682. *The Structures of Some Supposed Azetid-2 : 4-diones. Part III. The "Alloxan-5-o-dimethylaminoanil" of Rudy and Cramer, and its Alkali Hydrolysis Product.*

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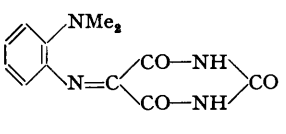
Neither the so-called "alloxan-5-*o*-dimethylaminoanil" nor the compound obtained from it by alkaline hydrolysis contains a dimethylamino-group and hence they cannot have the structures attributed to them by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329). The secondary product, hitherto regarded as mesoxalimide *o*-dimethylaminoanil, has been identified by synthesis as 1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4-methylglyoxalino(1′ : 5′-1 : 2)quinoxaline. It follows that the supposed alloxan anil is 1 : 2 : 3 : 4-tetrahydro-4-methylquinoxaline-2-*spiro*-5-(hexahydro-2 : 4 : 6-triketopyrimidine), formed as a result of a unique ring-closure involving a methyl group of the *o*-dimethylamino-substituent.

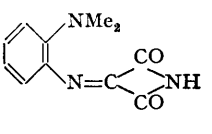
CONDENSATION of alloxan and *o*-dimethylaminoaniline in alcoholic solution leads to the formation of a compound believed by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329) to be the anil (I). This product, hereafter called A, is transformed by boiling 30% aqueous sodium or potassium hydroxide into a crystalline derivative B to which these authors have assigned the highly problematical mesoxalimide anil structure (II). Analyses, a colour reaction with hydrogen peroxide–hydrochloric acid said to be specific for the *o*-dimethylaminoanil grouping, and, in the case of B, a molecular-weight determination, are quoted as evidence for the proposed formulæ, and similar expressions have been used to represent the corresponding products derived from 2-dimethylamino-4 : 5-dimethylaniline. Nevertheless, the general properties of the compound B as recorded by Rudy and Cramer are incompatible with the structure (II). The supposed mesoxalimide anil is, for example, unaffected when heated with 50% aqueous sodium hydroxide or concentrated hydrochloric acid. This high degree of acid stability, which is characteristic too of the parent compound A, is unparallelled in the series of Schiff's bases, and Rudy and Cramer have consequently attributed the exceptional properties of the supposed anils A and B to the influence of the *o*-dimethylamino-substituent.

In view of these anomalous observations a further investigation of the problem has been undertaken. First, the postulated effect of the *o*-dimethylamino-group on anil stability was examined by reference to benzylidene-*o*-dimethylaminoaniline, whereupon it was observed that this new derivative, in contrast to the compounds A and B, exhibited the usual acid lability of the normal Schiff's base. Moreover, alloxan-5-*p*-dimethylaminoanil (Piloty and Finckh, *Annalen*, 1904, **333**, 37), a blue-black microcrystalline powder, also readily undergoes hydrolysis as is apparent from the immediate decolorisation of its deep blue-violet aqueous alcoholic solutions on the addition of dilute acid. Its isomer A, on the other hand, is light yellow, and the supposed anil B together with the *N*-methyl derivative prepared from it by the action of diazomethane are colourless. These marked differences between the prope ties of the authentic anil and the compounds A and B are quantitatively expressed by their respective ultra-violet absorption spectra (see figure) and render improbable the structures (I) and (II) proposed by Rudy and Cramer.

Evidence decisively excluding the anil structure (II) was obtained from a Herzig–Meyer analysis of the derivative B which gave a value indicative of the presence of only one *N*-methyl group in the molecule. It thus became apparent that in addition to the primary amino-group the *o*-dimethylamino-substituent of the constituent base had at one stage or the other reacted with the alloxan moiety. This further condensation we supposed to have taken place at the former alloxan-5-carbonyl group thus leading to a hydroquinoxaline system, since cyclisation at any other position would imply the formation of a ring larger than 6-membered. On this hypothesis it was possible to suggest for the alkali hydrolysis product B a new constitution (III; R = H) containing the hitherto unknown quinoxalino–hydantoin skeleton, which because of the ease of formation and general stability of the hydantoin ring afforded a more convincing interpretation of the properties of compound B than the structure (II) proposed by Rudy and Cramer.

