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Some Derivatives of 1,2-Dihydro-3-oxo-4H-cyclopent[*b*]indole & 6-Oxo-7,8,9,10-tetrahydro-5H-cyclohept[*b*]indole*

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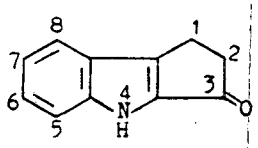
The synthesis of a number of derivatives of the ketones is reported. Under Mannich reaction conditions, the cyclopentanone (I) was alkylated on the nitrogen whereas the cycloheptanone (VIII) underwent C-alkylation.

A REPORT[1] on the antidepressant properties of 5-aminoalkyl-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indoles prompted us to prepare and biologically evaluate novel derivatives of the ketones (I) and (VIII). Ketone (I) was already known in the literature[2], whereas (VIII) had not been described then†. Several attempts were made to introduce an aminomethyl side chain on carbon 2 in (I) by a Mannich reaction under acidic conditions. Only in one experiment, using morpholine, paraformaldehyde and alcoholic hydrochloric acid, the desired product (III) was obtained, but in low yield. When the reaction was run on (I) in benzene, using aqueous formaldehyde, and a secondary amine (morpholine, N-methylpiperazine, hexamethylenimine, tetrahydroisoquinoline) in the absence of an acid, the products (II) were obtained in fair to high yields. Distinction between (II) and (III) was easily possible on the basis of IR : (II) lacked the NH bands, which were prominently seen at 3450 and 3220 cm^{-1} in the spectrum of (III).

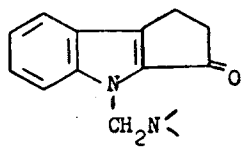
The reaction of acrylonitrile with (I) resulted first in the introduction of one β-cyanoethyl group on the indole nitrogen to afford (IV) and later two more on carbon atom 2 to yield (V). Ketone (I) was resistant to reduction with sodium borohydride, whereas the ketone (II) (>N=morpholino) was easily converted to the alcohol (VI). Probably the NH was bonded strongly to the carbonyl group in (I). Compounds (II) and (VI) were very unstable to dilute mineral acid. The former were cleaved to the parent ketone (I), while (VI) gave rise to highly coloured solutions, whose nature was not investigated.

Ketone (I) was alkylated on the nitrogen with γ-dimethylaminopropyl chloride using sodium hydride. IR showed that the product was (VII) and did not have the aminoalkyl side chain on carbon atom 2.

Treatment of cycloheptanone with ethyl formate followed by benzene diazonium chloride afforded cycloheptane-1,2-dione monophenyl hydrazone, which was cyclized by hot acid to the cyclohept-[*b*]indole ketone (VIII) in high yield. Sodium borohydride reduction readily yielded the alcohol (IX). It was not found possible to introduce an aminomethyl side chain on the nitrogen atom in (VIII) under the conditions used for the ketone (I). However, when the ketone (VIII) was heated under reflux with paraformaldehyde, and a secondary amine (morpholine, piperidine, 4-phenyl-4-*n*-propoxy-piperidine, 4-cyano-4-phenylpiperidine) in alcoholic hydrochloric acid, fair to high yields of the C-alkylated products (X) (NH band in IR)



I



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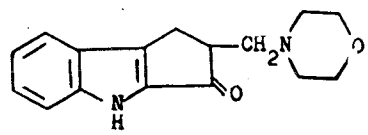

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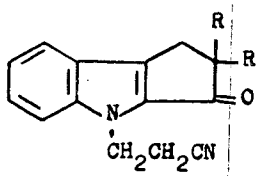
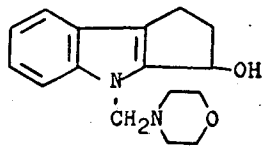
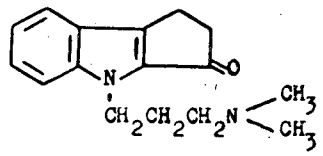


IV : R = H

V : R = $-CH_2CH_2CN$



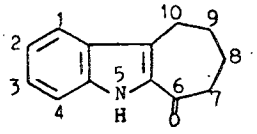
VI



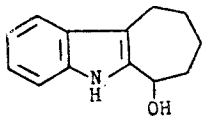
VII

*Contribution No. 145 from CIBA Research Centre, Goregaon, Bombay.

