458. *Ketolaudanosine.*

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Ketolaudanosine (II) has been prepared by reduction of papaveraldine methosulphate with borohydride and by Oppenauer oxidation of β-hydroxylaudanosine, to which it may be reduced by sodium borohydride. Autoxidation of ketolaudanosine methiodide gives the benzil (V). Narcotinediol (VI) is not oxidised under Oppenauer conditions, but gave the cyclic ether (VII), the structure of which was confirmed by degradation to compound (IX; R = $CH_2{\cdot}OH$). Reduction of papaverine methosulphate, papaveraldine, and papaverinol methosulphate by sodium borohydride has also been studied.

In connexion with other work, the previously unknown ketolaudanosine was required. Reduction of papaverine methosulphate * by sodium borohydride in water or alcohol was shown to afford (±)-laudanosine in excellent yield, the base remaining in solution as its methyl sulphate, $BH^+MeSO_4^-$, during the reaction. Papaveraldine (I) was reduced to the related secondary alcohol, papaverinol, by sodium borohydride in 2-ethoxyethanol, and the methosulphates of both of these bases in aqueous solution with sodium borohydride afforded, after neutralisation, β-hydroxylaudanosine, previously prepared by King *et al.*[1] The reduction of the heterocyclic nucleus of papaveraldine methosulphate precedes the reduction of the carbonyl group since reduction of this salt in aqueous solution in the presence of sodium carbonate to precipitate the initially formed base results in a good yield of ketolaudanosine (II), further reduction of which in methanol or acid then affords β-hydroxylaudanosine. The keto-base (II) was subsequently prepared in about 50% yield by Oppenauer oxidation of the easily accessible β-hydroxylaudanosine with potassium t-butoxide and benzophenone.

When ketolaudanosine methiodide was prepared by refluxing the base with methyl iodide and evaporating the mixture, recrystallisation of the residue from ethanol resulted in the formation of a small amount of a sparingly soluble dark red salt, the low carbon analysis of which is only explicable on the assumption that it contains the I_3^- anion. If this assumption is correct the salt is the product of an oxidation and the substance is formulated as the benzil (V), formed by autoxidation of the quaternary salt to the hydroperoxide (III), the O·OH group of which is reduced to hydroxyl by some iodide ion, the iodine thus formed being converted into tri-iodide I_3^-. The quaternary salt (IV) of the

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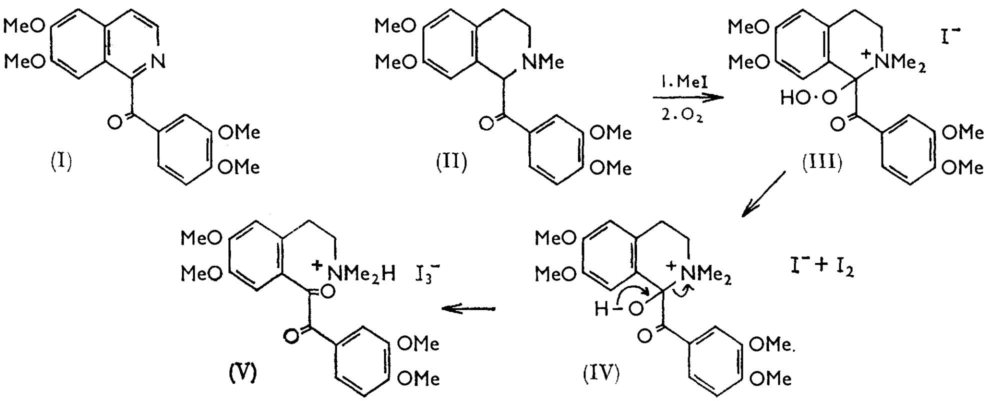
* Addition of " methosulphate " to a name denotes conversion of a tertiary nitrogen atom $\geqslant$N into $\geqslant$NMe$^+$ $MeSO_4^-$.