This new structure was confirmed by synthesis of 1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino(1′ : 5′-1 : 2)quinoxaline (III; R = Me), identical with the *N*-methyl derivative formerly obtained by Rudy and Cramer from the product B. A suitably substituted hydantoin was first prepared according to the general method of Frerichs and Breustedt (*J. pr. Chem.*, 1902, **66**, 231) by heating *N*-*o*-aminophenyl-*N*-methyltoluene-*p*-sulphonamide (IV) with chloroacetylurethane, of which an improved preparation is described. The resulting 1-*o*-(*N*-methyltoluene-*p*′-sulphonamido)phenylhydantoin (V) was hydrolysed by a mixture of acetic and sulphuric acids at 100° to 1-*o*-methylaminophenylhydantoin (VI; R = H), which


(I)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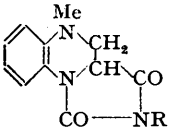
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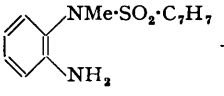

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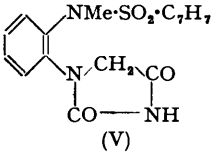
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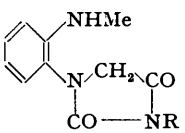
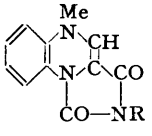
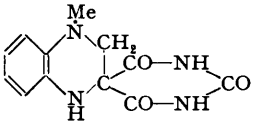
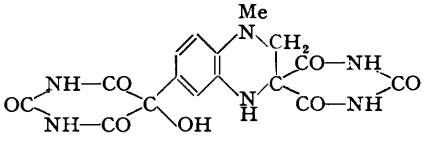


(VI)


(VII)


(VIII)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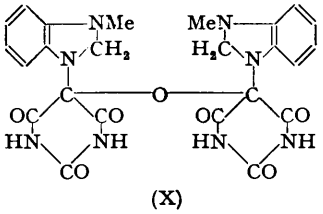

(X)

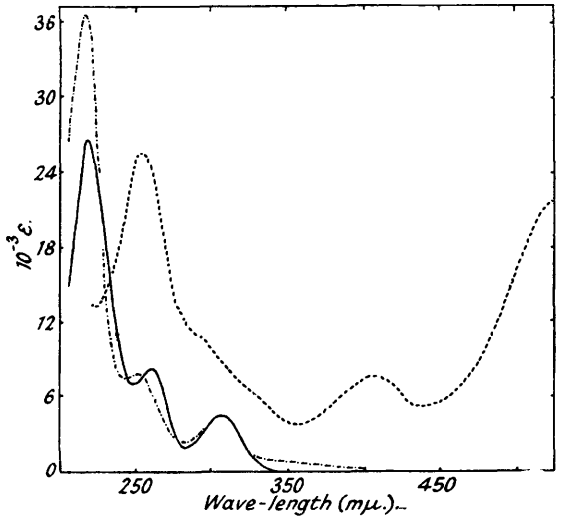
on methylation with diazomethane gave the 3-methylhydantoin (VI; R = Me) further characterised by its acetyl derivative. The intermediate (VI; R = Me) was alternatively obtained when the sulphonamidophenylhydantoin (V) was first methylated with methyl iodide–potassium carbonate and the methyl derivative then hydrolysed. The product (VI; R = Me) was then treated with powdered sodium in excess of ethyl formate, but instead of the expected intermediate sodium enolate of the 2-formylhydantoin, direct formation of the brilliant orange-yellow tetrahydrodiketoglyoxalinoquinoxaline (VII; R = Me) occurred. A similar condensation with ethyl acetate gave the 3-methyl homologue of (VII; R = Me), but the hydantoin (VI; R = Me) failed to react with ethyl benzoate.

Some difficulty was encountered in attempted catalytic reduction of the tetrahydro-compound (VII; R = Me), but tin and hydrochloric acid yielded the hexahydro-compound (III; R = Me) identical with the *N*-methyl derivative of compound B. Subsequently, the condensation of 1-*o*-methylaminophenylhydantoin (VI; R = H) and ethyl formate was effected, though less successfully than with the 3′-methyl derivative; reduction of the product yielded compound B, hitherto formulated as (II). It follows, furthermore, that a constitution analogous to (VII; R = H) may be assigned to the homologue of B obtained by alkaline hydrolysis of the so-called alloxan-2-dimethylamino-4 : 5-dimethylanil (Rudy and Cramer, *loc. cit.*).

