Aromatic Keto-enols. Part III. Some Heterocyclic Quinols.*

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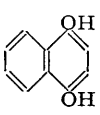
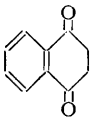
[Reprint Order No. 5506.]

Alkylated 4 : 7-dihydroxyindoles can be prepared by the Bischler synthesis. Attempts to tautomerise 5 : 8-dihydroxyquinoline, 4 : 7-dihydroxythionaphthen, 4 : 7-dihydroxy-2 : 3-dimethylindole, and 1 : 3- and 2 : 3-dihydroxynaphthalene were unsuccessful.

In previous papers * it has been shown that 1 : 4-dihydroxynaphthalene, 1 : 4-dihydroxyanthracene, and some related compounds can isomerise to diketones on fusion *in vacuo*, *e.g.*, (I) ⟶ (II). In this tautomeric change the gain in bond energies in the conversion enol → keto is counterbalanced by the lower resonance energy of the resulting diketone. That the balance is fine is evident from the fact that a diketone cannot be obtained unless both carbonyl groups are conjugated with the benzene ring (*e.g.*, as in II). Thus diketones could not be isolated by fusion of 1 : 3- or 2 : 3-dihydroxynaphthalene. The nature of the unsubstituted ring should therefore affect the position of equilibrium attained and it was of interest to prepare a number of quinols with fused heterocyclic rings and examine their behaviour on fusion. The quinols (III), (IV), and (V; R = Me) were therefore prepared but unfortunately were not sufficiently stable to yield satisfactory results. No carbonyl compounds could be detected after heating of the dienols above the melting points for several minutes followed by rapid cooling, but as considerable decomposition occurred this is inconclusive. 4 : 7-Dihydroxythionaphthen and 5 : 8-dihydroxyquinoline were obtained from the corresponding quinones. Indole-*p*-quinones and quinols are new and are discussed below.



(I)



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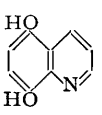

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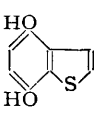

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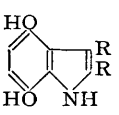

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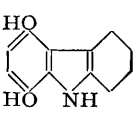

(VI)

Hydroxy- or methoxy-indoles have usually been prepared from suitably substituted *o*-nitrotoluenes (Blaikie and Perkin, *J.*, 1924, **125**, 307), 2 : β-dinitrostyrenes (Beer *et al.*, *J.*, 1948, 1605) or by the Fischer synthesis (Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1872). None of these methods is attractive for the synthesis of 4 : 7-dihydroxyindole (V; R = H) on account of the inaccessibility or instability of the required intermediates. 5 : 6-Dihydroxyindole has been obtained by oxidation of 3 : 4-dihydroxyphenylalanine (Harley-Mason and Bu'Lock, *J.*, 1951, 2248). The corresponding oxidation of 2 : 5-dihydroxyphenylalanine or 2-(2 : 5-dihydroxyphenyl)ethylamine seemed a possible route to 4 : 7-dihydroxyindole but after our preliminary experiments with the former had failed Cromartie and Harley-Mason (*J.*, 1952, 2525) showed that these oxidations took a different course and gave 5-hydroxyindole. Previously, with the intention of preparing the dihydroxyphenylethylamine from the corresponding β-nitrostyrene, we had attempted to condense 2 : 5-dihydroxybenzaldehyde with nitromethane. A variety of conditions were tried without success (cf. Remfry, *J.*, 1911, **99**, 282); when 2 : 5-diacetoxybenzaldehyde and piperidine as catalyst were used partial deacetylation occurred. The formation of indole and *N*-ethylindole by cyclisation of anilinoacetaldehyde diethyl acetal and its *N*-ethyl derivative has been claimed by Nencki and Berliner (G.P. 40,889) and by Räth (*Ber.*, 1924, **57**, 715) respectively. Although Janetsky, Verkade, and Meerburg (*Rec. Trav. chim.*, 1947, **66**, 317) were unable to repeat this work, an attempt to cyclise the more reactive 2 : 5-dimethoxyanilinoacetaldehyde diethyl acetal seemed worth while. However treatment of the latter under various acid conditions gave only amorphous solids from which no 4 : 7-dimethoxyindole could be isolated, in agreement with Janetsky *et al.*

* Parts I and II, *J.*, 1950, 1737; 1952, 2759.

