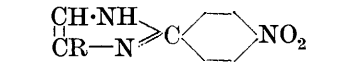
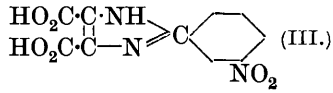
CVIII.—*The Nitration of Benzamidines.*

By Robert Forsyth, Vishvanath Krishna Nimkar, and Frank Lee Pyman.

Pyman and Stanley (J., 1924, **125**, 2484) showed that nitration of 2-phenylglyoxaline and its 4(5)-monocarboxylic acid gave mainly the *p*-nitro-compounds (I and II), whereas 2-phenylglyoxaline-4 : 5-dicarboxylic acid gave mainly the *m*-nitro-compound (III).



(I, R = H. II, R = CO_2H.)

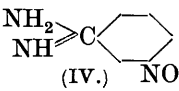


(III.)

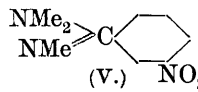
In view of the fact that 2-phenylglyoxaline and its monocarboxylic acid yield salts with mineral acids whereas its dicarboxylic acid does not, they suggested that the different character of the doubly-linked nitrogen atom, that is, the nitrogen atom which takes part in salt formation (compare Burtles and Pyman, J., 1923, **123**, 361), was responsible for the different results. In 2-phenylglyoxaline, this nitrogen atom would be regarded as saturated or positive by combination with acid according as to whether the hypotheses of Flürscheim or Lapworth were employed, whilst in the dicarboxylic acid it would be regarded as unsaturated or negative.

If this explanation were correct, then one would expect that nitration of benzamidine by the method employed for 2-phenylglyoxaline, that is, addition of the nitrate of the base to sulphuric acid, would yield mainly the *o*- and *p*-nitro-compounds, but as a matter of fact it proves to give more than 90% of *m*-nitrobenzamidine (IV).

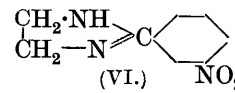
Various possible explanations of the essentially different results of nitrating 2-phenylglyoxaline and benzamidine have now been examined. It might be suggested that since glyoxalines do not readily yield acyl derivatives, we should not postulate nitroamine formation in this case, but might reasonably do so in the case of benzamidines. An explanation would then be furnished analogous to that devised by Holmes and Ingold (J., 1925, **127**, 1800) to explain the difference between the results of nitrating secondary and tertiary benzylamines. Such an explanation, however, was found to be inapplicable in our case, since the nitration of benzenyltrimethylamidine, which cannot yield a nitroamine, gave more than 80% of m-*nitrobenzenyltrimethylamidine* (V).



(IV.)



(V.)



(VI.)

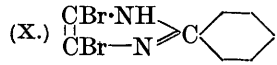
Next, it might be thought that the different results of nitrating 2-phenylglyoxaline and benzamidine might be due to the fact that the two nitrogen atoms were linked together by a closed chain in the former compound and might neutralise each other's influence. This view was disproved by the nitration of 2-phenyl-4 : 5-dihydroglyoxaline, which gave more than 80% of 2-m-*nitrophenyl*-4 : 5-*dihydroglyoxaline* (VI).

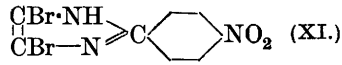
It seems to us that the noteworthy difference between the results of nitrating 2-phenylglyoxaline and its dihydro-derivative are probably associated with the fact that glyoxalines have aromatic character whereas their dihydro-derivatives have not. It thus appears that the amidinium ion, $\left[\cdot C\lessdot^{NHR}_{NR'R''}\right]^{\cdot}$, which is contained in the salts of benzamidine, benzenyltrimethylamidine, and 2-phenyl-4 : 5-dihydroglyoxaline, is strongly meta-directive, the nitrogen atoms exerting a similar influence to that of the oxygen atom in the carboxyl group. In the basic 2-phenylglyoxalines, the influence of the nitrogen atoms is suppressed, and the glyoxalinium ion produces an *op*-directive effect, due to the aromatic complex as a whole, and similar to that of phenyl in directing the *p*-nitration of diphenyl. The exceptional predominant *m*-nitration of the non-basic 2-phenylglyoxaline-4 : 5-dicarboxylic acid may be due possibly to the absence of salt formation in the case of this compound, and a difference in orienting properties between glyoxaline bases and glyoxalinium ions, for evidence of a difference in structure between glyoxalines and their salts may be found in the existence of the two isomeric bases 2 : 4- and 2 : 5-diphenylglyoxalines (VII and VIII), which yield a common ion (IX) (Burtles and Pyman, *loc. cit.*).