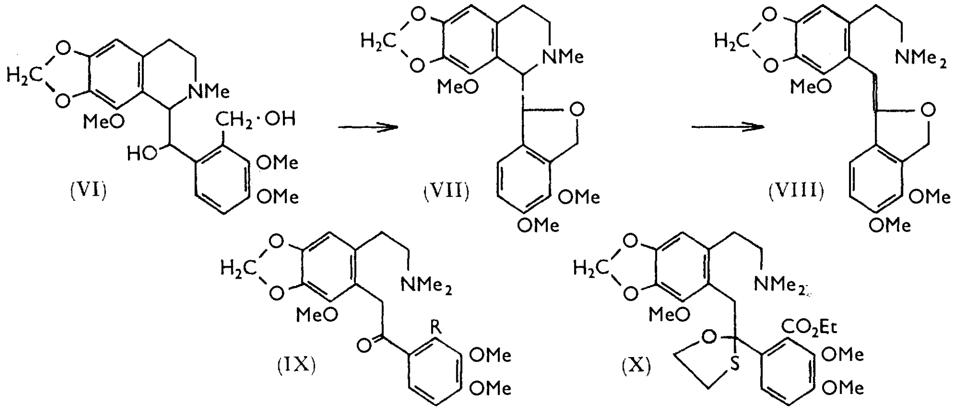
[1] King, L'Ecuyer, and Pyman, *J.*, 1936, 731.

carbinolamine resulting from this process has the correct composition for the red material; but this material is the isomeric keto-amine tri-iodide since its infrared spectrum contains a broad band at 1650 cm.$^{-1}$ assigned to the almost symmetrical benzil system, and the ultraviolet spectrum of the related hydriodide (obtained by reduction of the tri-iodide with sulphurous acid) is very similar to those of 3,4:3′,4′-bismethylenedioxybenzil and 3,3′,4,4′-tetramethoxybenzil.[2] An increase in the yield of this substance in the presence of acid is attributed to the faster oxidation of iodide ions by peroxides in acids. The material obtained in the presence of hydrochloric acid was found not to be identical with that obtained in neutral solution, since the analysis of the material indicated a somewhat higher carbon content, probably owing to the presence of the chloroiodoiodide (I_2Cl^- instead of I_3^-). The cation was the same in both cases, however, since reduction of material from the two sources with sulphurous acid afforded the same hydriodide.



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

Oppenauer oxidation of narcotinediol[3] (VI) failed to afford the desired keto-aldehyde, and gave instead the cyclic ether (VII), the structure of which was deduced from its infrared spectrum (no carbonyl or hydroxyl band), its ultraviolet spectrum (non-styrenoid), and its composition $C_{22}H_{25}NO_6$. Hofmann degradation of this base gave the enol ether (VIII), which was hydrolysed to the keto-alcohol (IX; R = $CH_2{\cdot}OH$) by hydrochloric acid, and this keto-alcohol was reduced to the corresponding diol which was identical with the product of reduction of the ethyl ester (IX; R = CO_2Et) by lithium aluminium hydride. An attempt to prepare the keto-alcohol (IX) by reduction with lithium aluminium hydride, and subsequent hydrolysis, of the monothioketal (X) (prepared from



(VI) (VII) (VIII) (IX) (X)

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[2] Leonard, Rapala, Herzog, and Blout, *J. Amer. Chem. Soc.*, 1949, **71**, 2997.

[3] Mirza and Robinson, *Nature*, 1950, **166**, 271.

the ethyl ester and 2-mercaptoethanol) failed owing to the insolubility of the thio-compound in solvents inert to the hydride.

EXPERIMENTAL

(±)-*Laudanosine*.—Papaverine methosulphate (5 g.) was dissolved in water (25 ml.) and a solution of sodium borohydride (1·0 g.) in water (10 ml.) was added. The mixture was set aside for 30 min. and the base was then precipitated completely with sodium carbonate, collected, washed with water, and recrystallised from aqueous ethanol; it was obtained as colourless needles (3·5 g., 91%), m. p. 115·5° alone or mixed with authentic (±)-laudanosine (Found: C, 70·4; H, 7·6. Calc. for $C_{21}H_{27}NO_4$: C, 70·6; H, 7·6%).

Papaverinol.—Papaveraldine (12 g.) and sodium borohydride (2·5 g.) were heated together in 2-ethoxyethanol (200 ml.) under reflux for 3 hr.; the mixture was then evaporated *in vacuo* and the residue was crystallised from ethanol, papaverinol (10 g.) being obtained as prisms, m. p. 139—139·5° (Found: C, 67·5; H, 6·0. Calc. for $C_{20}H_{21}NO_5$: C, 67·6; H, 5·9%).