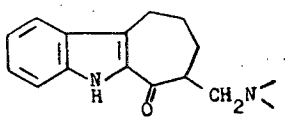
†Subsequent to our synthesis of (VIII), Ishizumi *et al* [Ishizumi, K., Shioiri, T. & Yamada, S., *Chem. pharm. Bull., Tokyo*, **15** (1967), 863] have reported its synthesis by the PPA cyclization of 5-(β-indolyl) pentanoic acid.



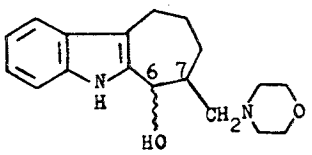
VIII



IX

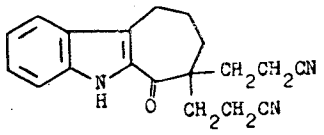


X

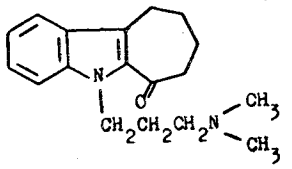


XI : 6,7-trans

XII : 6,7-cis



XIII



XIV

were obtained. We like to ascribe this difference in behaviour of the ketones (VIII) and (I) to the ability of the former to exist in the enol form (endo-double bond) more readily.

Sodium borohydride reduction of ketone (X) (>N=morpholino) gave, in 80% yield, a mixture of two amino alcohols, (XI), mp 179-81°, and (XII), mp 144-7°, in approximately equal proportions. In the NMR spectrum of (XI) in $CDCl_3$, containing a drop of D_2O, the proton on C-6 was seen as a doublet at 4·90 ppm ($J = 9$ *cps*); in the spectrum of (XII), this proton was a broad singlet. On these grounds, we like to assign *trans*- and *cis*-stereochemistry respectively to (XI) and (XII), with the morpholinomethyl group preferentially equatorial. The NH proton signals in (VIII), (XI) and (XII) were seen at 9·42, 8·89 and 8·95 ppm respectively.

Base-catalysed addition of acrylonitrile to (VIII) afforded the *bis*-cyanoethyl derivative (XIII), while the action of γ-dimethylaminopropyl chloride on (VIII) in the presence of sodium hydride yielded (XIV). IR spectra indicated reaction to have occurred in the former case on C-7 and on the indole nitrogen in the latter.

The compounds prepared in this study were examined mainly for potential antidepressant properties but were found to be devoid of these. They also exhibited no hypotensive, hypoglycaemic, anti-fertility or diuretic activity. They had no action on bacteria, fungi and helminths.

Subsequent to the completion of this work, a patent has appeared[3], claiming antidepressant properties for the cyclooctindole analogue of (XIV).

Experimental Procedure

All melting points are uncorrected. NMR spectra were run in $CDCl_3$ solutions on a Varian A60 spectrometer, using TMS internal standard. IR spectra were taken in CH_2Cl_2 solutions, unless otherwise stated.

