876. *The Search for Chemotherapeutic Amidines. Part XVI.* Amidinoanilino-1,3,5-triazines and Related Compounds.*

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A series of amidinoanilino-1,3,5-triazines has been prepared. Only 2,4-di-*p*-amidinoanilino-6-amino-1,3,5-triazine had significant activity against *Trypanosoma congolense*. Attempts to improve this activity by various modifications to the structure gave less active products.

In the diamidines of the general formula (I) which have been described so far in this series of papers, the group Y has been a hydrocarbon chain, or a nitrogen-, oxygen-, or sulphur-containing chain. The present paper describes a series of diamidines and related compounds in which Y is derived from the heterocyclic 1,3,5-triazine ring. The active trypanocide, Surfen C (II), consists of two 4,6-diaminoquinaldine rings joined to an amino-1,3,5-triazine ring. Since 4-aminoquinoline can be regarded as a vinylogue of 2-aminoquinoline, which is itself a cyclic amidine, Surfen C could be considered as equivalent to two amidinoanilino-groups joined to an amino-1,3,5-triazine ring. It was decided to synthesise the diamidine (III) in the hope that it would have significant trypanocidal activity. This indeed proved to be the case, and although the product, as the trihydrochloride (M & B 2242),† was less active, it was also much less toxic, than the trypanocides in current use (see Table 1).

Table 1. *Comparison of activity of* M & B 2242 *with antrycide and dimidium against* T. congolense *in mice.*

Compound	Toxicity (LD50; mg./g., s.c.)	Activity * (CD50; mg./g., s.c.)
M & B 2242	4·7	0·0375
Antrycide (methylsulphate)	0·03	0·0015
Dimidium (chloride)	0·06	0·0006

* These activities were determined by direct comparison on an acute strain of *T. congolense* isolated in Tanganyika in 1933 and received by us in 1952 from the Wellcome Laboratories of Tropical Medicine, Euston Road, London. This strain killed mice within 7 days.

Unfortunately the tri- and di-hydrochloride of this diamidine were only slightly soluble in water and the solutions formed gels very rapidly. The following salts, either as solids or in the form of aqueous solutions, were prepared in an endeavour to eliminate these drawbacks, but none was satisfactory: di- and tri-methanesulphonate, diphosphate, di(chloromethanesulphonate), and di- and tri-isethionate. The isethionate salts were prepared from the diamidine base and isethionic acid. An attempt was also made to prepare an isethionate from the trihydrochloride, using the procedure described by Phillips and Baltzly;[1] this involves the conversion of amine hydrobromides and hydriodides into the corresponding hydrochlorides by evaporation of a solution of the amine salt in excess of methanolic hydrogen chloride on the steam-bath. In the present instance, the conversion using the trihydrochloride and isethionic acid was not complete and the resulting salt, although mainly isethionate, still contained some hydrochloride. Subsequently the (—)-di-*o*-*p*-toluoyltartrate[2] was prepared; this was an insoluble salt and aqueous suspensions did not form gels.

Several methods were investigated for the synthesis of compound (III), and it was prepared finally as follows:

Reaction of cyanuric chloride with ammonia at —15° gave 2-amino-4,6-dichloro-1,3,5-triazine[3] which was condensed with *p*-aminobenzonitrile (2 mol.) in boiling anisole to

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* Part XV, Davis, *J.*, 1958, 907.

† This compound is claimed in B.P. 714,449/1954.

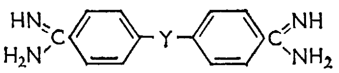
[1] Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 5231.

[2] May and Baker Ltd., B.P. 824,908/1959.

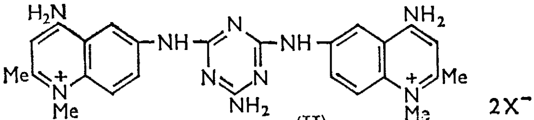
[3] Diels, *Ber.*, 1899, **32**, 691.

give 2-amino-4,6-di-*p*-cyanoanilino-1,3,5-triazine; this was converted into the diamidine by the usual Pinner method, the dinitrile being first converted into a very fine paste with ethanol (this was essential in order to obtain a good yield of di-imidoate owing to the very slight solubility of the dinitrile in ethanol). The use of anisole, dioxan, or nitrobenzene as diluents or adjuncts had no significant effect on the rate of the reaction or the yield, and the presence of chloroform considerably decreased the amount of di-imidoate formed.

An alternative synthesis, which would have avoided the preparation of the sternutatory 2-amino-4,6-dichloro-1,3,5-triazine, was investigated. This required the condensation of *p*-aminobenzonitrile (2 mol.) with cyanuric chloride (1 mol.), but the reaction, when carried out in chloroform, acetone, or ethyl methyl ketone at temperatures from 25° to the b. p., gave only 2,4-dichloro-6-*p*-cyanoanilino-1,3,5-triazine. Addition of potassium iodide to the reactants in boiling acetone or ethyl methyl ketone led to the isolation of 2,4,6-tri-*p*-cyanoanilino-1,3,5-triazine, which was also the only product formed when cyanuric chloride and *p*-aminobenzonitrile were boiled together in acetic acid. This tricyano-compound was converted into the corresponding triamidine.



