The Stereochemistry of tetrasubstituted Sulphur.

A thesis submitted to the University of London for the degree of Doctor of Philosophy

by

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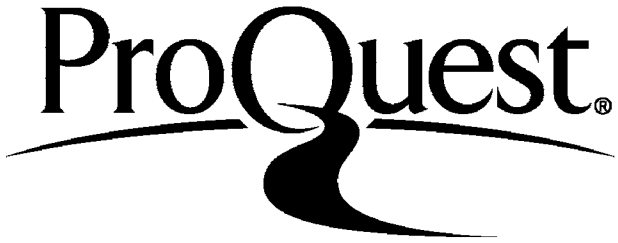

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Abstract.

This work describes the synthesis of an optically active chloramine-T analogue (Part I.) and its conversion into optically active forms of a derivative of tetrasubstituted Sulphur.(Part II.)

I thank Professor E.E.Turner for stimulation, Dr. D.M.Hall for several discussions and the Council of Bedford College for a post-graduate studentship.

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The Stereochemistry of tetrasubstituted Sulphur.

Part I.

The synthesis of Sodium 4-(3-menthyl)-benzenesulphonchloramide.

Introduction.

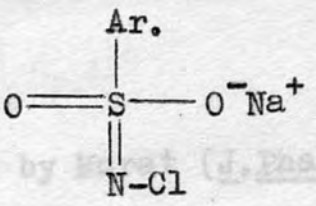
Chattaway (J., 1905, 148) first prepared sodium p-toluene sulphonchloramide , known as chloramine-T , by alkaline treatment of p-toluenesulphondichloramide (previously described by Kastle, Amer. Chem. J., 1895, 17, 704)

$$Ar.SO_2.NH_2 \xrightarrow[H^+]{Ca(OCl)_2} Ar.SO_2.NCl_2 \xrightarrow{NaOH} p(CH_3).C_6H_4.SO.(ONa):NCl$$

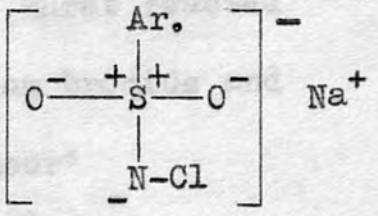
In 1916 Dakin, Cohen, Daufresne and Kenyon (Proc. Roy. Soc., 1916, 89B, 232) investigated the germicidal action of sodium hypochlorite and it appeared that this reagent was converting appropriate groups in protein to an :N-Cl function and this suggested biological testing of compounds containing this linkage . Chloramine-T was found to be active and its direct preparation by sodium hypochlorite treatment of the sulphonamide was described.

$$Ar.SO_2.NH_2 + NaClO = Ar.SO.(ONa):NCl + H_2O$$

Chloramine-T was first formulated as a derivative of isochloramine , (Chattaway, loc.cit.; Dakin, Cohen, Daufresne and Kenyon, loc.cit.; Mann and Pope, J., 1922, 1052)



Later workers suggested, (Clarke, Kenyon and Phillips, J., 1927, 188)



The aim of the present work was to prepare an optically pure 4-(3-menthyl)-benzenesulphonic acid and to convert this acid to the chloramine-T analogue with an optically pure menthyl residue replacing the methyl of the usual chloramine-T.

The preparation of the sulphonic acid was effected by sulphonation of the hydrogenation product of the known 3-phenylmenthene.

Discussion.

3-Phenylmenthene.

3-Phenylmenthene was first described by Murat (J.Pharm. Chim., 1911, 4 294; Chem.Zentr., 1911, II, 1449) as the dehydration product of 3-phenylmenthan-3-ol. Murat reacted l-menthone of $[\alpha]_D$ -23.6° with phenyl magnesium bromide and obtained a "liquid of menthol and camphor odour"
b.p. 175°/20mm., d^{20} 0.9843, n_D^{20} 1.527 , $[\alpha]_D^{20}$ -16.32
Treatment of this carbinol with oxalic acid, zinc chloride, or by passing over aluminium oxide at three hundred degrees gave a ~~three~~ 3-phenylmenthene having:
b.p. 268-272°/760mm., d^{20} 0.9621, n_D 1.537 , $[\alpha]_D$ +13.15°

Read and Watters repeated the carbinol preparation and oxalic dehydration in 1929 (J. 1929, 2165) . These workers starting from l-menthone of $[\alpha]_D^{16}$ -25.65° recorded the properties for the carbinol:
b.p. 170-172°/18mm., d_4^{25} 0.9872 , n_D^{25} 1.5265, $[\alpha]_D^{17}$ -22.87°
and for the dehydration product give:
b.p. 149-151°/18mm., d_4^{25} 0.9365, n_D^{25} 1.5275, $[\alpha]_D^{17}$ +43.48°

Similarly from d-isomenthone, $[\alpha]_D^{17}$ + 69.90° the carbinol had: b.p. 150-152°/9mm., d_4^{25} 0.9812, η_D^{25} 1.5265, $[\alpha]_D$ +0.44° and the oxalic acid dehydration product: b.p. 127-130°/5mm., η_D^{20} 1.527, $[\alpha]_D$ +16.3°

Read and Watters (loc.cit.) state "The alcohols are probably stereochemically heterogeneous because they are formed by partial asymmetric synthesis from equilibrium mixtures of l-menthone and d-isomenthone". In support of this contention these workers described the formation of addition compounds between magnesium dibromide and l-piperitone, d-isomenthone and l-menthone. On decomposition with water the l-piperitone had completely racemized and the other ketones had partially racemized. The addition complexes were therefore formulated by these workers as formed from the enol RC(H)—O - - - Mg(Br)(Br) - - - O(H)—CR and Schlenk and Schlenk (Ber., 1929, 62 920) haveproposed that the composition of the 'Grignard reagent' may be represented as $2RMgX \rightleftharpoons R_2Mg + MgX_2$. If this is so the reaction solution thus contains Read and Watter's 'enolisation reagent'.

Read and Watters (loc.cit.) point out the close similarity in physical properties of the olefins derived from the two ketones and that this may be taken to indicate a predominance of 3:4olefin formation. On empirical grounds this would be the expected path of elimination. Thus Harris and Turner ("Organic Chemistry", Longmans Green and Co., London, 1952, 58)state "Examination of a large number of alcohols of different type has led to a further generalization , that if an alcohol group is situated between carbon atoms attached to different numbers of hydrogen atoms water elimination will mainly involve that carbon bearing smaller number of hydrogen atoms". It was noted however that the olefin derived from l-menthone ~~had~~ had enhanced optical rotation.

More recently Carlin and his co-workers (J.Amer.Chem. Soc., 1945, 67 928; 1947, 69 50; 1953, 75 3969) have studied the dehydration of ortho-substituted 1-phenylcyclohexanols. They found that 1-(2:4-dimethylbenzene)-2:6-dimethylcyclo-hexanol , resistant to other reagents , was smoothly dehydrated by anhydrous oxalic acid at elevated temperatures,and showed

that possible rearrangement of the cycloalkyl ring did not occur in this and other analogous cases by conversion to diphenyl derivatives.

This work therefore indicated anhydrous oxalic acid as the preferred dehydration agent.

In the present work the carbinol obtained from l-menthone of $[\alpha]_D^{22}$ -28.23° had the properties : b.p. 138-140°/5mm., n^{25} 1.5232, $[\alpha]_D^{18.5}$ -25.39°, $[\alpha]_{5461}^{17.5}$ -30.15° and treatment with anhydrous oxalic acid at 180° gave the menthene b.p. 150-156°/22mm., n^{19} 1.5310, $[\alpha]_D^{21}$ +59.78°, $[\alpha]_{5461}^{21}$ +73.93°

It is noticeable that in the successive recorded preparations of these compounds the rotations have increased by significant amounts.

compound	rotation $[\alpha]_D$°	
3-phenylmenthan-3-ol	-16.32	(Murat, loc.cit.)
	-22.87	(Read and Watters, loc.cit.)
	-25.39	(This work)
3-phenylmenthene	+13.15	(Murat, loc.cit.)
	+43.48	(Read and Watters, loc.cit.)
	+59.78	(This work)

This may, perhaps, be accounted for by changes in Grignard technique. Dr. Chibber (Ph.D. Thesis, University of London, 1959)

has described the profound effects shown by increasing dilution and rate of stirring in suppressing side reactions such as diphenyl formation , in his Grignard studies. Also in this work an excess of magnesium was employed to further the prevention of self-coupling and only traces of diphenyl were isolated.

Le Brazidec (Bull. Soc. chim., (4), 17 106) treated 1-phenyl-4-methylcyclohexanol with anhydrous oxalic acid and oxidised the resultant olefin with permanganate. The product β-methyl-δ-benzoylvaleric acid showed that this dehydration resulted in a styryl compound. The 3-phenylmenthene ultra-violet spectrum(in cyclohexane) was found to be of the styrene type. Strong absorption bands were found at λ max.210mμ (log ϵ 4.08) λmin. occurred at 224mμ (log ϵ 3.76) and λmax.238mμ (log ϵ 3.87). Braude (Ann. Reports , 1945, 105) gives λmax.211mμ (log ϵ 4.20) and λ max.244mμ (log ϵ 4.08) for styrene.

R. Norman Jones (Chem. Reviews, 1943, 32 1) has discussed the spectra of the 1. and 2. propylidine benzenes

and the isomeric tetrahydro-naphthalenes and it is considered that the strong absorption band at 244mμ in styrene and the band in this region occurring in ~~this~~ the compounds of vinyl benzene structure is a conjugation band of the phenyl and olefin. In the present case the band at 238mμ is considered to be this conjugation band. The intensity, however , is somewhat lower than that reported for styrene itself and also for the similar band in 1-phenylcyclohexene which is reported as λ max. 247mμ (log ε 4.08) in cyclohexane. (Cope, Fawcett and Munn , J.Amer.Chem.Soc., 1950, 72 3399). Hirschberg (J.Amer.Chem.Soc. 1949, 71 3241) has described the effect of substituents on the styrene spectra and he records (in ethanol).

	λmax.	logε
Styrene	244	4.23
β -methylstyrene	246	4.25
α -methylstyrene	243.5	3.96
α:β -dimethylstyrene	244	3.94

The latter compound was oxidised by Klages (Ber., 1902, 2641) to acetophenone. The substituent methyl groups then tend to reduce the ability of the double-bond to conjugate with the aromatic ring as shown by the reduction in extinction coefficient.

Carlin and Landerl (J.Amer.Chem.Soc., 1953, 75 3973) have shown that the effect of successive introduction of methyl groups into the ortho-positions of the cyclohexyl ring in 1-phenyl-cyclohexenes is to lower the extinction and also move the position of the conjugation band to slightly lower wavelength.

Whilst the ultra-violet data in the present work only indicate a substantial amount of conjugated olefin , the shorter wavelength observed for the conjugation band is a definite diagnostic of restriction to complete conjugation. It seems then that in the postulated 3-phenyl-3:4-menthene the quite large iso-propyl group is exerting a steric effect thereby reducing the conjugation , and the ultra-violet result therefore is considered to be in accord with this structure.

The Hydrogenation of 3-phenylmenthene.

Hydrogenation of the main fraction of the oxalic acid dehydration product was slow, but uptake of hydrogen closely approaching one molecular proportion was observed after several days shaking with palladium-charcoal in ethanol. The possibility of aromatic reduction taking place on protracted hydrogenation was removed by an infinity run when uptake was observed during five days continuous shaking. The very slow absorption then ceased and two further days vigorous agitation caused no detectable uptake. The amount of hydrogen absorbed corresponded very closely to the one molecule required and there was no evidence that saturation of the benzene ring requiring a further three molecules of hydrogen, was occurring under the mild conditions used. Somewhat low hydrogen analytical data (H, 10.9, 10.8) were obtained by micro-analysis ($C_{16}H_{24}$ requires H, 11.2 per cent). These values suggest some sixty-three per cent reduction but a later repeat analysis gave a satisfactory figure. The initial low value may indicate that traces of diphenyl were present in the product (diphenyl requires H, 6.54 per cent).

Small fore-run fractions from the oxalic acid dehydration were obtained having lower rotation. Reduction of these fractions was found to be incomplete . Combined fore-run of rotation α_{5461} $+51^{\circ}$ was found to absorb seventy-six per cent of the molecular proportion of hydrogen, giving a product α_{5461} $+38.5^{\circ}$ This hydrogenation product was subjected to alumina adsorption chromatography in an effort to separate the suspected residual unsaturated material. The first eluted material , however , corresponded closely in properties $[\alpha]_{5461}$ +60.83 , n_D^{18} 1.5180 to the hydrogenation product of the main olefin fraction of higher rotation. Further elution gave material identified as carbinol.

The lower rotation and hydrogen absorption of the fore-runs is thus caused by thepresence of unchanged carbinol. A simple calculation on a weight-rotation basis indicated the presence of twenty-two per cent of the laevo rotating alcohol. This compares well with the observed hydrogen uptake of seventy-six per cent and is confirmed by the separation chromatographically of eighteen per cent of the carbinol. The hydrogen absorption gives therefore a diagnostic of olefin purity. It thus appears that the main dehydration fraction is substantially pure olefin.

The hydrogenation behaviour offers some support to the proposition that the dehydration of the 3-phenylmenthan-3-ol would result in the preferential formation of the 3:4 olefin. Styrene itself is readily reduced under mild conditions to ethylbenzene (Zartmann and Adkins, J.Amer.Chem.Soc., 1932, 54 1668) and with palladium-charcoal in ethanol , 1-phenylcyclohexene is easily reduced to phenylcyclohexane (Weinstock and Bordwell, J.Amer.Chem.Soc., 1955, 77 6706). The reduction of tertiary olefins is generally difficult. The rigidly held tetra-olefin in dodecahydrophenanthrene requires very drastic conditions, Raney nickel at 240°/200 atmospheres (Durland and Adkins , J.Amer.Chem.Soc., 1938, 60 1501) whereas Ott reports (Ber., 1928, 2124) reduction of cisdimethylstilbene in 39 minutes under mild conditions. Intermediate is the transdimethylstilbene which required 24 hours for its hydrogenation (Ott loc.cit.) and 1-methyl-2-1'-methylcyclohexylcyclohexene which was completely reduced in 15 hours with palladium-charcoal in ethanol at atmospheric pressure. (Bateman and Shipley, J., 1958, 2888). In comparison with the hydrogenation of the unsubstituted 1-phenylcyclohexene, one infers that the slow hydrogenation

observed in the present work , is an indication that the dehydration results in predominant formation of the 3:4,and therefore tetrasubstituted olefin,in accordance with classical and analogical conception.

The hydrogenation product ultra-violet spectrum shows negligable absorption in the region of 240mμ . This confirms the assignment of the strong band in this region in the olefin spectrum as a conjugation band involving the double-bond. The description of the material as a substantially reduced product was thus born out by spectral analysis and the physical properties are similar (apart from rotation) to those recorded by Ishikawa and Maeda (Science Reports Tokyo Burika Daigaku, 1937, A3 157 ; Chem.Abs.,31 7860^5) from synthesis based on alkylation of benzene with l-menthol.

Properties of 3-phenylmenthane			
density	refractive index	rotation	
0.934 /23°	1.5183 / 20°	$[\alpha]_{17}^{D}$ -3.898°	(Ishikawa and MAeda loc.cit.)
0.9305/21.5°	1.5175/ 21.5°	$[\alpha]_{5461}^{27}$ +61.04°	(This work)

During the course of this work two ~~complementry~~ papers appeared indicating the possibility of rearrangement occurring in simple dehydration of cyclohexanols. Schaeffer and Collins (J.Amer.Chem. Soc., 1956, 78 124) and independently Eliel, McCoy and Price (J.Org.Chem.,1957, 22 1533) observed that substantial rearrangement occurred on acid dehydration of 2-phenylcyclohexanol where the hydroxyl and tertiary hydrogen had a cis relative configuration. Some sixty per cent of their reduction product was found to be benzylcyclopentane whereas the latter workers found that ninety-seven per cent of the reduction product from the olefin derived from the trans isomer was phenylcyclohexane. Whilst there is a distinct structural dissimilarity in the alcohol dehydrated in the present work,it was felt necessary to confirm the hydrocarbon structure. The reduction product was therefore subjected to infra-red analysis. Prominent absorption bands were found at 3.38, 3.41, 3.47, 3.50, 6.86, 12.98, 13.28, 14.24 microns.

Jones and Sandorfy ("Chemical applications of Spectroscopy",Technique of Organic Chemistry, vol9,Interscience publishers Inc.,New York,1956,337) give the following correlation s.

Carbon-hydrogen stretching correlation.	Wavelength.
Asymmetric, in methyl group	3.38 microns
Asymmetric, in methylene group	3.42
Symmetric, in methyl group	3.48
Symmetric, in methylene group	3.50

The use of this region as a ring size diagnostic has been discussed by Plyler and Acquista (J. Res. Nat. Bur. Stand., 1949, 43 37) and by Hastings, Watson, Williams and Anderson (Analyt. Chem., 1952, 24 613). These workers find the methylene stretch sensitive to ring size. The first group give 3.42 and 3.51microns for the six membered, compared with 3.39 and 3.49microns for the five membered. The latter workers find 3.425 and 3.50microns for the six membered, in contrast to 3.385 and 3.48microns for the pentane type. The absorption found in the present work is thus, in the methylene stretch region, characteristic of the six membered ring.

The band at 6.86microns is probably an integration of several effects and is not useful as a diagnostic, but the strong sharp bands in the 13 to 14 microns region correlate well.

McMurray and Thornton (Analyt.Chem., 1952, 24 318) define "A correlation band as any band which empirical observation has demonstrated to be associated with a specific atom grouping. Its presence in the spectrum of a material indicates that the structure may be present ; its absence is certain evidence that the structure is missing." For monoalkyl benzenes these workers find strong sharp absorption at 14.27 to 14.40 microns. In addition benzyl type aromatics also absorb at 13.39 to 13.57, but in isopropyl type this second band shifts to about 13.10 to 13.19 microns. Potts (Analyt.Chem., 1955, 27 1027) states "In every case of a compound not having the alpha atom substituted there is a strong band at about 13.4 microns , never below 13.3 ; on the other hand , the great majority of the compounds having an alpha hydrogen substituted the strong band is at about 13.2 never above 13.3 microns." In the present work the strong band at 13.28 shows the isopropyl type of structure . Examination of cyclohexyl benzene spectra (American Petroleum Institute research project , 1956, 44 1844) showed bands in this region at 12.92, 13.29 and 14.35 microns,

whereas benzylcyclopentane (Obtained by courtesy of Professor Eliel , University of Notre Dame) absorbs strongly at 13.59 and 14.4 microns, and in the carbon-hydrogen stretching region methylene absorption occurs at 3.39 and 3.48 expected of the five membered ring present.

The pattern of absorption in the higher micron region shown by the reduction product confirms the absence of any styrene type olefin for which Thompson and Parkington (Proc. Roy. Soc., 1945, A184 3) record strong bands at 13.1 and 14.4 microns and also removes the possibility of the ~~alternant~~ 1:2 shift, as Ipatieff, Meisinger and Pines for 1-methyl-1-phenylcyclohexane find strong bands at 13.1 and 14.1 only. (J. Amer. Chem. Soc., 1950, 72 2772). The absence of absorption bands at 13.1 and between 13.4 and 13.6 microns in the spectrum of the hydrogenation product gives "certain evidence" that the structures of quaternary carbon aromatic and benzyl aromatic are absent, and this strong indication of absence of rearrangement is confirmed by correlations around 3.5 microns.

This is taken as a confirmation of Carlin's work on dehydration of ortho-substituted 1-phenylcyclohexanols (loc. cit)

and no report has appeared of rearrangement occuring on dehydration of an alcohol in which the hydroxyl group and a phenyl group are on the same carbon atom.

Barium 4-(3-menthyl)-benzenesulphonates.

The route involving the slow hydrogenation was persisted with, as sulphonation of the reduction product readily gave crystalline stable salts. The 3-phenylmenthane was stirred with warm, concentrated sulphuric acid till a test portion of the reaction gave a clear solution on dilution with water. Attempted isolation of the sodium sulphonate in the usual manner only gave tarry material. This was taken up in water and addition of barium ions gave the barium sulphonate as a sticky solid. Persistent recrystallisation from methanol gave small changes of rotation and eventually tedious fractionation gave a crop $[\alpha]_{5461}$ +70.16°, unchanged by further purification. Other salts were then prepared with intent to obtain a cleaner separation of isomers. The p-toluidine salt crystallised well but was very hygroscopic and was not pursued with.

The strychnine salt was next investigated. This salt crystallised nicely, and possessed the advantage ~~in~~ that the fractionation could be followed by melting point as well

as optical criteria, compared with the barium salts which were infusible up to 300°. Several crystallisations from ethanol gave a pure salt , which in itself provides a criterium of stereochemical purity of the sulphonic acid. This salt was very insoluble and was most conveniently decomposed by warm sodium methoxide and crystallising out the strychnine base. The resultant barium salt was identical in solubility characteristics and rotation with the barium salt obtained by persistent fractionation of the crude barium salt (i.e. the total sulphonation product). Further fractionation gave a second strychnine salt which afforded a barium sulphonate of markedly lower rotation. The alkaloid salt fractionation provided the readier separation of the optically pure 4-(3-menthyl)-benzenesulphonates.

4-(3-menthyl)-benzenesulphonamides.

Treatment of the active barium salts with phosphorus pentachloride gave the sulphonyl chlorides , which resisted acid hydrolysis but are reconverted to the barium salts by alkaline alcoholic treatment. Concentrated ammonia onthe

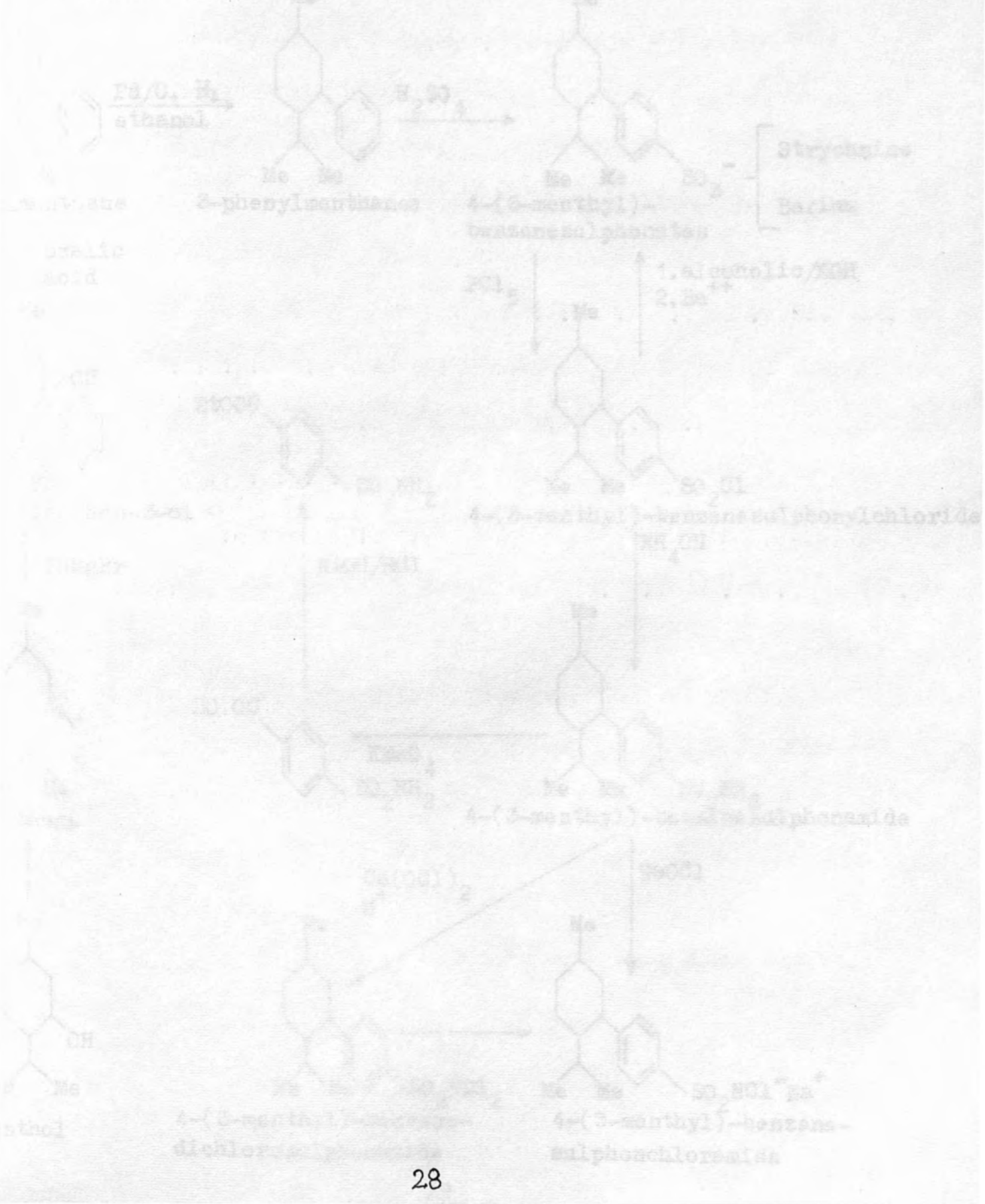
steam-bath gave the active sulphonamides in nearly quantitative yield. The sulphonamides were unchanged by further crystallisations, and on oxidation and subsequent esterification of the product, gave only ethyl-p-sulphonamidobenzoate, identical with an authentic specimen (Remsen, Annalen, 1875, 178 300).

The stereochemically pure sulphonamide of required orientation was therefore available for attempted conversion to the required chloramine-T analogue.

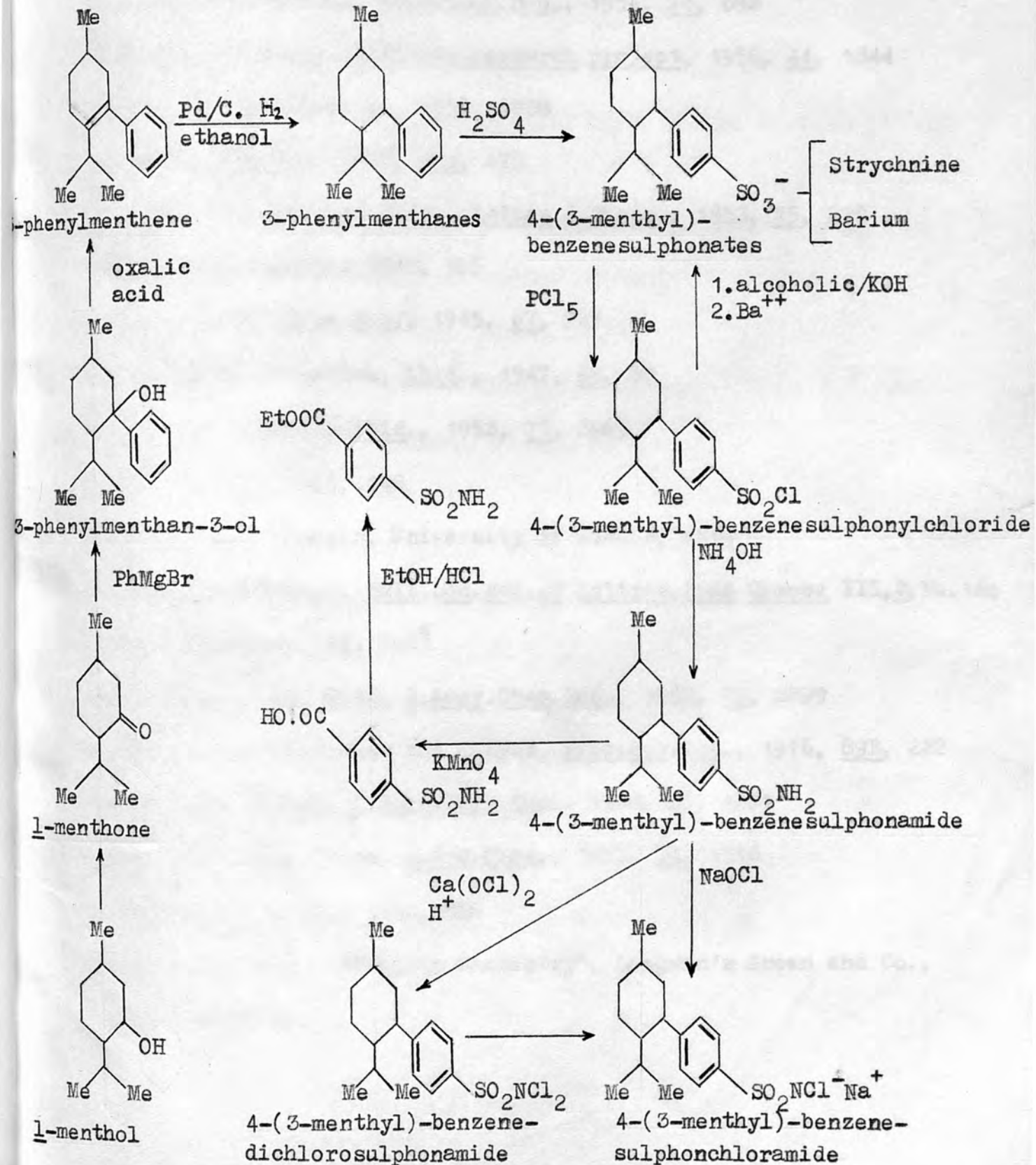
Sodium-4-(3-menthyl)-benzenesulphonchloramide.

