375. *Synthesis of Some Glyoxalino*(1′ : 2′-1 : 2)*quinolines.*

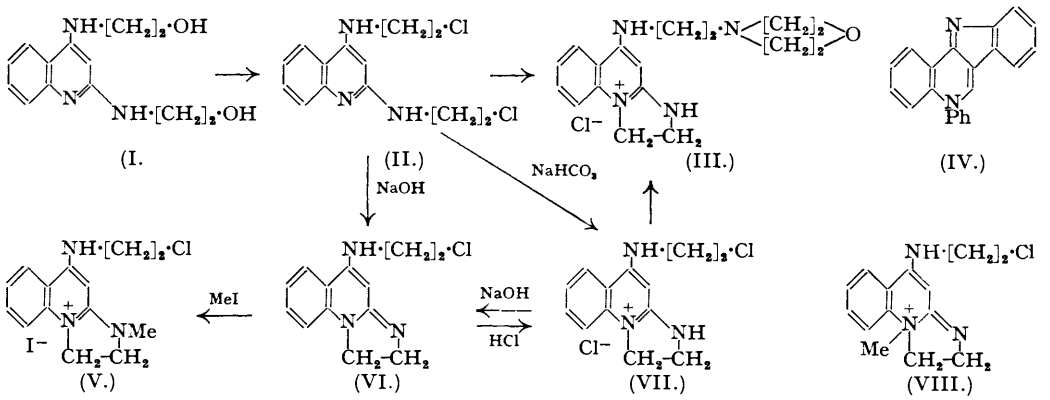
By J. M. Osbond.

In an attempt to prepare quinoline derivatives with two basic side chains, 2 : 4-dichloroquinoline was readily converted into the corresponding 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride. The base (II) derived from this, however, under the influence of bases such as morpholine or aqueous alkalis yielded a dihydroglyoxalinoquinoline by cyclisation of the side chain in the 2-position with the quinoline-nitrogen atom. Some reactions and derivatives of this type of ring system are described.

It has been demonstrated (Fulton, Joyner, King, Osbond, and Wright, *Proc. Roy. Soc.*, 1950, *B*, in the press) that certain 4-alkylaminoethylaminoquinaldines display high action against *Entamœba histolytica in vitro*, approaching in some cases the activity of emetine. In an attempt to extend this work, it was thought to be of interest to prepare 2 : 4-di(alkylaminoethylamino)-quinolines. It was hoped that 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride (cf. II) would, when condensed with various primary and secondary amines, afford a series of homologous quinolines. 2 : 4-Di-(2-hydroxyethylamino)quinoline (I), which was readily prepared by heating 2 : 4-dichloroquinoline with an excess of ethanolamine, was identical with a specimen previously obtained as a by-product in the condensation of ethanolamine and 2-anilino-4-chloroquinoline (Fulton *et al.*, *loc. cit.*).

This dihydroxy-base (I) with phosphorus oxychloride gave the hydrochloride of the corresponding dichloro-compound (II) in good yield. When this hydrochloride was condensed with morpholine the expected dimorpholino-derivative was not obtained. Instead, a quaternary chloride was isolated as the hydrochloride, $C_{17}H_{23}ON_4Cl,HCl$: the chlorine atom of the side-chain in the 4-position had been replaced by the morpholino-radical whereas the chlorine atom

in the side chain in the 2-position had formed a quaternary salt with the ring nitrogen atom, thus giving 4′ : 5′-dihydro-4-(2-morpholinoethylamino)glyoxalino(3′ : 2′-1 : 2)quinolinium