$$\underset{\text{(VII.)}}{\begin{matrix}CH\cdot NH\\ \|\\ CPh-N\end{matrix}\!\!>CPh} \longrightarrow \underset{\text{(IX.)}}{\left[\begin{matrix}CH-NH\\ \|\\ CPh\cdot NH\end{matrix}\!\!>CPh\right]^{\cdot}} \longleftarrow \underset{\text{(VIII.)}}{\begin{matrix}CPh\cdot NH\\ \|\\ CH-N\end{matrix}\!\!>CPh}$$

Nevertheless, the fact that the dicarboxylic acid yields 52% of the *m*- with 19% of the *p*-nitro-compound, whilst the monocarboxylic acid yields 52% of the *p*- with 19% of the *m*-compound, shows that the introduction of carboxyl groups into the glyoxaline nucleus of 2-phenylglyoxaline progressively diminishes the ratio of para- to meta-nitration of the benzene nucleus, and suggests, as an alternative explanation, for which we are indebted to Dr. King, that the results should be ascribed to the accumulation of acidic groups attached to the glyoxaline nucleus. In this sense, they are comparable with the results of nitrating benzyl chloride, benzylidene chloride, and benzotrichloride, where also the ratio of para- to meta-nitration is progressively diminished by the introduction of acidic groups

(Holleman, *Rec. trav. chim.*, 1914, **33**, 1). On the other hand, we found no support of this explanation, possibly owing to experimental difficulties, on the nitration of 4 : 5-*dibromo*-2-*phenylglyoxaline* (X),





which might be expected to yield a considerable proportion of the *m*-nitro-derivative, for here 4 : 5-*dibromo*-2-p-*nitrophenylglyoxaline* (XI) was isolated in a yield of 63% together with only 1·8% of an unidentified isomeride.

Nitration of 4(5)-*bromo*-2-*phenylglyoxaline* prepared by the reduction of the dibromo-compound with sodium sulphite proceeded less uniformly, possibly owing to nitration of the glyoxaline nucleus, but here the only product isolated was again the para-isomeride, 4(5)-*bromo*-2-p-*nitrophenylglyoxaline*. Another instance of the *p*-directive effect of the glyoxaline nucleus has been recorded by Tröger and Thomas (*J. pr. Chem.*, 1925, **110**, 42), who find that the nitration of lophine gives 2 : 4 : 5-tri-*p*-nitrophenylglyoxaline. Para-nitration of phenyl groups attached to the 2-position of glyoxalines having basic character thus seems to be the rule.

Experimental.

Nitration of Benzamidine.—Benzamidine nitrate,* prepared from the base and dilute nitric acid, crystallised from alcohol in large, colourless, rhombic prisms, m. p. 128° (corr.) after softening from 124°, which are anhydrous and very easily soluble in water or hot alcohol (Found : C, 45·7, 45·6; H, 4·9, 5·0. $C_7H_8N_2,HNO_3$ requires C, 45·9; H, 4·9%). This salt (10 g.) was added gradually to concentrated sulphuric acid (20 c.c.) cooled in ice and salt. After ½ hour, the solution was heated for 2 hours at 100°, then diluted and mixed with aqueous solutions of barium hydroxide (50 g., hydrated) and barium chloride (46·7 g., hydrated). After removing barium sulphate, the aqueous solution was evaporated to dryness under diminished pressure, and the residue crystallised fractionally from alcohol, when 10·1 g. of pure *m*-nitrobenzamidine hydrochloride were isolated, that is, 91·7%.† The salts remaining in the mother-liquors were hydrolysed by boiling with 40 c.c. of 17% aqueous sodium hydroxide until ammonia was no longer evolved. On addition of concentrated hydrochloric acid, 0·62 g. of *m*-nitrobenzoic acid (m. p. 135°) separated, whilst ether collected a further 0·08 g. of less pure material (m. p. 118—120°). Mixtures of

* This salt has not been described previously. The reference to it (*Jahresber.*, 1888, 1133) quoted by Beilstein is a mistake, and applies to the nitrite.

