CXXXV.—*Studies in Chemotherapy (Antimalarials). Part I. A Derivative of Glyoxalinoquinoline.*

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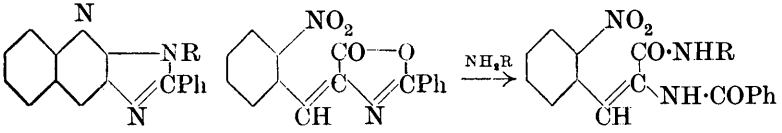
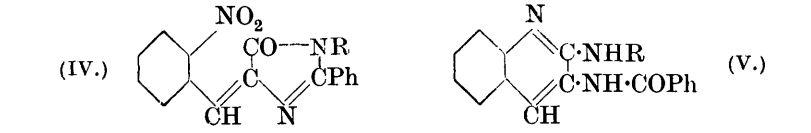
THREE lines of investigation on antimalarials derived from quinoline have been published recently, namely, aminoalkylaminoquinolines, similar to plasmoquine in structure (Baldwin, J., 1929, 2959), aminoalkylquinolinium salts (Seshadri, *ibid.*, p. 2952), and 4-piperidino- and 4-piperazino-derivatives of quinoline (Kermack and Smith, J., 1930, 1256). Mrs. Robinson (J., 1929, 2948) has described pyrroloquinolines having similarity in structure to harmine and harmaline, which are reputed antimalarials (Gunn and Marshall, *Proc. Roy. Soc., Edin.*, 1920, **15**, 145), and Chatterji (J., 1929, 2965) has recorded the preparation of β-benziminazolylethylamine derivatives.

The present investigation was undertaken with the object of preparing *glyoxalinoquinolines* (I). These substances are related to the iminazoles of Chatterji and also, partly, to the carbostyrils examined by Fourneau and his collaborators (*Ann. Inst. Pasteur*, 1930, **44**, 503).



(I.) (II.) (III.)

The *azlactone* (II), prepared by the condensation of *o*-nitrobenzaldehyde with hippuric acid by the method of Erlenmeyer, jr. (*Annalen*, 1904, **337**, 265 *et seq.*), when heated with an aromatic amine in presence of copper powder, furnished in most cases an



anilide (III) together with a small amount of a cyclic *imine* (IV). The substance (III) was smoothly converted into (IV) by phosphoryl

chloride on the steam-bath. On reduction with zinc dust in hot acetic acid, the substance (IV) furnished the glyoxalinoquinoline (I), but the anilide (III) gave 2-*anilino*-3-*benzamidoquinoline* (V).

A preliminary investigation, still incomplete, has indicated that some of the compounds described below are actively toxic to paramæcia in a dilution of 1 : 1000.

EXPERIMENTAL.

The azlactone (8 g.) prepared from piperonal and hippuric acid was heated with *m*-toluidine (3 g.) and a trace of copper-bronze at 160—170° for 2 hours. An extract of the cooled mass in hot acetic acid furnished, on cooling, *piperonylidenebenzamidoaceto*-m-*toluidide*, $CH_2{:}O_2{:}C_6H_3{\cdot}CH{:}C(NH{\cdot}COPh){\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}CH_3$, m. p. 233°, which gave a deep red solution in concentrated sulphuric acid (Found : C, 72·3; H, 5·0; N, 7·3. $C_{24}H_{20}O_4N_2$ requires C, 72·0; H, 5·0; N, 7·0%). The mother-liquor on dilution with much water furnished a second substance, m. p. 167° after crystallisation from hot dilute acid (charcoal) and alcohol (charcoal) (Found : N, 7·4. $C_{24}H_{18}O_3N_2$ requires N, 7·3%). This substance, which was presumably 5-*keto*-2-*phenyl*-1-m-*tolyl*-4-*piperonylidene*-4 : 5-*dihydroglyoxaline*, was also obtained when the aceto-*m*-toluidide (1 g.), dissolved in phosphoryl chloride (5 c.c.), was gently heated on the steam-bath, and the product decomposed with ice; after crystallisation from hot dilute alcohol (charcoal), it had m. p. and mixed m. p. 167°.

