175. *Carbazoles, Carbolines, and Related Compounds. Part II. Transformations of Some Quaternary Salts of Quindoline.*

By S. J. Holt and V. Petrow.

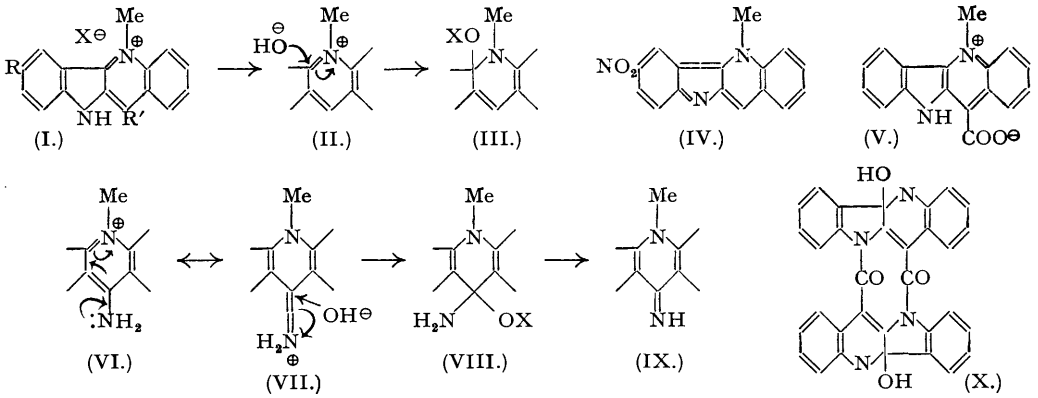
Pseudo-bases of two types have been prepared from quaternary salts of quindoline.

Pseudo-bases of type (III; X = H) are obtained from the quaternary *salts* of quindoline, 7-aminoquindoline, and bisquindolinoyl. These are unchanged by crystallisation from alcohols, and fail to give anhydronium bases. The quaternary *salt* from 7-nitroquindoline (I; R = NO_2, R′ = H, X = Cl), however, by virtue of the activating effect of the 7-nitro-grouping on the pyrrole hydrogen at 10, readily passes into the anhydronium base, 7-*nitro*-5-*methyl*iso*quindoline* (IV), on treatment with alkali.

A pseudo-base of type (VIII; X = H), on the other hand, is obtained from 11-*amino-quindoline methiodide* (I; R = H; R′ = NH_2; X = I). In contrast to pseudo-bases of type (III), (VIII; X = H) gives the corresponding *ethers* (VIII; X = Me and Et) on crystallisation from methyl or ethyl alcohol. These pass readily into the *anhydronium base* (IX) by loss of the alcohol.

We have now extended earlier work (Part I; Holt and Petrow, *J.*, 1947, 607) on the relationship between structure and biological activity in the quindoline series, by the preparation of some quaternary salts. Treatment of these with alkali has led to the formation of pseudo-bases, the transformations of which show certain points of interest.

Treatment of 5-methylquindolinium iodide (I; R = R′ = H, X = I) with alkali leads to the formation of a deep violet pseudo-base, readily soluble in chloroform (see Experimental), to which Fichter and Boehringer (*Ber.*, 1906, **39**, 3936; cf. Fichter and Probst, *ibid.*, 1907, **40**, 3478) assigned structure (III; X = H). Their evidence for this formulation rested largely on



the non-formation of a dihydroquindolinone on oxidation. Fichter and Probst (*loc. cit.*) remarked that crystallisation of this base from methyl alcohol failed to produce the corresponding methoxy-compound (III; X = Me), although substitution of hydrogen by alkyl in pseudo-bases by means of this method is a well-established reaction. We have confirmed the evidence submitted by the earlier workers in support of (III; X = H), and have also carried out systematic attempts to convert (III; X = H) into an anhydronium base, but without success. Its formation from (I; R = R′ = H, X = I), it may be added, probably proceeds by the mechanism indicated in (II).

