259. *Quinoline Derivatives. Part I. Furanoquinolines.*

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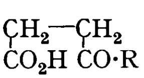
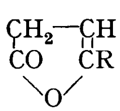
A base, $C_{12}H_9O_2N$, isolated from *Skimmia repens* (*Ber.*, 1930, **63**, 2045) and an alkaloid skimmianine from *Skimmia japonica* (Asahina and Inubuse, *ibid.*, p. 2052) have been formulated as 2 : 3-furano-(2′ : 3′)-quinoline derivatives, and a simple synthesis of substances having this skeleton is now described.

β-3 : 4-Dimethoxybenzoylpropionic acid (I) (Bargellini and Giua, *Gazzetta*, 1912, **42**, 197) when treated with acetic anhydride passes into the lactone (II), the structure of which is proved by the fact that it can be hydrolysed to the acid (I) and oxidised to veratric acid.

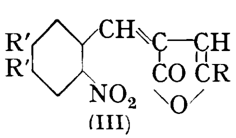


$$\begin{matrix} CH_2 - CH_2 \\ CO_2H \quad CO{\cdot}R \end{matrix}$$

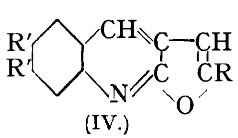
(I.)



(II.)



(III)



(IV.)

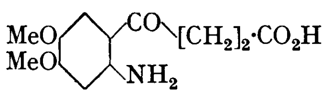
(R = 3 : 4-Dimethoxyphenyl.)

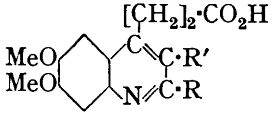
The acid (I) easily condenses with aromatic aldehydes to give the highly coloured arylidene derivatives (III) of the lactone (II), the structure following from the fact that these derivatives can be converted into the related keto-acids by fission of the ring with alkali, showing that the α- (and not the β-) carbon atom is involved in the condensation. The keto-acids are only very faintly coloured owing to the destruction of the long conjugated chain.

The substances of type (III) from *o*-nitrobenzaldehyde, 6-nitropiperonal, and 6-nitroveratraldehyde, give furanoquinolines (IV) when reduced with zinc dust and acetic acid.

The acid (I), on nitration furnishes β-3 : 4-dimethoxy-6-nitrobenzoylpropionic acid;

on reduction, this gives the related *amino*-acid (V), which forms substituted quinoline-4-propionic acids (VI) by condensation with acetaldehyde, acetophenone, acetylacetone,


(V.)


(VI.)

or dibenzoylmethane. The antimalarial properties of these compounds in alkaline solution are being studied.

EXPERIMENTAL.

β-3 : 4-*Dimethoxybenzoylpropionic Acid.*—To a cold solution of anhydrous aluminium chloride (27 g.) in nitrobenzene (65 c.c., freshly distilled), a solution of succinic anhydride (11 g.) and veratrole (14 g.) in the same solvent (20 c.c.) was slowly added during 30 minutes (stirring), and the mixture was kept at 0—10° for 24 hours with occasional shaking, then at 45° for 1 hour. Ice and hydrochloric acid were added, the nitrobenzene removed in steam, and the aqueous solution filtered hot. The acid crystallised, and after being purified by dissolution in sodium carbonate solution (10%) and reprecipitation, it had m. p. 165° (Bargellini and Giua, *loc. cit.*, give 160—161°); yield 22·5 g. (93%) (cf. Barnett and Saunders, this vol., p. 436) (Found : C, 60·4; H, 5·7. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 5·9%). The methyl ester had m. p. 89°.

The *lactone* (II) was prepared by heating the acid (1·2 g.) in acetic anhydride (3 c.c.) at 100° for 2 hours and pouring it into water (20 c.c.); it was washed successively with ice-cold 1% sodium carbonate solution and 1% acetic acid, and crystallised from hot water in pale orange-yellow, silky needles, m. p. 114—115° (Found : C, 65·5; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). It gives no ferric chloride reaction and is slightly soluble in cold dilute alkali giving a brownish solution, but in 5% sodium carbonate solution it dissolves very slowly, the colour deepening to a purple violet on exposure to air. In weaker sodium carbonate (0·5%) at 60°, it dissolves with a deep green colour, which slowly fades and vanishes completely at 40°, giving a pale orange solution which regains the green colour at 60°; at 100° hydrolysis occurs with formation of the acid, m. p. and mixed m. p. 164° (Found : C, 60·8; H, 5·9%). Oxidation with 5% permanganate solution at 60° gave veratric acid (m. p. and mixed m. p. 178°).

