CCCCXXVI.—*Attempts to find New Antimalarials. Part VI. Derivatives of 2-β-Aminoethylquinoline.*

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THE object of the following work was to prepare 2-β-aminoethylquinoline and its derivatives in order that the chemotherapeutic activity of these compounds might be investigated. In an attempt to obtain 2-β-aminoethylquinoline, previously prepared by Rupe and Schramme (*Z. physiol. Chem.*, 1928, **177**, 315) by the reduction of quinolylacetaldoxime (compare also D.R.-P. 380,918; *Chem. Zentr.*, 1924, i, 1446), from β-2-quinolylpropionic acid, β-2-*quinolylpropionylhydrazide* was prepared by the action of hydrazine hydrate at 140° on ethyl β-2-quinolylpropionate, obtained from the acid by esterification with ethyl alcohol and hydrochloric acid. Treatment of the hydrazide with nitrous acid or amyl nitrite in the presence of alcoholic hydrochloric acid failed to yield the desired β-2-quinolylpropionylazide. In all the experiments a gas was evolved and s.-*di*-(β-2-*quinolylpropionyl*)*hydrazide* was isolated: this was readily hydrolysed with concentrated hydrochloric acid to give hydrazine and β-2-quinolylpropionic acid. The abnormal behaviour of the hydrazide when treated with nitrous acid may be formulated as follows:

$$2C_9H_6N\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot NH_2 + 2HNO_2 = (C_9H_6N\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot)_2 + N_2 + N_2O + 3H_2O.$$

John (*Ber.*, 1925, **58**, 2779) found that the Curtius reaction proceeded normally when applied to β-(2-phenyl-4-quinolyl)propionylhydrazide, and the failure in the present instance to obtain the desired azide is difficult to understand.

Ketones containing an active methylene group have been shown by Mannich (*Ber.*, 1920, **53**, 1368; *Arch. Pharm.*, 1926, **264**, 741; 1927, **265**, 589) to condense with formaldehyde and secondary bases according to the equation

$$R_1\cdot CH_2\cdot CO\cdot CH_2R_2 + CH_2O + NHR_3R_4 = R_1\cdot CH_2\cdot CO\cdot CHR_2\cdot CH_2\cdot NR_3R_4 + H_2O.$$

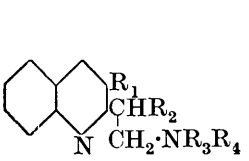
As the methyl group in quinaldine is reactive, this compound was substituted for the ketone in the reaction. When quinaldine, trioxymethylene, and piperidine were heated together at 140°, 2-β-piperidinoethylquinoline was obtained in small yield; it was isolated as the *monopicrate*, m. p. 155°. A compound of this formula was prepared by Loewe (D.R.-P. 380,918; *Chem. Zentr.*, 1924, i, 1446) by treatment of 2-β-bromoethylquinoline with piper-

idine and isolated as the dipicrate, m. p. 145°. Numerous experiments were carried out to improve the yield. The best result was obtained when 1 mol. of quinaldine hydrochloride, 2 mols. of formaldehyde, and 2 mols. of piperidine were used, the formaldehyde being in the form of commercial 40% formalin. By a similar method, 2-β-diethylaminoethylquinoline was obtained as the monopicrate, m. p. 123—124°, in 33% yield from diethylamine, 40% formalin, and quinaldine hydrochloride. In a paper which appeared after the present work was completed, Héou-Féo (*Compt. rend.*, 1931, **192**, 1242) described 2-β-diethylaminoethylquinoline (monopicrate, m. p. 122°), prepared by a method essentially the same as that described here. Quinaldine hydrochloride, formaldehyde, and monomethylaniline were heated at 37° for 2 days, and from the reaction mixture 2-β-phenylmethylaminoethylquinoline was isolated as the *picrate*, m. p. 175° (decomp.); the yield was relatively poor. Unsuccessful attempts were made to substitute acetaldehyde for formaldehyde in the above reactions. Although the methyl group in *o*-nitrotoluene possesses considerable activity, it was not found possible to condense piperidine, formaldehyde, and *o*-nitrotoluene so as to yield *o*-nitropiperidinoethylbenzene. Unsuccessful attempts were also made to substitute quinaldine methosulphate for quinaldine hydrochloride, tarring taking place even at the temperature of a freezing mixture.

