236. *Some Reactions of 2-(3-Oxindolyl)ethylamines.*

By P. J. Islip and A. C. White.

Catalytic reduction of 3-acetonyloxindole oxime in ethanolic hydrogen chloride over platinum oxide, followed by treatment with ketones, gave the oxazines (V). At high pressure and in the presence of ammonia, however, 3-acetonyloxindole oxime was hydrogenated over Raney nickel to give 3-(*o*-aminophenyl)-5-methyl-2-pyrrolidone (VIII).

Reduction of 3-acetonyl-3-hydroxy-1-methyloxindole oxime with lithium aluminium hydride afforded 1,2,3,3a,8,8a-hexahydro-2,8-dimethylpyrrolo-[2,3-*b*]indol-3a-ol (IX; R = Me).

It has been shown previously [1] that the oxindolyl oximes (I; R^1 = H or Me, R^2 = Alk, R^3 = H) are readily reduced with sodium and n-propanol to the corresponding α-alkyltryptamines (II), which may also be obtained by reduction of the dioxindolyl oximes (I; R^1 = H, R^2 = Alk, R^3 = OH) with lithium aluminium hydride or sodium borohydride–aluminium chloride.[2]

Catalytic reduction of the oxime (I; R^1 = R^3 = H, R^2 = Me) at atmospheric pressure in the presence of ethanolic hydrogen chloride and platinum oxide yielded a gum which afforded a crystalline product after treatment with acetone. It was thought likely that this compound $C_{14}H_{18}N_2O_2$,HCl, which contained three active hydrogen atoms and gave a dibenzoyl derivative, resulted from the internal Mannich reaction [3] between the amine (III; R^1 = H, R^2 = Me), formed in the hydrogenation, and acetone.

Accordingly, 1-methyl-2-(3-oxindolyl)ethylamine (III; R^1 = H, R^2 = Me), which was synthesized from α-methyltryptamine by the method of Witkop and his co-workers,[4] was treated with acetone, but the spiro-oxindole (IV) thus formed (pK_a 8·15) depressed the m. p. of the compound $C_{14}H_{18}N_2O_2$, and the infrared spectra were different.

Structure (V; R^1 = H, R^2 = Me) was assigned to the compound on the basis of the following evidence. Oxindoles are readily oxidized at the 3-position,[4,5] and colloidal platinum is known to effect catalytic oxidation.[6] Tetrahydro-1,3-oxazines are readily prepared by the acid-catalysed reaction between ketones and γ-amino-alcohols; [7] thus, the oxazine (V; R^1 = H, R^2 = Me) was formed by way of the proposed intermediate (III; R^1 = OH, R^2 = Me). The basicity (pK_a 4·65) and the infrared spectrum [8] were consistent with the oxazine structure, whilst the ultraviolet spectrum showed the shift in alkaline solution characteristic of oxindoles. Reduction of the oxime (I; R^1 = R^3 = H, R^2 = Me) in the presence of ethanolic hydrogen chloride at a pressure of 50 lb./in.^{2} was rapid, and uptake ceased when 2·0 mol. of hydrogen had been absorbed; the oxazine (V; R^1 = H, R^2 = Me) was then isolated (58% yield) as before. Reduction at atmospheric pressure gave the product in less than 40% yield. Oximes are generally assumed [9] to be reduced to the corresponding amine by way of the imine and not the hydroxylamine, and this, coupled with the fact that the theoretical amount of hydrogen was taken up and the product was isolated in good yield, enables the hydroxylamine structure (VI) to be ruled out. The hydrochloride yielded the free base, which could be reconverted into the

[1] Pietra and Tacconi, *Farmaco* (*Pavia*), (*a*) 1958, **13**, 893; (*b*) 1959, **14**, 854.
[2] Franklin and White, *J.*, 1963, 1335.
[3] Cf. Harley-Mason and Ingleby, *J.*, 1958, 3639.
[4] Freter, Weissbach, Redfield, Udenfriend, and Witkop, *J. Amer. Chem. Soc.*, 1958, **80**, 983.
[5] See, *e.g.*, Kendall and Osterberg, *J. Amer. Chem. Soc.*, 1927, **49**, 2047; Julian and Pikl, *ibid.*, 1935, **57**, 539; Julian, Printy, and Dailey, *ibid.*, 1956, **78**, 3501; Julian, Dailey, Printy, Cohen, and Hamashige, *ibid.*, 1956, **78**, 3503.
[6] Smidt, Hafner, Jira, Sedlmeier, Sieber, Rüttinger, and Kojer, *Angew. Chem.*, 1959, **71**, 176.
[7] Neuss and Gorman, *Tetrahedron Letters*, 1961, **6**, 206.
[8] Eckstein, Gluziński, Hofman, and Urbański, *J.*, 1961, 489.
[9] Breitner, Roginski, and Rylander, *J.*, 1959, 2918; Gilman, "Organic Chemistry," Vol. I, J. Wiley and Sons, London, 1949, p. 811.

