75. *The Search for Chemotherapeutic Amidines. Part XII.** NN′-*Di(amidinophenyl)amidines.*

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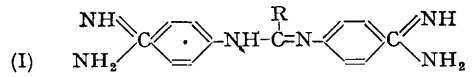
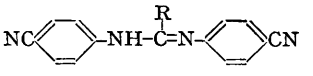
Some *NN′*-di(amidinophenyl)amidines, and some vinylogues of *NN′*-di(amidinophenyl)formamidine have been prepared and found to have slight trypanocidal activity.

DURING systematic investigation of the effect on trypanocidal activity of varying the central link between two *p*-amidinophenyl groups the preparation of compounds of type (I) was investigated. Such amidines appear not to have been described though Peyron and Peyron [1] reported a failure to prepare *N*-*p*-amidinophenyl-*N′*-phenylacetamidine from the corresponding nitrile, because of the difficulty of separating the very soluble amidine salt from ammonium chloride.



(I)



(II)

The amidines (I; R = Me, Et, or Ph) were prepared from the nitriles (II) which were obtained from the reaction of *p*-aminobenzonitrile with benzotrichloride (giving II; R = Ph) or with *N*-(*p*-cyanophenylimidoyl chlorides (giving II; R = Me and Et). Attempted condensation of anilides with *p*-aminobenzonitrile, using phosphorus trichloride [2] or phosphoric oxide,[1] gave only unchanged material.

The dinitriles (II) were converted into the diamidines (I) by Pinner's method. It was found that if the imidoate did not separate within 24 hours it was slowly hydrolysed and only *p*-aminobenzamidine was isolated on subsequent treatment with alcoholic ammonia.

NN′-Di-(*p*-cyanophenyl)formamidine was obtained from *p*-aminobenzonitrile and triethyl orthoformate. This nitrile (II; R = H) decomposed on treatment with alcoholic hydrogen chloride. The reaction of *p*-aminobenzamidine hydrochloride with triethyl orthoformate gave a product for which analyses corresponded approximately to those calculated for the desired diamidine (I; R = H); this product was however rapidly hydrolysed in aqueous solution to *p*-formamidobenzamidine hydrochloride. These observations are in agreement with the acid-catalysed hydrolysis [3] of *NN′*-diphenylformamidine:

$$Ph{\cdot}NH{\cdot}CH{:}NPh \longrightarrow Ph{\cdot}NH_2 + Ph{\cdot}NH{\cdot}CHO$$

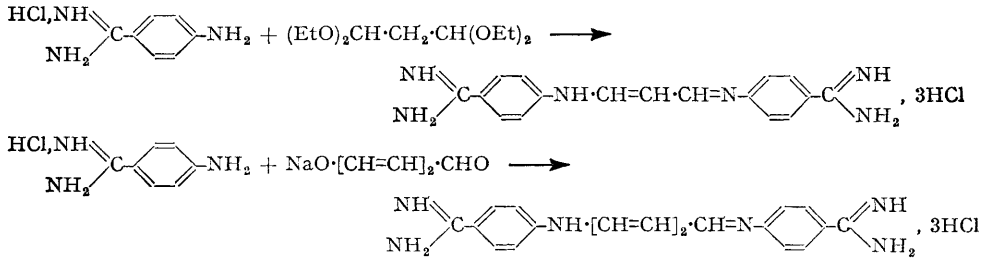
One nuclear-substituted amidine of type (I) was prepared. Bromination of *p*-acetamidobenzonitrile by Bogert and Wise's procedure [4] gave a dibromo-derivative. Bromination of *p*-aminobenzonitrile in chloroform–pyridine gave a monobromo-derivative which on acetylation gave a product corresponding to that described by Bogert and Wise.[4]

* Part XI, *J.*, 1951, 2588.

[1] Peyron and Peyron, *Bull. Soc. chim.* (*France*), 1953, 851.
[2] Sen and Rây, *J.*, 1926, 646.
[3] De Wolfe and Roberts, *J. Amer. Chem. Soc.*, 1953, **75**, 2942.
[4] Bogert and Wise, *ibid.*, 1912, **34**, 693.

