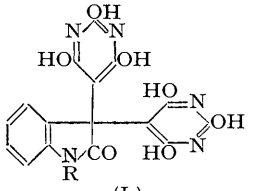
112. *The Condensation of Isatin and of* 1-*Methylisatin with Barbituric Acid.*

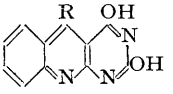
By F. E. KING. T. J. KING, and G. B. THOMPSON.

Isatin and barbituric acid react under aqueous acid conditions giving 3 : 3-*di*-(5-*barbituryl*)-*oxindole* (I, R = H), which is transformed by methanolic hydrogen chloride into *methyl* 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylate* (II, R = CO_2Me). Similar products, *i.e.*, (I, R = Me) and (VI, R = Me), can be prepared from 1-methylisatin. Hydrolysis of (II, R = CO_2Me) gave the corresponding *acid* (II, R = CO_2H) which was degraded to known 2-hydroxyquinolinecarboxylic acids. From the *acid chloride* the *amide* (II, R = $CO{\cdot}NH_2$) was obtained, and this was converted into 5-*amino*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine hydrochloride*.

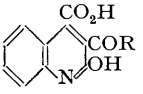
BECAUSE the heterocyclic system which they contain has several features in common with that of the *iso*alloxazines, a number of diaza-acridines were recently prepared as potential riboflavin antagonists (see F. E. and T. J. King, *J.*, 1947, 726). They were obtained by the action of *o*-aminobenzaldehyde on pyrimidines with tautomerisable groups in the 2 : 4 : 6-positions, a method of considerable flexibility, though limited in its application to *benz*-substituted diaza-acridines by the general inaccessibility of the necessary *o*-aminobenzaldehydes. With the idea of overcoming this disadvantage by using derivatives of isatin in place of the aminobenzaldehyde components—as in the Pfitzinger modification of Friedländer's quinoline synthesis—the condensation of isatin with barbituric acid as a typical pyrimidine was investigated. The carboxylic acids resulting from such condensations have a further interest in that they might be used in the preparation of the unknown 5-amino-1 : 3-diaza-acridines, analogues of the biologically active 5-aminoacridines.



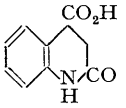
(I.)



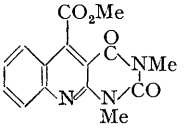
(II.)



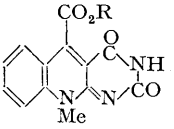
(III.)



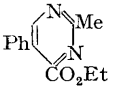
(IV.)



(V.)



(VI.)



(VII.)

From experience with *o*-aminobenzaldehyde in its reaction with the aminohydroxypyrimidines (F. E. and T. J. King, *loc. cit.*), isatin was not expected to condense with barbituric acid under the alkaline conditions of the normal Pfitzinger synthesis, and this was confirmed by experiment. Neither did any condensation occur in boiling water, but on addition of hydrochloric acid a colourless solid separated, which from analysis was evidently 3 : 3-*di*-(5-*barbituryl*)*oxindole* (I, R = H). In this respect, therefore, the pyrimidine behaves as a derivative of malonic acid, of which both the ethyl ester and dinitrile give similar di-substituted oxindoles (Zrike and Lindwall, *J. Amer. Chem. Soc.*, 1936, **58**, 49; Walter, *Ber.*, 1902, **35**, 1321).

The dibarbituryloxindole was decomposed by alkalis, and underwent hydrolysis into its components even on being heated with water, as was evident from the colour of the solution and from the isolation of isatin and barbituric acid in the form of derivatives. Conditions appropriate to the transformation of the dimalonyloxindoles to quinolines could not, therefore, be applied to the conversion of (I) into the required tricyclic system (II), and acid hydrolysis was therefore attempted. Heating with methanolic hydrogen chloride led (apparently by elimination of a barbituric acid residue) to the formation of a colourless *methyl* ester, and to this the constitution (II, R = CO_2Me) was assigned, since a barbiturylindogenide, the only likely alternative, would undoubtedly be coloured.

