1,3,4,5-Tetrahydrobenz[*cd*]indoles and Related Compounds. Part V.[1] Some Reactions of 1,2,4,5-Tetrahydropyrrolo[3,2,1-*ij*]quinolin-6-one

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Bromination, dehydrogenation, the Mannich reaction, the Cope–Knoevenagel reaction, and the Schmidt reaction of 1,2,4,5-tetrahydropyrrolo[3,2,1-*ij*]quinolin-6-one are described. The oxime derived from this ketone forms a *p*-tolylsulphonyl derivative, which under Neber reaction conditions (sodium ethoxide in benzene) yields the expected keto-amine hydrochloride. The latter has been converted into the corresponding keto-urethane, which has been subjected to dehydrogenation, hydrogenolysis, and reduction with both potassium borohydride and lithium aluminium hydride.

In Parts II[2] and III[3] the synthesis of a number of 1,3,4,5-tetrahydrobenz[*cd*]indoles for biological testing was reported. We now describe similar work on the isostere, 1,2,4,5-tetrahydropyrrolo[3,2,1-*ij*]quinolin-6-one[4] (1).

Treatment of the ketone (1) with tri-*N*-methylanilinium tribromide results in bromination in the aromatic ring, presumably at C-8, owing to the influence of the nitrogen atom. That aromatic substitution takes place is evident from the i.r. spectra of solutions of the compounds in cyclohexane; the ketone (1) absorbs at 746, 771, 778, and 786 cm^{-1}, whereas the bromo-ketone (2) absorbs weakly at 752 and 792 cm^{-1}, indicating a decreased contribution from the aromatic hydrogen out-of-plane deformation vibrations.

Dehydrogenation of the ketone (1) with activated manganese dioxide[5] in refluxing chloroform gave not a tricyclic indole derivative but the αβ-unsaturated ketone

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[1] Part IV, R. E. Bowman, D. D. Evans, J. Guyett, J. Weale, and A. C. White, *J.C.S. Perkin I*, 1973, 760.

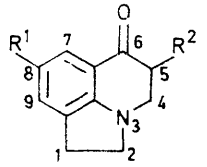
[2] Part II, R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, D. J. Weyell, and A. C. White, *J.C.S. Perkin I*, 1972, 1926.

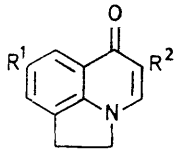
[3] Part III, R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, and D. J. Weyell, *J.C.S. Perkin I*, 1973, 438.

[4] H. Rapoport and J. R. Tretter, *J. Org. Chem.*, 1958, **23**, 248.

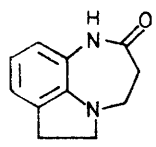
[5] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

(6), which has u.v. spectra similar to those reported [4] for the αβ-unsaturated ketone (7). Similarly the bromo-ketone (2) yielded the corresponding αβ-unsaturated bromo-ketone (8).

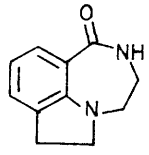




(1) $R^1 = R^2 = H$
(2) $R^1 = Br, R^2 = H$
(3) $R^1 = H, R^2 = CH_2NMe_2, HCl$
(4) $R^1 = H, R^2 = NH_2, HCl$
(5) $R^1 = H, R^2 = NH{\cdot}CO_2Me$
(6) $R^1 = R^2 = H$
(7) $R^1 = H, R^2 = CH_2Ph$
(8) $R^1 = Br, R^2 = H$
(9) $R^1 = H, R^2 = NH{\cdot}CO_2Me$



(10)



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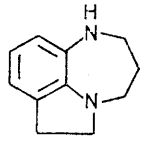

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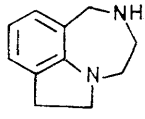

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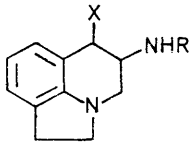
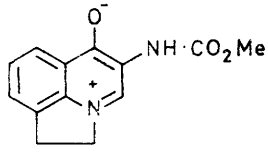


(14) X = H, R = CO_2Me
(15) X = OH, R = CO_2Me
(16) X = OH, R = Me



(17)

The ketone (1), under Mannich reaction conditions, gave the dimethylaminomethyl derivative (3) and with malononitrile in the Cope–Knoevenagel reaction [6] yielded the expected αβ-unsaturated dinitrile.

The Schmidt reaction [7] with the ketone (1) is reported [8] to yield a product for which no conclusive evidence of structure was available. In our hands the Schmidt reaction gave an intractable mixture of two diazepinones, probably (10) and (11). Evidence of such a mixture was obtained after reduction of the mixture with lithium aluminium hydride; two basic products were obtained. Potentiometric titration showed one to be a weak base, consistent with structure (12), and the other was a strong base (13). Use was made of this difference in basicity to separate the strong base as its tartrate salt.

