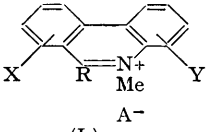
# 694. *The Synthesis of Amidinium Salts.**

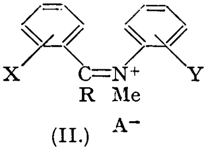
By C. G. Raison.

Amidinium salts * of the type (III) are obtained by methylation of fully substituted amidines (IV), a finding which confirms Pyman's conclusion relating to the mode of alkylation in amidine systems. An alternative synthesis of (III), involving condensation of disubstituted amides with secondary amines in the presence of phosphoryl chloride, has been shown to have wider applicability; in particular, it has enabled suggestions to be made as to the mechanism of the Vilsmeier–Haack aldehyde synthesis.

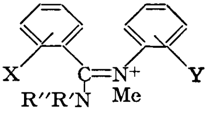
When considering new trypanocidal drugs based on Walls's phenanthridinium compounds (I) (*J. Soc. Chem. Ind.*, 1947, **66**, 182) it seemed possible that the synthetic work would be simplified if the ultimate dependence on diphenyl as a starting material could be avoided. Compounds (II) lacking the bridge between the benzenoid nuclei of phenanthridinium salts would be the metho-quaternary salts of anils and would certainly be unstable in aqueous solution (Decker and Becker, *Annalen*, 1913, **395**, 362; Reiber and Stewart, *J. Amer. Chem. Soc.*, 1940, **62**, 3026), but compounds (III) in which the complete amidine system is present seemed likely to possess greater stability, and their synthesis was therefore undertaken.



(I.)



(II.)



(III.)

(X, Y = H or $NH_2$; R = Ph or $p$-$NH_2 \cdot C_6H_4$.)

An obvious route to (III) was the methylation of completely substituted amidines, such as (IV), which are readily available by the condensation of imido-chlorides with secondary amines. Pyman (*J.*, 1923, **123**, 361 *et seq.*), during a study of the alkylation of open-chain and completely cyclic amidine systems, concluded that in these types alkylation occurs on the nitrogen atom which is doubly linked to carbon. He cited examples (Forsyth and Pyman, *J.*, 1926, 2502) to show that this conclusion probably also holds for partly cyclic amidines, but 2-dimethylaminopyridine appears to be an exception (Tschitschibabin and Konowalowa, *Ber.*, 1926, **59**, 2055).

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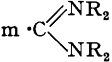
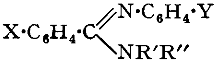
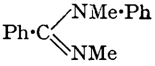
* " Amidinium salt " is used in this paper to mean the presence of the system  $\cdot C\begin{smallmatrix} \diagup\!\!\diagup \overset{+}{N}R_2 \\ \diagdown NR_2 \end{smallmatrix}$ in which no group R is hydrogen; when at least one such group is hydrogen, the expression " amidine salt " is used.

The majority of his work concerned amidines in which at least one hydrogen atom was present on nitrogen, but an observation of significance to the present work was that the isomeric amidines, *N'*-phenyl-*NN*-dimethylbenzamidine (IV; X = Y = H; R' = R'' = Me) and *N*-phenyl-*NN'*-dimethylbenzamidine (V) yielded the same salt, *N'*-phenyl-*NNN'*-trimethylbenzamidinium iodide (III; X = Y = H; R' = R'' = Me; A = I), m. p. 177—179°, with methyl iodide (*J.*, 1923, **123**, 3368). On repetition of Pyman's work, the identity of the salt derived from



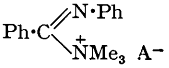
$X{\cdot}C_6H_4{\cdot}C\begin{smallmatrix}{/\!\!/}N{\cdot}C_6H_4{\cdot}Y\\ \diagdown NR'R''\end{smallmatrix}$

(IV.)



$Ph{\cdot}C\begin{smallmatrix}/NMe{\cdot}Ph\\ {\diagdown\!\!\diagdown}NMe\end{smallmatrix}$

(V.)

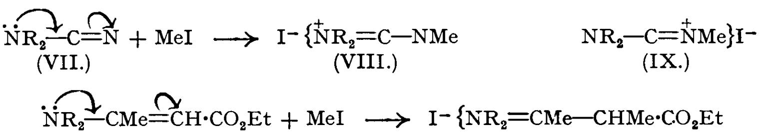


$Ph{\cdot}C\begin{smallmatrix}{/\!\!/}N{\cdot}Ph\\ \diagdown \overset{+}{N}Me_3\end{smallmatrix}\ A^-$

(VI.)

the two isomers was confirmed, but it had m. p. 144—145°; it was not until a few months later that all samples, representing several independent preparations by both routes, were found to be changing to a higher-melting form (180—182°), a change accelerated at 100°. Before this, however, it had been thought desirable to obtain further evidence of the structure of the salt, and this was achieved by degradation and by an alternative synthesis. On the one hand, alcoholic potassium hydroxide gave quantitatively benzoic acid, dimethylamine, and methylaniline; on the other hand, a synthesis which definitely indicated a structure such as (III) was realised in the condensation of benzodimethylamide with methylaniline in the presence of phosphoryl chloride, a reaction which is referred to later. An attempt to synthesise the isomeric amidinium salt (VI) by condensation of benzanilide imido-chloride with aqueous-alcoholic trimethylamine was fruitless; the product was a mixture of benzanilide and *N*-phenylbenzimino ethyl ether.