Ketolaudanosine.—(*a*) *From papaveraldine*. Papaveraldine (8 g.) and methyl sulphate (4 ml.) were heated together on the water-bath for 30 min. The methosulphate was precipitated from the resulting yellow solution by addition of ether, and crystallised from ethanol as pale yellow prisms (9·2 g.), m. p. 129—130° (Found: C, 55·0; H, 5·5. $C_{22}H_{25}NO_9S$ requires C, 55·1; H, 5·2%). The methosulphate (5 g.) was dissolved in water (50 ml.) containing sodium carbonate (2 g.), and a solution of sodium borohydride (1·5 g.) in water (20 ml.) was added; a sticky orange material was immediately precipitated. On cooling, this β-*ketolaudanosine* hardened to a brittle glass (2·7 g.) which did not crystallise. When passed in ethanol solution through charcoal and precipitated with ether it was obtained as an amorphous orange solid, m. p. 56—58·5° (Found: C, 67·6; H, 6·9; N, 3·6. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·7; N, 3·8%); $\lambda_{max.}$ 230 mμ (ε, 19,500); 282 mμ (ε, 10,300); 321 mμ (ε, 7,080); $\nu_{max.}$ 1675 cm.$^{-1}$ (aromatic C=O).

The *methiodide*, prepared by heating the base with one equivalent of methyl iodide for 30 min. under nitrogen and crystallising the product from ethanol, was obtained as colourless prisms, m. p. 213—214° (Found: C, 51·2; H, 5·7; I, 24·8. $C_{21}H_{25}NO_5,MeI$ requires C, 51·4; H, 5·5; I, 24·5%). The *methoperchlorate*, prepared from the methiodide and sodium perchlorate in aqueous solution, recrystallised from hot water as colourless plates, m. p. 208—210° (decomp.) (Found: C, 54·6; H, 5·6. $C_{21}H_{25}NO_5,MeClO_4$ requires C, 54·4; H, 5·8%). The *oxime* was prepared by refluxing the base in pyridine containing a small amount of ethanol with a large excess of hydroxylamine hydrochloride for 1 hr. The mixture was diluted with water and saturated with carbon dioxide, the precipitated oxime recrystallised from ethanol as pale yellow hexagonal plates, m. p. 63° (Found: C, 65·6; H, 6·9; N, 7·2. $C_{21}H_{26}N_2O_5$ requires C, 65·3; H, 7·3; N, 7·3%).

(*b*) *From* β-*hydroxylaudanosine*. Potassium (0·4 g.) was dissolved in dry t-butyl alcohol (10 ml.) and dry benzene (50 ml.). The alcohol was removed by distillation of its azeotrope with benzene. The apparatus was then flushed with dry nitrogen and β-hydroxylaudanosine (0·73 g.), benzophenone (6 g.), and dry benzene (25 ml.) were added. The mixture was refluxed under nitrogen for 2½ hr., cooled, and acidified with 2N-hydrochloric acid (30 ml.). The benzene layer was removed and extracted with 2N-acid (2 × 20 ml.). The combined acid solutions were washed with ether, then made alkaline with sodium hydroxide, and the liberated base was extracted with chloroform (3 × 50 ml.). Evaporation of the extract afforded ketolaudanosine (0·39 g.) identical with the product obtained as in (*a*) (infrared spectra). The methiodide, prepared under nitrogen, had m. p. 213—214° alone or mixed with material prepared as in (*a*).