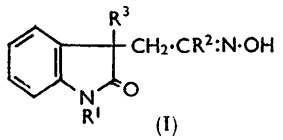
hydrochloride and was formulated as the Schiff's base (VII), the equilibrium between 1,3-tetrahydro-oxazines and Schiff's bases being well known.[10]

Treatment of the hydrogenation residue with ethyl methyl ketone, and hydrogenation of the oxime (I; $R^1 = R^2 = Me$, $R^3 = H$), followed by reaction with acetone, furnished the oxazines (V; $R^1 = H$, $R^2 = Et$) and (V; $R^1 = R^2 = Me$), respectively.

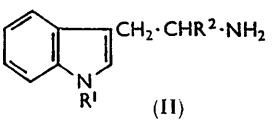
Reduction of the oxime (I; $R^1 = R^3 = H$, $R^2 = Me$), in ethanol saturated with ammonia, over Raney nickel at 60°/80 atm., afforded a product which did not crystallize, but which was distilled to give 3-(*o*-aminophenyl)-5-methyl-2-pyrrolidone (VIII). The hydrochloride had $\nu_{max.}$ (in Nujol) 1682 (C=O) cm.$^{-1}$, an ultraviolet spectrum similar to that of *o*-toluidine, and a pK_a of 3·2, and gave, after diazotization, an intense red precipitate with 2-naphthol. Potentiometric titration of the crude product before distillation indicated that it contained *ca.* 25% of the pyrrolidone (VIII) and 75% of the amine (III; $R^1 = H$, $R^2 = Me$) (pK_a 9·6).

The pyrrolidone alone was also obtained, in lower yields, by continuous ether extraction of a basic solution of the crude hydrogenation mixture, or by passage of the residue over activated alumina, and elution with chloroform. A similar rearrangement of oxindolylethylamine (III; $R^1 = R^2 = H$) was observed by Witkop and his co-workers [4] and by Hendrickson.[11]

Reduction of the oxime (I; $R^1 = R^2 = Me$, $R^3 = OH$) with lithium aluminium hydride in tetrahydrofuran, and isolation of the basic material, gave a compound



(I)



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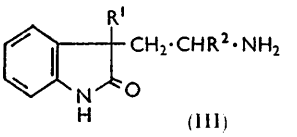

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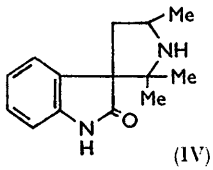

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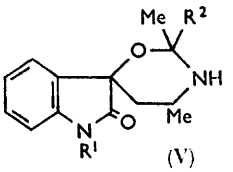

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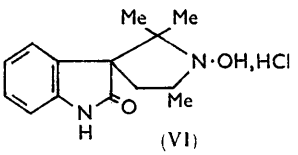
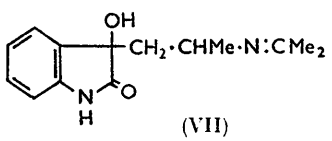
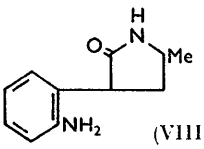


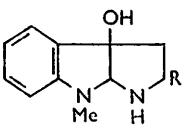
(VI)



(VII)



(VIII)



(IX)

$C_{12}H_{16}N_2O$ which had $\nu_{max.}$ (in CCl_4) 3555 (OH), 3170 (NH), 2785 (NMe) cm.$^{-1}$, and $\lambda_{max.}$ (in 0·1N-NaOH) 251, 309 mμ (ε 9048, 2395). Reduction with zinc and acetic acid yielded 1,α-dimethyltryptamine (II; $R^1 = R^2 = Me$), and on the basis of the above evidence the pyrroloindole structure (IX; R = Me) was assigned to this compound. The scission of the pyrrolidine ring by zinc and acetic acid is analogous to the formation of dihydroeserethole from eserethole.[12]

Finally, the oxime (I; $R^1 = Me$, $R^2 = Pr^i$, $R^3 = OH$) was reduced with lithium aluminium hydride to give the pyrroloindole (IX; $R = Pr^i$), which was converted into the tryptamine (II; $R^1 = Me$, $R^2 = Pr^i$) with zinc and acetic acid.

