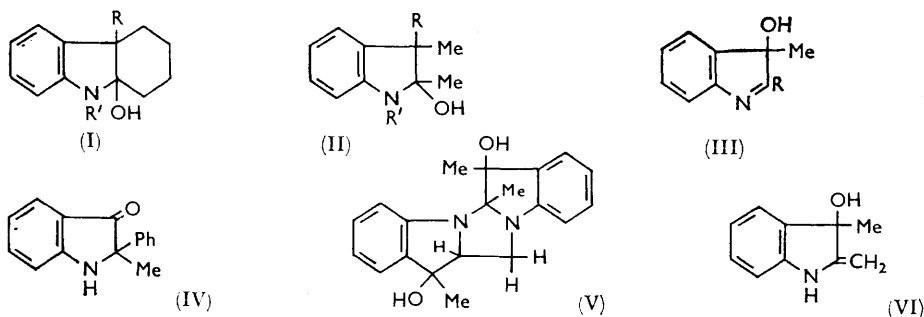


831. A New Rearrangement in the Indoline Series.

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cis-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline (II; R = OH, R' = Bz), when treated with aqueous alkali, gave 2,2-dimethylindoxyl. By contrast, the *trans*-isomer gave 2-methyl-2-phenylindoxyl (IV) and 3-hydroxy-3-methyl-2-phenyl-3*H*-indole (III; R = Ph). *cis*- and *trans*-Indolines are readily distinguished by their ultraviolet spectra.

WITKOP and his co-workers showed¹ that indoline glycols (*e.g.*, I; R = OH, R' = Ac) under alkaline conditions rearrange to indoxyls. They found that 3-hydroxy-3*H*-indoles behave similarly and suggested that the latter compounds were intermediates in the formation of indoxyls from indoline glycols. Whilst investigating the reactivity of the 2,3-bond of indoles towards oxidising agents we obtained² a glycol (II; R = OH, R' = Bz) from decomposition of the nitro-alcohol (II; R = NO₂, R' = Bz). The structure of the glycol was established by its oxidation with periodate to *o*-(*N*-acetylbenzamido)acetophenone. However, treatment with alkali gave only traces of the expected 2,2-dimethylindoxyl, the main products being an alcohol, C₁₅H₁₃NO, and an isomeric yellow ketone. The alcohol could also be prepared by catalytic oxidation of 3-methyl-2-phenylindole. The reactions and spectroscopic properties of the alcohol (see Experimental section) establish its structure as the 3*H*-indole (III; R = Ph). The yellow ketone had characteristic fluorescent properties and an absorption band at 404 mμ. It is therefore assigned the structure (IV). The formation of the alcohol (III; R = Ph) and the ketone (IV) from the glycol (II; R = OH, R' = Bz) is an example of a new rearrangement in the indoline series.



Plant and his co-workers³ showed that the glycols (I; R = OH, R' = Ac or Bz) gave the same yellow product when treated with alkali, and Witkop¹ found that its structure was indoxyl-2-spirocyclopentane. We repeated this work and obtained identical results. Thus, the products of the rearrangement of the hexahydrocarbazole (I; R = OH, R' = Bz) and the indoline (II; R = OH, R' = Bz) under the same conditions are not analogous. The same glycol (I; R = OH, R' = Bz) was obtained either by osmium tetroxide oxidation of 9-benzoyl-1,2,3,4-tetrahydrocarbazole or by decomposition of the nitro-alcohol (I; R = NO₂, R' = Bz). By contrast, oxidation of 1-benzoyl-2,3-dimethylindole with osmium tetroxide gave a new glycol, isomeric with that described previously,² which also gave *o*-(*N*-acetylbenzamido)acetophenone when oxidised with periodate. Only 2,2-dimethylindoxyl was isolated when the new glycol was treated with alkali. The ultraviolet spectra of the glycols obtained by hydrolysis of osmic esters (λ_{\max} , 272 mμ) and that of the nitro-alcohol (I; R = NO₂, R' = Bz) differed from the spectra of the *trans*-glycols (λ_{\max} , 250 mμ).

¹ Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614; Witkop and Patrick, *ibid.*, 1951, **73**, 2188.

² Atkinson, Kershaw, and Taylor, *J.*, 1962, 4426.

³ Perkin and Plant, *J.*, 1923, **123**, 676; Plant and Rutherford, *J.*, 1929, 1970.

