## 460. *The Rearrangement of Isoquinoline Alkaloid* N-*Oxides.*

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Oxidation of laudanosine *N*-oxide by potassium chromate affords norlaudanosine. In the same way the *N*-oxide of tetrahydro-anhydroepiberberine (IV; R = H) affords the carbinolamine (IV; R = OH), identical with norcryptopine, prepared from cryptopine (V; R = Me) through the *N*-cyano-nor-compound. This carbinolamine can be methylated to cryptopine and also to its *O*-methyl ether. Similarly the *N*-oxides of tetrahydroberberine and norcoralydine can be converted through the related carbinolamines into α-allocryptopine and cryptopalmatine, respectively.

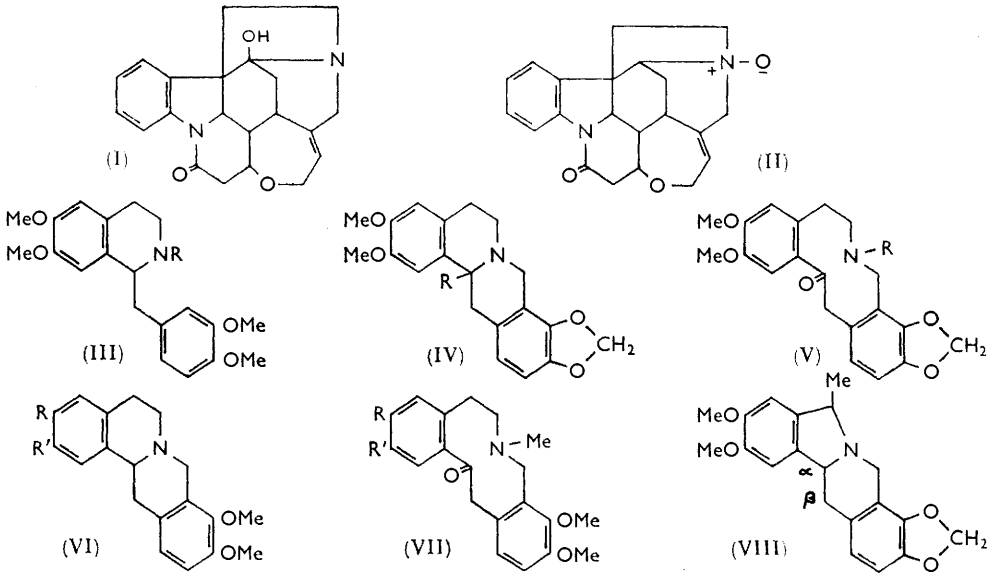
The biogenesis of halides of the protopine group is believed to involve oxidative fission of an N–C bond in a base of tetrahydroberberine type,[1] a reaction that has been accomplished only indirectly in the laboratory.[2-4] In analogy with the formation[5] of the carbinolamine ψ-strychnine (I) in 80% yield from strychnine *N*-oxide (II) on treatment with potassium chromate (this in turn is based on the conversion of codeine *N*-oxide into norcodeine by potassium chromate[6]), the *N*-oxide of laudanosine (III; R = Me) has been converted into norlaudanosine (III; R = H), and the *N*-oxide of anhydrotetrahydroepiberberine (IV; R = H) has been converted into the carbinolamine (IV; R = OH). The latter carbinolamine, which can be reduced with zinc and acid to the parent base (IV; R = H), should be tautomeric with the keto-secondary base norcryptopine (V; R = H) and an attempt was made to prepare it from cryptopine. This alkaloid (V; R = Me), on treatment with cyanogen bromide, affords a mixture of the methobromide, the hydrobromide, and *N*-cyanonorcryptopine (V; R = CN), whereas, as it contains a benzylamine system it might have been expected to suffer ring fission.[7] Hydrolysis of *N*-cyanonorcryptopine yielded the carbinolamine (IV; R = OH), which showed hydroxyl but no carbonyl absorption in the infrared spectrum.

