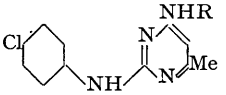
38. *Synthetic Antimalarials. Part XII. Some* 1 : 3 : 5-*Triazine Derivatives.*

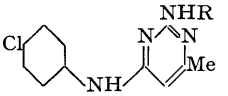
By F. H. S. Curd, J. K. Landquist, and F. L. Rose.

The series of 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines described in Part I (*J.*, 1946, 343), has been extended to corresponding and related 1 : 3 : 5-triazine derivatives. Some of these compounds were prepared by acylation and ring-closure of N^1-aryl-N^5-alkyldiguanides, others by stepwise reaction of cyanuric chloride with aryl- and alkyl-amines. No compound of the series showed antimalarial activity, and the theoretical implications of this are discussed.

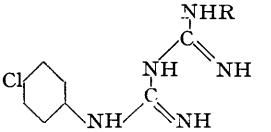
Part I of this series (Curd and Rose, *loc. cit.*) recorded the preparation and discovery of antimalarial activity in substances of which (I; R = $[CH_2]_2{\cdot}NEt_2$) was typical.



(I.)



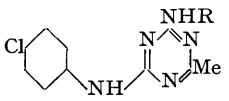
(II.)

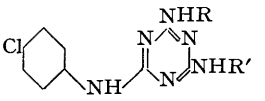


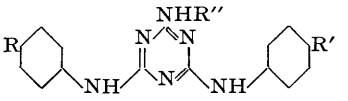
(III.)

Further development of this type has led to still other active structures such as the isomer (II) and the simple diguanides (III; R = alkyl). Consideration of these formulæ suggested the

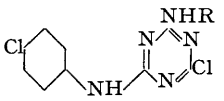
examination of 1 : 3 : 5-triazine analogues, for example, (IV), (V), (VI), and (VII). Not only did these bear an obvious molecular shape relationship to the earlier compounds, but they

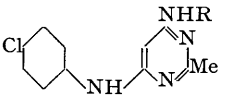

(IV.)


(V.)


(VI.)

appeared at first sight to present those features which we had come to consider essential for positive activity (Part X, Curd and Rose, *J.*, 1946, 729), namely, the existence within the molecule of two independent $-NH-C{=}N-$ systems associated severally with the aryl and the R group. In fact, not one of the many triazine preparations has exhibited any antimalarial

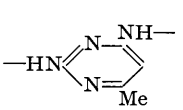

(VII.)

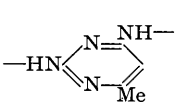

(VIII.)

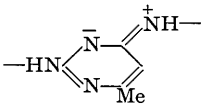
activity, and it is necessary to review our working hypothesis relating structure and biological effect in the light of this result.

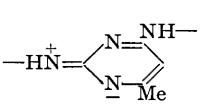
We are not yet prepared to differentiate between the apparent antimalarial significance of prototropic and electromeric phenomena. The amidino-group is such, however, that the two effects are closely interwoven and in the discussion which follows we have confined ourselves to the implications of resonance forms without attempting to define the position of the relevant hydrogen atoms.

On this basis, analysis of the active pyrimidine compounds (I) and (II) shows that, in addition to the Kekulé forms (IX*a*) and (IX*b*), the " independence " of the amidino-groups within the molecules permits the existence of structures such as (IX*c*) and (IX*d*); of these special sig-

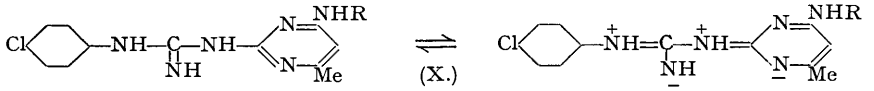

(IX*a*.)

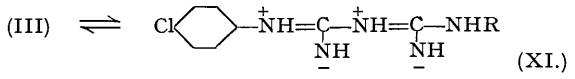

(IX*b*.)


(IX*c*.)