It was then apparent that the primary condensation product also might contain the quinoxaline system. This view was supported by the resemblance of the ultra-violet absorption spectra of the two compounds and was largely confirmed when it was shown that compound A

possessed only one *N*-methyl group instead of the two required by Rudy and Cramer's expression (I). Moreover, in the dimethyl derivative which may be prepared from A by the action of diazomethane (Rudy and Cramer, *loc. cit.*), the existence of a replaceable hydrogen atom has now been demonstrated both by the Zerewitinoff method and by the formation of a monoacetyl derivative. It is therefore concluded that the supposed anil (I) is in fact a spiran (VIII), the active group of the dimethyl derivative being the basic >NH of the tetrahydroquinoxaline ring; similar constitutions may be presumed for the compounds prepared from 2-dimethylamino-4-methyl-, -5-methyl-, and -4 : 5-dimethyl-aniline. The alkali degradation leading to (III; R = H) is thus analogous to the formation described in Part II of oxazolid-diones from dialuric acids, which is also effected under alkaline conditions. In both reactions the hexahydrotriketopyrimidine nucleus undergoes contraction to a 5-membered ring as a result of a preliminary loss of the residue $-CO\cdot NH-$, followed by subsidiary condensations involving in one series (the dialuric acids) the hydroxyl and in the other the secondary amino-group.

The condensation of alloxan with *o*-dimethylaminoanilines in boiling ethanol to form products of the type (VIII) appears to involve an entirely novel reaction. When assisted by



Absorption curves.

———— 1 : 2 : 3 : 4 : 2′ : 4′-*Hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = Me) *in* 95% *ethanol.*
– – – – – – – *Alloxan*-5-p-*dimethylaminoanil in methanol.*
— · — · — 1 : 2 : 3 : 4-*Tetrahydro*-4-*methylquinoxaline*-2-spiro-5-(*hexahydro*-2 : 4 : 6-*triketopyrimidine*) (VIII) *in methanol.*

a small quantity of hydrochloric acid the condensation will occur even at room temperature. Under no conditions, however, does the yield exceed 25%, and Rudy and Cramer have reported the isolation of two by-products. One of these, which can also be obtained from (VIII) by the further action of alloxan, is evidently a dialuric acid, to which Rudy and Cramer have attributed a structure based on the expression (I). On the new formulation of A this becomes (IX), the location of the second pyrimidine nucleus *para* to the quinoxaline-*N*-methyl group being substantiated by data already published (Rudy and Cramer, *loc. cit.*). The third product is believed by the German authors to have the formula (X). They have recorded that its oxidation with hydrogen peroxide in acetic acid gives 1-methylbenziminazole, but the remaining evidence for (X) is unconvincing, and pending a reinvestigation of this substance we reserve further comment on its structure.

Details are given in the Experimental section of intermediates prepared in other uncompleted syntheses of the glyoxalinoquinoxaline (III). *N*-*o*-Nitrophenylglycine, obtained as the ethyl ester from *o*-nitroaniline and ethyl bromoacetate, failed to give 1-*o*-nitrophenylhydantoin when heated with urea, and various other standard hydantoin syntheses were also unsuccessful, evidently owing to the influence of the *o*-nitro-group. Attempts were made to prepare an

o-nitro-derivative of 1-(3 : 4-dimethylphenyl)hydantoin, but the principal product was a dinitro-compound and only traces of a mononitrated substance were isolated. In other experiments connected with this problem it was observed that on heating *N*-methyl-*o*-nitroaniline with ethyl bromo-pyruvate or -oxaloacetate, 4-bromo-*N*-methyl-2-nitroaniline is obtained.

Experimental.

