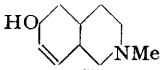
67. *Decahydroisoquinolines and Related Compounds. Part I. Some 6-Oxygenated Derivatives and an Example of Abnormal Ultraviolet Absorption.*

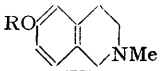
By Alan Marchant and A. R. Pinder.

The synthesis of some reduced 6-oxygenated *iso*quinolines is described. The constitution of the product obtained by the reduction, with sodium and liquid ammonia, and hydrolysis of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline has been proved by synthesis. This product, 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI), shows maximal ultraviolet absorption at an abnormally short wavelength.

The accepted structure of morphine,[1] confirmed by synthesis,[2] contains 1 : 2 : 3 : 4 : 5 : 6 : 9 : 10-octahydro-6-hydroxy-2-methyl*iso*quinoline (I) as one unit.[3] Since little is known of the chemistry of oxygenated octa- and deca-hydro*iso*quinolines, it seemed of interest to investigate the synthesis of such compounds, which may have interesting pharmacological properties.



(I)



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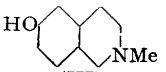


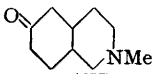
(III)

Only two *Bz*-hydroxydecahydro*iso*quinolines are known. Woodward and Doering [4] prepared decahydro-7-hydroxy-8-methyl*iso*quinoline and 2-acetyldecahydro-8-methyl-7-oxo*iso*quinoline, as intermediates in the synthesis of quinine, and Mannich and Hieronimus,[5] and Boekelheide and Schilling,[6] synthesised decahydro*iso*quinolines with angular hydroxyl substituents.

[1] Gulland and Robinson, *Mem. Manchester Lit. Phil. Soc.*, 1925, **69**, 79.
[2] Gates and Tschudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1109.
[3] Cf. Boekelheide, *ibid.*, 1947, **69**, 790.
[4] Woodward and Doering, *ibid.*, 1944, **66**, 849; 1945, **67**, 860.
[5] Mannich and Hieronimus, *Ber.*, 1942, **75**, 49.
[6] Boekelheide and Schilling, *J. Amer. Chem. Soc.*, 1950, **72**, 712; see also Grewe, Hamann, Jacobsen Nolte, and Riecke, *Annalen*, 1953, **581**, 85.

A convenient approach to 6-oxygenated reduced *iso*quinolines was from 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me), which was synthesised from *m*-hydroxybenzaldehyde (see p. 329). *O*-Demethylation of this base [7] afforded 1 : 2 : 3 : 4-tetrahydro-6-hydroxy-2-methyl*iso*quinoline (II; R = H), which on hydrogenation in presence of platinum oxide gave decahydro-2-methyl*iso*quinoline, in harmony with Woodward and Doering's observation [4] that 2-acetyl-1 : 2 : 3 : 4-tetrahydro-7-hydroxy-8-methyl*iso*quinoline gave much 2-acetyl-8-methyldecahydro*iso*quinoline under similar conditions.

Use of Raney nickel at high temperature and pressure, however, afforded smoothly an excellent yield of decahydro-6-hydroxy-2-methyl*iso*quinoline (III), without hydrogenolysis, and this on oxidation with chromic acid furnished decahydro-2-methyl-6-oxo*iso*quinoline (IV). Unsuccessful attempts were made to separate the crystalline picrate of this keto-base into *cis*- and *trans*-forms. It seems likely, therefore, that the ketone is stereochemically homogeneous; it is probably the *trans*-form, by analogy with Witkop's observations [8] that the reduction of 2-acetyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline with Raney nickel catalyst at high temperature and pressure gave only *trans*-2-ethyldecahydro*iso*-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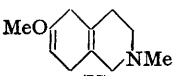
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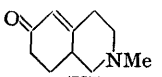
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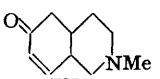
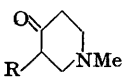

(VII)

quinoline. The infrared absorption of the ketone (IV) showed a carbonyl band at 5·85 μ, characteristic of a saturated ketone, with no band at 6 μ characteristic of a conjugated carbonyl group. It is evident, therefore, that there is in this amino-ketone no interaction between the carbonyl group and the nitrogen atom, resulting in transannular amide-type neutralisation, such as is shown by cryptopine and similar keto-bases containing a many-membered heterocyclic ring.[9] Molecular models of the ketone show that the carbonyl and the methylimino-group are widely separated, so that interaction would be unlikely.