Attention was then turned to more accessible alkylated 4 : 7-dihydroxyindoles. Reduction of the readily available 2 : 3-dimethyl-7-nitroindole (Schofield and Theobald, *J.*, 1949, 796) gave the amine which was coupled with diazotised sulphanilic acid in acid solution. Oxidation of the crude diamine, obtained by reduction of the azo-compound, with ferric chloride or acid dichromate gave red solutions but no quinone could be isolated. This general method for preparing quinones does not seem to be widely applicable to heterocyclic compounds. We experienced a similar failure in the oxidation of 4 : 7-diaminobenzothiadiazole (obtained as above), Fieser and Martin (*J. Amer. Chem. Soc.*, 1935, **57**, 1835) were unable to isolate a quinone after oxidation of 4-amino-7-hydroxybenzotriazole, and the oxidation of 5-amino-8-hydroxy*iso*quinoline is also anomalous (*idem, ibid.*, p. 1840).

A method of preparing 4 : 7-dihydroxyindoles was ultimately found in the Bischler synthesis. Condensation of 2 : 5-dimethoxyaniline with 1-bromoethyl methyl ketone gave 4 : 7-dimethoxy-2 : 3-dimethylindole from which the quinol (V; R = Me) was obtained by demethylation with aluminium chloride. The quinone was also prepared. 1 : 2 : 3 : 4-Tetrahydro-5 : 8-dimethoxycarbazole, and the corresponding quinol (VI) and quinone, were similarly obtained from 2 : 5-dimethoxyaniline and 2-chloro*cyclo*hexanone. The dimethyl ether was smoothly dehydrogenated with chloranil (Barclay and Campbell, *J.*, 1945, 530) to 1 : 4-dimethoxycarbazole but we were unable to demethylate this product. Attempts to dehydrogenate (VI) and the tetrahydrocarbazolequinone were also unsuccessful.

Experimental

7-Amino-2 : 3-dimethylindole.—(*a*) Sodium dithionite (2 g.) was added to a suspension of 2 : 3-dimethyl-7-nitroindole (0·57 g.) in a boiling mixture of alcohol (25 c.c.), water (40 c.c.), and sodium hydroxide (5 c.c., 2N). After 5 min. more dithionite (2 g.) was added and refluxing continued until an almost colourless solution was obtained (30 min.). This was diluted with water (50 c.c.) and extracted with ether. Evaporation of the dried extract yielded a solid which crystallised from water to give the amine as whitish-grey needles, m. p. 126° (decomp.) (40%). Recrystallisation was carried out rapidly as the amine decomposes at high temperatures. (*b*) 2 : 3-Dimethyl-7-nitroindole (0·48 g.) in 50% ethyl acetate–ethanol (20 c.c.) was hydrogenated in the presence of Raney nickel and the *amine* isolated by evaporation to dryness. It recrystallised from water in whitish-grey needles, m. p. 126° (decomp.) (45%) identical with those obtained as in (*a*) (Found: C, 75·2; H, 7·5; N, 17·5. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5%).

2 : 5-Dimethoxynitrobenzene.—The method described by Ungnade and Zilch (*J. Org. Chem.*, 1951, **16**, 64) gave dinitration products. The following procedure was found convenient: to a solution of 1 : 4-dimethoxybenzene (10 g.) in glacial acetic acid (40 c.c.) was added slowly with stirring a mixture of concentrated nitric acid (10 c.c.) and water (10 c.c.), the temperature being maintained below 40°. The yellow nitro-compound separated during the addition and was collected after dilution of the mixture with water (50 c.c.). Crystallisation from methanol yielded yellow needles, m. p. 72° (91%).

2 : 5-Dimethoxyaniline.—2 : 5-Dimethoxynitrobenzene (18·3 g.) in ethyl acetate (100 c.c.) was shaken with hydrogen and 5% palladised strontium carbonate until hydrogen uptake ceased (80 min.). The amine was obtained by evaporation to dryness and had m. p. 80° (98%).