Apart from hydrolysis of the ester group, giving 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic acid* (II, R = CO_2H), the new product was stable to boiling aqueous alkali, but at higher temperatures under pressure degradation to the 2-*hydroxy*-4-*carboxyquinoline*-3-*carboxy-amide* (III, R = NH_2) occurred. It is of interest to note that 2 : 4-dihydroxy-1 : 3-diaza-acridine

(II, R = H) is hydrolysed by alkali under pressure to 2-hydroxyquinoline-3-carboxylic acid (Conrad and Reinbach, *Ber.*, 1901, **34**, 1339), although the precise experimental conditions are not recorded.

From the amido-acid (III, R = NH_2) a *monomethyl* ester was obtained, and, by treatment in 40% sulphuric acid solution with sodium nitrite, the corresponding dicarboxylic acid (III, R = OH). This had already been prepared from 3 : 3-dimalonyloxindole (Zrike and Lindwall, *loc. cit.*), but, its melting point being outside the usual range, identification was uncertain. It was therefore reduced by zinc in acetic acid, as described by Zrike and Lindwall (*loc. cit.*); loss of the 3-carboxyl group then occurred, leading to the more easily identified 2-keto-tetrahydroquinoline-4-carboxylic acid (IV).

It was later found that the action of hot concentrated hydrochloric acid on the dibarbituryloxindole was an alternative method for the preparation of (II, R = CO_2H). Identity of the products from the two sources was established by their hydrolysis to the same amidoquinoline-carboxylic acid (III, R = NH_2), and from further evidence cited later.

Decarboxylation of the diaza-acridine (II, R = CO_2H) was attempted by heating with copper chromite in quinoline, but even in boiling solutions the acid remained unchanged. The inactivity of the carboxyl group in this derivative was also apparent from unsuccessful experiments on its re-esterification with methyl alcohol. By the action of boiling thionyl chloride, however, an *acid chloride* (II, R = COCl) was obtained which reacted with methanol to give the known methyl ester, and with ethanol to give its *ethyl* analogue (II, R = CO_2Et). When left in contact with ethereal diazomethane, both acid and methyl ester gave *methyl* 2 : 4-*diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylate* (V), the formation of this compound, one of the few in this series with an easily ascertainable melting point, both from the ester (II, R = CO_2Me) and from the acid prepared by acid hydrolysis of (I), affording definite proof of their identity. From the acid chloride and aqueous ammonia, the 5-*carboxyamide* (II, R = $CO{\cdot}NH_2$) was prepared, and the action of sodium hypobromite on this gave 5-amino-2 : 4-dihydroxy-1 : 3-diaza-acridine, isolated as *hydrochloride*. Hydrazoic acid under the usual conditions of the Schmidt process was without action on the diaza-acridine-5-carboxylic acid.

The investigation was concluded with some experiments on the condensation of barbituric acid with 1-methylisatin. Under acid conditions, the 3 : 3-*di*-(5-*barbituryl*)-1-*methyloxindole* (I, R = Me) was formed. With methanolic hydrogen chloride rearrangement occurred as in the case of (I, R = H), the resulting *methyl* ester (VI, R = Me) bearing the same relationship to the 1 : 3-diaza-acridines as do the *iso*alloxazines to the analogous alloxazines. As was expected, the new nucleus was markedly more chromophoric, the 10-methyldiaza-acridines being brilliant yellow. The hydrolysis of (VI, R = Me) with alkali gave a carboxylic *acid* which was indistinguishable from the product obtained from the action of concentrated hydrochloric acid on the dibarbituryl-1-methyloxindole.

An alternative synthesis of 5-hydroxy- or 5-amino-diaza-acridines was at one time considered, based on the preparation of suitable pyrimidines from *o*-nitrobenzoylmalonic esters, etc., followed by reduction of the nitro-group and ring-closure, but it was not completed. In connexion with preliminary experiments, using benzoyl compounds, an improved preparation of ethyl benzoylmalonate was devised, in the course of which *ethyl dibenzoylmalonate* was isolated. The oxidation of 5-benzylbarbituric acid as a possible source of the 5-benzoylpyrimidine led, with chromic acid as reagent, to the formation of 5-*benzyldialuric acid*. The action of acetamidine on ethyl ethoxymethylenebenzoylacetate did not give 4-hydroxy-5-benzoyl-2-methylpyrimidine but the 4-*carbethoxy*-5-*phenyl* derivative (VII).