Reduction of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me) with sodium and methanol in liquid ammonia gave a hexahydro*iso*quinoline, presumably (V), according to rules postulated by Birch [10] governing the mode of addition of hydrogen to anisole and its derivatives in such reductions. The product was not isolated; it gave on hydrolysis an unsaturated ketonic base, $\lambda_{max.}$ 227·5 mμ (ε 10,000). The expected structure for the base is 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI) (calc. $\lambda_{max.}$ 244 mμ), but the low value of $\lambda_{max.}$ agrees more satisfactorily with the structure (VII) (calc. $\lambda_{max.}$ 227 mμ), the calculated values being based on Woodward's rules [11] concerning the ultraviolet absorption of αβ-unsaturated carbonyl systems. Proof of structure (VI) was provided by unambiguous synthesis. Preliminary experiments showed that 3-cyano-1-methyl-4-piperidone (VIII; R = CN) and 3-methoxycarbonyl-1-methyl-4-piperidone (VIII; R = CO_2Me) condensed with 1 : 3-dichlorobut-2-ene [12] to give the chloro-ketones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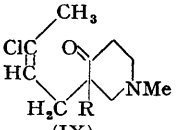
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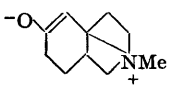
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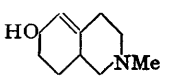
(XI)

(IX; R = CN) and (IX; R = CO_2Me) respectively, but these compounds could not be cyclised with sulphuric acid to *iso*quinolines. However, the ester (VIII; R = CO_2Me) with

[7] Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1769; Davies, Haworth, Jones, and Lamberton, *J.*, 1947, 191.
[8] Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559.
[9] Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944; Leonard and co-workers, *J. Amer. Chem. Soc.*, 1954, **76**, 630, 3463, 5708.
[10] Birch, *J.*, 1944, 430.
[11] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[12] Cf. Wichterle and co-workers, *Coll. Czech. Chem. Comm.*, 1947, **12**, 101, 129; 1948, **13**, 300.

4-diethylaminobutan-2-one methiodide (Robinson–Mannich reaction [13]) gave an intermediate product which on prolonged hydrolysis yielded 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI), $\lambda_{max.}$ 227·5 mμ, identical with the previous product.

The compound (VI) was synthesised simultaneously by Georgian [14] by a closely similar method. We are grateful to Professor Georgian for advance information about his investigations in this field.

It is evident, therefore, that the unsaturated keto-base (VI) shows ultraviolet absorption at an unexpectedly short wavelength. Other examples of this abnormal behaviour are at present under investigation, but it may be suggested here that the nitrogen atom, although not directly attached to the chromophore, raises the energy associated with the electronic disturbances therein, so that maximum ultraviolet absorption occurs at a shorter wavelength. A dipolar structure such as (X) may make an important contribution to the stable state of the molecule.

The methiodide of the base (VI) also shows this abnormality ($\lambda_{max.}$ 222 mμ; ε 27,400). Here the effect is enhanced, presumably by the positive charge carried by the nitrogen atom.

Catalytic hydrogenation of the base (VI) gave the saturated ketone (IV) or the alcohol (III), according to the conditions, and Meerwein–Ponndorf reduction afforded the unsaturated alcohol (XI).

We are indebted to Dr. J. Raventós, of Imperial Chemical Industries Limited (Pharmaceuticals), for a pharmacological test on decahydro-6-hydroxy-2-methyl*iso*quinoline (III). By the method of Davies, Raventós, and Walpole [15] it was found that the compound, injected intravenously into rats, was ineffective at 20 mg./kg., but at 100 mg./kg. gave an increase in the reaction time to painful stimulus similar to that obtained with 3 mg./kg. of morphine.