Lactone of α-*Piperonylidene*-β-3 : 4-*dimethoxybenzoylpropionic Acid* (as III; R′, R′ = CH_2O_2:).—A mixture of the acid (I) (1·2 g.), piperonal (0·8 g.), and acetic anhydride (5 c.c.) was heated at 100° for 1½ hours, and the purple-red solution poured into water. The viscous precipitate was treated with cold sodium carbonate solution (10%), stirred with cold acetic acid, and crystallised from acetic acid; yellow silky needles, m. p. 226° (Found : C, 68·2; H, 4·7. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%); the *lactone* is sparingly soluble in alcohol and ethyl acetate.

Similarly, *o*-nitrobenzaldehyde furnishes the *lactone* of α-2-nitrobenzylidene-β-3 : 4-dimethoxybenzoylpropionic acid, dark red needles, m. p. 200° (Found : N,* 4·0. $C_{19}H_{15}O_6N$ requires N, 4·0%). Hydrolysis of this lactone by alcoholic potash yielded the corresponding *acid*, m. p. 262°, nearly colourless needles from aqueous alcohol (Found : N, 4·0. $C_{19}H_{17}O_7N$ requires N, 3·8%).

The *lactone of* α-6-nitro-3 : 4-methylenedioxybenzylidene-β-3 : 4-dimethoxybenzoylpropionic acid (III; R′, R′ = CH_2O_2:), chocolate-coloured needles, prepared in an analogous manner, had m. p. 232° after crystallisation from acetic acid or pyridine (Found : N, 3·7. $C_{20}H_{15}O_8N$ requires N, 3·5%). The *lactone* of α-6-nitroveratrylidene-β-3 : 4-dimethoxybenzoylpropionic acid, vermilion-red needles, was crystallised from benzene, m. p. 206° (Found : N, 3·5. $C_{21}H_{19}O_8N$ requires N, 3·4%).

Reduction of the Lactones to the Related Furanoquinolines (IV).—The following is a typical example. To a mixture of zinc dust and boiling acetic acid, the lactone of α-*o*-nitrobenzylidene-β-3 : 4-dimethoxybenzoylpropionic acid was added in small portions with vigorous shaking, and the mixture then boiled until almost decolorised. The diluted filtered solution was basified with ammonia (ice-cold), and the precipitate washed with benzene and crystallised from methyl alcohol; colourless needles, m. p. 172° (Found : N, 4·8. $C_{19}H_{15}O_3N$ requires N, 4·6%).

In the reduction of the 6-nitropiperonylidene compound, the filtered solution of the reduced product in acetic acid was treated with concentrated hydrochloric acid and cooled; the hydrochloride of the base, which partly crystallised, was separated, and from the filtrate, the *base* (IV; R′,R′ = CH_2O_2:) was isolated in the usual manner. It crystallised from much acetone and had m. p. 262° (Found : N,* 4·1. $C_{20}H_{15}O_5N$ requires N, 4·0%). The *base* (IV; R′ = R′ = OMe) derived from the 6-nitroveratrylidene compound had m. p. 245° (from acetone) (Found : C, 68·6; H, 4·8; N, 4·2. $C_{21}H_{19}O_5N$ requires C, 69·0; H, 5·2; N, 3·8%); *picrate*, golden-yellow needles, m. p. 241° (from benzene) (Found : N,* 9·4. $C_{21}H_{19}O_5N,C_6H_3O_7N_3$ requires N, 9·4%).

