THE SYNTHESIS OF *NN'*-DISUBSTITUTED GUANIDINES AND SOME OBSERVATIONS ON THE MECHANISM OF THE TIEMANN REACTION

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Received October 28, 1952

In the course of experiments on structural variations of *N*-phenyl-*p*-*n*-hexyloxybenzamidine[1] which has been observed to exhibit high activity *in vitro* against *Mycobacterium tuberculosis*,[2] the corresponding *N*-phenylguanidine was required. It appeared not unlikely, if our speculations on the mechanism of the Tiemann reaction were correct, that *NN'*-disubstituted guanidines could be easily prepared from the readily accessible amidoximes.

In the Tiemann reaction an amidoxime is converted into an unsymmetrical urea by treatment first with benzenesulphonyl chloride and then with water.[3,4] The mechanism postulated involves conversion of the amidoxime (I) into its *O*-benzenesulphonyl derivative (II) which then undergoes a Beckman transformation to yield an *O*-benzenesulphonyl*iso*-urea (III); this is then stated to afford the unsymmetrical urea (IV) by hydrolysis.

$$\underset{\text{(I)}}{R\cdot C(:NOH)\cdot NH_2} \xrightarrow{PhSO_2Cl} \underset{\text{(II)}}{R\cdot C(:NOSO_2Ph)\cdot NH_2}$$

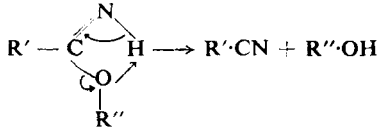
$$\underset{\text{(III)}}{RN:C(OSO_2Ph)\cdot NH_2} \xrightarrow{H_2O} PhSO_2\cdot OH + \underset{\text{(IV)}}{RNH\cdot CO\cdot NH_2}$$

In support of this supposition it was found that certain amidoximes yielded isolable *O*-benzenesulphonyl derivatives[4] and that these on heating with water gave the required urea, or its decomposition products, and benzenesulphonic acid.

Analogies for the formation and hydrolysis of the *iso*urea derivative (III) (or its tautomeride) are afforded by the hydrolysis, alcoholysis and aminolysis of the product of the Beckmann transformation of an oxime sulphonate[5,6]; an imidoyl sulphonate, $R\cdot C(O\cdot SO_2Ph):NR$, produced by acylation of an *N*-substituted amide, undergoes a similar aminolysis.[7] Nevertheless, it appeared more probable that the *iso*urea derivative (III) would decompose spontaneously into benzenesulphonic acid and a substituted cyanamide, $RNH\cdot CN$.[8] Hydrolysis of the cyanamide would then afford a urea; by reaction with an amine, a guanidine derivative could be produced. The urea is therefore to be regarded as a secondary product of the reaction and the isolable primary products would be benzenesulphonic acid and a substituted cyanamide. The existence of the *iso*urea derivative (III) can indeed be inferred only by analogy and from the nature of the reaction products.

Collateral evidence in support of this interpretation is provided by the

decomposition of imidoyl sulphonates $Ph{\cdot}SO_2{\cdot}O{\cdot}CR:NH$, into benzenesulphonic acid and a nitrile,[7,9] by the formation of arylsulphonylcyanamides when an arylurea is brought into reaction with a large excess of a sulphonyl chloride,[8,10,11] by the production of amidinourea from urea and benzenesulphonyl chloride.[8,10] Moreover, the process is then brought into line with a general mechanism for the production of cyanides[12] from a number of analogous structures. This may be represented, for simplicity, as an intramolecular process in which the hydrogen bond controls the subsequent electronic displacements:—

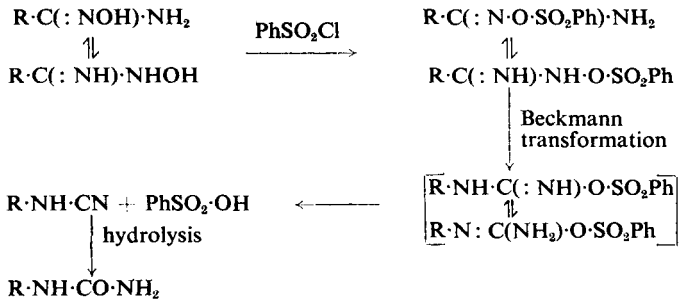


$R'' = SO_2Ar$ in an imidoyl sulphonate; $R'' =$ Et in an ethyl imidic ester; $R' =$ NHR, $R'' = SO_2Ar$ in an *O*-benzenesulphonyl*iso*urea.