Experimental

Most of the analyses are by Mr. F. C. Hall. Ultraviolet absorption measurements are in MeOH solution.

m-*Methoxyphenethylamine*.—*m*-Methoxybenzaldehyde, obtained by methylation of *m*-hydroxybenzaldehyde,[16] was condensed with nitromethane to give *m*-methoxy-ω-nitrostyrene.[17] The crystalline nitrostyrene (17 g.) in dry ether (800 c.c.) was added dropwise to a suspension of lithium aluminium hydride (12 g.) in dry ether (400 c.c.) during 1 hr., with constant shaking. After a further 2 hr. " Celite 545 " (3 g.) was added, followed by water (75 c.c.), cautiously, with shaking and ice-cooling. The ethereal solution was decanted, dried (KOH), and evaporated. The residual *m*-methoxyphenethylamine distilled at 140°/11 mm. (11·5 g.) [18] (Helfer [19] gives b. p. 122—123°/7 mm.).

1 : 2 : 3 : 4-*Tetrahydro*-6-*hydroxy*-2-*methyl*iso*quinoline* (II; R = H).—Application of the Pictet–Spengler synthesis to the foregoing base gave 1 : 2 : 3 : 4-tetrahydro-6-methoxy*iso*quinoline,[7,19] which on methylation with formaldehyde and formic acid [7,19] afforded 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me). The latter base (2·0 g.) was heated at 180° with concentrated hydrochloric acid (18 c.c.) for 3 hr.[7] The clear solution was evaporated to dryness *in vacuo*, the crystalline residue dissolved in water (15 c.c.), and the solution brought to pH 10—10·5 with solid potassium carbonate. The precipitated phenolic base was collected and washed with a little cold water. 1 : 2 : 3 : 4-*Tetrahydro*-6-*hydroxy*-2-*methyl*iso*quinoline* separated from water in diamond-shaped plates, m. p. 182—183° (1·7 g.) (Found: C, 73·8; H, 8·05. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%). The hydrochloride crystallised from ether–ethanol in pale cream-coloured nodules, m. p. 234—235° (decomp.) (Buck [7] gives m. p. 236°).

Decahydro-6-*hydroxy*-2-*methyl*iso*quinoline* (III).—The foregoing base (5 g.) in ethanol (50 c.c.) was hydrogenated at 160°/150 atm. in the presence of " W7 " Raney nickel [20] and a trace of

[13] Organic Reactions, Vol. I, p. 321.
[14] Georgian, *Chem. and Ind.*, 1954, 930.
[15] Davies, Raventós, and Walpole, *Brit. J. Pharmacol.*, 1946, **1**, 255.
[16] *Org. Synth.*, 1949, **29**, 64.
[17] Gulland and Virden, *J.*, 1929, 1791.
[18] Cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948 **70**, 3738; Erne and Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912.
[19] Helfer, *ibid.*, 1924, **7**, 945.
[20] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695; *Org. Synth.*, Coll. Vol. III, p. 181.

sodium hydroxide for 12 hr. The filtered solution gave on evaporation *decahydro-6-hydroxy-2-methylisoquinoline*, b. p. 150—160° (bath)/1 mm. (4·5 g.) (Found : C, 70·8; H, 11·25; N, 8·0. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·2; N, 8·3%), readily soluble in water and the usual organic solvents. Infrared absorption : strong hydroxyl band at 3·0 μ; no aromatic ring bands in the 6—7 μ region. The *methiodide* separated from ethanol in needles, m. p. 273° (Found : C, 42·2; H, 7·1. $C_{11}H_{22}ONI$ requires C, 42·2; H, 7·1%). The *α-naphthylurethane* crystallised from ethanol in plates, m. p. 74° (Found : C, 74·6; H, 7·75. $C_{21}H_{26}O_2N_2$ requires C, 74·6; H, 7·7%). The *picrate* separated from methanol in needles, m. p. 178° (Found : C, 48·4; H, 5·6. $C_{16}H_{22}O_8N_4$ requires C, 48·2; H, 5·5%).