Treatment of the carbinolamine (IV; R = OH) with warm absolute methanol gave the *O*-methyl ether (V; R = OMe) from which cryptopine hydriodide (20%) and methiodide (80%) were obtained by the prolonged action of methyl iodide. Cryptopine hydriodide was obtained in better yied (70%) by the direct action of methyl iodide on the carbinolamine. The *N*-oxides of tetrahydroberberine (VI; R = R′ = $CH_2O_2$<) and norcoralydine (VI; R = R′ = OMe) have also been converted into the carbinolamines and these in turn

[1] Manske, "Alkaloids," Academic Press, New York, Vol. IV, 1954, Chapter 25.
[2] Haworth and Perkin, *J.*, 1926, 445, 1769.
[3] Haworth, Koepfli, and Perkin, *J.*, 1927, 2261.
[4] Russell, *J. Amer. Chem. Soc.*, 1956, **78**, 3113.
[5] Bailey and Robinson, *J.*, 1948, 703.
[6] Diels and Fischer, *Ber.*, 1916, **49**, 1721.
[7] Hageman, *Organic Reactions*, 1953, **7**, 198.

can be methylated to α-allocryptopine (VII; R = R′ = $CH_2O_2$<) and cryptopalmatine (VII; R = R′ = OMe), respectively.

Cryptopalmatine has previously been prepared,[3] and our product, which crystallised in a solvated form, differs in melting point from that previously reported (unsolvated), but the colour reaction with sulphuric acid, the analysis, and the infrared spectrum




(carbonyl band 1665, cryptopine 1670, α-allocryptopine 1665 cm.$^{-1}$) all confirm our assignment of structure to the material.

An attempt to prepare a nine-membered-ring analogue of cryptopine by the potassium chromate rearrangement and subsequent methylation of the ψ-cryptopine derivative (VIII) gave only intractable material.

## Experimental

*Scission of Laudanosine N-Oxide by Potassium Chromate.*—The crude amine oxide [8] (1 g.) was dissolved in water (5 ml.) at 65° and cautiously treated with potassium chromate (0·5 g.) in water (10 ml.) at 65°; considerable frothing took place and a faint odour of formaldehyde was detected. After reaction had subsided, stirring and heating were continued for a further 15 min. The cold, brown solution was separated from tar and poured into an excess of ethanol, and inorganic material was removed by filtration. Evaporation afforded a brown gum (0·5 g.) which with ethanolic hydrogen chloride and dry ether gave the norlaudanosine hydrochloride; this crystallised from methanol–ethyl acetate as needles, m. p. 216—216·5° (Found: C, 63·4; H, 6·8. Calc. for $C_{20}H_{25}NO_4$,HCl: C, 63·2; H, 6·9%).

*Anhydrotetrahydroepiberberine N-Oxide.*—Anhydrotetrahydroepiberberine [9] (3·6 g.) in cold chloroform (20 ml.) was slowly added to an ice-cold solution of perbenzoic acid (2·8 g.) in chloroform (50 ml.) at <5°. Next day the solution was shaken with 10% aqueous sodium hydroxide and the latter was extracted with more chloroform. The syrup obtained from the chloroform extract solidified to a buff-coloured amorphous mass on trituration with 15% potassium hydroxide solution. The *oxide* crystallised from water as needles (2 g.), which sintered at 145° and melted at 150—152° (Found: C, 63·9; H, 6·4; N, 3·7. $C_{20}H_{21}NO_5$,$H_2O$ requires C, 64·1; H, 6·4; N, 3·6%). The *picrate* crystallised fom ethanol as prisms, m. p. 190° (decomp. from 165°) (Found: C, 53·5; H, 4·3; N, 9·4. $C_{20}H_{21}NO_5$,$C_6H_3N_3O_7$ requires C, 53·4; H, 4·1; N, 9·6%). The *hydrochloride* crystallised from water as needles which decomposed, with

[8] Bentley and Murray, preceding paper.
[9] Perkin, *J.*, 1916, **109**, 815; 1918, **113**, 492.

frothing, at 236—237·5° after darkening at 220° (Found: C, 61·1; H, 5·8. $C_{20}H_{21}NO_5$,HCl requires C, 61·3; H, 5·6%).

*Anhydrotetrahydrohydroxyepiberberine* (IV; R = OH).—Potassium chromate (0·6 g.) in water (10 ml.) was added, with stirring, to a solution of the amine oxide (1·7 g.) in water (25 ml.), and the mixture heated at 65° for 45 min. The cooled mixture was treated with dilute hydrochloric acid and chloroform, the chloroform removed, and the mother-liquor basified and continuously extracted with chloroform. The brown mass remaining after removal of the solvent was obtained from chloroform–ether as a pale yellow amorphous powder, m. p. 135—140°, which darkened considerably on storage and drying. It had $\lambda_{max.}$ 245 mμ (log ε 4·03), 292 mμ (log ε 3·80), $\nu_{max.}$ 3600 cm.$^{-1}$ (OH). This crystallised from aqueous ethanol, giving anhydrotetrahydrohydroxyepiberberine as needles, m. p. 144° alone or mixed with the product of hydrolysis of *N*-cyanonorcryptopine.

