698. *Ipecacuanha Alkaloids. Part VI.* The Absolute Stereochemistry at Position 1 of Emetine by Chemical Correlation with the Natural Amino-acids.*

By A. R. Battersby, R. Binks, and T. P. Edwards.

N-Acetylemetine has been degraded by Hofmann's method and the final product has been oxidised to yield the *N*-acetyl acid (X). This acid has been synthesised and resolved; its absolute configuration has been determined by a chemical correlation with the alkaloid (+)-calycotomine (XIII) which has been correlated earlier with the natural amino-acids. This provides the last piece of information to allow the complete absolute stereochemistry of emetine to be written.

Some of the optically active 1-substituted tetrahydroisoquinolines prepared in this work have been used to study further the method of rotation shifts for determinations of absolute configuration.

Previous parts of this series [1] have described the elucidation of the illustrated relative and absolute stereochemistry of the benzoquinolizidine system of emetine (I; R = H). The present paper is concerned with the absolute configuration of the isolated asymmetric centre at position 1 of this alkaloid. In order to isolate a fragment containing this centre, it was decided that the other sites of asymmetry should be destroyed by a multiple Hofmann degradation carried out on *N*-acetylemetine (I; R = Ac). This type of degradation has been studied previously [2,3] but now the various steps have been more fully examined and the intermediates characterised.

N-Acetylemetine (I; R = Ac) with methyl iodide gave the crystalline [3] *N*(b)-methiodide in 75% yield together with the remaining material as an amorphous methiodide. We regard these as diastereoisomeric methiodides corresponding to the two possible configurations of the asymmetric quaternary *N*(b)-nitrogen atom; the forms (II) and (III) are analogous to the *trans*- and *cis*-forms of 9-methyldecalin and there can be little doubt that the main crystalline product is the *trans*-form (II). Evidence for this comes from the Hofmann degradation of both methiodides to give the same methine (IV). This methine was reduced catalytically to dihydro-*N*-acetylemetinemethine (V) which was characterised as its crystalline picrate. After this Hofmann step and after subsequent ones, the products were reacetylated to ensure that any material which had been deacetylated under the alkaline conditions was again fully protected.

Hofmann degradation of the dihydromethine (V) gave, smoothly, dihydro-*N*-acetylemetinebismethine (VI) as an amorphous base which showed the ultraviolet absorption expected of a 3,4-dimethoxystyrene derivative. This time the double bond was not reduced before the next Hofmann degradation, so that the final double bond introduced might move into conjugation as shown in structure (VII); the illustrated arrangement of the diene system is for convenience, not to imply knowledge of the stereochemistry in this region. That the desired conjugated diene was formed in the last Hofmann degradation was indicated by the ultraviolet absorption of the neutral product which corresponded to conjugation extended beyond a 3,4-dimethoxystyrene system; further evidence is adduced below.

The diene (VII) was readily oxidised by permanganate in aqueous pyridine to yield 6-ethylveratric acid (VIII) as the main crystalline acidic product. When the diene (VII)

* Part V, *J.*, 1960, 717.

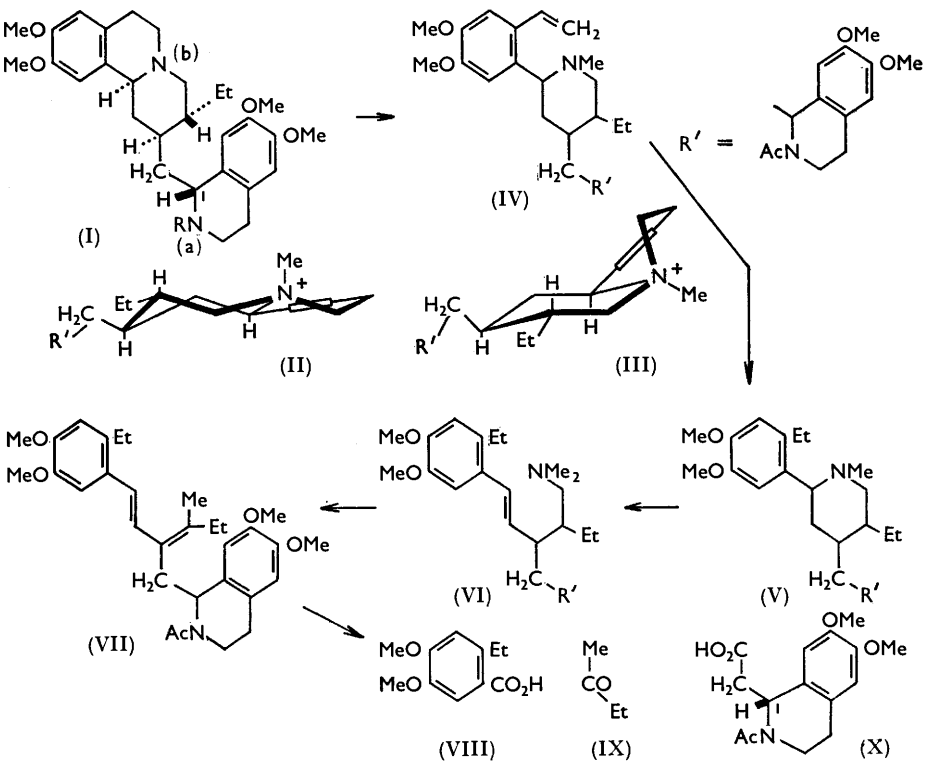
[1] Battersby, Binks, and Davidson, *J.*, 1959, 2704; Battersby and Garratt, *J.*, 1959, 3512; cf. Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *J.*, 1959, 3630; van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 6214; Ban, Terashima, and Yonemitsu, *Chem. and Ind.*, 1959, 568, 569.