Benzylidene-o-dimethylaminoaniline.—*o*-Dimethylaminoaniline was obtained by hydrogenation over Raney nickel of *NN*-dimethyl-*o*-nitroaniline (prepared from *o*-chloronitrobenzene as described by Campbell, *J. Amer. Chem. Soc.*, 1949, **71**, 740). With benzaldehyde the amine gave *benzylidene-o-dimethylaminoaniline* as a viscous yellow oil (Found : C, 79·8; H, 7·05; N, 12·5. $C_{15}H_{16}N_2$ requires C, 80·3; H, 7·2; N, 12·5%). Light absorption in ethanol (95%) : max. at 248 mμ (ε = 16,550), min. at 231 mμ (ε = 13,100). When cold dilute mineral acid was added to the anil, benzaldehyde was immediately liberated.

1 : 2 : 3 : 4-*Tetrahydro*-4-*methylquinoxaline*-2-spiro-5-(*hexahydro*-2' : 4 : 6-*triketopyrimidine*) (VIII).—This *spiran* was obtained in 15% yield from *o*-dimethylaminoaniline and alloxan hydrate by Rudy and Cramer's method (*loc. cit.*) and in 19% yield by keeping the reactants in aqueous ethanol at room temperature for 3 days in the presence of a few drops of concentrated hydrochloric acid. It crystallised from aqueous pyridine in small, yellow plates, m. p. 250° (decomp.) (Found : C, 55·0; H, 5·0; N, 20·9; NMe, 10·4. $C_{12}H_{12}O_3N_4$ requires C, 55·4; H, 4·7; N, 21·5; NMe, 11·2%). Light absorption in methanol : max. at 217 (ε = 36,450), 250 (ε = 7520) and 306 mμ (ε = 4500); min. at 242 (ε = 7250) and 283 mμ (ε = 2275). Methylation with ethereal diazomethane gave the *di*-N-*methyl* derivative, crystallising from ethanol in pale yellow prisms, m. p. 194° (Found : C, 59·0; H, 5·4; N, 19·6%; active H, 0·8 atom. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%); light absorption in 95% ethanol : max. at 218 (ε = 40,000), 250 (ε = 7710), and 306 mμ (ε = 5030); min. at 246 (ε = 7400) and 282 mμ (ε = 2280). When boiled with acetic anhydride for 1 hour the *N*-methyl derivative yielded an *acetyl* derivative which crystallised from ethanol in needles, m. p. 288° (Found : C, 58·4; H, 5·2. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5%).

The pale yellow colour of an alcoholic solution of the *spiro*-compound (VIII) was not discharged by shaking with zinc dust or by heating with magnesium (cf. Zechmeister and Truka, *Ber.*, 1930, **63**, 2883). The compound resisted catalytic hydrogenation over Adams's platinic oxide catalyst at room temperature and pressure. It gave a violet colour with hydrogen peroxide and concentrated hydrochloric acid.

Alloxan-5-p-*dimethylaminoanil* (Piloty and Finckh, *Annalen*, 1904, **333**, 37).—Condensation of *p*-dimethylaminoaniline and alloxan hydrate in boiling alcohol gave the Schiff's base as a nearly black powder. Light absorption in methanol : max. at 256 (ε = 26,400) and 405 mμ (ε = 7550); min. at 225 (ε = 13,240), 355 (ε = 3820), and 440 mμ (ε = 5220). The blue colour of an aqueous solution of the anil was immediately discharged by dilute mineral acid and was not restored on the dropwise addition of dilute aqueous sodium hydroxide. The colour of the liquid was also destroyed by shaking with zinc dust and by heating a methanolic solution with magnesium.

1 : 2 : 3 : 4 : 2' : 4'-*Hexahydro*-2' : 4'-*diketo*-4-*methylglyoxalino*(1' : 5'-1 : 2)*quinoxaline* (III; R = H).—When boiled with aqueous sodium hydroxide (30%) (cf. Rudy and Cramer, *loc. cit.*) the *spiro*-compound (VIII) (0·5 g.) gave the *quinoxalinohydantoin* (III; R = H) (0·2 g.) which crystallised from ethanol in needles, m. p. 240° (Found : C, 61·0; H, 5·2; N, 18·8; NMe, 14·1. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1; N, 19·3; NMe, 13·4%), and was coloured violet by a hydrogen peroxide–concentrated hydrochloric acid mixture.

