246. *Chemical Correlation of the Absolute Configurations of Salsolidine, Salsoline, and Calycotomine with the Amino-acids.*

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

The absolute configurations of (−)-salsolidine and (+)-salsoline have been elucidated by degrading the former base to *N*-2-carboxyethyl-L-alanine which has been synthesised from L-alanine for comparison. The stereochemistry of (+)-calycotomine has been correlated with that of (−)-salsolidine by chemical methods.

Support is given to the view that the method of rotation shifts is useful for the determination of absolute configurations provided that certain limitations are borne in mind. By this method, absolute configurations are assigned to the alkaloids anhalonine and lophophorine.

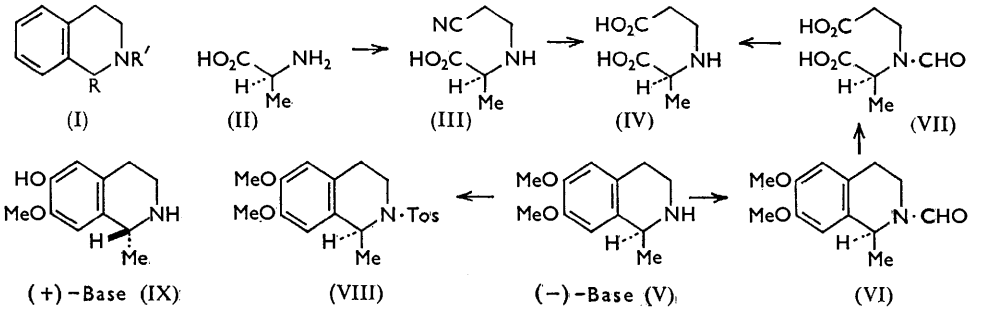
More than a dozen 1,2,3,4-tetrahydroisoquinoline alkaloids have been isolated, mainly from the Cactaceæ,[1] based upon the skeleton (I; R′ = H or Me) where R is an alkyl group or some simple derivative, for example, $-CH_2\cdot OH$. Of these bases, about half are optically active, but in no case has the absolute configuration been established. The biochemical interest of the absolute stereochemistry of natural products prompted a study of several isoquinoline alkaloids [2] and the present paper reports the elucidation of the absolute configurations of salsolidine (V), salsoline (IX) and calycotomine (X).

(−)-Salsolidine (V) occurs in *Salsola arbuscula* [3] together with partially racemic (+)-salsoline (IX). The former had been synthesised by the standard Bischler–Napieralski method followed by resolution,[4] but for our studies we found that (±)-salsolidine is more readily available by Pictet–Spengler condensation of acetaldehyde with 3,4-dimethoxyphenethylamine; resolution of the product was carried out by the recorded method.[4] It was planned to degrade (−)-salsolidine by vigorous ozonolysis,[5,6] the expected product

[1] Reti, "The Alkaloids," Ed. Manske and Holmes, Academic Press, New York, 1954, Vol. IV, p. 7; Djerassi, Nakano, and Bobbitt, *Tetrahedron*, 1958, **2**, 58 and refs. therein.
[2] Cf. Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86; *J.*, 1959, 3512.
[3] Orekhov and Proskurnina, *Bull. Soc. chim. France*, 1939, 144 and refs. therein.
[4] Späth and Dengel, *Ber.*, 1938, **71**, 113.
[5] Cf., *inter al.*, Schmid and Ebnother, *Helv. Chim. Acta*, 1951, **34**, 1041; Corrodi and Hardegger, *ibid.*, 1955, **38**, 2031, 2038; Barton and Miller, *J.*, 1955, 1028.
[6] Corrodi and Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889.

being *N*-2-carboxyethylalanine (IV or mirror image). This could then be correlated with L-alanine [7] (II).

To provide a reference sample of the previously unknown *N*-2-carboxyethyl-L-alanine (IV), L-alanine was cyanoethylated by the method of McKinney, Setzkorn, and Uhing [8] and the product (III) was hydrolysed with acid to the dicarboxylic acid (IV). This was conveniently separated from the alanine which was also produced in the hydrolysis by holding the dicarboxylic acid (IV) on a weak anion-exchange resin; it was then readily eluted with acetic acid.