*Anhydrotetrahydromethoxyepiberberine* (IV; R = OMe).—Crude anhydrotetrahydrohydroxyepiberberine, when heated with absolute methanol, gave *anhydrotetrahydromethoxyepiberberine* as prisms (from methanol), m. p. 233—235° (sintering at 205—210°) (Found: C, 67·8; H, 6·1. $C_{21}H_{23}NO_5$ requires C, 68·2; H, 6·2%). *The chromate*, m. p. 208—210°, was recovered from the methanolic mother-liquors [Found: C, 56·8; H, 5·2; N, 2·9. $(C_{21}H_{24}NO_5)_2CrO_4,4H_2O$ requires C, 56·5; H, 5·6; N, 3·1%].

*Reduction of Anhydrotetrahydrohydroxyepiberberine.*—Zinc dust (0·75 g.) was added to the base (0·3 g.), dissolved in hot 2N-hydrochloric acid (25 ml.), during 15 min. A solid was soon deposited. The mixture was then warmed on a water-bath for 30 min., after which the solution was clarified by addition of hot water, followed by a slight excess of saturated sodium carbonate solution. On cooling, the solid was collected and dried, and the organic material was separated from the zinc residue by treatment with hot chloroform. Removal of the solvent left a brown resin which crystallised from ethanol as pale brown needles, m. p. 169—170° alone and mixed with authentic anhydrotetrahydroepiberberine.

N-*Cyanonorcryptopine.*—Cyanogen bromide (2 g.) in chloroform (10 ml.) was added to a solution of cryptopine (5 g.) in chloroform (25 ml.), and the resulting mixture heated under reflux for 2 hr. When the pale yellow gum remaining after evaporation of the organic solvent *in vacuo* was boiled for 30 min. with water (50 ml.), and the solution filtered and cooled, cryptopine hydrobromide, m. p. 180—181° (0·35 g.), was deposited (Found: C, 55·0; H, 5·5. Calc. for $C_{21}H_{23}NO_5$,HBr,$\frac{1}{2}H_2O$: C, 55·0; H, 5·45%). The mother-liquor slowly deposited cryptopine methobromide, prisms (from aqueous ethanol), m. p. 222—225° (decomp.) (Found: C, 55·6; H, 5·6. Calc. for $C_{21}H_{23}NO_5$,$CH_3Br$,$\frac{1}{2}H_2O$: C, 55·8; H, 5·7%). Treating the water-insoluble gum with boiling ethanol gave N-*cyanonorcryptopine* as pale yellow prisms, m. p. 150—150·5° (Found: C, 66·4; H, 5·7. $C_{21}H_{20}N_2O_5$ requires C, 66·3; H, 5·3%), $\nu_{max.}$ 2220 (CN) and 1670 cm.$^{-1}$ (C=O).

*Norcryptopine.*—*N*-Cyanonorcryptopine (2 g.) was refluxed with 6% hydrochloric acid (60 g.) for 6 hr. and the solution was cooled and made alkaline with concentrated aqueous ammonia; a yellow amorphous mass was deposited. This crystallised from aqueous alcohol as needles (0·7 g.), m. p. 144° alone or mixed with *anhydrotetrahydrohydroxyepiberberine* (above) (Found: C, 67·8; H, 6·1; N, 3·7. $C_{20}H_{21}NO_5$ requires C, 67·6; H, 5·9; N, 3·9%). The ultraviolet and infrared spectra of the bases from the two sources were identical.

*Cryptopine from Anhydrotetrahydrohydroxyepiberberine and its* O-*Methyl Ether.*—Anhydrotetrahydromethoxypiberberine (0·4 g.), methyl iodide (30 ml.), and methanol (15 ml.) were heated together on a water-bath with frequent shaking for 3 days. The resulting pale yellow crystalline cake was dissolved in boiling aqueous methanol. On cooling, cryptopine methiodide (0·3 g.) rapidly separated as yellow prisms, m. p. 216—218° (lit., 215—217°) (Found: C, 49·9; H, 5·3. Calc. for $C_{21}H_{23}NO_5$,$CH_3I$,$H_2O$: C, 49·9; H, 5·3%), $\nu_{max.}$ 1685 cm.$^{-1}$ (cf. Anet *et al.*[10]). Evaporation of the methanolic mother-liquor yielded cryptopine hydriodide, which separated from boiling water as a jelly; on agitation, this produced prisms, m. p. 233—238° (effervescence) (lit.,[9] 235—240°) (Found: C, 49·0; H, 5·0. Calc. for $C_{21}H_{23}NO_5$,HI,$H_2O$: C, 48·9; H, 5·0%). Cryptopine hydriodide was also obtained by refluxing anhydrotetrahydrohydroxyepiberberine (0·3 g.) with methyl iodide (20 ml.) for 3 hr. Basification of an aqueous solution of the hydriodide with aqueous ammonia afforded cryptopine, prisms (from pyridine–ethanol), m. p. and mixed m. p. 218·5°, $\nu_{max.}$ 1670 cm.$^{-1}$ (spectrum identical with that of authentic cryptopine).

