CCCXVII.—*The Formation of 2-Substituted Benziminazoles.*

By MONTAGUE ALEXANDRA PHILLIPS.

IT has been shown (Phillips, this vol., p. 172) that 2-methylbenziminazoles are readily formed by the action of boiling dilute hydrochloric acid on mono- or di-acetyl-*o*-diamines and by the action of acetic anhydride and hydrochloric acid on *o*-phenylenediamines, and it was suggested that hydrolysis of the diacetyl to the monoacetyl compound constituted a stage in the formation of the ring compound from the former.

These reactions have now been extended to the formation of other 2-substituted benziminazoles, and it has been shown that *o*-phenylenediamine on condensation with formic, acetic, propionic, glycollic, lactic, and mandelic acids in the presence of boiling dilute hydrochloric acid gives good yields of the corresponding cyclic compound.

In view of the general nature of this reaction, it now seems possible, as an alternative to the above suggestion, that the mechanism of the formation of 2-substituted benziminazoles from mono- and di-acyl-*o*-diamines involves hydrolysis to the diamine with subsequent formation of the ring. Since traces of 4-nitro-*o*-phenylenediamine always seem to accompany 5-nitro-2-methylbenziminazole in the formation of the latter compound from 4-nitrodiacetyl-*o*-phenylenediamine (compare Phillips, *loc. cit.*) and the amount of diamine seems to be greater if the heating is not pro-

longed, it would seem that, in this case at least, the second view is the more correct. Experiments are contemplated which may decide between these two views.

The reduction of *o*-nitroacetanilide by iron and dilute acetic acid (a method which is generally employed for the production of *o*-aminoacylanilides) gives benziminazole only. The effect of a *p*-cyanomethyl group in stabilising the *o*-aminoformamido-structure is shown by the reduction of 3-nitro-4-formamidobenzyl cyanide by this method (Maron, Kontorowitsch, and Bloch, *Ber.*, 1914, **47**, 1377; D.R.-P. 283,448).

3-Amino-4-formamidobenzyl cyanide, 3-amino-4-acetamidobenzyl cyanide, and 3-amino-4-lactamidophenetole, which were shown by Maron and his co-workers (*loc. cit.*; *Ber.*, 1914, **47**, 718) to pass into the corresponding benziminazoles by prolonged treatment with formic or glacial acetic acid, readily give the same ring compounds by boiling with dilute hydrochloric acid. 3 : 4-Diformamidobenzyl cyanide also gives the benziminazole readily by similar treatment.

The condensation of *o*-phenylenediamine and oxalic, malonic, and succinic acids requires special notice. *o*-Phenylenediamine and oxalic acid in the presence of boiling dilute hydrochloric acid give a quantitative yield of 2 : 3-*dihydroxyquinoxaline*, no benziminazole derivative being detected, whilst malonic acid and *o*-phenylenediamine give a mixture of *o*-phenylenemalonamide (I) (compare Meyer and co-workers, *Annalen*, 1906, **347**, 17) and 2-*aminomalonanilic acid* (II), which readily passes into the heterocyclic compound on further treatment with boiling dilute mineral acid. No benziminazole-2-acetic acid was detected.

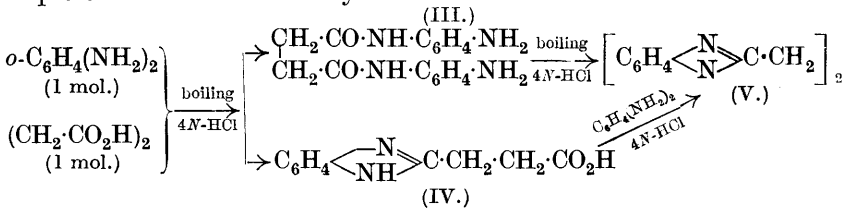
$$C_6H_4(NH_2)_2 + CH_2(CO_2H)_2 \longrightarrow$$

$$\text{(I.)}\ C_6H_4\begin{<}NH\cdot CO\\NH\cdot CO\end{>}CH_2 + C_6H_4(NH_2)\cdot NH\cdot CO\cdot CH_2\cdot CO_2H\ \text{(II.)}$$

2 : 3-Dihydroxyquinoxaline and *o*-phenylenemalonamide resemble each other in their insolubility in water and organic solvents, in their high melting points, and in the formation of very sparingly soluble monosodium salts.

