

## 226. *The Preparation of Quinoline Derivatives from Aromatic Amines and Ethyl Ethoxymethylenemalonate.*

By K. SCHOFIELD and J. C. E. SIMPSON.

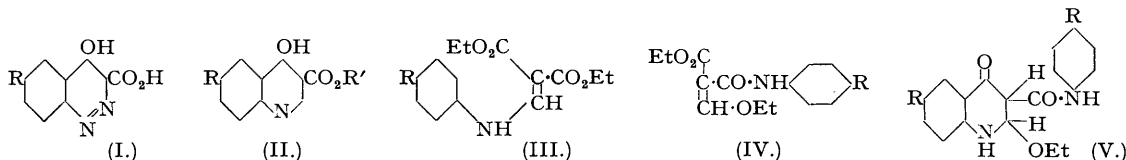
Interaction of aniline (or *p*-anisidine) and ethyl ethoxymethylenemalonate, followed by cyclisation, gives ethyl 4-hydroxyquinoline-3-carboxylate (II; R = H; R' = Et) [or its 6-methoxy-derivative (II; R = OMe; R' = Et)], together with unidentified products.

WORK on 4-hydroxycinnoline-3-carboxylic acid (I; R = H) and its 6-methoxy-derivative (I; R = OMe) (Schofield and Simpson, this vol. p. 472), necessitated the preparation of the corresponding quinoline acids (II; R = H and OMe; R' = H) for comparative purposes. 4-Hydroxyquinoline-3-carboxylic acid (II; R = R' = H) was first obtained by Camps (*Ber.*, 1901, **34**, 2703) by cyclisation of ethyl *o*-formamidophenylpropionate; short trial of this method, however, convinced us that it was unlikely to prove attractive, because esterification of *o*-aminophenylpropionic acid by alcoholic hydrogen chloride was apt to produce a considerable proportion of, apparently, 4-chloro-2-hydroxyquinoline (Baeyer and Bloem, *Ber.*, 1882, **15**, 2147), and attempted formylation of the ester, following the data supplied by Camps (*loc. cit.*), was unsuccessful.

The acid (II; R = R' = H) has also been prepared by Gould and Jacobs (*J. Amer. Chem. Soc.*, 1939, **61**, 2890) by cyclisation of ethyl anilinomethylenemalonate (III; R = H) at 250°. It is not clear from their paper whether quinoline acids or their esters were in all cases obtained by this method, and fission of the primarily formed esters into ethylene and the acids would appear to be possible [cf. the pyrolytic conversion of alkyl acrylates and methacrylates into the acids (Ratchford, Rehberg, and Fisher, *J. Amer. Chem. Soc.*, 1944, **66**, 1864)]; our own results, however, discount this possibility.

The ester (III; R = H) is described by Claisen (*Annalen*, 1897, **297**, 1) as the sole product of the interaction of aniline and ethyl ethoxymethylenemalonate, and Gould and Jacobs presumably were able to reproduce this result, as they state that all condensations between the ethoxy-ester and various arylamines "went smoothly

and apparently in only one sense." Our own experience, however, was notably different. We were able to obtain no crystalline products by condensation of aniline or *p*-anisidine with the ethoxy-ester, and cyclisation of the crude materials led to mixtures. Thus the reaction using aniline gave three products, one of which was the expected *ethyl 4-hydroxyquinoline-3-carboxylate* (II; R = H; R' = Et), identified by hydrolysis to the corresponding acid. A second substance, m. p. 318°, which gave analytical data in agreement with a formula C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub> or C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>, showed feebly acidic properties; it formed a crystalline sodium salt, but could not be hydrolysed in alkaline solution under ordinary conditions. The third component of the mixture was a *substance*, m. p. 118°, of formula C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub>. The reaction with *p*-anisidine gave rise to *ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate* (II; R = OMe; R' = Et), readily hydrolysed to the *acid* (II; R = OMe; R' = H), together with a *substance*, m. p. 133°, of formula C<sub>20</sub>H<sub>22</sub>O<sub>5</sub>N<sub>2</sub>.