(I)



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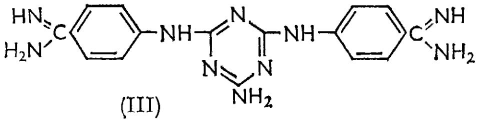
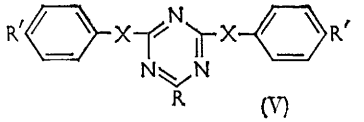
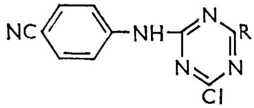


(III)

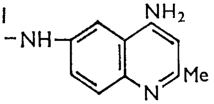
(IV)



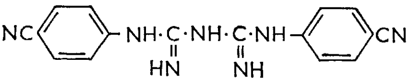
(V)



(VI)a: R =



(VI)b: R = $-NH\cdot[CH_2]_2\cdot NEt_2$



(VII)

(V)	R	X	R
a	NHEt	NH	CN
b	NHMe	NH	CN
c	NEt_2	NH	CN
d	OMe	NH	CN
e	NH_2	O	CN
f	NEt_2	O	CN
g	NH_2	NH	C(:NH)·NHMe
h	NH_2	NH	C(:NH)·NMe_2
i	NH_2	NH	NO_2
j	NEt_2	NH	NO_2
k	NH_2	NH	NMe_2
l	NH_2	NH	$NH\cdot[CH_2]_3\cdot NMe_2$

The preparation of amidines by fusion of a cyano-compound with ammonium benzenesulphonate in the presence of ammonia has been described by Oxley, Partridge, and Short.[4] When 2-amino-4,6-di-*p*-cyanoanilino-1,3,5-triazine was fused with ammonium benzenesulphonate the cyanophenyl groups were lost and melamine benzenesulphonate was formed. There was extensive decomposition when ammonium isethionate was used in a similar fusion.

In an attempt to improve the chemotherapeutic and physical properties of compound (III) the following modifications were made to the structure: (1) The amidino-groups were substituted or replaced by other basic groups. (2) The anilino-linkage was replaced by a phenoxy-linkage. (3) The heterocyclic amino-group was substituted, or replaced by

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[4] Oxley, Partridge, and Short, *J.*, 1948, 303.

other groups. (4) The *p*- was replaced by a *m*-amidino-group. (5) The *p*-amidinophenyl group was replaced by a dialkylaminoalkyl group. All these modifications caused very marked or complete loss of trypanocidal activity. In addition some unsuccessful attempts were made to prepare derivatives of compound (III) substituted in the benzene rings.

The substituted 4,6-dichloro-1,3,5-triazines (IV; R = NH_2, NHMe, NHEt, NEt_2, and OMe) were prepared by reaction of cyanuric chloride with the appropriate amine or alcohol. These dichlorotriazines were condensed with two equivalents of the appropriate amine (*m*- or *p*-aminobenzonitrile, *p*-nitroaniline) in boiling anisole; the condensations with *p*-dimethylaminoaniline and 3-dimethylaminopropylamine[5] were carried out in aqueous suspension whilst the reaction of the appropriate dichlorotriazine with *p*-hydroxybenzonitrile was effected in aqueous alkali.

The dicyano-compounds (Va—f) were converted into the di-imidoates and thence into the diamidines.

The *N*-substituted diamidines (Vg and h) were prepared by treatment of the requisite di-imidoate with the appropriate amine. Aqueous solutions (1%) of the dihydrochlorides of these diamidines rapidly formed gels.

The dinitro-compounds (Vi and j) were reduced with stannous chloride to the corresponding diamines, and these were condensed with cyanamide to give the diguanidines. The ditertiary amines (Vk and l) were converted into the diquaternary salts with methyl sulphate.

2,4-Dichloro-6-*p*-cyanoanilino-1,3,5-triazine condensed readily with 4,6-diaminoquinaldine or 2-diethylaminoethylamine to give the monochloro-compounds (VIa and b). Each of these reacted with *p*-aminobenzonitrile to give the dicyano-compounds which were converted into the respective diamidines.

Amination of 4,6-dichloro-2-*p*-cyanoanilino-1,3,5-triazine in phenol at 170° gave an excellent yield of 4,6-diamino-2-*p*-cyanoanilino-1,3,5-triazine which was converted into the amidine.

Demethylation of 4,6-di-*p*-cyanoanilino-2-methoxytriazine by benzylamine as described by Thurston *et al.*[6] (for demethylation of 4,6-dianilino-2-methoxy-1,3,5-triazine) gave the corresponding 2-hydroxy-derivative. This was a very insoluble compound and no attempt was made to convert it into a diamidine.

Condensation of *p*-aminobenzonitrile with dicyanimide gave N^1N^5-di-*p*-cyanophenyldiguanide (VII) which was converted into the corresponding diamidine; this was effective, but not curative, against *T. congolense* infections in mice. Condensation of the dicyano-compound with acetone, and with ethyl methyl ketone, gave the corresponding dihydrotriazines, which were converted into the respective diamidines.

EXPERIMENTAL

2-*Amino*-4,6-*dichloro*-1,3,5-*triazine*.—This was first prepared (0·5 molar scale) as described by Diels,[3] with ether as solvent for the cyanuric chloride; ammonia was admitted at such a rate that, with a cooling-bath at −20° to −25°, the internal temperature did not rise above −5°. The product (66—79%) crystallised from benzene in white prisms, m. p. 234—235° (decomp.). For the preparation of much larger amounts of this intermediate the following method was preferred: cyanuric chloride (553·5 g.; 3 moles), dissolved in dry chloroform (6 l.), was stirred whilst being cooled in a bath at −35°. When the internal temperature was −15°, ammonia was passed in for 48 min. at a rate of 3 l. per min. There was an exothermic reaction, but the temperature was never allowed to rise above −12°. The solid (658 g.; containing ammonium chloride) was filtered off and crystallised in batches of 100 g. from benzene (35 l.) The product (367 g., 74·5%) had m. p. 235—236°.