Further reactions which can be similarly interpreted are the decomposition of an amidine into a nitrile and an amine, of certain diamidides into a nitrile and an amidine, and of *N*-benzoyl-*N*-phenylbenzamidine into benzonitrile and benzanilide[13] and the fission of certain diamidides by acids.[12]

The formation of the *O*-benzenesulphonyl derivative of the amidoxime is readily demonstrated in the case of phenylacetamidoxime since the compound is stable and can be isolated and purified without decomposition[4]; *O*-benzenesulphonylbenzamidoxime is, however, too unstable to isolate. On heating in an inert solvent (trichloroethylene) *O*-benzenesulphonylphenylacetamidoxime readily undergoes the Beckmann transformation. The product isolated when the experimental conditions are chosen so as to exclude the possibility of hydrolysis is not an *iso*urea derivative (III). As the transformation proceeds, there separates a viscous oil which is readily characterised as benzenesulphonic acid (97 per cent.); the supernatant layer of the reaction mixture yields benzylcyanamide (50 per cent.). The same products (85 and 61 per cent. respectively) can be isolated when the transformation is conducted in pyridine solution starting with the sulphonyl derivative of the amidoxime formed *in situ*. The benzenesulphonyl ester of benzamidoxime, prepared in solution in pyridine, similarly affords benzenesulphonic acid and a molecular compound, $C_{21}H_{18}N_6{,}2C_7H_6N_2$, of phenylcyanamide and its trimer, 1 : 3 : 5-triphenyl*iso*melamine (79 per cent.). The thermal polymerisation of phenylcyanamide is well known[14] and in this reaction it is undoubtedly promoted by the exothermic character of the Beckmann transformation. We therefore suggest that the course of the Tiemann reaction is more correctly summarised on opposite page.

When the products of the transformation are heated with an amine, an *NN′*-disubstituted guanidine is obtained in good yield. The reaction involved in this stage would appear to be direct interaction of the substituted cyanamide and the benzenesulphonate of the amine, since, under



the same conditions, phenylcyanamide reacts with the benzenesulphonates of aniline and of *p-n*-hexyloxyaniline to afford the expected guanidines. In view of the facility with which this reaction takes place, it is probable that its mechanism is not identical with that operating when the benzenesulphonate of an amine is brought into reaction with a nitrile and it is suggested that the cyanamide reacts in the tautomeric form, RN: C: NH. The evidence of physical measurements on the tautomerism of cyanamides is inconclusive[15,16] but some support for this suggestion is provided by the observation that the presence of a mobile hydrogen in the cyanamide appears to be essential for its reaction with the hydrochloride of an amine.[17]

Attempts to use aniline as a Schotten-Baumann reagent as well as a participant in the reaction were unsuccessful. Obviously a suitable starting material for this method of synthesis of guanidines should be a urea; an example of this process is provided in the experimental section.

EXPERIMENTAL

O-Benzenesulphonylphenylacetamidoxime, prepared by the method of Pinnow,[4] had m.pt. 128° C. (decomp.); no melting point has previously been reported for this compound. Found: C, 58·0; H, 5·0; N, 9·4; calc. for $C_{14}H_{14}O_3N_2S$: C, 57·9; H, 4·8; N, 9·65 per cent. *O*-Benzenesulphonylphenylacetamidoxime is insoluble in aqueous alkalis.