The preparation of a series of compounds structurally analogous to (I) required experiments to ascertain whether Pyman's thesis of the position of alkylation could be extended to the following examples: (*a*) where NR'R'' in (IV) contained a phenyl residue, and (*b*) where X and/or Y = $NO_2$. Regarding (*a*), it was found that the amidine (IV; X = Y = H; R' = Me; R'' = Ph) with methyl iodide gave, quantitatively, *NN'-diphenyl-NN'-dimethylbenzamidinium iodide* (III; X = Y = H; R' = Me; R'' = Ph; A = I), also degraded by alkali to give a quantitative yield of methylaniline. Regarding (*b*), it was found that the influence of the nitro-group in (IV; X = H; Y = *p*-$NO_2$; R' = R'' = Me) was such that no reaction occurred with boiling methyl iodide; when, however, methyl sulphate at 115—120° was employed, an exothermic reaction gave *N'-p-nitrophenyl-NNN'-trimethylbenzamidinium iodide* (III; X = H; Y = *p*-$NO_2$; R' = R'' = Me; A = I) after treatment of the water-soluble product with potassium iodide. The same salt was obtained from benzodimethylamide and *p*-nitromethylaniline, and was degraded by alkali to give a high yield of *p*-nitromethylaniline The presence of a nitro-group in each ring, as in (IV; X = Y = *p*-$NO_2$; R' = R'' = Me), did not alter the general picture and again alkylation occurred at the doubly-linked nitrogen atom. This result may be explained on the assumption that in the system $(x)\ddot{N}R_2{-}C{=}N(y)$, the lone pair of electrons on N(*x*) is used to increase the nucleophilic character of N(*y*) by an electromeric effect [shown in (VII)] and that this effect predominates even when N(*y*) is deactivated, by a suitably placed nitro-group, to attack by an electrophilic reagent such as methyl iodide. The situation is then analogous to the alkylation of β-dialkylaminocrotonic esters (X) studied by Robinson



$\ddot{N}R_2{-}C{=}N + MeI \longrightarrow I^-\{\overset{+}{N}R_2{=}C{-}NMe \qquad NR_2{-}C{=}\overset{+}{N}Me\}I^-$

(VII.) (VIII.) (IX.)

$\ddot{N}R_2{-}CMe{=}CH{\cdot}CO_2Et + MeI \longrightarrow I^-\{NR_2{=}CMe{-}CHMe{\cdot}CO_2Et$

(X.)

(*J.*, 1916, **109**, 1038; 1947, 1297). In the present examples, however, the amidinium salts are stabilised by the resonance which is possible between forms such as (VIII) and (IX).

By the methods indicated above, compounds (III) have been prepared in which X and Y are substituents such as H, *m*- and *p*-$NH_2$, *p*-$NH{\cdot}COMe$, *p*-$NH{\cdot}CO_2Et$, and *p*-OMe and R'R'' are $Me_2$, $Et_2$, $<(CH_2)_5$, Me and Ph, and Me and $C_6H_4{\cdot}NH_2$. Nitroamidinium salts were reduced to the corresponding amino-compounds catalytically or by the use of neutral ferrous hydroxide. All the compounds made were examined for trypanocidal action by Mr. Goodwin and his colleagues of the Wellcome Laboratories of Tropical Medicine, but none possessed more than a trace of activity.

*The Condensation of Disubstituted Amides with Compounds having a Reactive Hydrogen Atom.*—Mention has been made above of the synthesis of amidinium salts by condensation of the benzoyl derivative of a secondary amine with an *N*-methylarylamine in the presence of phosphoryl chloride. This reaction is a development of the work of Sen and Rây (*J.*, 1926, 646; cf. Hill and Rabinowitz, *J. Amer. Chem. Soc.*, 1926, **48**, 732; Hill and Cox, *ibid.*, p. 3214; Sidiki and Shah, *J. Univ. Bombay*, 1937, **6**, 132). They extended an older synthesis by Hofmann for the preparation of *NN'*-diarylamidines and condensed primary amines (XI; $R_2 = H$) with either mono- (XII; $R_5 = H$) or di-substituted amides (XII), or secondary amines (XI) with

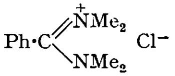
$$\underset{\text{(XI.)}}{NHR_1R_2} + \underset{\text{(XII.)}}{R_3{\cdot}CO{\cdot}NR_4R_5} \longrightarrow \underset{\text{(XIII.)}}{NR_1R_2{\cdot}CR_3(OH){\cdot}NR_4R_5} \qquad \underset{\text{(XIV.)}}{NR_1R_2{\cdot}CR_3{:}NR_4}$$

monosubstituted amides (XII; $R_5 = H$) in the presence of phosphorus trichloride or oxychloride. They postulated the intermediate (XIII) in the reaction, from which it is clear that so long as the nitrogen atoms in (XI) and (XII) carry, between them, at least two hydrogen atoms, the product will be an amidine salt * [*e.g.*, of (XIV) if only $R_5 = H$] formed by loss of a molecule of water. On the other hand, with a secondary amine and a disubstituted amide, the postulated intermediate cannot lose the elements of water to give an amidine, but there remained the possibility that, during the reaction or the subsequent working-up after addition of water, the change (XIII) ⟶ (XV) could lead to the formation of an amidinium salt,* by a re-arrangement similar to that encountered in the chemistry of such *pseudo*-bases as cotarnine (Hope and Robinson, *J.*, 1911, **99**, 2114).

$$\text{(XIII)} \xrightarrow{HA} NR_1R_2{\cdot}CR_3{:}\overset{+}{N}R_4R_5,\ A^- \qquad \text{(XV.)}$$

