CCCXCVII.—*Attempts to find New Anti-malarials. Introduction* by GEORGE BARGER and ROBERT ROBINSON. *Part I. Some Pyrroloquinoline Derivatives.*

By (MRS.) GERTRUDE MAUD ROBINSON.

Introduction.

THE memoirs comprising this series will describe the purely chemical aspects of a chemotherapeutical investigation planned as a campaign against malaria. Publication of the related biological work, which has been undertaken by Dr. R. Scott Macfie and Dr. T. Keilin, F.R.S., will follow in another place, and the co-operation thus implied has been fostered by the Joint Committee on Chemotherapy formed by the Medical Research Council and the Department of Scientific and Industrial Research.

The development follows three clues which are suggested by a consideration of the constitutions of (*a*) the *cinchona* alkaloids, (*b*) the *harmala* alkaloids, and (*c*) the synthetic compound known as *plasmoquine* or *beprochin* (Bayer).

Comment on the quinine analogies is unnecessary, except to remark that plasmoquine itself was based on them in the first instance; it is now convenient to regard this drug as a new point of departure. When the present research was initiated, nothing more was known of the nature of plasmoquine than was implied by the maker's description of the base as "a salt of alkylamino-6-methoxyquinoline." Simple tests and comparisons, however, gave valuable further information, and, when the I. G. Farbenind. A.-G. (*Arch. Schiff. Trop. Hyg.*, 1928, **32**, 382; chemical details by Schulemann, Schönhöfer, and Wingler will be published later) published the statement that plasmoquine base is 8-(diethylamino-*iso*pentylamino)-6-methoxyquinoline, it was found that some of the substances described in Part III (see p. 2959) were similarly constituted.

The *harmala* analogy is based on the work of Gunn and Marshall (*Proc. Roy. Soc. Edin.*, 1920, **15**, 145), who gave indications that harmaline, although inferior to quinine, possessed curative value in acute malaria (50% of the cases), whilst harmine was valueless in acute malaria but prevented the recurrence of attacks in three cases of relapsing malaria in which the administration of quinine had been tried and had failed.

In order to facilitate reference, the letters and numbers identifying specimens submitted for biological tests are given in the sequel in brackets following the names of new compounds.

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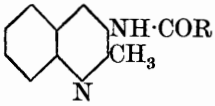
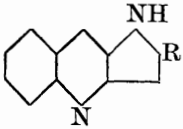
Part I.

KOENIGS AND FULDE (*Ber.*, 1927, **60**, 2106) obtained a methylpyrindole by heating 3-acetamido-γ-picoline with sodium ethoxide in a hydrogen atmosphere; it was sought to extend this method to the case of 3-acylamidoquinaldines (I), and so obtain derivatives of 2 : 3-pyrrolo(4′ : 5′)-quinoline (II).

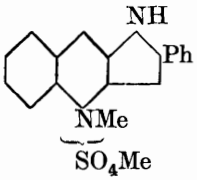
(I.) 

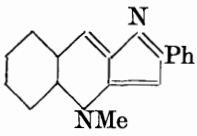


(II.)

This has been realised (R = H, Me, or Ph), but the conditions are critical, and the yields obtained were very poor until the device of mixing the materials with copper powder was adopted. This facilitated the conduction of heat and enabled the temperature of the mass to be rapidly and uniformly raised. The resulting bases contain the harmyrine nucleus with the benzene ring fused in a different position from that found in the *harmala* alkaloids, but, unlike the latter, they are quinoline derivatives, and it was thought that this might be advantageous from the chemotherapeutic standpoint.

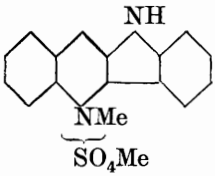
The behaviour of 2′-phenylpyrroloquinoline on methylation has been studied. Its methosulphate (III) is decomposed by sodium hydroxide in aqueous solution, with formation of a true anhydronium base (IV), an orange substance which could not be satisfactorily crystallised but was characterised by its analysis and properties.