[10] Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944.

(±)-*Tetrahydroberberine*.—Berberinium sulphate (3 g.) in warm water (100 ml.) was treated with an excess of sodium borohydride until the solution became colourless, the tetrahydroberberine being precipitated as a pale yellow, amorphous precipitate (2 g.) which crystallised from ethanol as pale yellow rectangular plates, m. p. 170—171° (Found: C, 71·0; H, 6·3. Calc. for $C_{20}H_{21}NO_4$: C, 70·8; H, 6·2%). The hydrochloride, which crystallised from water as lozenge-shaped plates, had m. p. 198—200° (Found: C, 63·6; H, 6·1. Calc. for $C_{20}H_{21}NO_4$,HCl: C, 63·9; H, 5·9%). The picrate was obtained in yellow plates (from ethanol), m. p. 185°.

*Tetrahydroberberine* N-*Oxide*.—A solution of tetrahydroberberine (1·6 g.) in chloroform (15 ml.) was slowly added to an ice-cold solution of perbenzoic acid (1·4 g.) in chloroform (30 ml.), and the solution was kept below 5° by immersion in ice. After 12 hr. the solution was shaken with 10% aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried, filtered, chloroform extract afforded *tetrahydroberberine* N-*oxide* as a buff-coloured, hygroscopic foam (1·1 g.) which crystallised from ethyl acetate as irregular plates, m. p. 158·5—159°. The *picrate* crystallised as yellow flakes (from ethanol), m. p. 196·5—197·5° (decomp.) (Found: C, 53·1; H, 4·1. $C_{20}H_{21}NO_5$,$C_6H_3N_3O_7$ requires C, 53·4; H, 4·1%.)

*Tetrahydromethoxyberberine*.—Tetrahydroberberine *N*-oxide (0·9 g.) in water (25 ml.) was isomerised as indicated above, with boiling potassium chromate (0·4 g.) in water (10 ml.). The brown syrup obtained by working up as above furnished, on trituration with and recrystallisation from methanol, *tetrahydromethoxyberberine* (0·5 g.), prisms, m. p. 178—179° (darkening at 160°) (Found: C, 67·9; H, 6·0. $C_{21}H_{23}O_5N$ requires C, 68·2; H, 6·2%).

α-*Allocryptopine*.—Tetrahydromethoxyberberine was refluxed in methanol with methyl iodide (20 ml.) for 24 hr. The solution was evaporated, and the residue was dissolved in boiling water and treated with concentrated potassium hydroxide solution. The small quantity of cream-coloured solid which was deposited was collected with chloroform and identified as α-allocryptopine, prisms (from ethyl acetate), m. p. 158—160° (lit.,[2] m. p. 160—161°) (Found: C, 68·2; H, 6·5. Calc. for $C_{21}H_{23}O_5N$: C, 68·3; H, 6·2), $\nu_{max.}$ 1665 cm.$^{-1}$ (cf. Anet *et al.*[10]). It dissolved in concentrated sulphuric acid to give a yellow solution which rapidly became violet and eventually red.

*Norcoralydine* N-*Oxide*.—The oxide was prepared by oxidising norcoralydine [11] (4 g.) with perbenzoic acid (3·5 g.) and working up the mixture with alkali and chloroform. Trituration of the syrup produced a pale brown mass which on recrystallisation from ethyl acetate afforded *norcoralydine* N-*oxide* as hygroscopic needles (1·7 g.), m. p. 159·5—160·5° (Found: C, 64·0; H, 6·9; N, 3·9. $C_{21}H_{26}NO_5$,$H_2O$ requires C, 64·6; H, 7·1; N, 3·6%). The *picrate* separated as pale yellow flakes (from ethanol), m. p. 254—255° (decomp.) (Found: C, 53·8; H, 4·7; N, 9·2. $C_{21}H_{25}NO_5$,$C_6H_3N_3O_7$ requires C, 54·0; H, 4·7; N, 9·3%).