Condensation of this 4-amino-3-bromobenzonitrile with *N*-*p*-cyanophenylacetimidoyl chloride gave *N'*-3-bromo-4-cyanophenyl-*N*-*p*-cyanophenylacetamidine, which was converted into the corresponding di(amidinophenyl)amidine by Pinner's method.

Two vinylogues of *NN'*-di-(*p*-amidinophenyl)formamidine were prepared by condensation of *p*-aminobenzamidine hydrochloride with malondialdehyde bisdiethyl acetal or with monosodium glutacondialdehyde in dilute hydrochloric acid :



These two diamidines, and three compounds of type (I) where R = Me, Et, and Ph, were examined for activity against trypanosome infections in mice. The most active compound (I; R = Me) was curative against *T. rhodesiense* [$LD_{50}/CD_{50} = 10$ (chemotherapeutic ratio = 10)] and *T. congolense* (ratio = 3) infections, but was ineffective in *T. evansi* infections. It was of no prophylactic value in *T. congolense* infections. The remaining compounds were less active or inactive. The compound (I; R = Me) had no antifungal activity *in vitro*.

Experimental

NN'-*Di*-(p-*cyanophenyl*)*benzamidine*.—*p*-Aminobenzonitrile (2·4 g., 0·02 mole), benzotrichloride (1·5 ml., 0·01 mole), nitrobenzene (10 ml.), and stannic chloride (0·1 ml.) were heated together at 160—170° for 30 min. A white solid separated; the mixture was cooled and diluted with alcohol (20 ml.), and the solid was collected, washed with alcohol, and ether, and dried at 75° (3·2 g.). It was then dissolved in pyridine (32 ml.); the solution was filtered and the filtrate added to water (32 ml.) with stirring, to give a yellow solid which was collected, washed with water, alcohol, and ether, and dried at 75° to a yellow powder (2·2 g., 69%), m. p. 198—200°. This amidine crystallised from alcohol as yellow prisms, m. p. 201—202° (Found : C, 78·2; H, 4·7; N, 17·0. $C_{21}H_{14}N_4$ requires C, 78·25; H, 4·35; N, 17·4%). Omission of stannic chloride caused the yield to fall to 40%.

NN'-*Di*-(p-*cyanophenyl*)*formamidine*.—*p*-Aminobenzonitrile (2·4 g., 0·02 mole) and triethyl orthoformate (1·8 ml., 0·01 mole) were heated on a steam-bath. A clear solution was formed which soon became solid, with the evolution of ethanol. Heating was continued for 30 min., then the crude solid crystallised from alcohol (125 ml.) as white feathery needles (1·7 g., 70%), m. p. 216—217° (Found : C, 73·5; H, 4·3; N, 22·7. $C_{15}H_{10}N_4$ requires C, 73·2; H, 4·1; N, 22·7%). A similar *amidine* was obtained when the reaction was carried out in acetic acid at room temperature.

NN'-*Di*-(p-*cyanophenyl*)*acetamidine*.—*p*-Acetamidobenzonitrile (1·6 g., 0·01 mole) was added to a cold solution of phosphorus pentachloride (2·1 g., 0·01 mole) in dry benzene (20 ml.). The mixture was refluxed, forming a clear solution after 5 min. Refluxing was continued for 10 min., then the hot solution was filtered and the solvent removed *in vacuo* at 50°. The residual solid was dissolved in hot dry benzene (20 ml.), and a solution of *p*-aminobenzonitrile (1·2 g., 0·01 mole) in hot dry benzene (10 ml.) was added with stirring. A white solid separated. The mixture was stirred and refluxed for 3 hr.; it was then cooled and the solid was collected, washed with light petroleum, and dried at 75°. The white powder (2·2 g.) was dissolved in pyridine (22 ml.); the solution was filtered and water (44 ml.) added to the filtrate to give a white precipitate which was filtered off, washed well with water, and dried at 75°. The white crystalline *product* (1·7 g., 65%), m. p. 216°, crystallised from benzene (100 ml./g.) or dioxan (5 ml./g.) as needles, m. p. 218° (Found : C, 73·6; H, 4·7. $C_{16}H_{12}N_4$ requires C, 73·9; H, 4·5%).