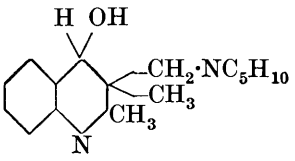
A second method for the formation of derivatives of 2-β-aminoethylquinoline has been developed in which *o*-aminobenzaldehyde is condensed with a compound of the general formula

$$CH_2R_1{\cdot}CO{\cdot}CHR_2{\cdot}CH_2{\cdot}NR_3R_4$$

(R_2 must not be H) to yield (I).



(I.)



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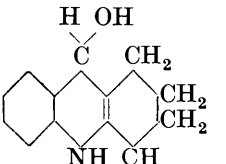

(III.)

Keto-bases of the required type are readily obtained by the Mannich reaction (Mannich and Hof, *Arch. Pharm.*, 1927, **265**, 589). Thus by the condensation of *o*-aminobenzaldehyde with α-piperidino-β-methylbutan-γ-one (prepared from piperidine, trioxymethylene, and methyl ethyl ketone; Mannich and Hof, *loc. cit.*), 2-β-piperidino*iso*propylquinoline was obtained (as the *monopicrate*, m. p. 167—168°) together with a by-product which was shown to be 2 : 3-dimethylquinoline.

The formation of the latter compound is most readily explained as the result of the regeneration of methyl ethyl ketone by the reversal of the Mannich reaction. The assumption of reversibility was supported by an experiment in which α-piperidino-β-methylbutan-γ-one was boiled in slightly alkaline solution under reflux for several hours. The distillate obtained after neutralisation contained a ketone which readily yielded 2 : 3-dimethylquinoline when treated with *o*-aminobenzaldehyde. The distillate therefore contained methyl ethyl ketone. An alternative assumption is the intermediate formation of (II), which might then be decomposed to yield 2 : 3-dimethylquinoline, piperidine, and formaldehyde.

In B.P. 321,974/1928 *o*-aminobenzaldehyde is condensed with α-diethylaminopentan-δ-one, but in this case the product is a derivative of 2-methyl-3-β-aminoethylquinoline. In our experiments, the presence of the group R_2 (not H) prevents the possibility of the formation of derivatives of 2-methyl-3-aminomethylquinoline.

In a similar way, *o*-aminobenzaldehyde condensed with 2-piperidinomethyl*cyclo*hexanone (Mannich and Honig, *Arch. Pharm.*, 1927, **265**, 602) to yield 1-piperidinomethyl-1 : 2 : 3 : 4-tetrahydroacridine, isolated as the *monopicrate*, m. p. 206°. When *o*-aminobenzaldehyde was condensed with 2-diethylaminomethyl*cyclo*hexanone (Mannich and Honig, *loc. cit.*) under exactly similar conditions, the expected base was not obtained but in its place an amorphous solid of somewhat indefinite m. p. (65—75°) was isolated. The analytical figures, which agree approximately with the formula $C_{14}H_{17}O_2N$, indicate that the diethylamino-radical has been lost. The *compound* may possibly be represented by the formula (III).

The difference in the ease of formation of the diethylamino- and the piperidino-compound is noteworthy. A similar difference has been observed in the Mannich reaction : methyl ethyl ketone, formaldehyde, and piperidine readily condense to give α-piperidino-β-methylbutan-γ-one, whereas the analogous diethylamino-compound could not be obtained by the condensation of diethylamine hydrochloride, formaldehyde, and methyl ethyl ketone under exactly similar conditions.

EXPERIMENTAL.

Ethyl β-2-*Quinolylpropionate*.—Saturated alcoholic hydrogen chloride (200 c.c.) was refluxed with β-2-quinolylpropionic acid (13 g.), and again after resaturation. After removal of the excess of alcoholic hydrogen chloride under reduced pressure, the non-crystallisable residue was dissolved in water. From the filtered solution, made alkaline, ether extracted the ester as a deep red oil, miscible with the usual organic solvents except light petroleum and ligroin (yield, 80%).