1,2-*Dihydro*-3-*oxo*-4*H*-*cyclopent*[*b*]*indole* (I)[2] — Starting with cyclopentanone (42 g), 55 g of cyclopentane-1,2-dione monophenyl hydrazone was obtained, mp 199-201° (from methanol). Cyclization with hot dil sulphuric acid afforded the ketone (I) (35 g), mp 248-50°; semicarbazone, mp 226° (decomp) (from aq ethanol) (Found: C, 63·39; H, 5·36; N, 24·08. $C_{12}H_{12}N_4O$ requires C, 63·14; H, 5·30; N, 24·55%); 2,4-dinitrophenylhydrazone, mp 325-7° (decomp) (from dimethylformamide-ethanol) (Found: C, 58·49; H, 4·04; N, 20·09. $C_{17}H_{13}N_5O_4$ requires C, 58·12; H, 3·73; N, 19·94%); oxime, mp 162-3° (from aq methanol) (Found: C, 70·68; H, 5·60; N, 15·38. $C_{11}H_{10}N_2O$ requires C, 70·95; H, 5·40; N, 15·05%).

4-*Aminomethyl*-1,2-*dihydro*-2-*oxo*-4*H*-*cyclopent*[*b*]-*indoles* (II) — These were prepared by the following typical procedure: A mixture of the ketone (I) (1·7 g), morpholine (1·75 g) and 38% aq formaldehyde (1·0 g) in benzene (35 ml) was stirred for sometime and then part of the solvent (15 ml) was distilled off. Again benzene (10 ml) was added and the mixture refluxed for 17 hr. The solution was extracted with dil hydrochloric acid, washed with water, dried and evaporated to give recovered (I) (0·8 g, 47%). The acid extract was made alkaline with sodium hydroxide and extracted with benzene. The benzene layer was worked up to give the solid basic product which was crystallized from benzene-hexane to give 1,2-dihydro-4-N-morpholinomethyl-3-oxo-4H-cyclopent[*b*]indole [1·2 g, 85% allowing for recovery of (I)], mp 134-5°; $\nu_{C=O}$ 1662 cm^{-1} (Found: C, 70·82; H, 6·63; N, 10·20. $C_{16}H_{18}N_2O_2$ requires C, 71·09; H, 6·71; N, 10·36%).

Similarly were prepared the following : 1,2-dihydro-4-N-(N'-methylpiperazino)methyl-3-oxo-4H-cyclopent[*b*]indole (85%) (from benzene-hexane), mp 116-19°; $\nu_{C=O}$ 1662 cm^{-1} (Found: C, 72·21; H, 7·81; N, 14·47. $C_{17}H_{21}N_3O$ requires C, 72·05; H, 7·47; N, 14·83%); 1,2-dihydro-4-N-hexamethyleniminomethyl-3-oxo-4H-cyclopent[*b*]indole (90%) (from ether-hexane), mp 96-97°; $\nu_{C=O}$ 1658 cm^{-1} (Found: C, 76·74; H, 7·93; N, 9·65. $C_{18}H_{22}N_2O$ requires C, 76·56; H, 7·85; H, 9·92%); and 1,2-dihydro-3-oxo-4-N-(1,2,3,4-tetrahydroisoquinolino)methyl-4H-cyclopent[*b*]indole (32%) (from benzene-hexane), mp 120-21°; $\nu_{C=O}$ 1660 cm^{-1} (Found: C, 79·71; H, 6·52; N, 8·96. $C_{21}H_{20}N_2O$ requires C, 79·71; H, 6·37; N, 8·85%).

1,2-Dihydro-2-N-morpholinomethyl-3-oxo-4H-cyclopent[b]indole (III) — A mixture of ketone (I) (1·7 g), morpholine hydrochloride (1·3 g) and paraformaldehyde (1·4 g) in alcohol (25 ml) containing concentrated hydrochloric acid (3 drops) was heated with stirring and under reflux for 15 hr. After evaporation of solvent, the residue was partitioned between dil hydrochloric acid and methylene chloride. The methylene chloride layer on evaporation gave recovered ketone (0·6 g). The acid extract was made alkaline with sodium hydroxide and extracted with methylene chloride. Evaporation of the organic layer gave a gum which became crystalline with methanol. Recrystallization from benzene-hexane afforded the Mannich product (III) (0·3 g, 18% based upon ketone used up), mp 164-6°; γ_{NH} 3450, 3220, $\gamma_{C=O}$ 1650 cm^{-1} (Found: C, 71·57; H, 6·96; N, 10·09. $C_{16}H_{18}N_2O_2$ requires C, 71·09; H, 6·71; N, 10·36%).