4,6-Dichloro-2-methylamino-1,3,5-triazine (82%), m. p. 160—161°, and 4,6-dichloro-2-ethylamino-1,3,5-triazine (84%), m. p. 106—107°, were prepared as described by Diels,[3] and

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[5] Nazarov and Shvekhgeimer, *Zhur. obshchei Khim.*, 1954, **24**, 163.

[6] Thurston, Schaefer, Dudley, and Holm-Hansen, *J. Amer. Chem. Soc.*, 1951, **73**, 2992.

4,6-dichloro-2-diethylamino-1,3,5-triazine (96%), m. p. 79—80°, and 4,6-dichloro-2-methoxy-1,3,5-triazine (61%), m. p. 90—91°, as described by Thurston *et al.*[7]

*2-Amino-4,6-di-*p*-cyanoanilino-1,3,5-triazine.*—2-Amino-4,6-dichloro-1,3,5-triazine (165 g., 1 mol.) in dry anisole (220 ml.) was added, in one portion, to a stirred solution of *p*-aminobenzonitrile (472 g., 4 mol.) in dry anisole (2400 ml.) in a bath at 100—110°. The bath-temperature was raised to 180—185°, an exothermic reaction then occurring. After being refluxed for 1·5 hr. the viscous mixture was cooled to 90—100° and filtered. After being washed with ethanol, the white solid was stirred with 2N-sodium hydroxide (10 l.) containing Lissapol-N (a nonylphenol–ethylene oxide condensate) (2 ml.) at 20—25° for 1 hr.; the mixture was refiltered, and the solid washed successively with water, ethanol, and ether. The *product* (325 g., 99·2%) crystallised from nitrobenzene (1 g. in 50 ml.) (or from pyridine or dimethylformamide) in pale yellow prisms, m. p. 339—341° (Found: C, 62·25; H, 4·0; N, 33·5. $C_{17}H_{12}N_8$ requires C, 62·2; H, 3·6; N, 34·2%).

The following 1,3,5-*triazines* were prepared by essentially similar methods: *4,6-di-*p*-cyanoanilino-2-methylamino-* (70%), pale yellow (from nitrobenzene), m. p. 281—282° (Found: C, 63·0; H, 4·3; N, 32·65. $C_{18}H_{14}N_8$ requires C, 63·15; H, 4·05; N, 32·8%); *4,6-di-*p*-cyanoanilino-2-ethylamino-* (67%), yellow prisms (from nitrobenzene), m. p. 249—251° (Found: C, 64·0; H, 4·3; N, 31·6. $C_{19}H_{16}N_8$ requires C, 64·05; H, 4·5; N, 31·45%); *4,6-di-*p*-cyanoanilino-2-diethylamino-* (60%), prisms (from anisole), m. p. 205—207° (Found: C, 65·4; H, 5·4; N, 29·0. $C_{21}H_{20}N_8$ requires C, 65·6; H, 5·2; N, 29·2%); *2-amino-4,6-di-*p*-nitroanilino-* (this was first prepared by our colleague, Mr. W. G. Leeds) (60%), greenish prisms (from nitrobenzene), m. p. >300° (Found: C, 48·6; H, 3·0; N, 30·6. $C_{15}H_{12}N_8O_4$ requires C, 48·9; H, 3·25; N, 30–4%); *2-diethylamino-4,6-di-*p*-nitroanilino-* (64%), yellow needles (from nitrobenzene), m. p. 316—317° (Found: C, 53·4; H, 4·7; N, 26·2. $C_{19}H_{20}N_8O_4$ requires C, 53·8; H, 4·7; N, 26·4%); *4,6-di-*p*-cyanoanilino-2-methoxy-* (87%), white needles (from acetic acid), m. p. >300° (Found: C, 62·8; H, 4·1; N, 28·4. $C_{18}H_{13}N_7O$ requires C, 63·0; H, 3·8; N, 28·6%); and 2-amino-4,6-di-*m*-cyanoanilino-1,3,5-triazine which crystallised from acetic acid as the *monoacetate* (58%), m. p. 240—242° (Found: C, 58·7; H, 4·3; N, 29·2. $C_{17}H_{12}N_8,C_2H_4O_2$ requires C, 58·8; H, 4·1; N, 28·9%).

*2,4-Dichloro-6-*p*-cyanoanilino-1,3,5-triazine.*—*p*-Aminobenzonitrile (70·8 g., 0·6 mole) in chloroform (250 ml.) was added dropwise during 1 hr. to a stirred solution of cyanuric chloride (55·35 g., 0·3 mole) in chloroform (500 ml.) at 15—20°. The pink solid, which separated, was filtered off and, after being washed with 2N-hydrochloric acid, the crude product (65 g., 83%) was used in further reactions. Crystallisation from acetone, ethyl methyl ketone, or dioxan gave the pure *product*, white rhombs, m. p. >300° (Found: Cl, 26·5; N, 26·3. $C_{10}H_5Cl_2N_5$ requires Cl, 26·7; N, 26·3%). Condensations carried out under similar conditions in acetone or ethyl methyl ketone at 30—35°, 45—50°, or 55—60° gave the same product; no 2-chloro-4,6-di-*p*-cyanoanilino-1,3,5-triazine was obtained.