From succinic acid and *o*-phenylenediamine (1 mol. of each) 2 : 2′-diaminosuccinanilide (III) and benziminazole-2-propionic acid (IV) were isolated, whilst with double the proportion of the diamine, αβ-dibenziminazolylethane (V) and traces of benziminazole-2-propionic acid were found. αβ-Dibenziminazolylethane, originally obtained by Walther and von Pulawski (*J. pr. Chem.*, 1899, **59**, 249) by the action of succinic anhydride on *o*-phenylenediamine at high temperatures, was also obtained from 2 : 2′-diaminosuccinanilide by treatment with hot dilute hydrochloric acid and by condensation

of benziminazole-2-propionic acid and *o*-phenylenediamine in the presence of the same catalyst :



The synthesis of 2-phenylbenziminazole by the above methods has not proved practicable, only traces of this compound having been isolated as picrate by treatment of *o*-aminobenzanilide and dibenzoyl-*o*-phenylenediamine with boiling dilute hydrochloric acid. The condensation of *o*-phenylenediamine with benzoic acid, benzoic anhydride, or benzoyl chloride in the presence of the above catalyst was also unsuccessful (compare, however, Walther and von Pulawski, *loc. cit.*).

That these reactions are not confined to the aromatic diamines is suggested by the ready conversion of $\alpha\alpha'$-diacetylethylenediamine into 2-methyl-4 : 5-dihydroglyoxaline by boiling with dilute hydrochloric acid; it is proposed to study the formation of glyoxalines from diacylethylenediamines by the above methods.

EXPERIMENTAL.

Condensation of o-*Phenylenediamine and Organic Acids in Presence of Boiling* 4N-*Hydrochloric Acid.*

o-Phenylenediamine (0·02 mol.), the requisite acid (0·03 mol.), and 20 c.c. of 4*N*-hydrochloric acid were boiled for 30—40 minutes under reflux. On neutralisation of the filtered solution with ammonia, the benziminazole separated. In no case except that of lactic acid was the benziminazole isolated readily when the condensation was attempted in the absence of the mineral acid.

All the benziminazoles described in the following table are readily soluble in dilute mineral acids and in excess of dilute caustic alkalis. They were recrystallised from water except where otherwise indicated.

Acid.	Benziminazole.	Crystalline form.	M. p.	Yield, %.	N, %. Found.	N, %. Calc.
Formic.	Unsubstituted.	Plates.	170°	60	23·6	23·7
Acetic.	2-Methyl.	Prisms.	176	60	21·3	21·2
Propionic.	2-Ethyl.	Prisms.*	177	70	19·0	19·1
Glycollic.	2-Hydroxymethyl	Plates.*	171—172†	65	18·7	18·9
Lactic.	2-α-Hydroxyethyl.	Plates.	178—179†	70	17·3	17·3
Mandelic.	2-α-Hydroxybenzyl.	Diamond plates.*	202—203†	50	12·4	12·5
Benzoic.	2-Phenyl.	(Traces isolated as picrate, m. p. 280°.)				

* Recrystallised from 50% alcohol.

† Compare Bistrzycki and Przeworski, *Ber.*, 1912, **45**, 3483.

Benziminazole was also obtained by reduction of *o*-nitroformanilide, using the method described for the preparation of *o*-aminoacetanilide (Phillips, *loc. cit.*) (Found : N, 23·5%), and by the action of boiling 4*N*-hydrochloric acid on *o-phenylenediamine monoformate* (Found : N, 23·6%).

3-Nitro-4-lactamidophenetole was obtained by warming a mixture of 5 g. of 4-*l*-lactamidophenetole (lactophenin) and 10 c.c. of 16% nitric acid for 5 minutes at 40°; the gum formed was poured into water (100 c.c.) and the resulting solid crystallised from 50% alcohol (4·5 g., yellow needles, m. p. 115°). The nitro-compound was reduced by iron and boiling dilute acetic acid as described previously; the amino-compound (yield 60%) crystallised from water in needles, m. p. 135—136° (compare Maron and Bloch, *Ber.*, 1914, **47**, 718). 5-Ethoxy-2-(α-hydroxyethyl)benziminazole was obtained in 50% yield by treating the above amino-compound (2 g.) with boiling 4*N*-hydrochloric acid (10 c.c.) for 30 minutes, with subsequent neutralisation. It forms white plates, m. p. 170—171°, from water, and is readily soluble in dilute mineral acids and in excess of dilute caustic alkali (Found : N, 13·5. Calc. for $C_{11}H_{14}O_2N_2$: N, 13·6%).

3-Nitro-4-formamidobenzyl cyanide was made by cautiously adding 4-formamidobenzyl cyanide to ten times its weight of nitric acid (*d* 1·5) at 5—6°. The nitration mixture on being poured on crushed ice deposited the nitro-compound, which was collected and washed within ten minutes to avoid hydrolysis of the formyl group; it crystallised from 60% alcohol in yellow prisms, m. p. 151—152° (yield 86%). On reduction with iron and acetic acid (Phillips, *loc. cit.*), a 50% yield of 3-amino-4-formamidobenzyl cyanide was obtained; white needles, m. p. 124°, from water (Found : N, 23·8. Calc. for $C_9H_9ON_3$: N, 24·0%).

