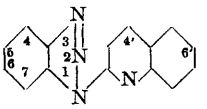
176. *Carbazoles, Carbolines, and Related Compounds. Part III. Quinindoline Derivatives.*

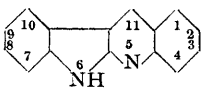
By S. J. Holt and V. Petrow.

Quinindoline (II), and its 11-*methyl*-, 2-*methoxy*-11-*methyl*-, and 8 : 9-*dimethoxy*-derivatives have been prepared by pyrolytic decomposition of the appropriate 1-α-*quinolylbenztriazoles* (I). 9-*Nitroquinindoline*, obtained by direct nitration of (II), was converted by reduction and acetylation into 6-*acetyl*-9-*diacetylaminoquinindoline*, the constitution of which followed from its alternative preparation from 2′ : 5-*dinitrobenzylideneoxindole*.

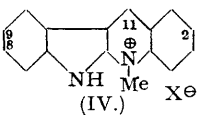
The corresponding *quinindolinium* salts (IV) failed to show outstanding biological activity. On treatment with alkali they passed into the *anhydronium bases* (V).

Work on the relationship between structure and biological activity in the azacarbazole series, initiated in Part I (Holt and Petrow, *J.*, 1947, 607), has now been extended to some derivatives of quinindoline (II). Although this compound may be prepared by the reduction of *oo*′-dinitro-α-cyanodibenzyl (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 3019), or of *o*-nitrobenzylideneoxindole (III; R = H) (Kirchner, *Nachr. K. Ges. Wiss. Göttingen*, 1921, 154), these methods proved unsuitable for our purpose. The required derivatives were obtained by the extension of the Graebe–Ullmann carbazole synthesis first described by Lawson, Perkin, and Robinson (*J.*, 1924, 627), whereby 1-α-quinolylbenztriazoles (I) are pyrolytically decomposed to give the quinindoline and nitrogen. Study of this reaction has now shown that pyrolytic decomposition of the triazoles (I) fails to occur in neutral or basic media such as nitrobenzene, quinoline, and liquid paraffin at their boiling points. In striking contrast, smooth decomposition at 170° takes place in syrupy phosphoric acid, a reagent first introduced for this purpose by Robinson and Thornley (*J.*, 1924, 2169), *i.e.*, under very much less drastic conditions than those obtaining in the absence of the acidic reagent. The mechanism of this facile decomposition in acidic media is being investigated.


(I.)


(II.)


(III.)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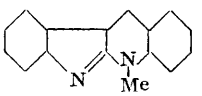
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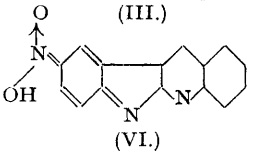
(VI.)

The required triazoles (I) were prepared by heating a mixture of the α-chloroquinoline, a slight excess of *o*-phenylenediamine, copper powder, and a little hydrochloric acid under reduced pressure, a procedure which gave somewhat improved yields, followed by treatment of the product with nitrous acid. 1-α-*Lepidylbenztriazole* and 1-α-(6′-*methoxylepidyl*)*benztriazole* were prepared in this way. 4 : 5-Diaminoveratrole and α-chloroquinoline gave 5 : 6-*dimethoxy*-1-α-*quinolylbenztriazole*. An attempt to prepare 8-nitrolepidyl-*o*-phenylenediamine by fusion of 2-chloro-8-nitrolepidine with *o*-phenylenediamine resulted in an explosion. Attempts to prepare 1-α-(4′-carboxyquinolyl)benztriazole from 2-chlorocinchoninic acid and *o*-phenylenediamine were unsuccessful, reaction only occurring at temperatures at which concomitant decarboxylation took place, so that treatment with nitrous acid led to the formation of (II).

Decomposition of these triazoles in syrupy phosphoric acid gave quinindoline (II) and its 11-*methyl*-, 2-*methoxy*-11-*methyl*-, and 8 : 9-*dimethoxy*-derivatives.