Models of hexahydrocarbazoles are difficult to construct when the cyclohexane ring is *trans*-fused to the indoline system but models of the *cis*-isomers appear to be free from strain. We therefore suggest that indolines with an absorption band at 272 $m\mu$ are *cis*-isomers. It is not known whether the acetyl group of the *trans*-glycol (II; R = OH, R' = Ac) is hydrolysed during its conversion into 2,2-dimethylindoxyl or whether it is involved in a rearrangement analogous to that of the *trans*-glycol (II; R = OH, R' = Bz). When the *trans*-glycol (II; R = OH, R' = Ac) was briefly treated with alkali, the imidazolidine (V) was isolated as well as 2,2-dimethylindoxyl, and an examination of the crude reaction mixture provided some evidence for the presence of the 3*H*-indole (III; R = Me). Further evidence for the formation of the imidazolidine (V) by a reaction such as the addition of the enamine (VI) to the unsaturated link of the 3*H*-indole (III; R = Me) was found when compound (V) was obtained by catalytic oxidation and then reduction of 2,3-dimethylindole. The formation of the imidazolidine (V) therefore suggests that the acetyl group of the glycol (II; R = OH, R' = Ac) is not hydrolysed but participates in the rearrangement.

The radiofrequency absorptions of the protons of the heterocyclic moiety of the indolines studied are given in the Experimental section. The bands due to the 3-hydroxy-hydrogen and the protons of the 3-methyl group in (II; R = OH, R' = Bz), (III; R = Ph), and (V) were found at τ 5.35, 8.88; 5.85, 8.45, and 6.14, 6.72, 8.60, 8.71, respectively. The nitro-alcohol (II; R = NO₂, R' = Bz), τ (CDCl₃) 7.78, 7.98, 8.07, 8.12, 8.22, 8.26, showed no bands upfield of τ 8.3 or downfield (apart from bands due to aromatic protons) of τ 7.6. Thus, the protons of the 3-methyl group in the nitro-alcohol are deshielded, as are the protons of the methyl groups of the osmic ester of (II; R = OH, R' = Bz). This may be regarded as evidence for the location of the nitro-group at position 3.

Decomposition of the *trans*-nitro-alcohol (II; R = NO₂, R' = Bz), λ_{\max} (EtOH) 250 $m\mu$ (log ϵ 4.11), results in liberation of dinitrogen tetroxide,² and a reaction scheme has been proposed that accounts for the products isolated. The decomposition of the *cis*-nitro-alcohol (I; R = NO₂, R' = Bz) did not proceed analogously, for a *cis*-glycol was isolated and the only other product obtained (45%) was 9-benzoyl-1,2,3,4-tetrahydro-7-nitrocarbazole.

EXPERIMENTAL

Spectroscopic measurements were obtained on numerous instruments in many parts of the world. Duplicate results obtained on different instruments were remarkably consistent. No bands due to absorptions by aromatic protons are given; values will be supplied to those interested. Intensities of proton absorption bands (given in parentheses) were obtained by weighing the peaks and dividing the total weight by the number of protons present.

cis-9-Benzoyl-1,2,3,4,4a,9a-hexahydro-4a,9a-dihydroxycarbazole.—(a) A solution of osmium tetroxide (0.79 g.) and 9-benzoyl-1,2,3,4-tetrahydrocarbazole (0.8 g.) in benzene (20 ml.) was set aside for 48 hr. and the crystalline precipitate (1.5 g.) collected. Hydrogen sulphide was passed into a solution of this osmic ester (0.5 g.) in methanol (10 ml.) for 0.5 hr. at 0°. The osmium sulphide was filtered off, washed with methanol, and the combined filtrate and washings evaporated. The residue was digested with benzene (5 ml.), separated from contaminating osmium sulphide, and the filtrate concentrated to 2 ml. The glycol separated from benzene as colourless prisms (0.2 g.), m. p. 143–145°, λ_{\max} (EtOH) 270 $m\mu$ (log ϵ 4.00), ν_{\max} (CS₂) 3610, 3430, (KBr) 1620, 1595, 1410, 1190, 1045, 776, 703 cm^{-1} .