Experimental.

3 : 3-*Di*-(5-*barbituryl*)*oxindole* (I, R = H).—A suspension of isatin (14·7 g., 1 mol.) and barbituric acid (25·6 g., 2 mol.) in hot water (50 c.c.) was treated with concentrated hydrochloric acid (10 c.c.) and the mixture shaken and heated to boiling for a few minutes. The product collected after cooling was well washed with alcohol and finally with ether, which left a pale cream granular powder (27 g., 67%). This was so sparingly soluble in the usual solvents that it was recrystallised by dissolving in cold sodium hydrogen carbonate solution, from which, on the addition of dilute hydrochloric acid, 3 : 3-*di*-(5-*barbituryl*)*oxindole* separated as a monohydrate in colourless microscopic rhombohedra, m. p. 270° (decomp.) (Found : C, 47·6; H, 3·3; N, 17·7. $C_{16}H_{11}O_7N_5,H_2O$ requires C, 47·5; H, 3·2; N, 17·4%). Its decomposition on dissolving in boiling water was apparent from the red colour of the solution, and from the formation on treatment with hydroxylamine of long yellow needles of isatin-β-oxime, m. p. and mixed m. p. 218—219°. Addition of benzaldehyde to a warm aqueous solution gave a colourless solid, m. p. after crystallisation from acetic acid, 258—259° alone or mixed with 5-benzylidene-barbituric acid.

Methyl 2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylate* (II, R = CO_2Me).—The dibarbituryloxindole (7·5 g.) was suspended in methanol (70 c.c.) previously saturated with hydrogen chloride and the

mixture heated under reflux for 3 hours. After cooling, the white solid was collected and the *ester* separated from any remaining dibarbituryloxindole, etc., either by washing with dilute sodium hydrogen carbonate solution or by heating with water. The purified product (3·8 g., 70%) crystallised from a large volume of acetic acid in colourless microscopic elongated rectangular plates, m. p. >320° (Found after drying at 100° in a vacuum : C, 57·3; H, 3·5; N, 15·5. $C_{13}H_9O_4N_3$ requires C, 57·6; H, 3·3; N, 15·5%). Its solution in acetic acid fluoresces bright green in ultra-violet light. The ester is also slightly soluble in dioxan and 2-ethoxyethanol, the solutions exhibiting a brilliant blue fluorescence. It does not dissolve in cold aqueous sodium carbonate, but with dilute sodium hydroxide a yellow solution with a green fluorescence is formed. From more concentrated solutions a *sodium* salt separates as the sesquihydrate in bright yellow fine needles, m. p. >310° (Found : C, 49·0; H, 3·4; N, 12·9. $C_{13}H_8O_4N_3Na,1\frac{1}{2}H_2O$ requires C, 48·75; H, 3·4; N, 13·1%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic Acid* (II, R = CO_2H).—(*a*) The diaza-acridine methyl ester (5 g.) was heated under reflux for 20—30 minutes with 2N-sodium hydroxide (50 c.c.). When the bright yellow solution was cooled, a pale yellow sodium salt crystallised which on treatment with hydrochloric acid gave a buff-coloured solid. It was purified by dissolving in warm dilute sodium hydrogen carbonate solution (charcoal) and reprecipitating with hydrochloric acid. The resulting 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic acid* was collected, and washed with water, alcohol, and ether (yield 4·4%). It is sparingly soluble in the ordinary organic solvents and was recrystallised from a large volume of acetic acid, from which it separated in colourless, microscopic, long, thin, rectangular prisms, m. p. >325° (Found : C, 52·5; H, 3·5; N, 15·4. $C_{12}H_7O_4N_3,H_2O$ requires C, 52·3; H, 3·3; N, 15·3%. Found in a specimen dried in a vacuum at 100° : C, 54·0; H, 3·4; N, 15·3; loss 2·9. $C_{12}H_7O_4N_3,\frac{1}{2}H_2O$ requires C, 54·1; H, 3·0; N, 15·8; loss 3·3%).