Direct ozonolysis of (−)-salsolidine (V) under many widely differing conditions gave none or only traces of the amino-acid (IV) detected chromatographically; this is in contrast to the successful direct degradation of (−)-tetrahydropapaverine (XVI; R = H) with ozone.[6] However, in simpler cases,[9] primary and secondary amines are completely destroyed by ozone. The secondary amino-function of (−)-salsolidine (V) was therefore protected by formylation, and the product (VI) was treated with a large excess of ozone followed by peracetic acid. After removal of the formyl group from the crude products by acid hydrolysis, the amino-acid fraction yielded *N*-2-carboxyethyl-L-alanine, shown by infrared absorption to be structurally identical with the sample prepared above from L-alanine. It is thus established conclusively that the absolute configuration of (−)-salsolidine is as shown in structure (V).

One must methylate (−)-salsoline in order to obtain [3] (−)-salsolidine (V), so it follows that the natural (+)-salsoline (IX) has the illustrated absolute configuration. This co-occurrence of closely related bases having opposite configurations in *Salsola arbuscula* can be compared with the presence of a similar pair, (+)-laudanosine (XVI; R = Me) and (−)-laudanidine (XVII) in *Papaver somniferum*.[10]

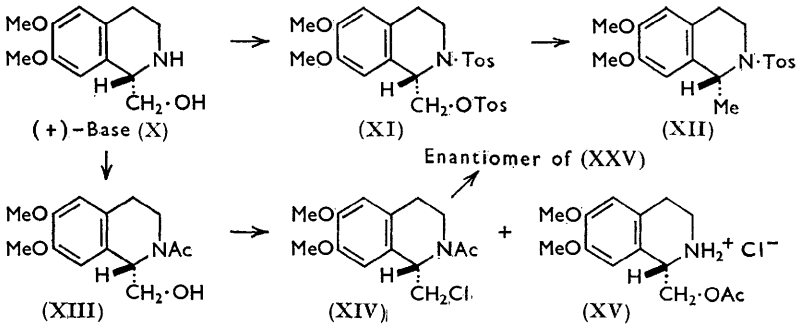
The third base included in the present study, calycotomine (X), is now available by synthesis [11] and its resolution was accomplished through the neutral (−)-*OO*-di-*p*-toluoyltartrate. To conserve material, the resolution was stopped when the base had $[\alpha]_D$ +16° (in H_2O). This material is quite sufficiently enriched with respect to the (+)-enantiomer for configurational studies; natural (+)-calycotomine has $[\alpha]_D$ +21° (in H_2O).

In order to correlate (+)-calycotomine (X) with (−)-salsolidine (V), the former was acetylated and the *ON*-diacetyl derivative then partially hydrolysed to give *N*-acetylcalycotomine (XIII). When this was treated with thionyl chloride, a mixture resulted which was not fully investigated though a crystalline salt was isolated having the composition corresponding to the expected product (XV) of acyl migration.[12] Reduction, by lithium aluminium hydride, of the mixture remaining after removal of the salt (XV)

[7] Brewster, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 178.
[8] McKinney, Setzkorn, and Uhing, *J. Amer. Chem. Soc.*, 1952, **74**, 1942.
[9] Homer, Schaefer, and Ludwig, *Chem. Ber.*, 1958, **91**, 75.
[10] Hesse, *Annalen*, 1894, **282**, 208; Späth and Bernhauer, *Ber.*, 1925, **58**, 200.
[11] Battersby and Edwards, *J.*, 1959, 1909.
[12] Cf., *inter al.*, Bergmann, Brand, and Dreyer, *Ber.*, 1921, **54**, 936; Elliott, *Biochem. J.*, 1952, **50**, 542; Welsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3500.

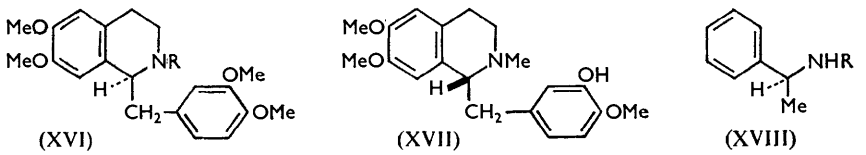
yielded (—)-*N*-ethylsalsolidine (enantiomer of XXV), presumably by way of the chloride (XIV). This sequence was not fully satisfactory, however, because of low yields, extensive racemisation and lack of crystalline intermediates.