*2-Amino-4,6-di-*p*-cyanophenoxy-1,3,5-triazine.*—2-Amino-4,6-dichloro-1,3,5-triazine (16·5 g., 0·1 mole) was added, with stirring, to *p*-hydroxybenzonitrile (23·6 g., 0·2 mole) in sodium hydroxide (8 g., 0·2 mole) and water (125 ml.) at 8—10°. The temperature was allowed to rise to 25° during 2 hr. and the mixture was then heated rapidly to 90—95° and after being kept at this temperature for 4 hr. the hot mixture was filtered. The *product* (23·5 g., 71%) crystallised from 2-ethoxyethanol (600 ml.) in white plates, m. p. 288—289° (Found: C, 61·9; H, 3·4; N, 25·2. $C_{17}H_{10}N_6O_2$ requires C, 61·8; H, 3·0; N, 25·5%). The following were prepared similarly: *4,6-di-*p*-cyanophenoxy-2-diethylamino-1,3,5-triazine* (72%), white needles (from ethanol), m. p. 144—145° (Found: C, 65·3; H, 4·9; N, 22·0. $C_{21}H_{18}N_6O_2$ requires C, 65·3; H, 4·7; N, 21·8%), and 2-amino-4,6-di-*p*-dimethylaminoanilino-1,3,5-triazine (57·5%) (from nitrobenzene), m. p. 283—286° [the *dihydrochloride* was deliquescent (Found: C, 50·3; H, 6·35; N, 25·0; H_2O, 3,65. $C_{19}H_{24}N_8,2HCl,H_2O$ requires C, 50·2; H, 6·15; N, 24·6; H_2O, 3·95%)]. The *bis(methosulphate)*, m. p. 274—276° (decomp.), prepared from the base and methyl sulphate in nitrobenzene at 100°, crystallised from methanol (Found: C, 43·0; H, 6·3; N, 17·6; S, 10·1; H_2O, 3·2. $C_{23}H_{36}N_8O_8S_2,H_2O$ requires C, 43·6; H, 6·0; N, 17·65; S, 10·1; H_2O, 2·85%).

*4,6-Di-*p*-cyanoanilino-2-hydroxy-1,3,5-triazine.*—4,6-Di-*p*-cyanoanilino-2-methoxy-1,3,5-triazine (3·4 g., 0·01 mole) and benzylamine (1 g., 0·01 mole) in nitrobenzene (100 ml.) were heated at 190° for 4—5 hr. A solid separated after 15 min. and the mixture thickened during

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[7] Thurston, Dudley, Kaiser, Hechenbleikner, Schaefer, and Holm-Hansen, *J. Amer. Chem. Soc.*, 1951, **73**, 2981.

the heating; after being cooled to 20°, the white solid was filtered off and washed with hot methanol. The product (1·3 g.) was insoluble in alcohols, hydrocarbons, acetic acid, dioxan, anisole, chlorobenzene, nitrobenzene, and cresylic acid. Analysis showed that it was probably the required *hydroxy-derivative* (Found: C, 61·3; H, 3·9; N, 29·2. $C_{17}H_{11}N_7O$ requires C, 62·0; H, 3·3; N, 29·8%).

2-*Amino*-4,6-*di*-p-*aminoanilino*-1,3,5-*triazine Dihydrochloride*.—2-Amino-4,6-di-*p*-nitroanilino-1,3,5-triazine (18·3 g.), suspended in boiling acetic acid (183 ml.), was treated with stannous chloride (183 g.) in concentrated hydrochloric acid (183 ml.) added in one portion. After being stirred at 100° for 2 hr. the mixture was cooled to 20°, and the pink stannichloride was filtered off and washed successively with concentrated hydrochloric acid and acetic acid. It was then ground with excess of 15% aqueous sodium hydroxide, and the pale red base was filtered off and treated with 2N-hydrochloric acid. The *dihydrochloride* crystallised from 2N-hydrochloric acid in white needles (9 g., 47·5%), m. p. >300° (Found: Cl, 18·7; N, 29·1. $C_{15}H_{16}N_8,2HCl$ requires Cl, 18·6; N, 29·4%). 4,6-*Di*-p-*aminoanilino*-2-*diethylamino*-1,3,5-*triazine* (61%), pink needles (from benzene), m. p. 196—197° (Found: C, 63·1; H, 6·7; N, 30·7. $C_{19}H_{24}N_8$ requires C, 62·6; H, 6·6; N, 30·8%) [*dihydrochloride*, m. p. >280° (Found, Cl, 16·4. $C_{19}H_{24}N_8,2HCl$ requires Cl, 16·2%), from 2N-hydrochloric acid], was prepared similarly.

2,4,6-*Tri*-p-*cyanoanilino*-1,3,5-*triazine*.—*p*-Aminobenzonitrile (23·6 g., 0·1 mole) in acetone (150 ml.) containing potassium iodide (0·05 g.) was added, in one portion, to 2,4-dichloro-6-*p*-cyanoanilino-1,3,5-triazine (13·3 g., 0·05 mole) in boiling acetone (600 ml.). The mixture was refluxed for 16 hr., and after 1 hr. a solid began to separate. The hot suspension was filtered, and the solid was crystallised from nitrobenzene (1120 ml.) to give the pale yellow *tricyano-derivative* (14·1 g., 66%), m. p. >300° (Found: C, 66·5; H, 3·7; N, 29·2. $C_{24}H_{15}N_9$ requires C, 67·1; H, 3·5; N, 29·4%).