[2] Pailer, *Monatsh.*, 1948, **79**, 127.

[3] Cf. Ahl and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 366.

was oxidised first with ozone and then with permanganate or peracetic acid, ethyl methyl ketone was isolated as its dinitrophenylhydrazone. The acidic products, after fractionation by countercurrent distribution, yielded a crystalline acid; this was the desired *N*-acetyl acid (X) as shown by its optical activity, $[\alpha]_D$ −144°, and its infrared spectrum [1628 cm.$^{-1}$ (>N·COMe); 1732, 2500—3500 cm.$^{-1}$ (CO_2H)] which was identical with that given by synthetic material below of unequivocal constitution (X). Experiments described later in this paper will establish the absolute configuration shown in formula (X).

The (±)-amino-ester corresponding to structure (XI) is readily available by synthesis [4] involving a Bischler–Napieralski ring-closure; by carrying out this cyclisation with phosphoric oxide spread on " Celite," [5] a useful increase in yield was obtained. Resolution of the (±)-ester was achieved slowly through the neutral (−)-*OO*-dibenzoyltartrate, and



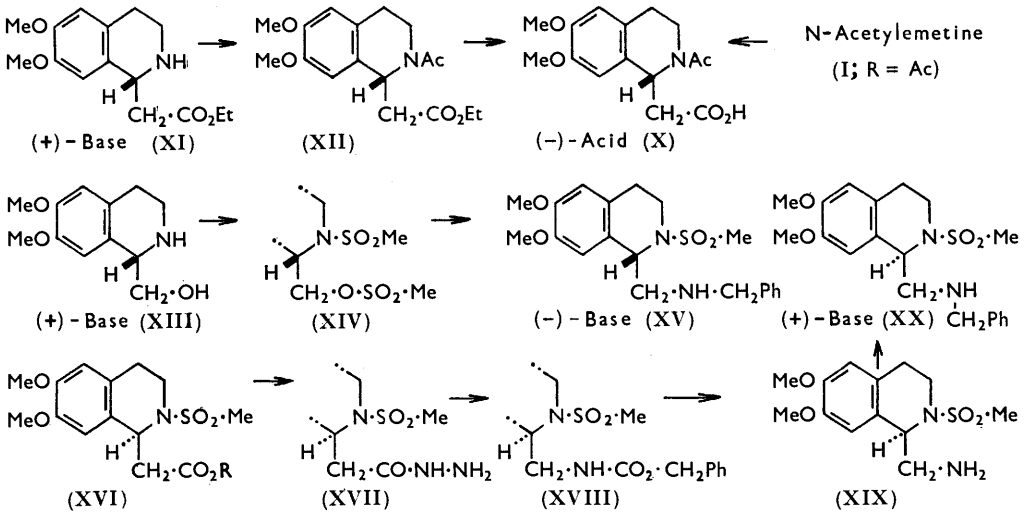
the (+)-base (XI), by acetylation and mild hydrolysis of the ester group, gave the same (−)-*N*-acetyl acid (X), $[\alpha]_D$ −141°, which had been obtained above from the degradation of emetine. The (+)-*N*-acetyl acid (enantiomer of X), $[\alpha]_D$ +145°, was prepared similarly from the (−)-amino-ester (enantiomer of XI). Some fractional crystallisation of both optically active synthetic acids (as X) was necessary to achieve the quoted rotations so that either the resolution of the amino-ester (as XI) is incomplete after twelve crystallisations of the dibenzoyltartrate or some racemisation occurs in the subsequent conversion of the bases (as XI) into the acids (as X).

Battersby and Edwards [6] have shown that (+)-calycotomine (XIII) has the illustrated absolute configuration by chemical correlation with the natural amino-acids. It thus remains to correlate the (+)-amino-ester (XI) with (+)-calycotomine in order to determine

[4] Battersby and Openshaw, *Experientia*, 1950, **6**, 387; Osbond, *J.*, 1951, 3464; Battersby, Openshaw, and Wood, *J.*, 1953, 2463.
[5] Nineham, *J.*, 1952, 635.
[6] Battersby and Edwards, *J.*, 1960, 1214.

the absolute configuration at position 1 of emetine (I; R = H). (+)-Calycotomine (XIII) was first converted by methanesulphonyl chloride in pyridine into the *NO*-dimethanesulphonyl derivative (XIV); the sulphonyloxy-group was then displaced by benzylamine, yielding the base (XV). This was carefully purified by countercurrent distribution and the final product showed a *negative* rotation.