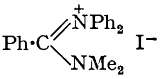
Experiments showed that amidinium salts are readily obtained in this manner and brought to light the following additional points: (i) phosphorus oxychloride is a more effective condensing agent than the trichloride, especially when nitro-groups are present; (ii) an increase in the acidity (decrease in basicity) of the secondary amine, or the use of the amine hydrochloride, facilitates the reaction; *e.g.*, in condensation with benzodimethylamide in comparable conditions, methylaniline, its hydrochloride, and *p*-nitromethylaniline gave yields of 50, 90, and 95%, respectively; (iii) the ability to use the amine salt increases the scope of the reaction to include gaseous aliphatic amines; thus, benzodimethylamide and dimethylamine hydrochloride gave a high yield of *NNN'N'*-tetramethylbenzamidinium chloride (XVI), characterised as the *picrate*. Now if (XIII) is an intermediate in these condensations, its formation may well be capable of such a hydrogen-ion catalysis. In addition it has been found that, in the *absence* of phosphoryl chloride, whereas benzodimethylamide and methylaniline are substantially unchanged after heating at 120°, the use of the amine hydrochloride leads to a 70% conversion to benzomethylanilide and dimethylamine hydrochloride. The existence of (XIII) in such an amide exchange must surely be assumed and this leads to the conclusion that one function of the phosphoryl chloride is to promote the subsequent step (XIII) ⟶ (XV).

As further examples of acidic secondary amines, the use of diphenylamine and carbazole was studied; condensed with benzodimethylamide, the former gave a 35% yield of N'N'-*di-phenyl*-NN-*dimethylbenzamidinium iodide* (XVII), but the latter gave *ca.* 80% of 9-benzoylcarbazole. When, however, the product from the carbazole experiment was carefully treated with ice-water, a clear yellow solution was obtained, which presumably contained the expected carbazolinium salt, but warming it caused the deposition of 9-benzoylcarbazole. It is suggested that resonance stabilisation between forms (XVIII) and (XIX) is of a low order and that, if the contribution of (XVIII) to the hybrid state were, for steric reasons, small, the molecule would approximate closely to structure (XIX) and the formation of benzoylcarbazole on hydrolysis would be expected. Similarly, thiophenol was condensed with benzodimethylamide to give, by careful treatment in the cold, a clear yellow aqueous solution which on warming deposited phenyl thiolbenzoate in *ca.* 40% yield. Here again, a stable product would presumably demand a high degree of hybridisation of the forms (XX) and (XXI) and, were the contribution of (XX) only small, the structure would approximate to (XXI), which is the metho-quaternary salt of an *N*-methylbenzimino phenyl thioether and would readily give phenyl thiolbenzoate



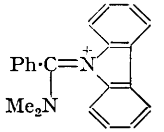
$$Ph{\cdot}C\begin{matrix}\nearrow \overset{+}{N}Me_2\\ \searrow NMe_2\end{matrix}\ Cl^-$$

(XVI.)

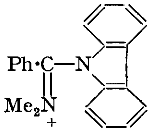


$$Ph{\cdot}C\begin{matrix}\nearrow \overset{+}{N}Ph_2\\ \searrow NMe_2\end{matrix}\ I^-$$

(XVII.)



(XVIII.)



(XIX.)

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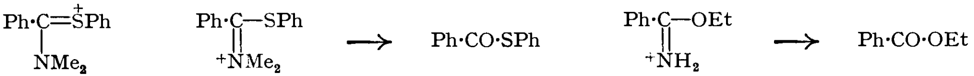
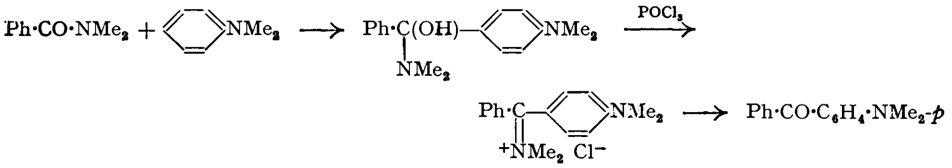
* See footnote, p. 3319.

on hydrolysis. In other words, the hydrolysis of (XXI) is held to be exactly analogous to the aqueous hydrolysis of imino-ether salts such as (XXII).

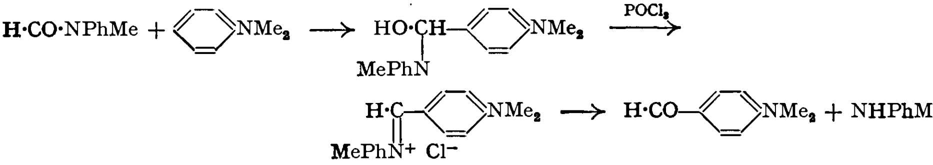


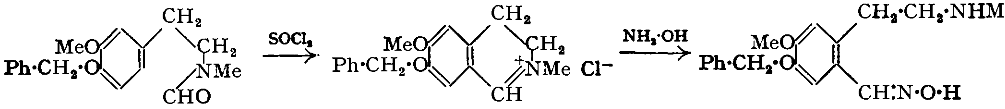
(XX.) (XXI.) (XXII.)

When the condensation was extended to dimethylaniline, it was found that the " reactive " hydrogen atom in the *p*-position to the substituent was able to function in the same manner as the " acidic " hydrogen atoms of secondary amines and thiophenol, for the product (60%) from benzodimethylamide was 4-dimethylaminobenzophenone and it seems reasonable to suppose that intermediate stages in the reaction can be visualised on lines already developed (cf. Shah, Deshpande, and Chaubal, *J.*, 1932, 642).