4-(β-Cyanoethyl)-1,2-dihydro-3-oxo-4H-cyclopent[b]indole (IV) — A mixture of ketone (I) (3·2 g), acrylonitrile (3·1 g) and solid sodium hydroxide (0·6 g) in benzene (50 ml) and dioxane (25 ml) was stirred for 24 hr. Again 25 ml dioxane were added to bring some undissolved, unreacted ketone into solution and the mixture stirred for an additional 16 hr. After adding water, the benzene layer was separated, dried and evaporated. The residue was crystallized from methanol to give the *N-cyanoethyl product* (IV) (3·1 g, 73%), mp 166-8°; γ_{CN} 2250, $\gamma_{C=O}$ 1672 cm^{-1} (Found: C, 75·12; H, 5·83; N, 11·92. $C_{14}H_{12}N_2O$ requires C, 74·99; H, 5·38; N, 12·49%).

2,2,4-Tris-(β-cyanoethyl)-1,2-dihydro-3-oxo-4H-cyclopent[b]indole (V) — A mixture of ketone (I) (5·1 g) and solid sodium hydroxide (1·5 g) in dioxane (200 ml) and acrylonitrile (20 ml) was stirred at room temperature for 3 days. The solvent was evaporated off and the residue taken up in benzene and washed with water. Evaporation of the benzene layer and crystallization form methanol gave the *tris-cyanoethyl product* (V) (3·5 g, 36%), mp 135-7°; γ_{CN} 2250, $\gamma_{C=O}$ 1680 cm^{-1} (Found: C, 72·89; H, 5·55; N, 16·48. $C_{20}H_{18}N_4O$ requires C, 72·70; H, 5·49; N, 16·96%).

1,2-Dihydro-3-hydroxy-4-N-morpholinomethyl-4H-cyclopent[b]indole (VI) — To a solution of the morpholinomethyl ketone (II) (>N=morpholino) (2·5 g) in methanol (100 ml) was added sodium borohydride (1·25 g) in small portions. After 6 hr at room temperature, water was added, the precipitate filtered off and crystallized from aq methanol to give the alcohol (VI) (1·8 g), mp 161-2°; γ_{OH} 3270 cm^{-1} (Found: C, 70·13; H, 7·49; N, 10·34. $C_{16}H_{20}N_2O_2$ requires C, 70·56; H, 7·40; N, 10·29%).

1,2-Dihydro-4-(3-dimethylaminopropyl)-3-oxo-4H-cyclopent[b]indole (VII) — To a stirred suspension of sodium hydride (0·17 g) in dimethyl formamide (12 ml) was added ketone (I) (0·85 g) in the same solvent (10 ml). After the mixture had been stirred at 30° for 1 hr, γ-dimethylaminopropyl chloride (0·65 g) was added and the mixture stirred at 50° for 2 hr and then at room temperature for 14 hr. It was then poured into water (60 ml) containing conc hydrochloric acid (2 ml) and the solution filtered. The filtrate was made basic with aq sodium hydroxide and extracted with ether. The basic product from the ether layer was converted to the *hydrochloride salt* which was crystallized from methanol-ether (0·25 g, 17%), mp 210-11° (for free base, no NH in IR; $\gamma_{C=O}$ 1670 cm^{-1}) (Found: C, 63·28; H, 7·82; N, 9·16. $C_{16}H_{21}ClN_2O.\frac{1}{2}H_2O$ requires C, 63·53; H, 7·93; N, 9·27%).