Turning now to the emetine series, the (−)-amino-ester (enantiomer of XI) similarly gave the corresponding *N*-methanesulphonyl derivative (XVI) which could be satisfactorily converted into its hydrazide (XVII) only under anhydrous conditions. When this product was subjected to the Curtius rearrangement in the presence of benzyl alcohol, the benzylurethane (XVIII) was formed which was then cleaved at the benzyloxy-residue by catalytic hydrogenation to give the amine (XIX). The sequence was completed by condensing the amine (XIX) with benzaldehyde followed by hydrogenation of the resultant Schiff's base to yield the benzylamine derivative (XX); this product had a *positive* rotation and it was shown by this and by its infrared spectrum to be the enantiomer of the benzylamine derivative (XV) prepared above from (+)-calycotomine (XIII). The enantiomeric relationship of the two bases (XV) and (XX) was confirmed by mixing equivalent amounts

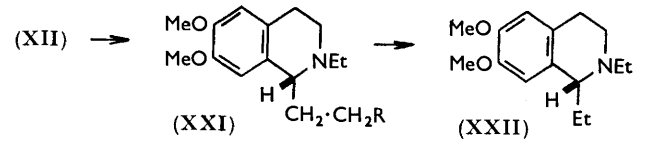


to yield the racemic benzylamine derivative (as XV) which had been obtained earlier in trial experiments. Thus the absolute configuration of the (−)-amino-ester (enantiomer of XI) is opposite to that established [6] for (+)-calycotomine (XIII), and it follows that the (+)-amino-ester (XI) has the *same* absolute configuration as (+)-calycotomine. Since the correlations described above established that the configuration at position 1 of emetine is the same as that of the (+)-amino-ester (XI), the illustrated arrangement at this position in structure (I; R = H) is proved; structure (I; R = H) now shows the complete absolute stereochemistry of emetine.

Several of the reaction sequences used in this work were studied first with racemic materials and these are described in the Experimental section.

Because of our interest [6] in the rotation-shifts method for determining absolute configurations of optically active amines, the rotation of the amino-ester (XI) was determined in a variety of solvents. In addition, the series of configurationally related bases was extended by reducing the acetamido-ester (XII) with lithium aluminium hydride to the alcohol (XXI; R = OH) which was isolated as its *O*-acetyl derivative (XXI; R = OAc). Treatment of the recovered alcohol (XXI; R = OH) with phosphorus pentachloride in chloroform yielded a mixture from which the chloride (XXI; R = Cl) was isolated by

countercurrent distribution; aluminium in moist ether then reduced the halide to yield the 1,2-diethyltetrahydroisoquinoline (XXII). This product and the other tertiary base (XXI; R = OAc) were included in the study of rotation shifts and the results are collected in the Table; the values are given as specific rotations because it was necessary, in order to conserve material, to use a sample of the amino-ester (XI) which had not been completely



resolved. The three bases studied are of the type [6] which should give satisfactory results by the method of rotation shifts. It is therefore satisfying to find that all show a clear negative shift of rotation as the polarity of the solvent is increased. This is the expected direction of shift [6,7] for 1-substituted tetrahydroisoquinoline bases having the absolute configuration established by the foregoing chemical work.

Rotations of tetrahydroisoquinolines in different solvents.

Base	C_6H_6	$CHCl_3$	EtOH	N-HCl
Amino-ester (XI)	+21·3°	+18·3°	+15·2°	*ca.* +15° [a]
N-Ethyl ester (XXI; R = OAc)	−5·8°	−9·7°	−10·7°	−20·6°
N-Ethyl 1-ethyl base (XXII)	+2·6°	−3·1°	−4·3°	−9·5°

[a] The solution in this solvent darkened considerably and the rotation was difficult to read.

Experimental

For general directions, see Battersby, Davidson, and Harper.[8]

N-Acetylemetine Methiodides (II) *and* (III).—*N*-Acetylemetine [3] was prepared by heating emetine (33 g.) with acetic anhydride (50 ml.) for 4 hr. at 90° and working up as usual for basic material. Part of this product (33 g.) in methanol (50 ml.) was heated under reflux for 12 hr. with methyl iodide (25 ml.). The solvents were then evaporated and the residue was crystallised from ethanol, to yield *N*-acetylemetine methiodide (34·8 g.), m. p. 208—210° (decomp.) [lit.,[2,3] m. p. 213—216° (corr.)]; concentration of the ethanolic mother-liquor gave only a gum. The total material in the mother-liquor was dissolved in aqueous ethanol, and this solution was extracted thoroughly with ether which removed a trace of basic material. Evaporation of the aqueous ethanol left the quaternary material as a gum (7·2 g.).

N-Acetyldihydroemetinemethine (V).—A solution of the foregoing crystalline methiodide (34·6 g.) in ethanol (240 ml.) and water (114 ml.) was shaken for 1 hr. at 55° with moist silver oxide (from 19 g. of silver nitrate). The silver salts were collected ("Filtercel") and the filtrate and washings, now free from iodide ion, were evaporated to *ca.* 20 ml., treated with potassium hydroxide (20 g.), and then evaporated to dryness. After the residue had been heated at 125° (bath)/1 mm. for 2 hr., it was partitioned between water (50 ml.) and ether (4 × 100 ml.), and a solution of ether-soluble material (25·5 g.) in ethanol (200 ml.) was shaken at room temperature and pressure with hydrogen and platinum oxide (0·5 g.). Uptake (1·0 mol.) was complete in 4 hr.; the catalyst was removed and the filtrate was evaporated to leave a gum, which was heated with acetic anhydride (50 ml.) at 90° for 4 hr. The gum remaining after evaporation of the anhydride was dissolved in N-hydrochloric acid (100 ml.), and the solution was extracted with ether (3 × 100 ml.) to remove the neutral products (0·91 g.). The basic material (25 g.) was recovered from the aqueous acid solution by basification and ether-extraction and was converted into the picrate by treatment with picric acid (12 g.) in ethanol (500 ml.). *N-Acetyldihydroemetinemethine picrate* separated as plates (31·55 g.), m. p. 132—133° unchanged by recrystallisation; on occasions the picrate crystallised as short prisms, m. p. 142—144° (Found: C, 59·1; H, 6·3; N, 9·0. $C_{38}H_{49}O_{12}N_5$ requires C, 59·4; H, 6·4; N, 9·1%).