4-(4-*Aminoquinaldin*-6-*ylamino*)-2-*chloro*-6-p-*cyanoanilino*-1,3,5-*triazine*.—4,6-Diaminoquinaldine (8·7 g., 0·05 mole) in acetic acid (200 ml.) was added to a stirred suspension of 2,4-dichloro-6-*p*-cyanoanilino-1,3,5-triazine (13·3 g., 0·05 mole) in acetic acid (200 ml.) at 35—40°. After being stirred at 40—50° for 3 hr. the solid was filtered off, washed with acetic acid and boiling acetone, and ground with 2N-sodium hydroxide. The *triazine* (8·4 g., 42%) separated from aqueous ethanol in pale yellow needles, m. p. >300° (Found: Cl, 8·4; N, 27·6. $C_{20}H_{15}ClN_8$ requires Cl, 8·8; N, 27·8%).

2-*Chloro*-6-p-*cyanoanilino*-4-2′-*diethylaminoethylamino*-1,3,5-*triazine*.—2-Diethylaminoethylamine (11·6 g., 0·1 mole) in acetone (100 ml.) was added dropwise to a suspension of 2,4-dichloro-6-*p*-cyanoanilino-1,3,5-triazine (13·3 g., 0·05 mole) in acetone (200 ml.). The temperature rose to 35° and a pale yellow solution was obtained. After being kept for 3 hr. the solution was evaporated *in vacuo* at 25—30°. The residual gum was dissolved in 2N-hydrochloric acid and the solution, after being treated with charcoal, was basified at 0—5° with 2N-sodium carbonate. The *base* crystallised from ethanol as white needles (10 g., 58%), m. p. 143—145° (Found: Cl, 9·8; N, 28·5. $C_{16}H_{20}ClN_7$ requires Cl, 10·3; N, 28·4%).

4-(4-*Aminoquinaldin*-6-*ylamino*)-2,6-*di*-p-*cyanoanilino*-1,3,5-*triazine*.—The last preceding 2-chloro-compound (16·1 g., 0·04 mole) and *p*-aminobenzonitrile (9·5 g., 0·08 mole) in anisole (120 ml.) were refluxed for 4 hr. (solid began to separate after 5 min.). The hot mixture was filtered and the residue was ground with 2N-sodium hydroxide. The *dinitrile* crystallised from ethylene glycol as pale brown prisms (8·1 g., 45%), m. p. >300° (Found: C, 66·4; H, 4·15; N, 28·9. $C_{27}H_{20}N_{10}$ requires C, 66·9; H, 4·1; N, 29·0%). 2,6-*Di*-p-*cyanoanilino*-4-2′-*diethylaminoethylamino*-1,3,5-*triazine* was prepared (40%) similarly from the corresponding 2-chloro-compound. It crystallised from ethanol in white prisms, m. p. 155—159° (Found: C, 64·2; H, 5·9; N, 29·4. $C_{23}H_{25}N_9$ requires C, 64·7; H, 5·9; N, 29·5%).

2,4-*Diamino*-6-p-*cyanoanilino*-1,3,5-*triazine*.—2,4-Dichloro-6-*p*-cyanoanilino-1,3,5-triazine (26·6 g., 0·1 mole) and phenol (80 g.) were heated in a bath at 182—189°, and ammonia was bubbled through the mixture for 6 hr. The internal temperature never rose above 188° and after 6 hr. the mixture solidified. The cold mass was ground with water (500 ml.), and the solid was filtered off, and washed with 2N-sodium hydroxide and water. The *diamine* crystallised in white prisms (18·3 g., 81%), m. p. 282—283°, from nitrobenzene (Found: C, 53·0; H, 4·0; N, 42·8. $C_{10}H_9N_7$ requires C, 52·8; H, 4·0; N, 43·2%).

N^1N^5-*Di*-p-*cyanophenyldiguanide*. (This compound was first prepared by our colleague, Dr. W. W. CUTHBERTSON.)—Sodium dicyanimide [8] (44·5 g., 0·5 mole) in water (250 ml.) was

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[8] Madelung and Kern, *Annalen*, 1922, **427**, 1.

added to *p*-aminobenzonitrile (129·8 g., 1·1 mole) in concentrated hydrochloric acid (110 ml.) and water (880 ml.). A precipitate was obtained after 5 min. and the mixture was heated under reflux on the steam-bath for 6 hr. The solid was filtered off, washed with water, and ground with 2N-sodium hydroxide; it was then filtered off and washed free from alkali. The *diguanide* crystallised from methanol (1 l.) in colourless needles (52·4 g.; 35%), m. p. 203—204° (slight decomp.) (Found: C, 63·5; H, 4·5; N, 32·4. $C_{16}H_{13}N_7$ requires C, 63·5; H, 4·3; N, 32·3%).

2,4-*Di*-p-*cyanoanilino*-1,3,5-*triazine* (cf. Clauder *et al.*[9]).—N^1N^5-Di-*p*-cyanophenyldiguanide (23 g.) in 90% formic acid (150 ml.) was refluxed for 3 hr. After being cooled to 30°, the solid was filtered off, ground with 2N-sodium hydroxide, and washed with water and methanol. The *product* (10·5 g., 50%) separated in white prismatic needles, m. p. >300°, from nitrobenzene (200 ml.) (Found: C, 64·8; H, 3·8; N, 31·2. $C_{17}H_{11}N_7$ requires C, 65·2; H, 3·5; N, 31·3%).