7-Nitroquindoline (Part I, *loc. cit.*), is readily converted into the corresponding 7-*nitro*-5-*methylquindolinium chloride* (I; R = NO_2, R′ = H, X = Cl). In contrast to the methochloride of the parent base (Armit and Robinson, *J.*, 1922, 829), however, this compound passes smoothly into the anhydronium base, 7-*nitro*-5-*methyl*iso*quindoline* (IV) on treatment with alkali in hot methanol. This compound is remarkable for its brilliant scarlet colour, which is not unexpected in view of its interesting and extensive conjugation. Reduction of 7-nitro-5-methylquindolinium chloride (I; R = NO_2, R′ = H, X = Cl) with reduced iron in aqueous alcohol containing a little calcium chloride gave 7-*amino*-5-*methylquindolinium chloride* (I; R = NH_2, R′ = H, X = Cl) which again failed to pass into an anhydronium base, yielding only the pseudo-base (III; R = NH_2, R′ = H, X = H) on treatment with alkali. All operations involving this pseudo-base had to be carried out in an inert atmosphere, as oxidation takes place very readily with formation of an insoluble, green compound. The atypical behaviour of the nitro-quaternary

salt (I; R = NO_2, R′ = H, X = Cl) in forming the anhydronium base (IV) is without doubt a direct result of the activating effect of the polar nitro-grouping on the reactivity of the pyrrole hydrogen atom in position 10.

The behaviour of 11-aminoquindoline (Part I, *loc. cit.*), on the other hand, followed a different pattern. Treatment with methyl iodide in boiling methanol gave *11-amino-5-methylquindolinium iodide* (I; R = H, R′ = NH_2, X = I). The constitution assigned to this compound followed from the observation that 10-acetyl-11-diacetylaminoquindoline (Part I, *loc. cit.*) gave the corresponding *11-amino-5-methylquindolinium chloride* on treatment with methyl sulphate followed by hydrolysis with dilute hydrochloric acid, both the chloride and the iodide obtained by the different routes giving the same alkoxyl pseudo-base and anhydronium base (see below). Treatment of an aqueous suspension of this methochloride with warm dilute ammonium hydroxide, or with cold dilute sodium hydroxide, precipitated a red, insoluble compound converted into the original quaternary salts on treatment with acids. Analytical results were not entirely satisfactory, but this compound is without doubt the corresponding pseudo-base. In striking contrast to compounds of type (III; X = H), however, its crystallisation from methyl or ethyl alcohol gave the respective *11-amino-11-methoxy-* (VIII; X = Me) or *11-amino-11-ethoxy-5-methyl-5 : 11-dihydroquindoline* (VIII; X = Et), passing smoothly on warming by loss of alcohol into the corresponding anhydronium base, *11-imino-5-methyl-5 : 11-dihydroquindoline* (IX). The latter passed into the original methochloride on treatment with hydrochloric acid. The observed experimental results receive a ready interpretation on the basis of formulæ (VIII) and (IX) assigned to the pseudo- and imino-bases. These formulations, too, are readily explicable along the lines indicated in (VI) ⟶ (VII) ⟶ (VIII). A similar rearrangement, it may be added, has been observed by Albert and Ritchie (*J.*, **1943**, 459), who obtained 5-imino-10-methylacridane from 5-amino-10-methylacridinium iodide by treatment with alkali followed by heating of the product to 130°. In contrast to the quaternary salt of 5-aminoacridine which readily gives 10-methylacridone on heating with 0·05N-sodium carbonate solution (*ibid.*), 11-amino-5-methylquindolinium iodide gives only the pseudo-base after prolonged heating under the same conditions.

Quindoline-11-carboxylic acid proved too insoluble for direct conversion into the quaternary salt. The latter was prepared by reaction of the readily soluble methyl ester (Part I, *loc. cit.*) with methyl sulphate in benzene solution giving (I; R = H, R′ = CO_2Me, X = $MeSO_4$), followed by hydrolysis with dilute hydrochloric acid whereby *11-carboxy-5-methylquindolinium chloride* (I; R = H, R′ = CO_2H, X = Cl) was obtained. This compound readily dissolved in hot sodium hydroxide from which the garnet-red *sodium* salt of the pseudo-base (III; R = H, R′ = CO_2Na, X = H) crystallised out on cooling. On boiling this compound with water, removal of the elements of sodium hydroxide occurred, giving the *zwitterion* (V). The latter was also obtained when (I; R = H, R′ = CO_2H, X = Cl) was heated with sodium acetate solution. It passed into the original chloride on treatment with hydrochloric acid.