The chloramine-T analogue was prepared by both Chattaway's procedure (loc.cit.) and by the later direct method (Hanby and Rydon, J., 1946, 866). Extreme difficulty was encountered in obtaining the dichlorosulphonamide pure. Eventually by several hypochlorite treatments satisfactory halogen values were obtained. The dichlorosulphonamide synthesis has been extensively discussed. (G.P.530,894., Chem.Abs., 1932, 26 153[3]; U.S.P.2,249,489., Chem.Abs., 44 7875[b]; Bhargava, Dhingra and Gupta, Indian J.Pharm., 1953, 15 229., Chem.Abs., 48 7586[g]; Zilberg, J.Gen.Chem., U.S.S.R., 1946, 16 2145., Chem.Abs., 42 144[e]; Akiyoshi and Okimo, J.Amer.Chem.Soc., 1954, 76 693 ; Chrzaszezewska, Bull. soc.sci.et lettres Lodz Classe III, 3 No.16., Chem.Abs., 49 212[e].) The crystallised dichlorosulphonamide when gently warmed with aqueous alkali, gave the sodium-4-(3-menthyl)-benzenesulphonchloramide, which, in characteristic manner, decomposed violently on direct heating , and gave calculated values on titration for active halogen. The preferred preparative procedure was the

direct treatment of the sulphonamide , dissolved in dilute alkali , with hypochlorite solution giving identical material.



Flow summary of synthetic work



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Part I. Experimental

Rotations were observed , at concentrations stated , in B.P. chloroform in a 20 cm. tube , on a polarimeter for which the calibrated error was $\pm 0.02^{\circ}$.

The preparation of l-menthone

Beckmann, (Annalen, 1889, 250, 325)

l-Menthol (90g.) was added in four portions to a stirred solution of potassium dichromate (117g.) and sulphuric acid (54c.c., 100g.) in water (600c.c.). The mixture was warmed to initiate the reaction . The internal temperature rose to about 70° and then fell after an hour when reaction was complete .

The mixture was extracted with ether , the ether washed three times with dilute sodium hydroxide , dried (Na_2SO_4) the ether evaporated , and the residue distilled.

The l-menthone (68g.,76%) had b.p. $93\text{-}94^{\circ}/18$mm., η^{21} 1.4520 , $[\alpha]^{22}_{5461}$ -33.94°, $[\alpha]^{22}_{D}$ -28.23° (homogeneous)

Beckmann,(loc.cit.), gives $[\alpha]_{D}$ -28.18° ; Vavon and Conduce, (Bull.Soc.chim.Belg.,36,59) give $[\alpha]^{24}_{5461}$ -34.60°.

The preparation of 3-phenylmenthan-3-ol.

Read and Watters, (J., 1929, 2171)

The Grignard reagent was prepared by the dropwise addition of bromobenzene (62.8 g., 0.40 mol., steam distilled and redistilled) to a stirred suspension of magnesium (12 g., 0.5 mol.) in dry ether (350 c.c.). The ether solution of the phenylmagnesiumbromide was decanted from the excess metal and l-menthone (37.5 g., 0.244 mol.) added dropwise with stirring . The reaction mixture was poured onto ice and then acidified with dilute sulphuric acid . The ether was separated, dried (Na_2CO_3) , evaporated and the residue distilled. After stripping off a lower boiling fraction , b.p. 100-120°/12 mm., (21 g.) , a fraction , b.p. 114-130°/5 mm. distilled which solidified in the water-cooled condenser. This solid (0.9 g.), crystallised from ethanol, had m.p. 70-72° and admixed with diphenyl The 3-phenylmenthan-3-ol (26.5 g., 47%) distilled at 138-140°/5mm. had n^{25} 1.5232 , $[\alpha]^{17.5}_{5461}$ -30.15°, $[\alpha]^{18.5}_{D}$ -25.39° (homogeneous) Read and Watters (loc.cit.), give n^{25} 1.5265, $[\alpha]^{17}_{D}$ -22.87°.

The preparation of 3-phenylmenthene

Read and Watters, (J., 1929, 2171)

The carbinol (21 g.) and anhydrous oxalic acid (42 g., Bowden, Org.Synth., 1941, Coll.Vol.I.,42) were heated at a bath temperature of 180° for three hours . After cooling the oil was decanted off and the residual solid oxalic acid washed three times with ether by decantation . The combined ether washes and the oil was washed thrice with water , dried (Na_2CO_3), evaporated and the residue distilled . After stripping off a small fore-run the 3-phenylmenthene distilled at 150-156°/22 mm. n^{19} 1.5310 , (17 g., 88%) , $[\alpha]^{21}_{5461}$ +73.93°, $[\alpha]^{21}_{D}$ +59.78°, (homogeneous), d^{23} 0.9256.

Read and Watters (loc.cit.), give b.p. 149-151°/18 mm., n^{25} 1.5275 $[\alpha]^{17}_{D}$ +43.38°, d^{25} 0.9365 .

The preparation of 3-phenylmenthane

The menthene (10.6 g.) and palladium charcoal (4g of 5%) in ethanol (120 c.c.) was shaken with hydrogen at room temperature (22°) and atmospheric pressure . After five days continuous shaking the uptake of hydrogen ceased when 1170 c.c. had been absorbed (Theoretical uptake 1210 c.c.).

The catalyst was filtered , the ethanol evaporated and the residue distilled. The 3-phenylmenthane had b.p. 130-136°/9 mm., $\eta^{21.5}$ 1.5175 , $\underline{d}^{21.5}$ 0.9305 , $[\alpha]^{27}_{5461}$ +61.04°(homogeneous). (Found: C,89.3, 89.2, 88.8; H, 10.9, 10.8, 11.3. Calc. for $C_{16}H_{24}$: C,88.8; H,11.2%). The infra-red spectrum(homogeneous) was 3.23 M, 3.26 M, 3.29 M, 3.38 S, 3.41S, 3.47 S, 3.50 S, 3.73 M br., 5.12 W, 5.22 W sh., 5.32 W, 5.43 W sh., 5.52 W, 5.70 W, 5.83 W, 6.21 M, 6.29 W, 6.67 M, 6.86 S, 7.20 M, 7.29 M, 7.40 W, 7.59 W, 7.70 W sh., 7.80 W sh., 7.93 W, 8.13 W, 8.28 W, 8.52 W, 8.63 W, 8.77 W, 8.86 W sh., 9.13 M, 9.22 M, 9.66 M, 9.78 W, 9.97 W, 10.19 W, 10.36 W, 10.42 W sh., 10.64 W, 10.83 W, 10.96 W, 11.30 W, 11.44 W, 11.60 W sh., 11.87 W, 12.98 S, 13.28 S, 14.24 microns S.

Chromatography of lower rotation reduction product

The small fore-runs from the dehydration were combined and had α_{5461} +51°. This material on protracted hydrogenation only absorbed 76% of the theoretical amount of hydrogen . The product (α_{5461} +38.50°) was chromatographed . As a result of small scale experiments,a column of 4 cms radius containing 500 g. of activated alumina (ex Hopkins and Williams and heated at

120° for four hours and cooled in a desiccator), gravity packed in petroleum ether 40/60°, was prepared. 20 g. of material α_{5461} +38.50° was added and the column developed with petroleum ether 40/60° and 25 c.c. fractions collected , the solvent evaporated , and residues distilled.

Fraction collected	Solvent	Weight	Properties
1 - 10	P.E. 40/60	-	-
11 - 16	same	10.7 g.	α_{5461} +54.03°
17 - 22	same	6.5 g.	α_{5461} +56.21°
23 - 28	same	-	-
Added further 18 g. of material (α_{5461} +38.50°)			
29 - 34	same	-	-
35 - 40	same	12 g.	α_{5461} +56.61°, n^{18} 1.5180
41 - 46	same	2.2 g.	α_{5461} +45.0°
47 - 52	10%benzene: P.E. 40/60°	-	-
53 - 58	same	-	-
59 - 64	20%benzene: P.E. 40/60°	-	-
65 - 70	5o%benzene: P.E. 40/60°	5 g.	α_{5461} -29.04°, n^{19} 1.5218
71 - 76	same	2 g.	α_{5461} -29.36°

Thus 38 g. of α_{5461} +38.50° yielded 29.2 g. corresponding closely in properties to the hydrogenation product of the main olefin fraction of higher rotation , and 2.2 g. of material of intermediate rotation, probably indicating saturation of the column. Stronger elution gave 7 g. of material having properties which identify it as carbinol.

The preparation of Barium 4-(3-menthyl)-benzenesulphonate.

The 3-phenylmenthane (21.6 g., 0.1 mol.) and concentrated sulphuric acid (19.6 g., 0.2 mol.) were stirred at 120° for 40 minutes . The resultant solution was then dissolved in water , neutralised with sodium carbonate , and saturated at the boil with sodium chloride . Only tarry material separated but addition of barium chloride solution gave a sticky pale yellow solid (32.5 g.). This was charcoaled and crystallised from methanol as prisms (19.5 g.) infusible up to 300°,

$[\alpha]^{24}_{5461}$ +52.32° (c 0.860)

(Found: Ba, 18.1 . $C_{16}H_{23}SO_3.0.5Ba.H_2O$ requires Ba, 18.0%)

This substance was readily soluble in chloroform but very sparingly in ethanol , isopropanol , acetone and ethyl acetate .

Persistent crystallisation of the barium salt from methanol gave small changes in rotation . Eventually successive crops were obtained $[\alpha]_{5461}$ +68.2°, +70.21°, +70.16°. This homogeneous, less soluble salt was better prepared through fractionation of the strychnine salt.

Strychnine 4-(3-menthyl)-benzenesulphonates.

The barium salt (113 g., 0.31 mol.) was finely powdered and added to a solution of strychnine hydrochloride (130 g., 0.32 mol.) in water (1200 c.c.) and stirred on the steam-bath for 7.5 hours. Filtered and washed with water, the salt 188.5 g.(94%) had $[\alpha]^{19}_{5461}$ +5.6°(c 1.072) . Several crystallisations from ethanol gave a crop (45 g.,25%) m.p. 285°,(changes at 207°), $[\alpha]^{18}_{5461}$ +18.76°,(c 1.172) unchanged by further crystallisation. (Found: C, 69.35; H, 7.1; N, 4.9. $C_{37}H_{41}O_5N_2S.(0.5H_2O)$ requires C, 69.5; H, 7.4; N, 4.4%)

Repeated crystallisation of the mother-liquor gave a second pure salt (9 g.,5%) m.p. 280°(admixed with less soluble salt m.m.p. 270-275°), $[\alpha]^{21}_{5461}$ +2.94°(c 1.532), (Found: C, 68.1; H, 7.4; N,4.3. $C_{37}H_{41}O_5N_2S.H_2O$ requires C, 68.5; H, 7.5; N, 4.3%)

Active barium 4-(3-menthyl)-benzenesulphonate.

The strychnine salt $[\alpha]^{18}_{5461}$ +18.76°(12.6 g.) was dissolved in hot methanol (120 c.c.) and added to a solution of sodium (0.5 g.) in methanol (10 c.c.) and refluxed for 3 hours. On cooling strychnine (6.5 g.) separated. The methanol was evaporated and the residue taken up in water (100 c.c.) and filtered to a clear solution. Addition of dilute barium chloride in slight excess gave the pure barium salt (7.3 g., quantitative), $[\alpha]^{22}_{5461}$ +70.0 (c 1.00) unchanged on repeated crystallisation from methanol whence it separates as characteristic prisms.

Similarly the strychnine salt $[\alpha]^{21}_{5461}$ +2.94° gave a second barium salt having $[\alpha]^{18}_{5461}$ +30.07°(c 0.4360)

Active 4-(3-menthyl)-benzenesulphonylchloride.

The barium salt $[\alpha]^{22}_{5461}$ +70.0 (7.3 g.,0.02 mol.) and phosphorus pentachloride (3.2 g.,0.15 mol.) were heated for 4 hours in a bath maintained at 150°. A homogeneous melt gradually formed, which was cooled and extracted four times with boiling benzene. The benzene was evaporated and the residue distilled.

The sulphonylchloride , 4.8 g.(76%), had b.p. 210°(bath)/2 mm. as a colourless,viscous oil freely soluble in all the common solvents with the exception of methanol. When methanol was cautiously added to a well cooled ether solution (-70°) solid separated. The sulphonylchloride melted at 13-14°and had $[\alpha]^{24}_{5461}$+67.56°(c 0.6040) . These properties were unchanged by similar precipitation. The sulphonylchloride was recovered unchanged after attempted hydrolysis with boiling 1:1 HCl. Hydrolysis with alcoholic potassium hydroxide was successful and addition of barium ions gave the barium salt. An attempted preparation of the free acid by treatment of the lead salt with hydrogen sulphide (Kursanoff, Annalen, 1901, 318, 309) only gave oily product.

Similarly the barium salt $[\alpha]^{18}_{5461}$ +30.07° gave the sulphonylchloride b.p.218°/3 mm. as a colourless oil $[\alpha]^{15}_{5461}$+33.58°, (c 0.5360) , (Found: C, 60.6; H, 7.4; Cl, 10.5. $C_{16}H_{23}SO_2Cl$ requires C, 61.0; H, 7.4; Cl 11.3%)

Active 4-(3-menthyl)-benzenesulphonamide.

The sulphonylchloride (2.5 g.) and concentrated ammonia (50 c.c.) were heated on the steam-bath and then evaporated , with vacuum , to dryness . The residue was taken up in benzene , washed with water and the benzene evaporated. The residue was crystallised from benzene/petroleum ether 40-60° whence the sulphonamide (2.2 g.,94%) separated as sheaves of stout needles m.p. 135°, $[\alpha]^{19}_{5461}$ +71.60° (c 0.740) unchanged by further crystallisation from the solvent mixture or from methanol.

(Found: C, 65.0; H, 8.6; N, 5.1; S, 10.8. $C_{16}H_{25}NSO_2$ requires C, 65.1; H, 8.5; N, 4.7; S, 10.8%)

Similarly the second sulphonylchloride gave a sulphonamide as needles from benzene/petroleum ether 40-60° m.p. 132 -133° (admixed with the first sulphonamide m.m.p. 110-114°), $[\alpha]^{19}_{5461}$ +34.03° (c 0.7640) , (Found: C, 64.4,65.3; H, 8.6,7.9; N, 5.7,4.8; S 10.7%).

The preparation of p-sulphonamidobenzoic acid.

p-Toluenesulphonamide (m.p.135-136°)(17.1 g.) was dissolved in a warm solution of sodium hydroxide (4.5 g.) in water (300 c.c.). Potassium permanganate (30 g.) was finely ground and added portionwise over four hours and stirring continued for a further two hours. Filtered and washed with hot water. The filtrate was decolourised with sodium meta-bisulphite and on making acid solid separated. The p-sulphonamidobenzoic acid (18.0 g.,90%) had m.p.292-293°d.(lit.280°d.)

The preparation of ethyl-p-sulphonamidobenzoate.

Remsen, (Annalen,1875, 178, 300)

The p-sulphonamidobenzoic acid (4 g.) was dissolved in warm ethanol (250 c.c.) and dry hydrochloric acid gas passed in till saturated (fourty minutes) without cooling . The ethanol was evaporated and the residue crystallised from water. Ethyl-p-sulphonamidobenzoate separated as stout needles m.p. 102-103°. Remsen (loc.cit.) gave m.p. 110-111°and 94-95° (Found: C,47.1;H,4.6;N,5.8.Calc. for $C_9H_{11}O_4NS$. C,47.1;H,4.8; N,6.1%).

The oxidation of 4-(3-menthyl)-benzenesulphonamides.

The two active sulphonamides (0.8 g.) were oxidised as described for the methyl analogue , with potassium permanganate (10 g.) in a warm solution of sodium hydroxide (2 g.) in water (100 c.c.) . The acidic products were in each case esterified and did not then depress the melting point of ethyl-p-sulphonamidobenzoate.

The preparation of chloramine-T.

Method 1. Chattaway, (J.,1905, 148); Soper, (J.,1924, 1909)

p-Toluenesulphonamide (8.6 g.) was dissolved in glacial acetic acid (125 c.c.) and on addition of bleaching powder solution (from 8g. of powder) the p-toluenesulphondichloramide precipitated and had m.p. 80-82°. (lit. 83°). This was (1.8g) added portionwise to sodium hydroxide solution (15 c.c. of 10%) at a bath temperature of 85°with stirring,so that each portion dissolved leaving a clear solution . On standing at room temperature long needles separated 1.6 g. (90%), m.p.180°(impetuous d.)

Method 2. Hanby and Ryden, (J., 1946, 866)

p-Toluenesulphonamide (8.6 g., 0.05 mol.) was dissolved in warm sodium hydroxide solution (5o c.c. of 10%), and sodium hypochlorite solution (50 c.c. of 10%) added dropwise with vigorous stirring. At the end of the addition, solid began to separate and, after cooling in ice water, was filtered. The chloramine-T 10.4 g. (90%) impetuously decomposed at 175°.

The titration of the chloramines.

The chloramine was dissolved in acetic acid and a calculated excess of potassium iodide in water added . The liberated iodine was titrated with a standardised sodium thiosulphate solution.

The material prepared above (0.0620 g.) was dissolved in acetic acid (25 c.c.). 10 c.c. portions were added to potassium iodide (0.5 g.) in water (10 c.c.) and the resultant solution titrated with thiosulphate solution (0.00992 N.) till colourless in the presence of freshly prepared starch paste. Titres were 19.05 c.c. and 18.9 c.c. Therefore found Cl, 13.51 13.4. $C_7H_7O_2NSCl.Na.2H_2O$ has 13.45% of active halogen.

4-(3-menthyl)-benzenedichlorosulphonamide.

The pure sulphonamide (0.77 g.) in acetic acid (2 c.c.) was treated with an excess of bleaching powder solution (from 0.5 g. of powder) when a viscous oil separated . This was washed and triturated with water to a sticky solid which was re-treated as above . The product was dried over phosphorus pentoxide to a free running powder (0.97 g.) . Crystallisation from purified petroleum ether 40-60° gave prisms m.p. 63-65°. (Found: Cl, 18.8 .$C_{16}H_{23}O_2NS.Cl_2$ requires Cl, 19.4%)

Sodium 4-(3-menthyl)-benzenesulphonchloramide.

Method 1.

The dichlorsulphonamide (0.3 g.) was added in small portions to stirred sodium hydroxide solution (1.5 c.c. of 10%) in a bath at 50°. On standing needles separated (0.13 g.) which impetuously decomposed at 152°, after sintering at 142°. (Found: Cl, 9.1 .$C_{16}H_{23}O_2NS.Cl.Na.2H_2O$ requires Cl, 9.1%) These properties were unaffected by reprecipitation from well cooled sodium hydroxide solution. A specimen dried over

magnesium perchlorate at 80°/ 5mm. for three hours decomposed vigorously at 170°. (Found Cl, 10.3. $C_{16}H_{23}O_2NS.Cl.Na$ requires 10.1%).

Method 2.

The pure 4-(3-menthyl)-benzenesulphonamide (0.65 g.) was dissolved at 40° in a stirred solution of sodium hydroxide (75 c.c.of 2%) and sodium hypochlorite solution (4 c.c. of 10%) added dropwise. After thirty minutes a further 2 c.c. of hypochlorite wereadded and stirring continued for a further thirty minutes . On cooling characteristic needles separated identical with the sodium 4-(3-menthyl)-benzenesulphonchloramide prepared by method 1.(0.77 g.,76%).

Part II.

Part II.

The Stereochemistry of tetrasubstituted Sulphur.

Introduction.

1. The Sulphonium compounds.

Pope and Peachey, (J., 1900, 1072.,) treated methylethyl sulphide with bromoacetic acid and formulated the reaction as

$$C_2H_5\text{-}S\text{-}CH_3 + Br\text{-}CH_2COOH \longrightarrow C_2H_5\text{-}\underset{\displaystyle Br}{\overset{\displaystyle CH_2COOH}{\overset{|}{\underset{|}{S}}}}\text{-}CH_3$$

Treatment with silver(+)camphorsulphonate gave the sulphonium-(+)camphorsulphonate which, as a result of protracted crystallisation, gave a fraction which was converted to the chloroplatinate having $[\alpha]_D$ +4.6 and $[M]_D$ +30.8°. Pope and Peachey formulated the carboxymethylmethylethylsulphonium chloroplatinate as, $\left[C_2H_5\text{-}\overset{\displaystyle CH_2COOH}{\overset{|}{\underset{|}{S}}}\text{-}CH_3\right]_2 PtCl_4$ and stated "_ _ _ succeeded in obtaining an optically active substance which owes its rotatory power to the presence of an asymmetric quadrivalent sulphur atom and have thus proved that in compounds of the type SX_4 the sulphur atom is truly quadrivalent" and conclude "_ _ _ sulphur atom acts as a centre of optical activity just as does the carbon one". Similarly Smiles, (J., 1900, 1174,) described the preparation of methylethylphenacylsulphonium picrates having

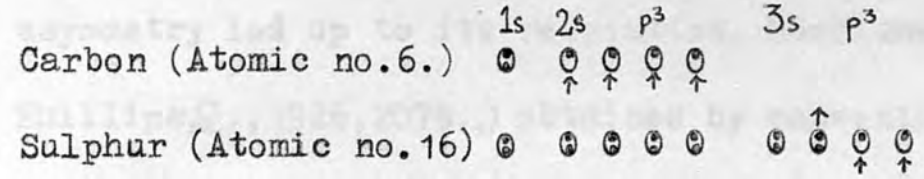
rotations of $[\alpha]_D$ -9.2 and $[\alpha]_D$ +8.1°.

These active sulphonium compounds became of exceptional interest several years later when Werner's views on directed and non-directional valencies became known. It appeared that their optical activity was due to the three rigidly held groups around the sulphur atom. The explanation of the optical activity by direct analogy with tetrasubstituted carbon was overthrown.

2.(a). The Sulphinic esters.

Optical activity in trisubstituted sulphur was confirmed when Phillips,(J., 1925, 2552,) described active sulphinates obtained by partial resolution involving ester interchange.

To account for the asymmetry, Phillips replaced the then accepted double bond formula, which if tetrahedral would give rise to a flat molecule, with a bond structure containing a semi-polar bond from sulphur to the oxygen atom, which received strong support from parachor measurement. Phillips stated as a preliminary hypothesis that "The sulphur atom is asymmetric since it has three different groups attached to it and possesses a lone pair of electrons which render the system analogous to that by which an asymmetric carbon is surrounded." The octet theory required that in a stable molecule, each atom would be surrounded by a shell of eight valency electrons. Many lines of evidence have suggested the following electron configurations when activated to the state involved in chemical bonding.



On this theory sulphur can complete its octet by joining in two normal covalencies and making a third singlet bond by donating one electron pair. The four pairs of electrons, the fourth pair is unbonded, would then be directed to the corners of a tetrahedron.

The sulphonium compounds were represented as $\left[C_2H_5\text{-}\overset{CHCOOH}{\overset{|}{S}}\text{-}CH_3\right]^+ X^-$, the loss of one electron by ionization enabling the sulphur atom to complete its octet with three covalencies, and again the fourth pair is unbonded, the optical activity being entirely due to the cation. This discussion replaces the direct analogy with tetrasubstituted carbon with an electronic one, but Phillips final thesis was "An atom can be asymmetric if it is attached to three disimilar groups and carries a positive charge" and he actually pictured the atom and the three substituents at the four corners of a tetrahedron.

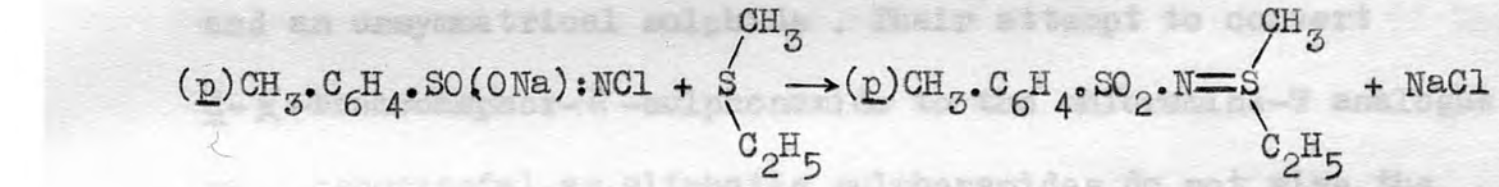
2.(b). The Sulphoxide.

The possibility of the sulphoxide existing as a semi-polar bond and fulfilling the Phillips requirement for

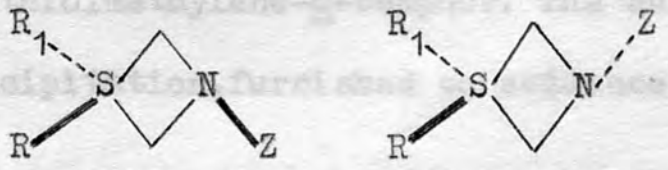
asymmetry led up to its resolution. Harrison, Kenyon and Phillips,(J., 1926, 2079.,) obtained by conventional methods 4-amino-4'-methyldiphenylsulphoxide $\pm$ 123° and 3-carboxyphenylmethylsulphoxide in forms having $[\alpha]_D$ +137 and -133°. Thus the double bond formula was replaced by $R_1R_2S^+--O^-$

3. The Sulphidimines.

Chloramine-T was found to condense readily with simple sulphides giving crystalline sulphidimines containing a new nitrogen-sulphur bond. Raper (Reports to the British Chemical Warfare department, 1917) found the derivative with 2:2'-dichlorodiethylsulphide useful for characterising small amounts of this compound, mustard gas. Mann and Pope (J., 1922, 1052) extended Raper's work by a study of the action of chloramine-T on other sulphides and formulated the reaction,



This formulation of the sulphidimine by Mann and Pope , would give rise to a planar configuration of four equivalent bonds around the sulphur , and predicts possible geometrical isomerism (of the oxime type).



where Z is tosyl

Many crystalline sulphidimines have been examined and no report has appeared of this type of compound occuring in two forms. It therefore appears that the possible isomerism due to the nitroger

configuration is unstable or that the nitrogen valencies exist in some alternate $^{iv}_{\wedge}$ configuration.

Later Mann and Pope (J.,1924, 911) were doubtful if the double bond between nitrogen and sulphur was a complete description of this linkage and commented "The problem here is whether the four valency units of IV S are all comparable with those of carbon, or whether one is coordinated". They suspected this type of compound would be asymmetric and attempted to prepare a sulphidimine from an optically active chloramine-T and an unsymmetrical sulphide . Their attempt to convert d-α-bromocamphor-π-sulphonamide to the chloramine-T analogue was unsuccessful,as aliphatic sulphonamides do not give the derivative (Cf. Clutterbuck and Cohen, J., 1922, 120; 1923,2501) As an alternative approach chloramine-T was condensed with the optically active ethylthiolmethylene-d-camphor. The sulphidimine, despite repeated reprecipitation,furnished no evidence of dC.dS. and dC.lS. isomerism.

Clarke, Kenyon and Phillips (J., 1927, 188) succeeded in obtaining evidence of asymmetry in this type of compound

and therefore replaced the double bond with a singlet donor bond from sulphur to nitrogen. They prepared the sulphidimine of m-carboxyphenylmethylsulphide and by conventional methods obtained it in forms ± 337°. One pair of enantiomorphs only was obtained in this case, and also in the resolution of the sulphidimine of m-carboxyphenylethylsulphide (Holloway, Kenyon and Phillips, J., 1928, 3000).

A historical description has been presented of four types of optically active trisubstituted sulphur compound. Phillips has represented the oxy-sulphur bond as a singlet linkage of the donor type and has accounted (in his more rational hypothesis) for the activity on the basis of four pairs of electrons in the valency shell arranged tetrahedrally . On this basis it is of interest to consider the stereochemical possibility when the spare (fourth) pair becomes bonded. Presumably a tetrahedral configuration would result and if the fourth substituent is unlike the other dissimilar three groups then optical activity would be expected. Clarke, Kenyon and Phillips (loc. cit.) attempted to study this possibility but on attempted oxidation

of S-m-carboxyphenyl-S-methyl-N-toluene-p-sulphonylsulphidimine with hydrogen peroxide degradation occured, p-toluenesulphonamide and m-carboxyphenylmethylsulphone only were isolated.