NN'-*Di*-(p-*cyanophenyl*)*propionamidine* was similarly prepared (64%) from *p*-propionamidobenzonitrile and crystallised from alcohol (10 ml./g.) as needles, m. p. 178—179° (Found : C, 74·5; H, 5·35; N, 20·2. $C_{17}H_{14}N_4$ requires C, 74·5; H, 5·1; N, 20·4%).

N′-2-*Bromo*-4-*cyanophenyl*-N-p-*cyanophenylacetamidine*, similarly prepared (50%) from *p*-acetamidobenzonitrile and 4-amino-3-bromobenzonitrile and crystallised from alcohol (20 ml./g.), had m. p. 184° (Found: C, 57·5; H, 3·65; Br, 23·1. $C_{16}H_{11}N_4Br$ requires C, 56·6; H, 3·25; Br, 23·6%).

NN′-*Di*-(p-*amidinophenyl*)*amidines.—General procedure.* The appropriate dinitrile was dissolved in dry chlorform (10—20 ml./g.), dry alcohol (2 ml./g.) added, and the solution saturated with dry hydrogen chloride. If an imidoate began to separate after 24 hr. the mixture was kept at room temperature for a further 7 days, then the solid was collected, washed with dry ether, dried *in vacuo* over sodium hydroxide, and treated with alcoholic ammonia as described below. If the imidoate did not separate after 24 hr., to avoid the slow decomposition in solution to *p*-aminobenzamidine the solvent was removed *in vacuo* at 50° and the residual solid triturated with ether, collected, dried *in vacuo* over sodium hydroxide, and treated with alcoholic ammonia as follows.

The crude ester was treated with a saturated solution of ammonia in dry alcohol (4 ml./g.), set aside at room temperature for 1 hr., kept at 55° for 6 hr., allowed to cool, and filtered, and the alcohol removed at 50° *in vacuo*. The resultant crude amidine hydrochloride was dissolved in water (10 ml./g.) and 2N-sodium carbonate (3 mol.) added with stirring to give a white solid which was collected, washed well with water to remove inorganic material and dried *in vacuo*. This solid was suspended in dry alcohol (10 ml./g.), and a saturated solution of dry hydrogen chloride in dry alcohol (1 ml./g.) added to give a yellow solution to which dry ether was added, precipitating a cream-coloured solid. This procedure was the only one by which the crude amidine could be freed from ammonium chloride. Yields were 30—70%. Like many of the diamidine salts described in the previous papers of this series, these amidine salts were strongly hygroscopic when thoroughly dried. To obtain a stable hydrate they were kept overnight in a closed vessel over water before analysis.

In this way were prepared:

NN′-*Di*-(p-*amidinophenyl*)*acetamidine trihydrochloride*, amorphous, decomp. above 300° [Found: C, 46·9; H, 5·35; N, 20·35; Cl, 26·9; loss at 100°/20 mm., 1·35; H_2O (Karl Fischer), about 1·0. $C_{16}H_{18}N_6,3HCl,\frac{1}{4}H_2O$ requires C, 47·0; H, 5·3; N, 20·6; Cl, 26·1; H_2O, 1·1%].

NN′-*Di*-(p-*amidinophenyl*)*propionamidine trihydrochloride*, amorphous, decomp. about 265° (Found: C, 48·7; H, 5·5; N, 19·6. $C_{17}H_{20}N_6,3HCl,\frac{1}{4}H_2O$ requires C, 48·4; H, 5·6; N, 19·9%).

NN′-*Di*-(p-*amidinophenyl*)*benzamidine trihydrochloride*, amorphous, m. p. above 300° (Found: C, 53·1; H, 5·5; N, 17·3; Cl, 22·7. $C_{21}H_{20}N_6,3HCl,\frac{1}{2}H_2O$ requires C, 53·1; H, 5·05; N, 17·65; Cl, 22·5%).

