115. *Contributions to the Chemistry of Synthetic Antimalarials. Part VI. Some Derivatives of* 1 : 3 : 5-*Triazine.*

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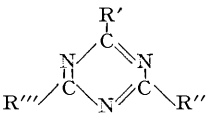
A number of basically substituted 1 : 3 : 5-triazines have been prepared. They exhibit no trypanocidal activity and little or no antimalarial activity.

As part of a programme for the examination of simple heterocyclic nuclei for chemotherapeutic activity several derivatives of 1 : 3 : 5-triazine have been prepared. The 1 : 3 : 5-triazine

nucleus has been the subject of several investigations in the realm of potential therapeutic agents; thus Jensch (U.S.P. 2,092,552) claimed that cyanuric quinoline derivatives were effective in diseases due to bacteria and protozoa. Friedheim (*J. Amer. Chem. Soc.*, 1944, **66**, 1775; U.S.P. 2,295,574) and Controulis *et al.* (*ibid.*, p. 1771) describe some arsenic substituted anilino-triazines, of which 4 : 6-diamino-2-(4′-arsenoanilino)-1 : 3 : 5-triazine has found application in African sleeping sickness (*Schweiz. Med. Woch.*, 1941, **5**, 116); while Controulis (*J. Amer. Chem. Soc.*, 1945, **67**, 1946) states that alkoxy-triazines possess the power to alleviate histamine shock in guinea pigs. While the work now reported was in progress Mosher and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 662) described the synthesis of a number of aminoalkylamino-1 : 3 : 5-triazines most of which contained the γ-piperidinopropylamino-grouping; no biological data, however, were quoted. A number of triazines similar to those now described have since been prepared by Curd, Landquist, and Rose (*J.*, 1947, 154), but none of these exhibited any anti-malarial activity. Some similarly constituted pyrimidines have been described by Curd and Rose (*J.*, 1946, 343); a number of these possess antimalarial activity.

In the present paper three types of triazine compound are described: (*a*) 6-methoxy-8-quinolylamino-, (*b*) δ-diethylamino-α-methylbutylamino-, and (*c*) *p*-chloroanilino-derivatives, the remaining positions in the triazine nucleus being substituted with other groups such as amino-, diethylamino-, *iso*propylamino-, and methoxy- (see Table).



Type.	R′.	R″.	R‴.	Type.	R′.	R″.	R‴.
I	A	NEt_2	Cl	III	C	$NHPr^{\beta}$	Cl
	A	NEt_2	NH_2		C	,,	NH_2
	A	NH_2	NH_2		C	,,	OMe
					C	,,	H
II	B	NH_2	Cl				
	B	NH_2	OMe				

(A = 6-methoxy-8-quinolylamino-; B = δ-diethylamino-α-methylbutylamino-; C = *p*-chloro-anilino-).

Most of the triazines were synthesised from cyanuric chloride in which all three chlorine atoms are reactive and capable of replacement either singly or completely, according to conditions. In general, the first chlorine atom is replaced at 0°, the second at room temperature, and the third at 120—140°. For example, reaction at 25° of 2 : 4-dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine with 2 mols. of *iso*propylamine in chloroform gave 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine. It was difficult to stop at the introduction of one methoxyl group when two or more chlorine atoms were present, owing to the ready reaction of these with alcohol alone. An attempted preparation of 2 : 4-dichloro-6-methoxy-1 : 3 : 5-triazine by reaction of cyanuric chloride at room temperature with one mol. of sodium methoxide in methyl alcohol gave 2 : 4 : 6-trimethoxy-1 : 3 : 5-triazine. On carrying out the reaction at 0° some monomethoxy-product was indeed isolated in one experiment, but the product generally appeared to be a mixture of all three substituted compounds.

Substances of type I gave crystalline salts whereas those of type II failed to do so. Indeed, the free base itself of the compound (R′ = B, R″ = NH_2, R‴ = Cl) could not be obtained in a pure state. On attempted distillation very little material distilled, and the remainder on cooling set to a hard glass which may be a condensation product of two or more molecules formed by elimination of hydrogen chloride.

In the case of substances of type III, an unsuccessful attempt was made to prepare 6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine* by selective dechlorination in the hetero-ring of the 2-chloro-derivative. Use of sodium in liquid ammonia (U.S.P. 2,385,761; (*Chem. Abs.*, 1946, **40**, 613)) led to complete dechlorination and the production of 6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*. Palladium–strontium carbonate and hydrazine (*J.*, 1935, 1283) had a similar effect, while the use of zinc and glacial acetic acid yielded only unchanged starting material. The structure of the completely dechlorinated product was proved by an alternative synthesis from cyanuric chloride by successive treatment with aniline and *iso*propylamine followed by dechlorination in the 6-position.

