## 461. *Reduction of Quaternary Salts of Isoquinoline Alkaloids by Sodium–Ammonia.*

By K. W. Bentley and A. W. Murray.

Reduction, by sodium–ammonia, of the methiodides of laudanosine, ketolaudanosine, β-hydroxylaudanosine, narcotinediol, and hydrastinediol proceeded with fission of the 1,2- C–N bond of the isoquinoline system; in addition, however, the two diols afforded nitrogen-free materials, suggesting that with these compounds 2,3-N–C bond fission occurs as a competing process.

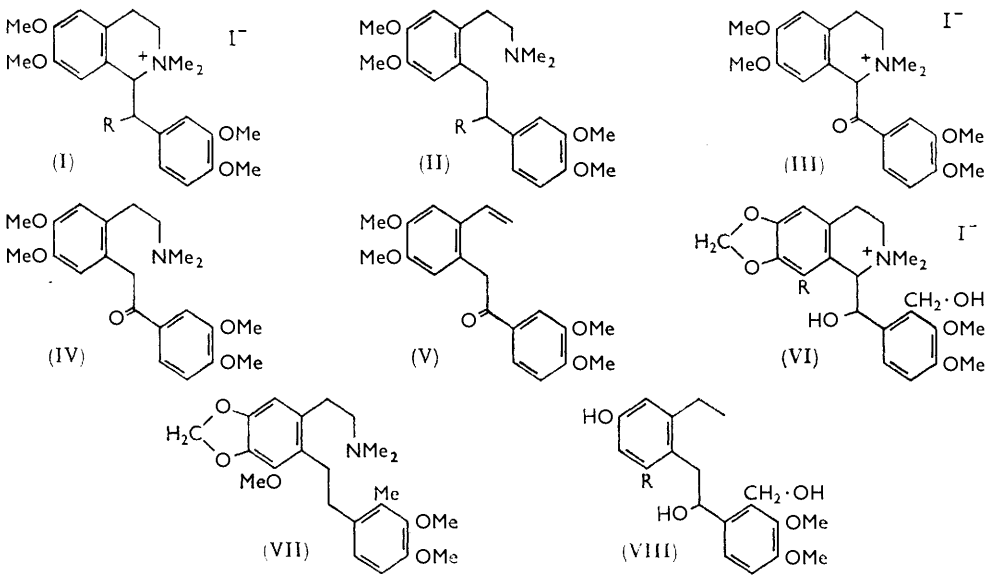
Reduction of alkaloidal quaternary salts by sodium and liquid ammonia has been shown [1,2] to be a convenient method of C–N bond fission, but its use when other reducible systems are present has not been widely examined. Its application to keto- and hydroxy-compounds in the benzyltetrahydroisoquinoline group has now been studied. As expected, laudanosine methiodide (I; R = H) afforded the dihydromethine (II; R = H), identified by subsequent Hofmann degradation to the N-free styrene which was reduced to a dihydro-derivative, identical with the product of reduction of laudanosene, the N-free product of exhaustive methylation of laudanosine.[3] A very small quantity of phenolic material (unidentified) was also obtained during the reduction (cf. the demethylation of laudanosine by lithium and liquid ammonia [4]).

With ketolaudanosine methiodide (III) [5] reduction of the carbonyl group did not occur in the absence of an alcohol, the product being the base (IV), the structure of which was

[1] Clayson, *J.*, 1949, 2016.
[2] Bentley and Wain, *J.*, 1952, 972.
[3] Decker and Galatty, *Ber.*, 1909, **42**, 1172.
[4] Tomita and Kunimoto, *J. Pharm. Soc. Japan*, 1961, **81**, 108.
[5] Bentley and Murray, *J.*, 1963, 2487.

proved by reduction with sodium borohydride to the base (II; R = OH) (also obtained from β-hydroxylaudanosine) and by Hofmann degradation to the styrene (V). No phenolic material was isolated from this reduction, possibly because the reduction product was very sparingly soluble in the reaction medium.

In the absence of an alternative proton source, hydrogenolysis of the benzyl alcoholic group was not observed during the reduction of the methiodide of β-hydroxylaudanosine




(I; R = OH) which afforded the dihydromethine (II; R = OH), identical with the product of reduction of the ketone (IV), and this base was degraded by Hofmann's method to the corresponding styrene. Narcotinediol methiodide (VI; R = OMe), however, afforded a small amount of the dihydromethine base (VII) in which both alcoholic hydroxyl groups had been eliminated by hydrogenolysis; the major product of this reduction was a non-basic phenolic oil separable into two components, $C_{20}H_{26}O_6$ and $C_{19}H_{24}O_5$. The $C_{20}$ component is formulated as (VIII; R = OMe) (compare the fission of the methylenedioxy-group of hydrocotarnine methiodide by sodium and ammonia [1]), and the $C_{19}$ component as (VIII; R = H) obtained by reductive removal of the methoxyl group as well (cf. the reduction of hydrocotarnine to hydrohydrastinine [1]); this $C_{19}$ compound was the sole isolable product of the reduction of hydrastinediol methiodide (VI; R = H).