Decahydro-2-methyl-6-oxoisoquinoline (IV).—The above hydroxy-base (4 g.) in acetic acid (12 c.c.) was treated with chromic acid (1·7 g.) in water (5 c.c.). After 6 hr. at 60—70° the solution was cooled, diluted, basified with potassium hydroxide, and extracted with ether. The extract was dried (K_2CO_3) and evaporated. The residual *decahydro-2-methyl-6-oxoisoquinoline* distilled at 120—130° (bath)/0·5 mm. (3·2 g.) (Found : C, 71·7; H, 10·2. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%). Infrared absorption : saturated carbonyl band at 5·85 μ; no hydroxyl band in 3 μ region. The *methiodide* crystallised from ethanol in needles, m. p. 243° (Found : C, 42·9; H, 6·6. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%). The *picrate* separated from methanol in needles, m. p. 142° (Found : C, 48·5; H, 5·0. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1%), but in a few days was transformed into a modification of m. p. 218° (Found : C, 48·5; H, 5·3%), which on crystallisation from methanol reverted to the form, m. p. 142°.

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-2-methyl-6-oxoisoquinoline* (VI).—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinoline (10 g.) in methanol (50 c.c.) was added to liquid ammonia (150 c.c.), followed by sodium (12 g.), in small portions during 30 min., with vigorous stirring, the blue colour being allowed to disappear between each addition. Ether was then added cautiously, followed by water, and the organic layer was separated. The aqueous layer was extracted several times with ether, and the combined extracts were dried and evaporated. The residual oil was boiled under reflux with 10% sulphuric acid (50 c.c.) for 1 hr. under nitrogen. The cooled solution was basified with potassium hydroxide and the product isolated with ether. Evaporation gave 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro-2-methyl-6-oxoisoquinoline*, b. p. 150—160° (bath)/12 mm. (5·0 g.) (Found : C, 72·6; H, 9·2. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%), as a very pale yellow oil, soluble in water and the usual solvents. Infrared absorption : αβ-unsaturated carbonyl band at 6·0 μ; no aromatic ring bands in the 6—7 μ region. The *methiodide* separated from ethanol in needles, m. p. 208° (Found : C, 43·0; H, 5·8. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%) (Georgian [14] gives m. p. 209—210°, $\lambda_{max.}$ 221 mμ). The *semicarbazone* crystallised from chloroform in plates, m. p. 198° (decomp.) (Found : C, 59·5; H, 8·0. $C_{11}H_{18}ON_4$ requires C, 59·5; H, 8·1%).

Catalytic Hydrogenation of 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-2-methyl-6-oxoisoquinoline*.—(*a*) The base (0·5 g.) in ethanol (10 c.c.) was shaken in hydrogen at room temperature and pressure with Adams platinum oxide. After 1½ hr. absorption had ceased (2 mols.). Evaporation of the filtered solution gave decahydro-6-hydroxy-2-methyl*iso*quinoline, b. p. 140—150° (bath)/0·5 mm. (0·5 g.), identical with the compound described previously. The methiodide had m. p. and mixed m. p. 273°.

(*b*) In a similar hydrogenation of the base (0·5 g.) in ethanol (10 c.c.) with 5% palladium–charcoal,[21] 1 mol. of hydrogen was absorbed in 3 hr. The product, worked up as before, was decahydro-2-methyl-6-oxo*iso*quinoline, b. p. 120—130° (bath)/0·5 mm., identical with the previous material. The methiodide had m. p. and mixed m. p. 243°.

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-6-hydroxy-2-methylisoquinoline* (XI).—The unsaturated keto-base (1·0 g.) was heated on the water-bath with aluminium *iso*propoxide (0·5 g.) and dry propan-2-ol (25 c.c.) so that slow distillation occurred, until no more acetone was detected in the distillate (45 min.). Propan-2-ol (10 c.c.) was added and the mixture refluxed on the water-bath for 30 min. After evaporation of the solvent 20% aqueous potassium hydroxide (20 c.c.) was added and the product isolated with ether. Evaporation of the dried extract gave 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro-6-hydroxy-2-methylisoquinoline*, b. p. 120—130° (bath)/0·5 mm. (0·9 g.) (Found : C, 72·0; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·3%). Infrared absorption : hydroxyl band at 3·0 μ; no carbonyl band in 6 μ region. On oxidation with manganese dioxide in benzene [22] it was transformed into the original unsaturated keto-base. The *picrate* separated from methanol in needles, m. p. 163° (Found : C, 48·5; H, 5·0. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1%).