The substance was eventually obtained by condensation of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide with ethyl formate (cf. Rackmann, *Annalen*, 1910, **376**, 170; Wagner, *J. Org.*

Chem., 1940, **5**, 133). Dechlorination yielded the previously obtained 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine. The above diguanide, which itself possesses a high antimalarial activity, was prepared by the method of Curd and Rose (*J.*, 1946, 729).

Salts of type III were readily hydrolysed and remained in solution only in presence of an excess of acid, although in one case (R′ = *p*-chloroanilino-, R″ = *iso*propylamino-, R‴ = NH_2) a pure *hydrobromide* was isolated. Treatment of 2-p-*chloroanilino*-4-iso*propylamino*-6-*methoxy*-1 : 3 : 5-*triazine* with hydrobromic acid led to demethylation and formation of the corresponding *triazone*, identified by analysis and reconversion into the 6-chloro-compound with phosphoryl chloride.

The substances were tested for therapeutic activity against *Trypanosoma equiperdum* in mice and *Plasmodium gallinaceum* in chicks; no activity was observed, except in the compound (R′ = *p*-chloroanilino-, R″ = *iso*propylamino-, R‴ = H) which had possibly a slight activity against *Plasmodium gallinaceum*.

Experimental.

Cyanuric chloride, m. p. 147°, was prepared by the method of Diels (*Ber.*, 1899, **32**, 691).

2 : 4-*Dichloro*-6-(6′-*methoxy*-8′-*quinolylamino*)-1 : 3 : 5-*triazine* (I).—8-Amino-6-methoxyquinoline (37·7 g.) in chloroform (100 c.c.) was added dropwise to a stirred solution of cyanuric chloride (20 g.) in chloroform (200 c.c.) at 0°. 8-Amino-6-methoxyquinoline hydrochloride separated as an orange powder together with the product. After removal of chloroform by distillation, the residue was extracted several times with boiling benzene. The combined extracts, on cooling, gave fine yellow needles of the *compound* (18·8 g.), m. p. 237° (Found : Cl, 21·7. $C_{13}H_9ON_5Cl_2$ requires Cl, 22·0%).

2-*Chloro*-6-(6′-*methoxy*-8′-*quinolylamino*)-4-*diethylamino*-1 : 3 : 5-*triazine* (II).—Diethylamine (5·6 g.) in chloroform (20 c.c.) was added dropwise to (I) (12·3 g.) in chloroform (50 c.c.) at room temperature. The chloroform solution was extracted with water, and evaporation of the dried solution gave the *compound* (11·5 g.) which crystallised from benzene in colourless prisms, m. p. 170° (Found : N, 23·5; Cl, 9·8. $C_{17}H_{19}ON_6Cl$ requires N, 23·4; Cl, 9·9%). The *hydrochloride* had m. p. 278° (decomp.) (Found : N, 19·25; OMe, 7·2. $C_{17}H_{19}ON_6Cl,HCl,2H_2O$ requires N, 19·4; OMe, 7·2%).

2-*Amino*-6-(6′-*methoxy*-8′-*quinolylamino*)-4-*diethylamino*-1 : 3 : 5-*triazine*.—The above chloro-compound (2·75 g.) was heated with saturated alcoholic ammonia (25 c.c.) in a sealed tube at 140° for 8 hours; the *product* formed yellow needles from alcohol, m. p, 191° (Found : N, 28·9. $C_{17}H_{21}ON_7$ requires N, 28·9%). The *hydrochloride* had m. p. 216° (decomp.) (Found : N, 21·8. $C_{17}H_{21}ON_7,2HCl,2H_2O$ requires N, 21·9%).

2 : 4-*Diamino*-6-(6′-*methoxy*-8′-*quinolylamino*)-1 : 3 : 5-*triazine*.—A mixture of (I) (1 g.) and saturated alcoholic ammonia (10 c.c.) was heated at 130° for 8 hours. The free base separated on cooling; it was insoluble in organic solvents, and was purified as the *hydrochloride*, m. p. 280° (decomp.) (Found : N, 25·0; Cl, 17·5; OMe, 7·6. $C_{13}H_{13}ON_7,2HCl,2H_2O$ requires N, 24·9; Cl, 18·1; OMe, 7·9%).

Attempted Preparation of 2 : 4-*Dichloro*-6-*methoxy*-1 : 3 : 5-*triazine*.—Treatment of cyanuric chloride (1 g.) in dry methanol (10 c.c.) with sodium (0·125 g.) in methanol (10 c.c.) at 0°, followed by distillation of the methanol under reduced pressure at 25°, and recrystallisation of the residue from ethyl acetate, gave a product, m. p. 130° which was obviously the trimethoxy-derivative (Found : OMe, 53·0. Calc. for $C_6H_9O_3N_3$: OMe, 54·3%); literature m. p. 134°.