The formulæ of the substances, m. p. 318°, 118°, and 133°, clearly indicate that two molecules of arylamine are involved. In view of the facility with which Michael-type additions of amines to unsaturated ketones occur (*e.g.*, Ruhemann and Watson, *J.*, 1904, **85**, 1170; Stewart and Pollard, *J. Amer. Chem. Soc.*, 1936, **58**, 1980; 1937, **59**, 2006, 2702; Cromwell *et al.*, *ibid.*, 1942, **64**, 2432; 1944, **66**, 872), analogous addition of arylamine to (III; R = H and OMe) or (IV; R = H and OMe) may be envisaged, and it may be significant that Surrey and Hammer (*ibid.*, 1946, **68**, 113) found that the yields of quinolines in the closely analogous synthesis from arylamines and oxaloacetic ester are diminished if the primary adduct contains free amine. Of the various possibilities which thus arise, the expression (V; R = H and OMe) [from (IV) by addition of arylamine and loss of alcohol] may be regarded as a tentative representation of the substances, m. p. 118° and 133°. An alternative explanation would be to formulate them as arylamidoarylaminoethylacetates (VI; R = H and OMe), isomeric with (V); the substance, m. p. 318°, would then be (VII). Each hypothesis is in conformity with the available evidence, and the second relates the substances, m. p. 118° and 318°, in a logical manner, although the analytical data for the second are not in good agreement with the formula, C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>, of (VII). That (V) should survive the conditions of the reaction without loss of ethyl alcohol would not, perhaps, be anticipated, but this criticism would also apply to (VI), and no definite decision between these alternatives is possible at present.



## EXPERIMENTAL.

(Melting points are uncorrected.)

*Products from Aniline and Ethyl Ethoxymethylenemalonate.*—In our hands, the conditions of Claisen (*loc. cit.*) for the preparation of the ethoxy-ester always gave extremely poor yields, the main product being an undistillable resin (15 mm.), and we were most indebted to Professor A. R. Todd, F.R.S., for details of a reliable method based on that of Wheeler and Johns (*Amer. Chem. J.*, 1908, **40**, 233). The oil formed by heating the ethoxy-ester (10 g., b. p. 164–168°/17 mm.) and aniline (4.3 g.) for  $\frac{1}{2}$  hour on the steam-bath, after removal of alcohol (reduced pressure) was added during 5 minutes to liquid paraffin at 255–265° under nitrogen with stirring. After 20 minutes' heating, during which sublimation occurred, the turbid solution was cooled and filtered; the solid was digested with boiling ligroin (b. p. 60–80°) and crystallised (5 g.) from acetic acid (100 c.c.), giving *ethyl 4-hydroxyquinoline-3-carboxylate*, which formed dull needles, m. p. 275–276° (shrinking at 267°) from alcohol (Found: C, 66.2; H, 5.3; N, 6.4. C<sub>12</sub>H<sub>11</sub>O<sub>3</sub>N requires C, 66.3; H, 5.1; N, 6.45%); the ester was soluble in  $\beta$ -ethoxyethyl alcohol and cyclohexanone in the hot, sparingly soluble in hot ethyl acetate and amyl formate, and insoluble in aqueous sodium bicarbonate. Hydrolysis on the steam-bath for  $\frac{1}{2}$  hour with aqueous sodium hydroxide (5%, 10 parts), followed by acidification, gave 4-hydroxyquinoline-3-carboxylic acid; the acid was easily soluble in aqueous sodium carbonate and bicarbonate, sparingly soluble in water and dilute hydrochloric acid, and formed colourless needles, m. p. 269–270° [efferv.; dependent on rate of heating; lit. m. ps., 266–267° (Camps), 267–268° (Gould and Jacobs)], from acetic acid (solubility in the hot, *ca.* 0.8%) (Found: C, 62.9; H, 3.5. Calc. for C<sub>10</sub>H<sub>7</sub>O<sub>3</sub>N: C, 63.5; H, 3.7%).