It was now clear that the present work might be related to the aldehyde synthesis of Vilsmeier and Haack (*Ber.*, 1927, **60**, 119; Ferguson, *Chem. Reviews*, 1946, **38**, 230), who found that, when *NN*-dialkylanilines and formomethylanilide condensed in the presence of phosphoryl chloride, the products were hydrolysed in acid solution to *p*-dialkylaminobenzaldehydes; and the reaction has been extended (see Ferguson, *loc. cit.*) to certain other compounds containing " reactive " hydrogen atoms. Vilsmeier and Haack were not very precise in expressing their views on the mechanism of their reaction. On the one hand, they suggested the intermediate formation of a compound such as $NPhMe{\cdot}CHCl_2$ and postulated the simultaneous formation of the *p*-dialkylaminobenzaldehyde and the formamidinium salt $NPhMe{\cdot}CH{:}\overset{+}{N}MePh\ Cl^-$, and on the other hand, in their experimental account, they state that half of the dialkylaniline does not react because it serves to bind the hydrochloric acid formed in the reaction. In a repetition of the condensation of equimolecular amounts of formomethylanilide and dimethylaniline, the identified products were *p*-dimethylaminobenzaldehyde (67%), dimethylaniline (impure picrate, 12%), and methylaniline (80%); there was no evidence of the formamidinium salt. Since the latter is readily isolated as its sparingly soluble iodide from the reaction product of formomethylanilide and either methylaniline (50%) or its hydrochloride (92%) under exactly the same conditions of treatment with phosphoryl chloride, it is probable that the methylaniline formed in the above reaction is liberated only during the working-up. For these reasons, it is suggested that the Vilsmeier–Haack reaction proceeds essentially through the stages shown, possibly with minor variations such as the initial formation of the formomethylanilide–phosphoryl chloride adduct isolated by those workers. Strong confirmation of these views has been provided by the work of Akabori (*Bull. Chem. Soc. Japan*, 1926, **1**, 96; see also Kindler and Peschke, *Arch. Pharm.*, 1932, **270**, 353) for a system in which a ring structure stabilised the type of charged intermediate postulated above.





## EXPERIMENTAL.

N′-*Aryl*-NN-*dialkylbenzamidines* (IV).—The following preparation of *N*′-phenyl-*NN*-dimethylbenzamidine (cf. von Pechmann, *Ber.*, 1895, **28**, 2372) may be taken as typical. Benzanilide imido-chloride (20 g.) was added gradually to a cooled and stirred mixture of 25% aqueous dimethylamine (100 c.c.) and alcohol (100 c.c.), which was afterwards kept at 40—50° for 3 hours and left overnight. After evaporation of the mixture to dryness in a vacuum, the amidine was extracted with dilute acetic acid and precipitated with aqueous ammonia. Crystallised from light petroleum it had m. p. 72—73° (yield, 80%). Von Pechmann gave m. p. 72°. The amidine hydriodide formed colourless prisms, m. p. 199—200°, from alcohol–ethyl acetate (Found : I, 36·5. Calc. for $C_{15}H_{17}N_2I$ : I, 36·1%) ; Pyman (*J.*, 1923, **123**, 370) gave m. p. 200°.

Other amidines which were prepared are recorded in Table I ; those containing nitro-groups were usually sparingly soluble in dilute acetic acid and were isolated with the aid of dilute hydrochloric acid. Nitro-compounds were reduced to amino-compounds catalytically and the latter were acetylated with acetic anhydride.

The anilides used as intermediates in the preparation of the above amidines were known compounds, with the exception of the following.

p-*Nitrobenzo*-p′-*carbethoxyaminoanilide*, prepared from *p*-carbethoxyaminoaniline, had m. p. 267° after crystallisation from pyridine (Found : N, 12·6. $C_{16}H_{15}O_5N_3$ requires N, 12·75%).

p-*Carbethoxyaminobenzo*-p′-*nitroanilide*, prepared from *p*-carbethoxyaminobenzoyl chloride (Walls, private communication) and *p*-nitroaniline, had m. p. 241° after crystallisation from 2-methoxyethanol (Found : N, 12·8%).

pp′-*Biscarbethoxyaminobenzanilide*.—The previous nitro-compound was reduced with hydrogen and palladium–charcoal in 2-methoxyethanol; the isolated p-*carbethoxyaminobenz*-p′-*aminoanilide* formed colourless leaflets (from methanol), m. p. 205—206° (Found : N, 13·9. $C_{16}H_{17}O_3N_3$ requires N, 14·0%). This was carbethoxylated with ethyl chloroformate in 2-methoxyethanol, in the presence of diethylaniline, to give the required *anilide*, m. p. 274—275° (evolves gases and resolidifies), after crystallising from 2-methoxyethanol in fine colourless needles (Found : N, 11·5. $C_{19}H_{21}O_5N_3$ requires N, 11·4%).

*Aniso*-p-*nitroanilide*, crystallised from 2-methoxyethanol, had m. p. 185° (Found : N, 10·0. $C_{14}H_{12}O_4N_2$ requires N, 10·3%). The m-*isomer*, crystallised from alcohol, had m. p. 176° (Found : N, 10·0%).