N′-4-*Amidino*-2-*bromophenyl*-N-p-*amidinophenylacetamidine dihydrochloride* was prepared similarly but crystallised from the alcoholic ammonia. It was therefore not purified *via* the base but by crystallisation from water (10 ml./g.) as needles, decomp. 295—296° (Found: C, 41·3; H, 4·6; N, 18·1; Br, 17·1; Cl^-, 15·8. $C_{16}H_{17}N_6Br,2HCl,H_2O$ requires C, 41·35; H, 4·5; N, 18·1; Br, 17·2; Cl,15·4%).

p-Aminobenzamidine hydrochloride was prepared similarly, but the crude amidine was purified by crystallisation from 17% aqueous sodium chloride and then alcohol, to give flakes, m. p. 221—222°. (Easson and Pyman [5] give m. p. 225—226° for a product prepared by reduction of *p*-nitrobenzamidine.)

Reaction between p-*Aminobenzamidine Hydrochloride and Triethyl Orthoformate.—p*-Aminobenzamidine hydrochloride (20 g.) was boiled with butanol (750 ml.); the hot solution was filtered and triethyl orthoformate (9 ml.) was added. The solution was refluxed for 90 min., a yellow solid separating. The hot mixture was filtered and the solid NN′-*di*-p-*amidinophenylformamidine dihydrochloride* washed with butanol and ether and dried *in vacuo*. The yellow powder, m. p. 265° (Found: C, 50·5; H, 5·35; N, 24·2. $C_{15}H_{16}N_6,2HCl$ requires C, 51·0; H, 5·1; N, 23·8%), crystallised from water as needles, m. p. 292°, probably p-*formamidobenzamidine hydrochloride* (Found: C, 48·0; H, 5·3; N, 20·9. $C_8H_9ON_3,HCl$ requires C, 48·1; H, 5·0; N, 21·1%).

1-p-*Amidinoanilino*-3-p-*amidinophenyliminoprop*-1-*ene Trihydrochloride.—p*-Aminobenzamidine dihydrochloride (41·6 g., 0·2 mole) was dissolved in 0·5N-hydrochloric acid (400 ml.). The solution was heated on a steam-bath and stirred while malondialdehyde bisdiethyl acetal (40 ml., 0·1 mole) was added; a yellow solid started to separate. Stirring and heating were continued for 3 hr. After cooling, the solid was filtered off, washed with dilute hydrochloric

[5] Easson and Pyman, *J.*, 1931, 2994.

acid, alcohol, and ether, and dried *in vacuo*. The *salt* (25·7 g., 62%) crystallised from dilute hydrochloric acid as yellow needles, m. p. about 265° (decomp.) [Found : C, 44·15; H, 5·95; N, 17·9; Cl, 22·6; loss at 100°/20 mm., 11·4; H_2O (Karl Fischer), about 11·8. $C_{17}H_{18}N_6$, $3HCl,3H_2O$ requires C, 44·2; H, 5·8; N, 17·9; Cl, 22·6; H_2O, 11·5%].

1-p-*Amidinoanilino*-5-p-*amidinophenyliminopenta*-1 : 3-*diene Trihydrochloride*.—*p*-Aminobenzamidine dihydrochloride (21 g., 0·1 mole) was dissolved in water, and a solution of the monosodium derivative of glutacondialdehyde dihydrate (7·8 g., 0·05 mole) in water (150 ml.) was added to give a deep red solution which was kept for 15 min. 2N-Hydrochloric acid (25 ml.) was then added to give a red solid which was filtered off, triturated with alcohol, washed with ether, and dried *in vacuo*, giving a red amorphous *product*, decomp. about 240° (15·6 g., 56%) (Found : C, 41·75; H, 6·35; N, 15·4. $C_{19}H_{20}N_6,3HCl,6H_2O$ requires C, 41·5; H, 6·4; N, 15·3%).

4-*Amino*-3-*bromobenzonitrile*.—*p*-Aminobenzonitrile (5·9 g., 0·05 mole) was dissolved in chloroform (50 ml.), and pyridine (4 ml.) added. The solution was stirred vigorously and bromine (2·5 ml., 0·05 mole) in chloroform (50 ml.) was added during 1 hr. The solution was then washed with water (2 × 250 ml.), and the chloroform removed to give a brown solid (8·8 g.). This *nitrile* crystallised from water as needles (5·35 g., 54%), m. p. 109—111° (Found : N, 14·3; Br, 40·9. $C_7H_5N_2Br$ requires N, 14·2; Br, 40·65%).

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