A convincing correlation of (+)-calycotomine (X) with (—)-salsolidine (V) involved treatment of the former with toluene-*p*-sulphonyl chloride in pyridine to yield the diacyl derivative (XI) which, with lithium aluminium hydride in boiling tetrahydrofuran, underwent reductive cleavage of the sulphonyloxy-residue. The resultant *N*-toluene-*p*-sulphonylsalsolidine (XII) had a strong negative rotation whereas the (+)-compound



(VIII) was obtained from (—)-salsolidine (V). Thus the natural forms of calycotomine and salsolidine have opposite absolute configurations; (+)-calycotomine is thereby proved to have the absolute stereochemistry (X).

The above work provides several 1,2,3,4-tetrahydroisoquinolines of firmly established absolute configuration and so it was possible to make a further study of the value of optical methods for configurational determinations in this series. It is known [13] that the molecular rotations of bases of type (I) and of simple α-phenylbenzylamines (cf. XVIII) are strikingly affected by the polarity of the solvent in which the observations are made. Moreover, Leithe [13] found in several cases that the rotations of bases having the same absolute configuration are shifted in the same direction as the polarity of the solvent is increased. In two cases, α-methylbenzylamine (XVIII; R = H) and *N*-ethyl-α-methylbenzylamine (XVIII; R = Et), the illustrated absolute configuration had been established by chemical means; [13] for these two bases, there was a marked shift in a positive direction as the polarity of the solvent was increased. (—)-Tetrahydropapaverine [6] (XVI; R = H) and (+)-laudosine [13] (XVI; R = Me) also show the same direction of shift, and Corrodi and Hardegger's recent chemical studies [6] have proved that these bases correspond in absolute configuration with (—)-α-phenethylamine (XVIII; R = H). Thus a positive shift in rotation brought about by increasing the polarity of the solvent has been taken as a strong indication that the base in hand has the absolute stereochemistry shown in formulæ (XVI) and (XVIII),



whereas a negative shift was taken as evidence for the mirror image of these structures. However, the failure of the method when attempts were made to extend it to more complex bases in the morphine–codeine group (ref. 14; cf. refs. 5 and 15) raised doubts [16] about its usefulness. Accordingly, the experiments below were carried out.

[13] Leithe, *Ber.*, 1934, **67**, 1261 and earlier papers.
[14] Bick, *Nature*, 1952, **169**, 755.
[15] Kalvoda, Buchschacher, and Jeger, *Helv. Chim. Acta*, 1955, **38**, 1847
[16] Beckett and Casy, *Nature*, 1954, **173**, 1231; *J.*, 1957, 3076.

The number of bases available for study by the rotation shift method was increased by methylating (—)-salsolidine (V) with formaldehyde and formic acid, to give *N*-methylsalsolidine (XIX). With methyl iodide, this readily gave the methiodide (XX) which was degraded by Hofmann's method. Catalytic hydrogenation of the total basic product resulted in the uptake of 1·03 mol. of hydrogen to yield dihydro-*N*-methylsalsolidinemethine. Without purification, this base showed $[\alpha]_D^{16}$ −76·5° ± 0·8° (*c* 9·14 in EtOH) and after purification as the picrate showed $[\alpha]_D^{22}$ −73·8° ± 0·8° (*c* 4·81 in EtOH). The optical activity of the dihydromethine proves that it has the structure (XXII), and the agreement in the rotations before and after purification shows that there is a high degree of specificity in the Hofmann degradation to give the base (XXI) rather than the optically inactive base (XXIII). This proof of the direction of Hofmann degradation for a 1,2,3,4-tetrahydro-1-methylisoquinoline is in agreement with the recent results of Childs and Forbes [17] in the deoxy-series.

Reduction of the *N*-acetyl derivative (XXIV) of (—)-salsolidine with lithium aluminium hydride in boiling ether gave a mixture of about 20% of (+)-*N*-ethylsalsolidine (XXV) and 80% of a secondary base, presumably recovered (—)-salsolidine (V). The high proportion of material resulting from reductive cleavage was unexpected though some fission of amide groups by lithium aluminium hydride has previously been observed.[18]

Molecular rotations [a] *in different solvents.*

Base	In C_6H_6	In $CHCl_3$	In EtOH	In N-HCl
(—)-Salsolidine (V)	−133°		−123°	−57°
(—)-*N*-Methylsalsolidine (XIX)	−115		−55	+17
(—)-Dihydro-*N*-methylsalsolidinemethine (XXII)	−244		−175	−20
(+)-*N*-Ethylsalsolidine (XXV)	*+14*	*+18°*	*+20*	*+30*
(+)-Calycotomine (X)		*≃0*	+6	*+25*
(—)-Anhalonine [c, d] (XXVI)		−124		−108 [b]
(—)-Lophophorine [d, e] (XXVII)		−111		−44 [b]