(*b*) 3 : 3-Di-(5-barbituryl)oxindole (15 g.) was heated with concentrated hydrochloric acid (75 c.c.) in an open flask on a steam-bath until most of the liquid had evaporated (*ca.* 3 hours). Water (50 c.c.) was added to the light brown residue which then turned reddish. The rose-pink solid (8·5 g.) was collected, and washed with water, alcohol, and ether. It was purified by precipitation with acid from a solution in sodium hydrogen carbonate and by crystallisation from acetic acid (Found : C, 52·5; H, 3·6. Found in a dried specimen : C, 54·5; H, 3·2; loss 3·7%).

The colourless recrystallised acid exactly resembled in form, and in the fluorescence of its solutions in the ultra-violet—which were green-yellow in acetic acid, bright blue in sodium hydrogen carbonate, intense green in sodium hydroxide, and bright blue in ethanol—the acid obtained from the methyl ester (II, R = CO_2Me). Unless several times recrystallised, however, the latter exhibited a bright yellow colour in concentrated sulphuric acid, which was also observed if the specimen derived directly from the dibarbituryloxindole by means of hydrochloric acid was treated with boiling 2N-sodium hydroxide. Both samples of recrystallised acid gave only a pale straw-yellow colour when dissolved in concentrated sulphuric acid. After being left for 2 days in a vacuum over sodium hydroxide both dissolved quite readily in warm acetic acid, but the products which very shortly afterwards separated then required the usual large volume of boiling acid for complete solution.

Methyl 2 : 4-*Diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylate*, (V).—A finely powdered specimen (1 g.) of 2 : 4-dihydroxy-1 : 3-diaza-acridine-5-carboxylic acid, dried at 120°, was treated with a solution of diazomethane (0·8 g.) in ether. Nitrogen was evolved as the suspension stood at room temperature, and after 24 hours the pale yellow solid (0·6 g.) was collected. The product, which was insoluble in sodium carbonate solution, was crystallised from methanol or aqueous acetic acid; the methylated *ester* was thus obtained as minute colourless needles, m. p. 220° (Found in specimen dried at 100° in a high vacuum : C, 60·0; H, 4·7; N, 14·0; OMe, 10·9. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·3; N, 14·0; OMe, 10·4%).

2-*Hydroxy*-4-*carboxyquinoline*-3-*carboxyamide* (III, R = NH_2).—2 : 4-Dihydroxy-1 : 3-diaza-acridine-5-carboxylic acid (2 g.) was heated with aqueous sodium hydroxide (6 c.c. of 20%) at 180° for 5 hours. The solution was diluted with water to dissolve the product, filtered, and treated with hydrochloric acid. The colourless product (1·5 g.) being very sparingly soluble in organic solvents, it was purified by precipitation with acid from its solution in sodium hydrogen carbonate, the 2-*hydroxy*-4-*carboxyquinoline*-3-*carboxyamide* forming microscopic short prisms, m. p. 245° (decomp.) after discolouration at *ca.* 200° (Found, after dying in a vacuum at 100° : C, 56·5; H, 3·7; N, 11·9. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·4; N, 12·1%).

Ethyl 2-*Hydroxy*-3-*carboxyamidoquinoline*-4-*carboxylate*.—The foregoing amido-acid (0·5 g.) was heated with refluxing ethanolic hydrogen chloride (100 c.c. of 3%) for 4 hours. The reddish solution was then evaporated, the residue treated with water, and the solid (0·4 g.) collected and washed with alcohol. The product was very sparingly soluble, dissolving only in warm aqueous sodium carbonate and in alcoholic hydrogen chloride. Precipitation from the latter with water gave the *ester* as a white microcrystalline powder, m. p. 258° (decomp.) (Found after drying at 80° in a vacuum : C, 59·4; H, 4·6; N, 10·9. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%).