(IX*d*.)

nificance is attached to (IX*d*), in which a conjugated path can be traced through alternate carbon and nitrogen atoms from the one extranuclear nitrogen atom to the other. Similar arrangements can be shown in certain polarised forms of the active guanidinopyrimidine type (X) (Part IV, Curd and Rose, *J.*, 1946, 362) and the diguanide type (XI) (Part X, *loc. cit.*). As with (I) and (II) conjugation extends from the anilino-nitrogen to the nitrogen

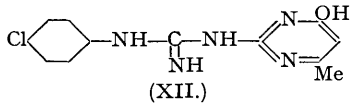

(X.)

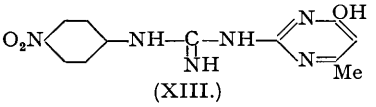

(XI.)

carrying the terminal alkyl group, and we now suggest that it is the contribution of this form to the resonance hybrid that is to be associated with the positive antimalarial activity of these compounds.

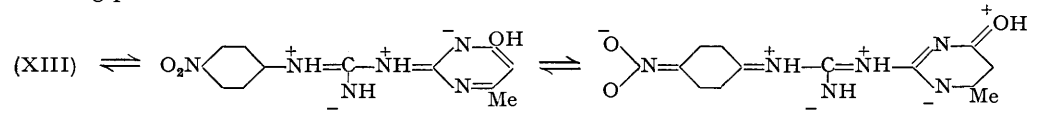
The existence of such structural possibilities should be reflected in physical and chemical behaviour, since a conjugated path of the type found therein might be expected to result in the facile transmission of an electronic effect from the anilino-nitrogen (or even from the benzene ring with which this nitrogen atom is also conjugated) to the terminal alkylamino group. This matter is now engaging our attention, but at present it is possible only to give one item of circumstantial evidence in favour of this view. Drug type (X) was prepared (see Part IV, *loc. cit.*) through the corresponding hydroxypyrimidine (XII). This substance

exhibited the properties of a feeble acid, dissolving somewhat in cold dilute sodium hydroxide. The corresponding *p*-nitrophenyl derivative (XIII) appeared to be a stronger acid giving a

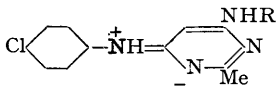

(XII.)

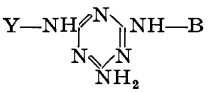

(XIII.)

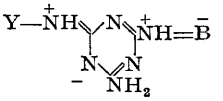
golden-yellow sodium salt. Both colour and increased acidity might be expected if the following processes were facile :



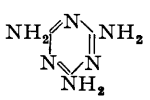
Examination of the inactive pyrimidine type (VIII) shows that the interdependence of the two amidine systems within the molecule (Part VIII, Basford, Curd, and Rose, *J.*, **1946**, 713) prevents the formation of a structure exhibiting the therapeutically significant features of the active substances. In this instance a fully conjugated path between the extranuclear atoms cannot be constructed through alternate nitrogen and carbon atoms, but only through C_4, C_5, and C_6 of the pyrimidine ring (XIV). Consideration on the same basis of the 1 : 3 : 5-triazine structures (IV), (V), (VI), and (VII) is difficult at this stage, but here again some

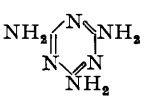

(XIV.)

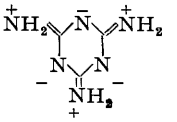

(XV.)

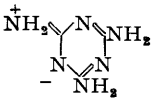

(XVI.)

circumstantial evidence is available to suggest how these structures might be expected to behave. Thus, the 1 : 3 : 5-triazine ring is well known in colour chemistry to function as a " chromophoric block ", that is to say, a dye molecule of type (XV) in which (Y) and (B) represent the terminal groupings of yellow and blue dye components, respectively, will produce a green shade not dissimilar from that obtained by a physical mixture of the two units. Accepting the current view that the colour of organic dyes is closely connected with resonance (see Pauling, " Gilman's Organic Chemistry ", New York, 1943, Chap. 26), this would suggest that asymmetrical structures such as (XVI), whose existence would have to be admitted in

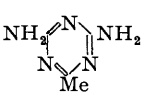

(XVII*a*.)

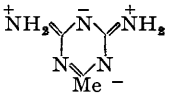

(XVII*b*.)

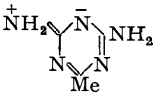

(XVII*c*.)