[a] The concentrations of solutions were kept approximately constant for a set of determinations on one base; probable maximum limits of error on present measurements are ±3°. [b] Determined as hydrochloride in aqueous solution. [c] Lewin, *Arch. exp. Pathol. Pharmakol.*, 1894, **34**, 374 and earlier papers. [d] Späth and Kesztler, *Ber.*, 1935, **68**, 1663. [e] Heffter, *Ber.*, 1896, **29**, 216.

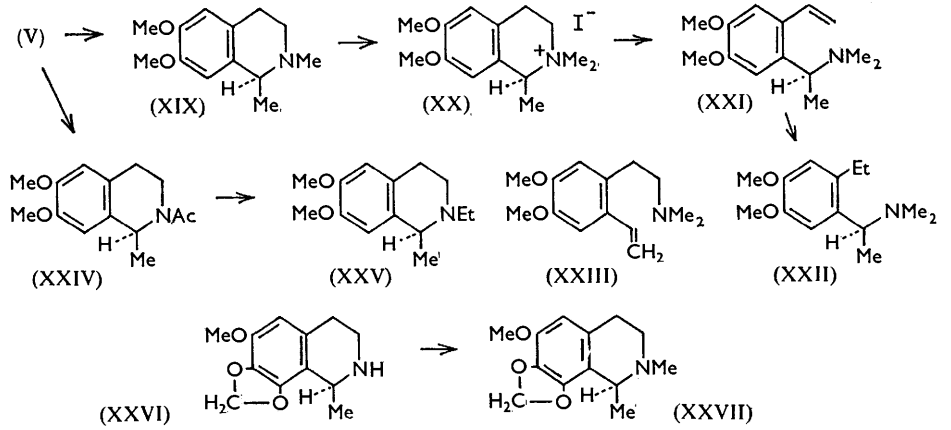
The Table gives molecular rotations for the 1,2,3,4-tetrahydroisoquinolines prepared as above. In the two cases having italicised figures, partially resolved material was used and the values given represent proportions of the true molecular rotations. These values are, however, no less useful than the others for the study of rotation shifts.

The first four bases in the Table, which we have proved to have the same absolute configuration as (—)-α-methylbenzylamine (XVIII; R = H) all show a positive shift of molecular rotation with increasing solvent polarity as was described above for the bases (XVI; R = H), (XVI; R = Me), and (XVIII; R = H and Me). Thus eight bases having the same absolute configuration show this positive shift. As shown above, (+)-calycotomine (X) has the opposite configuration, but nevertheless its rotations become more positive with increasing polarity of the solvent. This result is not unexpected since calycotomine (X) differs from all the other bases by having two strongly polar groups >NH and −OH close to the asymmetric centre; both groups will be affected by solvent polarity. The case of calycotomine emphasises again [19] the paramount importance of making optical comparisons only among strictly similar molecules.

On the basis of our results and those drawn from the literature cited above, we think that the method of rotation shifts is a useful one for the determination of absolute configuration *provided* that the base examined belongs to the α-methylbenzylamine or 1-benzyl- or 1-alkyl-1,2,3,4-tetrahydroisoquinoline series and that the nitrogen atom is the only

[17] Childs and Forbes, *J.*, 1959, 2024.
[18] *E.g.*, Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1190.
[19] Klyne, "Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York, 1955, p. 73.

strongly polar centre in the molecule. In this context, alkoxyl groups attached to aromatic rings are not considered to be strongly polar. It may be possible to enlarge this group as knowledge grows; for example, the protoberberine alkaloids will probably be included (cf. ref. 6) when more cases of established absolute configuration have been examined.