The production of nitrogen-free compounds during the reductions of the diol methiodides is explicable if fission of the 2,3-N–C bond of the isoquinoline is assumed to take place first, yielding a substituted benzylamine which then suffers hydrogenolytic removal of dimethylamine.

## Experimental

*Reduction of Laudanosine Methiodide.*—Sodium was added in thin slices to a stirred solution of laudanosine methiodide (6·1 g.) in liquid ammonia (250 ml.) until a nearly permanent blue colour developed. The mixture was stirred for a further 5 min. during which the excess of sodium was slowly removed by reaction with the ammonia, then poured continuously into cold water (1 l.); a bulky white precipitate was obtained. This was isolated by ether-extraction, and laudanosine dihydromethine was obtained as a colourless oil (4 g.), giving a yellow picrate as plates (from ethanol), m. p. 157·5—158° (lit.,[6] 153—156°) (Found: C, 55·6; H, 5·7; N, 9·0. Calc. for $C_{28}H_{34}N_4O_{11}$: C, 55·8; H, 5·7; N, 9·3%), and a methiodide (from 90% ethanol),

[6] Battersby and Harper, *J.*, 1962, 3526.

needles, m. p. 204° (lit.,[6] 197°) (Found: C, 53·4; H, 6·5. Calc. for $C_{22}H_{31}NO_4,CH_3I$: C, 53·6; H, 6·6%). Addition of ammonium chloride to the alkaline solution remaining after extraction of this base afforded a small amount of unidentified phenolic material.

*Dihydrolaudanosene* (*3′,4,4′,5-Tetramethoxy-2-vinyldiphenylethane*).—Laudanosine dihydromethine methiodide (1·4 g.) was boiled with 30% aqueous potassium hydroxide until evolution of trimethylamine ceased. The product, b. p. 195—197°/0·5 mm., isolated from the diluted reaction mixture by chloroform-extraction, crystallised as plates, m. p. 73° (lit.,[6] 74°), from ethanol (Found: C, 73·4; H, 7·4. Calc. for $C_{20}H_{24}O_4$: C, 73·2; H, 7·4%). It had $\lambda_{max.}$ 270 (ε 13,800) and 289 mμ (ε 9150), and $\nu_{max.}$ 915 cm.$^{-1}$ (vinyl).

*Tetrahydrolaudanosene* (*2-Ethyl-3′,4,4′,5-tetramethoxydiphenylethane*).—(*a*) Dihydrolaudanosene (0·5 g.), when hydrogenated in glacial acetic acid over platinum oxide, absorbed 1 mol. of hydrogen and gave tetrahydrolaudanosene as almost colourless plates (from aqueous acetic acid), m. p. 78° (lit.,[6,7] 78°) (Found: C, 73·4; H, 8·0 Calc. for $C_{20}H_{26}O_4$: C, 73·4; H, 7·9%).

(*b*) Laudanosene (3′,4,4′,5-tetramethoxy-2-vinylstilbene) [3] on hydrogenation as in (*a*) absorbed 2 mol. of hydrogen and gave tetrahydrolaudanosene, m. p. 78° alone or mixed with material prepared as in (*a*).

*Reduction of Ketolaudanosine Methiodide.*—Reduced as above with sodium and liquid ammonia (200 ml.), ketolaudanosine [5] methiodide (5 g.) afforded dihydroketolaudanosinemethine (IV) (2·3 g.) as an amber-coloured oil, giving a *methiodide*, hexagonal plates (from ethanol), m. p. 230° (Found: C, 52·4; H, 6·2; I, 23·8. $C_{22}H_{29}NO_5,CH_3I$ requires C, 52·2; H, 6·1; I, 24·0%), and a *methoperchlorate*, prisms (from ethanol), m. p. 159° (Found: C, 54·9; H, 6·5. $C_{22}H_{29}NO_5,CH_3ClO_4$ requires C, 55·1; H, 6·4%).

*Dihydroketolaudanosene* (V).—Dihydroketolaudanosinemethine methiodide (0·8 g.) was degraded by boiling 30% sodium hydroxide solution until evolution of trimethylamine ceased. Isolated by chloroform extraction, *dihydroketolaudanosene* had b. p. 117°/0·1 mm. (Found: C, 70·0; H, 6·5. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%), $\lambda_{max.}$ 230 (ε 33,150), 272 (ε 14,450), and 315 mμ (ε 6760), $\nu_{max.}$ 1680 (C=O) and 915 cm.$^{-1}$ (vinyl).