3 : 4-*Diformamidobenzyl Cyanide.*—3-Amino-4-formamidobenzyl cyanide (1·5 g.) and formic acid (98%, 2 c.c.) were heated under reflux for 20 minutes. After removal of excess formic acid, the gum was dissolved in alcohol, and the filtered solution allowed to evaporate in a vacuum. The semi-solid mass left was crystallised from alcohol–ether, 3 : 4-*diformamidobenzyl cyanide* being obtained as a hygroscopic, micro-crystalline solid, m. p. 92—95°, readily soluble in water, ethyl and methyl alcohols, and acetic and formic acids, but insoluble in ether or benzene (Found : N, 20·5. $C_{10}H_9O_2N_3$ requires N, 20·7%).

Nitration of 4-*Acetamidobenzyl Cyanide.*—This nitration was studied by Gabriel (*Ber.*, 1882, **15**, 836), who isolated only the 3-nitro-derivative; the following method led to the production of 4-acetamidophenylacetamide in addition. 4-Acetamidobenzyl cyan-

ide (8 g.) was fed slowly into nitric acid (*d* 1·5, 50 c.c.) at 5—10°, and then poured on ice; the gummy solid obtained was collected, dried at 50° (7 g.), and crystallised from 300 c.c. of 50% alcohol, 3 g. of crude 4-acetamidophenylacetamide, m. p. 212—215°, being obtained; further crystallisation gave the pure amide, m. p. 231° (compare Purgotti, *Gazzetta*, 1890, **20**, 599) (Found: N, 14·8. Calc.: N, 14·6%). The mother-liquors on concentration to half bulk gave deep golden-yellow plates of the nitro-compound, m. p. 112—113° (2 g.) (Found: N, 19·3. Calc.: N, 19·2%), slowly soluble in excess of dilute caustic alkalis to give an orange solution. 3-Amino-4-acetamidobenzyl cyanide was obtained by reduction of the above nitro-compound by iron and boiling dilute acetic acid. It forms white needles from hot water, m. p. 140° (compare Maron, Kontorowitz, and Bloch, *loc. cit.*) (Found: N, 22·4. Calc.: N, 22·2%).

5-*Cyanomethylbenziminazole.*—3-Amino-4-formamidobenzyl cyanide (1·5 g.) or 3 : 4-diformamidobenzyl cyanide (1·5 g.) was boiled under reflux with 4*N*-hydrochloric acid (10 c.c.) for 20 minutes. The crystals which separated on neutralisation and cooling were collected, washed, and crystallised from hot water. The yield was approximately 1·0 g. in either case (80%); 5-cyanomethylbenziminazole crystallises from hot water as anhydrous, diamond-shaped plates, m. p. 158—159° (compare Maron, Kontorowitz, and Bloch, *loc. cit.*) (Found: N, 26·8. Calc.: N, 26·7%).

5-*Cyanomethyl*-2-*methylbenziminazole.*—3-Amino-4-acetamidobenzyl cyanide (3 g.) was refluxed for 20—30 minutes with 20 c.c. of 4*N*-hydrochloric acid; on neutralisation and cooling, 5-cyanomethyl-2-methylbenziminazole separated (yield 65%); it crystallises from hot water in prisms, m. p. 206° (compare Maron, Kontorowitz, and Bloch, *loc. cit.*).

Condensation of o-*Phenylenediamine and Dibasic Organic Acids in Presence of Boiling* 4N-*Hydrochloric Acid.*

Oxalic acid. *o*-Phenylenediamine (5·5 g.), oxalic acid (dihydrate, 6·5 g.), and 4*N*-hydrochloric acid (30 c.c.) were heated to boiling, and a crystalline solid formed. After 10 minutes' further boiling, the reaction mixture was cooled and the solid, consisting of almost pure 2 : 3-dihydroxyquinoxaline, was collected, washed with water, and dried (yield, 8 g.) (Found: N, 17·4%). The *sodium* salt was obtained as white prisms, sparingly soluble in hot water (Found: N, 15·5; Na, 12·15. $C_8H_5O_2N_2Na$ requires N, 15·2; Na, 12·5%), and, on acidification with hydrochloric acid, it gave the pure *quinoxaline* as white needles, insoluble in hot water or the ordinary solvents and not melting below 350° (Found: N, 17·4.