† All yields are expressed in percentage of the theoretical.

these products with pure *m*-nitrobenzoic acid melted at 137° and 126—131°, respectively. The amount of these crops represents 7·8% of the theoretical yield, making in all 99·5%, whence it is clear that the nitration of benzamidine yields almost wholly the meta-isomeride.

m-*Nitrobenzamidine hydrochloride* crystallises from alcohol in clusters of cream-coloured, prismatic needles, m. p. 251° (corr.) after sintering from 248°. It is anhydrous and readily soluble in water or hot alcohol (Found: C, 41·9; H, 4·0; Cl, 17·6. Calc., C, 41·7; H, 4·0; Cl, 17·6%). Tafel and Enoch (*Ber.*, 1890, **23**, 1552), who prepared this salt by the interaction of the hydrochloride of *m*-nitrobenziminoethyl ether with ammonia, give m. p. 240°. The identity and purity of our preparation were established by hydrolysing the salt (1 g.) with 8·5% aqueous sodium hydroxide (40 c.c.), and adding concentrated hydrochloric acid, when 0·564 g. of *m*-nitrobenzoic acid, m. p. 140° (corr.), separated, and 0·25 g., m. p. 139°, was collected by ether, the total yield being 98·2%. The identity of these crops with *m*-nitrobenzoic acid was established by the mixed-melting point method. The first crop was also analysed (Found: C, 50·3; H, 3·0. Calc., C, 50·3; H, 3·0%).

Nitration of Benzenyltrimethylamidine.—Benzenyltrimethylamidine nitrate was prepared by the double decomposition of aqueous solutions of silver nitrate and the corresponding hydriodide, previously called dimethylamidobenzenylmethylimidine hydriodide (Pyman, J., 1923, **123**, 3372). It crystallises from alcohol in large, colourless, prismatic rods, m. p. 195—196° (corr.). It is anhydrous and readily soluble in water or hot alcohol (Found: C, 53·2; H, 6·5; N, 18·5. $C_{10}H_{14}N_2,HNO_3$ requires C, 53·3; H, 6·7; N, 18·7%). This salt (10 g.) was added gradually to concentrated sulphuric acid cooled in ice and salt. The solution was kept for 1 hour at the room temperature, heated for 2 hours at 100°, diluted with water, and mixed with aqueous solutions of barium hydroxide (50 g., hydrated) and barium chloride (46·7 g., hydrated). After removing barium sulphate, the aqueous solution was evaporated to dryness under diminished pressure, when a pale yellow syrup was obtained. Since the hydrochlorides showed little tendency to crystallise, the syrup was diluted and mixed with excess of aqueous sodium iodide, when the hydriodides separated as an oil which soon solidified. After numerous crystallisations from alcohol, using sulphur dioxide as a decolorising agent, 11·01 g. of pure *m*-nitrobenzenyltrimethylamidine hydriodide were isolated (yield 73·9%). The substance remaining in the mother-liquors was hydrolysed with aqueous sodium hydroxide; strong hydrochloric acid then precipitated 0·69 g. of *m*-nitrobenzoic acid, m. p. 133—137°. The filtrate was unfortunately lost.

On recrystallising the acid, 0·52 g. was obtained pure (m. p. 140°) and a further 0·164 g., m. p. 138°. They were identified as *m*-nitrobenzoic acid by the mixed-melting point method. The amount of these crops represents 9·3% of the theoretical yield, making in all 83·2%.

m-*Nitrobenzenyltrimethylamidine hydriodide* crystallises from alcohol in pale lemon-yellow needles, m. p. 243—246° (corr.; decomp.). It is anhydrous, and sparingly soluble in water or cold alcohol, but readily soluble in acetone (Found : C, 35·8; H, 4·1; I, 37·9. $C_{10}H_{13}O_2N_3,HI$ requires C, 35·8; H, 4·2; I, 37·9%).