Methylation with ethereal diazomethane formed 1 : 2 : 3 : 4 : 2' : 4'-*hexahydro*-2' : 4'-*diketo*-4 : 3'-*dimethylglyoxalino*(1' : 5'-1 : 2)*quinoxaline* (III; R = Me) which separated from ethanol in prisms, m. p. 154° (Found : N, 18·3. $C_{12}H_{13}O_2N_3$ requires N, 18·2%). Light absorption in ethanol (95%) : max. at 218 (ε = 26,500), 260 (ε = 8600), and 307 mμ (ε = 4700); min. at 248 (ε = 7590) and 284 mμ (ε = 1930). The picrate, which crystallised from ethanol in chocolate-brown needles, m. p. 133°, was unstable.

N-o-*Aminophenyl*-N-*methyltoluene*-p-*sulphonamide* (IV).—A suspension of powdered *N*-methyltoluene-*p*-sulphon-*o*'-nitroanilide (85 g.) (Usherwood and Whiteley, *J.*, 1923, 1084; Phillips, *J.*, 1929, 2820) in ethanol (300 ml.) was hydrogenated at room temp./6 atm. over Raney nickel. The product was dissolved by warming and the catalyst removed by filtration through kieselguhr, the filtrate depositing the *amide* (IV) as needles or prisms, m. p. 107—108° (62 g., 80%), soluble in dilute acids and sparingly soluble in water (Found : C, 61·0; H, 5·2; N, 10·2. $C_{14}H_{16}O_2N_2S$ requires C, 60·8; H, 5·8; N, 10·15%). A further quantity (10 g., total 94%) crystallised when the filtrate was concentrated.

Chloroacetylurethane.—Urethane (50 g.) was added to ether (300 c.c.) containing sodium wire (13 g.), and the mixture heated on a steam-bath until formation of the sodium salt was complete (5—6 hours). Ethyl chloroacetate (68·5 g.) was added to the cold suspension, and the mixture heated on a steam-bath for 5 hours and then left at room temperature for 14 hours. Ice and concentrated hydrochloric acid (56·5 c.c.) were then added alternately, and the ice-cold mixture shaken to complete decomposition of the sodium salt. The crystalline solid (72 g.) was collected and the remainder (5 g.) isolated by extraction of the aqueous layer with ether. Crystallisation from ethyl acetate gave chloroacetylurethane (70 g., 75%), m. p. 128—129°, also crystallising (in plates) from water, but with poor recovery (*ca.* 50%) presumably owing to hydrolysis (cf. Ruhemann and Priestley, *J.*, 1909, **95**, 453).

1-o-(N-*Methyltoluene*-p'-*sulphonamido*)*phenylhydantoin* (V).—A mixture of the amine (IV) (62 g., 1 mol.), chloroacetylurethane (37 g., 1 mol.), and dimethylaniline (27·2 g., 1 mol.) was heated at 120—

130° for 6 hours. The brownish-red product was treated with ether containing a little alcohol, and the solid residue washed in turn with ether, water, dilute hydrochloric acid, ethanol, and ether. Recrystallisation from ethanol gave the *hydantoin* (V) (44 g., 45%) as colourless prisms, m. p. 268—270° (Found: C, 57·0; H, 4·7; N, 11·5. $C_{17}H_{17}O_4N_3S$ requires C, 56·8; H, 4·8; N, 11·7%). The hydantoin is very sparingly soluble in hot water and in ethanol and only slightly soluble in aqueous sodium hydroxide. It was largely unchanged after being kept for 14 hours with sulphuric acid (90%) at room temperature, being then recovered when the mixture was poured into ice-water.

The use of alcohol in the above reaction, as in the experiments of Frerichs and Breustedt (*loc. cit.*), gave a poor yield of the hydantoin (V) (14%) together with N-o-(N-*methyltoluene*-p′-*sulphonamido*)-*phenylglycine ethyl ester* (8·5%), the latter being more soluble in alcohol and separating from it in prisms, m. p. 150° (Found: C, 59·5; H, 5·7; N, 7·7. $C_{18}H_{22}O_4N_2S$ requires C, 59·7; H, 6·1; N, 7·7%). When a mixture of the amine (IV) (2 mols.) and chloroacetylurethane (1 mol.) was kept at 100° for 18 hours and the product triturated and left with alcohol, a solid, m. p. 145—150°, was obtained consisting largely of the substituted glycine ester, m. p. 150° (65%) which was removed by a little hot ethanol leaving a residue of the hydantoin (V) (10%). After precipitation of excess of amine (IV) from the original alcoholic solution by ether, evaporation and sublimation of the residue gave ethyl carbamate, m. p. 50°.