When the same azlactone was similarly condensed with *p*-toluidine, and the product worked up as described above, *piperonylidenebenzamidoaceto*-p-*toluidide*, m. p. 248—249° after recrystallisation from hot acetic acid, was obtained (Found : C, 71·6; H, 5·0; N, 7·2%); the mother-liquor furnished 5-*keto*-2-*phenyl*-1-p-*tolyl*-4-*piperonylidene*-4 : 5-*dihydroglyoxaline*, which crystallised from alcohol in woolly needles, m. p. 230° (Found : N, 7·4%). The substance is only feebly basic, being reprecipitated from its solution in hot concentrated hydrochloric acid on dilution. Attempts to reduce it to the piperonyl compound were unsuccessful.

The *azlactone* (II) obtained from *o*-nitrobenzaldehyde and hippuric acid crystallised from hot acetic acid (charcoal) in golden-yellow rectangular plates, m. p. 166° (Found : C, 64·8; H, 3·4; N, 9·8. $C_{16}H_{10}O_4N_2$ requires C, 65·3; H, 3·4; N, 9·5%). It was very sparingly soluble in alcohol, but dissolved with the development of a deep red colour when treated with alkali hydroxide in the hot solvent; on acidification, it was not precipitated immediately.

The azlactone, on condensation with aniline in the above-described

manner, furnished o-*nitrobenzylidenebenzamidoacetanilide* (III; R = Ph), which crystallised from hot benzene in colourless hexagonal prisms, m. p. 213° (Found: C, 68·3; H, 4·4; N, 10·8. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·4; N, 10·85%). Hot alcoholic solutions deepened only slightly in colour when treated with alkali: solutions in concentrated sulphuric acid were colourless. The anilide was converted by phosphoryl chloride into 5-*keto*-1 : 2-*diphenyl*-4-o-*nitrobenzylidene*-4 : 5-*dihydroglyoxaline* (IV; R = Ph), which crystallised from hot alcohol in bright yellow, rectangular plates, m. p. 178°. The ring formation is attended with a remarkable development of colour (Found: N, 11·4. $C_{22}H_{15}O_3N_3$ requires N, 11·4%). The glyoxaline gives in concentrated sulphuric acid an almost colourless solution, from which it is precipitated on much dilution.

1 : 2-*Diphenylglyoxalino*-4 : 5(3′ : 2′)-*quinoline* (I; R = Ph).—A solution of the glyoxaline (IV; R = Ph) (0·5 g.) in acetic acid (50 c.c.) was boiled with zinc dust until it became almost colourless; it was then filtered, diluted with much water, and basified with sodium hydroxide solution. The colourless precipitate obtained formed needles (0·2 g.), m. p. 239°, from very dilute alcohol (Found: N, 12·8. $C_{22}H_{15}N_3$ requires N, 13·0%). The *glyoxalinoquinoline* is easily soluble in alcohol and strong acids, and forms a picrate in the usual way.

2-*Anilino*-3-*benzamidoquinoline* (V).—Reduction and ring closure of the anilides of type (III) to compounds of type (V) did not proceed smoothly and the method had to be modified in individual cases. The following, however, is a fairly typical example.

To a mixture of zinc dust and boiling acetic acid, *o*-nitrobenzylidenebenzamidoacetanilide (III; R = Ph) was added in small portions with vigorous shaking: after the final addition, the liquid was boiled for 15—30 minutes. (Prolonged heating considerably reduces the yield of the pure product.) The filtered solution, poured into much water, deposited an ochreous mass. This was separated, extracted with hot methyl alcohol, washed with dilute hydrochloric acid (the washings sometimes furnished a tetrahydroquinoline, usually mixed with other substances), and crystallised from acetic acid and then from alcohol; 2-*anilino*-3-*benzamidoquinoline* (V; R = Ph) thus obtained had m. p. 254° (Found: N, 12·5. $C_{22}H_{17}ON_3$ requires N, 12·4%). It gave a pale yellow solution in hot alcohol containing a little alkali, but was not precipitated on dilution with water.