[7] Leithe, *Ber.*, 1934, **67**, 1261 and earlier papers; Corrodi and Hardeger, *Helv. Chim. Acta*, 1956, **39**, 889.

[8] Battersby, Davidson, and Harper, *J.*, 1959, 1744.

The amorphous *N*-acetylemetine methiodide (7·2 g.) was degraded as above to yield the same dihydromethine picrate (V) (7·4 g.), m. p. and mixed m. p. 132—133°.

N-*Acetyldihydroemetinemethine Methiodide.*—A suspension of the foregoing picrate (38·9 g.) in ether (1 l.) was shaken with 50% aqueous ethanolamine (0·5 l.), and the aqueous layer was further extracted with ether (1 × 1 l.; 2 × 0·5 l.). The combined ethereal solutions were colourless after they had been shaken with 50% aqueous ethanolamine (6 × 80 ml.) and they were then washed with water (5 × 60 ml.), the final aqueous washing being neutral. Evaporation of the dried ethereal solution left a glass (26·64 g., 98%).

A solution of this base (1·83 g.) in methanol (10 ml.) was heated under reflux for 6 hr. with methyl iodide (4 ml.) and then evaporated to dryness. The residue crystallised from ethanol, to give the methiodide as pale yellow plates (1·62 g., 72%), m. p. 241—244° (decomp.), unchanged by recrystallisation [lit.,[2] m. p. 252—254° (corr.)] (Found: C, 57·9; H, 7·5; N, 4·1. Calc. for $C_{33}H_{49}O_5N_2I$: C, 58·2; H, 7·3; N, 4·1%).

N-*Acetyldihydroemetinebismethine* (VI) *and its Methiodide.*—Iodide ions were removed as above from a solution of the foregoing methiodide (1 g.) in ethanol (20 ml.) and water (10 ml.), and the residue left by evaporation of the solution was heated at 100°/15 mm. for 2 hr. The products were partitioned between ether (20 ml.) and water (10 ml.), and the aqueous layer was extracted again with ether (3 × 30 ml.) and then evaporated to dryness. After the residue had been heated at 110°/2 mm. for 2 hr., the ether-soluble products were extracted as before and combined with the ether solution from the first treatment, and the ether was evaporated to leave a resin (0·726 g.). This was heated at 70° for 1 hr. with acetic anhydride (6 ml.), the excess of anhydride was evaporated, and the residue was partitioned between ether and dilute hydrochloric acid. When the aqueous acidic solution was worked up for bases as above, a resin (0·673 g.) was obtained which did not crystallise and no crystalline salt was obtained.

A solution of this base (0·65 g.) in ether (15 ml.) was kept at room temperature in the dark with methyl iodide (2 ml.) for 50 hr.; the *methiodide* separated as an amorphous powder (0·79 g.) which was collected and washed thoroughly with ether (Found: C, 58·4; H, 7·5. $C_{34}H_{51}O_5N_2I$ requires C, 58·8; H, 7·4%). It had $\lambda_{min.}$ 248, 300, $\lambda_{max.}$ 267, 304—305 mμ (log ε 3·95, 3·82, 4·22, 3·83 respectively, in EtOH).

Hofmann Degradation of N-*Acetyldihydroemetinebismethine Methiodide.*—The foregoing methiodide (9·6 g.) in 50% aqueous ethanol (300 ml.) was converted into the corresponding methohydroxide as usual with moist silver oxide (from 5 g. of silver nitrate). The solution was evaporated to *ca.* 20 ml., potassium hydroxide (2·5 g.) was added and, after the solution had been evaporated to dryness, the residue was heated at 100°/15 mm. for 5 hr. After separation of the ether-soluble products as above, they were kept at room temperature with acetic anhydride (75 ml.) for 16 hr. and the anhydride was then evaporated. The neutral material (6·06 g., 87%) was isolated by partition of the products between dilute hydrochloric acid and ether; this final product was a resin, $[\alpha]_D^{16}$ −102° (*c*, 8·4 in EtOH), $\lambda_{min.}$ 251·5, $\lambda_{max.}$ 281·5 mμ (log ε 3·94, 4·24 respectively, in EtOH).

Oxidation of the Diene (VII).—(a) *With permanganate.* A solution of potassium permanganate (3·34 g.) in 50% aqueous pyridine (170 ml.) was added dropwise at room temperature to a stirred solution of the foregoing diene (2·01 g.) in 50% aqueous pyridine (150 ml.) containing 2N-sulphuric acid (9·25 ml.). After 40 min., 90 ml. of the oxidising solution had been added and there was a sharp break in the rate of oxidation. The oxidation was therefore continued at 40—45° and the rest of the permanganate was added during 1 hr. Filtration removed the manganese dioxide which was washed with 50% aqueous pyridine and ethanol; the filtrate was evaporated to low volume, adjusted to pH 7·5 with potassium carbonate, and extracted thrice with ethyl acetate, the organic extracts being back-extracted with aqueous sodium hydrogen carbonate. The total aqueous solution was acidified to pH 3 and shaken thrice with ethyl acetate which extracted the acidic fraction (0·99 g.). A solution of this fraction in hot ethyl acetate (3 ml.) was diluted with boiling light petroleum (b. p. 60—80°), and the clear supernatant liquor was decanted off from the solid residue. The latter was powdered and extracted twice with boiling light petroleum, and the combined petrol solutions were evaporated to dryness. The residue crystallised from water to give 6-ethylveratric (2-ethyl-4,5-dimethoxybenzoic) acid (VIII) (221 mg.), m. p. and mixed m. p. with a synthetic sample,[9] 142—143°.