4. Physical investigations.

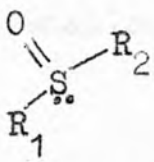
The rigorous application of the octet theory involving the donor singlet linkage to oxy-sulphur and related compounds has been discarded.

(a) The evidence provided by parachor is no longer regarded as conclusive.

(b) It is now believed that an element in the second row of the periodic table can expand its valency shell to contain more than eight electrons.

(c) Phillips, G.M., Hunter and Sutton, (J., 1945, 146,) found that the dipole moment which they associate with the oxy-sulphur link is only about one third of value required for full charge transference and that the oxy-sulphur separation is even shorter than that calculated on the basis of additivity for the sulphur to oxygen double bond.

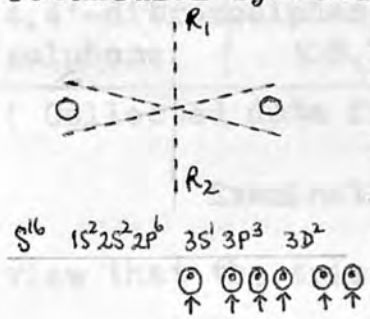
These workers favour the double type of linkage and proposed a trigonal bypyramid (Cf. PCl_5 and PF_5) arrangement i.e.



S^{16} $1s^2\ 2s^2 2p^6$ $3s^2$ $3p^3$ $3d^1$

This arrangement was derived on theoretical grounds by Kimball, (J. Chem. Physics, 1940, 8, 188) from SP^3D electron functions.

Extension of this system to sulphones having two double oxy-sulphur bonds is unsatisfactory, the electron functions involved are then D^2SP^3 i.e. six bonds which are known to have octahedral symmetry (Cf. $S F_6$). This system could give as a likely configuration the planar form shown. Since the sulphones are known to have a tetrahedral structure this picture is not stereochemically attractive.



The deductions of Sutton and coworkers are open to criticism and at present the details of the exact nature of the bonds around the sulphur atom are uncertain and in a state of flux.

Valency Angles obtained from Physical Studies.

Compound	∠ X-S-O	∠ X-S-X	Method
F_2SO	106.8°	92.8°	microwave
Cl_2SO	106.5°	114°	electron diffraction
$(CH_3)_2SO$	107°	100°	electron diffraction
$(C_6H_5)_2SO$	106.2°	97.3°	X-ray diffraction

Thus in the sulphoxides the three sulphur bonds form a shallow pyramid.

Passing on to the tetrasubstituted sulphur it may be noted that the sulphate type tend to the tetrahedral e.g. potassium ethyl sulphate ∠O-S-O is 109° (Jarvis, Acta. Cryst., 1953, 6327.)

Compound	∠ X-S-O	∠X-S-X	∠O-S-O	Method
F_2SO_2	107.1°	92.8°	129.6	microwave
Cl_2SO_2	106.5°	111.2°	119.8°	electron diffraction
$(CH_3)_2SO_2$	105°	115°	125°	electron diffraction
4,4'-dibromodiphenyl-sulphone	108.7°	100°	131°	X-ray diffraction

(Collected data from Abrahams, Quart. Reviews ,1956,X,407)

Examination of the physical data gives rise to the view that the trisubstituted compounds may be pictured as incipient tetrahedra and that the approximate tetrahedral angles are preserved on passage to the tetrasubstituted state.

Chemical attempts to investigate valency angle in oxy-sulphur compounds haveled to rather negative results (Cf. McLean and Adams, J.Amer.Chem.Soc.,1933,55 4683; Rule and Turner,H.M.,J.,1935,319; Luttringhaus and Bucholz ,Ber.,1939, 72B 2057.)

The Stereochemistry of tetrasubstituted Sulphur.

Discussion.

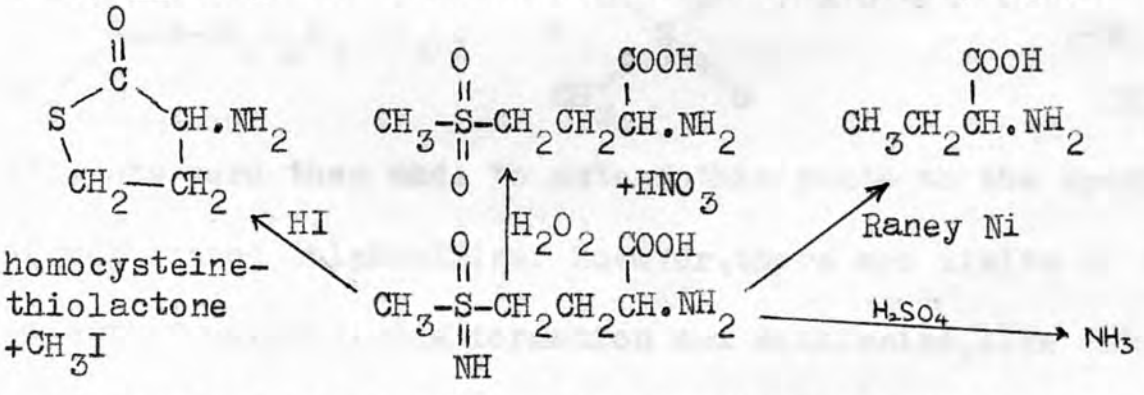
The Sulphoximines.

In the introduction a review was given of various optically active sulphur compounds. The concept emerged that the bond structure of unevenly trisubstituted sulphur may be pictured as an incipient tetrahedron and that this is born out by both physical studies and resolutions. A study of physical data has indicated that in passing from the tri- to the tetra-substituted state the approximate tetrahedral angles tend to be preserved. If this is so, then an unevenly tetrasubstituted sulphur compound should be optically active but this possibility has not been investigated owing to the ~~synthetic~~ unavailability of well defined potentially resolvable compounds.

Recently a new type of stable compound containing four different groups attached to sulphur has appeared on the chemical scene and may perhaps be described as an unnatural natural product. In 1946, Mellanby,(Brit.Med.J., 1946, 2 885) noted that wheat flour which had been 'improved' by treatment with nitrogen trichloride (agenised flour) produced symptoms in dogs similar to running fits : A flour which had not been agenised was not toxic. If the diet of agenised flour was

continued the animals became worse , developed epileptiform fits and died. In view of the widespread use of agenised flour it was important to isolate and determine the nature of the toxic substance.

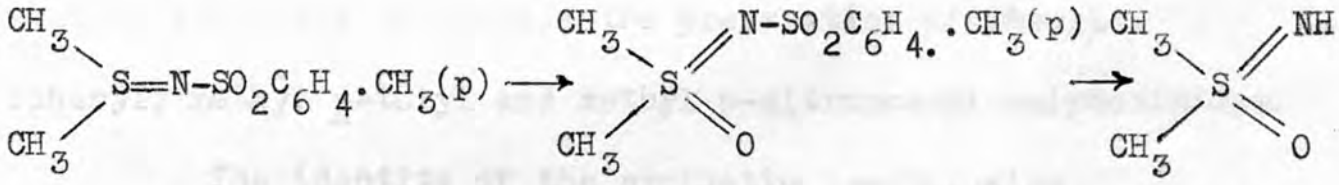
By tedious separation techniques three groups of workers isolated a crystalline substance which was toxic to small animals at a dosage of 2mg. or less. Bentley, McDermott, Whitehead and Moran ,(Nature, 1950 165 150,) gave analysis for $C_5H_{12}O_3N_2S$ and showed that on hydrogenolysis (over Raney nickel) ,α-aminobutyric acid was formed . They regarded the toxic substance as derived from methionine with the addition of an oxygen and an imino group. Coupled with further degradations by Misani, Fair and Reiner,(J.Amer.Chem.Soc. 1950, 73 459,) the tetrasubstituted structure emerges.



The substance was stable to N hydrochloric acid for one hour at reflux but 24 hours refluxing with 5N sulphuric acid liberated one molecule of ammonia.

The structure for the toxic substance as methionine sulphoximine derived from analytical and degradative evidence was accepted but its confirmation by synthesis proved very difficult. Exhaustive studies were made of the direct action of nitrogen trichloride on methionine and simple methionine peptides but no formation of toxic substance was detected.

In model experiments Bentley and Whitehead(J., 1950, 2081,) returned to the earlier attempts of the theoretical chemists (Clarke, Kenyon and Phillips J., 1927, 188) and succeeded in obtaining the first laboratory synthetic sulphoximine , the simplest member, by permanganate oxidation of SS-dimethyl-N-toluene-p-sulphonylsulphidimine followed by acid hydrolysis of the sulphoximide.



Attempts were then made to extend this route to the synthesis of methionine sulphoximine. However, there are limits to the extent of sulphidimine formation and methionine, like other heavier substituted sulphides , does not form one; with equimolecular quantities of chloramine-T, methionine sulphoxide is formed and in the presence of excess further oxidation at

the α-carbon occurs.

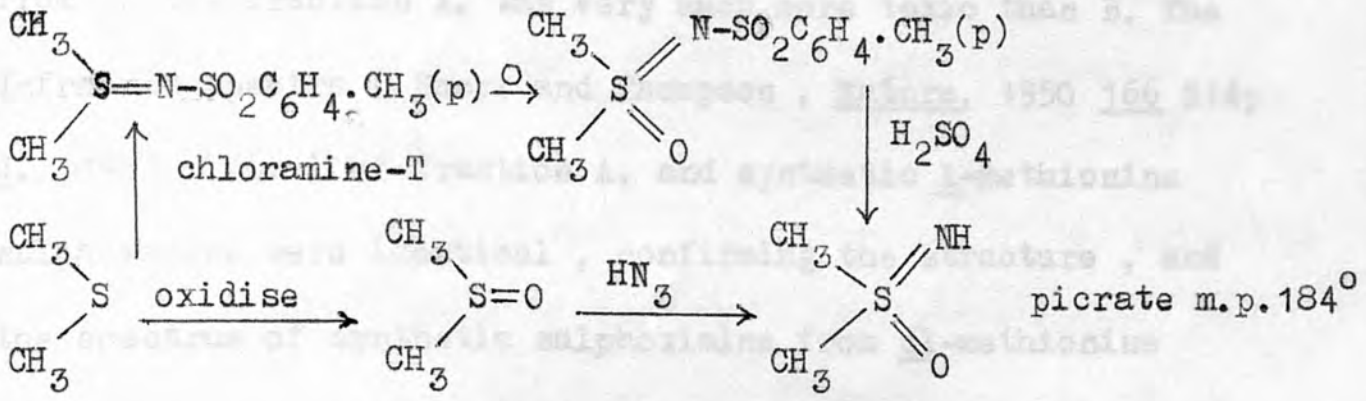
An alternate[iv] preparation of sulphidimines has been described by Tarbell and Weaver,(J.Amer.Chem.Soc.,1941, 63 2939,) which involves condensation of a sulphoxide with the sulphonamide, in presence of acidic dehydrating agents,but methionine sulphoxide failed to condense with toluene-p-sulphonamide.

After numerous unsuccessful attempts Bentley and co-workers,(Nature, 1950, 165 735,)eventually achieved the laboratory synthesis of methionine sulphoximine by the action of hydrazoic acid on methionine sulphoxide in presence of sulphuric acid under the conditions of the Schmidt rection. This synthesis was also described simultaneously by the Reiner group (Arch.Biochem.,1950, 27 234) who later extended the route to include the preparation of diamyl , diphenyl, methyl p-tolyl and methyl p-nitrophenyl sulphoximines.

The identity of the synthetic l-methionine sulphoximine with the isolated toxic substance was shown by melting point , mixed melting point , Rf. values of paper chromatograms in four solvents, elementary analysis and characteristic toxicity.

The structure of the product of this synthetic route as a tetrasubstiuted sulphur derivative was confirmed

by Bentley and co-workers when the sulphoximine obtained by reacting dimethyl sulphoxide with hydrazoic acid was shown to be identical with the acid hydrolysis product of SS-dimethyl-N-toluene-p-sulphonylsulphoximine.



Examination of Infra-red spectra of several sulphoximines has supported the proposed structure but certain anomalies appeared which merit discussion. In a more detailed account of the isolation of the toxic substance Bentley, McDermott, Pace, Moran and Whitehead., (Proc.Roy.Soc., 1950, B137 402) considered the tetrasubstituted sulphur as a possible asymmetric centre, and that the toxic substance , if the l-methionine centre is not racemized during the isolation , would be a mixture of two diastereoisomerides . Crystallisation of toxic substance picrate gave two fractions.

Toxic Substance. X. m.p.234°

picrate fractionation and then reconverted to bases.

A. m.p.248° B. m.p. 234°

The elementary analysis and Rf. values were indistinguishable from X. but fraction A. was very much more toxic than B. The Infra-red spectra (Short and Thompson , Nature, 1950 166 514; J., 1951,1746.) of fraction A. and synthetic l-methionine sulphoximine were identical , confirming the structure , and the spectrum of synthetic sulphoximine from dl-methionine sulphoxide only differed in small details,expected of such isomers,but the spectra of B. showed marked differences from A. The spectroscopists concluded that the"exact nature of fraction B. is undecided ", and Bentley and co-workers stated that the differences in spectra between A. and B. "appears to be greater than can be accounted for on the basis of stereoisomerism and it would appear that separation effected by picrates cannot be considered solely as a partial resolution of diastereoisomers."

From the data available it is difficult to assess the stereochemical significance of this work. Lavine,(J. Biol. Chem.,1947,477.) has described the separation of optically active l-methionine sulphoxides. He extended some unpublished results of Toennies and Kolb who obtained a sharp separation of the sulphoxide of dl-methionine as the picrates. Each fraction was

optically inactive and therefore consisted of the two possible racemates . Lavine oxidized l-methionine to the sulphoxide $[M]_D$+24.8 and succeeded in separating the active sulphoxides as their picrates having $[M]_D$ + 163.5° and $[M]_D$ -118.4° . Treatment with chloramine-T destroyed the methionine centre of asymmetry and rotations were obtained of +145 and -142° attributed to the sulphoxide group.

This analogous work is illustrative of the principle that a molecule containing two unlike asymmetric centres can exist in two inactive and four active forms. In view of the drastic conditions used in the separation of the toxic substance it seems likely that the methionine centre could well be racemized or partially racemized. The nature of the separation effected by picrate fractionation could therefore be clarified by examination of optical activity . No rotational evidence however has been disclosed. Reiner and co-workers (Trans. Amer. Assoc. Cereal Chemists ,1951, 9 1,.) were unable to separate their toxic substance into two picrate fractions and also found that the sulphoximines prepared (hydrazoic acid) from l-methionine-l-sulphoxide and l-methionine-d-sulphoxide had identical rotations , melting points and toxicities.

It may be said then that the work emanating from the isolation of the toxic substance does not provide a clear-cut demonstration of optical activity but showed that unevenly tetrasubstituted sulphurs exist as stable compounds and the gap is bridged between the resolved trisubstituted and the potentially resolvable tetrasubstituted.

The synthesis of an unsymmetrical sulphoximide.

The first member of a new class of sulphur compound, dimethyl sulphoximine , was prepared by permanganate oxidation of SS-dimethyl-N-toluene-p-sulphonylsulphidimine to SS-dimethyl-N-toluene-p-sulphonylsulphoximine , followed by acid hydrolysis.

As part of a study of the reactions of an optically active chloramine-T, the synthesis and properties of which have been described in section I, it seemed of interest to attempt its conversion to the sulphoximide of a mixed sulphide, in order to investigate possible isomerism of the dC.dS. and dC.lS. type suggested by the following facts.

Clarke, Kenyon and Phillips,(J., 1927, 188)have expressed the view that the sulphoxide bond and the sulphur-nitrogen link in the sulphidimines are stereochemically analogous . This analogy is furthered by the isolation of two forms of the sulphidimine sulphoxide and the disulphidimine, as well as two forms of the disulphoxide of 1:4-dithian, reported by Bell and Bennett,(J., 1927, 1798; 1928, 92.)On oxidation sulphoxides give sulphones for which physical data indicate an approximately tetrahedral arrangement of bonds. On the basis of these observations it is reasonable to assume that addition of an

oxy-sulphur bond to the sulphidimine would give an approximately tetrahedral bond structure.

Since Clarke, Kenyon and Phillips,(J.,1927, 188,) record that breakdown occurred on attempted oxidation of their mixed sulphidimine, model experiments with chloramine-T were first tried. The mixed sulphide chosen was p-nitrophenylmethyl as the alternate[iv] preparation of its sulphoximine by the hydrazoic acid route has been described. (Misani, Fair and Reiner, J.Amer. Chem.Soc.,1951 73 459).

Chloramine-T and p-nitrophenylmethylsulphide were reacted in warm aqueous ethanol. Crystallisation gave some sixty per-cent as a less soluble fraction which analysed for the sulphidimine. Fractionation of the mother-liquor yielded toluene-p-sulphonamide and some twenty per-cent of the sulphoxide. The preparation of the sulphidimine was also effected by the route of Tarbell and Weaver, (J.Amer.Chem.Soc., 1941, 63 2939,) When toluene-p-sulphonamide and p-nitrophenyl-methylsulphoxide were refluxed in chloroform, in presence of phosphorus pentoxide, identical material was obtained. The structure was also confirmed by acid hydrolysis which gave a nearly quantitative yield of toluene-p-sulphonamide and

p-nitrophenylmethylsulphoxide. The analytical data and alternate[iv] synthesis confirm that the deactivating nitro-group does not inhibit the normal sulphidimine formation. The Infra-red spectrum was similar to that of the dimethyl analogue and also that of the n-propylphenyl analogue. (Tarbell and McCall, J. Amer. Chem. Soc., 1952, 72, 48)

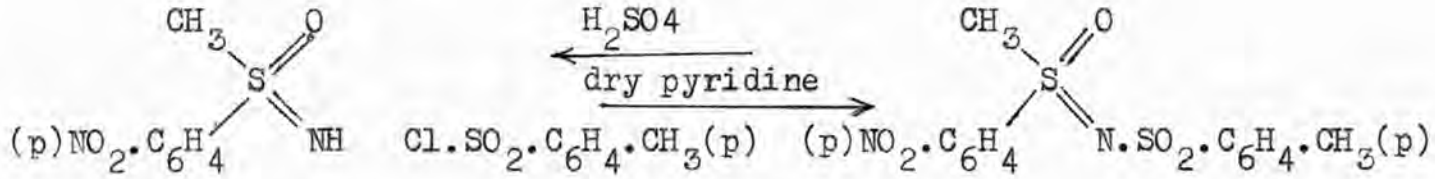
Permanganate oxidation of this mixed sulphidimine was attempted under conditions based on those successful in the case of the dimethyl analogue. When a mixture of the sulphidimine and a slight excess of aqueous alkaline permanganate were heated for five minutes on the steam-bath some ninety per-cent of starting material was recovered. The reaction repeated in aqueous acetone solution led to an initially vigorous reaction which rapidly subsided, and again a total heating period of five minutes was given. The work-up was hindered by tarry products but crystalline material, identified as starting material and toluene-p-sulphonamide, was isolated.

Similar experiences on attempted oxidation of quite simple mixed sulphidimines were described by Bentley and Whitehead , in a later paper (J., 1952, 1572)., and it appears

that oxidation to the sulphoximide , followed by acid hydrolysis , is not a general route to sulphoximines.

During the preparation of sulphoximines it is observed that after the hydrazoic acid reaction , the sulphoximine is found in the acid fraction , and the chloroform extract contains mainly unreacted sulphoxide. This indication of basic properties led up to the synthesis of the oxidation product , which was eventually prepared by a smooth condensation of toluene-p-sulphonylchloride with the sulphoximine , in dry pyridine , on the steam-bath for thirty minutes , reaction conditions typical of the tosylation of a weak base.

S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonylsulphoximine was obtained as a neutral stable compound m.p.203-204°. The Infra-red spectrumwas similar to that of the dimethyl analogue confirming the structure.

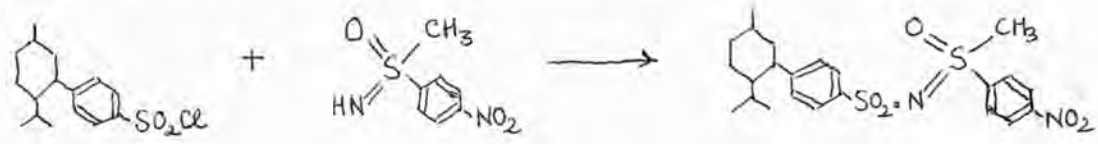


The acid stability of the sulphoximine (This remarkable stability is illustrated by the observation of Campbell, Work and Mellanby ,(Nature, 1950, 165,345) that treatment of

toxic substance for 48 hours with 6N hydrochloric acid at 110° did not completely destroy the sulphoximine structure) is shown by the course of hydrolysis of the sulphoximide . Whereas the sulphidimine was cleaved to sulphoxide and toluene-p-sulphonamide, acid treatment of the sulphoximide gave over eighty per-cent recovery of the free sulphoximine,identical with an analytical specimen.

The synthesis of an optically active unsymmetrical Sulphoximide

The model experiments confirmed the previous observations of the instability of sulphidimines of mixed sulphides , bearing more complex substituents than dimethyl , under oxidising conditions . The alternate[iv] preparation by condensation of the sulphonyl chloride with the sulphoximine proceeded smoothely giving a compound with the expected properties and merited further study. Condensation of the optically active 4-(3 -menthyl)-benzenesulphonylchloride $[\alpha]^{24}_{5461}$ +64.56° (prepared from the optically pure strychnine salt described in part I) with p-nitrophenylmethylsulphoximine in hot dry pyridine gave a product m.p. 133-136° $[\alpha]^{24}_{5461}$ +34.0°



The specific rotatory power was unchanged on standing for 24 hours in chloroform at room temperature. Changes in rotation were obtained by repeated recrystallisation from methanol or acetic acid and it became apparent that the less soluble fractions were of an enhanced laevo rotation. Eventually the less soluble form of the diastereoisomeride separated from methanol-chloroform .

Distinctive crystals in the form of thick hexagonal plates separated out having m.p. 150°, $[\alpha]^{21}_{5461}$ -155°, $[\alpha]^{21}_{D}$ -124° unchanged by further crystallisation. Intermediate crops separated as sheaves of needles , the melting points of which lay on a shallow eutectic with the initial material as minimum. Systematic fractionation of the mother-liquors gave an extreme crop m.p. 138-140°, $[\alpha]^{19}_{5461}$ +171.9°, $[\alpha]^{19}_{D}$ +138° . The Infra-red spectra of the extreme forms were almost identical and strongly resembled the spectra of the model compound and the dimethyl analogue.

The results obtained by repeated recrystallisation of the suspected diastereoisomeride give a strong indication of asymmetry at the tetrasubstituted sulphur atom. The molar rotations, calculated in the usual manner, for the sulphur group are numerically large . The less soluble form is considered optically pure but the rotation data suggest an optical purity of some ninety per-cent for the more soluble fraction. All attempts to find a solvent in which the solubility characteristics were reversed were unsuccessful.

Degradation of active Sulphoximides.

Fractionation of the menthyl sulphoximide produced forms having very different rotations. In order to account for this, calculation of the rotatory contribution for the sulphur group suggests a value of -454^{o} in the optically pure form isolated.

Hydrolysis of the laevo sulphoximide was first effected by heating with concentrated sulphuric acid for five minutes on the steam-bath. The neutralised solution was evaporated to dryness and extracted with benzene. The resultant solid was identified as the sulphoximine by solubility characteristics , melting and mixed melting point but it showed no rotation. Methanol extraction of the residue gave the active sulphonic acid identified as the strychnine salt. Experiments were then conducted to find the minimum conditions required for hydrolysis. Treatment of the sulphoximide for twenty minutes at room temperature with concentrated acid was found to break the sulphonimido bond but again the product was substantially racemic sulphoximine. The possibility of sulphone formation during hydrolysis was removed by preparation of an authentic specimen .

Attempts were then made to replace the sulphonyl group by acetyl. (Cf. Suter, "The Organic Chemistry of Sulphur", John Wiley and sons, New York ,1945, 583). Firstly the active sulphoximide and a slight excess of acetyl chloride were heated at 50° for an hour. The sulphoximide was recovered un-changed . The material was unchanged by heating in a solution of acetic acid and acetic anhydride , or standing at room temperature in this mixture with the addition of a trace of concentrated sulphuric acid,but when the latter mixture was kept for two hours on the steam-bath , the sulphoximide initially -155° was racemized to $[\alpha]_{5461}$ -112° .

Treatment of the sulphoximide with lithium aluminium hydride in tetrahydrofuran or with alcoholic potassium hydroxide gave no useful basic product.

Part II. Experimental.

The preparation of p-nitrophenylmethylsulphide.

Waldron and Reid, (J. Amer. Chem. Soc., 1923, 45, 2401); Zincke and Lenhardt, (Annalen, 1913, 400, 14).

p-Nitrochlorobenzene (m.p. 81-83°, lit. 83°, 157.5 g., 1 mol.) was suspended in ethanol (180 c.c.) and a solution of sodium disulphide (prepared from 240.2 g. $Na_2S_\Lambda^{9H_2O}$ and 32 g. powdered sulphur) in water (600 c.c.) was added dropwise with stirring. The reaction mixture was poured into water (2L.), filtered and on acidification of the filtrate the crude sulphide separated and was collected. This residue was taken up in sodium hydroxide solution (500 c.c. of 5%) at the boil and hot-filtered. The clear red solution was cooled and on addition of sodium hydroxide (120 g.) in water (300 c.c.) large red plates of the sodium salt of the sulphide separated.

Dimethylsulphate (24 g., 0.2 mol.) was gradually added to a solution of the sodium salt (28 g., 0.16 mol.) in sodium hydroxide (20%, 23 c.c.) and water (300 c.c.). The mixture was vigorously shaken when a pale yellow solid separated . This was

filtered, washed with water, vacuum dried and crystallised from methanol as flat rectangular plates (17.6 g., 63%) m.p. 69-71°, (lit. 71-72°).

The preparation of p-nitrophenylmethylsulphoxide.

Zincke and Lenhardt, (Annalen, 1913, 400, 14)

Concentrated nitric acid was added dropwise to a mixture of p-nitrophenylmethylsulphide (8.5 g.) and nitric acid (S.G. 1.15, 50 c.c.) till the boiling solution ceased to evolve brown fumes. Cooled, filtered , washed with water and dried to 8 g., m.p. 146-150°. An analytical specimen from benzene had m.p. 148-150° (Found: C, 45.9; H, 3.3; N, 7.5. Calc. for $C_7H_7O_3NS$: C, 45.4; H, 3.8; N, 7.6%). Zincke and Lenhardt (loc. cit.) give m.p. 149°.

S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonylsulphidimine.

Method (i).

p-Nitrophenylmethylsulphide (15.65 g., 0.092 mole.) was dissolved in ethanol (175 c.c.) and a solution of chloramine-T (26 g., 0.092 mole.) in water (100 c.c.) added, and the resultant solution heated on a steam-bath for one hour. On standing

overnight prisms separated (17.9 g.,57%) m.p. 161°. The analytical specimen prepared from a large volume of benzene separated as needles m.p. 161.5-162° (Found: C,50.3,49.7;H,4.1, 3.5; N,8.3 . $C_{14}H_{14}N_2S_2O_4$ requires C,49.7; H,4.2; N, 8.3%). (The hydroxysulphonamide, a possible by-product , requires C,47.2; H,4.5; N,7.9%).

The reaction mother-liquor provided a crop (3.15 g., 19%) m.p. 145-146°(admixed with authentic sulphoxide m.m.p. was 145-147°). On continued fractionation 1.35 g. of p-toluene-sulphonamide (melting point and mixed melting point 136-137°) was isolated.

Method (ii).

Tarbell and Weaver,(J.Amer.Chem.Soc., 1941,63,2939)

p-Toluenesulphonamide (0.85 g.), p-nitrophenylmethyl-sulphoxide (0.93 g.) and phosphorus pentoxide (1 g.) were heated in dried chloroform (5 c.c.) on the steam-bath for forty minutes , and then heated for a similar period with a further one gram of pentoxide. Ice water was added , the chloroform separated and then evaporated . The residue crystallised from ethanol, 0.5 g.,m.p.160-162°and admixed with the sulphidimine prepared by method (i).

The hydrolysis of S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonylsulphidimine.

Tarbell and Weaver,(loc.cit.)