2 : 5-Dimethoxyanilinoacetaldehyde Diethyl Acetal.—A mixture of 2 : 5-dimethoxyaniline (15·3 g.) and bromoacetal (19·9 g.) was refluxed in 95% ethanol (50 c.c.) in the presence of anhydrous sodium hydrogen carbonate (12·6 g.) for 48 hr. The solvent was then removed by evaporation on a water-bath and water added to the residue; an oil was precipitated. This was isolated with ether, dried ($MgSO_4$), and fractionated under reduced pressure to give (1) unchanged bromoacetal, b. p. 61—62°/10—11 mm., and (2) 2 : 5-dimethoxyaniline, b. p. 151°/10—11 mm. The latter solidified and was recrystallised from light petroleum (22% recovery). The high-boiling residue was distilled at 141°/1 mm., to give the required *acetal* as a colourless liquid (68%) (Found: C, 62·5; H, 8·65. $C_{14}H_{23}O_4N$ requires C, 62·45; H, 8·6%).

4 : 7-Dimethoxy-2 : 3-dimethylindole.—A mixture of 2 : 5-dimethoxyaniline (7·6 g.) and 1-bromoethyl methyl ketone (3·8 g.) was set aside overnight. The reddish-brown mixture was then heated in an oil-bath at 125° for 30 min., cooled, and brought to the boil with hydro-

chloric acid (35 c.c., 2N). After being chilled, the acid solution was decanted from a black tar. The tar was extracted with boiling ether (2 × 100 c.c.), and the extracts were dried and evaporated. Vacuum-distillation of the residual solid gave the *indole* as a brown liquid, b. p. *ca.* 135—140°/1—2 mm., which solidified. One recrystallisation from aqueous alcohol (charcoal) afforded plates, m. p. 103—104° (61%) (Found: C, 70·3; H, 7·4; N, 6·9. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·35; N, 6·8%). The *picrate* formed dark brown needles, m. p. 167° (from ethanol) (Found: C, 49·9; H, 3·9; N, 12·6. $C_{18}H_{18}O_9N_4$ requires C, 49·8; H, 4·15; N, 12·9%).

4 : 7-*Dihydroxy*-2 : 3-*dimethylindole*.—4 : 7-Dimethoxy-2 : 3-dimethylindole (1·8 g.) was refluxed in dry benzene (60 c.c.) with powdered anhydrous aluminium chloride (12·6 g.) for 12 hr. After cooling in ice the solid mass was broken up and treated with ice and hydrochloric acid. The product was collected and crystallised from benzene and then from water (containing a little sodium dithionite). The *quinol* separated as feathery crystals, m. p. 205—206° (decomp.) (bath preheated to 200°) (54%) (Found: C, 67·7; H, 5·95; N, 7·8. $C_{10}H_{11}O_2N$ requires C, 67·75; H, 6·2; N, 7·92%). The *diacetate* had m. p. 138° (from light petroleum) (Found: C, 64·2; H, 5·75; N, 5·5. $C_{14}H_{15}O_4N$ requires C, 63·9; H, 5·8; N, 5·35%).

2 : 3-*Dimethylindole*-4 : 7-*quinone*.—The above quinol (0·2 g.) was dissolved in acetone (20 c.c.) and water (10 c.c.) and treated with a solution of potassium dichromate (0·5 g.) in water (3 c.c.) containing concentrated sulphuric acid (0·5 c.c.). After 30 min. the red solution was diluted with water (30 c.c.) and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts afforded a red solid. Recrystallisation from benzene yielded the *quinone* in red leaflets, m. p. 215—217° (decomp.) (79%) (Found: C, 68·35; H, 5·4; N, 8·0. $C_{10}H_9O_2N$ requires C, 68·55; H, 5·2; N, 8·0%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 8-*dimethoxycarbazole*.—2 : 5-Dimethoxyaniline (10 g.), 2-chloro-*cyclo*hexanone (5 g.), and ethanol (30 c.c.) were refluxed for 14 hr. The amine hydrochloride gradually separated and was collected, after chilling of the mixture in ice, and was washed with ether. The combined filtrate and washings were evaporated to dryness and the semi-solid residue was extracted twice with boiling ether. The extract was washed with 2N-hydrochloric acid, water, aqueous sodium carbonate, and dried and evaporated. The residual sticky solid distilled at 150°/1 mm., to give a yellow oil which solidified. One recrystallisation from light petroleum (b. p. 80—90°) afforded the *tetrahydrocarbazole* in rosettes, m. p. 96° (52%) (Found: C, 72·5; H, 7·4; N, 6·15. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·1%). The *picrate* crystallised from ethanol in dark grey crystals, m. p. 153° (Found: C, 52·2; H, 4·25. $C_{20}H_{20}O_9N_4$ requires C, 52·2; H, 4·35%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 8-*dihydroxycarbazole*.—1 : 2 : 3 : 4-Tetrahydro-5 : 8-dimethoxycarbazole (0·5 g.) was refluxed in dry benzene (15 c.c.) with powdered anhydrous aluminium chloride (3·05 g.) for 12 hr. After decomposition with ice and hydrochloric acid the suspension obtained was extracted with ethyl acetate. Evaporation of the dried extract gave a brown solid which was crystallised first from benzene and then from aqueous alcohol (containing a little sodium dithionite). The *quinol* formed almost colourless needles, m. p. 225° (decomp.) (bath preheated to 205°) (48%) (Found: C, 70·6; H, 6·5; N, 6·8. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·45; N, 6·9%). The *diacetate* had m. p. 152° (from light petroleum) (Found: C, 67·1; H, 5·85; N, 4·8. $C_{16}H_{17}O_4N$ requires C, 66·85; H, 5·95; N, 4·9%).