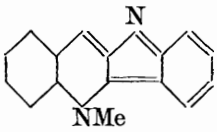
(III.) 



(IV.)

The behaviour of (III) is in marked contrast with that of quindoline methosulphate (V), which Armit and Robinson (J., 1922, **121**, 827) were unable to convert into a base of the formula (VI). Evidently, the longer route traversed by the valency changes in this case hinders the formation of the anhydro-derivative.

(V.) 



(VI.)

EXPERIMENTAL.

3-*Formamidoquinaldine* (I, R = H).—This amide was obtained in satisfactory yield when 3-aminoquinaldine (7 g.), accessible by the method of Lawson, Perkin, and Robinson (J., 1924, **125**, 638), was boiled with anhydrous formic acid (40 g.) until a minute test-portion, added to water, exhibited no fluorescence (2—3 hours). Water (100 c.c.) was added, and the derivative precipitated by means of sodium carbonate (about 5 g.); it was purified by crystallisation (charcoal) from boiling water (150 c.c.). The *substance* crystallised from benzene in clusters of needles, and from water in long, colourless needles, m. p. 163° (Found : C, 70·9; H, 5·2; N, 14·8. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

2 : 3-*Pyrrolo*(4′ : 5′)-*quinoline* (II, R = H).—The above formyl derivative shows a great tendency to give a sparingly soluble sodium salt, and difficulty was experienced in finding the correct procedure for its dehydration. Ultimately, the following conditions were adopted : A mixture of 3-formamidoquinaldine (2·0 g.), copper powder (2·0 g.), and dry sodium ethoxide (3·0 g.) was heated at 270° for 20 minutes in hydrogen. The resulting *base* was isolated as described below for its homologue; it crystallised from ethyl acetate in clusters of cream-coloured leaflets, m. p. 226° (yield of pure product, 0·4 g.) (Found, in material dried at 120° in a high vacuum : C, 78·6; H, 5·2. $C_{11}H_8N_2$ requires C, 78·5; H, 4·8%). The alcoholic solution of this base is colourless and fluoresces blue, but the yellow acid solutions exhibit a green fluorescence. The hydrochloride crystallises in colourless needles and is sparingly soluble in water.

3-*Acetamidoquinaldine* (I, R = Me).—3-Aminoquinaldine (10 g.) was acetylated by the addition of acetic anhydride (12 g.), the heat generated being sufficient to ensure the completion of the reaction. After isolation, the base was crystallised from benzene, and had m. p. 165° (Found : C, 72·0; H, 6·1. Calc. for $C_{12}H_{12}ON_2$: C, 72·0; H, 6·0%). Stark had previously obtained this substance in an entirely different manner, and quotes the m. p. 164° (*Ber.*, 1907, **40**, 3430). The hydrochloride (R. 2) crystallised from alcoholic hydrochloric acid in very pale yellow, elongated plates, m. p. 151°, after darkening at 149°.

2 : 3-(2′-*Methylpyrrolo*)(4′ : 5′)-*quinoline* (II, R = Me).—Many different condensing agents were tried without success in attempting the ring-closure of acetamidoquinaldine by dehydration. These included zinc chloride, sodium in hot xylene, phosphoryl chloride, phosphoric anhydride, fused potassium acetate, and sodamide. It is, apparently, necessary to resort to the use of the following reagents.

An intimate mixture of 3-acetamidoquinaldine (2·0 g.), copper powder (2·0 g.), and freshly prepared, dry sodium ethoxide (3·0 g.) was rapidly heated to 260° and maintained at this temperature for 15—20 minutes. The cooled mass was lixiviated with water and ammonia, and the mixed solids were collected and washed with a little hot water in order to eliminate unchanged acetamidoquinaldine and inorganic salts. The base was then extracted by means of hot, dilute hydrochloric acid, regenerated, and extracted by hot toluene. The residue (0·4 g.), after removal of the solvent, crystallised from benzene or from ethyl acetate in straw-coloured, elongated, flat prisms, m. p. 262°. Even after 4 hours at 100°, the *base* retains solvent of crystallisation (Found, in material dried at 120° in a high vacuum : C, 79·0; N, 5·8. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5%). In general properties and fluorescence, this base closely resembles its lower homologue.