The following compounds were prepared by methods described above: o-*nitrobenzylidenebenzamidoaceto*-o-*toluidide* (III; R = *o*-C_7H_7), pale yellow needles, m. p. 172—173° (Found: N, 10·7%); the corresponding m-*toluidide*, m. p. 215° after recrystallisation

from alcohol (charcoal) (Found: C, 68·7; H, 4·9; N, 10·8. $C_{23}H_{19}O_4N_3$ requires C, 68·6; H, 4·7; N, 10·5%); and the p-*toluidide*, m. p. 206° when similarly crystallised (Found: N, 10·8%). 2-o-*Toluidino*-3-*benzamidoquinoline* (V; R = *o*-C_7H_7), pale yellow needles, m. p. 247°, from acetic acid (Found: N, 12·0. $C_{23}H_{19}ON_3$ requires N, 11·9%); the 2-m-*toluidino*-analogue, pale yellow needles, m. p. 238—239°, from alcohol (Found: N, 12·1%), the substance being practically non-basic; and the p-*toluidino*-compound, m. p. 259° after crystallisation from acetic acid (obtained in very poor yield) (Found: N, 12·1%).

A mixture of 6-nitropiperonal (10 g.), hippuric acid (9·2 g.), freshly fused sodium acetate (10 g.), and acetic anhydride (25 c.c.), when heated on the steam-bath for 1¼ hours, gave the *azlactone* (6 g.), m. p. 196° after crystallisation from much boiling acetic acid (Found: N, 8·3. $C_{17}H_{10}O_6N_2$ requires N, 8·3%). It gave a scarlet solution in alcoholic alkali: after dilution, acidification with acetic acid precipitated the corresponding acid, which was not easily reconverted into the lactone.

This azlactone gave with aniline, *o*-toluidine, *m*-toluidine, and *p*-toluidine respectively, in the manner previously described, 6-*nitropiperonylidenebenzamidoacetanilide*, m. p. 225° (Found: C, 64·1; H, 4·0; N, 9·9. $C_{23}H_{17}O_6N_3$ requires C, 64·0; H, 4·0; N, 9·7%), the o-*toluidide*, golden-yellow plates, m. p. 223° (Found: N, 10·9%), the m-*toluidide*, bright yellow needles, m. p. 186°, from acetic acid (Found: C, 64·9; H, 4·5; N, 9·5. $C_{24}H_{19}O_6N_3$ requires C, 64·9; H, 4·6; N, 9·4%), and the p-*toluidide*, bright yellow needles, m. p. 229°, from acetic acid (Found: C, 64·5; H, 4·4; N, 9·4%). A second substance was isolated in bright orange needles, m. p. 259°, but not in sufficient amount for analysis.

The reduction and ring closure of the above substances presented considerable difficulty owing to their very sparing solubility in hot acetic acid. However, the quinoline derivatives were isolated in poor yield as follows:

6-Nitropiperonylidenebenzamidoacetanilide (5 g. in three portions) was reduced in boiling acetic acid (300 c.c.) until the deep orange colour of the solution changed to yellow. The filtered solution deposited a gelatinous precipitate, which became semi-crystalline in contact with dilute hydrochloric acid. Recrystallised from acetic acid, the 2-*anilino*-3-*benzamido*-6:7-*methylenedioxyquinoline* had m. p. 315° (Found: N, 11·3. $C_{23}H_{17}O_3N_3$ requires N, 11·0%). It gave a light red solution in concentrated sulphuric acid.

The 2-o-*toluidino*-compound, m. p. 298°, pale greenish-yellow needles (Found: N, 10·9. $C_{24}H_{19}O_3N$ requires N, 10·6%), 2-m-

toluidino-compound, m. p. 286° (Found : N, 11·1%), and 2-p-*toluidino*-compound, m. p. 305° (decomp.) (Found : N, 10·65%), were prepared similarly.

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