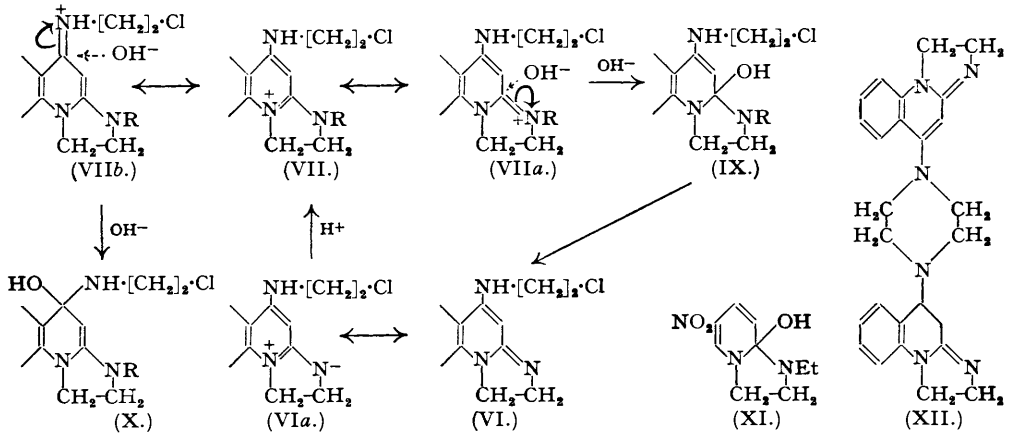


chloride hydrochloride (cf. III). When a solution of the hydrochloride of (II) was treated with cold saturated sodium hydrogen carbonate solution, the base (II) separated as a pale yellow oil which, if left in contact with the aqueous solution, soon dissolved. The oil could however be isolated by rapid extraction with ether, but the solution thus obtained, when kept at room temperature, soon became cloudy and deposited 4-(2-chloroethylamino)-4′ : 5′-dihydroglyoxalino(3′ : 2′-1 : 2)quinolinium chloride (VII) as colourless crystals, readily soluble in water, in which they gave rise to chlorine ions. When, however, dilute aqueous sodium hydroxide solution was added to a solution of the hydrochloride of (II) a colourless oil separated which rapidly became yellow; on gentle warming of the mixture for a short while, the oil solidified to a yellow solid melting above 320°. This contained halogen but not in an ionic form, and is the anhydronium base, 4-(2-chloroethylamino)-4′ : 5′-dihydroglyoxalino(1′ : 2′-1 : 2)quinoline (VI); with dilute hydrochloric acid, it gave (VII). Similarly, although the quaternary chloride (VII) was stable to sodium hydrogen carbonate solution, addition of aqueous sodium hydroxide gave (VI) which was identified by reconversion into (VII) and was further characterised as the corresponding quaternary bromide (cf. Armit and Robinson, *J.*, 1925, 1604; Holt and Petrow, *J.*, 1948, 922). Treatment of the quaternary salt (VII) with hot dilute alkali for a longer period gave an amorphous material insoluble in all the normal solvents and no longer giving a crystalline hydrochloride.

Since (VII) is readily converted into (VI), formation of the anhydronium base (VI) by treatment of the salt (II) with sodium hydroxide probably proceeds by way of (VII). The interconversion of (VI) and (VII) probably proceeds by the mechanism formulated below. The quaternary salt has the resonance forms (VII, VII*a*, and VII*b*; R = H), resembling those of an amidine salt, and gives in the presence of hydroxyl ions a quaternary hydroxide which readily loses water in its pseudo-base form (IX; R = H) to give the anhydronium base. This base can also exist in three resonance forms, two of which are (VI) and (VI*a*), and by the addition of a proton gives the quaternary salt (VII). Since the pseudo-base (IX; R = H) is a possible intermediate in the conversion of (VII) into (VI) an attempt was made to isolate it by treating (VII), in the cold, with alkali and then immediately extracting the base with chloroform. However, only the anhydronium base was isolated. Since, moreover, pseudo-bases readily form the corresponding methoxy- or ethoxy-derivative in the presence of methyl or ethyl alcohol respectively (cf. Decker, *Ber.*, 1900, **33**, 1715; *J. pr. Chem.*, 1892, **45**, 182; Holt and Petrow, *J.*, 1948, 919), a solution of the quaternary chloride (VII) in ethyl alcohol was made just alkaline with dilute aqueous sodium hydroxide and set aside at room temperature. From this a yellow crystalline material was isolated which did not contain halogen and in water gave a strongly alkaline solution. Analysis indicated it to be 1 : 4-bis-[4′ : 5′-dihydroglyoxalino(1′ : 2′-1 : 2)quinol-4-yl]piperazine (XII) derived from two molecules of (VI) by loss of hydrogen chloride (cf. Knorr, *Ber.*, 1905, **38**, 3135; 1906, **39**, 1420; Hanby and Rydon, *J.*, 1947, 513).