The identity and purity of this salt were established by hydrolysing 1·675 g. with aqueous sodium hydroxide, and acidifying the solution, when 0·67 g. of *m*-nitrobenzoic acid, m. p. 140°, was precipitated, and 0·16 g., m. p. 130°, collected from the filtrate by means of ether, the total yield being 99%. Both crops were identified as *m*-nitrobenzoic acid by the mixed-melting point method, and the first crop was also analysed (Found : C, 50·5; H, 3·0. Calc., C, 50·3; H, 3·0%).

2-*Phenyl*-4 : 5-*dihydroglyoxaline*.—Hofmann (*Ber.*, 1888, **21**, 2334) states, without giving any details, that this base is best prepared by heating dibenzoylethylenediamine in a stream of hydrogen chloride, and this method was adopted after it had been found that dibenzoylethylenediamine was completely hydrolysed by boiling with concentrated sulphuric acid (3 c.c. per g.) for 10 minutes, and was only slowly attacked by boiling concentrated hydrochloric acid (10 c.c. per g.) when, after 2 hours, 82% was recovered unchanged. Ten grams of dibenzoylethylenediamine (prepared from ethylenediamine monohydrate by the Schotten-Baumann method in 91% yield) were heated to 250°, and dry hydrogen chloride was passed through the molten substance for 1 hour. The product was dissolved in hot water; on keeping, benzoic acid and 0·3 g. of unchanged material separated. The filtrate was basified and extracted with ether, which gave 4·56 g. of 2-phenyl-4 : 5-dihydroglyoxaline, m. p. 100° (yield 83·7%). It crystallised from acetone in colourless, prismatic needles, m. p. 102—103° (corr.). Hofmann gives m. p. 101°.

The nitrate crystallises from acetone in large, colourless, rhombic prisms, which are hydrated to a variable extent. After drying at 98°, it is anhydrous and melts at 118—119° (corr.) after softening from 117°. On cooling, it resolidifies and then melts sharply at 123° (corr.), but on recrystallising this modification, it reverts to the original form, m. p. 118—119°. This salt was described previously by Forssel (*Ber.*, 1892, **25**, 2135), who does not record its m. p.

Nitration of 2-*Phenyl*-4 : 5-*dihydroglyoxaline*.—The anhydrous

nitrate (10·55 g.) was added to concentrated sulphuric acid (21 c.c.) cooled in ice and salt. The solution was kept for 1 hour at room temperature and then heated for 2 hours at 100°. The product was treated with barium hydroxide and barium chloride, just as the nitration product of benzamidine, to give the hydrochloride, which was crystallised from alcohol, when 10·47 g. of pure 2-*m*-nitrophenyl-4 : 5-dihydroglyoxaline hydrochloride were obtained, that is, 84·4%. The mother-liquors contained hydrochlorides (m. p. 195—200°) which could not be separated either as such or as hydriodide or picrate, and the material was therefore oxidised with alkaline permanganate, when a mixture of nitrobenzoic acids was obtained, from which pure *m*-nitrobenzoic acid was isolated in a yield of 3%.

2-m-*Nitrophenyl*-4 : 5-*dihydroglyoxaline hydrochloride* crystallises from alcohol in coarse, yellow needles containing $1H_2O$, which is lost at 100°. After drying, it has m. p. 249—251° (corr.). It is readily soluble in water or hot alcohol, but sparingly soluble in acetone (Found in air-dried salt : loss in a vacuum over H_2SO_4, 7·4, 7·3. $C_9H_9O_2N_3,HCl,H_2O$ requires H_2O, 7·3%. Found in dried salt : C, 47·6; H, 4·3; Cl, 15·6. $C_9H_9O_2N_3,HCl$ requires C, 47·5; H, 4·4; Cl, 15·6%). The *hydriodide* crystallises from water in pale yellow, prismatic needles, m. p. 207—209° (corr.), which are anhydrous and sparingly soluble in water (Found : I, 40·0. $C_9H_9O_2N_3,HI$ requires I, 39·8%).