The cactus *Lophophora williamsii* yields [20,21] two bases, (—)-anhalonine (XXVI) and (—)-lophophorine (XXVII), of unknown absolute configuration, which fall into the group of bases susceptible to study by rotation shifts. *N*-Methylation of the former base [22] yields the latter, showing that they have the same absolute configuration. In keeping with this, the values in the Table show a positive shift for each base as the polarity of the solvent increases so that they can be assigned the same absolute configuration as (—)-salsolidine (V), that is, as shown in structures (XXVI) and (XXVII). This assignment is supported by the fact that the change in molecular rotation brought about by methylation {$\Delta[M]$ for (XXVII) — (XXVI) = +64° for the hydrochlorides} corresponds well with that for the conversion of (—)-salsolidine into (—)-*N*-methylsalsolidine {$\Delta[M]$ for (XIX) — (V) = +74° for the hydrochlorides}.

Experimental

For general directions, see ref. 23.

N-2-*Cyanoethyl*-L-*alanine* (III).—A solution of L-alanine (2·97 g.) in N-sodium hydroxide (33·3 ml.) was cooled to 0° and treated with acrylonitrile (1·77 g.) at such a rate that the temperature was held below 30°. After the mixture had been kept at 5° overnight, glacial acetic acid (2 ml.) and ethanol (60 ml.) were added and the precipitated N-2-*cyanoethyl*-L-*alanine* was collected (2·56 g.); it had m. p. 240—245° (decomp.) after sintering at 220—225°, unchanged by recrystallisation from 50% aqueous ethanol (Found: C, 50·9; H, 7·0; N, 19·6. $C_6H_{10}O_2N_2$ requires C, 50·7; H, 7·0; N, 19·7%).

N-2-*Carboxyethyl*-L-*alanine* (IV).—The foregoing cyanide (5·26 g.) was heated under reflux for 24 hr. with 6N-hydrochloric acid (150 ml.), and the solution was then evaporated to dryness. Water (20 ml.) was added and the solution again evaporated to dryness; this process was repeated with two further portions of water. A solution of the final residue in water (20 ml.) was adjusted to pH 2·5—3·0 with sodium hydroxide and then run on to a column (3 × 20 cm.) of " Amberlite " IR-120 resin (H-form). The column was washed with water (1 l.), the final test samples being free from solute. Elution of the column with N-ammonia yielded the amino-acids (4·09 g.). This fraction was dissolved in the minimum volume of water, and the solution run on to a column (3 × 20 cm.) of " Amberlite " IR-4B resin (acetate form). After the column had been thoroughly washed with water, the acidic amino-acid fraction was eluted with N-acetic acid. Crystallisation from aqueous acetone gave N-2-*carboxyethyl*-L-*alanine*

[20] Lewin, *Arch. exptl. Pathol. Pharmakol.*, 1894, **34**, 374 and earlier papers.
[21] Heffter, *Ber.*, 1896, **29**, 216.
[22] Späth and Kesztler, *Ber.*, 1935, **68**, 1663.
[23] Battersby, Davidson, and Harper, *J.*, 1959, 1744.

(2·5 g.), m. p. 220—221° (Found: C, 44·8; H, 6·8; N, 8·7. $C_6H_{11}O_4N$ requires C, 44·7; H, 6·8; N, 8·7%), $[\alpha]_D^{22}$ +6·0° ± 0·5° (*c* 3·43 in H_2O).

(+)-*Salsolidine* (V).—Freshly distilled acetaldehyde (80 ml.) was added slowly at 0° to a solution of 3,4-dimethoxyphenethylamine (40 g.) in 6N-sulphuric acid (400 ml.). After the mixture had been heated under reflux for 0·5 hr., it was cooled to 0°, treated with a second portion of acetaldehyde (80 ml.), then heated under reflux for 3 hr. The black polymer was removed and the remaining solution was extracted thrice with ether. Basification of the aqueous solution with concentrated sodium hydroxide solution was followed by thorough ether-extraction which removed a gum (41 g.). This was fractionally distilled and the main fraction, b. p. 110—115°/0·03 mm., was (±)-salsolidine (33·4 g., 73%). A small portion was converted in ethanol into the picrate, m. p. 200—201°; Späth and Dengel [4] record m. p. 201—201·5°. The resolution of salsolidine was carried out by using (+)-tartaric acid as described by Späth and Dengel; [4] the $[\alpha]_D^{22}$ of pure base was −59·5° ± 0·5° (*c* 4·39 in EtOH) [lit.,[4] −59·7° (*c* 20 in EtOH)].