Finally, reaction of " bisquindolinoyl " (Part I, *loc. cit.*) with methyl sulphate gave a red product consisting of a mixture of two methosulphates. This conclusion followed from the results obtained on treating an aqueous solution of the methosulphates with alkali in the presence of chloroform. The red aqueous layer yielded 11-carboxy-5-methylquindolinium chloride (I; R = H, R′ = CO_2H, X = Cl) on treatment with hydrochloric acid. The blue chloroform-soluble fraction gave indigo-blue needles of a compound which was evidently the *pseudo-base* (X), although its analytical figures were not entirely satisfactory.

Experimental.

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

Pseudo-base from 5-Methylquindolinium Chloride (III; X = H).—Improved method of preparation: Chloroform (20 ml.) and 2N-sodium hydroxide (7·5 ml.) were added in turn to 5-methylquindolinium chloride (2·0 g.) (Armit and Robinson, *loc. cit.*), dissolved in warm water (200 ml.), in a separating funnel. After thorough agitation, the chloroform layer was washed, dried, filtered, and evaporated to 5 ml., whereupon dark, reddish-violet needles of the pseudo-base (600 mg.) separated (Found: C, 76·6; H, 5·5; N, 11·1. Calc. for $C_{16}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2%).

7-Nitro-5-methylquindolinium Chloride (I; R = NO_2, R′ = H, X = Cl).—7-Nitroquindoline (2·0 g.) in nitrobenzene (60 ml.) at 150° was treated with methyl sulphate (2·5 ml.). After 1½ hours the product was precipitated with benzene (300 ml.), hydrolysed for 15 mins. with concentrated hydrochloric acid (10 ml.) in methanol (200 ml.; charcoal), and the product which separated on cooling recrystallised from methanol. *7-Nitro-5-methylquindolinium chloride* (1·8 g.; 75%) formed small, bright yellow needles, m. p. 294—296° (decomp.) (Found: N, 13·3; Cl, 11·1. $C_{16}H_{12}O_2N_3Cl$ requires N, 13·4; Cl, 11·3%).

7-Nitro-5-methylisoquindoline (IV), crimson needles from methanol (90 mg.), m. p. 280—283° (Found:

C, 69·3; H, 4·3; N, 15·2. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0; N, 15·2%), was prepared by treating a boiling suspension of 7-nitro-5-methylquindolinium chloride (155 mg.) in methanol (20 ml.) with 2N-sodium hydroxide (0·28 ml.) under reflux for 15 mins.

7-*Amino-5-methylquindolinium Chloride* (I; R = NH_2, R′ = H, X = Cl).—This *salt*, a yellow, microcrystalline powder (600 mg.) from ethanol–hydrochloric acid (100 : 1, v/v) (Found: N, 14·6; Cl, 12·7. $C_{16}H_{14}N_3Cl$ requires N, 14·8; Cl, 12·5%), was prepared by reducing 7-nitro-5-methylquindolinium chloride (1·25 g.) with reduced iron (3·5 g.) in 80% ethanol (50 ml.) containing calcium chloride (100 mg.) for 12 hours under reflux.

Pseudo-base from 7-*Amino-5-methylquindolinium Chloride*.—7-Amino-5-methylquindolinium chloride (500 mg.) was dissolved in air-free water (50 ml.) in a separating funnel. Hydrogen was passed through to effect agitation, and freshly distilled chloroform (10 ml.) and air-free 2N-sodium hydroxide (20 ml.) were added in turn. After 5 minutes the chloroform layer was run off into another separating funnel containing air-free water (50 ml.) and a trace of sodium dithionite (hydrosulphite), and agitated by a stream of hydrogen. The washed chloroform layer was dried (Na_2SO_4) in hydrogen and concentrated to *ca.* 2 ml. Indigo-blue needles of the base crystallised out (Found: C, 72·6; H, 5·3; N, 15·9. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·8%).