The sulphidimine (3 g.) was heated on the steam-bath with concentrated hydrochloric acid (10 c.c.) for thirty minutes. The sulphidimine went into solution and subsequently an oil separated. Addition to the well cooled reaction mixture of sodium hydroxide solution (25 c.c. of 20%) precipitated a granular solid. This was filtered, washed with water and dried to 1.45 g., the melting point of which , 145-147° was not depressed on admixing with a specimen of authentic sulphoxide. Acidification (hydrochloric acid) of the filtrate gave a solid (1.25 g.) m.p. 137° and mixed with p-toluene-sulphonamide.

Attempted oxidation of S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonylsulphidimine.

Bentley and Whitehead,(J.,1950,2081; 1952,1572)

Method (i)

A mixture of powdered sulphidimine (3.5 g., 0.01 mole.), potassium permanganate (2.7 g.,0.015 mole.) and sodium hydroxide (0.6 g., 0.015 mole.) in water (25 c.c.) was heated for five

minutes on the steam-bath and efficiently stirred. Some darkening of the pink mixture occured. Sulphur dioxide was passed into the mixture and a colourless solid separated. This was triturated with water , sodium hydrogen carbonate solution and water. The material (2.95 g.) had m.p. 160-162° and admixed with the starting sulphidimine.

Method (ii).

The sulphidimine (3.5 g., 0.01 mole.) and sodium hydroxide (0.6 g.,0.015 mole.) were dissolved in water (25 c.c.) and acetone (75 c.c.) . Powdered potassium permanganate (2.37 g., 0.015 mole.) was added in portions , when the solution boiled ~~and~~ considerable dark solid separated . The total boiling period was five minutes . Protracted purification yielded p-toluenesulphonamide (0.1 g.) and the starting sulphidimine (0.9 g.), the identity being proved by mixed melting points.

The preparation of p-nitrophenylmethylsulphoximine.

Misani, Fair and Reiner, (J. Amer. Chem. Soc., 1951, 73, 459)

Sodium azide (2.21 g., 0.034 mole.) was added portion-wise, in the course of five hours, to a well stirred two-phase system of the sulphoxide of p-nitrophenylmethylsulphide (3.35 g., 0.018 mole.) in dry chloroform (33 c.c.) and sulphuric acid, at 50°, (d 1.84, 4.6 c.c., 0.1 mole.). Stirred for one hour after the addition was completed and then poured onto ice. The chloroform layer was separated and backwashed with dilute sulphuric acid. The combined acid aqueous layer was neutralised (Na_2CO_3) and evaporated to dryness under reduced pressure. The residue was codistilled with, and then extracted three times with, boiling benzene. Evaporation of the benzene gave the sulphoximine (1.8 g., 50%) m.p. 143-147°, (Reiner and co-workers (loc. cit.) give m.p. 139-141°). An analytical specimen separated from methanol as pale yellow prisms m.p. 146-147.5° (Found: C, 42.5; H, 3.7; N, 13.6. Calc. for $C_7H_8O_3N_2S$ C, 42.0; H, 4.0; N, 14.0%)

Evaporation of the chloroform extract gave a sticky residue, which on crystallisation from ethanol gave prisms (0.53 g. 16%) m.p. 146-149° and admixed with an authentic specimen of p-nitrophenylmethylsulphoxide.

S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonylsulphoximine.

The p-nitrophenylmethylsulphoximine (1.0 g.,0.005 mole.) was dissolved in warm,dry pyridine (6 c.c.),and p-toluene-sulphonylchloride (1.0 g.,0.005 mole.) added,and the resultant solution heated on the steam-bath, in an anhydrous apparatus, for one hour. The reaction mixture was then poured onto ice, when on stirring a solid separated which was filtered and washed with water. The crude solid product was taken up in chloroform, and washed with dilute hydrochloric acid , dilute sodium carbonate and water. The residue , after the evaporation of the chloroform, was crystallised from a mixture of acetone and methanol giving prisms (1.35 g.,) m.p.203-204°. The analytical specimen obtained from acetone-chloroform had unchanged m.p. (Found: C, 48.4,48.0; H,3.9,3.6; N, 7.5. $C_{14}H_{14}N_2O_5S_2$ requires C, 47.4; H, 4.0; N, 7.9%)

The infra-red spectrum(potassium bromide disc) showed prominent bands at 6.6 and 7.4 μ (aromatic nitro group) and 7.7, 8.1, 8.7, and 9.2 μ . Similar absorption in this latter region was found in the spectramof SS-dimethyl-N-toluene-p-sulphonyl-sulphoximine.(Dr.D.G.H.Daniels and the Research Director of the

Research Association of the British Flour-Millers are thanked for kindly providing specimens of this compound and the dimethyl sulphidimine for infra-red comparisons.)

The attempted preparation of p-nitrophenylmethylsulphoximine p-toluenesulphonate.

p-nitrophenylmethylsulphoximine (0.2 g.,0.001 mole.) was added to dry pyridine (2 c.c.) and dissolved on warming. p-Toluenesulphonic acid (0.2 g.,circa.0.001 mole.) was then added and heated on the steam-bath for an hour. When poured onto ice water the only product which separated after long standing was the sulphoximine, m.p. 145-148° and admixed with an authentic specimen.

The hydrolysis of S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonyl-sulphoximine.

Bentley and Whitehead (J., 1950,2081)

The sulphoximide (1.3 g.) was triturated with concentrated sulphuric acid (3 c.c.) and then heated on the steam-bath for five minutes giving a pale red solution. This was cautiously diluted with water (6 c.c.) , neutralised (Na_2CO_3)

and evaporated to dryness. The dry residue was extracted three times with boiling benzene and the benzene evaporated to a solid m.p.145-148°, mixed melting point with an analytical specimen of p-nitrophenylmethylsulphoximine was 144-147°. The weight of free sulphoximine base was 0.65 g.(81%).

The preparation of p-nitrophenylmethylsulphone.

Zincke and Lenhardt (Annalen, 1914, 400, 14)

p-Nitrophenylmethylsulphide (0.85 g.,0.005 mole.) in acetic acid solution (5 c.c.) was treated with hydrogen peroxide (6%W/V,5 c.c.) on the steam-bath for forty-five minutes, and after adding further hydrogen peroxide (15 c.c.), was heated for ninety minutes . On standing solid separated which was crystallised from methanol to 0.5 g., m.p. 140-141° (Zincke and Lenhardt,(loc. cit.) give m.p.141°) . The mixed melting point with the p-nitrophenylmethylsulphoximine (m.p.146-147.5°) was 130-144°.

S-p-nitrophenyl-S-methyl-N-[4-(3-menthyl)-benzenesulphonyl]-sulphoximine.

The p-nitrophenylmethylsulphoximine (2.32 g., 0.0116 mole.) was dissolved in warm, dry pyridine (15 c.c.), and the optically pure 4-(3-menthyl)-benzenesulphonylchloride (From Part I., 3.65 g., 0.0116 mole.) added, and the solution, in an anhydrous apparatus, heated on the steam-bath for one hour and then poured onto ice. On stirring, a pasty solid separated which was taken up in benzene and washed with dilute hydrochloric acid, dilute sodium hydroxide and water. The residue after evaporation of the benzene, was crystallised from methanol as sheaves of fine needles (4g., 72%) m.p. 133-136° $[\alpha]^{24}_{5461}$ +34.01° (c 1.1760). The rotatory power was unaffected on standing overnight in chloroform solution at room temperature. Changes of rotation were observed when this material was repeatedly recrystallised from methanol, acetic acid, and these solvents containing twenty per cent of chloroform, whereas ethanol crystallisation produced little or no change in physical properties. Eventually a crop was obtained from methanol-chloroform as large hexagonal plates m.p. 149-150°.

This fraction had $[\alpha]^{21}_{5461}$ -155°, $[\alpha]^{21}_{D}$ -124° (c 0.500) and these properties were unaffected by further crystallisations. (Found: C,57.7; H,6.2; N,6.0; S,13.5. $C_{23}H_{30}O_5N_2S_2$ requires C,57.7; H,6.3; N,5.9; S,13.4%)

Systematic and persistent fractionation of the mother-liquor from methanol and twenty per cent chloroform-methanol gave an extreme crop m.p. 138-140° as stout needles which had, $[\alpha]^{19}_{5461}$ +171.9°, $[\alpha]^{19}_{D}$ +138° (c 0.096) (Found: C,57.6; H,6.3; N,6.1; S,13.1%)

The infra-red spectra (potassium bromide disc) of these extreme forms were almost identical, and in the region of 7.5 to 11.5 μ the absorption pattern strongly resembled that of S-p-nitrophenyl-S-methyl-N-toluene-p-sulphonyl-sulphoximine and also SS-dimethyl-N-toluene-p-sulphonyl-sulphoximine.

The hydrolysis of active S-p-nitrophenyl-S-methyl-N- 4-(3-menthyl) -benzenesulphonyl -sulphoximine.

(i) The pure active laevo sulphoximide (0.25 g,) was triturated with concentrated sulphuric acid (0.5 c.c.) and then heated on the steam-bath for five minutes. The resultant pale red viscous solution was cautiously neutralised with sodium carbonate solution and evaporated to dryness under reduced pressure. The dry residue was extracted three times with hot benzene and evaporated to a pale yellow solid (0.065 g.), m.p. 144-147° and admixed with an authentic specimen of p-nitrophenylmethylsulphoximine. It showed no rotation.

The residue was extracted with boiling methanol, the methanol extract evaporated and an aqueous solution of strychnine hydrochloride added. The resultant strychnine salt had $[\alpha]^{18}_{5461}$ +18.54° (c 0.196) and its m.p. 283° was not depressed when mixed with authentic, less soluble strychnine 4-(3-menthyl)-benzenesulphonate.

(ii) The pure active laevo sulphoximide (0.13 g.) was triturated with concentrated sulphuric acid (0.75 c.c.) to a pale yellow solution. After twenty minutes at room temperature

addition of sodium carbonate solution produced a clear solution, in a test portion, so the mixture was poured onto ice, made just alkaline with ice cooling , and then added a slight excess of barium chloride solution. The resultant precipitate was filtered, and the filtrate exhaustively extracted with chloroform. Evaporation of the chloroform gave a solid residue (0.04 g.), m.p. 142–145°, the mixed melting point with sulphoximine was 146–148°, and with the sulphoximide (m.p. 149–150°) was 126–149°, $[\alpha]^{22}_{5461}$ -9.6° (c 0.160).

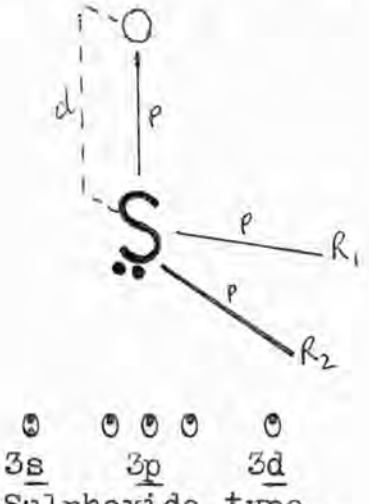
Conclusion.

In the introduction the stereochemical significance of the change from the classical double bond for the oxy-sulphur and related compounds , to the singlet donor bond was discussed. The recent physical investigations suggested that the linkage was best represented as a double bond, but the exact representation of the bonding has been the subject of further discussion.

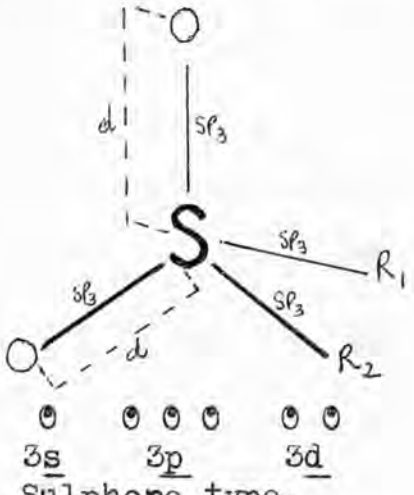
Wheland ("Advanced Organic Chemistry", John Wiley and Sons , New York , 1949 , 360) has advanced a resonance hybrid for the sulphoxide $R_2S^+—O^- \leftrightarrow R_2S{=}O$ This formulation explains the observed value of dipole but provides no stereochemical information.

Moffitt , (Proc.Roy.Soc., 1950, A200 409) has attempted,by an approximate molecular orbital analysis,to assess the contributions of the singlet and double bond forms. He found that the oxy-sulphur bonds are largely double in character and that the 3d electron orbitals of sulphur are of importance in formation of the bond.

Moffitt's work gives the following stereochemical picture.

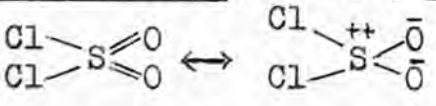


Sulphoxide type.



Sulphone type.

The make up of the oxy-sulphur bond is considered to be analogous to an ethylenic pi bond. For the sulphoxide type the sigma portion is derived from one of the 3p electrons and the pi bond is formed by the 3d electron. For the sulphones , a further promotion provides two 3d electrons to form two pi bonds on the sp_3 sigma framework.

In the case of sulphuryl chloride Nyholm and Gillespie , (Quart.Reviews , 1957 , 11 352) comment that this molecule  has bonds neither pure singlenor pure double,but have an intermediate character. For such a system they suggest that the stereochemistry is determined solely by the number of pairs of sigma electrons

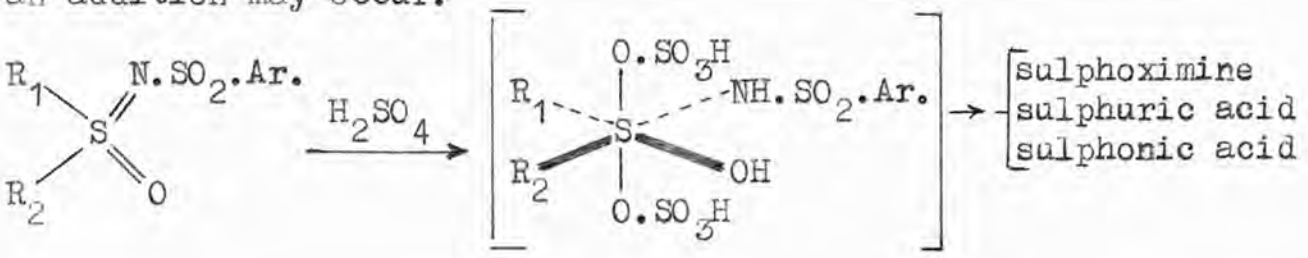
in the valency shell and that pi electrons can be ignored. The prediction that the four $\underline{sp}_3$ sigma bonding pairs would decide the stereochemistry is born out by an electron diffraction analysis which gave an approximate tetrahedral structure.

Bentley and Whitehead, (J., 1950, 2081) suggested that the properties of the sulphoximine would be accounted for by considerable resonance stabilization with extreme forms

The extension of the 3d pi bond theory to this molecule in an effort to obtain some stereochemical picture , does not seem unreasonable , and the demonstration of optical activity strengthens it.

The postulation of pi bonding between sulphur and nitrogen, as well as for the oxy-sulphur bond, offers an explanation of the racemization of the active forms on short treatment with cold concentrated acid. The addition to ethylenes under such conditions is well substantiated.

It is suggested,then,that during the course of hydrolysis an addition may occur.



The hexasubstituted sulphur derivative is postulated as a transient intermediate (written as shown has a plane of symmetry). This intermediate , it is suggested , would then breakdown to fragments of minimum energy content, in this case the sulphoximine and sulphonic acid.

This addition involving the passage to the hexacovalent or octahedral (SF_6) type of structure,and susequent breakdown, it is considered,could well account for the observed racemization.

It appears,then,that the results obtained in this work may be pictured in the framework of sigma orbitals intrinsic in the latest attempts to describe the nature of the oxy-sulphur bond. The passage from the incipient tetrahedron of trisubstituted sulphur

to the optically active tetrasubstituted derivatives has been a smooth one, but the attempts to obtain the active free sulphoximines have foundered , perhaps in the shallow waters of the hexasubstituted state.

Further information about the sulphoximine bond structure may soon be forthcoming. Hine and Rogers , (Chem. and Ind., 1956, 1428) in an investigation of asymmetric sulphoxides, using the powerful leading line of X-ray analysis, have expressed interest in this type of compound. It is to work of this type that one will look , in order to confirm the theme that the optical activity disclosed in this work indicates that the sulphoximine structure , like the sulphones and sulphuryl halides , has a near tetrahedral arrangement of bonds around the central sulphur atom.

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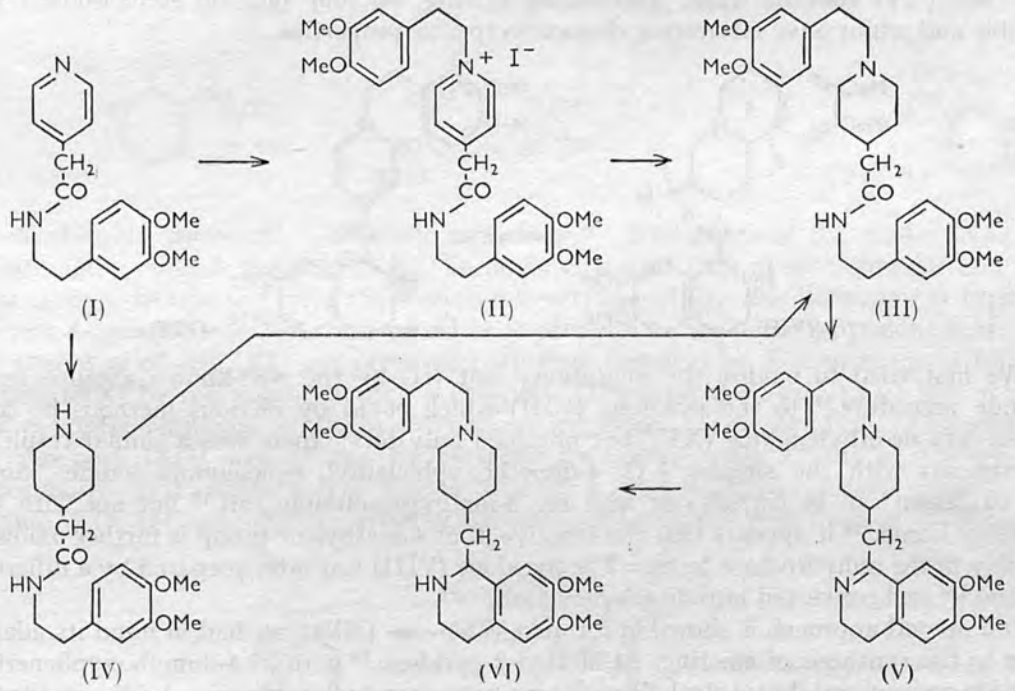
432. *Chemical Constitution and Amœbicidal Action. Part III.* Synthesis of an Analogue of Emetine and Two Stereoisomers of De-ethylemetine.*

By M. Barash and J. M. Osbond.

An open chain analogue (VI) of emetine has been prepared as a potential amœbicide. A new route to de-ethylemetine (XV) has also been developed which has allowed the synthesis of two stereoisomers of this base.

Although challenged by antibiotics and a range of relatively simple compounds effective in varying degrees, emetine [1] (VII) is still [2] pre-eminent in the treatment of amœbiasis.[3] Many attempts to obtain simple analogues having the same or enhanced activity have so far not had practical success: [4] it appears that emetine is very specific. So we decided to prepare a close analogue, (VI), formally derived from emetine (VII) by fission of the bonds *a*–*a* and *b*–*b* and then to utilise one of the intermediates, (II), for synthesis of de-ethylemetine (XV).



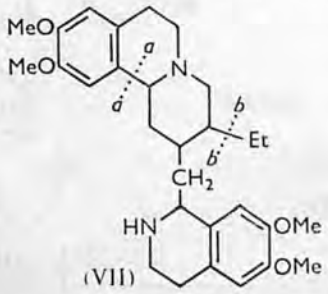
The starting material, 3 : 4-dimethoxyphenethyl iodide, was prepared from 3 : 4-dimethoxybenzyl cyanide, obtained by chloromethylation of veratrole [5] or from veratraldehyde. Catalytic reduction of the aldehyde gave 3 : 4-dimethoxyphenethyl alcohol which was converted into the chloride and nitrile; the derived ethyl ester was reduced by lithium aluminium hydride to 3 : 4-dimethoxyphenethyl alcohol. Alternatively veratraldehdye was condensed with ethyl chloroacetate (Darzens reaction) to give ethyl 3 : 4-dimethoxyphenylglycidate; [6] alkaline hydrolysis gave the sodium salt, which with aqueous oxalic acid gave 3 : 4-dimethoxyphenylacetaldehyde [8] whence lithium aluminium hydride afforded the alcohol. The alcohol with thionyl chloride gave 3 : 4-dimethoxyphenethyl chloride and thence the iodide.

* Part II, *J.*, 1952, 4785.

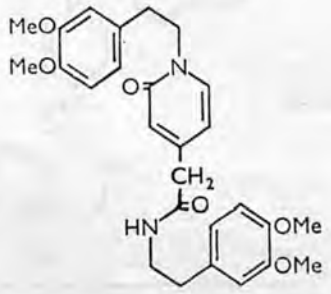
The other starting material, ethyl 4-pyridylacetate, was prepared either from 4-acetylpyridine [9] or from 4-vinylpyridine by the Kindler modification of the Willgerodt reaction [10] to give 4-4'-pyridyl(thioacetyl)morpholine (with some 4-ethylpyridine [11] and thioacetomorpholide). Alkaline hydrolysis of the morpholide gave the required acid which was esterified without isolation. Condensing ethyl 4-pyridylacetate with 3 : 4-dimethoxyphenethylamine gave the amide (I). Quaternisation of this with 3 : 4-dimethoxyphenethyl iodide in methanol gave the iodide (II), but reaction in benzene or without solvent gave a non-crystalline product having part of its iodine in non-ionic form.[12] The quaternary salt was reduced catalytically to the piperidine base (III). This base was also prepared by the route (I) ⟶ (IV) ⟶ (III), which confirms its structure. In a third attempt quaternisation of the 3 : 4-dimethoxyphenethyl iodide and ethyl 4-pyridylacetate and reduction of the quaternary salt to ethyl 1-(3 : 4-dimethoxyphenethyl)-4-piperidylacetate was successful, but the final step, condensation with the phenethylamine, gave no crystalline product.

The base (III) was readily cyclised by phosphorus pentachloride in chloroform or by phosphorus oxychloride in toluene to the dihydro*iso*quinoline (V), hydrogenation of which gave the required tetrahydro*iso*quinoline (VI).

Although de-ethylemetine * (XV) has already been prepared four times,[13] it has not been evaluated for amœbicidal properties and only one stereoisomer has been isolated. The base (XV) contains three asymmetric centres, so four racemic stereoisomers are possible and might have interesting chemotherapeutic properties.



(VII)



(VIII)

We first tried to oxidise the quaternary salt (II) by the well-known alkaline ferricyanide procedure [14] to the pyridone (VIII) which could by obvious methods be converted into de-ethylemetine (XV), but obtained only tars; there was a similar result in experiments with the simpler 1-(3 : 4-dimethoxyphenethyl)-4-picolinium iodide. Since this oxidation can be carried out with the 3-methylpyridinium salt [15] but not with the 2-methyl isomer [16] it appears that the reactive 2- or 4-methylene group is further oxidised possibly in the anhydro-base form. The pyridone (VIII) was later prepared by a different method [13d] and converted into de-ethylemetine.

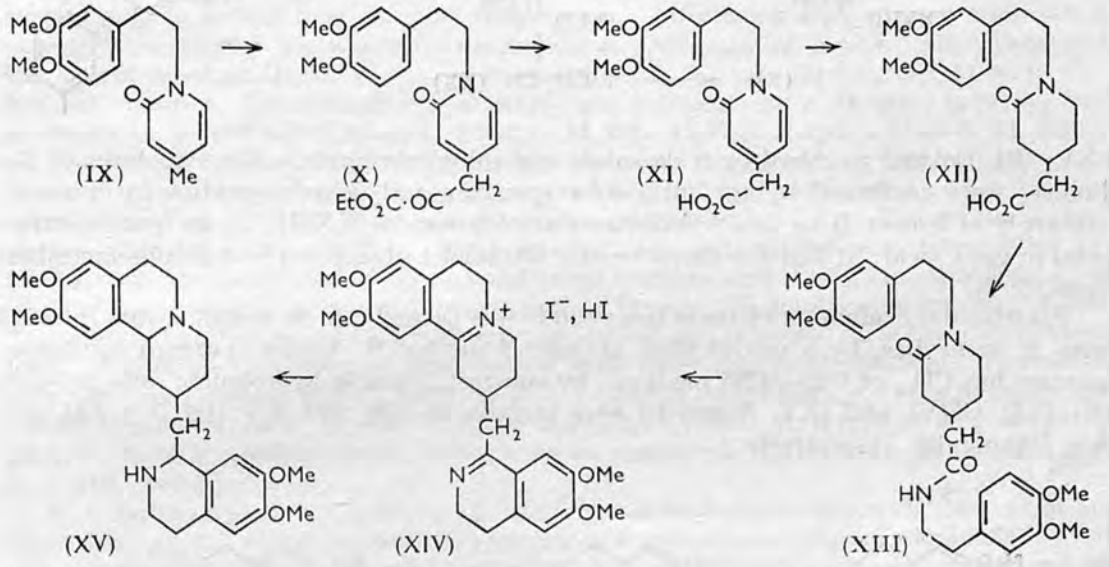
Our second approach is shown in formulæ (IX) ⟶ (XV); we had in mind its adaptation to the synthesis of emetine. 4-Methyl-2-pyridone [16] with 3 : 4-dimethoxyphenethyl iodide in aqueous *tert.*-butyl alcohol containing potassium hydroxide gave the *N*-substituted pyridone (IX); although under alkaline conditions the *N*-alkylpyridone is normally obtained, there are several recorded cases [17] where *O*-alkylation is the chief reaction; so, to confirm the structure of our compound, 2-bromo-4-methylpyridine [18] was converted by 3 : 4-dimethoxyphenethyl iodide into a (non-crystalline) salt (XVII) which on mild alkaline hydrolysis [19] gave the identical pyridone (IX).

This pyridone with ethyl oxalate in the presence of potassium ethoxide [16,17,20] gave the pyruvate ester (X). Attempts to oxidise the pyruvate ester or its potassio-derivative by alkali and hydrogen peroxide together [16] were unsuccessful. It was necessary first to hydrolyse the ester with dilute alkali at 0° and then to add hydrogen peroxide which gave

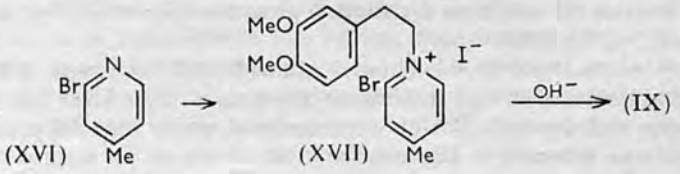
* The name bisnoremetine, previously used, is ambiguous as it could apply to emetine with 2OH replacing 2OMe. Ed.

a good yield of the pyridone-acid (XI); a more convenient route was to use the potassio-derivative of the ester (X) in this reaction. From the mother-liquor of the oxidation a small amount of the 4-methyl-2-pyridone (IX) was isolated, presumably as a result of a reverse Claisen reaction.

The structure of the acid (XI) was proved in two ways. The ester (X) or its potassio-derivative with hydroxylamine hydrochloride gave the hydroxyimino-ester (XVIII), hydrolysed by alkali to the acid (XIX), which afforded the nitrile (XX) by pyrolysis or,



preferably, on treatment with acetic anhydride.[21] Hydrolysis of the nitrile (XX) with dilute alkali yielded the acid (XI). Secondly, the acid (XI) at its decomposition point lost carbon dioxide and gave the 4-methyl-2-pyridone (IX); this behaviour is typical of 2- and 4-pyridylacetic acids and would be expected with a similar 2-pyridone-acid. The methyl ester of acid (XI) was prepared both from this acid by diazomethane or from the nitrile (XX) by methanolic hydrogen chloride. The piperidone-acid (XII) was obtained by catalytic reduction of the pyridone-acid by using Adams catalyst. The structure of the acid (XII) was proved by cyclising its methyl ester (XXI) in toluene with phosphorus oxychloride to the known 1 : 2 : 3 : 4 : 6 : 7-hexahydrobenzo[*a*]quinolizinium iodide [13b] (XXII), and the properties of the salt (XXII) agreed with those in the literature.