[9] Battersby and Openshaw, *J.*, 1949, S 59.

The material insoluble in light petroleum was examined by counter-current distribution as under (b), but the yield of other crystalline acids was very low.

(b) *With ozone.* Ozonised oxygen was passed through a solution of the diene (VII) (0·507 g.) in ethyl chloride (15 ml.) at −70°; two mols. of ozone were rapidly absorbed and the uptake then became slow. Passage of gas was stopped at this stage and the ethyl chloride was evaporated at low temperature to leave the crude ozonide which was heated under reflux for 30 min. with water (25 ml.). The solution was then evaporated to dryness, the distillate (*A*) was reserved, and the residue was dissolved in 50% aqueous pyridine (50 ml.). To this was added, dropwise at room temperature, a solution of potassium permanganate (0·34 g.) in 50% aqueous pyridine (17 ml.); the permanganate was rapidly consumed but the last few drops remained unused. After the solution had been warmed to coagulate the manganese dioxide, it was filtered and the pad was washed with aqueous pyridine and hot ethanol. The filtrate was evaporated until free from organic solvents, then adjusted to pH 8 with potassium carbonate and extracted thrice with ethyl acetate. Acidification of the aqueous layer released the acid products which were extracted into ethyl acetate (4 × 50 ml.) and recovered as a gum (0·32 g.) (*B*) by evaporation of the dried solution.

The distillate *A* above was treated with 2,4-dinitrophenylhydrazine sulphate, and the precipitated dinitrophenylhydrazones were collected, dried, and, as a solution in chloroform, run on a column made of well-mixed bentonite (3 g.) and kieselguhr [10] (12 g.). Elution was continued with chloroform to give a main band which crystallised from ethanol. This product was ethyl methyl ketone 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 113—114·5°.

A further portion (0·49 g.) of the diene (VII) was treated with ozone as above and the crude ozonide, in acetic acid (5·5 ml.), was treated with 30% hydrogen peroxide (3 ml.). After being kept at room temperature for 7 hr., the solution was warmed at 55° for 12 hr. Water (5·5 ml.) was then added to the cooled solution followed by platinum black (65 mg.) in small portions. When the decomposition of the per-acids was complete, the catalyst was removed, the filtrate was evaporated to dryness, and the residue was worked up for acidic material as in (a) above, to give a gum (0·29 g.). This fraction was combined with the gum *B* above and fractionated by countercurrent distribution (scattered in first three tubes) between ethyl acetate and an aqueous buffer made from 0·5M-KH_2PO_4 (100 vol.) and 0·5M-K_2HPO_4 (6·3 vol.). After 48 transfers, the material was recovered from the contents of tubes 0—38 of the machine by acidification and extraction with ethyl acetate. In this way a gum (193 mg.) was obtained which was crystallised from water (charcoal), ethyl acetate, and finally water to give the *N*-acetyl acid (X) as needles, m. p. and mixed m. p. with the synthetic acid below, 99—102° after slight sintering at 96°. The infrared spectra of the samples obtained by degradation and by synthesis were identical. The partition ratio, *K*, of the degradation acid in the above ethyl acetate–phosphate buffer system was determined as 0·226 by measurement of ultraviolet absorption at 282 mμ of the upper and the lower layer after the acid had been distributed between them (cf. *K* for synthetic acid below). The product had $[\alpha]_D^{19}$ −144° (*c* of anhydrous material, 2·4 in EtOH).

Preparation and Resolution of Ethyl 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylacetate* (as XI).—The (±)-ester was prepared by the published method [4] save that the cyclisation of *N*-cyanoacetyl-3,4-dimethoxyphenethylamide was improved. A solution of this amide (25 g.) in anhydrous toluene (300 ml.) was mixed with "Celite" (50 g.) which had been previously dried at 100°. Phosphoric oxide (42 g.) was added to the boiling solution and after the mixture had been heated under reflux for 30 min., a second portion (42 g.) of phosphoric oxide was added. The heating under reflux was continued for 2·5 hr. in all and during this period the mixture was occasionally agitated with a glass rod. The products were isolated as previously [4] and crystallised from ethanol to give 1-cyanomethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (15·8 g., 65%).

For resolution, the (±)-ester (as XI) (89 g.) was treated in ethanol (820 ml.) with (−)-*OO*-dibenzoyltartaric acid (58 g.) and after 3 days at room temperature the precipitated crystals were collected. These were recrystallised eleven times from ethanol to yield 17 g. of the tartrate. The bases were recovered from the crystalline salt after 6, 9, and 12 crystallisations and distilled at 160° (bath)/0·01 mm. for determination of rotation; the samples showed $[\alpha]_D$ in ethanol −21·8°, −24·8°, −26·9° respectively; samples of base were similarly recovered from the 1st,

[10] Linstead, Elvidge, and Whalley, "Modern Techniques of Organic Chemistry," Butterworths, London, 1955, p. 5.