With methyl iodide at room temperature (VI) gives a quaternary methiodide, which is formulated as 4-(2-chloroethylamino)-4′ : 5′-dihydro-1′-methylglyoxalino(3′ : 2′-1 : 2)quinolinium iodide (V), rather than the alternative (VIII). It has already been shown that the yellow anhydronium base (VI) gives by proton addition, colourless salts (VII) thus allowing the quinoline system to re-establish its conjugated structure; it therefore seems probable that

addition of methyl iodide (VI) will similarly give the more stable structure (V) rather than retain the less stable arrangement of bonds represented by (VIII). It is interesting that Mann (*J.*,



1949, 2816) discusses the somewhat similar case where treatment of the bright greenish-yellow base, 1-phenyl-ψ-indolo(3′ : 2′-3 : 4)quinoline (IV), which has a vinylogous relationship with the anhydronium base (VI), with acids gives a colourless cation owing to the formation of the normal aromatic structure of the indole and quinoline system but that the mono-methiodide and -ethiodide are buff-coloured, probably owing to a resonance hybrid. In the present case, however, the methiodide (V) like the other quaternary salt (VII) is colourless as would be expected. When the methiodide (V) was warmed on the water-bath with dilute sodium hydroxide a yellow gummy product was formed and 2-chloroethylamine was readily evolved. The unsubstituted quaternary salt (VII) did not undergo a similar change under these conditions but gave, as already described, the anhydronium base (VI). The cation of the monomethiodide (V) has also the resonance forms (VII, VII*a*, and VII*b*; R = Me), and the quaternary hydroxide can presumably give rise to the two possible pseudo-bases (IX and X; R = Me). In this case, owing to the lack of the necessary hydrogen on the nitrogen atom in the 1-position, (IX; R = Me) cannot readily lose water. The other pseudo-base form (X; R = Me), however, can give 2-chloroethylamine and a glyoxalinoquinolone.

The quaternary chloride (VII) readily condensed with morpholine or piperidine to give respectively the morpholino-derivative (III) already described and the analogous piperidino-compound.

Although four 4′ : 5′-dihydro-5′-ketoglyoxalino(3′ : 2′ : 1 : 2)quinolinium salts have been prepared by Harriman (U.S.P. 2,421,693; *Chem. Abstr.*, 1947, **41**, 6830) by the condensation of 2-aminoquinoline and the appropriate α-halogenated acyl halide, no properties or reactions of these compounds are given and no earlier reference to this ring system can be found. A parallel series of reactions has, however, been carried out with 2-(2-chloroethylamino)pyridine hydrochloride and its derivatives by Bremer (*Annalen*, 1935, **521**, 286) who found that this salt when warmed with strong alkali gave 4 : 5-dihydropyriminazole. The free base, 2-(2-chloroethylamino)pyridine, was isolated and gave a quaternary salt in the hot, but no properties or analyses for these two compounds are given. Of particular interest was the cyclisation of 2-(*N*-2-chloroethyl-*N*-ethylamino)-5-nitropyridine with potassium carbonate to a base which Bremer considers might be the pseudo-base (XI).

An attempt was made to prepare a 2 : 4-di(alkylaminoethylamino)quinoline by condensing 2 : 4-dichloroquinoline and diethylaminoethylamine in the presence of copper powder. Although a vigorous reaction took place no crystalline base or salt was obtained even after fractional extraction of the base with alkali (cf. Buchmann and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1357).

Compounds (I), (II), (III), and (VII), and the piperidino-analogue of (III), when tested against *E. histolytica* by the method of Laidlaw, Dobell, and Bishop (*Parasitology*, 1928, **20**, 207) by Dr. J. D. Fulton of this Institute, had only slight amœbicidal action.