Autoxidation of Ketolaudanosine Methiodide.—When ketolaudanosine (1·5 g.) was boiled under reflux with an excess (1·5 ml.) of methyl iodide without exclusion of oxygen for 2 hr. and the excess of halide was evaporated, a dirty orange material (2 g.) remained. On recrystallisation from methanol two substances were obtained, viz., ketolaudanosine methiodide, very pale yellow prisms, m. p. 212° (1·5 g.), soluble in hot methanol, identical with the methiodide previously obtained, and 2-2′-*dimethylaminoethyl*-4,5,4′,5′-*tetramethoxybenzil hydrotri-iodide* (0·3 g.) as dark red, rectangular plates, m. p. 111—115° (decomp.) (Found: C, 34·1; H, 3·5; I, 48·9. $C_{22}H_{27}NO_6,HI_3$ requires C, 33·7; H, 3·6; I, 48·7%). Addition of a small amount of methanolic hydrogen chloride to the solvent before the original crystallisation resulted in an increased yield (0·5 g.) of material obtained as irregular plates, m. p. ~140° (decomp.). This appeared to be the corresponding *hydrochloroiodoiodide* (Found: C, 37·8; H, 4·0; I, 36·5; Cl, 6·0. $C_{22}H_{27}NO_6,HI_2Cl$ requires C, 38·2; H, 4·0; I, 36·7; Cl, 5·1%). This salt (0·36 g.) was dissolved in warm aqueous ethanol (5 ml.), and sulphur dioxide was passed through the solution, which very rapidly changed from dark red to pale yellow. The solution was then boiled to expel sulphur dioxide and evaporated *in vacuo*. The solid residue was recrystallised from ethanol, 2-2′-*dimethylaminoethyl*-4,5,4′,5′-*tetramethoxybenzil hydriodide* being obtained as very pale yellow needles, m. p. 162·5—163·5° (Found: C, 50·0; H, 5·5; I, 23·7. $C_{22}H_{27}NO_6,HI$ requires C, 49·9; H, 5·3; I, 24·0%), $\lambda_{max.}$ 248 (ε 19,800), 287 (ε 11,500), and 237 mμ (ε 8500).

β-*Hydroxylaudanosine*.—(*a*) *From ketolaudanosine.* Ketolaudanosine (1 g.), ethanol (20 ml.), and sodium borohydride (0·2 g.) were heated together on the water-bath under reflux for 1 hr. When the hot solution was diluted with water and cooled slowly, β-hydroxylaudanosine (0·85 g.) was obtained as almost colourless needles, m. p. 98° (effervescence), m. p. after drying in a vacuum-desiccator 108° (lit.,[1] 108—109°). Recrystallised from light petroleum (b. p. 60—80°) it had m. p. 80·5—81° (colourless prisms). The hydrochloride had m. p. 235° (lit.,[1] 235°).

(*b*) *From papaverinol methosulphate.* Papaverinol (6 g.) and methyl sulphate (4 ml.) were heated together on a steam-bath for 30 min. The red mixture was freed from methyl sulphte by shaking it with benzene, and the solid product (7·7 g.) recrystallised from water, giving *papaverinol methosulphate* as almost colourless plates, m. p. 206° (Found: C, 55·2; H, 5·4. $C_{22}H_{27}NO_9S$ requires C, 54·9; H, 5·6%). This salt (1·5 g.) in methanol (50 ml.) with sodium borohydride (0·2 g.) was heated under reflux for 30 min., then more borohydride (0·2 g.) was added and the mixture boiled for a further 30 min. and finally evaporated *in vacuo*. The residue was dissolved in 2N-hydrochloric acid, and the base was precipitated with sodium carbonate, purified through the *picrate*, m. p. 177·5—178·5° (from ethyl methyl ketone) (Found: C, 54·0; H, 5·0; N, 9·4; $C_{21}H_{27}NO_5,C_6H_3N_3O_7$ requires C, 53·8; H, 4·9; N, 9·3%), and recrystallised from aqueous ethanol, giving β-hydroxylaudanosine, m. p. 108°.

(*c*) *From papaveraldine methosulphate.* Papaveraldine methosulphate (5 g.) in methanol (50 ml.) was reduced under reflux with sodium borohydride (1·5 g.) for 1½ hr. The mixture was evaporated, and the residual gum converted into β-hydroxylaudanosine hydrochloride, m. p. 235° (lit.,[1] 235°) (from ethanol), by trituration with ethanolic hydrogen chloride. The base recovered from the salt had m. p. 108° (from aqueous ethanol).

Anhydronarcotinediol (VII).—Narcotinediol (VI) (4·2 g.), dry benzophenone (9·5 g.), freshly prepared, powdered, dry potassium t-butoxide (2·9 g.) and dry benzene (50 ml.) were boiled under reflux under nitrogen for 6 hr., cooled, and extracted with dilute hydrochloric acid. The combined acid extracts were washed free from benzene with ether and then poured into ice and an excess of ammonia solution. The precipitated base was extracted with chloroform and obtained as a syrup on evaporation of the extract; this syrup, on being boiled with ethanol (20 ml.), afforded anhydronarcotinediol (0·9 g.) as colourless needles, m. p. 187—188·5°, $[\alpha]_D^{19}$ +28° (*c* 1·36 in $CHCl_3$) (Found: C, 65·8; H, 6·1; N, 3·4. $C_{22}H_{25}NO_6$ requires C, 66·1; H, 6·3; N, 3·5%). The mother-liquors afforded unchanged narcotinediol (2 g.).