N′-*Phenyl*-NNN′-*trimethylbenzamidinium Iodide* (III ; X = Y = H ; R′ = R″ = Me ; A = I).—*Preparation.* (*a*) The action of boiling methyl iodide on either *N*′-phenyl-*NN*- or *N*-phenyl-*NN*′-dimethylbenzamidine according to Pyman (*loc. cit.*) gave the same salt as colourless prisms (from acetone), m. p. 144—145° (later, 180—182°) (Found : I, 34·6. Calc. for $C_{16}H_{19}N_2I$ : I, 34·7%). (*b*) Benzodimethylamide (1·5 g.), methylaniline (1·1 c.c.), and phosphoryl chloride (10 c.c.) were heated at 120—130° for 5 hours. After evaporation of the mixture in a vacuum at 100°, the residual glass was dissolved in water, acidity to Congo-red removed with sodium acetate, and the solution extracted with ether. Addition of potassium iodide (2 g.) precipitated an oil which solidified on cooling. The product (yield, 50%), washed with ethyl acetate and dried, had m. p. 180—182°, undepressed by the salt obtained in (*a*). The use of phosphorus trichloride gave a yield of only 16%, but with oxychloride and an equivalent amount of methylaniline hydrochloride instead of the base, the yield was 90%.

TABLE I.

N′-*Aryl*-NN-*dialkylbenzamidines*, $X{\cdot}C_6H_4{\cdot}C(NR'R''){:}N{\cdot}C_6H_4Y$.

| X. | Y. | R′R″. | Formula. | Solvent. | M. p. | Found, N, %. | Reqd., N, %. |
|---|---|---|---|---|---|---|---|
| H | *p*-NO$_2$ | Me$_2$ | $C_{15}H_{15}O_2N_3$ | 60% EtOH | 107—108° | 15·9 | 15·6 |
| ,, | *m*-NO$_2$ | ,, | ,, | ,, | 104—105 | 15·4 | ,, |
| *m*-NO$_2$ | H | ,, | ,, | 80% EtOH | 119 | 15·45 | ,, |
| *p*-NO$_2$ | *p*-NO$_2$ | ,, | $C_{15}H_{14}O_4N_4$ | EtOH | 143—144 | 17·6 | 17·8 |
| ,, | *m*-NO$_2$ | ,, | ,, | ,, | 134—135 | 17·85 | ,, |
| *m*-NO$_2$ | *p*-NO$_2$ | ,, | ,, | ,, | 127 | 17·55 | ,, |
| ,, | *m*-NO$_2$ | ,, | ,, | 66% EtOH | 91 | 17·9 | ,, |
| H | *p*-NH$_2$ | ,, | $C_{15}H_{17}N_3$ | 25% EtOH | 81—82 | 17·4 | 17·6 |
| ,, | *m*-NH$_2$ | ,, | ,, | ,, | 77—78 | 17·3 | ,, |
| ,, | *p*-NHAc | ,, | $C_{17}H_{19}ON_3$ | 30% EtOH | 174·5—175·5 | 15·2 | 15·0 |
| ,, | *m*-NHAc | ,, | $C_{17}H_{19}ON_3,1\frac{1}{2}H_2O$ | ,, | 104—105·5 | 13·7 | 13·6 |
| *p*-NH$_2$ | *p*-NH$_2$ | ,, | $C_{15}H_{18}N_4$ | EtOAc–petrol | 91—92 | 22·2 | 22·05 |
| *p*-NHAc | *p*-NHAc | ,, | $C_{19}H_{22}O_2N_4$ | Aq. EtOH | 265—266 | 15·6 | 16·5 |
| *p*-NH·CO$_2$Et | *p*-NH·CO$_2$Et | ,, | $C_{21}H_{26}O_4N_4$ | (Amorphous) | — | 14·6 | 14·05 |
| ,, | *p*-NO$_2$ | ,, | $C_{18}H_{20}O_4N_4$ | ( ,, ) | — | 15·65 | 15·7 |
| *p*-NO$_2$ | *p*-NH·CO$_2$Et | ,, | ,, | Aq. EtOH | 111 | 15·75 | ,, |
| *p*-OMe | *p*-NO$_2$ | ,, | $C_{16}H_{17}O_3N_3$ | EtOH | 88 | 14·05 | 14·0 |
| ,, | *m*-NO$_2$ | ,, | ,, | 66% EtOH | 91 | 13·7 | ,, |
| *p*-NO$_2$ | *p*-NO$_2$ | [CH$_2$]$_5$> | $C_{18}H_{18}O_4N_4$ | MeO·CH$_2$·CH$_2$·OH | 202 | 15·3 | 15·8 |
| ,, | ,, | Et$_2$ | $C_{17}H_{18}O_4N_4$ | EtOH | 140 | 16·4 | 16·4 |

*Degradation.* A mixture of the salt (2 g.) and potassium hydroxide (3 g.) in alcohol (15 c.c.) was boiled for 3 hours, dimethylamine being evolved. Water (35 c.c.) was added and the mixture extracted exhaustively with ether. The aqueous residue, on treatment with sodium hydrogen sulphite and hydrochloric acid, yielded benzoic acid (0·6 g., 90%), identified by mixed m. p. The ethereal extract was evaporated to give an alcoholic solution, which was acidified with hydrochloric acid. The alcohol was evaporated and the aqueous residue treated with a little charcoal and filtered. Sodium hydroxide solution (3 c.c. ; 40%), toluene-*p*-sulphonyl chloride (1·4 g.), and pyridine (1 drop) were added, and the

TABLE II.