β-6-*Nitro*-3 : 4-*dimethoxybenzoylpropionic Acid.*—A hot solution of the acid (I) (1·0 g.) in acetic acid (4 c.c.) was quickly cooled, and into it nitric acid (*d* 1·42; 1·2 c.c.) was stirred. The solution became dark green but the colour faded on standing. Sulphuric acid (*d* 1·84; 4 drops) was added, and the mixture cooled. The *nitro-acid* which crystallised was collected after an hour and recrystallised from acetic acid, m. p. 212° (Found : N,* 5·2. $C_{12}H_{13}O_7N$ requires N, 5·0%). The *methyl* ester had m. p. 118° (greenish-yellow needles) (Found : N, 5·1. $C_{13}H_{15}O_7N$ requires N, 4·7%).

β-6-*Amino*-3 : 4-*dimethoxybenzoylpropionic acid* (V) was prepared by reducing a solution of the nitro-acid (1·0 g.) in ammonia (*d* 0·88; 8 c.c.) and water (7·5 c.c.) at 100° with a solution of hydrated ferrous sulphate (9·8 g.) for ¾ hour. After being filtered, the solution was partly neutralised with hydrochloric acid and acidified with acetic acid; a pale brown crystalline precipitate was formed, and the mother-liquor yielded a further amount to chloroform. Crystallised from hot water (charcoal), the *acid* had m. p. 118° (Found : N,* 5·5. $C_{12}H_{15}O_5N$ requires N, 5·5%); *benzoyl* derivative, m. p. 225° (from methyl alcohol) (Found : N, 3·9. $C_{19}H_{19}O_6N$ requires N, 3·8%); *acetyl* derivative, m. p. 187° (Found : N, 5·0. $C_{14}H_{17}O_6N$ requires N, 4·8%); *methyl* ester, m. p. 127° (from methyl alcohol) (Found : N, 5·5. $C_{13}H_{17}O_5N$ requires N, 5·3%).

6 : 7-*Dimethoxy*-3-*acetyl*-2-*methylquinoline*-4-*propionic Acid* (VI; R = Me, R′ = $CH_3{\cdot}CO$).—A mixture of the acid (V) (0·72 g.) and acetylacetone (0·3 g.) was heated at 110° for 1 hour. The resulting *acid* was washed with tepid water (2 × 5 c.c.), and crystallised successively from aqueous alcohol and methyl alcohol; m. p. 245° (decomp.) (Found : C, 64·0; H, 5·9; N,* 4·5. $C_{17}H_{19}O_5N$ requires C, 64·35; H, 6·0; N, 4·4%).

The acid from dibenzoylmethane, similarly condensed at 115°, was isolated by suspending the mixture in dilute alcohol and treating it with hydrochloric acid (15%). The residue was dissolved in sodium carbonate solution (10%) and then precipitated by acetic acid. 6 : 7-*Dimethoxy*-3-*benzoyl*-2-*phenylquinoline*-4-*propionic acid* crystallised in cream-coloured needles from aqueous methyl alcohol (50%) (charcoal), m. p. 229° (decomp.) (Found : N, 3·4. $C_{27}H_{23}O_5N$ requires N, 3·2%).

A mixture of the amino-acid (V) (1·6 g.) and acetophenone (0·6 g.) was heated at 110° for ¼ hour, then zinc chloride (1·0 g.) was added, and the heating continued for 8 hours. 6 : 7-*Dimethoxy*-2-*phenylquinoline*-4-*propionic acid* (VI; R = C_6H_5, R′ = H), isolated as in the previous case, crystallised from alcohol in colourless needles, m. p. 231—232°, showing a strong bluish-violet fluorescence in solution (Found : N,* 4·3. $C_{20}H_{19}O_4N$ requires N, 4·2%).

6 : 7-*Dimethoxyquinoline*-4-*propionic acid* (VI; R = R′ = H) was prepared by heating the acid (V) (1·0 g.) with acetaldehyde (1·5 g.) in alcohol (10 c.c.) with sodium hydroxide solution (3 c.c. of 50%) for 10 hours. After removal of the solvent, the residue was dissolved in hot water, and the *acid* isolated by acidification with acetic acid. It crystallised from water (charcoal) in glistening needles, m. p. 120—121° (m. p. 141° after drying at 100°) (Found, in dry material : N,* 5·4. $C_{14}H_{15}O_4N$ requires N, 5·4%), a non-acidic portion (not investigated) remaining undissolved in the water.

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[*Received, June* 19*th*, 1933.]