Ozonolysis of N-*Formylsalsolidine* (VI).—A solution of (−)-salsolidine ($[\alpha]_D^{22}$ −11° in EtOH) (1·56 g.) in 98—100% formic acid (12·5 ml.) was heated with acetic anhydride (4·1 ml.) at 35° for 0·5 hr. Evaporation of the solvents left *N*-formylsalsolidine as a gum. This was dissolved in chloroform–methanol (10 : 1 by vol.; 75 ml.), and the solution was divided equally among three Drechsel bottles which were connected in series. Ozonised oxygen (3% ozone) was passed through the bottles at 200 ml./min. for 7·5 hr. The bottles were interchanged after 2·5 hr. and 5 hr. so that each bottle was the first in the series for 2·5 hr. Formic acid (98—100%; 17 ml.) and hydrogen peroxide (30-vol.; 17 ml.) were added to the combined solutions, the chloroform–methanol was evaporated, and the mixture was heated under reflux for 1 hr. The oil which had separated was dissolved by the addition of methanol, and the peracids were destroyed with palladium black (0·2 g.); this was completed by warming the mixture at 60° for 1 hr. After removal of the catalyst, the solution was evaporated to dryness and the residue was heated under reflux for 2 hr. with 4N-hydrochloric acid (25 ml.). The solution was extracted thrice with chloroform, the aqueous layer was taken to dryness, and the residue in the minimum volume of water was run on to a column (2·5 × 13 cm.) of " Amberlite " IR-120 resin (H-form). The procedure used above in the synthesis of *N*-2-carboxyethyl-L-alanine was then followed, to give the acidic amino-acids (341 mg.). This fraction crystallised from aqueous acetone to give partially racemic *N*-2-carboxyethyl-L-alanine (115 mg.), m. p. 209—210° (Found: C, 44·5; H, 6·8; N, 8·6. Calc. for $C_6H_{11}O_4N$: C, 44·7; H, 6·8; N, 8·7%), $[\alpha]_D^{22}$ +2·8° ± 0·8° (*c* 2·55 in H_2O). The infrared spectrum of this product was identical with that of the synthetic sample of *N*-2-carboxyethyl-L-alanine (IV) above.

Resolution of (±)-*Calycotomine* (cf. X).—(±)-Calycotomine [11] (2·25 g.) in the minimum volume of ethanol was treated with (−)-*OO*-di-*p*-toluoyltartaric acid [24] (1·93 g.) in ethanol (total vol. of solution 75 ml.). After crystallisation had been initiated by seeding with material from a trial resolution, it was allowed to continue for 2 days at room temperature. The crystals (8·13 g.) from four such resolutions were dissolved in water, and the solution was basified with a large excess of potassium carbonate and extracted exhaustively with ether–chloroform (4 : 1). Evaporation of the extracts left the optically active base (3·68 g.), $[\alpha]_D^{22}$ −16° (*c* 2·26 in H_2O), whose infrared spectrum was identical with that of (±)-calycotomine.

The mother-liquors from the first crops of calycotomine ditoluoyltartrate slowly deposited a second crop (total 5·7 g.) from which the base (2·64 g.) was recovered as above, having $[\alpha]_D^{22}$ +16° (*c* 1·68 in H_2O).

(±)-N-*Acetylcalycotomine* (cf. XIII).—(±)-Calycotomine (512 mg.) was heated with acetic anhydride (10 ml.) for 1·25 hr., the excess of anhydride was evaporated and the residue in ether (150 ml.) was shaken with an excess of 2N-sulphuric acid (total 10 ml.). Evaporation of the ether left a neutral gum (677 mg.) which was dissolved in 0·25N-methanolic potassium hydroxide (10 ml.) and kept overnight. After addition of hydrochloric acid to pH 5, the solution was freed from methanol by evaporation and then shaken with an excess of N-hydrochloric acid and ether. The ether afforded a solid (433 mg.) which crystallised from ethyl acetate to yield (±)-N-*acetylcalycotomine*, m. p. 166—167° (Found: C, 63·3; H, 7·4; N, 5·7. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·3%).

N-*Ethylsalsolidine*.—(a) *From* (+)-*calycotomine*. The foregoing experiment was repeated but with (+)-calycotomine (3·68 g.) ($[\alpha]_D^{22}$ +16° in H_2O), and the total *N*-acetyl derivative was

[24] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 922.

dissolved in dry chloroform (60 ml.). Thionyl chloride (10 ml.) was added, the solution was kept overnight, then evaporated to dryness, and the residue in chloroform (60 ml.) was heated with thionyl chloride (1 ml.) at 60° for 1·5 hr. The residue left by evaporation of the solvents was extracted with warm tetrahydrofuran, and the insoluble solid (1·64 g.), probably *1-acetoxymethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride* (XV), was recrystallised thrice from ethanol; it had m. p. 190—191° (Found: C, 56·1; H, 6·7; N, 4·6. $C_{14}H_{20}O_4NCl$ requires C, 55·7; H, 6·6; N, 4·6%).