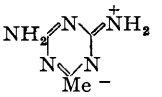

(XVII*d*.)

the event of any observed mixing of the chromophoric systems, contribute little to the colour resonance hybrid. Further, Hughes (*J. Amer. Chem. Soc.*, **1941**, **63**, **1737**), from *X*-ray studies on the crystal structure of melamine, concludes that the three principal structures are (XVII*a*), (XVII*b*), and (XVII*c*), with only minor contributions from the asymmetrical forms such as (XVII*d*). This would accord with the mechanism of the chromophoric block effect suggested in the case of the dye (XV). It might be anticipated therefore that drug structures based on (V) and (VI) would be inactive since the asymmetric disposition of bonds necessary to give an arrangement analogous to that of (IX*d*) in the biologically active pyrimidine series


(XVIII*a*.)


(XVIII*b*.)

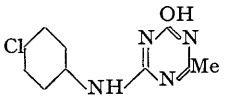

(XVIII*c*.)

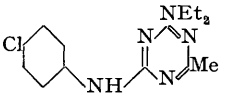

(XVIII*d*.)

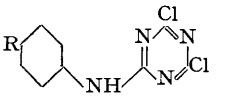
(that is, necessary to provide conjugation through alternate carbon and nitrogen atoms) is unlikely. On the other hand, 2 : 4-diamino-6-methyltriazine (XVIII*a*), of which (IV) is a

derivative, cannot provide a structure analogous to (XVII*c*), the nearest approach being (XVIII*b*). If this asymmetrical arrangement is permissible then there would appear to be less reason for excluding the possible existence of the other asymmetrical forms (XVIII*c*) and (XVIII*d*) which exhibit those structural features tentatively suggested as necessary for antimalarial activity. These points can only be settled with the aid of precise physical data relating to the resonance states of these substances, and until these are available it is not possible to say whether the biological results obtained with the triazine drugs support or invalidate our postulates.

The methods tried for the preparation of the triazine derivatives (IV) were (*a*) acetylation and ring-closure of (III), (*b*) replacement of the hydroxyl group of (XIX), itself obtained from acetic anhydride and *p*-chlorophenyldicyandiamide (compare the preparation of acetoguan-

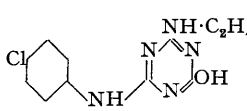

(XIX.)

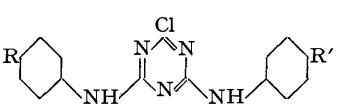

(XX.)

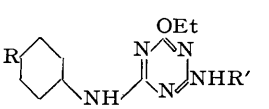

(XXI.)

amine, Andreasch, *Monatsh.*, 1927, **48**, 145) by halogen and subsequent interaction with amines, and (*c*) interaction of (IV; R = H) with amines, *e.g.*, $Et_2N{\cdot}[CH_2]_n{\cdot}NH_2$, with loss of ammonia. The requisite diguanides (III; R = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) for method (*a*) were described in Part X (*loc. cit.*); by successive treatment with acetic anhydride and alcoholic sodium hydroxide they gave the corresponding triazines (IV). The nature of the initial condensates with acetic anhydride was not investigated since they could not be obtained solid for characterisation, but in a parallel experiment starting with (III; R = H), the product at this stage analysed as (IV; R = Ac) and dissolved in alcoholic sodium hydroxide, presumably as a sodium salt, with the almost immediate deposition of the de-acetylated compound (IV; R = H). The related (XX) was formed analogously from the corresponding N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide. Method (*b*) was successful as far as (XIX), but attempts to replace hydroxyl by chlorine failed. Similarly, no condensation took place by method (*c*) with temperatures up to 170°.