6-Oxo-7,8,9,10-tetrahydro-5H-cyclohept[b]indole (VIII) — This was prepared by the same method as that described for the analogous cyclopent[*b*]-indole derivative[2]. Starting with cycloheptanone (56 g), a total of 65·1 g of cycloheptane-1,2-dione monophenyl hydrazone was obtained in two forms: hexane-soluble isomer (57·5 g), crystallized from methanol, mp 55-56° (Found: C, 72·26; H, 7·84; N, 13·18. $C_{13}H_{16}N_2O$ requires C, 72·19; H, 7·46; N, 12·95%), and hexane-insoluble isomer* (7·6 g), crystallized from aq dimethyl formamide, mp 101-3° (Found: C, 71·83; H, 7·71; N, 12·74%). Cyclization of either isomer (5·4 g) with 10% sulphuric acid (100 ml) under reflux for 6 hr afforded the cycloheptindolone (VIII) (4·1 g), mp 145-7° (from acetone-methanol); γ_{NH} 3440, 3320, $\gamma_{C=O}$ 1610 cm^{-1} (Found: C, 77·96; H, 6·36; N, 7·43. $C_{13}H_{13}NO$ requires C, 78·36; H, 6·58; N, 7·03%).

6-Hydroxy-7,8,9,10-tetrahydro-5H-cyclohept[b]indole (IX) — A solution of the ketone (2·5 g) in methanol (50 ml) was treated with sodium borohydride (1 g). After 1 hr at room temperature, water was added. The crystalline *alcohol* that precipitated out was recrystallized from aq methanol to give (IX) (2·35 g), mp 103-5°; $\gamma_{OH,NH}$ 3600, 3450 cm^{-1} (Found: C, 77·23; H, 7·75; N, 6·56. $C_{13}H_{15}NO$ requires C, 77·58; H, 7·51; N, 6·96%).

7-N-Aminomethyl-7,8,9,10-tetrahydro-5H-cyclohept[b]indole — A mixture of ketone (VIII) (2·0 g), morpholine hydrochloride (2·5 g) and paraformaldehyde (1·35 g) in ethanol (25 ml) containing concentrated hydrochloric acid (4 drops) was heated under reflux with stirring for 16 hr. The solvent was then evaporated off and the residue extracted with 2*N* hydrochloric acid. The acid extracts were neutralized with sodium bicarbonate and extracted with ether. Evaporation of the ether layer gave the *Mannich product*, which was crystallized from benzene-hexane to give (X) (>N= morpholino), mp 148-9°; γ_{NH} 3440, 3320 cm^{-1}, $\gamma_{C=O}$ 1610 cm^{-1} (Found: C, 72·30; H, 7·34; N, 9·46. $C_{18}H_{22}N_2O_2$ requires C, 72·45; H, 7·43; N, 9·39%). The hydrochloride had mp 171-2° (from methanol-ether) (Found: C, 64·63; H, 7·35; N, 7·93. $C_{18}H_{23}ClN_2O_2$ requires C, 64·60; H, 6·92; N, 8·37%). By a similar procedure were prepared: 7-N-piperidinomethyl-6-oxo-7,8,9,10-tetrahydro-5H-cyclohept[*b*]indole (77%), mp 144-5° (from ether-hexane); γ_{NH} 3440, $\gamma_{C=O}$ 1620 cm^{-1} (Found: C, 77·39; H, 8·37; N, 9·85. $C_{19}H_{24}N_2O$ requires C, 76·99; H, 8·16, N, 9·45%); 6-oxo-7-[N-(4-phenyl-4-*n*-propoxy)-piperidinomethyl]-7,8,9,10-tetrahydro-5H-cyclohept-[*b*]indole hydrochloride (37%), mp 170-72° (from methanol); $\gamma_{C=O}$ 1645 cm^{-1} (Nujol) (Found: C, 71·46; H, 7·75; N, 5·75. $C_{28}H_{35}ClN_2O_2$ requires C, 71·99; H, 7·55; N, 6·00%); and 7-[N-(4-cyano-4-