Beckmann Transformation of O-*Benzenesulphonylphenylacetamidoxime.* (i) The amidoxime sulphonate (2·9 g.) was boiled for 3 hours in solution in dry trichlorethylene (40 ml.); as the reaction proceeded, a viscous oil separated. The supernatant layer was decanted and the viscous oil was washed with further small successive quantities of dry trichloroethylene. The solvent was evaporated under reduced pressure and the residue was dissolved in 4N sodium hydroxide (15 ml.). After removal of a trace of insoluble material, the solution was adjusted to *p*H 7 by the addition of acetic acid and thoroughly extracted with ether. The dried ethereal solution, after concentration, deposited benzylcyanamide (0·67 g.; 50 per cent.) as plates, m.pt. 40 to 42° C., raised to 42·5° C. on crystallisation from ether and undepressed on admixture with an authentic specimen. The viscous oil remaining in the reaction flask was dissolved in water and on being neutralised with sodium hydroxide and treated with an excess of *S*-benzylthiouronium chloride afforded *S*-benzylthiouronium benzenesulphonate (3·15 g.; 97 per cent.), m.pt. and mixed m.pt. 148° C.

(ii) When the reaction was conducted in boiling toluene a considerable quantity of tar was produced and benzenesulphonic acid was the only product which could be unequivocally characterised.

(iii) To a solution of phenylacetamidoxime (10 g.) in anhydrous pyridine (25 ml.) benzenesulphonyl chloride (11·8 g., 1 mol.) was added drop by drop during 15 minutes at 0° C. The mixture was kept at 0° C. for 5 hours and then heated on a steam bath for 30 minutes; a vigorous exothermic reaction occurred. Water (50 ml.) was added and the solution was thoroughly extracted with ether. From the ethereal extract, benzylcyanamide (5·4 g.; 61 per cent.), m.pt. 40 to 41° C. was isolated. The aqueous layer yielded *S*-benzylthiouronium benzenesulphonate (18·5 g.; 85 per cent.) m.pt. 147 to 148° C. on treatment with an excess of *S*-benzylthiouronium chloride.

Beckmann Transformation of O-*Benzenesulphonylbenzamidoxime.* A solution of benzamidoxime (13·6 g.) in anhydrous pyridine (24 ml.) was cooled to 0° C. and benzenesulphonyl chloride (17·65 g., 1 mol.) was added drop by drop during 15 minutes at 0° C. The mixture was kept at 0° C. for 5 hours and then heated on a steam bath for 30 minutes; an exothermic reaction occurred. Water (40 ml.) was added and the mixture was thoroughly extracted with ether. The dried, ethereal extract was evaporated and pyridine was distilled off from the residue under reduced pressure. Repeated crystallisation of the solid remaining (9·3 g., 79 per cent.) from ethanol afforded a compound of phenylcyanamide and 1 : 3 : 5-triphenyl*iso*melamine as prisms, m.pt. 175° C.; yield 5·2 g. (44 per cent.). Found: C, 71·7; H, 5·0; N, 23·5; $(C_7H_6N_2)_n$ requires C, 71·2; H, 5·1; N, 23·7 per cent. Arndt[14] described such a compound, $(C_{21}H_{18}N_6)_2$, $C_7H_6N_2$, m.pt. 185° C. Accordingly the compound we isolated was separated into the alkali-insoluble 1 : 3 : 5-triphenyl*iso*melamine, m.pt. 209 to 210° C., undepressed by an authentic specimen, and the alkali-soluble phenylcyanamide, m.pt. and mixed m.pt. 40 to 40·5° C. Found: 1 : 3 : 5-triphenyl*iso*melamine, 62·4; phenylcyanamide, 34·0; $C_{21}H_{18}N_6,2C_7H_6N_2$ requires $C_{21}H_{18}N_6$, 60; $C_7H_6N_2$, 40 per cent. The mother liquors from the first crystallisation of the double compound, treated in the same way, afforded 1 : 3 : 5-triphenyl*iso*melamine (1·8 g.; 15 per cent.) and phenylcyanamide (1·8 g.; 15 per cent.). The identity of the phenylcyanamide was confirmed by converting it into its benzenesulphonyl derivative, m.pt. and mixed m.pt. 64° C. For confirmation of the identity of the triphenyl-*iso*melamine, it was hydrolysed to 1 : 3 : 5-triphenyl-4 : 6-dioxo-2-iminohexahydro-1 : 3 : 5-triazine, m.pt. 272° C., undepressed by an authentic specimen. Found: C, 71·2; H, 4·6; N, 15·6; M (Rast) 341; calc. for $C_{21}H_{16}O_2N_4$: C, 70·8; H, 4·5; N, 15·7 per cent.; M, 356.