The remaining compounds were obtained starting with cyanuric chloride. The stepwise reaction of this compound with aniline to give (XXI; R = H) has been described by Fierz-David and Matter (*J. Soc. Dyers and Col.*, 1937, **53**, 424). By the same method (XXI; R = Cl) and (XXI; R = OMe) were made. (XXI; R = Cl) reacted with *iso*propylamine, β-diethylaminoethylamine, or αγ-bisdiethylamino*iso*propylamine in warm acetone to give {VII; R = Pr^{β}, $[CH_2]_2{\cdot}NEt_2$, or $CH(CH_2{\cdot}NEt_2)_2$}, and interaction of this secondary product at 100° with ammonia gave {V; R = Pr^{β}, $[CH_2]_2{\cdot}NEt_2$, or $CH(CH_2{\cdot}NEt_2)_2$ R′ = H}, and with *p*-chloroaniline gave (VI; R = R′ = Cl; R″ = $[CH_2]_2{\cdot}NEt_2$). In a similar manner (XXI; R = H) and (XXI; R = OMe) reacted successively with β-diethylaminoethylamine and ammonia to give compounds analogous to (VII; R = $[CH_2]_2{\cdot}NEt_2$) and (V; R = $[CH_2]_2{\cdot}NEt_2$, R′ = H). Boiling 2N-hydrochloric acid hydrolysed the secondary product (VII; R = $[CH_2]_2{\cdot}NEt_2$) to (XXII). *p*-Chloroaniline or *p*-anisidine reacted with (XXI; R = Cl or OMe)

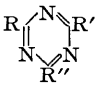

(XXII.)


(XXIII.)


(XXIV.)

in benzene at 80° to give the 2 : 4-diarylamino-6-chloro-1 : 3 : 5-triazine (XXIII; R = R′ = Cl or OMe) and in one experiment some 2 : 4 : 6-triarylamino-1 : 3 : 5-triazine (VI; R = R′ = OMe, R″ = *p*-C_6H_4Cl). With ammonia in ethanol at 120—140° (XXIII; R = R′ = Cl or OMe) gave the melamine derivative (VI; R = R′ = Cl or OMe, R″ = H), but with β-diethylaminoethylamine in ethanol at 120—140° (XXIII; R = R′ = OMe) gave the ethoxy-derivative (XXIV, R = OMe, R′ = *p*-$C_6H_4{\cdot}OMe$). An ethoxy-compound (XXIV; R = Cl, R′ = Pr^{β}) was also obtained when (VII; R = Pr^{β}) reacted similarly with *iso*propylamine.

Compounds Tested for Antimalarial Activity.—Antimalarial activity was determined by the method described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139) against *P. gallinaceum* in the chick.

General formula : 

Ref. No.	R.	R′.	R″	Dose, mg./kg.	Activity.
3492	$Cl\cdot C_6H_4\cdot NH$	$Et_2N\cdot[CH_2]_3\cdot NH$	Me	100	—
3919	,,	$Et_2N\cdot[CH_2]_2\cdot NH$	,,	80	—
3469	,,	,,	Cl	300	—
3667	,,	,,	NH_2	100	—
3689	,,	,,	OH	500	—
5354	,,	,,	$Cl\cdot C_6H_4\cdot NH$	120	—
5232	,,	$(Et_2N\cdot CH_2)_2CH\cdot NH$	Cl	240	—
5237	,,	,,	NH_2	120	—
3468	$Ph\cdot NH$	$Et_2N\cdot[CH_2]_2\cdot NH$	Cl	200	—
3559	,,	,,	NH_2	150	—
3670	$MeO\cdot C_6H_4\cdot NH$	,,	Cl	200	—
3343	$Cl\cdot C_6H_4\cdot NH$	NH_2	Me	200	—
4176	,,	NEt_2	,,	400	—
5200	,,	$NHPr^{\beta}$	Cl	80	—
5228	,,	,,	NH_2	120	—
5292	,,	,,	OEt	240	—
3875	,,	$Cl\cdot C_6H_4\cdot NH$	NH_2	400	—
3874	,,	$MeO\cdot C_6H_4\cdot NH$	,,	400	—
3766	,,	,,	$MeO\cdot C_6H_4\cdot NH$	400	—
3541	NH_2	,,	,,	100	—

Experimental.

2-p-*Chloroanilino*-6-*acetamido*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = Ac).—*p*-Chlorophenyldiguanide (10 g.) and acetic anhydride (25 c.c.) were heated at 100° for 1 hour. Water (100 c.c.) was added and the solid *product* collected, recrystallised successively from β-ethoxyethanol and glacial acetic acid, washed with ethanol, and dried at 100°, giving 1·7 g., m. p. 269—271° (Found : C, 51·3; H, 4·0; N, 24·7. $C_{12}H_{12}ON_5Cl$ requires C, 51·9; H, 4·3; N, 25·2%).