3-*Benzamidoquinaldine* (I, R = Ph).—A practically quantitative yield of this *base* is obtained in the following manner. A mixture of aminoquinaldine (4·0 g.), glacial acetic acid (8·0 g.), and benzoyl chloride (8·0 g.) with an excess of potassium acetate, was gently heated until a diluted test-portion did not exhibit fluorescence. The mass was decomposed by means of ice-cold, aqueous sodium carbonate, and the solid was isolated and crystallised from benzene (charcoal). The derivative crystallises also from toluene, ethyl acetate, or acetone in colourless needles. These seem to contain solvent of crystallisation, for they soften on heating, harden again, and then melt at 161° (Found, in material dried at 120° : C, 77·7; H, 5·3; N, 10·3. $C_{17}H_{14}ON_2$ requires C, 77·9; H, 5·3; N, 10·7%).

2 : 3-(2′-*Phenylpyrrolo*)(4′ : 5′)-*quinoline* (II, R = Ph).—The method was like that previously described, the crude product from 2 g. of the benzamide being washed with 300 c.c. of boiling water. Extraction in this case by dilute hydrochloric acid was unsatisfactory, and boiling acetic acid (100 c.c.) was used. The isolated *base* (0·8 g.) crystallised from toluene in pale yellow, elongated, rhombic prisms, and from ethyl acetate in yellow needles, m. p. 268° (Found, in material dried at 120° in a high vacuum : C, 83·6; H, 4·9; N, 11·3. $C_{17}H_{12}N_2$ requires C, 83·6; H, 4·9; N, 11·5%). As in other cases, a small quantity of an organo-copper compound was formed in the condensation reaction. The alcoholic solution has a purer blue fluorescence than in the two previous examples, and, as before, the yellow acid solutions exhibit a green fluorescence. The hydrochloride is extremely sparingly soluble, but the acetate (R. 18) is soluble in weak acetic acid solutions. This salt separates in yellow needles on slow evaporation of a solution of the base in glacial acetic acid in a desiccator over potassium hydroxide. It

shrinks at 120° and melts at 130° but, on prolonged heating at 100°, is resolved into its components.

The *methosulphate* was prepared in hot toluene solution, and crystallised from alcohol–ether in sheaves of glistening, canary-yellow needles, m. p. 345° (decomp.) (Found : S, 8·7. $C_{19}H_{18}O_4N_2S$ requires S, 8·7%). This salt crystallises from hot water in flocculent needles ; its yellow aqueous and alcoholic solutions exhibit an intense bluish-green fluorescence.

Anhydro-2 : 3-(2′-*phenylpyrrolo*)(4′ : 5′)-*quinoline Methohydroxide* (IV).—Addition of sodium hydroxide to a hot, aqueous solution of the above-described methosulphate gives a yellowish-orange precipitate which is soluble in neutral organic solvents to orange-yellow, non-fluorescent solutions. The *base* was extracted by hot toluene, and the solution dried by sodium hydroxide and concentrated by distillation in a vacuum. Light petroleum was then added, and, on keeping in a well-sealed flask in the ice-chest, an orange crust gradually separated. The substance slowly shrinks to a resin above 100° and does not give a sharp m. p. It was dried at 120° in hydrogen (Found : C, 84·0; H, 5·6. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4%). It dissolves in alcohol to a yellow, fluorescent solution evidently containing the related methohydroxide (or ethoxide), and in acid solutions the metho-salts are regenerated. When pure, dry methyl sulphate was added to a dry toluene solution, combination occurred immediately and a new methosulphate of the anhydro-base was precipitated in yellow needles. This methosulphate gives yellow solutions, exhibiting a striking greenish-blue fluorescence, but the addition of sodium hydroxide to its aqueous solutions either causes no apparent change or, in concentrated solutions, precipitates the methohydroxide. No toluene-soluble base was produced, and this experiment affords a sure proof of the correctness of the view of the orange base that has been suggested.

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