The aqueous layer, on treatment with an excess of *S*-benzylthiouronium chloride, afforded the corresponding benzenesulphonate which after recrystallisation from ethanol had m.pt. 148° C.; yield 17·3 g. (53 per cent.).

N-*Benzyl*-N′-*phenylguanidine.* (i) *O*-Benzenesulphonylphenylacetamidoxime (5·8 g.) and aniline (1·86 g., 1 mol) were boiled together in solution in dry toluene (15 ml.) for an hour. The residue obtained by

evaporating the solvent under reduced pressure was dissolved in ethanol (20 ml.) and the solution was poured into 2N sodium hydroxide (50 ml.). Basic material was extracted from the precipitate with aqueous lactic acid, decolorised with charcoal and recovered by the addition of sodium hydroxide. Yield 2·9 g. (64 per cent.); leaflets, m.pt. 122 to 123° C., from aqueous ethanol or light petroleum (b.pt. 100 to 120° C.). Found: N, 18·5; $C_{14}H_{15}N_3$ requires N, 18·6 per cent. Its nitrate crystallised as needles, m.pt. 134 to 135° C. (decomp.) from water or *iso*propanol. Found: N, 19·25; $C_{14}H_{16}O_3N_4$ requires N, 19·4 per cent.

The same yield (64 per cent.) was obtained when the period of heating was 2½ hours and also when the reaction was conducted in trichloroethylene.

(ii) Phenylacetamidoxime (7·5 g.) dissolved in a mixture of anhydrous pyridine (7·9 g., 2 mols.) and dry toluene (15 ml.) was treated at 0° C. with benzenesulphonyl chloride (8·8 g., 1 mol.) added drop by drop during 15 minutes. The solution was boiled for 5 minutes, aniline (4·65 g., 1 mol.) was added and boiling was continued for 2½ hours. On working up as described above, *N*-benzyl-*N'*-phenylguanidine (5·2 g.; 46 per cent.) m.pt. 122 to 123° C., was obtained.

(iii) The yield was 45 per cent. when benzamidoxime and benzylamine were employed as described in (ii) above.

N-*Benzyl*-N'-p-*methoxyphenylguanidine*. A solution of *O*-benzenesulphonylphenylacetamidoxime (2·9 g.) and *p*-anisidine (2·46 g., 2 mols.) in dry trichloroethylene (40 ml.) was boiled for 2 hours. The *N*-benzyl-*N'*-*p*-methoxyphenylguanidinium benzenesulphonate, m.pt. 152 to 153° C. (3·15 g.; 76 per cent.) which separated on cooling crystallised as prisms, m.pt. 154° C., from aqueous ethanol. Found: N, 10·1; $C_{21}H_{23}O_4N_3S$ requires N, 10·15 per cent. The base separated as platelets, m.pt. 122 to 123° C., from ethanol. Found: N, 16·1; $C_{15}H_{17}ON_3$ requires N, 16·4 per cent.

N-*Benzyl*-N'-2-*naphthylguanidine*. By interaction of *O*-benzenesulphonylphenylacetamidoxime (2·9 g.) and 2-naphthylamine (2·56 g., 2 mols.) in boiling trichloroethylene (40 ml.) for 4 hours and basification of the crystalline product, *N*-benzyl-*N'*-2-naphthylguanidine (1·4 g.; 51 per cent.) was obtained; by recrystallisation from benzene this separated as platelets m.pt. 172° C. Found: N, 15·2; $C_{18}H_{17}N_3$ requires N, 15·25 per cent. The benzenesulphonate crystallised from water as platelets, m.pt. 185° C. Found: N, 9·6; $C_{24}H_{23}O_3N_3S$ requires N, 9·7 per cent. Its picrate was obtained as yellow needles from ethanol and had m.pt. 152° C. Found: N, 16·4; $C_{24}H_{20}O_7N_6$ requires N, 16·65 per cent. The nitrate crystallised as rosettes, m.pt. 128° C., from *iso*propanol. Found: N, 16·2; $C_{18}H_{18}O_3N_4$ requires N, 16·5 per cent.