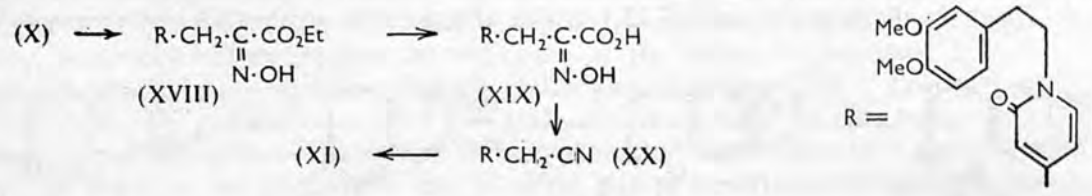


The triethylammonium salt of the 2-oxo-4-piperidylacetic acid (XII) in dimethylformamide with ethyl chloroformate gave, in the usual way,[22] the ethoxycarbonyloxy-derivative, which without isolation was treated with 3 : 4-dimethoxyphenethylamine in the presence of triethylamine to give the amide (XIII) in two crystalline forms, m. p. 120—121° and m. p. 130—131°, which were interconvertible. This amide had previously been prepared by Tomitsu [13b] as a gum and, after our work was complete, Sugasawa and Oka [13d] reported it as having m. p. 130—131°.

Phosphorus oxychloride in toluene effected double ring closure of the amine (XIII) to the quaternary compound, characterised as the iodide hydriodide (XIV) and bromide

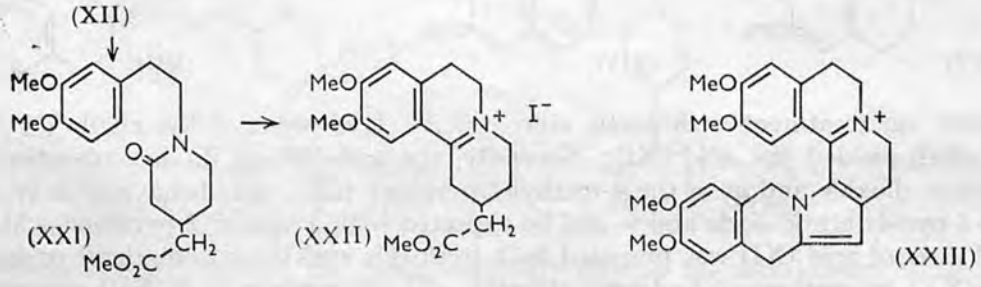
hydrobromide, both crystalline; the ultraviolet absorption spectrum was in agreement with this structure.

Catalytic reduction of the iodide hydriodide was slow but complete, and the first racemate of de-ethylemetine (XV; A) separated as a crystalline dihydriodide and afforded a dihydrobromide and dihydrogen dioxalate. The mother-liquors yielded a second isomer



(XV; B), isolated as dihydrogen dioxalate and dihydrobromide. The structures of the isomers were confirmed by the ultraviolet spectrum and dehydrogenation by mercuric acetate [23] of isomer B to de-ethylrubremetinium bromide (XXIII) as an orange-scarlet solid in good yield; it had the characteristic ultraviolet absorption [13b] (cf. rubremetinium bromide [24]).

Amœbicidal evaluation of these compounds was carried out on weanling rats infected with *E. histolytica*, by a modification of Jones's method.[25] Under standard conditions emetine has CD_{50} of 6·25—12·5 mg./kg.; by contrast, suitable hydrohalide salts of bases (V), (VI), (XIV), and (XV, A and B) were inactive at 250, 500, 5 × 100, 5 × 100, and 5 × 100 mg./kg., respectively.



Experimental

3 : 4-*Dimethoxybenzyl Alcohol.*—Veratraldehyde (120 g.; m. p. 43·5—45°) was hydrogenated in methanol in the presence of Raney nickel (*ca.* 10 g. in methanol) at 90° with an initial pressure of 50 atm., substantially completely in 2 hr. The mixture was cooled, filtered, and concentrated to a viscous oil which on distillation gave the alcohol (116 g., 95·5%), b. p. 112—120°/0·25—0·35 mm., n_D^{19} 1·5520.

3 : 4-*Dimethoxyphenylacetonitrile.*[27]—Thionyl chloride (17 c.c.) was added in 25 min. to 3 : 4-dimethoxybenzyl alcohol (25 g.) in benzene (20 c.c.) at 0°. After the initial reaction had subsided the benzene and thionyl chloride were removed under reduced pressure on the water-bath. The residue was refluxed in benzene (*ca.* 100 c.c.) with potassium cyanide (14·6 g.) in water (50 c.c.) for $2\frac{3}{4}$ hr. with stirring. The phases were separated and the aqueous phase was re-extracted with benzene. The benzene extracts were dried and distilled. The residue was distilled to give the nitrile (16·7 g., 63%), b. p. 128—130°/0·1—0·25 mm., m. p. 60—61°.

Ethyl 3 : 4-*Dimethoxyphenylacetate.*—A solution of the above nitrile [5] (90 g.) in dry ethanol (500 c.c.) was saturated with hydrogen chloride, then cooled to 0°. The nitrile which separated gradually redissolved to give a purple solution. The mixture was kept at 0° overnight, then most of the alcohol was removed under reduced pressure at 35°. Dry ether was added to the residue and the crystalline *ethyl* 3 : 4-*dimethoxyphenylacetimidoate hydrochloride* was collected and washed with dry ether; it recrystallised from cold ethanol–ether in prisms, m. p. 114·5—115° (Found: N, 5·7; Cl, 13·4. $C_{12}H_{18}O_3NCl$ requires N, 5·4; Cl, 13·7%). The salt was dissolved in water; after a few minutes at room temperature an oil separated and this was

extracted with ether. The aqueous solution was then kept in contact with ether for 18 hr., the ether extracts being separated from time to time. The ether extracts were combined, washed with dilute sodium carbonate solution and with water, and dried (Na_2SO_4). The residue after removal of the ether was distilled, to give the ester (94·3 g., 83%), b. p. 132—136°/0·1—0·3 mm., n_D^{20} 1·5192 (Found: C, 64·5; H, 8·0. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

Ethyl 3 : 4-*Dimethoxyphenylglycidate*.—A mixture of 3 : 4-dimethoxybenzaldehyde (redistilled; 66·4 g.) and ethyl chloroacetate (redistilled; 41·3 c.c.) was added during 4 hr. to a stirred solution from sodium (9·4 g.) and absolute ethanol (133·2 c.c.) at −10°. Stirring was continued for a further 6 hr. at room temperature. After being kept at room temperature overnight the mixture was poured on ice containing acetic acid (*ca.* 5 c.c.). The yellow solid was filtered and dried (P_2O_5; vac.). After several days a dry solid (81·5 g., 77·1%), m. p. 49—51°, was obtained. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *ester* as needles, m. p. 52·5—53·5° (Found: C, 62·1; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·8; H, 6·3%).

3 : 4-*Dimethoxyphenylacetaldehyde*.—The glycidic ester (12·6 g.) in ether (100 c.c.) was added in 15 min. to a solution from sodium (1·25 g.) in methanol (17 c.c.) and water (1 c.c.) at 5°. The mixture was kept at 0° for 19 hr., and ether (20 c.c.) added after 7 hr. The sodium 3 : 4-dimethoxyphenylglycidate (12·05 g., 98%) was collected and washed with ether. The salt (18·9 g.) was dissolved in water (75 c.c.) and added to oxalic acid (13·5 g.) in water (60 c.c.) at 95—100° with a rapid stream of nitrogen passing through the solution, during 15—20 min. The solution was then heated for a further 5 min., cooled, and extracted three times with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4). Distillation gave the pure aldehyde (8·6 g., 62%), b. p. 115—121°/0·7—1·0 mm., n_D^{20} 1·5430 (lit.,[28] n_D^{20} 1·5431) (Found: C, 66·3; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%). The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate as orange-red needles, m. p. 168—169° (lit.,[28] m. p. 169—169·5°).

3 : 4-*Dimethoxyphenethyl Alcohol*.—(1) Ethyl 3 : 4-dimethoxyphenylacetate (33·6 g.) in dry ether (150 c.c.) was added dropwise with stirring to a suspension of lithium aluminium hydride (7·5 g.) in dry ether (150 c.c.); after 0·5 hour's heating on a water-bath a fairly granular precipitate was obtained. Ethyl acetate (25 c.c.) was added, followed by 2N-sulphuric acid (excess) with ice-cooling. The aqueous phase was extracted with ether six times, the combined extracts were washed with sodium carbonate solution, dried, and evaporated. Distillation gave the alcohol (25·2 g., 92%), b. p. 126—128°/0·3—0·7 mm., m. p. 45—46·5° (lit.,[29] m. p. 48°) (Found: C, 66·4; H, 8·2. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). The *toluene*-p-*sulphonate*, prepared in pyridine at 0—5°, separated from ether–light petroleum and had m. p. 49—51·5° (1·04 g. from 1·82 g.) (Found: C, 60·9; H, 6·1; S, 9·4. $C_{17}H_{20}O_5S$ requires C, 60·7; H, 6·0; S, 9·5%).

(2) 3 : 4-Dimethoxyphenylacetaldehyde (8·63 g.) was reduced by lithium aluminium hydride (2 g.) in ether (100 c.c.), as above, to the alcohol (6·6 g., 75%), b. p. 112—118°/0·3 mm., m. p. 41—43°.

3 : 4-*Dimethoxyphenethyl Chloride*.—Thionyl chloride (8·92 g., 0·075 mole) in dry benzene (15 c.c.) was added with stirring to a solution of 3 : 4-dimethoxyphenethyl alcohol (9·1 g., 0·05 mole) and diethylaniline (7·93 c.c., 0·05 mole) in benzene (60 c.c.) during 0·5 hr. The mixture was kept at room temperature for 1·5 hr., then heated on a boiling-water bath for 10 min. Two-thirds of the benzene was removed under reduced pressure and the resulting solution was washed with water, dilute aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the chloro-compound (9·45 g., 94%), b. p. 126°/0·3 mm., laths, m. p. 37·5—39·5° [from ether–light petroleum (b. p. 40—60°) at −15°] (Found: C, 59·8; H, 6·7; Cl, 17·3. Calc. for $C_{10}H_{13}O_2Cl$: C, 59·9; H, 6·5; Cl, 17·7%).

3 : 4-*Dimethoxyphenethyl Iodide*.—(1) Sodium iodide (132 g.; dry and powdered) was refluxed in dry ethyl methyl ketone (1 l.) for 1·5 hr. The mixture was then cooled, 3 : 4-dimethoxyphenethyl chloride (117 g.) in dry ethyl methyl ketone (200 c.c.) was added, and the mixture refluxed for a further 10 hr. Precipitated sodium chloride was removed, most of the ketone was distilled off, and the residue was dissolved in ether and water. The aqueous layer was extracted six times with ether and washed with sodium thiosulphate solution and water. The ether extract was dried and evaporated and the residue distilled, to give the iodo-compound (157 g., 92%), b. p. 112°/0·3 mm., prisms, m. p. 45—47° [from ether–light petroleum (b. p. 40—60°)] (Found: I, 42·9. Calc. for $C_{10}H_{13}O_2I$: I, 43·4%).

(2) 3 : 4-Dimethoxyphenethyl toluene-*p*-sulphonate (1·68 g.) was refluxed in dry acetone

(25 c.c.) with sodium iodide (0·82 g.) for 3 hr. The sodium toluene-*p*-sulphonate (0·92 g.) was filtered off and the acetone was removed under reduced pressure, and the product was obtained as in (1), having m. p. and mixed m. p. 45·5—48°.

4-4′-*Pyridyl(thioacetyl)morpholine.*—Redistilled 4-vinylpyridine (10·5 g., 0·1 mole), sulphur (4·8 g., 0·15 mole), and morpholine (13·0 g., 0·15 mole) were refluxed at 160° for 16 hr. The resultant dark mass was dissolved in ethanol (15 c.c.) and cooled to 0°. The morpholide (11·83 g., 53%) was collected and recrystallised from ethanol as yellow prisms, m. p. 105—107° (lit.,[9] m. p. 104—105·5°). The alcoholic mother-liquor was basified with aqueous potassium hydroxide and extracted 6 times with ether. Distillation of the ether-soluble material gave 4-ethylpyridine (1·35 g.), b. p. 50°/12 mm., n_D^{20} 1·4988 (lit., 1·5022) [picrate, m. p. and mixed m. p. 167—169° (from alcohol)], and thioacetomorpholide (0·6 g.), b. p. 143—146°/12 mm., m. p. 90—92° (lit.,[29] m. p. 89—91·2°) (Found: C, 49·7; H, 7·8; N, 9·6; S, 22·1. Calc. for $C_6H_{11}ONS$: C, 49·6; H, 7·6; N, 9·6; S, 22·0%).

Ethyl 4-*Pyridylacetate.*—4-4′-Pyridyl(thioacetylmorpholine (33·3 g., 0·15 mole) was refluxed with potassium hydroxide (23 g.) in alcohol (180 c.c.) for 16 hr. Water (360 c.c.) was added and the solution concentrated to half-volume under reduced pressure; then water (180 c.c.) was added and the solution was evaporated nearly to dryness, made just acid with 2N-hydrochloric acid, evaporated to dryness, and co-distilled with ethanol (twice) and benzene. The dry residue was suspended in absolute ethanol (200 c.c.), saturated with hydrogen chloride without cooling, and kept overnight at room temperature. The alcohol was removed and dilute sodium carbonate and ether were added. The residue from the ether-extracts was distilled, to give the ester (18·9 g., 76%), b. p. 86—90°/0·2—0·4 mm. The *hydrochloride* separates from ethanol as prisms, m. p. 165—168° (decomp.) (Found: C, 54·0; H, 6·1; N, 6·9. $C_9H_{12}O_2NCl$ requires C, 53·7; H, 6·0; N, 6·9%).

Ethyl 1-(3 : 4-*Dimethoxyphenethyl*)-4-*piperidylacetate.*—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and ethyl 4-pyridylacetate (1·65 g.) were heated on a boiling-water bath for 2 hr., to give a quaternary salt which was hydrogenated in ethanol (60 c.c.) and triethylamine (1·6 c.c.) and at 145—150°/75 atm. for 3 hr. in the presence of Raney nickel. The product after removal of the alcohol was treated with excess of 2N-sodium carbonate, and extracted with ether three times. The extract was dried (Na_2SO_4) and distilled (b. p. 188—192°/0·6 mm.; 1·16 g.), affording the *product* which after several recrystallisations from ether–light petroleum (b. p. 40—60°) at −20° formed prisms, m. p. 38·5—40° (Found: C, 68·4; H, 8·9; N, 3·8. $C_{19}H_{29}O_4N$ requires C, 68·0; H, 8·7; N, 4·2%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-4-*pyridylacetamide* (I).—3 : 4-Dimethoxyphenethylamine (9·05 g.), ethyl 4-pyridylacetate (8·25 g.), and a few drops of dry pyridine were heated at 180° for 3 hr., then dissolved in benzene from which the crude amide (11·3 g., 75%) separated. Recrystallisation from benzene gave the *amide* (10·5 g.) as needles, m. p. 93·5—95° (Found: C, 68·3; H, 7·3; N, 9·2. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-4-*piperidylacetamide* (IV).—The foregoing amide (3 g.) was shaken in ethanol (40 c.c.) with Raney nickel for 1½ hr. The suspension was filtered and the nickel was washed with glacial acetic acid. Further acetic acid (60 c.c.) was added to the filtrate which was then hydrogenated in the presence of Adams catalyst. The product after removal of solvent was partitioned between dilute sodium carbonate and chloroform. Several chloroform extracts were obtained, washed with water, and dried (Na_2SO_4). The solid residue crystallised from benzene–light petroleum (b. p. 40—60°), to give the *amide* (1·72 g.), m. p. 93—96°, needles (Found: C, 67·0; H, 8·4; N, 8·8. $C_{17}H_{26}O_3N_2$ requires C, 66·6; H, 8·5; N, 9·1%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-[N-(3 : 4-*dimethoxyphenethyl*)*carbamoylmethyl*]*pyridinium Iodide* (II).—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and *N*-(3 : 4-dimethoxyphenethyl)-α-4-pyridylacetamide (3·0 g.) were refluxed in absolute methanol (25 c.c.) in nitrogen for 16 hr. After concentration of the solution to *ca.* 10 c.c. the quaternary salt (4·87 g.), m. p. 142—146°, slowly separated. Recrystallisation from absolute ethanol gave the *pyridinium iodide*, m. p. 146—148° (softens at 145°), as yellow prisms (Found: C, 53·4, 53·7; H, 6·0, 6·0; I′, 22·2, 22·2. $C_{27}H_{33}O_5N_2I,H_2O$ requires C, 53·1; H, 5·8; I′, 20·8%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-(3 : 4-*dimethoxyphenethyl*-4-*piperidyl*)*acetamide* (III).—(1) The iodide (II) (11·85 g.) in methanol (300 c.c.) was hydrogenated at atmospheric pressure and room temperature in the presence of Adams catalyst (0·5 g.) (uptake 1560 c.c.; theor., 1555 c.c.). The solution was filtered, concentrated, and basified with 2N-sodium hydroxide, and the base extracted with chloroform (5 times). The recovered *base* (8·25 g., 88%) separated from ethyl

acetate as needles, m. p. 135·5—136° (Found: C, 68·8; H, 8·0; N, 6·1. $C_{27}H_{38}O_5N_2$ requires C, 68·9; H, 8·1; N, 5·9%).

3 : 4-Dimethoxyphenethyl iodide (0·73 g.), the amide (IV), and potassium carbonate (0·52 g.) were refluxed in dry benzene (20 c.c.) for 3 hr. The solution was washed with water and evaporated. The residual solid crystallised from ethyl acetate, to give the amide (II) (0·6 g.), m. p. and mixed m. p. 133—135·5° (from ethyl acetate).

4-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)-1-(3 : 4-*dimethoxyphenethyl*)*piperidine* (V).—(i) Phosphorus pentachloride (3 g.) was added to the amide (III) (2·46 g.) in dry chloroform (30 c.c.) at 5°. The mixture was kept at 0° for 0·5 hr. with intermittent shaking, then at room temperature for 18 hr. Most of the chloroform was removed under reduced pressure and ice and excess of 2N-sodium hydroxide were added. The basic material was extracted with chloroform, washed with water, and recovered. The residue dissolved in warm ether and after removal of some flocculent material was recovered as an oil. Dilute hydrochloric acid was added, and the yellow solution evaporated to a yellow foam. After distillation of the residue 3 times with alcohol it was dissolved in ethanol to which ether was added. The *dihydrochloride* separated as yellow prisms (2·42 g., 88%), m. p. 105—110°. Recrystallisation from ethanol–ether with a trace of dry hydrogen chloride gave pale yellow prisms which, after drying at 50—60° *in vacuo*, had m. p. ~180—185° (softening at 160°, doubtless owing to hydration). The salt was very hygroscopic and its dilute ethanolic solution had a bright blue fluorescence (Found: C, 59·9; H, 7·1; N, 5·2. $C_{27}H_{36}O_4N_2,2HCl,H_2O$ requires C, 59·7; H, 7·4; N, 5·1%).

The *dihydrobromide* was less hygroscopic and crystallised from ethanol as pale yellow prisms, m. p. (air-dried) m. p. 131—136° (meniscus and frothing at 155—160°) (Found: C, 48·1, 48·3; H, 6·2, 6·6; N, 3·9; Br, 23·9; H_2O, 10·2. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2; Br, 23·9; H_2O, 8·1%).

The *base*, crystallised from light petroleum (b. p. 60—80°) containing a few drops of ether, had m. p. 99—102·5° (Found: C, 71·8; H, 8·4; N, 5·8. $C_{27}H_{36}O_4N_2$ requires C, 71·6; H, 8·0; N, 6·2%).

(ii) The amide (III) (2·35 g.) was refluxed in dry toluene (15 c.c.) and phosphorus oxychloride (10 c.c.) for 1 hr., cooled, washed by decantation with light petroleum (b. p. 60—80°), and dissolved in aqueous alcohol. Excess of 50% sodium hydroxide solution was added and the basic material extracted with ether (3 times) and washed with water. The recovered base was converted into the dihydrobromide which separated from ethanol as yellow prisms (2·32 g., 75%), m. p. (air-dried) and mixed m. p. 131—136°.

1-(3 : 4-*Dimethoxyphenethyl*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)-*piperidine* (VI).—The dihydrobromide (V) (3·07 g.) was hydrogenated at room temperature and atmospheric pressure in methanol (50 c.c.) with Adams catalyst (0·2 g.). The filtered solution was concentrated to 25—30 c.c. and treated with hydrobromic acid, to give a dihydrobromide (2·55 g., 92%), m. p. 188—192°. Recrystallisation from methanol gave the *tetrahydroisoquinoline dihydrobromide* as prisms, m. p. (air-dried) 190—196° (Found: C, 50·3; H, 6·6; N, 4·5; Br, 24·2; H_2O, 5·1. $C_{27}H_{38}O_4N_2,2HBr,2H_2O$ requires C, 49·7; H, 6·80; N, 4·3; Br, 24·5; H_2O, 5·5. Found, in a sample dried at 90° *in vacuo*: loss, H_2O, 2·5; C, 51·9; H, 6·4. $C_{27}H_{38}O_4N_2,2HBr,H_2O$ requires H_2O, 2·8; C, 51·1; H, 6·7%).

In a preliminary reduction the tetrahydro*iso*quinoline was isolated as the *dihydrogen dioxalate*, needles (from methanol–ether), m. p. 173·5—175° (decomp. 180—185°) (Found: C, 58·2; H, 6·8; N, 4·7. $C_{27}H_{38}O_4N_2,2H_2C_2O_4$ requires C, 58·6; H, 6·7; N, 4·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*picolinium Iodide*.—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and γ-picoline (0·93 g.) were heated on a boiling-water bath for 2 hr. The crystalline precipitate was dissolved in ethanol from which the quaternary *salt* separated as yellow needles (6·6 g.), m. p. 184—187° (Found: C, 50·2; H, 5·3; N, 3·6. $C_{16}H_{20}O_2NI$ requires C, 49·9; H, 5·2; N, 3·6%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*methyl*-2-*pyridone Hydrochloride* (IX).—(i) To potassium hydroxide (6·6 g.), dissolved in water (3 c.c.) and *tert.*-butyl alcohol (80 c.c.), 4-methyl-2-pyridone (10·9 g., 0·1 mole) was added and the solution was heated for a few minutes to obtain complete dissolution. 3 : 4-Dimethoxyphenethyl iodide (29·2 g., 0·1 mole) was added and the solution was refluxed for 2·75 hr. The solvent was then removed and the residue was partitioned between benzene and 2N-sodium hydroxide. The aqueous layer was extracted 3 times with benzene which was then removed, and the residue was dissolved in a very small volume of ethanol and treated with excess of ether saturated with dry hydrogen chloride. The *hydro-*

chloride (24·45 g., 79%) recrystallised from ethanol–ether as needles, m. p. 170—172° (Found: C, 62·6; H, 6·8; N, 4·5. $C_{16}H_{19}O_3N$,HCl requires C, 62·0; H, 6·2; N, 4·5%).

(ii) 4-Methyl-2-pyridone (5·45 g.) was warmed with a solution from potassium (1·95 g.) and *tert.*-butyl alcohol (40 c.c.) for a few minutes, 3 : 4-dimethoxyphenethyl chloride (11·1 g.) was added, the whole refluxed for 6 hr., and the product obtained as described above as the hydrochloride (11·09 g., 71·6%) m. p. 165—166°.

(iii) 3 : 4-Dimethoxyphenethyl iodide (5·84 g.) and 2-bromo-4-methylpyridine were heated on a boiling-water bath for 5 hr. The residue was lixiviated with dry ether, dissolved in aqueous ethanol, treated with excess of 2N-sodium hydroxide at room temperature, and kept overnight. The solution was extracted with chloroform, dried, and evaporated. The residue gave on distillation a fraction (1·4 g.), b. p. 200—202°/0·5 mm., which gave the pyridone hydrochloride, m. p. 165—169°, when treated with ether saturated with dry hydrogen chloride. Recrystallisation gave the pure hydrochloride, m. p. 169—172°, identical with the compound prepared as above (Found: Cl, 11·4. $C_{16}H_{19}O_3N$,HCl requires Cl, 11·4%).

Ethyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylpyruvate* (X).—Absolute ethanol (16·6 c.c.) was added to potassium (2·53 g.) under dry ether (14·4 c.c.), and dissolution completed by warming. Ethyl oxalate (9·48 g.) in ether (60 c.c.) was added dropwise at *ca.* 10°. After 10 min. 1-(3 : 4-dimethoxyphenethyl)-4-methyl-2-pyridone [from the hydrochloride (18·6 g.)] in benzene (90 c.c.) was added dropwise in 8 min. at 0°. After 2 days an oil separated which became solid on addition of ether (*ca.* 90 c.c.). This yellow potassio-derivative salt (19·0 g.) was filtered off after 4 days and washed with dry ether. From the filtrate a further 3·8 g. (total 91·2%) were obtained.

The potassio-derivative (10·3 g.) was added portionwise to 2N-sulphuric acid (32·5 c.c.), ice (17 g.) and chloroform (55 c.c.) with vigorous shaking. The chloroform was separated and the aqueous layer was re-extracted with chloroform; this was repeated again after adjustment of the pH of the aqueous extract to pH 7 with dilute ammonia. The combined extracts yielded the solid *pyruvate* which crystallised twice from ethanol or ethyl acetate as pale yellow prisms (7·9 g., 85% yield from potassio-derivative), m. p. 157—158·5° (Found: C, 64·5; H, 6·3; N, 3·4. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·7%).

Ethyl β-[1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridyl*]-α-*hydroxyiminopropionate* (XVIII).—(i) The pyruvate (X) (3·73 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and anhydrous sodium acetate (0·88 g.) for 0·5 hr.; the solution was cooled and water (5 c.c.) added. The *oxime* (3·17 g., 82%), recrystallised from alcohol, had m. p. 186·5—189·5° (Found: C, 61·1; H, 6·3; N, 7·2. $C_{20}H_{24}O_6N_2$ requires C, 61·8; H, 6·2; N, 7·2%).

(ii) The crude potassio-derivative (3·8 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and sodium acetate (0·88 g.) for 0·5 hr., then concentrated to half its volume. The oxime (2·08 g., 58%) had m. p. and mixed m. p. 182—184°.

This ester (3·17 g.) was converted by 2N-sodium hydroxide (12·5 c.c.) on a boiling-water bath in 1·5 hr. into the *acid*, needles, m. p. 166—168° (2·50 g., crude) (Found: C, 59·9; H, 5·8; N, 7·8. $C_{18}H_{20}O_6N_2$ requires C, 60·0; H, 5·6; N, 7·8%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetonitrile* (XX).—The hydroxyimino-acid (2·76 g.) was heated in acetic anhydride (5 c.c.) on a water-bath for 10 min., the anhydride removed under reduced pressure, and ethanol was added and then removed under reduced pressure. The crystalline *nitrile* was precipitated from a small volume of benzene by a few drops of light petroleum (b. p. 60—80°) as needles (1·82 g., 80%), m. p. 118—121° (Found: C, 68·4; H, 6·1; N, 10·0. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1; N, 9·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetic Acid* (XI).—(i) The acetonitrile (0·23 g.) was refluxed overnight with ethanol (10 c.c.) and 2N-sodium hydroxide (5 c.c.). The alcohol was then removed and the aqueous alkaline solution extracted with benzene and then filtered. The filtrate was made acid by concentrated hydrochloric acid, and the precipitated red oil extracted with chloroform. After removal of the solvent the residue was dissolved in methanol from which prisms (0·23 g.), m. p. 158—161° (decomp.), were deposited. Crystallisation from methanol gave the *acetic acid*, m. p. 156·5—157° (decomp.) (Found: C, 64·3; H, 6·1; N, 4·7. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

(ii) The ester (X) (6·5 g.) was kept in 10% aqueous sodium hydroxide (31·2 c.c.) at 0° for 4·5 hr., then treated with 30% hydrogen peroxide (6·05 c.c.) and ice (*ca.* 17 g.) and kept for a further 16 hr. at 0°. Thereafter a further 2·6 c.c. of hydrogen peroxide were added and the

solution was kept at 0° for a further 24 hr. Manganese dioxide (*ca.* 1 g.) was added, the solution filtered, and the filtrate made just acid to Congo-Red paper with concentrated hydrochloric acid. The oil was extracted with chloroform (3 × 25 c.c.), washed with water, and evaporated. The colourless solid residue was dissolved in methanol from which the acid (4·36 g., 78%), m. p. and mixed m. p. 157° (decomp.), separated.