11-*Amino-5-methylquindolinium iodide* (I; R = H, R′ = NH_2, X = I), yellow microscopic needles (2·15 g.) from methanol, which decomposed on heating with liberation of iodine (Found: N, 11·3; I, 33·6. $C_{16}H_{14}N_3I$ requires N, 11·2; I, 33·8%), was obtained by heating 11-aminoquindoline (2·4 g.) with methyl iodide (10 ml.) in methanol (25 ml.) under reflux for 4 hours.

11-*Amino-5-methylquindolinium Chloride*.—Triacetyl-11-aminoquindoline (1·0 g.) in nitrobenzene (20 ml.) at 160° was treated with methyl sulphate (0·4 ml.) for 30 minutes. The product, precipitated with benzene (100 ml.), was heated under reflux with 2N-hydrochloric acid (100 ml.) for 30 minutes, and the solid which separated on cooling recrystallised from methanol. 11-*Amino-5-methylquindolinium chloride* (500 mg.) formed yellow micro-needles charring at 375° (Found: N, 14·8; Cl, 12·5. $C_{16}H_{14}N_3Cl$ requires N, 14·8; Cl, 12·5%).

11-*Amino*-11-*ethoxy*-5-*methyl*-5 : 11-*dihydroquindoline* (VIII; X = Et), reddish-orange needles (150 mg.) from ethanol (Found: C, 73·9; H, 6·4; N, 14·2; OEt, 15·2. $C_{18}H_{19}ON_3$ requires C, 73·8; H, 6·5; N, 14·3; OEt, 15·4%), was prepared by adding 2N-sodium hydroxide (0·55 ml.) to a boiling suspension of 11-amino-5-methylquindolinium iodide (375 mg.) in pure ethanol (10 ml.), heating the mixture under reflux for 5 mins., and allowing the filtered solution to cool.

11-*Amino*-11-*methoxy*-5-*methyl*-5 : 11-*dihydroquindoline* (VIII; X = Me), prepared as above but using methanol (20 ml.), formed long, orange needles (200 mg.) from methanol (Found: C, 73·4; H, 6·0; N, 15·1; OMe, 10·8. $C_{17}H_{17}ON_3$ requires C, 73·2; H, 6·1; N, 15·1; OMe, 11·1%). On treatment of its methanolic solution (200 mg. in 40 ml.) with concentrated hydrochloric acid (0·2 ml.), 11-amino-5-methylquindolinium chloride separated on standing (Found: N, 14·8; Cl, 12·4%), identical with the product described above.

11-*Imino*-5-*methyl*-5 : 11-*dihydroquindoline* (IX), a vermilion powder or needles decomposing at *ca.* 172° (Found: C, 78·0; H, 5·5; N, 16·9. $C_{16}H_{13}N_3$ requires C, 77·8; H, 5·3; N, 17·0%), was prepared by heating finely powdered analytically pure 11-amino-11-methoxy-5-methyl-5 : 11-dihydroquindoline at 110°/10 mm. for 15 minutes. With acids it gave the corresponding 11-aminoquindoline quaternary salts.

11-*Carbomethoxy*-5-*methylquindoline* 5-*methosulphate* (I; R = H; R′ = CO_2Me, X = $MeSO_4$), red needles (3·2 g.) from methanol, m. p. 274° (decomp.) (Found: C, 56·7; H, 4·6; N, 7·2; OMe, 15·2. $C_{19}H_{18}O_6N_2S$ requires C, 56·7; H, 4·5; N, 7·0; OMe, 15·4%), was prepared by treating a solution of 11-carbomethoxyquindoline (7·0 g.) in benzene (250 ml.) with methyl sulphate (3·6 ml.) under reflux for 5 hours.