6th, 9th, and 12th mother-liquors and showed $[\alpha]_D$ in ethanol +23·8°, −7·3°, −16·8°, −25·4° respectively.

(±)-*Ethyl* N-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylacetate and the* (+)-*Enantiomer* (as XII).—A solution of the (±)-amino-ester (as XI) (0·5 g.) in acetic anhydride (15 ml.) was heated at 100° for 1·5 hr., then evaporated to dryness and the residue was crystallised from water. The (±)-N-*acetyl ester* (as XII) separated as clumps of needles (445 mg.), m. p. 94—95° (Found, in material dried at 78°: C, 63·6; H, 7·3; N, 4·1. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·1; N, 4·4%).

The (−)-amino-ester (enantiomer of XI) having $[\alpha]_D$ −26·9° was acetylated in the same way, to give after crystallisation from water the (+)-N-*acetyl ester* (enantiomer of XII), m. p. 113—114°, $[\alpha]_D^{20}$ +124° (*c*, 1·16 in EtOH) (Found: C, 63·7; H, 7·4; N, 4·4%).

(±)-N-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylacetic Acid and the* (−)- *and* (+)-*Enantiomers* (as X).—The above (±)-*N*-acetyl ester (as XII) (445 mg.) in ethanol (15 ml.) was treated with N-sodium hydroxide (1·5 ml.; 1·1 equiv.), and the solution was kept at room temperature overnight. After removal of the ethanol, the solution was made strongly alkaline with potassium carbonate, extracted thrice with ether, acidified, and extracted thrice with ethyl acetate. The solid obtained by evaporation of the latter solvent crystallised from water to give the (±)-N-*acetyl acid* (as X) (353 mg.), m. p. 154—155° (Found: C, 61·7; H, 6·6; N, 5·0. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·7%). The partition ratio, *K*, was determined as 0·227 in the same solvent system and by the same method as were used for the degradation acid (X) above.

The crude (−)-*N*-acetyl ester (XII) (2·3 g.), prepared as above from the (+)-amino-ester (XI), $[\alpha]_D$ +23·8°, was hydrolysed as for the (±)-ester, and the acidic products were crystallised from ethyl acetate. The first crop (781 mg.) had $[\alpha]_D$ −25° (in EtOH) and the second crop (854 mg.) had $[\alpha]_D$ −110° (in EtOH). Crystallisation of the latter from ethyl acetate gave, by seeding with the (±)-acid (as X), a small crop of optically inactive material; after repetition of this operation on the material held in the mother-liquor, the (−)-acid was crystallised twice from water to give the optically pure (−)-N-*acetyl acid* (X), m. p. 99—102° after slight sintering at 95° (Found, in material dried first at 78° and then at 100°: Loss, 5·6; C, 61·7; H, 6·2; N, 4·7%), $[\alpha]_D^{20}$ −141° (*c* 1·23 in EtOH).

Although the starting material was from the twelfth crop of crystals in the above resolution, it was also necessary to carry out fractional crystallisation of the (+)-N-*acetyl acid* (enantiomer of X) in order to obtain optically pure material, $[\alpha]_D^{20}$ +145° (*c* 1·14 in EtOH) (Found, in material dried first at 78° and then at 100°: C, 61·6; H, 6·7; N, 4·9%).

NO-*Dimethanesulphonylcalycotomine* (XIV).—Methanesulphonyl chloride (2·5 g.) was added dropwise at 0° to a stirred solution of (+)-calycotomine [6] (XIII) (557 mg.), having $[\alpha]_D$ +16° (in H_2O), in dry pyridine (15 ml.). After the solution had been stirred for 2 hr., it was kept at 5° for 3 days, then poured on an excess of ice and extracted thrice with chloroform. The combined extracts were washed with 5N-hydrochloric acid and water, dried, and evaporated. Crystallisation of the residue from ethanol gave NO-*dimethanesulphonylcalycotomine* (704 mg.), m. p. 127—128° (Found: C, 44·3; H, 5·8. $C_{14}H_{21}O_7NS_2$ requires C, 44·3; H, 5·8%).

(+)-*Ethyl* 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-2-*methanesulphonyl*-1-*isoquinolylacetate* (XVI; R = Et).—The (−)-amino-ester (enantiomer of XI) (973 mg.), $[\alpha]_D$ −26·9° (in EtOH), was treated with methanesulphonyl chloride (0·9 g.) in dry pyridine (15 ml.) as in the preceding experiment, to give the *ester* (XVI; R = Et) (954 mg.). After crystallisation from ethanol, it had m. p. 114—115° and $[\alpha]_D$ +30° (*c* 1·9 in $CHCl_3$) (Found: C, 54·0; H, 6·7; N, 3·9. $C_{16}H_{23}O_6NS$ requires C, 53·8; H, 6·4; N, 3·9%).

(±)-1,2,3,4-*Tetrahydro*-2-*methanesulphonyl*-6,7-*dimethoxy*-1-*isoquinolylacetic Acid* (XVI; R = H).—A solution of the foregoing ester (512 mg.) in dioxan (5 ml.) and N-sodium hydroxide (1·6 ml.) was kept at room temperature overnight, then evaporated to dryness and the residue was partitioned between dilute sodium hydroxide and chloroform. After the aqueous layer had been extracted twice more with chloroform, it was acidified and extracted with chloroform to give a gum (441 mg.). This crystallised from ethanol to give the (±)-*acid* (XVI; R = H) (0·2 g.), m. p. 120° (decomp.) after previous sintering, $[\alpha]_D$ 0° (Found: C, 51·3; H, 5·5; N, 4·3. $C_{14}H_{19}O_6NS$ requires C, 51·1; H, 5·8; N, 4·2%).