Experimental

3-Hydroxy-1-methyl-3-(3-methyl-2-oxobutyl)oxindole.—A mixture of *N*-methylisatin (25 g.), isopropyl methyl ketone (45 c.c.), and diethylamine (12 c.c.) was stirred at room temperature

[10] Watanabe and Conlon, *J. Amer. Chem. Soc.*, 1957, **79**, 2825.
[11] Hendrickson, Ph.D. Thesis, Harvard, 1954.
[12] Polonovski, *Bull. Soc. chim. France*, 1918, [iv], **23**, 356.

for 4 hr., and then left overnight.[13] Addition of ether afforded the *ketone* (18·7 g.), needles, m. p. 103—104° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 68·1; H, 6·6; N, 5·5. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9; N, 5·7%).

3-*Hydroxy*-1-*methyl*-3-(3-*methyl*-2-*oxobutyl*)*oxindole Oxime*.—The foregoing ketone (15·5 g.), hydroxylamine hydrochloride (8·4 g.), and anhydrous sodium acetate (19·9 g.), in ethanol (150 c.c.), were refluxed for 2½ hr. After removal of most of the solvent, the residue was poured into water (150 c.c.). The crude product was washed with water, and recrystallized from benzene–methanol, to give platelets of the *oxime* (13·0 g.), m. p. 178—179° (Found: C, 64·2; H, 6·8; N, 10·3. $C_{14}H_{18}N_2O_3$ requires C, 64·1; H, 6·9; N, 10·7%).

The following compounds were prepared similarly: **3-*acetonyl*-3-*hydroxy*-1-*methyloxindole oxime***, from the ketone,[14] m. p. 157—159° (from ethanol) (Found: C, 61·8; H, 6·1; N, 11·7. $C_{12}H_{14}N_2O_3$ requires C, 61·5; H, 6·0; N, 12·0%); **3-*acetonylidene*-1-*methyloxindole oxime***, from the ketone,[14] m. p. 189—190° (from ethanol) (Found: C, 66·9; H, 5·7; N, 12·6. $C_{12}H_{12}N_2O_2$ requires C, 66·6; H, 5·6; N, 13·0%).

3-*Acetonyl*-1-*methyloxindole Oxime*.—3-Acetonylidene-1-methyloxindole oxime (6·5 g.), in ethanol (150 c.c.), was hydrogenated over 5% palladised charcoal (0·5 g.). Hydrogenation was interrupted when 1·1 mol. of hydrogen had been absorbed. Filtration and evaporation gave the *oxime*, rhombs, m. p. 112—113° (from ethanol) (Found: C, 66·3; H, 6·3; N, 13·3. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%).

3′,4′,5′,6′-*Tetrahydro*-2′,2′,4′-*trimethylindoline*-3-*spiro*-6′-2H-1,3-*oxazin*-2-*one Hydrochloride* (V; R^1 = H, R^2 = Me).—3-Acetonyloxindole oxime [1a] (4·1 g.), in ethanol (100 c.c.) containing three equivalents of dry hydrogen chloride, was hydrogenated over platinum oxide (0·25 g.) at atmospheric pressure. Hydrogenation was interrupted when 2·1 mol. of hydrogen had been absorbed, and the filtered solution was evaporated. The residue, an amorphous powder which could not be crystallized, was refluxed with acetone (50 c.c.) and methanol (3 c.c.) until crystallization occurred. The solid was collected, and the process repeated until no further crystals were deposited (2·0 g.). Recrystallization from methanol–acetone afforded the *oxazine hydrochloride*, rhombs, m. p. 227—230° (Found: C, 60·0; H, 7·0; Cl, 12·9; N, 10·0; H^+, 1·0. $C_{14}H_{18}N_2O_2$,HCl requires C, 59·5; H, 6·8; Cl, 12·6; N, 9·9; $3H^+$, 1·1%), pK_a 4·65 (in 50% ethanol). The hydrochloride liberated acetone (identified as the 2,4-dinitrophenylhydrazone) when boiled with 2N-hydrochloric acid, and its infrared spectrum showed no trace of NH or OH absorption. The free *base*, m. p. 202—204 (from ethanol), had pK_a ~3·5, $\nu_{max.}$ (in CCl_4) 3600 (OH), 3452 (free NH), 3295 cm.$^{-1}$ (bonded NH), $\nu_{max.}$ (in tetrahydrofuran) 1639 cm.$^{-1}$ (C=N). The *picrate* separated from methanol as pale yellow needles, m. p. 199—200° (decomp.) (Found: C, 51·0; H, 4·4; N, 14·9. $C_{20}H_{21}N_5O_9$ requires C, 50·5; H, 4·4; N, 14·7%). The *dibenzoyl derivative* (benzoyl chloride and pyridine), rhombs (from dilute ethanol), had m. p. 167—169° (Found: C, 73·7; H, 6·1; N, 6·3. $C_{28}H_{26}N_2O_4$ requires C, 74·0; H, 5·8; N, 6·2%).