(iii) The potassio-derivative (5·15 g.) was kept in 10% aqueous sodium hydroxide (22·5 c.c.) at 0° for 17 hr. Ice (12·5 g.) and 30% hydrogen peroxide (4·4 c.c.) were added and the solution kept at 0° for 24 hr. A further 1·88 c.c. of hydrogen peroxide were added and the solution left for 3 days longer at 0°, then worked up as in (ii), to give the acid (2·91 g., 73·5%), m. p. 152—156° (decomp.). This reaction was repeated with the potassio-derivative (51·5 g.); after removal of the pyridylacetic acid (28 g.) the mother-liquor was concentrated to a syrup and treated with ethereal hydrogen chloride. The partially crystalline hydrochloride, after recrystallisation, gave 4-methyl-2-pyridone hydrochloride (3 g.), m. p. and mixed m. p. 166—167°.

Methyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetate*.—(i) The nitrile (XX) (1·49 g.), suspended in dry methanol, was saturated at 0° with hydrogen chloride. After 20 hr. at 0° the methanol was removed under reduced pressure, and the residue dissolved in chloroform, washed with 2N-sodium carbonate, and evaporated. The residual ester was treated in a small volume of methanol with ethereal hydrogen chloride, which precipitated a slightly hygroscopic hydrochloride (1·37 g., 74%). Two recrystallisations from methanol–ether with a trace of dry hydrogen chloride gave the pure *hydrochloride*, m. p. 116·5—120° (Found: N, 4·3. $C_{18}H_{22}O_5NCl$ requires N, 3·8%). The hydrochloride in water dissociated to an oil; basification (2N-sodium carbonate) and extraction with chloroform gave the free *ester* which separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 64·5—67° (from ether at −10°) (Found: C, 64·9; H, 6·4; N, 4·7. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·4; N, 4·2%).

(ii) The acid (XI) (0·63 g.) was treated in methanol (3 c.c.) with ethereal diazomethane [from methylnitrosourea (1·17 g.)]. Next morning unchanged acid (0·133 g.) was filtered off and the ester converted by ethereal hydrogen chloride into the hydrochloride, m. p. and mixed m. p. 117—120°. The base had m. p. and mixed m. p. 67—69°.

1-(3 : 4-*Dimethoxyphenethyl*)-2-*oxo*-4-*piperidylacetic Acid* (XII).—The acid (XI) (4·76 g.) was hydrogenated in methanol (140 c.c.) at room temperature and pressure in the presence of Adams catalyst (0·2 g.). (Uptake in 24 hr., 820 c.c. Theor., at 23°/757 mm., 797 c.c.) The catalyst was removed and the filtrate concentrated to *ca.* 20 c.c. to which ether (*ca.* 100 c.c.) was added. The *piperidylacetic acid* (4·13 g., 86%), m. p. 146—148°, separated from methanol–ether in prisms, m. p. 147·5—149·5° (Found: C, 63·4; H, 7·4; N, 4·6. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·2; N, 4·4%).

1 : 2 : 3 : 4 : 6 : 7-*Hexahydro*-9 : 10-*dimethoxy*-2-*methoxycarbonylmethylbenzo*[a]*quinolizinium Iodide* (XXII).—The acid (XII) (0·23 g.) was dissolved in warm methanol (20 c.c.), and hydrogen chloride was passed into the solution to saturation at 0°. The solution was kept at room temperature overnight, then the solvent was removed. The residue was dissolved in chloroform and washed with 2N-sodium carbonate and water. Removal of the solvent gave the oily methyl ester (XXI). Without being crystallised (Pailer and Strohmayer [13b] record m. p. 57—58°) this was cyclised by phosphorus oxychloride (1 c.c.) and toluene (4 c.c.) at 95° for 5—10 min. The iodide was isolated as described by Pailer and Strohmayer and crystallised from water as yellow needles, m. p. 218—219·5° (lit., 218—220°) (Found: C, 48·5; H, 5·5; N, 2·9. Calc. for $C_{18}H_{24}O_4NI$: C, 48·5; H, 5·4; N, 3·1%), $\lambda_{max.}$ 232 (log ε 4·29), 300 (log ε 3·96), and 245 mμ (log ε 3·97) in water.

1-(3 : 4-*Dimethoxyphenylethyl*)-4-N-(3 : 4-*dimethoxyphenethyl*)*carbamoylmethyl*-2-*oxopiperidine* (XIII).—Ethyl chloroformate (1·19 g.) was added to a solution of the acid (XII) (3·21 g.) and triethylamine (1·01 g.) in dry dimethylformamide (12·5 c.c.) at −15° to −20° during 10—15 min. The mixture was kept at −10° for 10 min., then allowed to warm to 0° for 10 min., cooled to −5°, treated with 3 : 4-dimethoxyphenethylamine (2·71 g.) and triethylamine (1·01 g.) in dimethylformamide (5 c.c.), kept at room temperature overnight, and evaporated. The residue was dissolved in chloroform and washed with 2N-hydrochloric acid (20 c.c.), 2N-sodium carbonate (20 c.c.), and water. The chloroform was removed and the residue dissolved in ethyl acetate. The amide (4·05 g., 84%), m. p. 126—128°, separated in needles on cooling and an analytical sample, obtained from ethyl acetate, had m. p. 120—121° or 130—131°; these forms are interconvertible (Found: C, 67·3; H, 7·6; N, 5·9. Calc. for $C_{27}H_{36}O_6N_2$: C, 66·9; H, 7·5; N, 5·8%). Sugasawa and Oka [13c] give m. p. 130—131°.

2-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-2-iso*quinolylmethyl*)-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizinium Iodide Hydriodide* (XIV).—The amide (XIII) (9·70 g.) was heated in dry toluene (80 c.c.) with phosphorus oxychloride (20 c.c.) at 95° for 0·5 hr. Toluene and excess of phosphorus oxychloride were then removed and the residue was washed twice with dry light petroleum (b. p. 60—80°) by decantation. The residue was dissolved in water (100 c.c.) and a few c.c. were distilled under reduced pressure. On cooling, a small amount of crystalline material, m. p. 150°, was removed and, to the filtrate, sodium acetate (*ca.* 30 g.) and then sodium iodide (24 g.) in water (40 c.c.) were added. The precipitated red oil was extracted with chloroform and washed with water. The recovered red gum was dissolved in methanol (*ca.* 60 c.c.) from which the *iodide hydriodide* (12·1 g., 85%), m. p. 193—195° (softens at 170°), separated; recrystallisation from methanol gave material of m. p. 193—195° (Found, in a sample dried at 60° *in vacuo*: C, 44·9; H, 5·0; N, 3·7; I, 36·0. $C_{27}H_{33}O_4N_2I,HI,H_2O$ requires C, 44·9; H, 5·0; N, 3·9; I, 35·1%). An air-dried sample had an indistinct m. p. (90—195°) owing to hydration (Found: C, 44·0; H, 5·1; N, 3·2. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires C, 43·8; H, 4·9; N, 3·8%): at 100° *in vacuo* (2 hr.) it lost one molecule (Found: loss, 2·9. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires H_2O, 2·4%). The absorption spectrum (solution in water) had maxima at 227·5 (log ε 4·61), 302·5 (log ε 4·29), and 455 mμ (log ε 4·29).

Use of sodium bromide instead of sodium iodide gave the *bromide hydrobromide*, pale yellow prisms, m. p. 193—195° (from methanol–ether) (Found: C, 50·2; H, 6·0; N, 4·1; Br, 24·1. $C_{27}H_{33}O_4N_2Br,HBr,2H_2O$ requires C, 50·3; H, 5·9; N, 4·3; Br, 24·8%), $\lambda_{max.}$ (in water) 242·5 (log ε 4·5), 305 (log ε 4·25), and 452 mμ (log ε 4·25). 1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)pentane dihydrobromide [30] had $\lambda_{max.}$ 242·5 (log ε 4·43), 305 (log ε 4·2), and 452 mμ (log ε 4·15).

(±)-*De-ethylemetine Dihydriodide* (XV).—*Racemate A*. The iodide hydriodide (XIV) (3·52 g.) was hydrogenated in methanol (150 c.c.) with Adams catalyst (0·2 g.) at room temperature and pressure. Absorption was slow but after 24 hr. the theoretical amount of hydrogen had been taken up and reduction ceased. The pale yellow solution was filtered and concentrated, prisms (1·5 g., 42%), m. p. 236—240° (softening at 234°), separating. Crystallisation from methanol gave the *dihydriodide A*, m. p. 247—249° (softening at 243°) (Found: C, 45·6, 45·2; H, 5·5, 5·6; N, 4·0, 3·3; I, 35·8. $C_{27}H_{36}O_4N_2,2HI$ requires C, 45·8; H, 5·4; N, 4·0; I, 35·8%). The base did not crystallise. Ethereal hydrobromic acid gave the *dihydrobromide*, m. p. 218—220° (from ethanol–ethyl acetate) (m. p. less sharp than for the dihydriodide, possibly owing to hydration) (Found: C, 48·4; H, 6·7; N, 3·8. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2%), $\lambda_{max.}$ (in water) 227 (log ε 4·17) and 282 mμ (log ε 3·85). The *dihydrogen dioxalate*, prepared from the dihydrobromide in the normal way, formed prisms (from methanol–ether) which softened at 120° and had m. p. 123—125° (meniscus at 140°) (Found: C, 56·0; H, 6·3; N, 4·3. $C_{27}H_{36}O_4N_2,2H_2C_2O_4,2H_2O$ requires C, 55·6; H, 6·6; N, 4·2%).

Racemate B. After separation of the dihydriodide A no further material could be obtained crystalline. However, evaporation gave a non-hygroscopic yellowish, amorphous powder, m. p. 210—220° (softening at 205°) (Found: C, 44·2; H, 5·7; N, 3·6%).

In a similar experiment, this product was dissolved in water, and the solution was made alkaline and extracted with chloroform. The base was treated with ethanolic oxalic acid. Ether was added. The precipitated oil crystallised slowly (1·06 g., 33%); on crystallisation from methanol–ethyl acetate, the *salt B* separated very slowly as prisms, m. p. 180° (decomp.) (Found: C, 59·4; H, 6·7; N, 4·5%). A mixed m. p. with the racemate A dihydrogen dioxalate was 112—140°.

In another experiment the amorphous dihydriodide (1·31 g.) was dissolved in methanol with warming; from the cooled solution ethereal hydrobromic acid precipitated a yellow gum. Crystallisation from methanol–ethyl acetate gave pale yellow prisms (0·31 g.), m. p. 225—230°. Recrystallisation gave prisms, soften at 218°, m. p. 224—228° (mixed m. p. with the dihydrobromide of racemate A, 212—227° (Found: C, 50·0; H, 6·7; N, 4·1; Br, 24·1. $C_{27}H_{36}O_4N_2,2HBr,2H_2O$ requires C, 49·8; H, 6·5; N, 4·3; Br, 24·6%), $\lambda_{max.}$ (in water) 228 (log ε 3·91) and 282 mμ (log ε 3·55).

De-ethylrubremetinium Bromide (XIII) (cf. ref. 23).—The amorphous racemates of de-ethylemetine dihydriodide, after removal of the crystalline racemate A—1·5 g. obtained from the mother-liquor by evaporation to dryness—were heated with potassium acetate (0·25 g.), mercuric acetate (5 g.) and acetic acid (1 c.c.) in water (32 c.c.) for 1 hr., then filtered. The mercurous acetate was washed with water, alcohol, and acetone. The washings were added to the first

filtrate and the alcohol and acetone were removed under reduced pressure. A further quantity of mercuric acetate (2·5 g.) was added and the solution refluxed again for 2 hr. The solution was filtered and the mercurous acetate washed with water. The filtrate was heated to 90° and hydrogen sulphide was passed into the solution. Mercuric sulphide was filtered off and extracted exhaustively with boiling ethanol. The total filtrates were concentrated under reduced pressure to *ca.* 30 c.c. and treated with excess of 48% aqueous hydrobromic acid. The orange-scarlet needles (0·80 g., 72%), m. p. 237—240° (soften at 230°), which separated, were collected. Recrystallisation from dilute hydrobromic acid gave *de-ethylrubremetinium bromide*, m. p. 233—235° (Found: C, 57·8; H, 5·9; N, 4·8. $C_{27}H_{29}O_4N_2Br,2H_2O$ requires C, 57·7; H, 5·9; N, 5·2%).

This oxidation product was also obtained by Pailer and Strohmayer [13b] but no experimental details or analyses are given; they record m. p. 215°.

Our product had $\lambda_{max.}$ (in H_2O) 257·5 (log ε 4·28), shoulder 283 (log ε 4·24), 300 (log ε 4·26), and 437·5 mμ (log ε 4·47). The absorption curve is identical with that given by Pailer and Strohmayer for this compound and with that for rubremetinium bromide.[24]

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CHEMICAL CONSTITUTION AND AMŒBICIDAL ACTION. PART IV. SYNTHESIS OF EMETINE AND STEREOISOMERS OF EMETINE

BY
M. BARASH
J. M. OSBOND
AND
J. C. WICKENS

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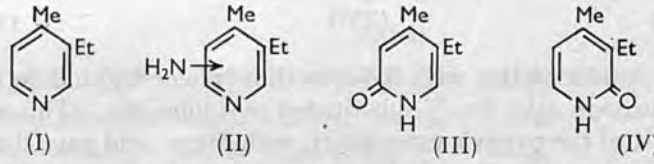
710. *Chemical Constitution and Amœbicidal Action. Part IV.* Synthesis of Emetine and Stereoisomers of Emetine.*

By M. Barash, J. M. Osbond, and J. C. Wickens.

Stereoisomers of emetine (XXII) have been synthesised by three routes: (1) Catalytic reduction of the four dehydroemetines (XXI) has given 4 stereoisomers of emetine (XXII) (Aa_1, Ab_2, Bc_1, and Bd_1). Paper chromatography showed only one of these isomers (Aa_1) to be inseparable from emetine. The physicochemical properties were in close agreement with those of emetine, and (±)-Aa_1 had slightly more than half the amœbicidal activity of (+)-emetine dihydrochloride. Resolution of the base of (±)-Aa_1 gave optically active salts indistinguishable from natural emetine salts. (2) Catalytic reduction of tetradehydroemetinium chloride hydrochloride (XXIII; A) led to the predominant formation of (±)-isoemetine (Ab_2) with a small amount of (±)-emetine (Aa_1). (3) Catalytic reduction of the esters (XXV; A and B) with subsequent transformations led to the formation of the above four emetine isomers.

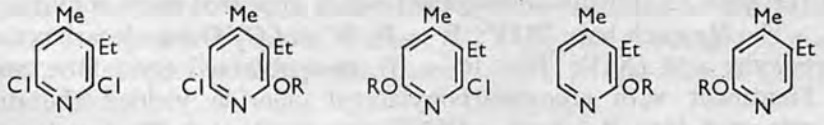
The correct structure (XXII) for emetine, suggested by Robinson [1] on biogenetic grounds, was confirmed independently by Openshaw [2] and Pailer [3] and their co-workers, and (±)-rubremetinium bromide has been synthesised by three groups of workers.[4,5,6] In addition a total synthesis of emetine has been described by Preobrazhenski and Evstigneeva and their co-workers,[7] and a partial synthesis by Battersby, Davidson, and Harper.[8] A summary [9] of our synthetic work was followed by a stereospecific synthesis of emetine by Battersby and Turner,[10] which caused us to re-examine some of our conclusions and to make a correction.[11]

As emetine (XXII) has four asymmetric centres (positions 2, 3, 11b, and 1′), 8 racemic and 16 optical isomers are possible. To apply the synthesis of de-ethylemetine, described in Part III,* to emetine, it was necessary to prepare the pyridone (III).



(I) (II) (III) (IV)

β-Collidine (I) with sodamide in dimethylaniline gave a mixture of the 2- and 6-aminopyridine (II) which was converted into the pyridones (III) and (IV) and separated by crystallisation, but the yield was low and the unwanted isomer (IV) predominated. An alternative route employed 2,6-dichloro-5-ethyl-4-methylpyridine [12] (V) which with one equivalent of sodium isopropoxide, sodium benzyloxide, or potassium diphenylmethoxide gave a mixture of the isomers (VI) and (VII) (R = Pr^i, CH_2Ph, or $CHPh_2$). It was hoped



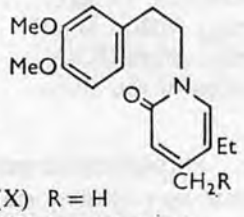
(V) (VI) (VII) (VIII) (IX)

that the condensation with a bulky group (*e.g.*, diphenylmethyl) would occur chiefly at the less hindered 2-position. The mixture (VI + VII; R = Pr^i) was dechlorinated by hydrogenolysis to give the ethers (VIII + IX; R = Pr^i) which on acid hydrolysis gave the pyridones (III; 47%) and (IV; 9%). Alternatively, the mixture (VI + VII; R =

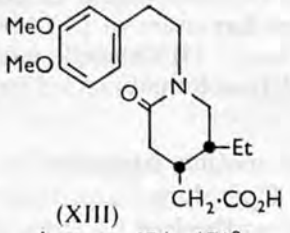
* Part III, *J.*, 1959, 2157.

Pr^i) was hydrolysed and then dechlorinated. The mixture of benzyl ethers (VI + VII) was hydrogenated to give predominantly the pyridone (III). The condensation with potassium diphenylmethoxide was the most favourable as it gave chiefly the ether (VII; R = $CHPh_2$). Hydrogenolysis gave the pure pyridone (III) in one step.

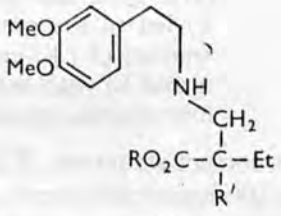
The structures of the pyridones (III) and (IV) were assigned on the following considerations. By analogy [13] it was expected that, in the amidation of β-collidine (I), isomer (IV) would predominate, whereas in the condensation of the dichloro-compound (V) with potassium diphenylmethoxide the isomer (III) was expected. The pyridone (III) had $\lambda_{max.}$ 298 mμ, and the isomer (IV) 293 mμ; 5- and 3-methyl-2-pyridones [13] showed a parallel difference, namely 303 and 295 mμ respectively (cf. also ref. 14). Compound (III) was converted into the two acetic acid derivatives (XIII; A and B) (see below) which were identical with those obtained by a different route [5] and were converted eventually into (±)-rubremetinium bromide (XXIV).



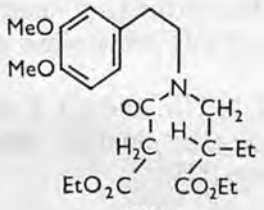
(X) R = H
(XI) R = CO·CO_2Et
(XII) R = CO_2H



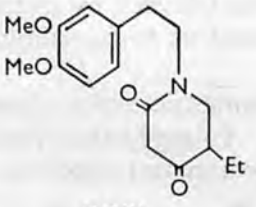
(XIII)
A, m.p. 154–156°
B, m.p. 152–153°



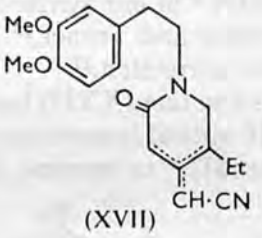
(XIV)



(XV)



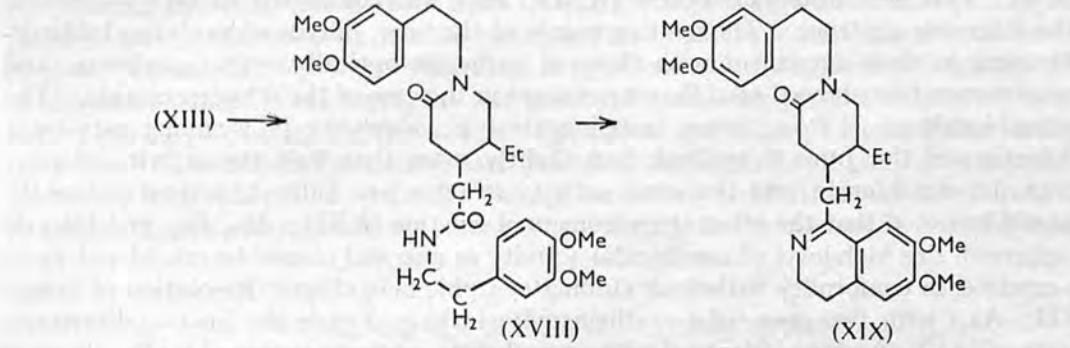
(XVI)

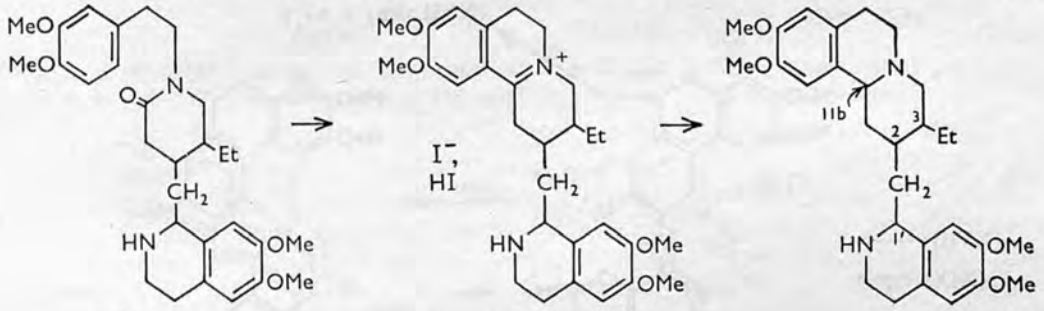


(XVII)

Condensing the pyridone (III) with 3,4-dimethoxyphenethyl iodide in t-butyl alcohol with potassium hydroxide gave the *N*-substituted pyridone (X). This with ethyl oxalate gave the potassio-salt of the pyruvic ester which with dilute acid gave the ester [15] (XI). It was assumed that only the active 4-methyl group would participitate in this reaction. Oxidation of the ester (XI) or the potassio-salt with alkaline hydrogen peroxide gave the corresponding acetic acid (XII) which, on melting, is decarboxylated to the pyridone (X). Hydrogenation of the acetic acid (XII) with Adams catalyst gave the two stereoisomeric 2-piperidone acids (XIII), A, m. p. 154—156° (70%), and B, m. p. 152—153° (15%); a mixed m. p. between the two gave a strong depression. It was later shown [16] that the A series has the *trans*- and the B series the *cis*-configuration. Ban [5] later described a synthesis of the acids (XIII) (non-crystalline) which appeared more convenient than the above route. The Mannich base (XIV; R = H, R′ = CO_2H) was decarboxylated to give the monocarboxylic acid (XIV; R = R′ = H), now obtained crystalline, and esterified (R = Et). Treatment with ethoxycarbonylacetyl chloride yielded the diester (XV) which was converted into the ketone (XVI) and then crystallised as a monoethanol solvate. However, several attempts to repeat the condensation of the ketone (XVI) with ethyl cyanoacetate and subsequent transformations under Ban's conditions [5] gave only a trace of crystalline acid (XIII; A). However, condensing the ketone (XVI) with cyanoacetic acid gave a good yield of mixed unsaturated nitriles (XVII), which on esterification, reduction, and hydrolysis gave the two crystalline acids (XIII) A (56%) and B (12%) in good overall yield.

Treatment of the separated acids (XIII) A and B with triethylamine and ethyl chloroformate gave the corresponding ethoxyformic anhydrides, which with 3,4-dimethoxyphenethylamine afforded the amides (XVIII, A and B). It has already been shown [17] that cyclisation of *NN'*-bis-(3,4-dimethoxyphenethyl)glutardiamide with phosphoric oxide in toluene resulted in γ-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)-*N*-(2-3,4-dimethoxyphenethyl)butyramide as well as 1,3-bis-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)propane. Application of this method to the two amides (XVIII) resulted in good yields of the mono-





Aa,HI, m. p. 214—216°	Aa, m. p. 215—222°	Aa_1,2HCl, m. p. 252—257°
Ab,HI, m. p. 207—208·5°	Ab, m. p. 195—196°	Ab_2,2HCl, m. p. 250—270°
Bc,HI, m. p. 241—243°	Bc, m. p. 190—197° *	$Bc_1$2HCl, m. p. 261—267°
Bd,HI, m. p. 204—207°	Bd, m. p. 237—242°	Bd_1,2HCl, m. p. 215—220°

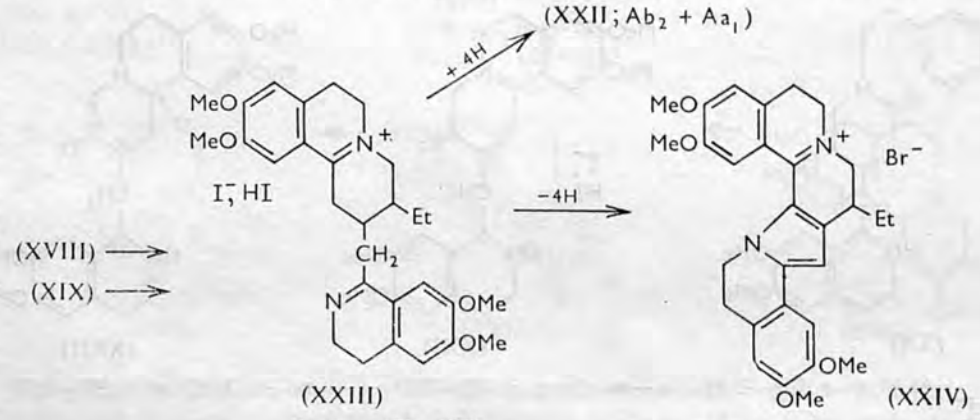
* Amorphous.

cyclised dihydroisoquinolines (XIX), isolated as their hydriodides: it will be shown later that the possible alternative cyclisation involving the piperidone did not occur. The structure of compound (XIX) was confirmed by cyclising isomer A further with phosphorus oxychloride to the benzo[*a*]quinolizinium salt (XXIII A) (see below). Hydrogenation of compound (XIX) was effected with Adams catalyst in methanol or dilute acid, or with Raney nickel or sodium borohydride. Isomer (XIX A) gave a mixture of products (XX; Aa, 55% and Ab, 45%); similarly, the isomer (XIX B) gave more (XX; Bc, 55%) than (XX; Bd, 26%).

The hydriodides of bases (XX) were cyclised by phosphorus oxychloride in chloroform and toluene in uniformly high yield.

The final step involves reduction of the dehydroemetinium salts (XXI) at the 11b centre either catalytically (Adams) or with potassium borohydride. Each dehydroemetinium salt (XXI) yielded essentially only one stereoisomer of emetine, isolated as their dihydrochlorides which were the most suitable for biological testing. *E.g.*, the salt (XXI; Aa) gave the emetine isomer (XXII; Aa_1) in 80% yield. Two isomers are

theoretically possible in these reductions and in some cases a very small amount of a second compound was detected. *E.g.*, in addition to (XXII; Aa_1), 5—10% of a non-crystalline material considered to be (XXII; Aa_2) was found by paper chromatography and isolated; however, its structure was not established with certainty. In order to ensure homogeneity of the isomers (XXII) and to detect (±)-emetine, paper chromatography was employed extensively. By this means all four isomers Aa_1, Ab_2, Bc_1, and Bd_1 were separated and only one (XXII; Aa_1) could not be separated from emetine (see Table 1). This most abundant isomer (XXII; Aa_1) was considered to be (±)-emetine on the following evidence. The melting points of the base, dihydrochloride, and dihydriodide were in close agreement with those of authentic optically active specimens, and infrared comparison showed no differences except in the case of the dihydrochloride. The dihydrochloride of (±)-Aa_1, when tested against *E. histolytica* in weanling rats by a modification of the Jones [18] method, had slightly more than half the activity of (±)-emetine dihydrochloride, and the same activity *in vitro* (see Table 1, revised values [11]). It should be noted that the other stereoisomers of emetine (XXII; Ab_2, Bc_1, and Bd_1) do not approach this high level of amœbicidal activity *in vivo* and cannot be considered to be (±)-emetine, in conformity with their chromatographic behaviour. Resolution of isomer (XXII; Aa_1) with two mols. of (+)-dibenzoyltartaric acid gave the bis-(−)-dibenzoyltartrate of (Aa_1), which was identical with an authentic specimen prepared by Dr. Brossi [19] as shown by m. p., mixed m. p., paper chromatography, infrared spectra, and rotation.



A, m. p. 172—175°.
B, m. p. 185—188°.

From the synthetic bis-(−)-dibenzoyltartrate, the (+)-dihydrochloride and (+)-dihydriodide were prepared, and again comparison with authentic specimens showed no differences (see p.). It follows if compound (XXII; Aa_1) is (±)-emetine, then isomer (XXII;

TABLE 1.