Nitration of quinindoline to a mononitro-derivative had previously been carried out by Graebe and Eschenbach (*loc. cit.*), who failed to orient their product. As indole derivatives generally nitrate *para* to the pyrrole nitrogen (cf. quindoline ⟶ 7-nitroquindoline, Part I, *loc. cit.*), we assigned the constitution of a 9-*nitroquinindoline* to this product, a formulation confirmed by its reduction and acetylation to 6-*acetyl*-9-*diacetylaminoquinindoline*, identical with an authentic specimen. The latter was prepared by an extension of Kirchner's quinindoline synthesis (*loc. cit.*) by fusion of 5-nitro-oxindole (Sumpter, Miller, and Magan, *J. Amer. Chem. Soc.*, 1945, **67**, 499) with *o*-nitrobenzaldehyde to give 2′ : 5-*dinitrobenzylideneoxindole* (III; R = NO_2), followed by catalytic reduction and acetylation.

Conversion of some of the above derivatives into the quaternary salts (IV) gave 5-*methyl*-, 5 : 11-*dimethyl*-, 2-*methoxy*-5 : 11-*dimethyl*-, and 9-*nitro*-5-*methyl*-*quinindoliniu*m *chloride*. Treatment of these with alkali gave the corresponding anhydronium bases (V) : 5-*methyl*-, 5 : 11-*dimethyl*-, 2-*methoxy*-5 : 11-*dimethyl*-, and 9-*nitro*-5-*methyl*-iso*quinindoline*. These regenerated the quinindolinium salts (IV) on treatment with acids, and were used in the preparation of the soluble methoacetates (IV; X = OAc) employed for biological testing (see Experimental), the methochlorides proving too insoluble for this purpose. Attempts to condense 5 : 11-*dimethylquinindolinium iodide* with *p*-dimethylaminobenzaldehyde to the styryl derivative by Petrow's method (*J.* 1945, 18) were not successful, probably owing to the very sparing solubility of the quaternary salt. There was evidence of reaction, however, as indicated by the appearance of a deep red coloration.

Treatment of an aqueous-alcoholic solution of 9-nitroquinindoline with sodium hydroxide gave a bright reddish-orange solution. This coloration is certainly due to the formation of the sodium salt of the ψ-nitrolic acid (VI). In contrast, the corresponding anhydronium base, 9-nitro-5-methyl*iso*quinindoline, which *a priori* cannot undergo prototropic change to a ψ-nitrolic acid, fails to give a coloration with alkali.

Experimental.

(M. p.s are corrected; semimicroanalyses are by Mr. S. Bance, B.Sc., A.R.I.C., Microanalytical Dept., May and Baker Ltd.).

1-α-*Quinolylbenztriazole*.—α-Chloroquinoline (16·36 g.), *o*-phenylenediamine (12 g.), copper powder (0·5 g.), and concentrated hydrochloric acid (2 drops) were mixed in a flask fitted with a reflux air-condenser, the top of which was connected to a water-pump. The mixture was heated at 155°/30 mm. for 30 mins., and the product dissolved in alcohol (200 ml.), filtered, and added to 2N-hydrochloric acid (250 ml.). The resulting solution was cooled to 0°, and then slowly added to a solution of sodium nitrite (25 g.) in water (200 ml.) at 0° with mechanical stirring. After 30 minutes the precipitate was collected, washed with water, and crystallised from ethanol. 1-α-Quinolylbenztriazole formed faintly-coloured needles, (16 g., 65%), m. p. 145—146° (Found : N, 22·9. Calc. for $C_{15}H_{10}N_4$: N, 22·9%).

1-α-*Lepidylbenztriazole* was prepared from 2-chlorolepidine (*Org. Synth.*, **24**, p. 28). It separated from alcohol as a cotton-wool-like mass which changed, on standing overnight in contact with the solvent, into stout, white needles, m. p. 164—165° (Found : C, 73·7; H, 4·8; N, 21·9. $C_{16}H_{12}N_4$ requires C, 73·8; H, 4·7; N, 21·5%). Yield, 58%.

1-α-(6-*Methoxylepidyl*)*benztriazole*, prepared from 2-chloro-6-methoxylepidine (Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 84), formed pale yellow plates (51%) from acetic acid, m. p. 162—163° (Found : C, 70·1; H, 4·9; N, 19·2. $C_{17}H_{14}ON_4$ requires C, 70·3; H, 4·8; N, 19·3%).

5 : 6-*Dimethoxy*-1-α-*quinolylbenztriazole*, prepared from 4 : 5-diaminoveratrole, formed pale buff-coloured needles (27%) from alcohol, m. p. 193—194° (Found : C, 66·5; H, 4·7; N, 18·3. $C_{17}H_{14}O_2N_4$ requires C, 66·6; H, 4·6; N, 18·3%).