1-o-*Methylaminophenylhydantoin* (VI; R = H).—The hydantoin (V) (3 g.) was heated for 1 hour on a steam-bath with 6 c.c. of a solution prepared by mixing acetic acid (41 c.c.) and concentrated sulphuric acid (92·5 c.c.). Recrystallisation, from ethanol, of the precipitate formed by pouring the solution into ice-water gave 1-o-*methylaminophenylhydantoin* (VI; R = H) (1·45 g., 85%) in plates, m. p. 224—226° (Found: C, 58·1; H, 5·4; N, 20·7. $C_{10}H_{11}O_2N_3$ requires C, 58·5; H, 5·4; N, 20·5%). The hydantoin is soluble in dilute mineral acids and in hot ethanol, and sparingly soluble in water.

3-*Methyl*-1-o-*methylaminophenylhydantoin* (VI; R = Me).—(i) Methylation of (VI; R = H) with ethereal diazomethane for 18 hours gave 3-*methyl*-1-o-*methylaminophenylhydantoin* (VI; R = Me), crystallising from ethanol in prisms, m. p. 153—154° (Found: C, 60·3; H, 5·9; N, 19·0. $C_{11}H_{13}O_2N_3$ requires C, 60·3; H, 6·0; N, 19·2%), and sparingly soluble in water, but soluble in dilute mineral acids and in organic solvents.

(ii) A mixture of 1-*o*-(*N*-methyltoluene-*p*′-sulphonamido)phenylhydantoin (V) (8·4 g.), acetone (50 c.c.), methyl iodide (23 g.), and anhydrous potassium carbonate (30 g.) was heated under reflux for 36 hours. The solvent was removed under reduced pressure and, after being washed with water to remove inorganic salts, the residual clear gum (*ca.* 8 g.) was crystallised from benzene–light petroleum. The resulting 3-*methyl*-1-o-(N-*methyltoluene*-p′-*sulphonamido*)*phenylhydantoin* formed plates, m. p. 134—135° (Found: N, 11·0. $C_{18}H_{19}O_4N_3S$ requires N, 11·3%). Hydrolysis with acetic–sulphuric acid mixture as in the preparation of (VI; R = H) gave 3-methyl-1-*o*-methylaminophenylhydantoin (VI; R = Me) (60%), m. p. 153—154°. With acetic anhydride the product (1 g.) afforded 3-*methyl*-1-o-N-*methylacetamidophenylhydantoin* (0·9 g., 75%), prisms (from ethanol), m. p. 187—188° (Found: N, 16·5; $C_{13}H_{15}O_3N_3$ requires N, 16·1%).

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = Me).—A mixture of 3-methyl-1-*o*-methylaminophenylhydantoin (VI; R = Me) (4 g., 1 mol.) and ethyl formate (17·5 g.) was heated with powdered sodium (0·4 g., 1·05 equiv.) on a steam-bath for 2 hours. A brisk evolution of hydrogen occurred and the solution deposited an orange-yellow solid (3·5 g., 85%), which was collected after 12 hours at room temperature. Crystallisation of the solid from hot ethanol, after washing with dilute hydrochloric acid, water, and alcohol, gave 1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = Me) as lustrous orange-yellow long hair-like needles, m. p. 260° (Found: C, 62·9; H, 4·8; N, 18·2. $C_{13}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). The glyoxalinoquinoxaline is slightly soluble in dilute mineral acids and readily soluble in acetic acid. It gives a violet colour with nitric acid, but is unaffected by hydrogen peroxide–hydrochloric acid. The compound could not be reduced by sodium and boiling ethanol or catalytically although slowly undergoing partial hydrogenation at N.T.P. over platinic oxide.