NN'-*Diphenylguanidine*. (i) A solution of benzamidoxime (6·8 g.) in a mixture of dry benzene (15 ml.) and dry pyridine (7·9 g., 1 mol.) was cooled to 0° C. Benzenesulphonyl chloride (8·8 g., 1 mol.) was added drop by drop during 15 minutes at 0° C. and the mixture was allowed to stand at room temperature for 30 minutes. The transformation was effected by heating at 80° C. for 5 minutes; aniline (4·65 g., 1 mol.) was added and the

reaction was completed by heating the two-layered mixture for 30 minutes on a steam bath. After removal of the solvent under reduced pressure, the residue was poured into excess 2N sodium hydroxide; liberated basic material was collected in chloroform, dried and recovered. Yield 7·5 g. (71 per cent.), m.pt. 141 to 142° C., raised to 149° C. by crystallisation from aqueous ethanol. Found: N, 19·8; calc. for $C_{13}H_{13}N_3$: N, 19·9 per cent. The nitrate had m.pt. and mixed m.pt. 195 to 196° C. (decomp.). Found: N, 20·1; calc. for $C_{13}H_{14}O_3N_4$: N, 20·4 per cent. Its picrate had m.pt. 170 to 171° C. Found: N, 19·05; calc. for $C_{19}H_{16}O_7N_6$: N, 19·1 per cent.

When the period of heating to effect the transformation was prolonged to 15 minutes, the yield of guanidine was 65 per cent. Addition of aniline before effecting the transformation lowered the yield to 57 per cent. When aniline (1 and 2 mols.) was used both as a Schotten-Baumann reagent and as a participant in the reaction, 1 : 3 : 5-triphenyl*iso*melamine (73 per cent.) together with benzenesulphonanilide (11 per cent.) and phenylcyanamide (54 per cent.) respectively were isolated.

(ii) Phenylcyanamide hemihydrate (6·4 g.) and anilinium benzenesulphonate (12·65 g., 1 mol.) were boiled together in a mixture of pyridine (7·9 g.) and benzene (15 ml.) for 30 minutes. An aqueous ethanolic solution of the residue obtained by removing the solvent under reduced pressure afforded, on basification, *NN'*-diphenylguanidine (6·6 g.; 63 per cent.), m.pt. and mixed m.pt. 149° C.

When phenylcyanamide, rendered anhydrous by azeotropic drying with benzene, was employed, the yield of the guanidine was 73 per cent.

(iii) Phenylurea treated in the same manner as that described above for benzamidoxime afforded *NN'*-diphenylguanidine in 59 per cent. yield.

N-p-*Bromophenyl*-N'-*phenylguanidine* was prepared from benzamidoxime, *p*-bromoaniline, benzenesulphonyl chloride and pyridine in benzene solution in the usual way in 66 per cent. yield. The base crystallised in leaflets, m.pt. 167 to 168° C. from aqueous ethanol. Found: N, 14·5; $C_{13}H_{12}N_3Br$ requires N, 14·5 per cent. *N-p*-Bromophenyl-*N'*-phenylguanidinium benzenesulphonate crystallised as needles, m.pt. 184 to 185° C., from *iso*propanol. Found: N, 9·2; $C_{19}H_{18}O_3N_3BrS$ requires N, 9·35 per cent. Its picrate was obtained as rosettes of needles, m.pt. 189 to 191° C., from aqueous ethanol. Found: N, 16·1; $C_{19}H_{15}O_7N_6Br$ requires N, 16·2 per cent.