[21] *Org. Synth.*, 1946, **26**, 78.
[22] Cf. Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62.

3-(3-*Chlorobut*-2-*enyl*)-3-*cyano*-1-*methyl*-4-*piperidone* (IX; R = CN).—To an ice-cold solution of sodium (1·8 g.) in absolute ethanol (60 c.c.) was added 3-cyano-1-methyl-4-piperidone hydrochloride [23] (6·6 g.) in absolute ethanol (300 c.c.). 1 : 3-Dichlorobut-2-ene (5 g.) in absolute ethanol (10 c.c.) was added dropwise with shaking. The mixture was refluxed for 3 hr., then cooled, diluted, and extracted with chloroform. The dried extract was evaporated, leaving 3-(3-*chlorobut*-2-*enyl*)-3-*cyano*-1-*methyl*-4-*piperidone*, b. p. 85—90° (bath)/0·5 mm. (2·6 g.) (Found: C, 58·2; H, 6·6; Cl, 15·4. $C_{11}H_{15}ON_2Cl$ requires C, 58·3; H, 6·6; Cl, 15·7%).

3-(3-*Chlorobut*-2-*enyl*)-3-*methoxycarbonyl*-1-*methyl*-4-*piperidone* (IX; R = CO_2Me).—A cognate experiment with 3-methoxycarbonyl-1-methyl-4-piperidone [24] (6 g.) in absolute ethanol (10 c.c.), sodium (1 g.) in absolute ethanol (50 c.c.), and 1 : 3-dichlorobut-2-ene (4·4 g.) in absolute ethanol (10 c.c.) for 5 hr. gave the *piperidone ester*, b. p. 120—125° (bath)/0·5 mm. (3·0 g.) (Found: C, 55·5; H, 7·0; N, 5·3. $C_{12}H_{18}O_3NCl$ requires C, 55·5; H, 6·9; N, 5·4%).

Robinson–Mannich Reaction with 3-*Methoxycarbonyl*-1-*methyl*-4-*piperidone*.—4-Diethylaminobutan-2-one [25] (7·15 g.) was converted into its methiodide as described by Cornforth and Robinson.[26] 3-Methoxycarbonyl-1-methyl-4-piperidone (8·55 g.) in dry benzene (40 c.c.) was added and the apparatus filled with nitrogen. A solution of potassium metal (3·25 g.) in absolute ethanol (50 c.c.) was added with swirling and ice-cooling during 5 min., swirling being continued for a further 30 min. The mixture was kept at 0° for 1 hr., then refluxed on the water-bath for 30 min. Excess of 2N-sulphuric acid was added, followed by water, the organic layer was separated, and the aqueous layer basified and extracted several times with ether. The combined extracts were dried and evaporated, and the residual oil (5·5 g.) was boiled for 6 hr. with 6N-hydrochloric acid (70 c.c.). The cooled solution was basified with potassium hydroxide; the product, isolated with ether, distilled at 150—160° (bath)/12 mm. (2·1 g.) (Found: C, 72·6; H, 8·9. Calc. for $C_{10}H_{15}ON$: C, 72·7; H, 9·1%). Ultraviolet absorption: max. at 227·5 mμ (ε 9500). The methiodide (Found: C, 42·8; H, 6·0. Calc. for $C_{11}H_{18}ONI$: C, 43·0; H, 5·9%) had m. p. 208—209° (decomp.), and the semicarbazone (Found: C, 59·6; H, 8·0. Calc. for $C_{11}H_{18}ON_4$: C, 59·5; H, 8·1%) had m. p. 198° (decomp.), both alone and mixed with the corresponding derivatives obtained from the reduction and hydrolysis of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline.

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[23] Cook and Reed, *J.*, 1945, 399.
[24] Cf. Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233; McElvain and Rorig, *ibid.*, 1948, **70**, 1820.
[25] Wilds and Shunk, *ibid.*, 1943, **65**, 469.
[26] Cornforth and Robinson, *J.*, 1949, 1855.