The oxime [8] derived from the ketone (1) has now been converted to its *p*-tolylsulphonyl derivative, which in the Neber reaction [9] gave the keto-amine hydrochloride (4). The latter was converted by standard methods into its formamido-derivative and the keto-urethane (5). Hydrogenolysis of (5) gave the urethane (14), and reduction with potassium borohydride yielded the hydroxy-urethane (15). Reduction of the keto-urethane (5) with lithium aluminium hydride or sodium dihydridobis-(2-methoxyethoxy)aluminate gave the methylamino-alcohol (16). Dehydrogenation of the keto-urethane (5) with activated manganese dioxide in methylene chloride at room temperature results in the introduction of unsaturation into the six-membered heterocyclic ring. This is evident from the n.m.r. spectrum of the product, which shows the presence of two pairs of protons identified as those at C-1 and C-2. However, the remarkable similarity of its u.v. spectra (solvent ethanol) to those of 3-acetamido-4-hydroxyquinoline [10] suggests that this compound is better represented by the zwitterionic structure (17) rather than that of the unsaturated ketone (9).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. U.v. and i.r. spectra were determined for ethanolic solutions and Nujol mulls, respectively, unless otherwise specified. Potentiometric titrations were carried out in aqueous ethanol (1 : 1) and [$^2H_6$]dimethyl sulphoxide was used as solvent for n.m.r. spectra (Varian A60 spectrometer). All compounds gave satisfactory analytical figures. The data are tabulated in Supplementary Publication No. SUP 20891 (4 pp.).*

8-Bromo-1,2,4,5-tetrahydropyrrolo[3,2,1-ij]*quinolin-6-one* (2).—A solution of tri-*N*-methylanilinium tribromide (18·8 g) in tetrahydrofuran (80 ml) was added dropwise to a stirred solution of the ketone (1) (8·66 g) in tetrahydrofuran (100 ml) and triethylamine (18 ml) at 0°, and the mixture was set aside overnight at room temperature. Ether and saturated sodium hydrogen carbonate solution were added and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue (12·1 g) was digested with hot ether, and the solution was decanted from a brown gum. Concentration and cooling of the solution gave the *bromo-ketone* (2) (2·3 g), m.p. 103·5—104·5°.

1,2-Dihydropyrrolo[3,2,1-ij]*quinolin-6-one* (6).—A stirred mixture of the ketone (1) (10·0 g) and activated manganese dioxide (50 g) in chloroform (200 ml) was refluxed overnight under a Dean–Stark head. The manganese dioxide was filtered off, and the filtrate was evaporated to dryness *in vacuo* to give a solid (9·76 g), m.p. 135—165°. Two recrystallisations from benzene gave the *ketone* (6), m.p. 184—186·5°.

Slmilarly obtained was *8-bromo-1,2-dihydropyrrolo*[3,2,1-ij]*quinolin-6-one* (8), m.p. 200—203° (from ethanol).

5-(Dimethylaminomethyl)-1,2,4,5-tetrahydropyrrolo[3,2,1-ij]*-quinolin-6-one Hydrochloride* (3).—A stirred mixture of the ketone (1) (4·16 g), dimethylamine hydrochloride (2·93 g), paraformaldehyde (2·16 g), and concentrated hydrochloric acid (0·4 ml) in 96% ethanol (40 ml) was

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1972, Index Issue. Items less than 10 pp. are supplied as full size copies.

[6] G. Jones, *Org. Reactions*, 1967, **15**, 204.
[7] H. Wolff, *Org. Reactions*, 1946, **3**, 307; D. Evans and I. M. Lockhart, *J. Chem. Soc.*, 1965, 4806.
[8] B. D. Astell and V. Boekelheide, *J. Org. Chem.*, 1958, **23**, 316.
[9] V. Bažant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus, and J. Málek, *Tetrahedron Letters*, 1968, 3303.
[10] E. M. Tanner, personal communication.

heated under reflux for 2 h. The yellow solid which crystallised on cooling was filtered off and washed with 96% ethanol (20 ml) followed by ether (80 ml) to give the *dimethylaminomethyl hydrochloride* (3) (2·87 g), pK_a 7·63, equiv. 265.