2-*Hydroxyquinoline*-3 : 4-*dicarboxylic Acid* (III, R = OH) (cf. Zrike and Lindwall, *loc. cit.*).—The above amido-acid (1 g.) dissolved in the minimum of 40% sulphuric acid (*ca.* 10 c.c.) was cooled to 0° and treated with a concentrated solution of sodium nitrite in water. The yellow solution had turned green at the end point, and on standing and dilution with water a pale yellow solid appeared. This could be crystallised from boiling water giving the quinolinedicarboxylic acid in short colourless needles (0·5 g.), m. p. >325° (Found after drying at 100° in a vacuum : C, 57·1; H, 3·0; N, 6·2. Calc. for $C_{11}H_7O_5N$: C, 56·7; H, 3·0; N, 6·0%).

2-*Hydroxytetrahydroquinoline*-4-*carboxylic Acid*.—The hydroxyquinolinedicarboxylic acid (0·6 g.) was heated on a steam-bath with acetic acid (15 c.c.) and zinc dust (1·5 g.). After 1½ hours the suspension was filtered, and the filtrate diluted with water (10 c.c.) and left overnight. 2-Hydroxytetrahydroquinoline-4-carboxylic acid separated in long colourless needles which after crystallisation from water had m. p. 219°, as recorded by Zrike and Lindwall (*loc. cit.*) (Found : C, 63·4; H, 4·6; N, 7·1. Calc. for $C_{10}H_9O_3N$: C, 62·9; H, 4·7; N, 7·3%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxyl Chloride* (II, R = COCl).—The dried carboxylic acid (1 g.) was heated with thionyl chloride under reflux for 1 hour. Hydrogen chloride was evolved and the mixture became bright yellow. Excess of thionyl chloride was removed under diminished pressure leaving the *acid chloride* as a yellow powder, decomp. 250°. It could not be crystallised, though slightly soluble in boiling dioxan and acetic acid, and it was well washed with ethyl acetate before analysis (Found : Cl, 12·2. $C_{12}H_6O_3N_3Cl$ requires Cl, 12·8%). Reaction with methanol as described in the preparation of the ethyl ester (below) gave the known methyl diaza-acridinecarboxylate (Found : C, 57·2; H, 3·5; N, 14·9. Calc. for $C_{13}H_9O_4N_3$: C, 57·6; H, 3·3; N, 15·5%).

Ethyl 2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxylate* (II, R = CO_2Et).—The acid chloride (1 g.) was heated with ethanol (100 c.c.) under reflux for 2—3 hours. The solution originally yellow was then virtually colourless, and on cooling a pale yellow crystalline solid (0·7 g.) separated. This was insoluble in sodium hydrogen carbonate solution, but dissolved in boiling dioxan, from which the *ethyl* ester separated on adding water as a microcrystalline powder, m. p. >320° (Found : C, 59·2; H, 4·1; N, 14·5. $C_{14}H_{11}O_4N_3$ requires C, 59·0; H, 3·9; N, 14·7%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxyamide* (II, R = $CO{\cdot}NH_2$).—The diaza-acridine acid chloride (4 g.) was added to aqueous ammonia (300—400 c.c., *d* 0·88) which was gently heated under reflux. At first a clear solution was obtained, but within ½ hour solid separated, which was collected after the addition of water. The resulting *amide* (2·5 g.) did not dissolve in aqueous sodium hydrogen carbonate but formed with sodium carbonate a sparingly soluble salt. The amide was precipitated from its solution in warm sodium carbonate by carbon dioxide, and if crystallised from formamide separated in a mass of colourless minute needles, m. p. >310° (Found after drying at 100° in a vacuum : C, 56·3; H, 3·3; N, 21·2. $C_{12}H_8O_3N_4$ requires C, 56·1; H, 3·1; N, 21·8%).