*These are most probably geometric isomers. The compound, mp 101-3°, on recrystallization from methanol, gave the lower melting isomer.

phenyl)-piperidinomethyl]-6-oxo-7,8,9,10-tetrahydro-5H-cyclohept[*b*]indole hydrochloride (63%), mp 189-90°; $\nu_{C=O}$ 1600 cm^{-1} (Nujol) (Found: C, 71·53; H, 6·72; N, 9·55. $C_{26}H_{28}ClN_3O$ requires C, 71·96; H, 6·50; N, 9·68%).

7,7-*Bis*(β-*cyanoethyl*)-6-*oxo*-7,8,9,10-*tetrahydro*-5*H*-*cyclohept*[*b*]*indole* (XIII) — A mixture of ketone (VIII) (2·5 g), acrylonitrile (2·0 g) and solid sodium hydroxide (0·5 g) in benzene (50 ml) was stirred overnight. The solution was washed with water, dried and evaporated. Crystallization of the residue from acetone-methanol afforded the *bis-cyanoethyl product* (XIII) (2·0 g, 53%), mp 178-80°; ν_{NH} 3440, ν_{CN} 2245, $\nu_{C=O}$ 1610 cm^{-1} (Found: C, 75·02; H, 6·00; N, 13·33. $C_{19}H_{19}N_3O$ requires C, 74·73; H, 6·27; N, 13·76%).

Cis- and trans-6-*hydroxy*-7-*N*-*morpholinomethyl*-7,8,9,10-*tetrahydro*-5*H*-*cyclohept*[*b*]*indole* — To a solution of the morpholinomethyl ketone (X) (7·5 g) in methanol (50 ml) was added, in small portions, sodium borohydride (3·0 g). After 2 hr at room temperature, the solution was concentrated to half its volume and cooled. The *trans*-alcohol (XI) crystallized was filtered off and recrystallized from methanol (2·6 g); mp 179-81°; ν_{NH} 3320 (Nujol); 3460, 3100 (broad) (CH_2Cl_2) (Found: C, 72·28; H, 8·11; N, 9·37. $C_{18}H_{24}N_2O_2$ requires C, 71·97; H, 8·05; N, 9·33%). The mother liquors were combined, concentrated and diluted with water. The crystalline precipitate was recrystallized from benzene to give the *cis-alcohol* (XII) (2·9 g), mp 144-7°; ν_{NH} 3340 (Nujol); 3460, 3140 (broad) (CH_2Cl_2) (Found: C, 72·36; H, 8·27; N, 9·51. $C_{18}H_{24}N_2O_2$ requires C, 71·97; H, 8·05; N, 9·33%). The mother liquor from the above crystallization was evaporated and the residue fractionally crystallized to give more *trans*- and *cis*-alcohols. The total yield of *trans*-alcohol was 3·0 g (40%) and of *cis*-alcohol was 3·1 g (41%).

5-(3-*Dimethylaminopropyl*)-6-*oxo*-7,8,9,10-*tetrahydro*-5*H*-*cyclohept*[*b*]*indole* (XIV) — Alkylation of the ketone (VIII) (5·0 g) with γ-dimethylaminopropyl chloride (3·6 g) was carried out in dimethylformamide (70 ml) using sodium hydride (1·5 g), under the conditions employed for alkylation of the cyclopentindolone. Two grams of starting material were recovered; the N-γ-dimethylaminopropyl derivative was obtained as the hydrochloride (1·4 g, 29%, based on ketone used up), mp 173-4° (from ethanol); $\nu_{C=O}$ 1640 cm^{-1} (for free base in Nujol) (Found: C, 67·17; H, 7·90; N, 8·48. $C_{18}H_{25}ClN_2O$ requires C, 67·38; H, 7·85; N, 8·73%).

Acknowledgement

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