2,4-*Di*-p-*cyanoanilino*-1,6-*dihydro*-6,6-*dimethyl*-1,3,5-*triazine*.—N^1N^5-Di-*p*-cyanophenyldiguanide (20 g.), acetone (60 ml.), and piperidine (0·9 ml.) were mixed, and refluxed for 2·5 hr. After one hr. a solution was obtained, and after a further 10 min. the product began to separate. After being cooled to 20°, the *dinitrile* was filtered off; it crystallised from methanol in needles (18·5 g., 81·5%), m. p. 269—271° (decomp.) (Found: C, 66·1; H, 5·05; N, 28·4. $C_{19}H_{17}N_7$ requires C, 66·45; H, 4·95; N, 28·6%). 2,4-*Di*-p-*cyanoanilino*-6-*ethyl*-1,6-*dihydro*-6-*methyl*-1,3,5-*triazine* (85%) was similarly prepared by using ethyl methyl ketone and crystallised from this solvent in white needles, m. p. 244—246° (Found: C, 67·15; H, 5·1; N, 27·3. $C_{20}H_{19}N_7$ requires C, 67·2; H, 5·35; N, 27·45%).

2-*Amino*-4,6-*di*-p-*guanidinoanilino*-1,3,5-*triazine Dihydrochloride*.—2-Amino-4,6-di-*p*-aminoanilino-1,3,5-triazine dihydrochloride (5·0 g.), cyanamide (2·5 g.), and ethanol (100 ml.) were refluxed together overnight. The pink solution was evaporated under reduced pressure. The residue was dissolved in water (100 ml.), the solution filtered (charcoal), and the filtrate basified at 0—5° with 2N-sodium hydroxide. The solid was dissolved in hot 2N-hydrochloric acid (50 ml.); the *product* (4·0 g.; 65%) separated in white needles, m. p. >360° (Found: Cl, 14·0; N, 33·4; H_2O, 7·5. $C_{17}H_{20}N_{12},2HCl,2H_2O$ requires Cl, 14·15; N, 33·5; H_2O, 7·2%).

2-*Diethylamino*-4,6-*di*-p-*guanidinoanilino*-1,3,5-*triazine* was similarly prepared from 4,6-di-*p*-aminoanilino-2-diethylamino-1,3,5-triazine dihydrochloride. The base (84%) separated in white prisms (from propan-2-ol), m. p. 174—175° (decomp.) (Found: C, 56·4; H, 6·2; N, 37·2. $C_{21}H_{18}N_{12}$ requires C, 56·25; H, 6·25; N, 37·5%).

4,6-*Di*-p-*amidinoanilino*-2-*amino*-1,3,5-*triazine Trihydrochloride*.—2-Amino-4,6-di-*p*-cyanoanilino-1,3,5-triazine (500 g.), suspended in dry ethanol (1·5 l.), was ground to a paste, in a ball-mill, for 4 days. After the addition of dry ethanol (6 l.), the fine suspension was saturated at −10° with dry hydrogen chloride (cooling-bath at −15° to −20°) during 12 hr. The mixture was kept for 4 weeks at room temperature, with occasional shaking; it thickened considerably. The white solid was filtered off (through coarse filter paper), washed with dry ether (5 l.), and kept overnight over calcium chloride *in vacuo*. The yields of di-imidoate hydrochloride (containing solvent) in two experiments were 1400 g. and 1250 g. (a 2% w/v aqueous solution was clear at 25—30°). The white cake was stirred to a paste with dry ethanol (1·5 l.) and carefully added to liquid ammonia (1·5 l.) in dry ethanol (6 l.) at 20—25°. A solution was obtained at the beginning of the addition, then a solid separated, and the fine suspension was stirred for 2 hr. The temperature was raised to 50—55° during 2 hr. and the mixture was stirred at this temperature for 6 hr. After being cooled, the white solid was filtered off and added to 0·5N-hydrochloric acid (20 l.) at 90°. The mixture was boiled, filtered, treated with charcoal, re-filtered (hot), and cooled to 25°. Concentrated hydrochloric acid (2·5 l.) was added, and the mixture was cooled at 5—10° for 2 hr. The solid was filtered off, washed with 2N-hydrochloric acid, and dried at 30—35° for 3 days. The pale yellow solid was ground to a paste with acetone in a ball-mill, filtered off, and washed with acetone, and the crude product (804 g., and 606 g. in 2 experiments) was crystallised as follows: A solution of the white solid (50 g. batch) in hot methanol (6 l.) was cooled to 25°, treated with charcoal, filtered, and treated with concentrated hydrochloric acid (300 ml.). On scratching, crystallisation occurred to give white needles (20—25 g.) of the *trihydrochloride dihydrate*, m. p. >360° (sintering slightly above 200°) (Found: Cl, 20·9; N, 27·9; H_2O, 7·1. $C_{17}H_{18}N_{10},3HCl,2H_2O$ requires Cl, 21·0; N, 27·9; H_2O, 7·1%).

The amorphous *diamidine base* (80%), m. p. 195—198° (decomp.) (Found: C, 56·0; H, 4·8;

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[9] Clauder, Zemplen, and Bulesu, Austrian Pat. 168,063/1951.

N, 38·2. $C_{17}H_{18}N_{10}$ requires C, 56·35; H, 4·9; N, 38·7%), was obtained by grinding the trihydrochloride with methanol–2N-sodium hydroxide, and did not crystallise. The *diphosphate*, no m. p. below 290° (Found: N, 24·8. $C_{17}H_{18}N_{10},2H_3PO_4$ requires N, 25·1%), was prepared from the base and orthophosphoric acid in methanol.