N-*Phenyl*-N'-p-*tolylguanidine* was obtained in 77 per cent. yield; m.pt. and mixed m.pt. 123 to 124° C. Found: N, 18·6; calc. for $C_{14}H_{15}N_3$: N, 18·65 per cent. The picrate separated from aqueous ethanol as rosettes of needles, m.pt. 172 to 173° C. Found: N, 18·2; $C_{20}H_{18}O_7N_6$ requires N, 18·5 per cent.

p-n-*Hexyloxybenzamidoxime*. A solution of *p-n*-hexyloxybenzonitrile (20·3 g.) in ethanol (80 ml.) was mixed with a solution by hydroxylamine prepared from hydroxylamine hydrochloride (13·9 g.) and anhydrous sodium carbonate (10·6 g.) in water (25 ml.) and heated at 70° for 24 hours. The solvent was removed under reduced pressure and basic material was extracted from the residue with aqueous lactic acid (10 per cent.; 60 ml.). Neutralisation of this extract to Brilliant Yellow with solution of ammonia

afforded the amidoxime which crystallised from aqueous ethanol or light petroleum (b.pt. 80 to 100° C.) as large plates, m.pt. 110° C.; yield 11·9 g. (50 per cent.). Found: N, 11·8; $C_{13}H_{20}O_2N_2$ requires N, 11·85 per cent. The non-basic fraction gave on recrystallisation from ethanol, *p-n*-hexyloxybenzamide (2·4 g.), m.pt. and mixed m.pt. 154° C.

N-p-n-*Hexyloxyphenyl*-N'-*phenylguanidine.* (i) To a cooled solution of *p-n*-hexyloxybenzamidoxime (5·9 g.) in dry benzene (25 ml.) and dry pyridine (4 g., 1 mol.), benzenesulphonyl chloride (4·4 g., 1 mol.) was added drop by drop during 15 minutes; the mixture was kept at 0° C. for 20 minutes and then heated on a steam bath for 20 minutes; aniline (2·3 g., 1 mol.) was added and the mixture was boiled for an hour. After removal of the solvent under reduced pressure, the residue was dissolved in ethanol (25 ml.) and basic material was precipitated by pouring the solution into ice-cooled 2N sodium hydroxide. Crystallisation of the precipitate from light petroleum (b.pt. 60 to 80° C.) afforded the required guanidine as leaflets, m.pt. 94° C. Yield 6·8 g. (87 per cent.). Found: N, 13·3; $C_{19}H_{25}ON_3$ requires N, 13·5 per cent. The picrate crystallised from benzene as yellow plates, m.pt. 51 to 52° C. Found: N, 15·7; $C_{25}H_{28}O_8N_6$ requires N, 15·55 per cent.

(ii) Phenylcyanamide hemihydrate (7·6 g.) and *p-n*-hexyloxyanilinium benzenesulphonate (22·6 g., 1·1 mols.) were brought into reaction by boiling in ethanol (70 ml.) for 3 hours. On working up as described above, the reaction mixture afforded an oil; this was collected in ether, dried and recovered. Material soluble in cold light petroleum (b.pt. 40 to 60° C.) was removed and the residue on crystallisation from light petroleum (b.pt. 60 to 80° C.) yielded the crude guanidine (6·4 g.; 34 per cent.), m.pt. 88 to 89° C. Further recrystallisation (with charcoal) afforded the pure material, m.pt. 94° C., undepressed on admixture with the compound prepared in the foregoing manner.

p-n-*Hexyloxyanilinium Benzenesulphonate* was prepared by neutralisation of *p-n*-hexyloxyaniline[18] with aqueous benzenesulphonic acid and crystallised from water; m.pt. 165° C. Found: C, 61·4; H, 6·9; N, 3·9; $C_{18}H_{25}O_4NS$ requires, C, 61·5; H, 7·1; N, 4·0 per cent.

SUMMARY

1. The mechanism of the Tiemann reaction is discussed.

2. Evidence is presented to show that the first isolable products of this reaction are a cyanamide and a sulphonic acid.

3. A synthesis of *NN'*-disubstituted guanidines which exploits the Tiemann reaction is described.

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