Reduction of 1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline*.—A solution of the glyoxalinoquinoxaline (VII; R = Me) (1·4 g.) in acetic acid (20 c.c.) was mixed with concentrated hydrochloric acid (100 c.c.), and heated on a steam-bath with the gradual addition of granulated tin (25 g.). When reduction was complete (3 hours), the solution was cooled and filtered, and the filtrate cooled in ice-water and strongly basified with aqueous sodium hydroxide (40%). Crystallisation of the organic precipitate from the minimum quantity of hot ethanol gave 1 : 2 : 3 : 4 : 2′ : 4′-*hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = Me) (0·664 g., 47%) as colourless prisms, m. p. 154° alone or mixed with the product obtained by the method of Rudy and Cramer (Found: C, 62·1; H, 5·5; N, 18·2. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·7; N, 18·2%). The *picrate* crystallised in chocolate-brown needles (from ethanol), m. p. 133° (Found: C, 46·8; H, 3·6; N, 18·1. $C_{12}H_{13}O_2N_3,C_6H_3O_7N_3$ requires C, 47·0; H, 3·5; N, 18·3%). The compound gave a violet colour with hydrogen peroxide–concentrated hydrochloric acid and with sulphuric acid containing nitric acid.

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4-*methylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = H).—A mixture of 1-*o*-methylaminophenylhydantoin (VI; R = H) (1·7 g., 1 mol.), ethyl formate (15 c.c.), and powdered sodium (0·4 g., 2·1 equivs.) was heated on a steam-bath for 1 hour and then left at room temperature for 14 hours. Neutralisation with aqueous acetic acid gave 1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-4-*methylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = H) (0·5 g., 28%) which crystallised from ethanol in yellow needles, m. p. 270° (Found: C, 60·9; H, 4·8; N, 19·8. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2; N, 19·5%). Unused hydantoin (VI; R = H) (0·75 g., 44%), m. p. 226°, was recovered by chloroform extraction of the original aqueous solution.

Reduction of the compound (VII; R = H) with tin and hydrochloric acid, as for the homologue (VII; R = Me), removal of the tin as sulphide, and neutralisation with aqueous ammonia gave

1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4-methylglyoxalino(1′ : 5′-1 : 2)quinoxaline (III; R = H) (*ca.* 0·1 g.), m. p. 239°, identical with that obtained by the method of Rudy and Cramer (*loc. cit.*).

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-3 : 4 : 3′-*trimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline*.—A mixture of 3-methyl-1-*o*-methylaminophenylhydantoin (VI; R = Me) (2 g., 1 mol.), ethyl acetate (20 c.c.), and powdered sodium (0·4 g., 1·9 equivs.) was heated on a steam-bath for 5 hours. The excess of ethyl acetate was removed under reduced pressure and water was added, the yellow solid which consisted of 1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-3 : 4 : 3′-*trimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* crystallising from ethanol in small yellow needles, m. p. 190—191° (Found : C, 64·6; H, 5·7; N, 16·9. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%). 3-Methyl-1-*o*-methylaminophenylhydantoin (0·9 g., 45%) was recovered from the filtrate by extraction with chloroform. When (VI; R = Me) was treated in a similar manner with ethyl benzoate and sodium (1 equiv.) no reaction took place.

N-*o*-*Nitrophenylglycine Ethyl Ester*.—A mixture of ethyl bromoacetate (62 g., 1 mol.) and *o*-nitroaniline (103 g., 2 mols.) was heated in an oil bath at 120—135° for 4½ hours, and then diluted with ether and filtered from *o*-nitroaniline hydrobromide (52 g.). The filtrate was evaporated under reduced pressure, crystallisation of the residue from ethanol (*ca.* 150 ml.) giving N-*o*-*nitrophenylglycine ethyl ester* (50 g., 60%) as long yellow needles, m. p. 77—78°, raised to 80° by recrystallisation from ethanol (Found : C, 53·5; H, 5·3; N, 13·1. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). The ester failed to react when heated with ethyl chloroformate alone or in the presence of pyridine, 85% being recovered. It was not hydrolysed after several hours by boiling aqueous or alcoholic alkali, but evaporation with concentrated hydrochloric acid gave *N*-*o*-nitrophenylglycine (90%), orange prisms, m. p. 199°, a method of preparation superior to that of Plöchl (*Ber.*, 1886, **19**, 7).