The mother-liquors contained the optically active acid (XVI; R = H); they were not fully examined.

Curtius Degradation of the N-*Methanesulphonyl Ester* (XVI; R = Et).—The (+)-ester (XVI;

R = Et) (1 g.) was heated under reflux for 23 hr. with anhydrous hydrazine (2·5 ml.) and anhydrous methanol (2·0 ml.). Water (17 ml.) was added to the cooled solution to precipitate (±)-1,2,3,4-*tetrahydro*-2-*methanesulphonyl*-6,7-*dimethoxy*-1-*isoquinolylacethydrazide* (as XVII) which recrystallised from ethanol as needles (0·28 g.), m. p. 71—72°, $[\alpha]_D$ 0° (*c* 1·57 in $CHCl_3$) (Found, in material dried first at 65° then at 78°: C, 49·3; H, 6·0; N, 12·7. $C_{14}H_{21}O_5N_3S$ requires C, 48·9; H, 6·1; N, 12·2%).

The mother-liquor from the racemic hydrazide was acidified, extracted thrice with chloroform, then basified with potassium carbonate and re-extracted with chloroform to yield the crude optically active hydrazide (XVII) as a gum (0·5 g.), $[\alpha]_D^{20}$ +21·5° (*c* 2·24 in EtOH).

A solution of dry hydrogen chloride (55·3 mg.) in anhydrous ethanol (0·8 ml.) was added to a solution of the above optically active hydrazide (517 mg.) in anhydrous ethanol (2 ml.). After the ethanol had been evaporated, the residue was dissolved in dry benzyl alcohol (5 ml.), and a solution of pentyl nitrite (0·2 g., 1·1 equiv.) in dry benzyl alcohol (0·9 ml.) was added. The solution was heated under reflux at 60° for 10 min., then at 103° for 14 hr., and finally the solvents were evaporated at 100°/0·1 mm. The residue in chloroform (150 ml.) was washed with dilute sulphuric acid, aqueous potassium carbonate, and water; evaporation of the chloroform left the crude urethane (XVIII) as a gum (575 mg.). A solution of this gum in methanol (15 ml.) and acetic acid (0·5 ml.) was shaken with palladium black (0·1 g.) while a stream of hydrogen was bubbled through. After 2½ hr., the evolution of carbon dioxide ceased; the catalyst was removed, the solvents were evaporated, and the residue was distributed between dilute sulphuric acid and chloroform. The acidic layer was extracted twice with chloroform, then basified and extracted again thrice with chloroform. Evaporation of the second set of chloroform extracts gave 1-*aminomethyl*-1,2,3,4-*tetrahydro*-2-*methanesulphonyl*-6,7-*dimethoxyisoquinoline* (XIX) as a gum (0·11 g.), $[\alpha]_D^{20}$ +21° (*c* 2·1 in EtOH). A portion was converted into the *picrate* in ethanol, and the salt was recrystallised from the same solvent, m. p. 218—219° (decomp.) (Found: C, 42·9; H, 4·3; N, 12·9. $C_{19}H_{29}O_{11}N_5S$ requires C, 43·1; H, 4·3; N, 13·2%).

1-*Benzylaminomethyl*-1,2,3,4-*tetrahydro*-2-*methanesulphonyl*-6,7-*dimethoxyisoquinoline* (XV) *and* (XX).—(a) *Emetine series.* A solution of the foregoing amine (XIX) (312 mg.) and benzaldehyde (150 mg.) in anhydrous ethanol (10 ml.) was evaporated to dryness at 40°. The residue was dissolved in anhydrous ethanol (10 ml.), the ethanol was evaporated as before, and this process was repeated twice more. Platinic oxide (0·1 g.) was added to a solution of the final residue in ethanol (70 ml.) and water (3 ml.), and the mixture was shaken with hydrogen at room temperature and pressure; uptake was 1·15 mol. After the catalyst and solvents had been removed, the products were dissolved in an excess of dilute sulphuric acid, this solution was extracted thrice with 4 : 1 ether–chloroform, then basified with potassium carbonate and extracted again with 4 : 1 ether–chloroform to yield a gum (280 mg.). Purification was achieved by countercurrent distribution of this gum (scattered in first 3 tubes) between ethyl acetate and aqueous buffer made from 0·5M-KH_2PO_4 (150 vol.) and 0·5M-K_2HPO_4 (2·4 vol.); after 96 transfers, one main peak (*K*, 0·75) was detected. The base was recovered from the contents of tubes 27—51 thus: the ethyl acetate layer was shaken with an excess of 2N-hydrochloric acid, and the aqueous extracts were combined with the original aqueous buffer solution, which was then basified and extracted thrice with 4 : 1 ether–chloroform. Evaporation of the dried extracts left the benzylamine (XX) as a gum, $[\alpha]_D^{20}$ +18·1° (*c* 1·38 in $CHCl_3$), infrared spectrum ($CHCl_3$) identical with those of the (±)- and (−)-isomers below.