β-2-*Quinolylpropionylhydrazide.*—The ester (12 g.) was refluxed for 3 hours with hydrazine hydrate (50 c.c. of 50% by weight) at 140°. The crystals which separated on cooling were washed with water, dried, and recrystallised from light petroleum, forming silvery leaflets (12 g.), m. p. 165° (Found : N, 19·6. $C_{12}H_{13}ON_3$ requires N, 19·5%), easily soluble in dilute mineral acids, alcohol, and benzene, less readily in acetone, and insoluble in cold but moderately easily soluble in hot ligroin and light petroleum. The *hydrazide* reduces Fehling's solution on gentle warming, and ammoniacal silver nitrate.

Treatment of β-2-*Quinolylpropionylhydrazide with Nitrous Acid.*—When a solution of the hydrazide (1 g.) in *N*-hydrochloric acid (10 c.c.) was treated dropwise with sodium nitrite (0·36 g. in 5 c.c. of water), gas was slowly evolved, the solution became turbid, and a greenish crystalline material was deposited. This was removed, the filtrate made alkaline, and the white precipitate that separated was collected and dried. The two deposits were essentially identical, both blackening at 220° and melting at 240—250°, and yielding silvery leaflets, m. p. 265°, on recrystallisation from ligroin. Alternatively, to a solution of β-2-quinolylpropionylhydrazide (4·4 g.) in absolute alcohol (40 c.c.), freshly distilled amyl nitrite (2·4 g.) was added, and 4·5*N*-alcoholic hydrogen chloride (3·3 c.c.) run in with constant shaking. The mixture was boiled under reflux for 8 hours, and the white solid that separated on cooling was washed, dried, and recrystallised from ligroin; m. p. 265° (yield, 3·2 g.) (Found : C, 71·6; H, 5·5; N, 14·3. $C_{24}H_{22}O_2N_4$ requires C, 72·3; H, 5·5; N, 14·1%).

This compound dissolves in dilute mineral acids to form clear colourless solutions. It does not reduce Fehling's solution or ammoniacal silver nitrate. It is insoluble in cold and sparingly soluble in hot alcohol or benzene. The compound was refluxed with concentrated hydrochloric acid (20 c.c.) for 8 hours. Crystals of hydrazine hydrochloride, m. p. 200°, slowly separated after cooling. The mother-liquor was evaporated to dryness, an aqueous solution of the residue was made alkaline with ammonia and again evaporated to dryness, and the residue was heated on the water-bath for 8 hours to decompose the ammonium salt of the amphoteric β-2-quinolylpropionic acid. This acid was obtained pure, m. p. 122—123°, by extracting the residue with acetone and recrystallising from benzene the solid remaining after distillation of the acetone. The analysis and properties of the compound, m. p. 265°, show it to be s.-*di*-(β-2-*quinolylpropionyl*)*hydrazide.*

2-β-*Piperidinoethylquinoline.*—To a mixture of 40% formalin (6 c.c.) and piperidine (6·8 g.) at room temperature, quinaldine hydrochloride (7·1 g.) was slowly added with constant shaking, gentle

heat being finally applied to effect complete solution. The mixture was heated on the water-bath for 18 hours, the deep red product basified with sodium hydroxide solution and steam-distilled to remove unchanged quinaldine and formaldehyde, and the non-volatile oil dissolved by the addition of hydrochloric acid. The solution was boiled with animal charcoal, filtered, and made alkaline, and the thick yellow oil produced was extracted and dried in ether, recovered, and treated in benzene solution with picric acid. The *picrate* crystallised from alcohol in long, fine, yellow needles, m. p. 155° (yield, 72%) (Found: C, 56·1; H, 4·9; N, 14·9. $C_{16}H_{20}N_2,C_6H_3O_7N_3$ requires C, 56·3; H, 4·9; N, 14·9%).