2 : 4-*Dichloro*-6-*amino*-1 : 3 : 5-*triazine* (III) (Diels, *loc. cit.*).—Cyanuric chloride (5 g.) in dry ether (100 c.c.) was treated at 0° with dry ammonia. Recrystallisation of the product from ether, then benzene, gave colourless needles (3 g.), m. p. 237°.

2-*Chloro*-6-*amino*-4-*methoxy*-1 : 3 : 5-*triazine* (IV).—Sodium methoxide solution (0·42 g. of sodium in 42 c.c. of methanol) at room temperature was added gradually to (III) (3 g.). The product separated as a white mass, which was collected and washed with water to remove sodium chloride. Recrystallisation from ethyl acetate gave colourless plates (1·8 g.), m. p. > 300° (Found : N, 34·9; Cl, 21·8; OMe, 19·35. $C_4H_5ON_4Cl$ requires N, 34·9; Cl, 22·1; OMe, 19·3%).

6-*Amino*-2-(δ-*diethylamino*-α-*methylbutylamino*)-4-*methoxy*-1 : 3 : 5-*triazine*.—A mixture of (IV) (2·9 g.) and δ-diethylamino-α-methylbutylamine (17·4 g.) was heated in a sealed tube at 120° for 4 hours. Excess of diamine was removed by distillation; the viscous brown residue, b. p. 210°/0·1 mm. (3·9 g.), failed to crystallise. Decomposition of the pure *dipicrate*, m. p. 190° (Found : C, 41·0; H, 4·8; N, 22·7. $C_{13}H_{26}ON_6,2C_6H_3O_7N_3$ requires C, 40·5; H, 4·3; N, 22·7%), gave the pure *base* as a pale yellow syrup, b. p. 195—200°/0·03 mm. (Found : N, 29·8. $C_{13}H_{26}ON_6$ requires N, 29·7%).

2-*Chloro*-6-*amino*-4-(δ-*diethylamino*-α-*methylbutylamino*)-1 : 3 : 5-*triazine*.—A solution of (III) (5 g.) in chloroform (50 c.c.) was treated gradually with δ-diethylamino-α-methylbutylamine (9·6 g.) in chloroform (25 c.c.) at room temperature. The solution was extracted with water to remove diamine hydrochloride, and evaporation of the dried solution gave a viscous brown syrup. Only a small amount distilled at 250°/0·3 mm., and the remainder solidified to a hard glass. The latter may be a condensation product of two molecules formed by elimination of hydrogen chloride. The distillate was impure (Found : N, 30·8. $C_{12}H_{23}N_6Cl$ requires N, 29·3%) and failed to give a crystalline picrate, styphnate, or picrolonate.

2 : 4-*Dichloro*-6-p-*chloroanilino*-1 : 3 : 5-*triazine*.—*p*-Chloroaniline (6·9 g.) in chloroform (50 c.c.) was added dropwise to a stirred solution of cyanuric chloride (5 g.) in chloroform (100 c.c.) at 0°. The precipitated *p*-chloroaniline hydrochloride was removed by filtration and washed with chloroform, and the filtrates were extracted with water. Evaporation of the dried solution gave the crude product (7 g.) which crystallised from benzene in colourless microcrystals, (4·2 g.), m. p. 188° (Found : N, 20·3. Calc. for $C_9H_5N_4Cl_3$: N, 20·3%).

2-*Chloro*-6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—*iso*Propylamine (3·5 c.c.) in chloroform (25 c.c.) was added gradually to a solution of the above dichloro-compound (5·56 g.) in chloroform (50 c.c.)

at room temperature. The product formed colourless microcrystals (4·6 g.) from benzene, m. p. 172° (Found : N, 23·6. Calc. for $C_{12}H_{13}N_5Cl_2$: N, 23·5%).

2-*Amino*-6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—The above chloro-compound (5 g.) was heated with saturated alcoholic ammonia (75 c.c.) at 140° for 8 hours. Evaporation of the alcohol and extraction with chloroform gave a colourless syrup (5·1 g.) which crystallised on trituration with acetone. The *compound* formed colourless microcrystals (3·16 g.) from ethyl acetate, m. p. 166° (Found : N, 29·9; Cl, 12·6. $C_{12}H_{15}N_6Cl$ requires N, 30·2; Cl, 12·7%). The *hemistyphnate* had m. p. 239° (Found : N, 26·1. $2C_{12}H_{15}N_6Cl,C_6H_3O_8N_3$ requires N, 26·2%), and the *hydrobromide*, m. p. 223° (Found : N, 22·5. $C_{12}H_{15}N_6Cl,HBr,H_2O$ requires N, 22·2%). The hydrochloride has been described by Curd, Landquist, and Rose (*loc. cit.*).