The solution in tetrahydrofuran was added dropwise to a stirred suspension of lithium aluminium hydride (2·1 g.) in tetrahydrofuran (200 ml.), and the mixture was heated under reflux for 1 hr. After the excess of hydride had been destroyed with the minimum amount of water, the suspension was filtered, and the filtrate evaporated to dryness. The residue was heated at 100° with acetic anhydride (25 ml.) for 1 hr., the excess of anhydride was evaporated, and the residue shaken with dilute sulphuric acid and chloroform. Basification of the aqueous layer with a large excess of potassium carbonate followed by ether-extraction yielded the basic products (0·5 g.) as a gum. This was purified by countercurrent distribution (150 transfers) between ethyl acetate and aqueous buffer made from 0·5M-potassium dihydrogen phosphate (85 vol.) and 0·5M-dipotassium hydrogen phosphate (15 vol.). The contents of tubes 98—122 were worked up for base as usual, to give (−)-*N*-ethylsalsolidine (251 mg.), b. p. 110—115° (bath)/0·01 mm., $[\alpha]_D^{22}$ −1·5° ±0·5° (*c* 5·6 in EtOH), infrared spectrum (in CCl_4) identical with that of authentic *N*-ethylsalsolidine below.

(b) *From* (−)-*salsolidine*. This base (2·29 g., $[\alpha]_D$ −17·5° in EtOH) was heated with acetic anhydride (50 ml.) for 1 hr. at 100° and the excess of anhydride was evaporated; the residue was worked up for neutral material (2·8 g.) as usual. A solution of this product in anhydrous ether (150 ml.) was added gradually to a stirred suspension of lithium aluminium hydride (1·4 g.) in boiling ether (100 ml.). After the mixture had been heated under reflux for 2 hr., it was cooled and treated with the minimum volume of water necessary to decompose the hydride, and the solid was then filtered off. The latter was extracted with ethanol, and the ethanolic and ethereal solutions were combined and evaporated to give a gum (2·26 g.). This was acetylated as above, the product was shaken with 2N-sulphuric acid and chloroform, and the aqueous layer was extracted twice more with chloroform. The tertiary base (423 mg.) was recovered from the aqueous solution by basification and ether extraction. It was purified by countercurrent distribution as above and distilled at 110°(bath)/0·01 mm., to give (+)-*N*-ethylsalsolidine, $[\alpha]_D^{22}$ +8·3° ± 0·5° (*c* 6·04 in EtOH).

Part of this base was converted into the *hydrochloride* which, crystallised from ethanol, had m. p. 173—174° (Found: C, 61·7; H, 8·1; N, 5·4. $C_{14}H_{22}O_2NCl$ requires C, 61·8; H, 8·1; N, 5·1%).

(+)-N-*Toluene*-p-*sulphonylsalsolidine* (VIII).—Toluene-*p*-sulphonyl chloride (0·3 g.) in dry pyridine (5 ml.) was added dropwise at 0° to a stirred solution of (−)-salsolidine (0·2 g. of optically pure base) in dry pyridine (5 ml.). After the mixture had been kept at 5° for 2 days, it was treated with crushed ice and extracted with chloroform. The extracts were washed twice with 6N-hydrochloric acid, then with water, and finally dried and evaporated to a gum. This crystallised from ethanol to give (+)-N-*toluene*-p-*sulphonylsalsolidine* (143 mg.), m. p. 172—173°, $[\alpha]_D^{22}$ +127° ± 1·5° (*c* 1·64 in $CHCl_3$) (Found: C, 63·6; H, 6·6; N, 3·9 $C_{19}H_{23}O_4NS$ requires C, 63·1; H, 6·4; N, 3·9%).