In another experiment, the hydrogenation product was treated with ethyl methyl ketone, to give **2′-*ethyl*-3′,4′,5′,6′-*tetrahydro*-2′,4′-*dimethylindoline*-3-*spiro*-6′-2H-1,3-*oxazin*-2-*one hydrochloride*** (V; R^1 = H, R^2 = Et), rhombs, m. p. 208—210° (decomp.) (from methanol–ethyl methyl ketone) (Found: C, 60·4; H, 7·1; Cl, 12·1; N, 9·7. $C_{15}H_{20}N_2O_2$,HCl requires C, 60·7; H, 7·1; Cl, 11·9; N, 9·4%).

3′,4′,5′,6′-*Tetrahydro*-1,2′,2′,4′-*tetramethylindoline*-3-*spiro*-6′-2H-1,3-*oxazin*-2-*one Hydrochloride* (V; R^1 = R^2 = Me).—This was prepared in a similar manner by the reduction of 3-acetonyl-1-methyloxindole oxime (1·65 g.) over platinum oxide, followed by treatment of the hydrogenation residue with acetone. The *oxazine hydrochloride* (0·71 g.) needles (from methanol–acetone), had m. p. 210—211° (decomp.) (Found: C, 60·7; H, 7·3; Cl, 11·7; N, 8·9; H^+, 0·78. $C_{15}H_{20}N_2O_2$,HCl requires C, 60·7; H, 7·1; Cl, 11·9; N, 9·4; $2H^+$, 0·68%).

High-pressure Reduction of **3-*Acetonyloxindole Oxime*.**—The oxime [1a] (4·1 g.) was catalytically reduced, in ethanol (100 c.c.) previously saturated with dry ammonia, at 60°/80 atm. in the presence of Raney nickel (*ca.* 3·0 g.). After 5 hr., the cooled mixture was filtered, and the filtrate evaporated. The residue, which did not crystallize, was distilled (slight decomposition), to give a viscous oil (2·3 g.), b. p. 174—182°/0·05 mm., which was converted into the hydrochloride in the normal manner. **3-(o-*Aminophenyl*)-5-*methyl*-2-*pyrrolidone hydrochloride*** (VIII) separated (in low yield) from methanol–ethyl acetate as plates, m. p. 189—190° (sinters at *ca.* 180° and

[13] Cf. Lindwall and Maclennan, *J. Amer. Chem. Soc.*, 1932, **54**, 4739.
[14] Braude and Lindwall, *J. Amer. Chem. Soc.*, 1933, **55**, 325.

does not clear before decomp. at 227°) (Found: C, 58·4; H, 7·0; N, 12·3. $C_{11}H_{14}N_2O$,HCl requires C, 58·3; H, 6·7; N, 12·4%), pK_a 3·2 (in 50% ethanol). The *picrate* crystallized from methanol as yellow needles, m. p. 166—168° (decomp.) (Found: C, 48·3; H, 4·1; N, 16·5. $C_{17}H_{17}N_5O_8$ requires C, 48·7; H, 4·1; N, 16·7%).

Chromatography on alumina (elution with chloroform), or continuous ether extraction of a basic solution of the crude hydrogenation residue, also afforded the pyrrolidone.

Reduction of 3-Acetonyl-3-hydroxy-1-methyloxindole Oxime with Lithium Aluminium Hydride.—The oxime (I; $R^1 = R^2 = Me$, $R^3 = OH$) (16·0 g.) in tetrahydrofuran (250 c.c.) was added to a stirred suspension of lithium aluminium hydride (10·0 g.) in ether (300 c.c.). The mixture was stirred and refluxed for 10 hr., then treated successively with water (18 c.c.) and 50% sodium hydroxide solution (82 c.c.). The solid was filtered off and washed with hot ethyl acetate. Isolation of the basic material from the filtrate with ethyl acetate furnished *1,2,3,3a,8,8a-hexahydro-2,8-dimethylpyrrolo*[2,3-b]*indol-3a-ol* (IX; R = Me) (4·0 g.) as needles, m. p. 178—180° [from benzene–light petroleum (b. p. 60—80°), then ethyl acetate] (Found: C, 70·3; H, 8·1; N, 13·9. $C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9; N, 13·7%). The *hydrochloride* separated from methanol–ethyl acetate as needles, m. p. 214—215° (decomp.) (Found: C, 59·7; H, 7·1; N, 11·4. $C_{12}H_{16}N_2O$,HCl requires C, 59·9; H, 7·1; N, 11·6%). The *picrate* crystallized from 50% ethanol as yellow needles, m. p. 186° (decomp.) (Found: C, 50·0; H, 4·4; N, 16·0. $C_{18}H_{19}N_5O_8$ requires C, 49·9; H, 4·4; N, 16·2%).