(b) 9-Benzoyl-1,2,3,4,4a,9a-hexahydro-9a(4a)-hydroxy-4a(9a)-nitrocarbazole³ (4 g.), λ_{\max} (EtOH) 272 $m\mu$ (log ϵ 3.97), ν_{\max} (KBr) 1630, 1540, 1475, 1250, 1075, 1025, 948, 865, 855, 791, 763, 705, 677 cm^{-1} , alumina (5 g.), and ethanol-water (19 : 1; 75 ml.) were stirred and heated together under reflux for 1 hr. The mixture was filtered hot, the alumina washed with hot methanol (3 \times 50 ml.), and the combined filtrate and washings evaporated. The residue was digested with ethanol and the yellow precipitate (1.7 g.; m. p. 120°) collected. 9-Benzoyl-1,2,3,4-tetrahydro-7-nitrocarbazole separated from ethanol as yellow needles, m. p. 123–124° (Found: C, 71.6; H, 5.3; N, 9.0. C₁₉H₁₆N₂O₃ requires C, 71.3; H, 5.0; N, 8.75%), λ_{\max} (EtOH)

239, 324, 362 $m\mu$ ($\log \epsilon$ 4.32, 4.05, 4.12), ν_{\max} . (KBr) 1670, 1600, 1510, 1320, 1210, 913, 835, 790, 781, 750, 740, 735 cm^{-1} . The mother-liquors from this nitro-compound were evaporated and the residue digested with benzene and set aside overnight. The colourless precipitate was collected and gave the glycol, prisms (1.1 g.), m. p. 143° (from benzene), identical with the glycol prepared as described under (a) above.

(c) When the 9a(4a)-nitrohexahydrocarbazole (10 mg.) was heated under reflux with ethanol for 0.5 hr., the glycol (5 mg.; m. p. 143°) was obtained.

1,2,3,4-Tetrahydro-7-nitrocarbazole.—9-Benzoyl-1,2,3,4-tetrahydro-7-nitrocarbazole (70 mg.), methanol (10 ml.), and sodium hydroxide solution (2N; 0.5 ml.) were heated together under reflux for 0.5 hr. The mixture was evaporated, and the benzene-soluble products adsorbed from benzene on alumina (20 g., Brockmann grade I). A single red band was eluted with benzene and gave 1,2,3,4-tetrahydro-7-nitrocarbazole, m. p. 174—175° [Perkin and Plant⁴ report m. p. 172° for the 5(?)-nitro-compound and m. p. 174° for its acetyl derivative] on evaporation. 9-Acetyl-1,2,3,4-tetrahydro-7-nitrocarbazole, m. p. 175—176°, was obtained when the above tetrahydrocarbazole (30 mg.) was heated under reflux with sodium acetate (0.5 g.) and acetic anhydride (8 ml.) for 5 hr.⁵

Treatment of cis-9-Benzoyl-1,2,3,4,4a,9a-hexahydro-4a,9a-dihydroxycarbazole with Alkali.—The glycol (0.8 g.) and sodium hydroxide solution (N; 50 ml.) were steam-distilled until 600 ml. of distillate were obtained. The indoxyl¹ (0.3 g.), m. p. 77—78°, λ_{\max} . (EtOH) 402 $m\mu$, was obtained from the distillate as described previously for 2,2-dimethylindoxyl.² The residue in the distillation flask was extracted with chloroform and the extract adsorbed from benzene-light petroleum (b. p. 40—60°) (1:1) on alumina (20 g.; Brockmann grade I). Elution with this solvent gave more indoxyl (0.1 g.; total 88%). The aqueous residue from the chloroform extraction was acidified and the precipitate gave benzoic acid (0.18 g.; 58%), m. p. 120° (from water).