The *picrate* crystallises from water or alcohol in fine, lemon-yellow needles, m. p. 224—225° (corr.). It is anhydrous and sparingly soluble in hot water or hot alcohol, but very readily soluble in acetone.

The orientation of the nitro-group in 2-*m*-nitrophenyl-4 : 5-dihydroglyoxaline was established by oxidation. The hydrated hydrochloride (1·23 g.) in hot water (50 c.c.) was boiled with 17% aqueous sodium hydroxide (20 c.c.) and sufficient aqueous potassium permanganate to give a permanently pink solution. After adding alcohol and filtering, the solution was concentrated and acidified with hydrochloric acid, when 0·577 g. of *m*-nitrobenzoic acid, m. p. 140° (corr.), was deposited, whilst ether extracted a further 0·048 g., m. p. 125—128°, from the mother-liquor. Mixtures of the two crops with pure *m*-nitrobenzoic acid had m. p. 140° (corr.) and 132—135°, respectively. The total yield is 74·9%.

Bromination of 2-Phenylglyoxaline.—A solution of 1·75 c.c. of bromine (1 mol.) in chloroform (15 c.c.) was added gradually to 2-phenylglyoxaline (5 g.) in chloroform (40 c.c.). After keeping for 15 minutes, the colourless precipitate of 4 : 5-dibromo-2-phenylglyoxaline hydrobromide, m. p. 250—255°, was collected, and this

gave on repeated treatment with cold water the base (4·3 g.), m. p 137—138°. The chloroform mother-liquors were distilled with steam to remove solvent and excess of bromine, and the aqueous residue deposited 0·5 g. of the crude dibromo-base, m. p. 136—138° The total yield is thus 46%. The final mother-liquors were basified with sodium carbonate and gave crude 2-phenylglyoxaline (2·5 g.; m. p. 138—140°).

4 : 5-*Dibromo*-2-*phenylglyoxaline* crystallises from acetone in colourless cubes, which decompose at about 141° (corr.) after darkening earlier (Found : C, 36·0; H, 2·0; Br, 52·8. $C_9H_6N_2Br_2$ requires C, 35·8; H, 2·0; Br, 53·9%). It is insoluble in cold water and resinifies when heated with water. It is soluble in warm dilute mineral acids, aqueous sodium hydroxide, or ammonia. It is readily soluble in alcohol or acetone, and fairly readily soluble in ether or chloroform.

The *hydrochloride* crystallises from dilute hydrochloric acid in colourless needles, m. p. 235—237° (corr.). It yields the base on treatment with water. The *picrate* forms yellow plates, from alcohol, m. p. 170—172° (corr.).

Nitration. Potassium nitrate (3·3 g.; 1 mol.) was added to a cold solution of 4 : 5-dibromo-2-phenylglyoxaline (10 g.) in concentrated sulphuric acid (40 c.c.). After heating for 2 hours at 100°, the solution was poured into water, when 4: 5-dibromo-2-*p*-nitrophenylglyoxaline was precipitated; the filtrate was basified with sodium carbonate, when an isomeric base separated. After crystallising these products from alcohol, 7·0 g. of the *p*-nitro-compound (yield 63%) and 0·2 g. of the isomeride (yield 1·8%) were obtained in a pure state.

4 : 5-*Dibromo*-2-p-*nitrophenylglyoxaline* crystallises from alcohol in orange needles, m. p. 220—222° (corr.) (Found in air-dried base : loss in a vacuum over H_2SO_4, 9·3, 9·3. $C_9H_5O_2N_3Br_2,2H_2O$ requires $2H_2O$, 9·4%. Found in dried base : C, 31·2; H, 1·8; N, 12·1; Br, 45·8. $C_9H_5O_2N_3Br_2$ requires C, 31·1; H, 1·4; N, 12·1; Br, 46·1%). It is insoluble in cold water, and resinifies on heating with water. It is insoluble in cold dilute mineral acids, but dissolves slightly on warming. It dissolves in aqueous sodium hydroxide, ammonia, and sodium carbonate, giving red, orange, and yellow solutions, respectively. It is readily soluble in alcohol, acetone, or ether. On oxidation with alkaline permanganate, it gave *p*-nitrobenzoic acid, which was identified by the mixed-melting point method. 4 : 5-*Dibromo*-2-o(or m)-*nitrophenylglyoxaline* crystallises from dilute alcohol in lemon-yellow, glistening plates, m. p. 181—182° (corr.), which are anhydrous (Found : C, 31·0; H, 2·0; N, 12·1. $C_9H_5O_2N_3Br_2$ requires C, 31·1; H, 1·4; N, 12·1%). It is insoluble