In another experiment (with Dr. S. C. R. Meacock) 3-hydroxy-1-methyl-3-(3-methyl-2-oxobutyl)oxindole oxime (22·4 g.) was reduced with lithium aluminium hydride (16·0 g.) to give *1,2,3,3a,8,8a-hexahydro-2-isopropyl-8-methylpyrrolo*[2,3-b]*indol-3a-ol* (IX; R = Pr^i) (8·0 g.), prisms [from benzene–light petroleum (b. p. 60—80°)], m. p. 165—167° (Found: C, 72·0; H, 8·7; N, 12·0. $C_{14}H_{20}N_2O$ requires C, 72·4; H, 8·7; N, 12·1%). The *hydrochloride*, prisms (from methanol–ethyl acetate), had m. p. 198—199° (Found: C, 62·0; H, 7·9; N, 10·7. $C_{14}H_{20}N_2O$,HCl requires C, 62·5; H, 7·9; N, 10·4%). The *picrate* separated from 50% ethanol as long yellow needles, m. p. 192° (decomp.) (Found: C, 51·8; H, 5·0; N, 15·0. $C_{20}H_{23}N_5O_8$ requires C, 52·1; H, 5·0; N, 15·2%).

1,α-Dimethyltryptamine.—The pyrroloindole (IX; R = Me) (1·0 g.), zinc dust (3·5 g.), acetic acid (10 c.c.), and a few drops of concentrated hydrochloric acid were refluxed for 2 hr. The filtered mixture was poured into water and basified, and the product was isolated with ether. Evaporation furnished a gum, which was converted into the hydrochloride, m. p. 226—228° (from methanol–ethyl acetate), identical in all respects with a sample [15] of 1,α-dimethyltryptamine hydrochloride.

Similarly, the pyrroloindole (IX; R = Pr^i) furnished *α-isopropyl-1-methyltryptamine hydrochloride* as prisms, m. p. 260° (from propan-2-ol–ether) (Found: C, 67·1; H, 8·5; N, 10·6. $C_{14}H_{20}N_2$,HCl requires C, 66·6; H, 8·4; N, 11·1%).

1-Methyl-2-(3-oxindolyl)ethylamine (III; $R^1 = H$, $R^2 = Me$).—The *amine hydrochloride*, prepared [4] from α-methyltryptamine,[15] formed prisms, m. p. 200—204° (from propan-2-ol) (Found: C, 57·4; H, 6·7; N, 11·9. $C_{11}H_{14}N_2O$,HCl,0·25H_2O requires C, 57·2; H, 6·6; N, 12·1%), pK_a 9·6 (in 50% ethanol).

2′,2′,5′-Trimethylindoline-3-spiro-3′-pyrrolidin-2-one Hydrochloride (IV.—The foregoing oxindole (4·0 g.) was dissolved in warm methanol–acetone; on cooling, needles of the *product* crystallized, m. p. 249—252° (decomp.) depressed to 214—216° (decomp.) on admixture with the oxazine (V; $R^1 = Me$, $R^2 = H$) (Found: C, 57·5; H, 7·9; Cl, 12·5; N, 9·2. $C_{14}H_{18}N_2O$,HCl,1·5H_2O requires C, 57·2; H, 7·6; Cl, 12·1; N, 9·5%), pK_a 8·15 (in 50% ethanol). The free *base*, isolated in the normal manner, formed prisms, m. p. 172—174° (from ethyl acetate) (Found: C, 73·0; H, 8·1; N, 11·8. $C_{14}H_{18}N_2O$ requires C, 73·0; H, 7·9; N, 12·2%). The *picrate* crystallized from ethanol as yellow needles, m. p. 231—233° (decomp.) (Found: C, 52·4; H, 4·7; N, 14·9. $C_{20}H_{21}N_5O_8$ requires C, 52·3; H, 4·6; N, 15·2%).

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Parke, Davis and Company, Staines Road,
Hounslow, Middlesex. [*Received, April 3rd,* 1963.]

[15] Heinzelman, Anthony, Lyttle, and Szmuszkovicz, *J. Org. Chem.*, 1960, **25**, 1548.