2-β-Piperidinoethylquinoline is a pale yellow, viscous oil which decomposes on attempted vacuum distillation. It is readily soluble in dilute acetic and mineral acids. The amorphous yellow chloroplatinate becomes black and decomposes on attempted recrystallisation. The brownish-red chloroaurate also is amorphous and cannot be recrystallised. The monopicrate is sparingly soluble in cold alcohol and benzene, easily soluble in alcohol, and less readily in benzene when hot, insoluble in hot ligroin and light petroleum, and freely soluble in cold acetone. It is decomposed by dilute sodium hydroxide solution, and from a benzene extract of the product the hydrochloride of the base is precipitated by hydrogen chloride as a white crystalline compound, m. p. 184—185°.

2-β-*Diethylaminoethylquinoline.*—Diethylamine (5·8 g.) was condensed with 40% formalin (6 c.c.) and quinaldine hydrochloride (7·1 g.) in the same way as piperidine. The pale yellow, viscous oil obtained gave, in benzene solution, a picrate, which formed long, fine, yellow needles, m. p. 123—124°, after recrystallisation from alcohol (yield, 33%) (Found: C, 55·1; H, 5·1; N, 15·4. Calc. for $C_{15}H_{20}N_2,C_6H_3O_7N_3$: C, 55·1; H, 5·0; N, 15·3%).

2-β-Diethylaminoethylquinoline and its picrate closely resemble the analogous piperidine compounds. The yellow chloroplatinate and the deep red chloroaurate are amorphous and decompose on attempted recrystallisation. The hydrochloride is very deliquescent.

2-β-*Phenylmethylaminoethylquinoline.*—Quinaldine hydrochloride (7·1 g.) was slowly added with vigorous shaking to a mixture of monomethylaniline (8·6 g.) and 40% formalin (6 c.c.). The whole was kept, and occasionally shaken, for 24 hours at 37° and then for 2 days at room temperature. The supernatant liquid was decanted, the red viscous oil dissolved in water containing a few drops of concentrated hydrochloric acid, and the filtered solution made alkaline with saturated aqueous sodium carbonate. The sticky amorphous material which separated before the neutral point was reached was filtered off; when exposed to air or kept in a vacuum

desiccator, it became red and oily. When the addition of sodium carbonate was continued, a red mobile oil separated. The mixture was then steam-distilled, and the non-volatile red oil was extracted with ether, recovered, and treated in benzene with picric acid. The precipitate thus obtained was partly insoluble in hot water; after two crystallisations the *picrate* formed large greenish-yellow plates (1 g.), m. p. 175° (decomp.) (Found : C, 48·4; H, 3·9; N, 15·4. $C_{18}H_{18}N_2,2C_6H_3O_7N_3,H_2O$ requires C, 48·8; H, 3·5; N, 15·2%), slightly soluble in hot benzene and alcohol (from which it separated as a greenish-yellow amorphous powder), insoluble in hot ligroin and light petroleum, and readily soluble in cold acetone. The base could not be regenerated from the picrate, because the latter blackened and decomposed when treated with dilute sodium hydroxide solution.

2-β-*Piperidino*iso*propylquinoline*.—α-Piperidino-β-methylbutan-γ-one hydrochloride (Mannich and Hof, *loc. cit.*) (8·4 g.), dissolved in water (20 c.c.), was added to a solution of *o*-aminobenzaldehyde (4·8 g.) in alcohol (10 c.c.), and 10*N*-sodium hydroxide (4·8 c.c.) slowly run in with constant shaking. The slightly alkaline, clear yellow solution was kept at 37° for 3 days while a thick yellow oil separated. The mixture was steam-distilled and the non-volatile oil was extracted with ether, dried over anhydrous potassium carbonate, recovered, dissolved in benzene, and converted into the *picrate*, which crystallised from alcohol in fine, yellow, rectangular prisms (5·5 g.), m. p. 167—168° (Found : C, 56·7; H, 5·0; N, 14·7. $C_{17}H_{22}N_2,C_6H_3O_7N_3$ requires C, 57·1; H, 5·2; N, 14·5%).

The steam-distillate contained an oil, which was extracted with ether. After the extract had been dried with anhydrous potassium carbonate, and the ether removed, the residual pale yellow, viscous oil crystallised in large plates. These, alone or mixed with authentic 2 : 3-dimethylquinoline prepared from *o*-aminobenzaldehyde and methyl ethyl ketone, melted at 63—64°. Both samples gave identical picrates, m. p. 224—225°.