Experimental.

2 : 4-*Di*-(2-*hydroxyethylamino*)*quinoline* (I).—2 : 4-Dichloroquinoline (19·7 g., 1 mol.), prepared from 2 : 4-dihydroxyquinoline by the method of Buchmann and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**,

1357), and ethanolamine (30 c.c., 5 mols.) were heated in an oil-bath until the external temperature reached 110°. When the internal temperature reached 95—100° the two layers mixed and the temperature rose to 125°. The flask was then removed from the oil-bath and, when the internal temperature rose to 150°, the reaction was moderated by cooling the flask. The mixture was then heated for a further 20 minutes at 145° and poured into water (800 c.c.), and the yellow oil which separated dissolved by warming the mixture to 40°. The yellow solution was made alkaline by the addition of excess of 2N-sodium hydroxide, and the precipitated crystalline base was collected and crystallised from ethanol, (1 l.), separating in colourless needles (21 g.), m. p. 190—191° (Found : N, 16·6. Calc. for $C_{13}H_{17}O_2N_3$: N, 17·0%). A mixed m. p. with a specimen (m. p. 193°) supplied by Dr. H. King showed no depression. Treatment of the base with N-hydrobromic acid gave a *monohydrobromide* which separated from ethanol as clusters of prisms, m. p. 184° (Found : C, 47·9; H, 5·7. $C_{13}H_{17}O_2N_3$,HBr requires C, 47·6; H, 5·5%).

2 : 4-*Di*-(2-*chloroethylamino*)*quinoline Hydrochloride* (II).—The dihydroxy-base (24·7 g.) was added to phosphorus oxychloride (120 c.c.). After 1 minute a vigorous reaction started at room temperature, the mixture was vigorously shaken, and the flask plunged into cold water. When the reaction had subsided the clear solution was heated on a water-bath for 1 hour. The excess of phosphorus oxychloride was removed on the water-bath under reduced pressure and the syrupy residue poured into water (300 c.c.) and warmed slightly to facilitate decomposition of the complex. The mixture was left overnight at 0°. The solid was collected and crystallised from methanol–ethyl acetate from which the *hydrochloride* separated slowly in rosettes of long slender prisms (30 g.), m. p. 133° (Found : C, 46·2; H, 5·3; N, 12·4; Cl^-, 11·3; H_2O, 5·0. $C_{13}H_{15}N_3Cl_2$,HCl,H_2O requires C, 46·1; H, 5·3; N, 12·4; Cl^-, 10·8; H_2O, 5·3%). After being dried at 100° the anhydrous *hydrochloride* has m. p. 145° (Found : C, 48·95; H, 5·1. $C_{13}H_{15}N_3Cl_2$,HCl requires C, 48·7; H, 5·0%).

4′ : 5′-*Dihydro*-4-(2-*morpholinoethylamino*)*glyoxalino*(3′ : 2′-1 : 2)*quinolinium Chloride Hydrochloride* (III).—(*a*) The hydrochloride (II) (5 g.) and morpholine (15 c.c.) were heated on a water-bath for 30 minutes. The salt dissolved and after 15—20 minutes a heavy solid was precipitated. The mixture was cooled to 0°, ether was added, and the solid material collected and dissolved in slight excess of dilute hydrochloric acid. The solution was taken to dryness and the resulting solid gave after several recrystallisations from ethanol the quaternary *chloride hydrochloride* (2·5 g.) in sheathes of woolly needles, m. p. 290° (Found : C, 52·7; H, 6·95; N, 13·9; H_2O, 5·5. $C_{17}H_{23}ON_4Cl$,HCl,H_2O requires C, 52·4; H, 6·7; N, 14·4; H_2O, 4·6%). A specimen was analysed after drying at 115° for 5 hours (Found : C, 55·0; H, 7·0. $C_{17}H_{23}ON_4Cl$,HCl requires C, 55·0; H, 6·5%).

(*b*) Prepared in the same way as the piperidino-compound recorded below, from (VII) and morpholine, the salt separated from alcohol in needles, m. p. 290°, undepressed on admixture with that recorded in (*a*).