$C_8H_6O_2N_2$ requires N, 17·3%). That this compound is not the isomeric benziminazole-2-carboxylic acid is indicated by its weak acidity and by the sparing solubility of its sodium salt. Moreover, benziminazole-2-carboxylic acid has been obtained by oxidation of 2-methylbenziminazole (Bistrzycki and Przeworski, *loc. cit.*). The analogous 2 : 3-dihydroxyquinoxaline-6-arsinic acid, made from 3 : 4-diaminophenylarsinic acid by the above method, gives an arseno-compound which is insoluble in caustic alkali or alkali carbonate solutions, showing that this cannot be a benziminazole derivative (unpublished work).

Malonic acid. *o*-Phenylenediamine (5 g.), malonic acid (5 g.), and 4*N*-hydrochloric acid (30 c.c.) were boiled under reflux for 30 minutes. A white crystalline precipitate which had separated from the hot solution was collected after cooling (A); the filtrate on being made alkaline to litmus with 50% sodium hydroxide solution gave a crystalline precipitate (B). The solid A was further purified by means of its *mono-sodium* salt (compare dihydroxyquinoxaline, above), white, sparingly soluble cubes (Found : N, 14·5; Na, 11·4. $C_9H_7O_2N_2Na$ requires N, 14·1; Na, 11·6%), and was proved to be *o*-phenylenemalonamide (Found : N, 15·9. Calc. : N, 15·9%), white prisms, m. p. over 300°, insoluble in boiling water and the ordinary solvents, resembling dihydroxyquinoxaline in these particulars. The solid B (1·5 g.) crystallised from boiling water as white prisms of *2-aminomalonanilic acid*, m. p. 175—176° (Found : N, 14·4. $C_9H_{10}O_3N_2$ requires N, 14·4%), an amphoteric substance; when its solution in dilute hydrochloric acid is boiled for ½ hour, *o*-phenylenemalonamide is formed in quantitative yield.

Succinic acid. (i) *o*-Phenylenediamine (8 g.), succinic acid (10 g.), and 4*N*-hydrochloric acid (60 c.c.) were boiled under reflux for 40 minutes. On cooling, a crystalline solid (A) separated. The filtrate on basification with 50% sodium hydroxide gave an amorphous precipitate (B); the filtrate from this, on neutralisation to Congo-red with hydrochloric acid, gave a crystalline precipitate (C). The last precipitate (4·5 g.) was further crystallised from hot water and shown to be benziminazole-2-propionic acid, white prisms, m. p. 224°, sparingly soluble in cold but readily soluble in boiling water, in dilute mineral acids, and in ammonia, sodium carbonate, etc. The solid A (9 g.) consisted of a mixture of succinic acid with the hydrochloride of the base B. The latter (2 g.) was found to be 2 : 2′-diaminosuccinanilide (compare Meyer, *Annalen*, 1903, **327**, 1), a white, amorphous solid, m. p. above 300°, insoluble in boiling water and in the ordinary solvents; its hydrochloride is sparingly soluble in cold water, from which it forms white, hexagonal plates (Found : N, 15·3; Cl, 19·1. Calc. : N, 15·1; Cl, 19·1%).

No trace of *o*-phenylenesuccinamide or of 2-aminosuccinanilic acid was detected.

(ii) *o*-Phenylenediamine (4·2 g., 2 mols.) and succinic acid (2·3 g., 1 mol.) were boiled for 1 hour with 4*N*-hydrochloric acid (30 c.c.). The solid which was precipitated on cooling was collected and crystallised from hot water (A); the filtrate on neutralisation to litmus gave 0·5 g. of benziminazole-2-propionic acid. The solid A (1·5 g.) was shown to be αβ-dibenziminazolylethane dihydrochloride (Found: N, 16·5; Cl, 20·9. Calc.: N, 16·7; Cl, 21·2%), white needles, sparingly soluble in water; this was also obtained by boiling for 1 hour under reflux a mixture of benziminazole-2-propionic acid (2 g.), *o*-phenylenediamine (1 g.), and 4*N*-hydrochloric acid (14 c.c.), and cooling (Found: N, 16·3; Cl, 20·9%), or by treatment of 2 : 2′-diaminosuccinanilide with boiling 4*N*-hydrochloric acid. The base is a white amorphous solid, m. p. above 300°.

2-*Methyl*-4 : 5-*dihydroglyoxaline*.—Diacetylethylenediamine, made by reduction of aminoacetonitrile hydrochloride (Fargher, J., 1920, **117**, 1351), followed by acetylation, was boiled for 30 minutes with five times its weight of 4*N*-hydrochloric acid and gave a 55% yield of the above glyoxaline, m. p. 107° (Found: N, 33·0. Calc.: N, 33·3%).

RESEARCH LABORATORIES, MESSRS. MAY AND BAKER, LTD.,
WANDSWORTH, S.W. 18. [*Received, June 16th*, 1928.]