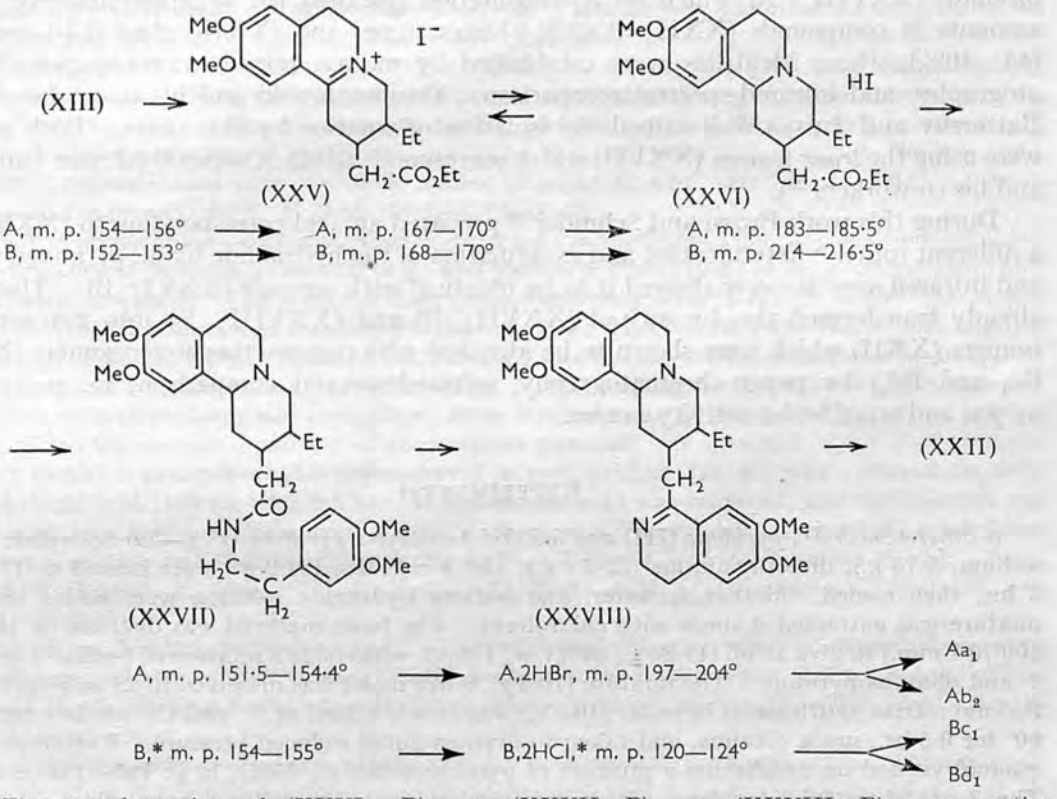
Stereoisomer of emetine,2HCl	Amœbicidal *in vivo* test: CD_{50} (mg./kg.)	Amœbicidal *in vitro* test: m.c. (g./ml.)	R_F (emetine = 1) *
Aa_1	6·25	10	1·00
Ab_2	64·6	10,000	0·62 †
Bc_1	133	1000	0·79 †
Bd_1	200	1000	0·67 †
(+)-Emetine,2HCl	6·25—12·5, 4—8	10—100	1·00

* These values are: Distance travelled by substance/Distance travelled by emetine, in ethyl methyl ketone–2N-aqueous hydrochloric acid on Whatman No. 1 paper.
† Separation from emetine can be effected.

Ab_2) is isoemetine as this isomer is epimeric with emetine at position 1′.

The above work located (±)-emetine as being in the A series; in addition, the paper-chromatographic, physical, and biological properties of compound (XXII; Aa_1) in relation to the other isomers allowed a second approach to be made, namely, the simultaneous

reduction of the two double bonds in tetradehydroemetine (cf. XXIII; A). Cyclisation of the amide (XVIII; A) to give a pentacyclic base (XXIII; A) was best effected with phosphorus oxychloride alone; alternatively, cyclisation of the base (XIX; A) gave the same iodide hydriodide A of (XXIII). Similarly, the isomeric amide (XVIII; B) gave the quaternary salt B of (XXIII). Dehydrogenation of a salt of (XXIII; A) with mercuric acetate, etc., gave (±)-rubremetinium bromide (XXIV) in good yield, and comparison with an authentic specimen showed them to be identical. Catalytic reduction (Adams) of the chloride hydrochloride derived from (XXIII; A) gave (±)-isoemetine (XXII; Ab_2) (in 60% yield), identified by the R_F value, infrared spectrum, and amœbicidal activity *in vivo*. The mother-liquor gave mixtures of (±)-isoemetine (Ab_2) and (±)-emetine (Aa_1), as shown by paper chromatography, but the small quantities present did not allow us to obtain pure (±)-emetine by this route. Openshaw and Wood [20] showed that catalytic reduction of a tetradehydroemetine salt, probably as (XXIII),[20,21] gave only isoemetine. Reduction with other catalysts under various conditions and with potassium borohydride in methanol gave substantially the same result. Catalytic reduction of an isomeric chloride



* The transformation of (XXVI; B) ⟶ (XXVII; B) ⟶ (XXVIII; B) ⟶ emetine isomers (XXII; Bc_1) and (Bd_1) was carried out by Brossi and Schnider.[19] Their compounds have been included in the above chart for completeness. The conditions used by Brossi and Schnider for the above reactions were used by us in the corresponding A series.

hydrochloride (cf. XXIII; B) gave rise almost certainly to the emetine isomer (XXII; Bc) as shown by the melting point and paper chromatography, but this was not firmly established. Evstigneeva and her co-workers [8] obtained a salt (XXIII) (m. p. 257—258°; A or B?) by a different route which on hydrogenation (Adams) gave an isomer considered to be (±)-emetine, together with a second isomer.

A third approach to the synthesis of stereoisomers of emetine was carried out as shown in the flow sheet above. Esterification of the acids (XIII; A and B) gave the corresponding esters, which without isolation were cyclised to give the quaternary iodides (XXV; A and B). These on catalytic reduction (Adams) gave in each case only one isomer, isolated

as their hydriodides (XXVI) in 91 and 95% yield respectively. In the case of salt (XXV; A) many experiments were carried out with different catalysts under varying conditions and by chemical reduction, such as potassium borohydride, alkaline sodium dithionite,[22] formic acid on the anhydro-base,[23] in an attempt to obtain the other isomer, but in all cases only the isomer (XXVI; A) was obtained; zinc and hydrochloric acid [24] gave no crystalline material. Treatment of salts (XXVI; A and B) with mercuric acetate gave the dehydro-esters (XXV; A and B) in high yield.

Condensing of the amino-acid corresponding to (XXVI; A) with 3,4-dimethoxyphenethylamine gave the amide (XXVII; A). Brossi and Schnider [19] later obtained the amide (XXVII; A) from 3-ethyl-1,2,3,4,5,6-hexahydro-9,10-dimethoxy-2-oxo-11b*H*-benzo[*a*]-quinolizine,[4,25] identity being provided by m. p., mixed m. p., and infrared-spectral comparison. The hydriodide, m. p. 227—228°, of base (XXVII; A) was not identical with either hydriodide of base (XX; Aa or Ab), and this confirms the view that in our first synthesis the direction of monocyclisation was (XVIII) ⟶ (XIX). Cyclisation of the base (XXVII; A) with phosphorus oxychloride gave (±)-*O*-methylpsychotrine dihydrobromide (XXVIII; A) which on hydrogenation (Adams) led to approximately equal amounts of compounds (XXII; Ab_2) [(±)-isoemetine] and (XXII; Aa_1) [(±)-emetine] (45, 40%), whose identities were established by m. p.s, mixed m. p.s, paper chromatography, and infrared-spectral comparison. Preobrazhenski and his co-workers [7] and Battersby and Turner [10] described the isolation of emetine by this route. Both groups were using the *trans*-isomer (XXVII) which corresponds to our A series [16] (cf. van Tamelen and his co-workers [26]).

During this work Brossi and Schnider [19] prepared an acid corresponding to (XXVI) by a different route. Esterification and examination of the hydriodide by m. p., mixed m. p., and infrared spectroscopy showed it to be identical with our salt (XXVI; B). They had already transformed this by way of (XXVII; B) and (XXVIII; B) into two emetine isomers (XXII) which were shown to be identical with our emetine stereoisomers (XXII; Bc_1 and Bd_1) by paper chromatography, infrared-spectral comparison, m. p.s, mixed m. p.s, and amœbicidal activity *in vivo*.

Experimental

5-Ethyl-4-methyl-2-pyridone (III) *and 3-Ethyl-4-methyl-2-pyridone* (IV).—(*a*) Sodamide (from sodium, 5·75 g.), dimethylaniline (22·5 c.c.), and β-collidine (24·2 g.) were heated at 170° for 5 hr., then cooled. Methanol, water, and sodium hydroxide solution were added and the mixture was extracted 6 times with chloroform. The basic material was distilled (b. p. 80—100°/0·7 mm.) to give an oil (11·35 g., 42%), n_D 1·5562, which was a mixture of 5-ethyl-4-methyl-2- and -6-aminopyridine. The mixture (10·8 g., 0·079 mole) was dissolved in 2N-sulphuric acid. Sodium nitrite (0·079 mole) in water (10 c.c.) was slowly added at 5°, and the whole warmed to 90° for 0·5 hr., made alkaline, and taken to dryness under reduced pressure. Extraction with ethanol yielded on distillation a mixture of pyridones (8·2 g., 75%), b. p. 150—158°/0·9 mm. The *3-ethyl-4-methyl-2-pyridone*, which was predominant, crystallised from ethyl acetate as plates, m. p. 169·5—172° (Found: C, 70·25; H, 8·2; N, 10·3. $C_8H_{11}ON$ requires C, 70·1; H, 8·1; N, 10·2%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·67), 293 mμ (log ε 3·83). After crystallisation from ethyl acetate the required *5-ethyl-4-methyl-2-pyridone*, m. p. 160·5—161·5°, was obtained in low yield as prisms (Found: C, 70·4; H, 7·9; N, 10·65%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·81), 298 (log ε 3·77).

(*b*) (i) To a solution of sodium (2·54 g.) in dry benzyl alcohol (90 c.c.) was added 2,6-dichloro-5-ethyl-4-methylpyridine [12] (18·9 g.). The solution was heated on a boiling-water bath for 9 hr., then under reflux for 0·75 hr. The benzyl alcohol was removed, water was added, the whole was extracted with ether, and the extract was washed with water and dried (K_2CO_3). Two distillations gave essentially *6-benzyloxy-2-chloro-3-ethyl-4-methylpyridine* (VII; R = CH_2Ph) (23·07 g., 88%), b. p. 150°/0·6 mm., n_D^{20} 1·5680 contaminated with a certain amount of the other isomer (Found: C, 69·3; H, 6·1; N, 5·4; Cl, 13·1. $C_{15}H_{16}ONCl$ requires C, 68·85; H, 6·2; N, 5·35; Cl, 13·45%).

This base (2·5 g.) was hydrogenated (palladium–charcoal) in methanol at room temperature and atmospheric pressure, yielding essentially the hydrochloride (0·9 g.), m. p. 161—168°, of 5-ethyl-4-methyl-2-pyridone. This salt yielded a base whence crystallisation from ethyl acetate afforded pure 5-ethyl-4-methyl-2-pyridone as prisms, m. p. 160—162°, identical with that prepared by method (a), together with a small amount of the 3-ethyl-4-methyl-2-pyridone.

(ii) Potassium (8·6 g.) was refluxed with diphenylmethanol (55·2 g.) in xylene (400 c.c.) in a nitrogen atmosphere for 20 hr. 2,6-Dichloro-3-ethyl-4-methylpyridine (38 g.) was then added and refluxing continued for a further 24 hr. The xylene was washed with water and evaporated to dryness under reduced pressure. The residue was crystallised twice from methanol, to give *2-chloro-6-diphenylmethoxy-3-ethyl-4-methylpyridine* (VII; R = $CHPh_2$) (26·1 g.), m. p. 104—105° (Found: C, 75·2; H, 5·95; N, 4·2; Cl, 10·3. $C_{21}H_{20}ONCl$ requires C, 74·7; H, 6·0; N, 4·15; Cl, 10·5%). The other isomer, *6-chloro-2-diphenylmethoxy-3-ethyl-4-methylpyridine* was isolated in small amount from the mother-liquor and after crystallisation from methanol had m. p. 94—95° (Found: C, 74·0; H, 5·8; N, 4·0%). The 2-chloro-ether (26·1 g.) in ethanol (600 c.c.) and water (10 c.c.) containing sodium acetate (14 g.) was hydrogenated (3 g. of palladium–charcoal) at room temperature and atmospheric pressure. This yielded the 5-ethyl-4-methyl-2-pyridone (8·57 g.), m. p. 160—161°. In a similar way the other isomer yielded on hydrogenolysis the 3-ethyl-4-methyl-2-pyridone.

(*c*) 2,6-Dichloro-3-ethyl-4-methylpyridine (19 g.) in dry xylene (100 c.c.) was added to sodium isopropoxide [from sodium (2·3 g.) in propan-2-ol (75 c.c.)] suspended in xylene (100 c.c.) and refluxed for 16 hr. The solution was filtered and the product distilled, to give essentially *2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine* (VII; R = Pr^i) (17·77 g.), b. p. 78—80°/0·8 mm., n_D 1·5075, contaminated with the other isomer (Found: C, 61·5; H, 7·7; N, 6·45; Cl, 16·6. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·55; N, 6·6; Cl, 16·6%).

(*c'*) The above chloro-isopropoxypyridine (15·4 g.) in methanol (150 c.c.) was hydrogenated in the presence of palladised charcoal (4 g.) and sodium acetate (12 g.) at room temperature and atmospheric pressure. The *5-ethyl-2-isopropoxy-4-methylpyridine* (IX; R = Pr^i) (14·73 g.), b. p. 132—134°/7·2 mm., was distilled (Found: C, 73·8; H, 9·8; N, 7·55. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6; N, 7·8%). This product (2·4 g.) was heated with concentrated hydrochloric acid (15 c.c.) in a sealed tube at 118° for 4·5 hr. The resulting 5-ethyl-4-methylpyridone was extracted with chloroform and crystallised from ethyl acetate as prisms (47%), m. p. 159·5—162°. From the mother-liquor 9% of the isomeric pyridone was obtained.

(*c''*) Crude 2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine (42 g.) was refluxed in 48% hydrobromic acid (400 c.c.) for 0·5 hr. Hydrobromic acid was removed, and the solution was made slightly alkaline with aqueous sodium carbonate. The solid that separated crystallised from ethyl acetate and then alcohol, to give *6-chloro-5-ethyl-4-methyl-2-pyridone* (9·47 g.), m. p. 174—176° (Found: C, 55·9; H, 5·4; N, 7·8; Cl, 20·8. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·9; N, 8·2; Cl, 20·7%).

The above 6-chloro-2-pyridone (1·55 g.) in methanol (25 c.c.) was hydrogenated at room temperature and atmospheric pressure in the presence of sodium acetate (1·5 g.) and palladised charcoal (1 g.), yielding 5-ethyl-4-methyl-2-pyridone (0·75 g.), m. p. 159—161°, identical with that obtained above.

3-Methyl-2-pyridone.—Sodium nitrite (3·7 g.) in water (10 c.c.) was added to 2-amino-3-methylpyridine (5·0 g.) in sulphuric acid (concentrated acid 5·5 c.c., in water, 42 c.c.) at 5°. After 1 hr. at 10° the solution was heated at 90° for 1 hr. Potassium carbonate was added, and the solution concentrated to dryness. The residue was extracted with boiling ethanol. The ethanol extracts were combined, evaporated, and sublimed at 100°/0·5 mm. to give the pyridone (2·7 g.), which on crystallisation from benzene had m. p. 141—143° (Seide [13] gives m. p. 140°), $\lambda_{max.}$ (in H_2O) 226 (log ε 3·84), 295 mμ (log ε 3·93).

5-Methyl-2-pyridone.—This *isomer* (2·9 g.) was prepared similarly from 2-amino-5-methylpyridine (5 g.) and after sublimation at 110°/1·0 mm. and crystallisation from benzene had m. p. 184—188° (Found: C, 66·0; H, 6·5; N, 12·8. C_6H_7ON requires C, 66·1; H, 6·5; N, 12·8%), $\lambda_{max.}$ (in H_2O) 227 (log ε 3·91); 303 mμ (log ε 3·79).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-4-methyl-2-pyridone (X).—5-Ethyl-4-methyl-2-pyridone (2·72 g.) was added to a solution of potassium hydroxide (1·32 g.) in water (1 c.c.) and t-butyl alcohol (80 c.c.), followed by 3,4-dimethoxyphenethyl iodide (5·84 g.), and the solution was refluxed for 4 hr. The butanol was removed, water added, the whole extracted 3 times with

benzene, the extracts were washed with water, and the product converted into the *hydrochloride* (4·28 g.), m. p. 199—201·5° (decomp.) (Found: C, 64·2; H, 7·3; N, 4·0; Cl, 10·5. $C_{18}H_{23}O_3N$,HCl requires C, 64·5; H, 7·2; N, 4·15; Cl, 10·5%).

The *pyridone*, obtained from the hydrochloride separated from ethyl acetate–ether as prisms, m. p. 72—75·5° (Found: N, 4·7. $C_{18}H_{23}O_3N$ requires N, 4·65%).

Ethyl 1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-1,2-*dihydro*-2-*oxo*-4-*pyridylpyruvate* (XI).—Absolute ethanol (2·85 c.c.) was added dropwise to potassium (0·43 g.) under dry ether (10 c.c.), followed by ethyl oxalate (1·6 g.) in ether (6 c.c.) at 0°. The pyridone (X) (3·01 g.) in dry benzene (40 c.c.) and ether (140 c.c.) was added and the solution refluxed for 24 hr. After cooling to 0° for 4 hr. the yellow potassio-salt (3·01 g., 85% based on pyridone used) was filtered off and washed with ether. Treatment of this salt with 2N-sulphuric acid, extraction with chloroform, and crystallisation from ethyl acetate gave the *ester*, m. p. 141·5—142·5° (Found: C, 65·7; H, 7·0; N, 3·4. $C_{22}H_{27}O_6N$ requires C, 65·8; H, 6·8; N, 3·5%).

The potassio-salt of the pyruvate (3 g.) in 10% aqueous sodium hydroxide (12·4 c.c.) was kept at 0° for 18 hr. A small amount of ice was added, followed by 30% hydrogen peroxide (2·41 c.c.); after 24 hr. at 0° a further quantity of hydrogen peroxide (1·03 c.c.) was added. After a further 24 hr. at 0° manganese dioxide (0·1 g.) was added, the mixture was filtered, and the filtrate made slightly acid with hydrochloric acid and extracted with chloroform. Treatment of the product with ethereal hydrogen chloride gave the *acetic acid hydrochloride* (cf. XII) which crystallised from methanol–ether as prisms (1·92 g., 76·5%), m. p. 160·5—162·5° (decomp.) (Found: C, 59·3; H, 6·7; H, 3·3. $C_{10}H_{24}O_5HCl$ requires C, 59·8; H, 6·3; N, 3·7%). The free *acid* (obtained from the hydrochloride) and crystallised from methanol had m. p. 154° (decomp.) (Found: N, 4·2. $C_{19}H_{24}O_5NCl$ requires N, 4·1%), $\lambda_{max.}$ (in 2N-HCl) 228, 285, and 303 mμ (log ε 3·99, 3·68, and 3·71 respectively).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-2,4-*dioxopiperidine* (XVI).—The 2,4-dioxopiperidine was prepared by Ban's method [5] with some improvement of yield and crystallisation of intermediates. 3,4-Dimethoxyphenethylamine was condensed with formaldehyde and ethylmalonic acid to give the Mannich base, m. p. 157—158°. Decarboxylation was then effected in 60% acetic acid to give α-(3,4-dimethoxyphenethylaminomethyl)butyric acid, m. p. 155—156° (Found: C, 64·1; H, 8·2; N, 4·9. Calc. for $C_{15}H_{23}O_4N$: C, 64·2; H, 8·2; N, 4·9%), the overall yield for the two steps being 75%. Esterification of the acid with ethanol and hydrogen chloride, followed by treatment with the acid chloride of ethyl hydrogen malonate gave ethyl α-[*N*-(ethoxycarbonylacetyl)-*N*-(3,4-dimethoxyphenethyl)aminomethyl]butyrate. Dieckmann cyclisation, by sodium in xylene, of the diester, hydrolysis by 10% acetic acid, and decarboxylation gave the ketone as a crystalline *ethanol solvate*, m. p. 38—40°, in 62% overall yield (Found: C, 65·3; H, 8·1; N, 4·2. $C_{17}H_{23}O_4N,C_2H_5{\cdot}OH$ requires C, 64·95; H, 8·3; N, 4·0%).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-1,2-*dihydro*-2-*oxo*-4-*piperidylacetic Acids* (XIIIA *and* B).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-pyridylacetic acid (6·91 g.) was hydrogenated in methanol (400 c.c.) in the presence of Adams catalyst (0·3 g.) at room temperature and atmospheric pressure. After 2—3 days the slow uptake of hydrogen ceased (*ca.* 2 mol.). The *acetic acid* (A) separated from methanol as prisms (4·56 g., 70%), m. p. 154—156° (Found: C, 65·2; H, 8·35; N, 4·5. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

From the mother-liquor, on concentration, the *acid* (B) separated as prisms (0·94 g., 14%), m. p. 152—153°. A mixed m. p. between A and B gave a marked depression (m. p. 130—135°) (Found: C, 65·3; H, 7·9; N, 3·9. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

(ii) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2,4-dioxopiperidine ethanol solvate (70·3 g., 0·2 mole), dry cyanoacetic acid (39 g., 0·459 mole), dry ammonium acetate (5 g.), and glacial acetic acid (5 ml.) were dissolved in benzene (500 ml.) and refluxed in a Dean and Stark apparatus at 110° for 3 hr. Cyanoacetic acid (12 g., 0·141 mole), ammonium acetate (3 g.), and glacial acetic acid (5 ml.) were added and the whole was refluxed for a further 4 hr. Ammonium acetate (3 g.) was added and the mixture refluxed for a further 6 hr., then the bath-temperature was raised to 120°, the benzene distilling. The residual syrup was heated in the bath for a further 12 hr. at 120°, dissolved in benzene (200 ml.), washed 3 times with 2N-sodium carbonate, then with water, dried (Na_2SO_4), and evaporated. The mixture of unsaturated nitriles (XVII) (80 g.) was dissolved in absolute alcohol (600 ml.), saturated with hydrogen chloride at 0°, and refluxed for 2½ hr. with continued passage of hydrogen chloride. The alcohol was removed and water (*ca.* 300 ml.) added. The solution was extracted 3 times with benzene, washed twice

with 2N-sodium carbonate, and dried (Na_2SO_4). The benzene was removed, and the resulting ethyl esters (75 g.) were hydrogenated in methanol (650 ml.) at room temperature and atmospheric pressure in the presence of Adams catalyst (0·5 g.) (uptake 4·4 l.) (theor. 4·9 l.). The catalyst was removed, and the solution was concentrated to *ca.* 600 ml., treated with potassium hydroxide (20·7 g.) in water (20 c.c.), and refluxed for 3¼ hr.; water was then added and the methanol removed under reduced pressure. The aqueous solution was acidified, extracted 3 times with chloroform, dried (Na_2SO_4), and co-distilled twice with methanol; the residue was dissolved in methanol (300 ml.) and the first main crop was the almost pure acetic acid A. Fractional crystallisation of the mother-liquor gave a total amount of the pure A isomer, m. p. 154—156° [identical with A prepared as in (i)] (39·49 g., 56·5%). The isomer (B), m. p. 152—153° (8·34 g., 12%), was identical with the B isomer prepared in experiment (i). When the original Ban process [5] was attempted the gummy mixture of acids at the end yielded only a trace of acetic acid A after being seeded with our crystalline material.

N-(3,4-*Dimethoxyphenethyl*)-α-[1-(3,4-*dimethoxyphenethyl*)-5-*ethyl*-2-*oxo*-4-*piperidyl*]*acetamide* (XVIII; A *and* B).—The acetic acid (XIII; A) (2·79 g.) was treated in dry dimethylformamide (25 c.c.) at 0° with triethylamine (0·85 g.), followed by ethyl chloroformate (1·12 g.) in dry dioxan (4 c.c.) at −30° during 10 min. The mixture was kept at −30° for a further 5 min. and at −10° for 10 min. Then 3,4-dimethoxyphenethylamine (1·6 g.) and triethylamine (0·85 g.) in dimethylformamide (20 c.c.) were added during 10 min. with stirring, and the mixture was kept at room temperature overnight. The solution was concentrated to a thick syrup, dissolved in chloroform, and washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water and dried (Na_2SO_4). This yielded a pale yellow gum (quantitative yield) which did not crystallise. In a similar way the acetic acid (XIII; B) was also converted into the amide (XVIII; B). Compounds of similar structure have been prepared by a different route by Evstigneeva *et al.*,[7] also non-crystalline.

4-(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-1-(3,4-*dimethoxyphenethyl*)-5-*ethyl*-2-*piperidone Hydriodides* (cf. XIX; A *and* B).—The amide (XVIII; A) [prepared from the corresponding acetic acid (XIII; A) (5·28 g.)] was treated in dry refluxing toluene (140 c.c.) with phosphoric oxide (50 g.) for ¾ hr. Further oxide (50 g.) was added and refluxing continued for a further 1¼ hr. The toluene was decanted and the residual material added to ice. The solution was extracted with ether, and aqueous potassium iodide was added. The *hydriodide* was extracted three times with chloroform, dried, and evaporated. The residue crystallised from methanol–ethyl acetate as yellow prisms [8·05 g.; 85% for the two steps from (XIII; A)], m. p. 190—192° (Found: C, 56·15; H, 6·5; N, 4·5. $C_{29}H_{38}O_5N_2$,HI requires C, 56·0; H, 6·3; N, 4·5%). $\lambda_{max.}$ (in H_2O) 230, 287 sh, 303, and 354 mμ (log ε 4·44, 3·81, 3·96, and 3·95 respectively). The *base* crystallised from ethyl acetate as pale yellow prisms, m. p. 122·5—124° (Found: C, 70·2; H, 7·8; N, 5·35. $C_{29}H_{38}O_5N_2$ requires C, 70·4; H, 7·7; N, 5·7%).

A similar result was obtained by using polyphosphoric acid instead of phosphoric oxide, although the yield was lower.

Similarly the amide (XVIII; B) was cyclised to give the corresponding *hydriodide*, m. p. 195·5—197·5°, as yellow prisms (from methanol–ethyl acetate) [76% yield (from XIII; B)] [mixed m. p. with (XIX; A) 187—189°] (Found: C, 56·25; H, 6·2; H, 4·3%].

1-(3 : 4-*Dimethoxyphenethyl*)-5-*ethyl*-4-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-2-*piperidone Hydriodides* [XX; Aa, Ab, (Bc), *and* (Bd)].—The hydriodide (5·0 g.) of base (XIX; A) was hydrogenated in methanol (75 c.c.) with Adams catalyst (0·1 g.) at room temperature and atmospheric pressure until one mol. had been absorbed. The solution was filtered and concentrated; on cooling, the *hydriodide* (cf. XX; Aa) separated as colourless prisms (2·6 g., 51·8%), m. p. 214—216° (Found: C, 55·5; H, 6·6; N, 4·4. $C_{29}H_{40}O_5N_2$,HI requires C, 55·8; H, 6·6; N, 4·5%), $\lambda_{max.}$ (in H_2O) 226 and 280 mμ (log ε 4·43 and 3·74). On concentration the second *hydriodide* (cf. XX; Ab) was obtained which after two recrystallisations separated from methanol–ether as pale yellow plates (2·05 g., 41%), m. p. 207—208·5° [mixed m. p. between (Aa) and (Ab) 203—208°] (Found: C, 56·3; H, 6·6; N, 4·5; I, 20·9%).

The amide hydriodide (cf. XIX; B) (4·26 g.) was reduced with potassium borohydride (1·0 g.) in methanol (100 c.c.) at room temperature to give two stereoisomers (XX; Bc and Bd). The hydriodide (cf. XX; Bc) (2·02 g., 55%) separated from methanol, in which it was sparingly soluble, as yellow plates, m. p. 244—246°. Catalytic reduction with Adams catalyst in methanol raised the amount to 82% (Found: C, 55·6; H, 6·8; N, 4·8%). From the mother-liquor of the potassium borohydride reduction, the epimer (XX; Bd) was isolated as the *hydriodide* after

several crystallisations from methanol–ether as pale yellow clumps (1·21 g., 26%), m. p. 203—205° (Found: C, 56·3; H, 7·0; N, 4·7%).