6a,7,12a,13-Tetrahydro-7,13-dihydroxy-7,12a,13-trimethyl-6H-indolo[3,4:1',2']imidazo[1,2-a]-indole (V).—(a) *trans*-1-Acetyl-2,3-dihydroxy-2,3-dimethylindoline² [1 g.; λ_{\max} . (MeOH) 204, 248 $m\mu$ ($\log \epsilon$ 4.59, 4.41), τ (CDCl₃) 5.69 (0.65), 7.82 (1.0), 7.99 (2.1), 8.13 (2.4), 8.29 (2.3), 8.47 (1.35), 8.58 (1.2)] and sodium hydroxide solution (N; 50 ml.) were heated together under reflux for 1 hr. The benzene-soluble products were adsorbed from benzene on alumina (20 g.; Brockmann grade III) and 2,2-dimethylindoxyl [0.3 g.; m. p. 89°, τ (CDCl₃) 8.63] was eluted from the column with benzene. Elution with ether-methanol (19:1) evaporation, and treatment of the residue (0.3 g.) with isopropyl ether gave a precipitate, m. p. 141—142°, λ_{\max} . (EtOH) 218, 258 $m\mu$ ($E_{1\%}^{1\text{cm}}$. 690, 209), ν_{\max} . (KBr) 1595, 1135, 1015, 1105, 950, 868, 778, 759 cm^{-1} . The whole ether-methanol eluate was digested with hot isopropyl ether until a solution was obtained, which, on cooling, gave the *diol*, colourless prisms, m. p. 214—215° (from benzene) (Found: C, 74.8; H, 6.5; N, 8.7%; *m/e* 322. C₂₀H₂₂N₂O₂ requires C, 74.5; H, 6.8; N, 8.7%; *M*, 322), λ_{\max} . (EtOH) 204, 244, 297 $m\mu$ ($\log \epsilon$ 4.05, 3.54, 3.26), ν_{\max} . (KBr) 3600, 3450, 1605, 1490, 1205, 880, 769, 755 cm^{-1} , τ (CDCl₃) 5.35 (1), 6.14 (1), 6.72 (1), 7.60 (2), 8.50 (3), 8.60 (3), 8.71 (3); after deuteration, 5.35, 7.60, 8.50, 8.60, 8.71.

(b) Platinum oxide (0.2 g.) and ethyl acetate (100 ml.) were shaken together in an atmosphere of hydrogen until no more gas was absorbed. 2,3-Dimethylindole (1.45 g.) was added and the mixture stirred under oxygen until absorption ceased (18 hr.; uptake 210 ml.). The vessel was evacuated and filled with hydrogen; both processes were repeated twice. The mixture was shaken until 210 ml. of hydrogen had been absorbed (5—10 min.), filtered, and evaporated. The residue was adsorbed from benzene on alumina (20 g.; 12 × 2 cm.; Brockmann grade III) and 2,3-dimethylindole (0.1 g.; m. p. 106°) eluted with benzene. The diol (0.71 g.; m. p. 214°), identical with that described above, was eluted with benzene-ether (1:4).

cis-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline.—A solution of 1-benzoyl-2,3-dimethylindole² (1 g.), osmium tetroxide (1 g.), and pyridine (0.2 ml.) in benzene (50 ml.) was kept at 20° for 48 hr. The crystalline precipitate [2.2 g.; m. p. *ca.* 150°, τ (CDCl₃) 8.03, 8.25] was dissolved in methanol (50 ml.) and hydrogen sulphide passed into the stirred solution at 0° for 1 hr. The osmium sulphide was filtered off, the filtrate evaporated, and the residue adsorbed from ether on alumina (20 g., Brockmann grade III). Evaporation of the ether eluate gave a colourless glass. After several months and numerous preparations of this glass, a crystal was

⁴ Perkin and Plant, *J.*, 1921, **119**, 1825.

⁵ Atkinson, Simpson, and Taylor, *J.*, 1954, 165.

found by chance in an old preparation. Subsequently all preparations were crystallised, with difficulty, by seeding the glass immersed in isopropyl ether or cyclohexane. Crystals are available if necessary. *cis*-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline separated from cyclohexane as colourless needles, m. p. 104–105° (Found: C, 71.8; H, 6.2; N, 4.9%; *m/e*, 283. C₁₇H₁₇NO₃ requires C, 72.0; H, 6.0; N, 4.95%; *M*, 283), λ_{\max} . (EtOH) 272 m μ (log ϵ 4.14), ν_{\max} . (CS₂) 3500, 3400, 3090, 3000, (CCl₄) 1705, 1670, 1580, (KBr) 765, 710, 685 cm.⁻¹, τ (CDCl₃) 5.70 (1), 7.89 (0.5), 8.05 (3.5), 8.26 (3).