Attempts to prepare 1-*o*-nitrophenylhydantoin from *N*-*o*-nitrophenylglycine or its ester by standard methods were unsuccessful. Heating chloroacetylurethane (1 mol.) with *o*-nitroaniline (2 mols.) led to *s*-di-*o*-nitrophenylurea (8%), m. p. 223—224°.

N-3 : 4-*Dimethylphenylglycine Ether Ester*.—A mixture of 3 : 4-dimethylaniline (43 g., 2 mols.) and ethyl chloroacetate (20 g., 1 mol.) was heated at 100° for 1 hour. The solid was treated with hot water and the oily product extracted with ether and washed with 2N-hydrochloric acid. Removal of the ether and crystallisation of the residue from light petroleum gave N-3 : 4-*dimethylphenylglycine ethyl ester* (23·1 g., 67·5%), as prisms, m. p. 49—50°, or plates from aqueous ethanol (Found : N, 6·9. $C_{12}H_{17}O_2N$ requires N, 6·8%).

1-(3 : 4-*Dimethylphenyl*)*hydantoin*.—Heating 3 : 4-dimethylaniline (21·2 g., 2 mols.) with chloroacetylurethane (14·5 g., 1 mol.) (cf. Frerichs and Breustedt, *loc. cit.*) gave 1-(3 : 4-*dimethylphenyl*)*hydantoin* (12 g., 70%), which crystallised from ethanol in long needles, m. p. 206—207° (Found : C, 65·2; H, 6·1; N, 14·3. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). It was also obtained by heating *N*-(3 : 4-dimethylphenyl)glycine ester with urea at 150—160° (cf. Schwebel, *Ber.*, 1877, **10**, 2048).

Methylation of the hydantoin (10·7 g.) with methyl iodide and potassium carbonate in acetone gave 1-(3 : 4-*dimethylphenyl*)-3-*methylhydantoin* (9 g., 79%), needles (from ethanol), m. p. 169—170° (Found : C, 65·5; H, 6·1; N, 12·8. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·5; N, 12·8%). An identical product was obtained by methylation with ethereal diazomethane. Treatment of the 1-(3 : 4-dimethylphenyl)-3-methylhydantoin with concentrated nitric–sulphuric acids for 10 minutes at 0° gave a *dinitro*-derivative (34%) which crystallised from ethanol in pale yellow prisms, m. p. 226°, and was also obtained by nitration with sulphuric acid containing potassium nitrate (1 mol.) (Found : C, 47·0; H, 4·0; N, 18·9. $C_{12}H_{12}O_6N_4$ requires C, 46·8; H, 3·9; N, 18·3%). Nitration of the methylated hydantoin (0·5 g.) with nitric acid (1 c.c.) in glacial acetic acid (9 c.c.) at room temperature for 14 hours yielded a *mononitro*-derivative crystallising from ethanol in pale yellow prisms (0·067 g., 10%), m. p. 130—132° (Found : C, 55·0; H, 4·8; N, 16·0. $C_{12}H_{13}O_4N_3$ requires C, 54·8; H, 5·0; N, 16·0%).

Reaction of o-*Nitromethylaniline with Ethyl Bromo-oxaloacetate and Ethyl Bromopyruvate*.—*o*-Nitromethylaniline (7·5 g.) and ethyl bromo-oxaloacetate (13·2 g.) were heated together for 4 hours at 130—135° and then added to light petroleum (100 c.c.; b. p. 100—120°). Crystallisation of the solid (6·15 g., 54%) from light petroleum (b. p. 60—80°) gave orange prisms of 4-bromo-2-nitromethylaniline (5 g.), m. p. 93—94°, raised by two crystallisations to 99—100° undepressed by an authentic specimen (Found : C, 37·0; H, 2·7; N, 12·3. Calc. for $C_7H_7O_2N_2Br$: C, 36·4; H, 3·0; N, 12·3%). Heating *o*-nitromethylaniline with ethyl bromopyruvate at 120—130° for 4 hours gave 4-bromo-2-nitromethylaniline (35%) and a dark tar. When the reactants were heated in pyridine no bromonitroaniline was obtained and *o*-nitromethylaniline (80%) was recovered.

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