(b) *Calycotomine series.* *NO*-Dimethanesulphonylcalycotomine (XIV) (0·2 g.) was dried at 65° for 1 hr. and then heated under reflux with freshly distilled benzylamine (5 ml.) for 2 hr. The excess of benzylamine was distilled off at 100°/0·1 mm. and the residue was worked up for bases as for the hydrogenation product under (a) above. A gum (175 mg.) was obtained which crystallised from ethanol to give (±)-1-*benzylaminomethyl*-1,2,3,4-*tetrahydro*-2-*methanesulphonyl*-6,7-*dimethoxyisoquinoline* (as XV) (44 mg.), m. p. 176—177°, $[\alpha]_D$ 0° (Found: C, 61·8; H, 6·7; N, 7·2. $C_{20}H_{26}O_4N_2S$ requires C, 61·5; H, 6·7; N, 7·3%).

This preparation was repeated on a larger scale and the crude basic fraction without crystallisation was purified by countercurrent distribution for 97 transfers in the solvent system named in (a) above. A well-separated peak (*K*, 0·86) was detected by analysis and the contents of tubes 30—56 were worked up as before, to give the benzylamine (XV) as a gum, $[\alpha]_D^{20}$ −16·5° (*c* 1·72 in $CHCl_3$), infrared spectrum (in $CHCl_3$) identical with those of the (±)- and (+)-isomers above.

The (+)-benzylamine from (a) above (73·2 mg.) and the (−)-isomer from (b) above (81·5 mg.) were dissolved together in hot ethanol (3 ml.). On cooling, the (±)-benzylamine (as XV) separated (128 mg.; 83%), m. p. and mixed m. p. 177—177·5°, infrared spectrum (in $CHCl_3$) identical with that of the (±)-sample obtained earlier, $[\alpha]_D$ 0° (*c*, 1·77 in $CHCl_3$).

(−)-1-2′-*Acetoxyethyl*-2-*ethyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (XXI; R = OAc).—The amino-ester (XII), $[\alpha]_D$ +15·2° (in EtOH), was dried at 65° for 4 hr. and it (4·4 g.) was then extracted from a Soxhlet thimble into a stirred suspension of lithium aluminium hydride (1·6 g.) in boiling anhydrous ether (250 ml.). After the mixture had been heated under reflux for 6·5 hr., the excess of hydride was decomposed with water (10 ml.) and 15% potassium carbonate solution (5 ml.), and the solids were filtered off and washed with ether. The filtrate was worked up as usual to give a neutral and a basic fraction (3·25 g.), and the latter was heated at 100° with acetic anhydride (75 ml.) for 1·5 hr. Evaporation of the anhydride left a gum which was separated as before into a neutral and a basic fraction (1·86 g.); distillation of the latter in a short-path still at 165° (bath)/0·01 mm. gave the N-*ethyl ester* (XXI; R = OAc) (Found, in freshly distilled material: C, 65·8; H, 8·3; N, 4·7%; equiv., 298. $C_{17}H_{25}O_4N$ requires C, 66·4; H, 8·1; N, 4·6%; equiv., 307).

(−)-1,2-*Diethyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (XXII).—A solution of the foregoing ester (XXI; R = OAc) (0·84 g.) in 2N-hydrochloric acid (75 ml.) was heated under reflux for 15 hr., then evaporated to 20 ml., basified with potassium carbonate, and extracted thrice with ether to give the crude alcohol (XXI; R = OH) as a gum (0·71 g.). This was distilled at 150° (bath)/0·01 mm. and the distillate in dry chloroform (35 ml.) was stirred at 0° with calcium carbonate (1·3 g.) while phosphorus pentachloride (2·1 g.) was added during 45 min. After the mixture had been stirred at room temperature overnight, it was filtered, the pad was washed with chloroform, and the filtrate was evaporated to dryness. The residue was fractionated without delay by countercurrent distribution between ethyl acetate and 0·5M-phosphate buffer (pH 7·6). Five transfers of the *lower* layer were carried out and the upper layers from tubes 0 and 1 were then shaken with an excess of dilute hydrochloric acid; basification of the acidic solution and extraction with ether (600 ml.) gave a solution of the crude chloride (XXI; R = Cl). Meanwhile, the reducing agent had been prepared as follows. Small pieces of aluminium foil (20 g.) were covered with 2N-sodium hydroxide and, when the reaction was brisk, the alkali was decanted and the metal was washed thoroughly with water, ethanol, and ether. The ethereal solution of the chloride (XXI; R = Cl) was quickly added together with mercuric chloride (6 g.), and the mixture was shaken until amalgamation was complete; water (70 ml.) was then added and the mixture was kept at room temperature for 15 hr. with occasional shaking. After the ethereal solution had been decanted, the solids were washed with ether, and the combined ethereal solution and mercuric chloride (2·5 g.) were added to fresh aluminium foil (16 g.) prepared as above; water (50 ml.) was added and, after 15 hr., the treatment with fresh aluminium (16 g.), mercuric chloride (2·5 g.), and water (50 ml.) was repeated. Evaporation of the final ether solution gave the 1-*ethylisoquinoline* (XXII) as a gum (316 mg.), purified by distillation at 130° (bath)/0·01 mm. (Found, in freshly distilled material: C, 69·5; H, 9·0; N, 5·2. $C_{15}H_{23}O_2N$ requires C, 69·5; H, 8·9; N, 5·4%).

The alumina residues from the above reductions were extracted with ether in a Soxhlet apparatus to give more (56 mg.) of the same base which was converted in ethanol into the *picrate*, m. p. 137—138° (Found: C, 52·3; H, 5·7. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·4%).

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