1 : 2 : 3 : 4-*Tetrahydrocarbazole*-5 : 8-*quinone*.—The above quinol (0·2 g.) in a mixture of acetone (25 c.c.) and water (10 c.c.) was oxidised by addition of potassium dichromate (0·75 g.) in water (3 c.c.) containing concentrated sulphuric acid (1 c.c.). After 30 min. the red solution was diluted with water and extracted with ether. The extract yielded a dark red solid which was crystallised from benzene. The *quinone* separated in red rosettes, m. p. 208—210° (decomp.) (68%) (Found: C, 71·55; H, 5·8; N, 6·8. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 6·95%).

1 : 4-*Dimethoxycarbazole*.—A mixture of 1 : 2 : 3 : 4-tetrahydro-5 : 8-dimethoxycarbazole (5·25 g.), chloranil (11·1 g.), and sulphur-free xylene (112 c.c.) was refluxed for 24 hr. After cooling, the tetrachloroquinol was filtered off and washed with ether, and the combined filtrate and washings were further diluted with ether, shaken with aqueous sodium hydroxide and then water, and dried. The solvent was evaporated and the residual dark blue oil distilled under reduced pressure, to give a faintly brown liquid, b. p. *ca.* 180—185°/1 mm., which solidified. Crystallisation from aqueous alcohol afforded small plates, m. p. 109—110° (72%). On a smaller scale the blue oil was conveniently purified by passing a benzene solution through a short column of alumina (Found: C, 74·2; H, 5·7; N, 6·5. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%). The carbazole gave a violet fluorescence in hydrocarbon solvents.

4 : 7-*Dihydroxythionaphthen*.—Thionaphthen-4 : 7-quinone (0·83 g.) in ethyl acetate

(20 c.c.) was reduced with hydrogen and Adams catalyst. The *quinol* was isolated by evaporation to small bulk and precipitation with light petroleum. It crystallised from benzene in felted needles, m. p. 171—172° (decomp.) (83%) (Found : C, 57·8; H, 3·2; S, 19·0. $C_8H_6O_2S$ requires C, 57·8; H, 3·6; S, 19·3%). The *diacetate* formed plates, m. p. 147° (from light petroleum) (Found : C, 57·6; H, 4·0; S, 12·6. $C_{12}H_{10}O_4S$ requires C, 57·6; H, 4·0; S, 12·8%).

5 : 8-*Dihydroxyquinoline*.—Quinoline-5 : 8-quinone (2·8 g.) in ethyl acetate (100 c.c.) was hydrogenated in presence of 5% palladised barium sulphate. The quinol separated from benzene in needles, m. p. 180° (68%).

5-*Acetoxy*-2-*hydroxybenzaldehyde*.—Piperidine (10 small drops) was added to 2 : 5-diacetoxybenzaldehyde (1 g.) in ethanol (20 c.c.) containing nitromethane (0·4 g.). After 24 hr. the mixture was poured into water; the precipitate crystallised from light petroleum (b. p. 50—60°) in needles, m. p. 77—77·5° (62%) (Found : C, 59·9; H, 4·6. Calc. for $C_9H_8O_4$ C, 60·0; H, 4·5%). The same compound was obtained when the experiment was repeated in the absence of nitromethane.

2 : 3-*Diacetoxynaphthalene* crystallises from aqueous alcohol in blades, m. p. 106° (Found : C, 68·85; H, 4·9. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%).

One of us (A. B.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance.

THE UNIVERSITY, OLD ABERDEEN. [*Received, June* 30*th*, 1954.]