The acid-insoluble material obtained in the amination stage was essentially the corresponding 4,4′-dicarboxamide (Found: C, 53·1; H, 4·2; Cl, 9·45; N, 28·5. $C_{17}H_{16}N_8O_2,HCl$ requires C, 51·0; H, 4·0; Cl, 8·9; N, 28·0%).

2-*Amino*-4,6-*di*-p-(*ethoxyiminomethyl*)*anilino*-1,3,5-*triazine*.—The corresponding dihydrochloride (10·6 g.) was ground with 2N-sodium hydroxide (50 ml.), ice (25 g.), and Lissapol N (0·2 ml.). The white solid *di-imidoate* (7 g.) was filtered off, washed free from alkali with water, and dried at 10 mm. over sulphuric acid; it decomposed at 255° (Found: C, 61·2; H, 5·7; N, 27·2. $C_{21}H_{24}N_8O_2$ requires C, 60·0; H, 5·7; N, 26·7%). It was insoluble in hydrocarbon solvents, and only slightly soluble in hydroxylic solvents. When it was treated in aqueous ethanol with ammonium chloride, a 12% yield of the diamidine was obtained, together with the dicarboxamide. When ammonium isethionate was used in this conversion only the dicarboxamide was obtained.

Fusion of 2-*Amino*-4,6-*di*-p-*cyanoanilino*-1,3,5-*triazine with Ammonium Benzenesulphonate*.—A mixture of 2-amino-4,6-di-*p*-cyanoanilino-1,3,5-triazine (3·5 g., 0·01 mole) and ammonium benzenesulphonate (3·5 g., 0·02 mole) was heated at 300° in a stream of ammonia for 2·5 hr. After being cooled to 30°, the brown melt was powdered, dissolved in boiling water (15 ml.), and filtered (charcoal). The filtrate deposited pale yellow needles of *melamine benzenesulphonate* (2·3 g.; 81%) which, after being crystallised from water, had m. p. >300° (Found: N, 29·75; S, 10·85. $C_3H_6N_6,C_6H_6O_3S$ requires N, 29·6; S, 11·25%). Treatment of a hot aqueous solution with sodium hydroxide gave melamine. Concentration of the aqueous crystallising liquors to one-third volume gave white needles (0·2 g.), m. p. 180—183°, probably *p*-aminobenzamide. Extraction of the initial aqueous mother-liquor with ether gave *p*-aminobenzonitrile (0·1 g.), m. p. 86—88°.

The diamidines in Table 2 were prepared from the respective nitriles by the Pinner method.

TABLE 2. *Diamidines* [V; R′ = C(:NH)·NH_2].

No.	X	R	Alcohol and solvent (imidoate prep.)	Time (imidoate prep.) (days)	Amidine salt	Cryst. from	Yield (%)
1	NH	NEt_2	EtOH	10	2HCl	MeOH	42
2	O	NH_2	EtOH–$CHCl_3$	5	2HCl	MeOH–$COMe_2$	33
3	O	NEt_2	EtOH–$CHCl_3$	5	2HCl	MeOH–$COMe_2$	45
4	NH	NHMe	EtOH	14	2HCl	Aq. NaCl	53
5	NH	NHEt	EtOH	21	2HCl	Aq. NaCl	55
6	NH	$NH(CH_2)_2NEt_2$	EtOH–$CHCl_3$	6	3HCl	MeOH–$COMe_2$	42
7	NH	4-Aminoquinaldin-6-ylamino	EtOH–Ph·NO_2	21	3HCl	MeOH	26·5
8	NH	OMe	EtOH	21	2HCl	MeOH–$COMe_2$	41
9	NH	*p*-Amidinoanilino	HO·$[CH_2]_2$·OEt	30	4Me·SO_3H	MeOH	23·3
10	NH	H	EtOH	21	2Me·SO_3H	MeOH	60

No.	M. p.	Formula	Found (%)		Requires (%)	
			Cl	N	Cl	N
1	>300°	$C_{21}H_{26}N_{10},2HCl$	14·3	28·2	14·45	28·5
2	160 [a]	$C_{17}H_{16}N_8O_2,2HCl,0{\cdot}5H_2O$	15·7	24·8	15·9	25·05
3	255—257 [a]	$C_{21}H_{24}N_8O_2,2HCl$	14·4	23·0	14·4	22·7
4	319—320 [a] (loses H_2O at 262°)	$C_{18}H_{20}N_{10}2HCl,2H_2O$ [b]	14·6	28·7	14·6	28·85
5	275—276 [a] (loses H_2O at 258—260°)	$C_{19}H_{22}N_{10},2HCl,2H_2O$	14·3	27·8	14·2	28·05
6	245—247 [a]	$C_{23}H_{31}N_{11},3HCl$	18·8	26·8	18·65	27·0
7	>300	$C_{27}H_{26}N_{12},3HCl$	16·7	26·6	17·0	26·8
8	>300	$C_{18}H_{19}NO,2HCl$	15·7	27·8	15·8	28·0
9	212—214 [a] (shrinks at 176—178°)	$C_{24}H_{24}N_{12},4CH_4O_3S,3H_2O$ [d]	—	18·6	—	18·3
10	306—308 [a] (darkens at 277°)	$C_{17}H_{17}N_9,2CH_4O_3S$ [e]	—	23·2	—	23·4

[a] With decomp. [b] Found: H_2O, 7·5. Required: H_2O, 7·4%. [c] Found: H_2O, 7·0. Required: H_2O, 7·2%. [d] Found: C, 37·1; H, 5·1; S, 14·2; H_2O, 5·7. Required: C, 36·6; H, 5·0; S, 13·95; H_2O, 5·9%. [e] Found: S, 11·6. Required: S, 11·9%.