Quinindoline.—1-α-Quinolylbenztriazole (15 g.) in syrupy phosphoric acid (150 ml.) was heated to 150°. When the brisk evolution of gas had slackened, the dark solution was heated to 180° for one minute, cooled, and poured on crushed ice (500 g.). The yellow solid was collected, basified by warming with 2N-ammonium hydroxide, and crystallised from pyridine. Quinindoline formed flat, pale yellow needles (36%), m. p. 346° (Found : C, 82·6; H, 4·6; N, 12·8. Calc. for $C_{15}H_{10}N_2$: C, 82·6; H, 4·5; N, 12·9%).

11-*Methylquinindoline*, prepared from 1-α-lepidylbenztriazole, formed faintly yellow needles (26%) from pyridine, m. p. 274—275° (Found : C, 82·6; H, 5·1; N, 12·2. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%). Its 6-*acetyl* derivative, prepared by heating the base with acetic anhydride for ten minutes under reflux, formed fine white needles from alcohol, m. p. 171·5—172° (Found : N, 10·2. $C_{18}H_{14}ON_2$ requires N, 10·2%).

2-*Methoxy*-11-*methylquinindoline*, prepared from 1-α-(6-methoxylepidyl)benztriazole, formed pale yellow needles (24%) from pyridine, m. p. 305—307° (Found : C, 77·7; H, 5·3; N, 10·6. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%). The 6-*acetyl* derivative formed flat needles from acetic anhydride, m. p. 182—183° (Found : N, 9·2. $C_{19}H_{16}O_2N_2$ requires N, 9·2%).

8 : 9-*Dimethoxyquinindoline*, prepared from 5 : 6-dimethoxy-1-α-quinolylbenztriazole, formed light lemon-yellow needles (4%) from ethanol, m. p. 277—278° (Found : C, 73·2; H, 5·1; N, 10·2. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%). The 6-*acetyl* derivative formed pale yellow needles from acetic anhydride, m. p. 183—184° (Found : N, 8·8. $C_{19}H_{16}O_3N_2$ requires N, 8·8%).

9-*Nitroquinindoline*.—Quinindoline (2·0 g.) was heated with nitric acid (20 ml., *d* 1·42) until solution was complete. After standing overnight at room temperature, the product was poured into water, the solids collected, basified by warming with N-ammonium hydroxide, and crystallised from glacial acetic acid. 9-*Nitroquinindolinium acetate* formed yellow needles (1·96 g.) (Found : loss in wt. on drying, 18·5. $C_{15}H_9O_2N_3,CH_3{\cdot}CO_2H$ requires $CH_3{\cdot}CO_2H$, 18·6%), which lost acetic acid on heating to give 9-nitroquinindoline, m. p. 377—378° (Found : C, 68·4; H, 3·5; N, 16·0. Calc. for $C_{15}H_9O_2N_3$: C, 68·5; H, 3·4; N, 16·0%).

9-*Aminoquinindoline*.—9-Nitroquinindoline (2·63 g.), reduced iron (10·0 g.), calcium chloride (200 mg.), and 70% alcohol (100 ml.) were heated under reflux for 72 hours, and the mixture filtered hot. The iron residues contained some yellow crystalline material which was extracted with alcohol (Soxhlet). The bulked filtrates yielded 9-*aminoquindoline* (45%), which formed a microcrystalline yellow powder from butanol (Found, in dried sample : C, 77·1; H, 4·5; N, 17·9. $C_{15}H_{11}N_3$ requires C, 77·2; H, 4·8; N, 18·0%). The 6 : 9 : 9-*triacetyl* derivative formed small needles from alcohol, m. p. 223·5—224·5° (Found : C, 70·2; H, 4·9; N, 11·8. $C_{21}H_{17}O_3N_3$ requires C, 70·3; H, 4·7; N, 11·7%).

2′ : 5-*Dinitrobenzylideneoxindole* (III).—A mixture of 5-nitro-oxindole (2·65 g.) (Sumpter, Miller, and Magan, *loc. cit.*) and *o*-nitrobenzaldehyde (2·5 g.) was heated at 170° for 15 minutes, reaction then having occurred and the mass become solid. The product, from chlorobenzene, gave 2′ : 5-*dinitrobenzylideneoxindole*, yellow needles (57%) from alcohol, m. p. 253—254° (Found : C, 57·7; H, 3·1; N, 13·3. $C_{15}H_9O_5N_3$ requires C, 57·8; H, 2·9; N, 13·5%). Catalytic reduction of this product in glacial acetic acid in the presence of 10% palladised charcoal, followed by acetylation with acetic anhydride, gave 6-acetyl-9-diacetylaminoquinindoline, m. p. 223·5—224·5° (Found : C, 70·2; H, 4·8; N, 11·8%), not depressed in admixture with a sample prepared from the nitroquinindoline (above).