5-*Amino*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine* (II, R = NH_2).—The suspension of sodium salt obtained on cooling a solution of the diaza-acridine-5-carboxyamide (2·6 g.) in warm 2N-sodium hydroxide (20 c.c., 2 mols.) was treated with sodium hypobromite prepared by dissolving bromine (1·6 g.) in 2N-alkali (20 c.c.). After 3 hours at room temperature the residual solid was collected; it was identified as the amide sodium salt by treating it with mineral acid and recrystallising the product from formamide (Found : C, 56·1; H, 3·3%). Sodium hydroxide (8—10 g.) was added to the dark orange filtrate and the liquid was then gradually heated and maintained at 80° for 1—2 hours. The aminodiaza-acridine (1 g.) was precipitated from the cold solution by neutralisation with acetic acid. Although very sparingly soluble in alcohols, esters, etc., it dissolved freely in warm formamide, but on cooling the solution formed a gel. The product was readily dissolved by hot 2N-hydrochloric acid from which the *hydrochloride* separated in clusters of colourless prisms, m. p. >300° (Found after recrystallising from water and drying in a vacuum at 100° : C, 50·1, 50·3; H, 3·7, 3·4; Cl, 13·2. $C_{11}H_8O_2N_4$,HCl requires C, 49·9; H, 3·4; Cl, 13·4%).

3 : 3-*Di*-(5-*barbituryl*)-1-*methyloxindole* (I, R = Me).—1-Methylisatin (8·05 g., 1 mol.), prepared by the method of Borsche and Jacobs (*Ber.*, 1914, **47**, 361) and separated from the less soluble isatin by shaking with a small quantity of chloroform, was dissolved in boiling water (30—35 c.c.) with the addition of a little ethanol. Barbituric acid (12·8 g., 2 mol.) was introduced and the mixture heated until a clear solution resulted; concentrated hydrochloric acid (8 c.c.) was then added.

After further heating a solid was precipitated, which was collected and washed with alcohol. To purify the very sparingly soluble *dibarbituryl*-1-*methyloxindole*, it was dissolved in aqueous sodium hydrogen carbonate and precipitated with hydrochloric acid; if acetic acid is used, fairly concentrated solutions give a sodium salt which separates in flat rectangular prisms. 3 : 3-Di-(5-barbituryl)-1-methyloxindole forms colourless rhombohedra, m. p. 250° (decomp.) (Found after drying at 100° in a vacuum : C, 50·9; H, 3·6; N, 17·2. $C_{17}H_{13}O_7N_5$ requires C, 51·1; H, 3·3; N, 17·6%). As with the lower homologue, heating with water effects hydrolysis to the original components.

Methyl 2 : 4-*Diketo*-10-*methyl*-2 : 3 : 4 : 10-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylate* (VI, R = Me).—Methanolic hydrogen chloride (200 c.c. of 8%) containing the dibarbiturylmethyloxindole (8 g.) was refluxed for 5 hours. The cold solution was filtered from a small residue (0·55 g.) and the orange-yellow filtrate evaporated. The remaining solid was washed with sodium hydrogen carbonate solution and dissolved in a large volume of boiling water; the *methyl* ester (VI, R = Me) (2·3 g.) separated on cooling as a mass of brilliant yellow fine prisms, m. p. 280—282° (Found : C, 58·8; H, 4·0; N, 14·4. $C_{14}H_{11}O_4N_3$ requires C, 59·0; H, 3·9; N, 14·7%). The sodium hydrogen carbonate washings contained unchanged dibarbiturylmethyloxindole (3·5 g.). The bright yellow solution of the ester in aqueous sodium hydroxide was only feebly fluorescent, but in acetic acid and alcohol it fluoresced brilliant yellow-green.

2 : 4-*Diketo*-10-*methyl*-2 : 3 : 4 : 10-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylic Acid* (VI, R = H).—(*a*) The methyl ester (1 g.) was heated under reflux with 2N-sodium hydroxide (15 c.c.) for 20 minutes; the originally orange solution had then become light yellow. On cooling, a sodium salt separated as a thick paste which with careful acidification gave a deep yellow crystalline powder (*ca.* 1 g.). By dissolving in warm sodium hydrogen carbonate solution and precipitating with hydrochloric acid, the very sparingly soluble *methyldiaza-acridine-5-carboxylic acid* was obtained as microscopic yellow short prisms, m. p. >300° (Found : C, 57·7; H, 3·7; N, 15·7. $C_{13}H_9O_4N_3$ requires C, 57·6; H, 3·3; N, 15·5%).