4-(2-*Chloroethylamino*)-4′ : 5′-*dihydroglyoxalino*(3′ : 2′-1 : 2)*quinolinium Chloride* (VII).—(*a*) To a suspension of 2 : 4-di-(2-chloroethylamino)quinoline hydrochloride (10 g.) in water (300 c.c.) was added a cold saturated solution of sodium hydrogen carbonate (250 c.c.). The pale yellow oil precipitated was rapidly extracted with ether (3 × 100 c.c.). If the free base is not extracted at onee it cyclises spontaneously and dissolves in the aqueous solution. The filtered ethereal extract rapidly became cloudy and when kept at room temperature deposited colourless crystals. The therc was distilled off and the resulting white solid was recrystallised from ethanol from which the quaternary *chloride* separated in long prisms (4·0 g.), m. p. 220—221° (Found : C, 52·1; H, 6·1; N, 14·3; Cl^-, 11·4; H_2O, 6·3. $C_{13}H_{15}N_3Cl_2$,H_2O requires C, 51·7; H, 6·3; N, 13·9; Cl^-, 11·7; H_2O, 6·0%). The salt was dried for analysis at 115° (Found : C, 55·3; H, 5·0; N, 14·3. $C_{13}H_{15}N_3Cl_2$ requires C, 54·9; H, 5·3; N, 14·8%). Treatment with excess of N-hydrochloric acid gave the quaternary chloride unchanged. An aqueous solution of the salt is unaffected by treatment with sodium hydrogen carbonate or sodium carbonate solution, but a yellow base is precipitated when 2N-sodium hydroxide is added (see below).

(*b*) The crude anhydronium base (VI) [see below; from (II) (30 g.)] was treated with hot N-hydrochloric acid (75 c.c.), and the resulting solution was concentrated under reduced pressure. After cooling, the white crystalline mass (20 g.) was collected and crystallised from ethanol in long prisms (19·5 g.), m. p. 219—221°, identical with the chloride described above (mixed m. p.). Similar treatment with aqueous hydrogen bromide gave the corresponding *bromide* as colourless needles (from ethanol), m. p. 220° (Found : C, 47·4; H, 4·9; N, 12·8. $C_{13}H_{15}N_3ClBr$ requires C, 47·5; H, 4·6; N, 12·8%).

4-(2-*Chloroethylamino*)-4′ : 5′-*dihydroglyoxalino*(1′ : 2′-1 : 2)*quinoline* (VI).—(*a*) To a solution of 2 : 5-di-(2-chloroethylamino)quinoline hydrochloride (17 g.) in warm water (150 c.c.) was added 2N-sodium hydroxide (50 c.c.). The white oil, which separated, rapidly became yellow and, after warming of the mixture at 40° for 5 minutes, the yellow oil solidified. The mixture was cooled rapidly and the yellow *glyoxalinoquinoline* collected and crystallised from ethanol as bunches of fine yellow prisms or from ethyl acetate, in which it is only sparingly soluble, as stout yellow prisms, m. p. >320° (Found : C, 63·2; H, 5·8; N, 16·2. $C_{13}H_{14}N_3Cl$ requires C, 63·0; H, 5·65; N, 16·95%). The base, which gives a positive Beilstein test, gives with potassium dichromate and concentrated sulphuric acid a greyish-green colour which develops through reddish-brown to olive-green.

(*b*) The chloride (VII) (1·4 g.) in water (10 c.c.) was treated with 2N-sodium hydroxide (20 c.c.); the yellow oil which separated solidified on slight warming and scratching. The base (VI), when collected, washed with water, and dried, had m. p. <320°. Treatment with dilute hydrobromic acid gave the quaternary bromide, which separated from ethanol in colourless needles, m. p. 219°, and gave no depression of m. p. when admixed with the bromide described above.