*Hydroxynorcoralydine* (VI; R = R′ = OH).—Isomerisation of norcoralydine *N*-oxide (1·5 g.) with potassium chromate (0·6 g.) as described above yielded the impure hydroxynorcoralydine (0·9 g.) as dirty brown crystals, $\nu_{max.}$ 3620 cm.$^{-1}$ (OH). The *picrate*, precipitated from an acetone solution of the base and picric acid by ether, crystallised from acetone–ether as needles, m. p. 273—275° (decomp.) (Found: C, 54·0; H, 4·5; N, 9·5%. $C_{21}H_{25}NO_5$,$C_6H_3N_3O_7$ requires C, 54·0; H, 4·7; N, 9·3%).

*Methoxynorcoralydine* (VI; R = R′ = OMe).—Trituration of the crude carbinolamine with boiling methanol afforded *methoxynorcoralydine* as yellow prisms (from methanol), m. p. 215° (decomp.) (Found: C, 68·2; H, 6·9. $C_{22}H_{27}NO_5$ requires C, 68·5; H, 7·1%). Evaporation of the methanolic mother-liquor nearly to dryness furnished the *chromate* as yellow needles. This was purified by precipitation from a methanolic solution with ether [Found: C, 59·4; H, 6·2. $(C_{22}H_{28}NO_5)_2CrO_4$ requires C, 59·4; H, 6·3%].

*Cryptopalmatine* (VII; R = R′ = OMe).—Methoxynorcoralydine (0·5 g.), dissolved in the minimum of methanol, was refluxed with methyl iodide (20 ml.) for 48 hr. Removal of volatile material afforded a dirty residue which was dissolved in boiling water. The aqueous solution was made alkaline with aqueous potassium hydroxide; the precipitated off-white amorphous material (0·1 g.) crystallised from chloroform–methanol as prisms, m. p. 210—212·5° (Found: C, 67·3; 67·1; H, 7·5, 7·4; N, 3·1, 3·2. $C_{22}H_{27}NO_5$,$\frac{1}{2}CH_3{\cdot}OH$ requires C, 67·3; H, 7·2; N, 3·5%), $\nu_{max.}$ 3500 (OH from methanol), 1665 cm.$^{-1}$ (C=O).

*Nor-ψ-cryptopine* (VIII; $\Delta^{\alpha\beta}$).—Finely powdered ψ-cryptopine chloride [9] (1·2 g.) was

[11] Craig and Tarbell, *J. Amer. Chem. Soc.*, 1948, **70**, 2783.

cautiously heated at 10 mm. until all moisture had been removed. The temperature was then raised rapidly to 230° where decomposition began with frothing and formation of a reddish-brown viscous mass; as soon as the loss of methyl chloride became rapid the temperature was allowed to fall to about 200°. The crude, reddish-brown product was boiled with water, to extract unchanged ψ-cryptopine chloride and a dark brown impurity, and the residue triturated with methanol; it then afforded *nor-ψ-cryptopine* as buff-coloured crystals (0·3 g.) which recrystallised from acetone as pale yellow needles, m. p. 218—220° (decomp.) (Found: C, 71·1; H, 5·4. $C_{20}H_{19}NO_4$ requires C, 71·2; H, 5·6%). A trace of the substance in a few drops of glacial acetic acid, gave, on the addition of concentrated sulphuric acid, an orange solution with a green fluorescence.

*Dihydronor-ψ-cryptopine* (VIII).—Crude nor-ψ-cryptopine (2 g.) was dissolved in glacial acetic acid (25 ml.) and hydrogenated in the presence of Adams catalyst (0·1 g.). After the absorpion of 1 mol. the catalyst was removed, the solution basified with aqueous ammonia, and the amorphous precipitate isolated with methylene chloride. *Dihydronor-ψ-cryptopine* (1·8 g.), obtained on evaporation the solvent, did not crystallise and was purified through the picrate which separated as an amorphous precipitate, m. p. 125° (decomp.), from aqueous ethanol. The recovered base was a yellow glass (Found: C, 71·0; H, 6·3. $C_{20}H_{21}NO_4$ requires C, 70·8; H, 6·2%), $\lambda_{max.}$ 292 mμ (log ε 3·72). The amine oxide, obtained by use of perbenzoic acid, was characterised as its *picrate*, yellow needles (from ethanol), m. p. 116—118° (decomp.) (Found: C, 53·2; H, 4·1. $C_{20}H_{21}NO_5,C_6H_3N_3O_7$ requires C, 53·4; H, 4·1%). Rearrangement of the *N*-oxide with potassium chromate followed by methylation afforded no identifiable product.

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