1,2,5,6-*Tetrahydro*-4H-*pyrrolo*[3,2,1-ij]*quinolin*-6-*ylidene-malononitrile*.—Toluene (10 ml) was added to a stirred solution of the ketone (1) (519 mg) in acetic acid (5 ml), followed by malononitrile (2·28 g) and ammonium acetate (1·0 g), and the mixture was heated under reflux for 3·5 h under a Dean–Stark head. Most of the toluene was evaporated off *in vacuo*, water was added to the residue, and a dark red solid was filtered off. The solid was dissolved in ethyl acetate–methylene chloride and the solution was washed with water, saturated sodium hydrogen carbonate solution, and water again until neutral. Evaporation of the dried solution gave a red solid which was shaken with ether and filtered off to give the *dicyano-compound* (360 mg), m.p. 180—182° $\lambda_{max.}$ 249, 321, and 467 nm (ε 9950, 13,150, and 9550) (Found: C, 75·8; H, 5·05; N, 19·2. $C_{11}H_{11}N_3$ requires C, 76·0; H, 5·0; N, 19·0%). Evaporation of the mother liquors to dryness and shaking again with ether gave a second crop (173 mg), m.p. 178—180°.

5-*Amino*-1,2,4,5-*tetrahydropyrrolo*[3,2,1-ij]*quinolin*-6-*one Hydrochloride* (4).—2N-Sodium hydroxide (3 ml) and toluene-*p*-sulphonyl chloride (1·0 g) were added succesively to a stirred solution of 1,2,4,5-tetrahydropyrrolo[3,2,1-*ij*]-quinolin-6-one oxime (940 mg) in acetone at 0°. The cooling bath was then removed, and stirring was continued for 1 h. Concentration gave a solid which was filtered off, washed with ether, and dried to give the *p*-tolyl-sulphonyl derivative (1·67 g), m.p. 120—122°. Since this compound darkened rapidly it was used immediately in the following reaction. To a stirred suspension of the *p*-tolylsulphonyl derivative (1·67 g) in anhydrous benzene (10 ml) was added a solution of sodium ethoxide [from sodium (125 mg)] in ethanol (2·5 ml) and stirring was continued for 3 days. The mixture was filtered through Hyflo supercel and the filtrate was shaken with successive portions of 2N-hydrochloric acid until the aqueous acidic phase remained colourless. The aqueous acidic solutions were combined, decolourised with charcoal, filtered, and evaporated to dryness to give a solid (1·09 g), m.p. 192—194°. A sample crystallised from ethanol–ether gave the *keto-amine hydrochloride* (4), m.p. 193—194°, pK_a 6·38, equiv. 242; N-*formyl derivative*, m.p. 188—190°.

Subsequent experiments were carried out by stirring overnight instead of for 3 days.

Methyl 1,2,5,6-*Tetrahydro*-6-*oxo*-4H-*pyrrolo*[3,2,1-ij]-*quinolin*-5-*ylcarbamate* (5).—Methyl chloroformate (2·0 ml) and potassium hydrogen carbonate (4·0 g) were added successively to a stirred solution of the keto-amine hydrochloride (4) (675 mg) in water (20 ml); stirring was continued for 1 h and the yellow solid was filtered off, washed with water, and dried to give a solid (640 mg), m.p. 155—159°. Recrystallisation of a sample from 96% ethanol gave the *keto-urethane*, m.p. 160—160·5°.

Methyl 1,2,5,6-*Tetrahydro*-4H-*pyrrolo*[3,2,1-ij]*quinolin*-5-*ylcarbamate* (14).—The keto-urethane (5) (4·93 g) was hydrogenated in acetic acid (140 ml) and conc. sulphuric acid (7 ml) over 10% palladised charcoal (1·25 g). After 2 h the catalyst was filtered off, the filtrate was diluted with three volumes of water, sodium acetate was added to bring the pH to *ca.* 4, and the solution was concentrated *in vacuo*. Ethyl acetate was added and the mixture was basifed with 2N-sodium hydroxide. The aqueous phase was separated and the ethyl acetate extract was washed with water until neutral. Drying and evaporation gave a brown solid (4·46 g) which was dissolved in ether. The solution was decolourised with charcoal and filtered, and the filtrate was concentrated to give the *urethane* (14) (2·77 g), m.p. 111—114°.

Methyl 1,2,5,6-*Tetrahydro*-6-*hydroxy*-4H-*pyrrolo*[3,2,1-ij]-*quinolin*-5-*ylcarbamate* (15).—Potassium borohydride (4 g) was added to a stirred solution of the keto-urethane (5) (8 g) in a mixture of tetrahydrofuran (150 ml) and methanol (150 ml) and the solution was stirred for 1 h. A mixture of acetic acid (8 ml) and water (16 ml) was added, the organic solvents were evaporated off *in vacuo*, and the residue was basified with saturated sodium hydrogen carbonate solution. The product was extracted with ether–methylene chloride and the extract was washed neutral with sodium chloride solution, dried ($MgSO_4$), filtered, and evaporated to an oil. A solution of the oil in ether was decolourised with charcoal and filtered, and the filtrate was concentrated until crystallisation set in. The solid (5·77 g), m.p. 118—125°, was filtered off and recrystallised from ethyl acetate (10 ml) to give the *hydroxy-urethane* (15) (4·65 g), m.p. 124—126°.