1 : 4-*Bis*-[4′ : 5′-*dihydroglyoxalino*(1′ : 2′-1 : 2)*quinol*-4-*yl*]*piperazine* (XII).—The chloride (VII) (1·45 g.) in ethanol (50 c.c.) was kept in 2N-sodium hydroxide (2 c.c.) for several weeks at room temperature. After filtration, the yellow solution was evaporated to dryness under reduced pressure. The yellow solid residue was triturated with ether and filtered off. The *piperazine* separated from benzene in short stout yellow prisms, m. p. 167°; it does not melt sharply, and gradually forms a meniscus above 167° (Found : C, 73·9; H, 6·0; N, 19·7. $C_{26}H_{26}N_6$ requires C, 73·9; H, 6·1; N, 19·9%).

4-(2-*Chloroethylamino*)-4′ : 5′-*dihydro*-1′-*methylglyoxalino*(3′ : 2′-1 : 2)*quinolinium Iodide* (V).—Methyl iodide (0·28 g.) was set aside overnight at room temperature in a solution of (VI) (0·5 g.) in methyl alcohol. The long slender needles, m. p. 225—226°, which separated (0·3 g.), were recrystallised from methanol to give the colourless quaternary *methiodide*, m. p. 226° (Found : C, 42·7; H, 4·5; N, 10·9. $C_{14}H_{17}N_3ClI$ requires C, 43·1; H, 4·4; N, 10·8%).

Action of Dilute Alkali on the Methiodide (V).—The methiodide (V) (1·0 g.) was boiled with 2N-sodium hydroxide (15 c.c.) for 10 minutes and the basic vapour, which was readily evolved, was passed into dilute hydrochloric acid. The acid solution was taken to dryness under reduced pressure, and ethyl alcohol was added and then removed under reduced pressure, to give a colourless hygroscopic salt (0·03 g.). Aqueous sodium picrate was added to this and a yellow picrate in long needles, m. p. 140—141°, separated at 0°. Recrystallisation from a small amount of water gave 2-chloroethylamine picrate, m. p. 141—142°. A mixed m. p. with an authentic specimen (m. p. 142—143°) showed no depression (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914, gives m. p. 142—143°). No crystalline material has yet been obtaind from the yellow gummy product which remained in the distilling flask.

4′ : 5′-*Dihydro*-4-(2-*piperidinoethylamino*)*glyoxalino*(3′ : 2′-1 : 2)*quinolinium Bromide Hydrobromide*.—The chloride (VII) (2·8 g., 1 mol.) was heated on the water-bath with piperidine (10·9 c.c. 10 mols.) for 30 minutes. The salt gradually dissolved and after 15—20 minutes a red oil separated which gradually solidified on further heating to give a heavy yellow precipitate. The mixture was cooled to 0°, ether was added, and the solid collected and washed with ether. Treatment of the solid with N-hydrobromic acid (40 c.c.), evaporation to dryness under reduced pressure, and crystallisation from ethanol gave the *bromide hydrobromide* in colourless short needles, m. p. 292° (Found : C, 46·7; H, 5·8; N, 12·0. $C_{18}H_{25}N_4Br,HBr$ requires C, 47·2; H, 5·7; N, 12·2%). The *chloride hydrochloride* separated from ethanol in microcrystalline form, m. p. 295° (Found : C, 55·7; H, 7·3; N, 14·3; H_2O, 5·2. $C_{18}H_{25}N_4Cl,HCl,H_2O$ requires C, 55·8; H, 7·2; N, 14·5; H_2O, 4·7%).

Reaction between Diethylaminoethylamine and 2 : 4-*Dichloroquinoline*.—2 : 4-Dichloroquinoline (1·97 g., 1 mol.), 2-diethylaminoethylamine (6·9 g., 6 mols.), and copper powder (0·25 g.) were heated in an oil-bath. At 120° a vigorous reaction ensued and the mixture was then heated at 140° for a further 3 hours. The mixture was treated with dilute alkali and the bases were extracted with chloroform. The chloroform and excess of base were removed by distillation at 130° under reduced pressure. The remaining red gummy base could not be induced to crystallise or to give a crystalline salt. The base was fractionally extracted from N-hydrobromic acid (40 c.c.) with N-sodium hydroxide (4 × 10 c.c.) and chloroform in 10 fractions. No crystalline base or salt could be obtained.

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