N′-*Aryl*-NNN′-*trialkylbenzamidinium salts*, $X{\cdot}C_6H_4{\cdot}C(NR'R'')\overset{+}{:}NMe{\cdot}C_6H_4Y\ A^-$.

| X. | Y. | R′R″. | Method of preparation. | Formula. | Solvent. | M. p. | Found, %. N. | Found, %. I. | Required, %. N. | Required, %. I. |
|---|---|---|---|---|---|---|---|---|---|---|
| H | *p*-$NH_2$ | $Me_2$ | *b, c, d* | $C_{16}H_{20}N_3I$ | MeOH | 261—262° | 11·1 | 33·5 | 11·0 | 33·4 |
| ,, | *m*-$NH_2$ | ,, | *b* | ,, | (Amorphous) | — | 10·8 | 33·3 | ,, | ,, |
| *p*-$NH_2$ | H | ,, | *d* | ,, | EtOH | 167·5—168·5 | 10·95 | 33·5 | ,, | ,, |
| *m*-$NH_2$ | ,, | ,, | *b* | ,, | ,, | 164—165 | 11·3 | 33·6 | ,, | ,, |
| H | *p*-NHAc | ,, | *a* | $C_{18}H_{22}ON_3I$ | ,, | 247—248 | — | 30·0 | — | 30·0 |
| *p*-NHAc | ,, | ,, | *a* | $C_{20}H_{25}O_2N_4I$ | ,, | 256—257 | — | — | — | — |
| H | *m*-$NO_2$ | ,, | *a* | $C_{16}H_{18}O_2N_3I$ | ,, | 184·5—185·5 | 10·2 | 31·1 | 10·2 | 30·9 |
| *m*-$NO_2$ | ,, | ,, | *a* | $C_{16}H_{17}O_4N_4I$ | MeOH | 216 | 12·05 | 27·7 | 12·3 | 27·85 |
| *p*-$NH{\cdot}CO_2Et$ | *p*-$NH{\cdot}CO_2Et$ | ,, | *a* | $C_{22}H_{29}O_4N_4I$ | (Amorphous) | — | 10·7 | 23·6 | 10·4 | 23·5 |
| ,, | *p*-$NH_2$ | ,, | *b* | $C_{19}H_{25}O_2N_4Br$ | $H_2O$ | 275 | 13·2 | (18·9) * | 13·3 | (19·0) * |
| *p*-$NH_2$ | *p*-$NH{\cdot}CO_2Et$ | ,, | *b* | $C_{19}H_{25}O_2N_4I$ | EtOAc–$COMe_2$ | 145—150 | 11·9 | 27·3 | 12·0 | 27·1 |
| *p*-OMe | *p*-$NH_2$ | ,, | *b* | $C_{17}H_{22}ON_3I$ | EtOH | 222 | 10·25 | 30·8 | 10·5 | 31·7 |
| ,, | *m*-$NH_2$ | ,, | *b* | ,, | ,, | 183—184 | 10·3 | 30·85 | | |
| *p*-$NH_2$ | *p*-$NH_2$ | ,, | *b, c, d* | $C_{16}H_{21}N_4I$ | MeOH | 275—276 | 14·15 | 32·1 | 14·1 | 32·1 |
| ,, | *m*-$NH_2$ | ,, | *b* | $C_{16}H_{21}N_4I,H_2O$ | $H_2O$ | 229 | 13·5 | 30·5 | 13·55 | 30·7 |
| *m*-$NH_2$ | *p*-$NH_2$ | ,, | *b, d* | ,, | Aq. MeOH | 262 | 13·7 | 30·7 | ,, | ,, |
| ,, | *m*-$NH_2$ | ,, | *b* | $C_{16}H_{21}N_4I$ | EtOH | 195 | 14·15 | 32·6 | 14·15 | 32·1 |
| *p*-$NH_2$ | *p*-$NH_2$ | $[CH_2]_5>$ | *b* | $C_{19}H_{25}N_4I$ | MeOH | 243 | 12·4 | 29·9 | 12·9 | 29·3 |
| ,, | ,, | $Et_2$ | *b* | $C_{18}H_{25}N_4Br$ | EtOH | 248 | 15·4 | (22·0) * | 15·85 | (22·65) * |

* Br.

mixture was well shaken, a further quantity of sodium hydroxide (2 c.c.) being added later; the mixture was warmed gently and then shaken till cold. A crystalline precipitate (1·3 g., 90%) was filtered off and dried, and had m. p. 90—92°; crystallisation from benzene–light petroleum raised this to 93·5—94·5°, undepressed by an authentic specimen of toluene-*p*-sulphonmethylanilide. The alkaline filtrate from the acylation gave no precipitate on acidification.

NN′-*Diphenyl*-NN′-*dimethylbenzamidinium Iodide* (III; X = Y = H; R′ = Me; R″ = Ph; A = I).—*Preparation.* (*a*) The condensation of benzanilide imido-chloride with methylaniline in benzene gave *NN*′-diphenyl-*N*-methylbenzamidine, b. p. 230—235°/16 mm., in 80% yield (von Braun and Weissbach, *Ber.*, 1932, **65**, 1574, gave b. p. 226—228°/13 mm.). Boiling methyl iodide converted this quantitatively into the required *salt*, pale yellow prisms (from alcohol–ethyl acetate), m. p. 171—172° (Found: I, 29·5, 29·9. $C_{21}H_{21}N_2I$ requires I, 29·7%). (*b*) Benzomethylanilide (2·1 g.), methylaniline (1·1 c.c.), and phosphoryl chloride (10 c.c.) were heated at 120° for 5 hours. Working up as before gave an iodide (2 g.; 50%), m. p. 167—169°, raised by crystallisation to 170—172°, undepressed by the salt obtained in (*a*).

*Degradation.* Treatment of the salt (2 g.) with alcoholic potassium hydroxide in the manner described above gave toluene-*p*-sulphonmethylanilide (2·2 g., 90%), m. p. 91—93°, identified by mixed m. p.