6-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = H).—The above acetyl derivative (3·7 g.) was heated with methanol (50 c.c.) and 10N-sodium hydroxide (5 c.c.) added. The initial solution rapidly deposited crystals which were collected and recrystallised from butanol, giving the *base* as colourless needles, m. p. 195—196° (Found : N, 29·2. $C_{10}H_{10}N_5Cl$ requires N, 29·6%). The two stages were conveniently combined for the preparation of larger amounts by warming into solution a mixture of *p*-chlorophenyldiguanide hydrochloride (46 g.), dioxan (100 c.c.), 10N-sodium hydroxide (50 c.c.), and water (50 c.c.) and cautiously stirring in acetic anhydride (40 c.c.). Restoring alkalinity with more sodium hydroxide and adding water (700 c.c.) precipitated 40 g. of a nearly pure product, m. p. 191°.

2-p-*Chloroanilino*-6-β-*diethylaminoethylamino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = $[CH_2]_2\cdot NEt_2$) (3919). —N^1-*p*-Chlorophenyl-N^5-β-diethylaminoethyldiguanide (9 g.) and acetic anhydride (25 c.c.) were refluxed for 1 hour, diluted with water (150 c.c.), and made alkaline with sodium hydroxide. The precipitated oil was washed with water by decantation and boiled for 3 minutes in methanol (90 c.c.) and 10N-sodium hydroxide (9 c.c.). On adding water (150 c.c.) the crude *triazine* crystallised out and after drying gave colourless needles (5·2 g.) from light petroleum (b. p. 100—120°), m.p. 145—146° (Found : C, 57·35; H, 6·7; N, 24·3. $C_{16}H_{23}N_6Cl$ requires C, 57·3; H, 6·9; N, 25·1%).

2-p-*Chloroanilino*-6-γ-*diethylaminopropylamino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = $[CH]_3\cdot NEt_2$) (3492). —Similarly prepared from N_1-*p*-chlorophenyl-N_5-γ-diethylaminopropyldiguanide (5 g.) and acetic anhydride (12·5 c.c.), the *triazine* formed colourless crystals from light petroleum (b. p. 100—120°), m. p. 125° (Found : C, 57·8; H, 7·0; N, 23·8. $C_{17}H_{25}N_6Cl$ requires C, 58·5; H, 7·1; N, 24·1%).

2-p-*Chloroanilino*-6-*diethylamino*-4-*methyl*-1 : 3 : 5-*triazine* (XX) (4176).—Similarly prepared from N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide, the *triazine* formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 112° (Found : C, 58·2; H, 6·4; N, 23·6. $C_{14}H_{18}N_5Cl$ requires C, 57·6; H, 6·15; N, 24·0%).

2-p-*Chloroanilino*-4-*hydroxy*-6-*methyl*-1 : 3 : 5-*triazine* (XIX).—*p*-Chlorophenyldicyandiamide (10 g.) and acetic anhydride (20 c.c.) were heated for 10 minutes under reflux and cooled, and the product (3·75 g.) was filtered off and washed with acetic acid. The *triazine* gave crystals from acetic acid, m. p. 341—344° (Found : C, 50·5; H, 4·1; N, 23·5; Cl, 14·3. $C_{10}H_9ON_4Cl$ requires C, 50·7; H, 3·8; N, 23·65; Cl, 15·0%). A *dihydrate*, m. p. 292—294°, was obtained by dissolving in sodium hydroxide solution and precipitating with acetic acid; it crystallised unchanged from dimethylformamide but gave the anhydrous compound, m. p. 340°, when crystallised from acetic acid (Found : C, 44·7; H, 4·1; N, 20·1; Cl, 12·4. $C_{10}H_9ON_4Cl,2H_2O$ requires C, 43·9; H, 4·75; N, 20·5; Cl, 13·0%).