1,2,5,6-*Tetrahydro*-5-*methylamino*-4H-*pyrrolo*[3,2,1-ij]-*quinolin*-6-*ol* (16).—A stirred mixture of the keto-urethane (5) (1·23 g) and lithium aluminium hydride (1·23 g) in anhydrous tetrahydrofuran (60 ml) was heated under reflux overnight, cooled, treated with ethyl acetate–tetrahydrofuran, and then poured into a stirred, iced, aqueous solution of potassium sodium tartrate. Ethyl acetate was added; the aqueous phase was separated and the ethyl acetate phase was washed with sodium chloride solution. The ethyl acetate solution was extracted with aqueous citric acid solution, and the aqueous acid phase was separated and basified with 5N-sodium hydroxide. The basic product was extracted with ethyl acetate, and the extract was washed with water until neutral. Drying and evaporation gave an oil (945 mg) which slowly solidified. Trituration with ether gave a tan-coloured solid (420 mg), m.p. 109—119°, pK_a 7·65, equiv. 205. Three recrystallisations from ethyl acetate gave the *hydroxy-methylamino-compound* (16), m.p. 120—121·5°, τ 7·60 (s, NMe), 7·44 (s, NH and OH) and 5·58 and 5·5 (d, 5-H and 6-H). In another experiment the lithium aluminium hydride was replaced, for convenience, by sodium dihydridobis-(2-methoxyethoxy)aluminate in benzene (70% solution) and the same product was obtained.

Methyl 1,2-*Dihydro*-6-*oxo*-6H-*pyrrolo*[3,2,1-ij]*quinolin*-5-*ylcarbamate* (17).—A mixture of the keto-urethane (5) (1·23 g) and manganese dioxide (5 g) in methylene chloride (25 ml) was stirred at room temperature for 24 h and filtered through Hyflo supercel; the filtrate, evaporated to dryness *in vacuo*, gave a yellow solid (1·0 g). A sample recrystallised from methanol yielded the *unsaturated keto-urethane* (17), m.p. 225—230° (decomp.), τ 6·64—6·37 (2H, m), 6·2 (3H, s), 5·58—5·32 (2H, m), 2·82—2·69 (2H, d), 2·06—1·90 (2H, m), and 1·2 (1H).

1,2,3,4,6,7-*Hexahydropyrrolo*[1,2,3-ef][1,5]*benzodiazepine Dihydrochloride* (12) *and* 1,2,3,4,6,7-*Hexahydropyrrolo*-[3,2,1-jk][1,4]*benzodiazepine Tartrate* (13).—Conc. sulphuric acid (24 ml) was added dropwise to an ice-cooled solution of the ketone (1) (5·20 g) in chloroform (30 ml), and to the solution sodium azide (2·9 g) was added during 30 min.

Stirring was then continued at room temperature for 1 h and the mixture was diluted with iced water (150 ml) and basified with potassium carbonate. The mixture was filtered; the chloroform phase of the filtrate was separated, dried, and evaporated to dryness *in vacuo* to give a pale brown solid (5·38 g), m.p. 105—120°, $\nu_{max.}$ 1653 and 3210 cm^{-1}. A solution of the solid (5·38 g) in tetrahydrofuran (90 ml) was added, dropwise, to a stirred suspension of lithium aluminium hydride (1·5 g) in tetrahydrofuran (20 ml). The mixture was heated under reflux overnight, cooled, treated with saturated ammonium chloride solution, and filtered through Hyflo supercel, and the tetrahydrofuran phase was separated and evaporated to dryness. Potentiometric titration of the residue (3·6 g) indicated the presence of two basic compounds, pK_a *ca.* 4·3 and 7·75 in the ratio *ca.* 1 : 3. The mixture of bases and (+)-tartaric acid (2·45 g) were dissolved in warm 96% ethanol (20 ml), the solution was allowed to cool, and ether was added to complete the crystallisation. The solid (4·7 g), m.p. 182—184°, which separated was filtered off and recrystallised from aqueous ethanol to give the benzodiazepine tartrate (3·25 g), m.p. 183—184°; the *free base* (13) (2·29 g) had m.p. 64—65°; *acetyl derivative*, m.p. 78—83°.

The weaker base (12) was recovered from the filtrate of the tartrate salt preparation. The filtrate was washed with saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), filtered and evaporated to dryness. A solution of the residue in ether was treated with ethereal hydrogen chloride, and the solid which precipitated was crystallised from ethanol to give the *hydrochloride* of (12), m.p. 212—214°, pK_a 2·34 and 4·45, equiv. 125 ($C_{11}H_{16}Cl_2N_2$ requires 247).

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