N′-p-*Nitrophenyl*-NNN′-*trimethylbenzamidinium Iodide* (III; X = H; Y = *p*-$NO_2$; R′ = R″ = Me; A = I).—*Preparation.* (*a*) *N*′-*p*-Nitrophenyl-*NN*′-dimethylbenzamidine (2·7 g.) and acid-free methyl sulphate (1·05 c.c.) were heated to 115—120°; when the exothermic reaction had ceased, the product was washed with benzene and then dissolved in water, and potassium iodide (1·8 g.) was added. The precipitated orange oil solidified on cooling to a pale yellow solid (3·8 g., 93%), which separated from alcohol–ethyl acetate as a mixture of pale yellow prisms and fine needles. This was a *monohydrate*, melting indefinitely >90° (Found, after drying in a vacuum at 60°: I, 29·4; loss at 115°, 4·7. $C_{16}H_{18}O_2N_3I,H_2O$ requires I, 29·6; $H_2O$, 4·2%).

(*b*) Benzodimethylamide (1·5 g.), *p*-nitromethylaniline (1·5 g.), and phosphoryl chloride (10 c.c.) were heated at 120—130° for 6 hours. Working up as before gave an iodide (3·9 g., 95%) identical with that obtained in (*a*). Phosphorus trichloride gave a tar.

*Degradation.* Treatment of the salt with alcoholic potassium hydroxide in the usual manner was unsuccessful, a considerable amount of brown amorphous material being formed. The salt (2·06 g.) was dissolved in warm water (15 c.c.) and N-sodium hydroxide (1 mol) added; after refluxing for 6 hours the mixture was cooled and the separated crystals were extracted with ether. The residue, after evaporation of ether, was digested with cold benzene to leave orange prisms (0·42 g.), m. p. 149—152° (mixed m. p. with *p*-nitroaniline, 114—117°; with *p*-nitromethylaniline, 150—152°). A pale yellow oil obtained from the benzene washing was heated for 2½ hours with alcohol (10 c.c.) and concentrated hydrochloric acid (5 c.c.); evaporation and basification gave a product which, washed with benzene, left greenish-brown crystals (0·18 g.), m. p. 150—152°, depressed to 114—117° by *p*-nitroaniline, but undepressed by *p*-nitromethylaniline. The total recovery of *p*-nitromethylaniline was 80%.

N′-*Aryl*-NNN′-*trialkylbenzamidinium Salts* (III).—The remaining compounds of this type are given in Table II. The methods of preparation were: (*a*) methylation of the appropriate amidine (IV); (*b*) methylation of the corresponding nitro-amidine, followed by reduction; (*c*) methylation of the corresponding acetamidoamidine, followed by hydrolysis with hydrochloric acid; (*d*) condensation of the appropriate amide and secondary amine, followed by reduction. Amidinium salts containing nitro-groups did not, in general, give crystalline iodides and were in such examples reduced without characterisation to the corresponding amino-compounds. This reduction was carried out either catalytically or with neutral ferrous hydroxide.

NN′-*Diphenyl*-N-*methyl*-p-*nitrobenzamidine* (IV; X = *p*-$NO_2$; Y = H; R′ = Me; R″ = Ph).—*p*-Nitrobenzanilide imido-chloride (from 24·2 g. of anilide), methylaniline (10·6 g.), and benzene (100 c.c.) were heated under reflux for 24 hours. The separated solid was filtered off, dissolved in water, and basified with aqueous ammonia. The precipitated *amidine*, m. p. 86°, separated in orange cubes from alcohol (Found: N, 12·6. $C_{20}H_{17}O_2N_3$ requires N, 12·7%).

NN′-*Diphenyl*-NN′-*dimethyl*-p-*aminobenzamidinium Iodide* (III; X = *p*-$NH_2$; Y = H; R′ = Me; R″ = Ph; A = I).—The above nitro-amidine (5 g.) was heated at 115—120° with methyl sulphate (2·1 c.c.), and the water-soluble product precipitated as the iodide (m. p. $\nless$250°), which could not be recrystallised. It was therefore reduced with ferrous hydroxide (from 18·2 g. of ferrous sulphate and 20·6 g. of barium hydroxide) on the steam-bath; after cooling, the mixture was filtered, the solid was extracted exhaustively with methanol, and the combined filtrate and extract were evaporated to dryness in a vacuum (3·7 g.; m. p. 262°). Crystallised from 2-ethoxyethanol, the *iodide* had m. p. 265° (Found: N, 9·2; I, 28·1. $C_{21}H_{22}N_3I$ requires N, 9·5; I, 28·6%).

NNN′N′-*Tetramethylbenzamidinium Chloride* (XVI).—Benzodimethylamide (4·3 g.), dimethylamine hydrochloride (2·35 g.), and phosphoryl chloride (10 c.c.) were heated at 120—130° for 5 hours. After evaporation in a vacuum, the residue was dissolved in water and added to a hot solution of picric acid (7·5 g.) in water (150 c.c.). When the precipitated oil had solidified, it was filtered off, dried (10·9 g.), and crystallised from methanol to give yellow needles of the *picrate*, m. p. 130—132°, in *ca.* 70% yield (Found: C, 50·85; H, 4·7; N, 17·3, 17·4. $C_{17}H_{19}O_7N_5$ requires C, 50·4; H, 4·7; N, 17·3%). The chloride, regenerated from pure picrate, was a glass; when boiled with dilute sodium hydroxide, it evolved dimethylamine and yielded benzoic acid by acidification.