N^1N^5-*Di*-p-*amidinophenyldiguanide*.—This was prepared by the general method using 2-ethoxyethanol as the alcohol; the imidoate preparation was kept for one month; the *diamidine trihydrochloride* (13·2%) separated from dilute sodium chloride in white crystals, m. p. 355—356° (decomp.) (Found: Cl, 23·55; N, 28·2. $C_{16}H_{19}N_9,3HCl$ requires Cl, 23·85; N, 28·2%).

6-p-*Amidinoanilino*-2,4-*diamino*-1,3,5-*triazine* was prepared by the general method using ethanol as alcohol; the reaction mixture was kept for 4 weeks. The *hydrochloride* (61%) crystallised from water in white prisms, m. p. 306—308° (decomp.) (Found: Cl, 12·2; N, 37·6; H_2O, 5·7. $C_{10}H_{12}N_8,HCl,H_2O$ requires Cl, 11·9; N, 37·5; H_2O, 6·0%).

2,4-*Di*-p-*amidinoanilino*-1,6-*dihydro*-6,6-*dimethyl*-1,3,5-*triazine* was prepared similarly. The imidoate preparation was kept for 3 days only and the *diamidine trihydrochloride* (62%) separated from methanol–acetone in white prisms, m. p. >300° (Found: Cl, 21·3; N, 26·55. $C_{19}H_{23}N_9,3HCl$ requires Cl, 21·9; N, 26·0%). 2,4-*Di*-p-*amidinoanilino*-6-*ethyl*-1,6-*dihydro*-6-*methyl*-1,3,5-*triazine trihydrochloride* (70%), white prisms (from methanol–acetone), m. p. >300° (Found: Cl, 21·1; N, 25·0. $C_{20}H_{25}N_9,3HCl$ requires Cl, 21·3; N, 25·15%), was prepared similarly.

The following two *N*-alkylamidines were obtained from the di-imidoate trihydrochloride and the requisite amine in ethanol: 2-*amino*-4,6-*di*-p-N-*methylamidino*- (56%) (from methanol–ether) (Found: C, 44·4; H, 4·8; N, 26·9; H_2O, 3·8. $C_{19}H_{22}N_{10},3HCl,H_2O$ requires C, 44·2; H, 5·2; N, 27·05; H_2O, 3·5%), and 2-*amino*-4,6-*di*-p-NN-*dimethylamidino-anilino*-1,3,5-*triazine dihydrochloride* (from methanol–ether) (Found: C, 48·9; H, 4·9; Cl, 13·8; N, 27·1; H_2O, 3·8. $C_{21}H_{26}N_{10},2HCl,H_2O$ requires C, 49·5; H, 5·9; Cl, 13·95; N, 27·5; H_2O, 3·55%).

2-*Amino*-4,6-*di*-(3-*dimethylaminopropylamino*)-1,3,5-*triazine*.—3-Dimethylaminopropylamine [9] (20·4 g., 0·2 mole) was added to a stirred suspension of 2-amino-4,6-dichloro-1,3,5-triazine (16·5 g., 0·1 mole) in water (50 ml.). The mixture was heated slowly to the b. p., and a solution of sodium hydroxide (8 g., 0·2 mole) in water (40 ml.) was added during 1 hr. After being boiled for a further 2 hr. the cooled mixture was filtered and the filtrate saturated with salt and extracted with chloroform (2 × 100 ml.). The extract afforded a pale yellow viscous liquid, b. p. 200° (air-bath temp.)/0·2 mm., which solidified to a hygroscopic glass (7·5 g., 25%). This base (5·8 g.) was dissolved in dry ethanol (50 ml.) and when treated with a solution of tartaric acid (5·7 g.) in dry ethanol (25 ml.) gave the hygroscopic *di*(*hydrogen tartrate*), m. p. 78—80° (Found: C, 41·4; H, 7·1; N, 18·0. $C_{13}H_{28}N_8,2C_4H_6O_6$ requires C, 41·1; H, 6·85; N, 18·2%). The above tertiary base (7·2 g.), dissolved in acetone (50 ml.), was treated with methyl iodide (3·5 ml.), and the mixture was heated to the b. p. and then cooled. The methiodide was filtered off, dissolved in the minimum amount of water, and the solution added to aqueous diammonium 4,4′-diaminostilbene-2,2′-disulphonate (1 mol.). The mixture was heated on the steam-bath for 5 min. and, after it had cooled, alcohol was added to precipitate the product. This was removed and ground with alcohol; it recrystallised from 1 : 1 v/v water–methanol and afforded the bisquaternary 4,4′-*diaminostilbene*-2,2′-*disulphonate* as a pinkish powder, m. p. 283—285° (decomp.) (Found: C, 48·4; H, 6·7; N, 19·7; H_2O, 2·9. $C_{15}H_{34}N_8,C_{14}H_{14}N_2O_6S_2,H_2O$ requires C, 48·4; H, 6·7; N, 19·65; H_2O, 2·5%).

4,6-*Di*-m-*amidinoanilino*-2-*amino*-1,3,5-*triazine*.—This was prepared by the standard method using ethanol as the alcohol. The preparation was kept for 3 weeks and afforded the *dihydrochloride*, m. p. >300°, from methanol (Found: C, 44·8; H, 5·3; N, 30·7. $C_{17}H_{18}N_{10},2HCl,H_2O$ requires C, 45·0; H, 4·9; N, 30·8%).

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