*Dihydro-β-hydroxylaudanosinemethine* (II; R = OH).—(*a*) Dihydroketolaudanosinemethane (1 g.), sodium borohydride (0·3 g.), and methanol (50 ml.) were heated together under reflux for 1 hr., then concentrated to 10 ml. and diluted with water. Isolated by chloroform-extraction, dihydro-β-hydroxylaudanosinemethine was an oil; it gave a *methiodide*, prisms (from ethanol), m. p. 199—200° (Found: C, 52·2; H, 6·3; I, 23·9. $C_{22}H_{31}NO_5,CH_3I$ requires C, 52·0; H, 6·4; I, 23·9%), and a *methoperchlorate*, needles (from ethanol), m. p. 147° (Found: C, 54·9; H, 6·9; $C_{22}H_{31}N_5O,CH_3ClO_4$ requires C, 54·8; H, 6·8%).

(*b*) β-Hydroxylaudanosine methiodide (2 g.) was reduced with sodium and liquid ammonia (200 ml.) in the same way as laudanosine methiodide. The dihydromethine was obtained as an oil [methiodide, m. p. 200°; methoperchlorate, m. p. 147°; both identical with material prepared as in (*a*)].

*Reduction of Narcotinediol Methiodide* (VI; R = OMe).—Narcotinediol methiodide (7 g.) was reduced with sodium and liquid ammonia (500 ml.) as described for the reduction of laudanosine methiodide. The mixture was poured into cold water (500 ml.) and extracted continuously with chloroform for 24 hr. The extract yielded a syrup that crystallised after several days and recrystallised from methanol, giving NN-*dimethyl*-2-(3,4-*dimethoxy*-2-*methylphenethyl*)-4,5-*methylenedioxy*-3-*methoxyphenethylamine* (VII) as colourless needles, m. p. 168° (Found: C, 68·6; H, 8·0; OMe, 23·2. $C_{23}H_{31}NO_5$ requires, C, 68·75; H, 7·8; OMe, 23·2%). Saturated aqueous ammonium chloride was added to the aqueous layer remaining after the chloroform-extraction, a yellow phenolic material being precipitated. This was isolated by chloroform-extraction and crystallised slowly from 50% aqueous ethanol, giving 2-*ethyl*-4-*hydroxy*-α-(2-*hydroxymethyl*-3,4-*dimethoxyphenyl*)-6-*methoxyphenethyl alcohol* (VIII; R = OMe); this was soluble in aqueous sodium hydroxide and precipitated by carbon dioxide; it was obtained as colourless needles, m. p. 122—123° (Found: C, 64·8; 64·9; H, 7·2, 7·4; OMe, 26·1; *C*-Me, 7·2. $C_{20}H_{26}O_6,\frac{1}{2}H_2O$ requires C, 64·7; H, 7·3; OMe, 25·2; *C*-Me, 8·1%).

Dilution of the mother-liquors from this crystallisation with water and extraction of the precipitated oil afforded, finally, 2-*ethyl*-4-*hydroxy*-1-(2-*hydroxymethyl*-3,4-*dimethoxyphenyl*)-*phenethylalcohol* (VIII; R = H), b. p. 120°/0·1 mm., soluble in aqueous sodium hydroxide and reprecipitated by carbon dioxide (Found: C, 68·4; H, 7·0. $C_{19}H_{24}O_5$ requires C, 68·7;

[7] Robinson and Sugasawa, *J.*, 1932, 789.

H, 7·2%). The *tribenzoyl derivative* was prepared in pyridine and crystallised from aqueous ethanol or light petroleum (b. p. 80—90°) as irregular plates, m. p. 42·5° (Found: C, 74·0; H, 5·4. $C_{40}H_{36}O_8$ requires C, 74·4; H, 5·6%).

*Reduction of Hydrastinediol Methiodide* (VI; R = H).—Hydrastinediol methiodide (1·3 g.) was reduced with sodium and liquid ammonia (100 ml.). Chloroform-extraction of the aqueous solution resulting from dilution of the mixture with water afforded no product, but addition of ammonium chloride to the aqueous solution resulted in precipitation of a phenol. This was isolated by chloroform-extraction and was shown after distillation (b. p. 126°/0·11 mm.) to be identical (infrared spectrum) with the dimethoxy-compound (VIII; R = H) obtained from narcotinediol methiodide. The benzoyl compound, m. p. 42·5°, was identical with that reported above.

One of us (A. W. M.) thanks the Carnegie Trust for the Universities of Scotland for financial assistance.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN. [*Received, October 24th*, 1962.]