2-β-Piperidino*iso*propylquinoline is a viscous, pale yellow oil, closely resembling its lower homologue, piperidinoethylquinoline, described above. The picrate is moderately easily soluble in hot benzene and alcohol, freely soluble in cold acetone, but insoluble in light petroleum and ligroin. A small quantity of picrate insoluble in alcohol was recrystallised from hot water, forming long, narrow, rectangular prisms, m. p. 201°. This is probably the *dipicrate*, but there was insufficient for complete investigation (Found : N, 15·5. $C_{17}H_{22}N_2,2C_6H_3O_7N_3$ requires N, 15·7%). The chloroplatinate formed a buff-coloured, and the chloroaurate a deep red, amorphous precipitate. The hydrochloride, prepared from the purified picrate

through the base in benzene, is a deliquescent solid which darkens on exposure to air.

1-*Piperidinomethyl*-1 : 2 : 3 : 4-*tetrahydroacridine*.—A solution of *o*-aminobenzaldehyde (9·3 g.) in alcohol (15 c.c.) was mixed with a solution of 2-piperidinomethyl*cyclo*hexanone (Mannich and Honig, *loc. cit.*) (5·7 g.) in water (5 c.c.), and 10*N*-sodium hydroxide solution (2·6 c.c.) added. After 4 days, no oil having separated, the mixture was refluxed for ½ hour to complete the reaction. The alcohol was distilled off, and the residue steam-distilled. The non-volatile oil was extracted and dried in ether, recovered, and converted in benzene into the *picrate*, which, recrystallised from alcohol, formed long, fine, silky, yellow needles (5·5 g.), m. p. 206° (Found : N, 13·9. $C_{19}H_{24}N_2,C_6H_3O_7N_3$ requires N, 13·8%).

1-Piperidinomethyl-1 : 2 : 3 : 4-tetrahydroacridine is a pale yellow, slightly basic, viscous oil closely similar to the other piperidine derivatives described above. It yields a pale yellow amorphous chloroplatinate and a deep red amorphous chloroaurate, both of which decompose when recrystallisation is attempted. The picrate is readily soluble in hot alcohol and less soluble in hot benzene, soluble in cold acetone, but insoluble in hot light petroleum and ligroin. The hydrochloride, obtained from the base regenerated by decomposition of the picrate, is extremely deliquescent and tends to darken on exposure to air.

Condensation of 2-*Diethylaminomethyl*cyclo*hexanone and* o-*Aminobenzaldehyde*.—A solution of diethylaminomethyl*cyclo*hexanone hydrochloride (5·5 g.) in water (5 c.c.) was mixed with a solution of *o*-aminobenzaldehyde (3 g.) in alcohol (15 c.c.), and 10*N*-sodium hydroxide solution (2·6 c.c.) added. After standing at 37° for 4 days, the mixture was refluxed for ½ hour and then steam-distilled. The non-volatile dark-coloured oil changed on cooling to a hard reddish-brown mass. This was separated from the aqueous layer, washed with water, dissolved in hot dilute hydrochloric acid, and a flocculent basic material precipitated from the filtered solution by the addition of sodium hydroxide. This substance was washed, dried, and extracted with hot ligroin, and the extract treated with animal charcoal. On cooling, the *compound* separated first as an oil and then settled as a pale yellow, amorphous powder. This was washed, dried, dissolved several times in hot ligroin, and precipitated by cooling. The m. p. 65—75° of the powder was not improved by this treatment (Found : C, 74·1; H, 7·5; N, 6·1. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·1%). The compound is freely soluble in cold alcohol, benzene, and acetone and moderately easily soluble in hot ligroin and light petroleum. It is precipitated as an amorphous powder by alkali from dilute mineral acid solution.

A picrate is not obtained from its solution in benzene. The chloroplatinate and the chloroaurate are respectively obtained as brownish-yellow and reddish-brown precipitates which blacken and decompose on attempted recrystallisation.

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