5-*Methylquinindolinium Chloride*.—Quinindoline (2 g.) in dry nitrobenzene (50 ml.) was heated with methyl sulphate (2·5 ml.) at 160° for one hour. The cooled product was added to dry benzene (250 ml.). The crude methosulphate, collected after one hour, was dissolved in hot water (100 ml.), and the filtered solution (charcoal) treated with concentrated hydrochloric acid (5 ml.). Light yellow needles of 5-*methylquinindolinium chloride* (2·1 g.) separated on cooling, m. p. 278—280° (decomp.) (Found on dried sample : C, 71·4; H, 4·6; N, 10·4; Cl, 13·1. $C_{16}H_{13}N_2Cl$ requires C, 71·5; H, 4·8; N, 10·4; Cl, 13·2%).

5-*Methyl*iso*quinindoline*, orange-yellow needles from a large bulk of hot water, m. p. 108—110° (Found : C, 82·4; H, 5·2; N, 12·0. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%), was precipitated when the foregoing chloride (1·0 g.), dissolved in hot water at 60°, was treated with 2N-sodium hydroxide solution until the mixture was alkaline to phenolphthalein.

5 : 11-*Dimethylquinindolinium iodide*, prepared *via* the methosulphate, formed orange needles from water, m. p. 288—289° (Found : C, 54·5; H, 4·1; N, 7·4; I, 33·6. $C_{17}H_{15}N_2I$ requires C, 54·6; H, 4·0; N, 7·5; I, 33·9%). The *methochloride* formed pale yellow needles, m. p. 280—282° (Found : C, 72·2; H, 5·2; N, 9·8; Cl, 12·4. $C_{17}H_{15}N_2Cl$ requires C, 72·2; H, 5·3; N, 9·9; Cl, 12·6%).

5 : 11-*Dimethyl*iso*quinindoline* formed orange-yellow needles from 50% ethanol, m. p. 218—219° (Found : C, 82·7; H, 5·6; N, 11·3. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

2-*Methoxy*-5 : 11-*dimethylquinindolinium chloride*, prepared *via* the methosulphate, formed small plates from N-hydrochloric acid, m. p. 272—274° (decomp.) (Found : C, 69·1; H, 5·6; N, 8·8; Cl, 11·2. $C_{18}H_{17}ON_2Cl$ requires C, 69·2; H, 5·5; N, 8·9; Cl, 11·4%).

2-*Methoxy*-5 : 11-*dimethyl*iso*quinindoline* formed orange micro-needles from water, m. p. 159—160° (Found : C, 78·1; H, 5·6; N, 10·2. $C_{18}H_{16}ON_2$ requires C, 78·2; H, 5·8; N, 10·1%).

9-*Nitro*-5-*methylquinindolinium chloride*, prepared *via* the methosulphate, separated from dilute hydrochloric acid as a microcrystalline, yellow solid, m. p. 295—300° (decomp.) (Found : C, 61·2; H, 3·7; N, 13·3; Cl, 11·1. $C_{16}H_{12}O_2N_3Cl$ requires C, 61·3; H, 3·9; N, 13·4; Cl, 11·3%).

9-*Nitro*-5-*methyl*iso*quinindoline* formed orange needles from a large volume of alcohol, m. p. 262° (Found : C, 69·5; H, 3·9; N, 15·0. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0; N, 15·2%).

Biological Data.—Dr. R. Wien, Biological Division, May and Baker Ltd., has very kindly reported the following results : The quaternary salts were inactive against *T. equiperdum* and *T. congolense* with the exception of 5 : 11-dimethylquinindolinium acetate, which showed a slight, but no curative, effect against the latter organism. 5 : 11-Dimethyl-, and 2-methoxy-5 : 11-dimethyl-quinindolinium acetates were active *in vitro* against *Staph. aureus* in broth at dilutions of 1 : 128,000 and 1 : 256,000, but the activity fell to 1 : 16,000 and <1 : 8000 in the presence of blood. Activity against *B. coli* and *Ps. pyocyanea* was not appreciable.

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