N′N′-*Diphenyl*-NN-*dimethylbenzamidinium Iodide* (XVII).—Benzodimethylamide (1·5 g.), diphenylamine (1·7 g.), and phosphoryl chloride (10 c.c.) were heated at 120° for 5 hours and then evaporated in a vacuum. The residue was treated with hot water, cooled, acidity to Congo-red removed with sodium acetate and extracted with ether. Addition of potassium iodide (2 g.) precipitated an oil which eventually solidified in the cold. After drying, it was crystallised from ethyl acetate–methyl ethyl ketone and then from the latter alone to give the above *iodide*, pale yellow prisms or bright yellow needles, m. p. 215—216° (Found: N, 6·5; I, 30·4. $C_{21}H_{21}N_2I$ requires N, 6·5; I, 29·7%).

*Condensations of Benzodimethylamide.*—(1) *With carbazole.* (*a*) Benzodimethylamide (1·5 g.), carbazole (1·67 g.), and phosphoryl chloride were heated at 120° for 5 hours and then evaporated in a vacuum. When the remaining glass was heated with water, an insoluble oil was formed which solidified on cooling (2·7 g.; m. p. *ca.* 90°). Crystallisation from alcohol gave long needles (80%) of 9-benzoylcarbazole, m. p. 97—98°, identified by mixed m. p. (*b*) The crude product left after removal of phosphoryl chloride was stirrred with water and ether at 0° until dissolution was complete. The yellow aqueous solution was re-extracted with ether, buffered with sodium acetate, and warmed on the steam-bath; the colour was at once discharged, and an oil separated, which solidified on cooling. This was identified by its mixed m. p. as 9-benzoylcarbazole.

(2) *With thiophenol.* Benzodimethylamide (1·5 g.), thiophenol (1 c.c.), and phosphoryl chloride (10 c.c.) were heated at 120—130° for 5 hours and then evaporated in a vacuum. The remaining glass dissolved in ice-cold water to leave only a little residue, taken into ether. The clear golden-yellow solution was buffered with sodium acetate and warmed on the steam-bath; the colour rapidly disappeared and an oil separated which solidified on cooling (1 g.). Purified by chromatography on alumina in light petroleum solution, this gave 0·8 g. (37%) of phenyl thiolbenzoate, m. p. and mixed m. p. 55·5—56·5°.

(3) *With dimethylaniline.* Benzodimethylamide (3 g.), dimethylaniline (2·5 c.c.), and phosphoryl chloride (10 c.c.) were heated at 120° for 5 hours and then evaporated in a vacuum. The dark-green glass dissolved completely in a little water, but dilution precipitated an oil; the pH was raised until the solution was only faintly acid to Congo-red, and the mixture cooled to 0°. The solid product (2·7 g., 60%) had m. p. 88—89°, raised to 90·5—91·5° by crystallisation from methanol and was identified by mixed m. p. as 4-dimethylaminobenzophenone.

*Condensations of Formomethylanilide.*—(1) *With methylaniline.* Formomethylanilide (2·7 g.), methylaniline hydrochloride (2·9 g.), and phosphoryl chloride (10 c.c.) were heated at 50—60° for 2 hours and then on the steam-bath for ½ hour. After evaporation in a vacuum, the remaining syrup was dissolved in warm water, and potassium iodide (4 g.) was added. The precipitated oil quickly solidified (6·5 g., 92%) and had m. p. 162—164°. Crystallisation from alcohol yielded the formamidinium iodide as colourless plates, m. p. 163—164° (Found: N, 7·6; I, 36·2. Calc. for $C_{15}H_{17}N_2I$: N, 7·95; I, 36·1%). Vilsmeier and Haack (*loc. cit.*) gave m. p. 160—161°. When methylaniline was used in place of its hydrochloride, the yield was only 50% and the product was not so easy to purify.

(2) *With dimethylaniline.* Formomethylanilide (2·7 g.), dimethylaniline (2·5 c.c.), and phosphoryl chloride (10 c.c.) were heated at 50—60° for 2¼ hours and then on the steam-bath for ½ hour. After evaporation in a vacuum, the reddish-brown glass was warmed with water. When an exothermic reaction had ceased, a little brownish-yellow solid was undissolved (0·4 g.; m. p. $\not<$250°) and was filtered off. The filtrate was treated carefully with sodium hydrogen carbonate until only faintly acid to Congo-red, thus producing a very pale yellow precipitate, which, after cooling at 0° overnight, was filtered off and dried (2·0 g., 67%). It had m. p. 73—74°, not depressed by authentic *p*-dimethylaminobenzaldehyde.

When the filtrate was further basified to pH 7·5—8, an oil was precipitated and taken into ether. (Subsequent addition of potassium iodide gave no precipitate of the formamidinium iodide.) The ethereal extract yielded an oil (2·5 g.) which was acylated by the portionwise addition of toluene-*p*-sulphonyl chloride (7·5 g.) and 2N-sodium hydroxide with shaking and gentle warming. The semi-solid product was taken into benzene, washed with sodium hydroxide solution, and then extracted with hydrochloric acid. The benzene yielded 4·05 g. (80%) of toluene-*p*-sulphonmethylanilide, m. p. 90—93°, identified by mixed m. p. The acid extract was basified and extracted with ether to give an oil (0·6 g.); extraction with methanol and addition of methanolic picric acid yielded a greenish-yellow powder (0·85 g., 12%), m. p. *ca.* 155°. Crystallisation from alcohol raised the m. p. to 156—158°, not depresssed by authentic dimethylaniline picrate.

The author is indebted to Mr. A. Bennett for the micro-analyses and to Messrs. Armitage and West for technical assistance.

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[*Received, September 1st*, 1949.]