in hot or cold water, slightly soluble in dilute mineral acids, and readily soluble in aqueous sodium hydroxide, ammonia, or sodium carbonate, giving red, orange, and yellow solutions. The quantity available did not permit the identification of the acid produced on oxidation.

Reduction of 4 : 5-*Dibromo-2-phenylglyoxaline.*—Hot solutions of 4 : 5-dibromo-2-phenylglyoxaline (5 g.) in alcohol (125 c.c.) and hydrated sodium sulphite (20·5 g.) in water (200 c.c.) were mixed and boiled for 8 hours under reflux. After the alcohol had been removed, a crystalline precipitate (m. p. 185—187°) was deposited, which was separated, by fractional precipitation by hydrochloric acid from its solution in aqueous sodium hydroxide, into 4(5)-bromo-2-phenylglyoxaline (1·43 g.; m. p. 205—206°; yield 39%) and unchanged dibromo-base (1·36 g.).

4(5)-*Bromo-2-phenylglyoxaline* crystallises from dilute alcohol in small, white needles, m. p. 206—207° (corr.) (Found: C, 48·3; H, 3·1; N, 12·2; Br, 35·7. $C_9H_7N_2Br$ requires C, 48·4; H, 3·1; N, 12·6; Br, 35·9%). It is slightly soluble in hot water, readily soluble in alcohol or acetone, and moderately readily soluble in ether. It is soluble in warm dilute acids, aqueous sodium hydroxide, or ammonia, but insoluble in aqueous sodium carbonate.

The *hydrochloride* crystallises from dilute hydrochloric acid in hard, white needles, which lose $1H_2O$ in a vacuum over sulphuric acid and then melt at 118—119° (corr.) (Found in air-dried salt: loss in a vacuum over H_2SO_4, 6·6. $C_9H_7N_2Br,HCl,H_2O$ requires H_2O, 6·5%. Found in dried salt: Cl, 13·8. $C_9H_7N_2Br,HCl$ requires Cl, 13·7%). On heating at 100°, the vacuum-dried salt suffers a further loss owing to dissociation. The *picrate* crystallises from alcohol in yellow plates, m. p. (air-dried) 164—165° (corr.).

Nitration. Potassium nitrate (0·76 g.; 1 mol.) was added to a cold solution of 4(5)-bromo-2-phenylglyoxaline (2 g.) in concentrated sulphuric acid (4 c.c.). After heating for 2 hours at 100°, the solution was poured into water, filtered from a yellow precipitate (1·0 g.; m. p. 95—110°), which was not worked up, and basified with sodium carbonate, when a further precipitate (1·7 g.; m. p. 180—182°) was collected. After crystallisation from dilute alcohol, this gave pure 4(5)-bromo-2-*p*-nitrophenylglyoxaline (0·75 g.; yield 31%).

4(5)-*Bromo*-2-p-*nitrophenylglyoxaline* crystallises from glacial acetic acid in yellow needles, m. p. 222—223° (corr.) (Found: loss at 100°, 18·1. $C_9H_6O_2N_3Br,CH_3{\cdot}CO_2H$ requires loss of $CH_3{\cdot}CO_2H$, 18·3%. Found in substance dried at 100°: C, 40·0; H, 2·5; N, 15·8. $C_9H_6O_2N_3Br$ requires C, 40·3; H, 2·2; N, 15·7%).

It is insoluble in hot water, readily soluble in alcohol, ether, acetone, or glacial acetic acid, and moderately readily soluble in

chloroform. It is soluble in aqueous mineral acids, and dissolves in aqueous alkalis, including sodium carbonate, giving yellow to red solutions.

On oxidation with alkaline permanganate, it gave *p*-nitrobenzoic acid, which was identified by the mixed-melting point method.

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