Anhydronarcotinediol methiodide, prepared from the base and methyl iodide under reflux for 3 hr., was obtained as colourless prisms, m. p. 104·5—205·5°, from ethanol (Found: C, 50·8; H, 5·5; I, 23·2. $C_{22}H_{25}NO_6,CH_3I$ requires C, 51·0; H, 5·3; I, 23·5%).

Anhydronarcotinediolmethine (VIII).—Potassium hydroxide (1 g.) was added to anhydronarcotinediol methiodide (0·7 g.) in boiling water (10 ml.), and the solution boiled for 30 min., then concentrated to 3 ml. *in vacuo*. The mixture was then extracted with ether, which afforded 0·62 g. of brown oil. When crystallised from ethanol (charcoal), this gave *anhydronarcotinediolmethine* as plates, m. p. 135° with solidification to needles remelting at 212—213° (Found: C, 66·8; H, 6·3; N, 3·2. $C_{23}H_{27}NO_6$ requires C, 66·8; H, 6·5; N, 3·4%).

NN-*Dimethyl*-2-(2-*hydroxymethyl*-3,4-*dimethoxyphenacyl*)-3-*methoxy*-4,5-*methylenedioxyphenethylamine* (IX; R = $CH_2{\cdot}OH$).—Anhydronarcotinediolmethine (0·55 g.) in 38% hydrochloric acid (4 ml.) was kept for 48 hr. at 20°. The solution was diluted and the base was precipitated with aqueous ammonia and isolated by ether-extraction which afforded a viscous oil, part of which was crystallised from aqueous ethanol, affording the *ketone* (IX; R = $CH_2{\cdot}OH$) as off-white prisms, m. p. 176° (Found: C, 63·8; H, 6·8. $C_{23}H_{29}NO_7$ requires C, 64·0; H, 6·7%).

NN-*Dimethyl*-2-(β-*hydroxy*-2-*hydroxymethyl*-3,4-*dimethoxyphenethyl*)-3-*methoxy*-5-*methylenedioxyphenethylamine*.—(*a*) *From the ketone* (IX; R = $CH_2{\cdot}OH$). The crude ketone (0·4 g.) was reduced with lithium aluminium hydride (0·05 g.) in ether (2 hr.). The mixture was poured into an excess of aqueous sodium hydroxide, the ether was separated, and the aqueous layer submitted to continuous ether-extraction. The combined ether solutions were dried and evaporated, affording the diol as a colourless oil (0·3 g.). The *methiodide* was obtained as prisms, m. p. 192—193°, from aqueous ethanol (Found: C, 48·6; H, 5·9; I, 21·1. $C_{23}H_{31}NO_7,CH_3I,H_2O$ requires C, 48·6; H, 6·1; I, 21·4%). The *methoperchlorate*, prepared from the methiodide and sodium perchlorate, was obtained as needles (from ethanol), m. p. 203—204° (Found: C, 52·6; H, 6·4. $C_{23}H_{31}NO_7,CH_3ClO_4$ requires C, 52·6; H, 6·2%).

(*b*) *From the ethyl ester* (IX; R = CO_2Et). The ester (0·6 g.) was reduced with lithium aluminium hydride (0·05 g.) in ether. The product, isolated as in (*a*), was a colourless oil [methiodide, m. p. 192—193°; methoperchlorate, m. p. 203—204°, each undepressed on admixture with the corresponding salt prepared as in (*a*)].

Condensation of the Ethyl Ester (IX; R = CO_2Et) *with* 2-*Mercaptoethanol*.—The ester (0·65 g.) and 2-mercaptoethanol (1 ml.) in glacial acetic acid (10 ml.) were treated with the boron trifluoride–ether complex (2 ml.). After 24 hr. methanol was added and the precipitate was recrystallised from ethanol, giving the *ethylene monothioketal* (X) as white prisms (0·33 g.), m. p. 188·5—189° (Found: C, 60·4; H, 6·4. $C_{27}H_{35}NO_8S$ requires C, 60·7; H, 6·6%).

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