(*b*) When the methyloxindole derivative (I, R = Me) (5 g.) was heated under reflux for 3 hours with concentrated hydrochloric acid (40 c.c.), a trace of *n*-octanol being added to prevent frothing, the 2 : 4-diketo-10-methyl-2 : 3 : 4 : 10-tetrahydro-1 : 3-diaza-acridine-5-carboxylic acid was again formed. It was isolated by evaporating the mineral acid, washing the residue with water, and shaking with warm dilute sodium hydrogen carbonate, the filtered solution (charcoal) depositing the microcrystalline yellow product on acidification (Found : C, 57·4; H, 3·6; N, 15·5%). The acid formed with saturated sodium hydrogen carbonate solution a yellow mass of hair-fine needles, which dissolved in water to form a brilliant blue-green fluorescent solution. The sodium salt obtained with sodium hydroxide does not separate but gives a yellow solution fluorescing green. The fluorescence in acetic acid is green-yellow and in ethanol blue. In sulphuric acid solution the diaza-acridine gives only a pale straw-yellow colour.

Ethyl Benzoylmalonate (cf. Bulow and Hailer, *Ber.*, 1902, **35**, 934).—Powdered sodium (11·5 g., 2 mols.) and ethyl malonate (40 g., 1 mol.) in dry ether (500 c.c.) were heated under reflux to complete the form-

ation of sodium salt. The suspension was shaken while benzoyl chloride (35 g., 1 mol.) was added, and the mixture was then set aside for 24 hours. After addition of water (700 c.c.) and a slight excess of hydrochloric acid, the ether layer was removed, dried, and evaporated. Distillation gave ethyl benzoylmalonate (40 g., 60%), and *ethyl dibenzoylmalonate* (6 g., 6·5%), b. p. 186°/0·03 mm., as a pale yellow opalescent oil (Found: C, 68·3; H, 5·7. $C_{21}H_{20}O_6$ requires C, 68·4; H, 5·4%). The monobenzoyl ester (4 g., 1 mol.) treated with ethylamine (0·68 g., 1 mol.) in dry ether deposited the *ethylamine* derivative (4·6 g., 98%). This dissolved freely in water and alcohol, and crystallised from ethanol–petroleum in long needles, m. p. 92° (Found: C, 62·35; H, 7·4; N, 4·4. $C_{14}H_{16}O_5,C_2H_7N$ requires C, 62·1; H, 7·4; N, 4·5%). Heating to 120° for 30 minutes gave ethyl malonate and *N*-ethylbenzamide.

5-Benzyldialuric Acid.—5-Benzylbarbituric acid (Kast, *Ber.*, 1912, **45**, 3124) (2 g.) and chromic acid (1·4 g.) were heated in refluxing acetic acid (30 c.c.) for 2 hours. Removal of the solvent under reduced pressure left a green friable gum which was dissolved in boiling water (50 c.c.). From the cold solution *5-benzyldialuric acid* (3·6 g., 67%) crystallised in large colourless plates which after crystallisation from water had m. p. 213—215° (slight decomp.) (Found: C, 56·0; H, 4·4; N, 12·1. $C_{11}H_{10}O_4N_2$ requires C, 56·4; H, 4·3; N, 12·0%).

Ethyl 5-Phenyl-2-methylpyrimidine-4-carboxylate (VII).—A solution of sodium (0·25 g., 1 mol.) in alcohol (75 c.c.), acetamidine hydrochloride (1 g., 1 mol.) and ethyl ethoxymethylenebenzoylacetate (Feist, Delf, and Langenkamp, *Ber.*, 1926, **59**, 2958) (2·6 g., 1 mol.) were heated under reflux for 5 hours. The deposit of sodium chloride was removed, the solution evaporated, and the residue distilled, giving *ethyl 5-phenyl-2-methylpyrimidine-4-carboxylate* (1·8 g., 69%) as a colourless oil, b. p. 115°/0·04 mm. (Found: C, 69·7; H, 6·0. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

The award of a studentship by the Medical Research Council to one of us (T. J. K.) is gratefully acknowledged. We thank Messrs. Genatosan, Loughborough, for a gift of barbituric acid.

DYSON PERRINS LABORATORY, OXFORD. [*Received, May 3st*, 1947.]