The acetic acid filtrate from the crude quinoline ester was evaporated (exhausted desiccator); the residue, after repeated digestion with alcohol and crystallisation from acetic acid, gave colourless hexagonal plates of the substance, m. p. 318–320° [Found (two samples): C, 71.75, 71.8; H, 4.6, 4.6; N, 10.9, 11.0. Calc. for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 72.7; H, 4.6; N, 10.6. Calc. for C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 71.4; H, 4.8; N, 11.1. Calc. for C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>: C, 72.1; H, 5.3; N, 10.5%]. The substance, which gave no ferric reaction, was almost insoluble in hydrochloric acid (dilute and concentrated), slightly soluble in aqueous sodium carbonate, and readily in warm aqueous sodium hydroxide, from which a colourless sodium salt separated on cooling. It was recovered unchanged after boiling with 10% sodium hydroxide for 3 hours under reflux, and was precipitated from alkaline solution at pH 9.5–10 (it could thus be separated from 4-hydroxyquinoline-3-carboxylic acid). It was only slightly attacked by acetic anhydride (3 hours under reflux; m. p. and mixed m. p. of product, 270–275°); reaction with phosphorus pentachloride–oxygen mixture at 90° gave an oil which did not yield a crystalline product after condensation with aniline.

The original liquid paraffin filtrate and ligroin extracts deposited solid on standing; this was digested with hot ligroin (b. p. 40–60°), and crystallised from the same solvent, yielding long, faintly yellow needles of the *substance*, m. p. 118–119° (Found: C, 69.4; H, 5.75; N, 9.2. C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub> requires C, 69.7; H, 5.8; N, 9.0%), insoluble in hot aqueous

sodium carbonate, in cold aqueous sodium hydroxide, and in cold 2*N*-hydrochloric acid. Hydrolysis of the substance resulted when it was heated for  $\frac{3}{4}$  hour on the steam-bath with aqueous-alcoholic sodium hydroxide (5%; 40 parts), but the acid, m. p. 172—173° (efferv.), obtained on acidification was amorphous and seemed to decompose on attempted crystallisation from acetic acid.

*Products from p-Anisidine and Ethyl Ethoxymethylenemalonate.*—The oil obtained by heating *p*-anisidine (6.75 g.) and the ester (12 g.) for  $\frac{3}{4}$  hour on the steam-bath was freed from alcohol and added during 7—8 minutes to liquid paraffin as already described. After a total of 20 minutes, the mixture was cooled and filtered, and the solid, after digestion with boiling ligroin (b. p. 40—60°), crystallised from acetic acid, giving *ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate* (4.3 g.) as tiny straw-coloured prisms, m. p. 280—281° (Found: C, 62.85; H, 5.25.  $C_{15}H_{13}O_4N$  requires C, 63.1; H, 5.3%). Hydrolysis was effected by heating the ester (2 g.) for 1 hour on the steam-bath with 5% aqueous sodium hydroxide (40 c.c.); *4-hydroxy-6-methoxyquinoline-3-carboxylic acid* (1.7 g.), obtained by acidification, was easily soluble in aqueous sodium bicarbonate, and very sparingly soluble in acetic acid, from which it formed almost colourless feathery needles, m. p. 278—279° (efferv.) (Found: C, 60.2; H, 4.2; N, 6.55.  $C_{11}H_9O_4N$  requires C, 60.3; H, 4.1; N, 6.4%).

Digestion with ether of the solid which slowly separated from the liquid paraffin and ligroin filtrates gave material which, on crystallisation from alcohol, furnished lemon-yellow, prismatic needles of the *substance*, m. p. 132—133° (1.85 g.) (Found: C, 64.6; H, 6.0; N, 8.0.  $C_{20}H_{22}O_5N_2$  requires C, 64.85; H, 6.0; N, 7.6%). This substance, which was insoluble in cold sodium hydroxide, was hydrolysed by heating it (0.5 g.) for 1 hour on the steam-bath with 10% aqueous sodium hydroxide (3 c.c.), alcohol (10 c.c.), and water (3 c.c., added after  $\frac{1}{4}$  hour). Dilution with water and ether-extraction gave an oil, acetylation of which yielded *acet-p-anisidide* (0.15 g.), m. p. and mixed m. p. 126—128°. Acidification of the alkaline solution after ether-extraction gave an amorphous acid (70 mg.), m. p. 174—177° (efferv.), which yielded only traces of crystalline material on attempted esterification (alcoholic sulphuric acid). In another similar hydrolysis of the substance, m. p. 133°, the acid fraction had m. p. 198—200°, and was either insoluble in, or decomposed on attempted crystallisation from, numerous solvents.

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DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.  
WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,  
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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