3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*isoquinolylmethyl*)*benzo*[a]*quinolizinium Iodide Hydriodides* (cf. XXI; Aa, Ab, Bc, and Bd).—The reduced hydriodide (cf. XX, Aa) (4·0 g.) was dissolved in dry chloroform (40 c.c.) of which 5 c.c. were removed by distillation. Dry toluene (30 c.c.) and phosphorus oxychloride (14 c.c.) were added and the solution was refluxed on a water-bath for 0·5 hr. The reagents were removed and the resulting red gum was dissolved in hot water (4 extractions) to which potassium iodide was added and the *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms (3·8 g., 81%), m. p. 215—222° (decomp.) (Found: C, 47·9; H, 5·4; N, 3·7. $C_{29}H_{39}O_4N_2I$,HI requires C, 47·4; H, 5·5; N, 3·8%).

The reduced hydriodide (cf. XX; Ab) (2·4 g.) was cyclised in a similar way. The resulting *iodide hydriodide* separated as yellow prisms, m. p. 195—196° (2·25 g., 79%) (Found: C, 47·2; H, 5·7; N, 3·6%). An air-dried sample had m. p. 186—193° with softening at 180° (Found: C, 45·9; H, 5·7; N, 3·8; I, 34·0; H_2O, 4·1. $C_{29}H_{39}O_4N_2I$,HI,1·5H_2O requires C, 45·7; H, 5·7; N, 3·6; I, 33·3; H_2O, 3·5%), $\lambda_{max.}$ (in H_2O) 227, 290, 302·5, and 350 mμ (log ε 4·7, 3·8, 3·88, and 3·9).

The *isomer* (XXI; Bc) was obtained in a similar manner in good yield but did not crystallise. The amorphous salt separated from ethanol as a yellow solid, m. p. 190—197° (Found: C, 46·3; H, 5·1; N, 3·9; I, 34·6. $C_{29}H_{39}O_4N_2I$,HI,0·5H_2O requires C, 46·9; H, 5·5; N, 3·8; I, 34·2%).

The *iodide hydriodide* (XXI; Bd) was obtained in 70% yield as pale yellow crystalline nodules (from ethanol), m. p. 237—242° (Found: C, 46·95; H, 5·5; N, 3·65; I, 34·1%).

2-(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide Hydriodide* (*Tetradehydroemetinium Iodide Hydriodide*) (XXIII; A).—(*a*) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-piperidylacetic acid (XIII; A) (0·69 g.) was converted into the amide (XVIII; A), which was dissolved in phosphorus oxychloride (13 c.c.), and heated at 95° for 0·5 hr. The excess of reagent was removed and the gum, after being washed once with light petroleum, was dissolved in ethanol and water and treated with excess of potassium iodide. The *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms, m. p. 172—175° (1·10 g., 75%) (Found, in air-dried sample: C, 44·2; H, 5·95; N, 3·5; I, 33·0; loss on drying 6·0. $C_{29}H_{37}O_4N_2I$,HI,2·5H_2O requires C, 44·8; H, 5·6; N, 3·6; I, 32·65; 2·5H_2O, 5·8. Found, in dried sample: C, 48·1; H, 5·4; N, 3·7; I, 34·9. $C_{29}H_{37}O_4N_2I$,HI requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·6, 4·52, 4·20, and 4·19).

(ii) 4-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-piperidone hydriodide (cf. XIX; A) (2·0 g.) was cyclised in chloroform (10 c.c.), toluene (11 c.c.), and phosphorus oxychloride (7 c.c.) at 95° for 0·75 hr. The iodide hydriodide was obtained as described above as yellow prisms (2·07 g.; 87%), m. p. and mixed m. p. 175—177°.

The acetic acid (XIII; B) (0·69 g.) was converted into the amide (XVIII; B), as in the example above, and cyclised with phosphorus oxychloride (2 c.c.) and toluene (10 c.c.) for 15 min. The product (XXIII; B) crystallised from methanol as the sparingly soluble *iodide hydriodide* (0·36 g., 66%), m. p. 185—188°, yellow prisms (Found: C, 47·6; H, 5·75; N, 3·6; I, 34·1. $C_{29}H_{37}O_4N_2I$,HI requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·80, 4·51, 4·20, 4·18 respectively).

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide* (XXV; A).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidylacetic acid (XIII; A) (1·05 g.; m. p. 155·5—157°) was esterified with absolute ethanol (30 c.c.) and hydrogen chloride at room temperature for 18 hr. The ethanol and hydrogen chloride were removed and the resulting ester hydrochloride was cyclised in toluene (5 c.c.) by phosphorus oxychloride (3 c.c.) at 95° for 0·5 hr. The quaternary *iodide*, prepared in the usual way, was extracted with chloroform and crystallised from ethanol–ethyl acetate with a few drops of ether, as yellow needles (1·26 g., 86%), double m. p. 135—140° and 167—170° (Found: C, 51·8; H, 6·0; N, 2·9; I, 26·4. $C_{21}H_{30}O_4NI$ requires C, 51·75; H, 6·2; N, 2·9; I, 26·0%), $\lambda_{max.}$ (in H_2O) 235, 302, and 348 mμ (log ε 4·34, 4·0, and 4·1).

(ii) The hydriodide (XXVI; A) (1·2 g.) was treated in methanol (5 c.c.) with excess of 2N-sodium carbonate, and the base extracted with ether, recovered, and heated in glacial acetic acid (30 c.c.) with mercuric acetate (2·4 g.) at 60° for 2·5 hr. Mercurous acetate separated after

10 min. The solution was cooled, diluted with water, and filtered. The filtrate was treated with hydrogen sulphide, the metal sulphide was filtered off, and the filtrate concentrated to 50 c.c. and acidified with hydrochloric acid. Potassium iodide was added and the quaternary iodide ester was extracted with chloroform and crystallised from methanol–ether as yellow plates (0·94 g., 78%), m. p. and mixed m. p. 170·5—171·5°.

Similarly the acetic acid (XIII; B) (2·52 g.) gave the *ester iodide* (XXV; B) as yellow prisms (3·01 g.) (from methanol–ethyl acetate–ether), m. p. 168—170° (Found: C, 52·35; H, 6·1; N, 2·9%).

Also the quinolizine hydriodide (XXVI; B) (0·27 g.) was dehydrogenated with mercuric acetate in acetic acid to give the ester iodide (XXV; B) (0·20 g.), m. p. and mixed m. p. 168—170°.

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine Hydriodide* (XXVI; A).—(i) The iodide ester (XXV; A) (0·97 g.) was hydrogenated in methanol (10 c.c.) with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After filtration, concentration, and dilution with ether, the *hydriodide* separated as colourless needles (0·89 g., 91%), double m. p. 163—165° and 183·5—184·5° (Found: C, 51·5; H, 6·3; N, 3·0; I, 26·3. $C_{21}H_{31}O_4N$,HI requires C, 51·5; H, 6·6; N, 2·9; I, 25·9%).

(ii) The iodide ester (XXV; A) (1·22 g.) was dissolved in methanol (40 c.c.) and saturated aqueous sodium hydrogen carbonate (40 c.c.) and treated at room temperature with sodium dithionite (4·0 g.) in two portions during 0·5 hr. The solution was left overnight, made strongly alkaline with 2N-sodium hydroxide, and extracted with ether. The hydriodide of the extracted base separated from ethanol as needles, m. p. 180—184° (1·02 g., 83%), identical with the previous preparation.

(iii) The iodide ester (1·2 g.) was treated in methanol (5 c.c.) with 2N-aqueous sodium carbonate. The anhydronium base was extracted with ether, dried (K_2CO_3), and recovered. To it was added 98% formic acid (0·17 g.) and the whole was kept at 60° for 2·25 hr., then dissolved in 2N-hydrochloric acid. Potassium iodide was added. The hydriodide crystallised from methanol–ether as needles, m. p. and mixed m. p. 178—181° (1·0 g., 82%).

The isomeric iodide ester (XXV; B) (2·25 g.) was hydrogenated as described in (i) above. The *hydriodide* (2·17 g.) separated from methanol–ether as needles, m. p. 214·5—216·5° (Found: C, 51·8; H, 6·7; N, 2·9%).

A sample of the acid (m. p. 170—171°) corresponding to structure (XXVI) obtained from Drs. Brossi and Schnider [19] was esterified with ethanol and hydrogen chloride at room temperature; the ethyl ester was characterised as the hydriodide and crystallised from methanol–ether as needles, m. p. 214—216°. A mixed m. p. with the above sample showed no depression and infrared comparison of the two samples showed them to be identical (Found: C, 52·0; H, 6·6; N, 3·0%).

2-[N-(3,4-*Dimethoxyphenethyl*)*carbamoylmethyl*]-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine* (XXVII; A).—The ester hydriodide (XXVI; A) (2·44 g.) was hydrolysed with aqueous-alcoholic 10% potassium hydroxide (30 c.c.) at 95° for 2 hr. The alcohol was removed, the pH of the solution adjusted to pH 7, and the acid extracted with chloroform. The gummy acid was refluxed with 3,4-dimethoxyphenethylamine (1·8 g.), acetic acid (0·2 c.c.), and ammonium acetate (0·2 g.) in xylene (30 c.c.), in a Dean–Stark apparatus with separation of water, for 12 hr. The xylene was removed, water added, and the yellow solid filtered off and washed with water and ether. The *amide* separated from ethyl acetate as needles, m. p. 151·5—154·5° (1·58 g., 64%) (Found: C, 70·2; H, 8·1; N, 5·6. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1; N, 5·6%). The hydriodide had m. p. 227—228°. An amide of the same structure (XXVII; A) was later prepared by Brossi and Schnider [19] by a different route and had m. p. and mixed m. p. 152—154°; infrared comparison in Nujol showed them to be identical.

2-(3,4-*Dihydro*-6,7-*dimethoxy*-2-*isoquinolylmethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine Dihydrobromide* (XXVIII, *A*) [(±)O-*Methylpsychotrine*].—The amide (XXVII; A) (2·42 g.) was heated in benzene (40 c.c.) with phosphorus oxychloride (6 c.c.) for 0·5 hr., whereupon a red oil separated. The solvent was removed and the residue dissolved in water and basified with 2N-sodium carbonate. The base was extracted with ether (3 times) and converted into the dihydrobromide which separated from methanol–ether as yellow nodules (2·25 g., 68%), m. p. 197—204°, softens at 195° [(+)-*O*-Methylpsychotrine dihydrobromide [27] has m. p. 190—200°] (Found, in air-dried specimen: C, 51·4; H, 6·25; N,

4·4. $C_{29}H_{38}O_4N_2,2HBr,2H_2O$ requires C, 51·5; H, 6·6; N, 4·1%). Drying at 100° did not remove the water of crystallisation and the same analysis was obtained.

(±)-*Emetine* (XXII; Aa_1) *and its Resolution*: *Stereoisomers* (XXII; Ab_2, Bc_1, Bd_1).—1*st Route. Reduction of stereoisomers of dehydroemetinium salts* (XXI). (i) (±)-Emetine (XXII; Aa_1). Dehydroemetinium iodide hydriodide (XXI; Aa) (1·46 g.) was converted into the chloride hydrochloride by shaking it with silver chloride in aqueous methanol, and the solution was filtered and evaporated to dryness. The residue was dissolved in methanol (20 c.c.) and hydrogenated with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After rapid uptake of 1 mol. of hydrogen the solution was filtered and ether was added. The *dihydrochloride* (1·0 g.) of base (XXII; Aa_1) crystallised as prisms, m. p. 252—257° (sinters at 247°). A mixed m. p. with (+)-emetine dihydrochloride gave no depression. An infrared comparison in Nujol showed the two to be very similar but not identical (Found: C, 59·5; H, 7·9; N, 5·4; Cl, 12·4. $C_{29}H_{40}O_4N_2,2HCl,2H_2O$ requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%. Found, in sample dried at 100°: C, 61·9; H, 7·7; N, 5·0. $C_{29}H_{40}O_4N_2,2HCl,0·5H_2O$ requires C, 61·9; H, 7·7; N, 5·0%). The dihydriodide, obtained by treatment of an aqueous solution of the dihydrochloride with sodium iodide, separated from methanol as woolly needles, m. p. 227—228°. A mixed m. p. with (+)-emetine dihydriodide (m. p. 228—229·5°; lit.,[28] m. p. 215—216°, 228—230°, 235—238°) showed no depression and a comparison of the two salts' infrared spectra showed no difference (Found in air-dried sample: C, 45·0; H, 5·6; N, 3·7; I, 32·5; H_2O, 4·3. $C_{29}H_{40}O_4N_2,2HI,2H_2O$ requires C, 45·1; H, 5·7; N, 3·6; I, 32·85; H_2O, 4·9. Found, in sample dried at 100°: C, 47·3; H, 5·2; N, 3·9; I, 34·5. $C_{29}H_{40}O_4N_2,2HI$ requires C, 47·2; H, 5·7; N, 3·8; I, 34·5%). The base, derived from an aqueous solution of the hydrochloride by treatment with alkali, was a colourless amorphous solid, m. p. 68—70° (meniscus at 74°). A mixed m. p. with (−)-emetine (m. p. 74°) gave no depression and the infrared spectra (in CS_2) of the two were identical. The (±)-base (XXII; Aa_1) (0·5 g.) in methanol was treated with (+)-dibenzoyltartaric acid (0·57 g., 2 mol.) in methanol–ethyl acetate: ethyl acetate was then added to turbidity and the solution seeded with the authentic salt. The (−)-*emetine bisdibenzoyltartrate* slowly crystallised and after two recrystallisations from methanol–ethyl acetate had m. p. 182—182·5° (decomp.), $[\alpha]_D^{20}$ −61·4° ±0·5° (*c* 1·002 in MeOH). An authentic specimen had m. p. 180—181°, $[\alpha]_D^{20}$ −62° (*c* 1·00 in MeOH); a mixed m. p. gave no depression and the infrared spectra were identical (Found: C, 64·6; H, 6·5; N, 2·7. $C_{29}H_{40}O_4N_2,C_{36}H_{28}O_{16},H_2O$ requires C, 64·9; H, 5·9; N, 2·3%). The (−)-base, obtained from this salt, with hydrochloric acid and sodium iodide gave the (+)-dihydriodide (sparingly soluble in water), needles (from methanol–ether), m. p. 228—230° (sinters at 225°), $[\alpha]_D^{19}$ +26·25° ±1·75° (*c* 0·571 in chloroform). An authentic sample had m. p. 228—229°, $[\alpha]_D^{19}$ +22·2° ±0·9° (in chloroform) (Found, in sample dried at 100°: C, 46·5; H, 5·8; I, 33·7. Calc. for $C_{29}H_{40}O_4N_2,2HI,H_2O$: C, 46·2; H, 5·9; I, 33·65%). In addition the (+)dihydrochloride was prepared from the (−)-dibenzoyltartrate in 82% yield, as needles (from methanol–ethyl acetate–ether), m. p. 235—250°, $[\alpha]_D^{20}$ +44·85° ±0·95° (*c* 1·07 in chloroform). An authentic specimen had m. p. 235—250°, $[\alpha]_D^{23}$ +46° (in chloroform) {lit.,[29] m. p. 235—250°, $[\alpha]_D^{20}$ +55° (in chloroform)} (Found: C, 57·0; H, 8·35; N, 4·4; H_2O, 8·0. Calc. for $C_{29}H_{40}O_4N_2,2HCl,3H_2O$: C, 57·3; H, 8·0; N, 4·6; H_2O, 8·9%). A mixed m. p. between these salts and authentic samples gave no depression and the infrared spectra (in KBr) of each pair were identical.

From the mother-liquor, after removal of a further small amount of the dihydriodide of base (XXII; Aa_1), the second isomer (cf. XXII; Aa_2) was obtained only as amorphous salts. The *dihydrochloride* had m. p. 235—240° (Found: C, 60·0; H, 7·5; N, 4·9; Cl, 12·6. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%).

(ii) The dehydroemetinium iodide hydriodide (XXI; Ab) (1·80 g.) was converted into the chloride hydrochloride and reduced as described above. The *dihydrochloride* of base (XXII; Ab_2) crystallised readily as prisms (0·8 g.), m. p. 250—270°, softening at 240° (Found, in air-dried sample: C, 60·35; H, 8·3; N, 4·5. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9%). This stereoisomer was examined by paper chromatography by the method described below and was found to be homogeneous and readily separated from emetine.

(iii) (*a*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (0·8 g.) in methanol (10 c.c.) was treated portionwise with sodium borohydride (1·0 g.) at 20°. After 0·5 hr. the solvent was removed and the residue treated with 2N-sodium carbonate and benzene. The benzene extracts were washed with water, then evaporated, and the product was converted into

the *dihydrochloride* of base (XXII; Bc_1). This salt crystallised from methanol–ether as colourless prisms (0·28 g.), m. p. 261—267° (sinters at 258°). It can be separated readily from emetine by paper chromatography in the usual solvent system, and gave only one spot (Found, in air-dried sample: C, 59·3; H, 7·7; N, 4·8; Cl, 12·1. $C_{29}H_{40}O_4N_2,2HCl,2H_2O$ requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%). The other epimer was not obtained. Comparison with an emetine isomer prepared by Drs. Brossi and Schnider [19] by m. p., mixed m. p., paper chromatography, toxicity, amœbicidal evaluation *in vivo*, and infrared spectroscopy showed them to be identical.

(*b*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (2·0 g.) was converted into the chloride hydrochloride in water and methanol with silver chloride (from 0·25 g. of silver nitrate) and hydrogenated in methanol (30 c.c.) with platinum oxide (0·18 g.). The solution was filtered, concentrated and diluted with ether and hydrochloric acid (0·1 c.c.). The dihydrochloride of base (XXII; Bc_1) separated as prisms (0·8 g.), m. p. 267—274° (decomp.), identical with the above specimen on paper chromatography.

(iv) Dehydroemetinium iodide hydriodide (XXI; Bd) (0·75 g.) was treated in methanol (15 c.c.) with potassium borohydride (0·3 g.) at 0°. The product was isolated after 1 hr. at 20° as the *dihydrochloride* of base (XXII; Bd), prisms (0·17 g.) (from methanol–ether), m. p. 215—220° (Found, in air-dried sample: C, 55·0; H, 7·8; N, 4·5; Cl, 11·9; loss on drying at 100°, 8·1. $C_{29}H_{40}O_4N_2,2HCl,4{\cdot}5H_2O$ requires C, 54·8; H, 8·1; N, 4·4; Cl, 11·1; $3H_2O$, 6·75. Found, in sample dried at 100°: C, 60·0; H, 7·6; N, 4·9. $C_{29}H_{40}O_4N_2,2HCl,1{\cdot}5H_2O$ requires C, 60·0; H, 7·8; N, 4·8%). Paper chromatography gave a single spot, easily separated from that of the salts of emetine and (XXII; Bc_1). This isomer (Bd_1) was also obtained by Drs. Brossi and Schnider [19] and m. p., mixed m. p., infrared spectroscopy, and paper chromatography showed them to be identical.

2nd Route. From stereoisomers of tetradehydroemetinium salts (XXIII). (i) *Salts of bases* (XXII; Ab_2 *and* Aa_1). Tetradehydroemetinium iodide hydriodide (XXIII; A_1) (2·07 g.) was shaken in hot water (75 c.c.) with silver chloride (from silver nitrate, 2 g.). The resulting chloride hydrochloride in methanol (20 c.c.) was reduced catalytically with platinum oxide (0·1 g.) at room temperature and pressure. After two mols. of hydrogen had been taken up the solution was filtered, concentrated, and diluted with ether. The *dihydrochloride* of base (XXII; Ab_2) separated as prisms (1·0 g., 60%), m. p. 245—260°, sinters 235°. Paper chromatography gave a single spot identical with that of isomer (Ab_2) obtained as described above. This identity was confirmed by the amœbicidal activity (Found: C, 60·43; H, 7·75; N, 4·6; Cl, 12·2. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%). The mother-liquor yielded on concentration two small further crops of dihydrochlorides which were mixtures (XXII; Aa_1 and Ab_2). Unfortunately (Aa_1) was present in only very small amounts and could not be purified.

Sodium borohydride reduction in methanol gave isomer (Ab_2) in 50% yield.

(ii) *Salt of base* (XXII; Bc_1). The tetradehydroemetinium iodide hydriodide (XXIII; B) (0·5 g.) was converted into the chloride hydrochloride and hydrogenated in methanol (25 c.c.) with platinum oxide (0·1 g.). The dihydrochloride produced crystallised as prisms (0·15 g.), m. p. 255—265°, and had the same R_F value as (XXII; Bc_1) with which on this basis it was considered to be identical.

3rd Route. From (±)-O-*methylpsychotrine* (XXVIII; A). *Salts of bases* (XXII; Aa_1 *and* Ab_2). (±)-*O*-Methylpsychotrine dihydrobromide (XXVIII; A) (2·25 g.) was hydrogenated (1 mol.) in methanol (50 c.c.) with Adams catalyst (0·2 g.). The solution was then warmed and filtered. The alcohol was removed, water and 2N-sodium carbonate were added, and the base was extracted with ether and converted into mixed dihydrochlorides. Crystallisation from methanol–ether gave the dihydrochloride of base (XXII; Ab_2) as needles (0·88 g., 45%), m. p. 249—263° (Found, in sample dried at 100°: C, 62·1; H, 7·8; N, 5·0. $C_{29}H_{40}O_4N_2,2HCl,0{\cdot}5H_2O$ requires C, 61·9; H, 7·7; N, 5·0%). This isomer was identified as Ab_2 by its R_F value and mixed m. p. Concentration of the mother-liquor and addition of ether gave the dihydrochloride (0·84 g.), m. p. and mixed m. p. 247—257°, of base (XXII; Aa_1) (Found, in sample dried at 100°: C, 61·9; H, 7·65; N, 5·0%). Isomer (Aa_1) [(±)-emetine] was more difficult to free from traces of (Ab_2), as shown by paper chromatography, and three crystallisations were necessary to obtain a homogeneous sample, but the R_F of the final sample was the same as that of Aa_1 and emetine.

Paper Chromatography of Emetine Stereoisomers.—Ethyl methyl ketone (600 c.c.) was shaken with 2N-hydrochloric acid (200 c.c.). The ketone layer was used as the eluant in descending

chromatography. Emetine dihydrochloride was used as a marker spot and given R_F 1 (distance travelled = 31 cm.). The R_F values are given in Table 1; in addition to the isomers (Ab_2, Bc_1, and Bd_1) in Table 1 which could be separated from emetine it was possible to separate isomers (Bc_1) and (Bd_1). The spots were detected with a reagent described by Brossi, Hafliger, and Schnider.[30]

(±)-*Rubremetinium Bromide* (XXIV).—Tetradehydroemetinium iodide hydriodide (XXIII; A) (0·37 g.) was oxidised in dilute acetic acid containing potassium acetate and mercuric acetate according to the procedure of Battersby, Openshaw, and Wood.[4] The bromide crystallised from dilute hydrobromic acid as orange-red needles (0·16 g.). When dried at 50° *in vacuo* for 1·5 hr. the salt had m. p. 177—185° with the meniscus at 197—205°, behaviour similar to natural (+)-rubremetinium bromide (Pyman [29] records m. p. 160—180°, meniscus at 195—205°) (Found, in air-dried specimen: C, 58·3; H, 6·2; N, 4·7. Calc. for $C_{29}H_{33}O_4N_2Br,2{\cdot}5H_2O$: C, 58·2; H, 6·4; N, 4·7%. Found, in sample dried at 100°: C, 62·2; H, 5·9; Br, 14·9. Calc. for $C_{29}H_{33}O_4N_2Br$: C, 62·9; H, 6·0; Br, 14·4%). The (±)-salt had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·22, 4·22, 4·44). (+)-Rubremetinium bromide had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·20, 4·21, 4·40). The infrared spectra (hexachloroethane KBr, Nujol) and the R_F (butanol, acetic acid, and water) were the same.

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SYNTHESIS OF EMETINE AND STEREOISOMERS OF EMETINE

By M. Barash and J. M. Osbond

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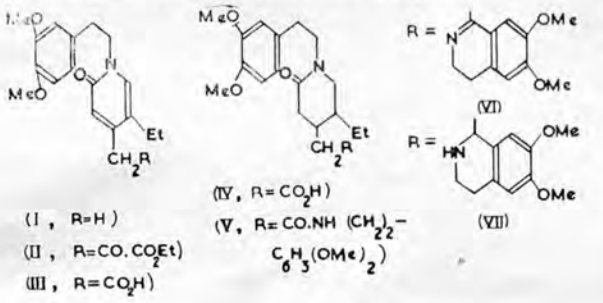
Emetine has structure[1] (X); a synthesis has been claimed by Evstigneeva *et al.*[2] A new total synthesis and resolution is now reported, together with the isolation of six other stereoisomers of emetine.

Hydrogenolysis (Pd/C) of the product obtained by condensing 2:6-dichloro-3-ethyl-4-methylpyridine[3] with sodium benzyloxide (1M), gave 3-ethyl-4-methyl- (m.p. 170–172·5°) and 5-ethyl-4-methyl-2-pyridone (m.p. 160–161·5°). The latter compound with β-(3:4-dimethoxyphenyl)ethyl iodide gave compound (I). Oxidation (H_2O_2) of the pyruvate ester (II;

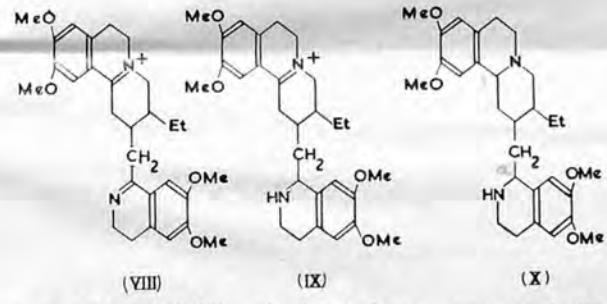


(I, R=H)
(II, R=CO.CO$_2$Et)
(III, R=CO$_2$H)

(IV, R=CO$_2$H)
(V, R=CO.NH(CH$_2$)$_2$C$_6$H$_3$(OMe)$_2$)

(VI)

(VII)



(VIII) (IX) (X)

m.p. 141·5–142·5°), obtained from compound (I) and ethyl oxalate, resulted in formation of compound (III) which on reduction (PtO_2/MeOH) afforded the two 2-piperidone-4-acetic acids (IV; *dl*-A, m.p. 154–156° and *dl*-B, m.p. 152–153°). The homoveratrylamide (V, *dl*-A) of (IV, *dl*-A) was cyclized ($POCl_3$) to a tetradehydroemetinium salt (VIII) (iodide hydroiodide, m.p. 172–176° (decomp.) which was dehydrogenated[4] to (±) rubremetinium bromide.

Compound (VI), *dl*-A (m.p. 122·5–124°) obtained from (V), *dl*-A by monocyclization[5] (P_2O_5/toluene), was reduced to a mixture of (VII) (*dl*-Aa hydriodide m.p. 214–216° and *dl*-Ab hydriodide m.p. 207–208·5°). Cyclization of (VII *dl*-Ab) afforded the dehydroemetinium salt (IX *dl*-Ab) (iodide hydriodide m.p. 195–196°), which on reduction (PtO_2 or $NaBH_4$) yielded two of the eight stereoisomeric racemates of emetine (X) (*dl*-Ab_1 and *dl*-Ab_2). *dl*-Ab_1 is considered to be *dl*-emetine on the evidence provided in the two tables. In addition, 5 other isomers have been obtained in a similar manner.

	dl-Ab_1	*Emetine*	*Infrared comparison*
Dihydrochloride	m.p. 249–56°	m.p. 235–55°	Similar but not identical
Dihydroiodide	m.p. 237–238°	m.p. 236–37°	Identical
Base	m.p. 70–73°	m.p. 74°	Identical
Bis(-)dibenzoyl tartrate	m.p. 180–182° (decomp.) $[\alpha]_D^{20}$–62·2 (*c.*, 0·744 in MeOH)	m.p. 180–181° (decomp.) $[\alpha]_D^{20}$–62 (*c.*, 1·0 in MeOH)	Identical

Stereoisomer of emetine	*Amoebicidal activity in vivo* CD50 mg./kg.	*in vitro* mcg./ml.	*Toxicity LD50* mg./kg.	R_F *methylethylketone/* 2N *HCl.*
Aa_1	>50	1000	35–40	1·00
Aa_2	—	—	—	0·60†
Ab_1	19·5	1000	25	1·00
Ab_2	64·6	10000	>200	0·62†
Bc_1	133	1000	>250	0·79†
Bd_1	200	1000	>500	0·67†
Bd_2	—	—	—	0·73†
Emetine	6·25–12·5	10–100	40	1·00

† Separation from emetine can be effected.

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