11-*Carboxy*-5-*methylquindolinium chloride* (I; R = H, R′ = CO_2H, X = Cl), orange needles giving an amorphous red powder (900 mg.) on drying at 100°/10 mm., m. p. 268° (decomp.) (Found: N, 8·8; Cl, 11·6. $C_{17}H_{13}O_2N_2Cl$ requires N, 9·0; Cl, 11·4%), was obtained when an aqueous solution of the foregoing ester (1·5 g.) was heated under reflux with concentrated hydrochloric acid (5 ml.) for 30 minutes and the mixture allowed to cool. The product was very soluble in water, and was washed with 2N-hydrochloric acid and dried over potash in a vacuum.

The sodium salt of the pseudo-base from 11-carboxy-5-methylquindolinium chloride, garnet-red needles (500 mg.) (Found: C, 64·6; H, 4·0; N, 9·0. $C_{17}H_{13}O_3N_2Na$ requires C, 64·5; H, 4·1; N, 8·9%), was obtained when a hot solution of the chloride (500 mg.) in water (10 ml.) was added to hot 2N-sodium hydroxide (10 ml.), and the mixture heated until solution was complete and allowed to cool.

The corresponding *zwitterion* (V) was obtained when (*a*) the foregoing sodium salt (400 mg.) was heated under reflux with water (20 ml.) for 20 minutes and the mixture allowed to cool, m. p. 265° (decomp.) (Found: N, 10·2. $C_{17}H_{12}O_2N_2$ requires N, 10·2%), or (*b*) solid sodium acetate (5·0 g.) was added to a hot solution of 11-carboxy-5-methylquindolinium chloride (1·0 g.) in water (50 ml.). Concentrated hydrochloric acid was then carefully added just to redissolve the flocculent precipitate, followed by a further quantity of sodium acetate (5·0 g.). The hot filtered solution (charcoal) deposited yellow needles of the zwitterion, m. p. 265° (decomp.) (Found: C, 73·9; H, 4·5; N, 10·2. Calc.: C, 73·9; H, 4·4; N, 10·2%), identical with the product obtained under (*a*).

Quaternisation of "Bisquindolinoyl".—Bisquindolinoyl (2·4 g.) in nitrobenzene (50 ml.) was treated at 160° for 1½ hours with methyl sulphate (3 ml.). The red crystalline product (1·8 g.), dissolved in water (150 ml.) in a separating funnel, was treated with chloroform (50 ml.) followed by 2N-sodium hydroxide until alkaline to phenolphthalein. After thorough shaking, the dark blue chloroform layer was separated, the aqueous layer extracted with fresh chloroform (25 ml.), and the combined extracts washed, dried, and concentrated to *ca.* 7·5 ml. under reduced pressure. The product from chloroform (5 ml.) gave lustrous blue-black needles of the *pseudo-base* (X) (500 mg.), m. p. *ca.* 173° (with previous decomp.) (Found on sample dried at 56°/10 mm.: C, 73·6; H, 4·7; N, 9·9. $C_{34}H_{24}O_4N_4$ requires C, 74·1; H, 4·4; N, 10·1%). Acidification of the reddish-purple aqueous layer with hydrochloric acid

gave orange-red needles on standing, identified as 11-carboxy-5-methylquindolinium chloride (400 mg.), m. p. 268° (decomp.), alone or in admixture with an authentic specimen (Found: N, 8·9. Calc. for $C_{17}H_{13}O_2N_2Cl$: N, 9·0%).

Biological Data.—Dr. R. Wien, Biological Division, May and Baker Ltd., has very kindly reported the following results: 7-Amino- and 11-amino-quindolines are inactive as trypanocidal or anti-malarial substances. Of the quaternary salts, only 11-amino-5-methylquindolinium acetate slowed a slight, but not curative, effect against *T. congolense*. Some of the compounds showed greater potentialities as antibacterial agents. Three, namely 11-aminoquindoline, and the 7-nitro- and 11-amino-quindolinium salts, were active *in vitro* against *B. coli* at a dilution of 1 : 128,000. Against *Staph. aureus* they showed fairly high activity in broth. This was reduced in the presence of blood to 1 : 16,000—64,000, except in the case of the 5-methylquindolinium chloride which was active at 1 : 128,000.

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