Periodate Oxidation of cis-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline.—The glycol (0.15 g.) in ethanol (20 ml.) was added to a solution of sodium metaperiodate (0.5 g.) in water (60 ml.). Borate buffer (pH 7.0; 0.5M; 5 ml.) was added, the mixture kept at 20° for 48 hr., then evaporated, diluted with water (100 ml.), and extracted with ether. The dried (Na₂SO₄) extract, on evaporation, gave *o*-(*N*-acetylbenzamido)acetophenone (0.13 g.),² m. p. 126°.

Treatment of cis-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline with Aqueous Alkali.—The glycol (0.3 g.) and sodium hydroxide solution (0.5N; 40 ml.) were steam-distilled until no more fluorescent distillate was obtained (700 ml.). 2,2-Dimethylindoxyl (60 mg.; m. p. 86–87°) was obtained from the distillate by extraction and chromatography as described previously.

Treatment of trans-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline with Aqueous Alkali.—The glycol [0.85 g.; λ_{\max} . 253 m μ (log ϵ 4.15), ν_{\max} . (CS₂) 3650, 3400 (unaffected by dilution), τ (CDCl₃) 5.35 (1), (8.03, 8.09) (1), 8.28 (3), 8.88 (3)] and sodium hydroxide solution (N; 25 ml.) were heated under reflux for 2 hr. An ether extract was adsorbed on alumina (20 g.; Brockmann grade I) from light petroleum (b. p. 60–80°) and a fluorescent yellow band eluted with benzene–light petroleum (b. p. 60–80°) (9:1; 275 ml.). 2-Methyl-2-phenylindoxyl separated from light petroleum (b. p. 40–60°) as blades, m. p. 113° (Found: C, 81.0; H, 6.4; N, 6.0; O, 7.2. C₁₅H₁₃NO requires C, 80.7; H, 5.8; N, 6.3; O, 6.9%), λ_{\max} . (EtOH) 234, 255, 402 m μ (log ϵ 4.53, 4.12, 3.67), ν_{\max} . (KBr) 3350, 1680, 1605, 1480, 1320, 975, 882, 755, 719, 695 cm.⁻¹. Ethanol solutions of the indoxyl showed a green fluorescence in daylight which was quenched when the solution was basified or acidified; the fluorescence was regenerated when such solutions were neutralised. Blue fluorescent solutions were obtained in non-polar solvents. The alumina column was washed with benzene (100 ml.) then ether (200 ml.). The ether eluate provided 3-hydroxy-3-methyl-2-phenyl-3H-indole, needles, m. p. 145° [from light petroleum (b. p. 60–80°)] (Found: C, 81.05; H, 6.3; N, 6.0%), λ_{\max} . (EtOH) 239, 247, 317 m μ (log ϵ 4.29, 4.27, 4.22), ν_{\max} . (saturated solution in CS₂) 3700, 3400, 3150, 3050, 3000, (KBr) 1550, 1479, 1105, 870, 775, 755, 700, 690 cm.⁻¹, τ (CDCl₃) 5.85 (1), 8.45 (3); after deuteration, 8.45 (3).

Oxidation of 3-Methyl-2-phenylindole.—3-Methyl-2-phenylindole (1 g., prepared from propiophenone phenylhydrazone with boron trifluoride in acetic acid⁵) was added to freshly reduced platinum (from 0.2 g. PtO₂) in ethyl acetate (100 ml.) and stirred in an atmosphere of oxygen for 12 hr. (100 ml. absorbed). The vessel was evacuated and filled with hydrogen, when a rapid uptake of 100 ml. of hydrogen occurred. The mixture was filtered and the solutes in the filtrate adsorbed from benzene on to alumina (30 g.; Brockmann grade III). A small fluorescent band was eluted with benzene (200 ml.) and a further 200 ml. of benzene was washed through the column, which was finally washed with ether (300 ml.). The ether eluate provided 3-hydroxy-3-methyl-2-phenyl-3H-indole (0.4 g.), m. p. 145°.

Treatment of 3-Hydroxy-3-methyl-2-phenyl-3H-indole with Aqueous Alkali.—The 3H-indole (70 mg.) and sodium hydroxide solution (2N; 15 ml.) were heated together under reflux overnight. The cooled mixture was diluted with water (15 ml.) and the chloroform-soluble products adsorbed from benzene on alumina (15 g.; Brockmann grade I). A yellow fluorescent band, eluted with benzene gave 2-methyl-2-phenylindoxyl (60 mg.), m. p. 112–113°.

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