(−)-N-*Toluene*-p-*sulphonylsalsolidine* (XII) *from* (+)-*Calycotomine* (X).—(+)-Calycotomine {306 mg. of base $[\alpha]_D^{22}$ +16° (in H_2O)} was converted into the amorphous *ON*-ditoluene-*p*-sulphonyl derivative (783 mg.) as in the foregoing experiment, though proportionately twice the amount of toluene-*p*-sulphonyl chloride was used. A solution of this product in anhydrous tetrahydrofuran (30 ml.) was added dropwise in 0·5 hr. to a stirred suspension of lithium aluminium hydride (0·3 g.) in tetrahydrofuran (20 ml.). After the mixture had been heated under reflux for 2 hr., it was treated with an excess of wet ethyl acetate, and the precipitate was dissolved by the addition of 5N-hydrochloric acid. The aqueous layer was extracted twice more with ethyl acetate, and the combined organic layers were dried and evaporated to leave a gum (615 mg.). Crystallisation from ethanol (15 ml.) gave (−)-N-*toluene*-p-*sulphonylsalsolidine* (229 mg.), m. p. 168—169°, $[\alpha]_D^{22}$ −94° ± 1·5° (*c* 1·65 in $CHCl_3$) (Found: C, 63·0; H, 6·8; N, 4·2%). The infrared spectrum of this product was identical with that of the foregoing (+)-enantiomer.

(−)-N-*Methylsalsolidine* (XIX) (with Dr. R. Binks).—Optically pure (−)-salsolidine

(2·06 g.) was dissolved at 0° in 90% formic acid (11 ml.), and 40% aqueous formaldehyde (10 ml.) was then added. The solution was heated at 100° for 11 hr., cooled, treated with 4N-hydrochloric acid (10 ml.) and evaporated to dryness. A solution of the residue in water (20 ml.) was basified strongly with potassium hydroxide and a large excess of potassium carbonate and extracted with ether (6 × 80 ml.). The ethereal solution was washed with saturated sodium sulphate solution, dried, and evaporated to leave an oil (2 g.). Part was converted into the picrate as usual which was recrystallised from methanol to give (−)-N-*methylsalsolidine picrate*, m. p. 233—234° (decomp.) (Found: C, 50·95; H, 5·2. $C_{19}H_{22}O_9N_4$ requires C, 50·65; H, 4·9%).

The base (91 mg.) was recovered by passing the pure picrate (189 mg.) in chloroform (25 ml.) and methanol (5 ml.) down a column of alumina. Distillation of the base at 100°(bath)/0·02 mm. gave (−)-*N*-methylsalsolidine as an oil, $[\alpha]_D^{22}$ −24·9° ± 0·5° (*c* 4·45 in EtOH).

Hofmann Degradation of (−)-N-*Methylsalsolidine* (XIX) (with Dr. R. Binks).—Methyl iodide (2·8 ml.) was added to a solution of (−)-*N*-methylsalsolidine (1·85 g.) in ether (20 ml.), and the mixture was kept at room temperature overnight. The precipitate (2·76 g.) was collected and recrystallised from methanol, to yield (−)-N-*methylsalsolidine methiodide*, m. p. 229—231° (decomp.) (Found: C, 46·4; H, 6·3; N, 3·9. $C_{14}H_{22}O_2NI$ requires C, 46·3; H, 6·1; N, 3·9%).

A solution of the methiodide (2·47 g.) in warm water (150 ml.) was shaken for 2 hr. with silver oxide freshly prepared from silver nitrate (6 g.), and the solids were then filtered off. The filtrate was evaporated to dryness and the residue was heated at 100°/12 mm. for 2 hr. before it was cooled and shaken with water and ether. Evaporation of the ether left an oil (1·44 g.) which in ethanol (30 ml.) was shaken with hydrogen and platinum at room temperature and pressure; uptake (1·03 mol.) ceased after 18 min. After removal of the catalyst, the ethanol was evaporated and the residual base distilled at 110°(bath)/0·05 mm.; $[\alpha]_D^{16}$ of the distillate was −76·5° ± 0·8° (*c* 9·14 in EtOH). The distillate was converted into the picrate which recrystallised from ethanol to give *dihydro*-N-*methylsalsolidinemethine picrate*, m. p. 165—166° (decomp.) (Found: C, 51·4; H, 6·0; N, 11·9. $C_{20}H_{26}O_9N_4$ requires C, 51·5; H, 5·6; N, 12·0%).

The base was recovered from the pure picrate as above and after redistillation had $[\alpha]_D^{22}$ −73·8° ± 0·8° (*c* 4·81 in EtOH).

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