6-p-*Chloroanilino*-4-iso*propylamino*-2-*methoxy*-1 : 3 : 5-*triazine*.—2-Chloro-6-*p*-chloroanilino-4-*iso*-propylamino-1 : 3 : 5-triazine (2·98 g.) was refluxed with sodium methoxide solution (0·25 g. of sodium in 50 c.c. of methanol) for 4 hours. Evaporation of the alcohol gave a syrup (2·9 g.), b. p. 205°/0·03 mm., which crystallised on trituration with ether. The *compound* crystallised from ether–light petroleum (b. p. 40—60°) in fine needles (1·5 g.), m. p. 137° (Found : N, 23·6; Cl, 12·2. $C_{13}H_{16}ON_5Cl$ requires N, 23·8; Cl, 12·1%). An attempt to prepare the hydrobromide gave material, m. p. 337° (Found : N, 21·55; OMe, 0·85%), which was probably the hydrobromide of 6-*p*-chloroanilino-4-*iso*propylamino-2-triazone. Addition of ammonia to an alcoholic solution of this gave the free *base*, which formed an amorphous white powder from aqueous pyridine, m. p. 365° (Found : N, 24·95. $C_{12}H_{14}ON_5Cl$ requires N, 25·0%). The triazone (1·1 g.) was refluxed for 4 hours with phosphoryl chloride (10 c.c.), and the mixture was poured into ice–water and neutralised with ammonia. Recrystallisation from benzene gave 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. and mixed m. p. with authentic sample, 170°.

Attempted Preparation of 6-p-*Chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—Sodium (0·4 g.) was added during 1 hour to 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine (2·07 g.) in liquid ammonia (40 c.c.). Ammonium chloride (1 g.) was then added, and the ammonia allowed to evaporate. The residue was extracted with hot benzene which, on cooling, deposited crystals (0·77 g.), m. p. 197—198°. Recrystallisation from the same solvent gave 6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine* (Found : C, 62·7; H, 6·6; N, 30·4; Cl, 0·00. $C_{12}H_{15}N_5$ requires C, 62·8; H, 6·5; N, 30·5%). An attempted reduction by zinc and glacial acetic acid in alcohol was carried out as follows. The chloro-compound (2·6 g.), alcohol (75 c.c.), glacial acetic acid (12·5 c.c.), and zinc powder (7·5 g.) were stirred mechanically at room temperature for 8 hours. After standing overnight, a further quantity of acetic acid (10 c.c.) was added and stirring continued for 8 hours. Excess of zinc was removed by filtration, and the filtrate was poured into water and extracted with chloroform. Evaporation of the dried extract gave a crude product (2·3 g.) which, after recrystallisation from benzene, was shown by mixed m. p. to be identical with the starting material.

Reduction by Hydrazine and Palladium–Strontium Carbonate in Alcohol.—A solution of 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine (1·72 g.) in alcohol (100 c.c.) was boiled for 30 minutes with alcoholic potassium hydroxide (100 c.c.; 10%), palladised strontium carbonate (10 g.; 2%), and hydrazine hydrate (4 c.c.; 50%). Evaporation of alcohol from the filtered solution, and extraction of the residue with benzene, gave 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine (0·7 g.), m. p. 199°.

2 : 4-*Dichloro*-6-*anilino*-1 : 3 : 5-*triazine* (Fierz-David and Matter, *J. Soc. Dyers Col.*, 1937, **53**, 424).—This was prepared from aniline (3·1 g.) in chloroform (15 c.c.) and cyanuric chloride (3·15 g.) in chloroform (40 c.c.). It formed colourless needles (2·78 g.) from benzene–light petroleum (b. p. 60—80°), m. p. 136—137° (Found : N, 23·2; Cl, 29·2. Calc. for $C_9H_6N_4Cl_2$: N, 23·2; Cl, 29·4%).

2-*Chloro*-6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—The above dichloro-compound (2 g.) in chloroform (20 c.c.) was treated gradually with *iso*propylamine (1·4 c.c.) in chloroform (10 c.c.). The *product* (1·35 g.) separated in colourless microcrystals from benzene–light petroleum (b. p. 60—80°), m. p. 127—128° (Found : N, 26·3; Cl, 13·25. $C_{12}H_{14}N_5Cl$ requires N, 26·6; Cl, 13·5%).

Dechlorination by hydrazine and palladised strontium carbonate gave 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. 199°, identical with the product obtained previously.

6-p-*Chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—N^1-*p*-Chlorophenyl-N^5-*iso*propyldiguanide (3·2 g.), methyl alcohol (20 c.c.), and ethyl formate (10 c.c.) were heated under reflux for 1 hour. The *product* separated from the mixture and formed colourless microcrystals from methyl alcohol, m. p. 228° (Found : N, 26·6; Cl, 13·75. $C_{12}H_{14}N_5Cl$ requires N, 26·6; Cl, 13·5%). Dechlorination by hydrazine and palladised strontium carbonate furnished 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. 199°.

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