2 : 4-*Dichloro*-6-p-*chloroanilino*-1 : 3 : 5-*triazine* (XXI; R = Cl).—Cyanuric chloride (30·75 g.) dissolved in benzene (400 c.c.) was stirred below 10° and *p*-chloroaniline (42·5 g.) dissolved in benzene (250 c.c.) added dropwise. The mixture was stirred for 1 hour at 20°. The precipitated *triazine* was collected, stirred with 2N-hydrochloric acid (250 c.c.), filtered off, and washed with water until free from *p*-chloroaniline hydrochloride. The residual solid (36 g.) melted at 184—186° (evaporation of the benzene mother liquors yielded a further 8·25 g., m. p. 180—184°) and gave colourless needles from benzene, m. p. 185—186° (Found : N, 20·2; Cl, 37·8. $C_9H_5N_4Cl$ requires N, 20·35; Cl, 38·65%).

2 : 4-*Dichloro*-6-p-*anisidino*-1 : 3 : 5-*triazine* (XXI; R = OMe).—Similarly prepared from cyanuric

chloride and *p*-anisidine, the *triazine* formed colourless needles from benzene, m. p. 168—170° (Found : Cl, 25·8. $C_{10}H_8ON_4Cl_2$ requires Cl, 26·2%).

2-*Chloro*-4-*anilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3468).—2 : 4-Dichloro-6-anilino-1 : 3 : 5-triazine (12·1 g.) in acetone (30 c.c.) was mixed with *β*-diethylaminoethylamine (5·4 g.) in acetone (20 c.c.). After the initial reaction the mixture was boiled under reflux for 30 minutes. The white microcrystalline *hydrochloride* (12·5 g.) was filtered off and washed with acetone; it gave flat microscopic needles from water, m. p. 156° (Found : C, 47·95; H, 6·6; N, 22·0; Cl, 19·0. $C_{15}H_{21}N_6Cl,HCl,H_2O$ requires C, 48·0; H, 6·4; N, 22·4; Cl, 18·95%). The free base gave plates from ethanol, m. p. 150—151°.

2-*Chloro*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (VII; R = $[CH_2]_2{\cdot}NEt_2$) (3469).—Prepared from 2 : 4-dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine and *β*-diethylaminoethylamine, the *triazine* gave irregular white platelets from benzene, m. p. 174—175° (Found : N, 23·0; Cl, 18·5. $C_{15}H_{20}N_6Cl_2,H_2O$ requires N, 22·55; Cl, 19·05%). The *hydrochloride* gave colourless prisms from water, m. p. 228° (Found : C, 45·9; H, 5·5; N, 21·3; Cl, 27·0. $C_{15}H_{20}N_6Cl_2,HCl$ requires C, 46·0; H, 5·35; N, 21·45; Cl, 27·2%).

2-*Chloro*-4-p-*anisidino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3670).—Prepared similarly, this thiazine gave the *hydrochloride* as colourless crystals from water, m. p. 120—121° (Found : C, 46·9; H, 6·5; N, 20·1; Cl, 17·4. $C_{16}H_{23}ON_6Cl,HCl,H_2O$ requires C, 47·3; H, 6·4; N, 20·75; Cl, 17·55%).

2-*Chloro*-4-p-*chloroanilino*-6-*αγ*-*bisdiethylamino*iso*propylamino*-1:3:5-*triazine* [VII; R=$CH(CH_2{\cdot}NEt_2)_2$] (5232).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (7 g.) and *αγ*-bisdiethylamino*iso*propylamine (5 g.) were refluxed with acetone (30 c.c.) for 30 minutes. The *monohydrochloride* separated as a white crystalline powder, m. p. 199—200° (Found : Cl, 21·5; Cl′, 7·0. $C_{20}H_{31}N_7Cl_2,HCl,H_2O$ requires Cl, 21·6; Cl′, 7·2%). The *base* gave white prisms, m. p. 156°, from benzene (Found : N, 22·2; Cl, 15·6. $C_{20}H_{31}N_7Cl_2$ requires N, 22·25; Cl, 16·15%).

2-*Chloro*-4-p-*chloroanilino*-6-iso*propylamino*-1 : 3 : 5-*triazine* (VII; R = Pr*β*) (5200).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (14 g.), *iso*propylamine (5 c.c.), and acetone (65 c.c.) refluxed for 30 minutes, filtered from insoluble matter, and diluted with N/2-sodium hydroxide solution (200 c.c.), formed a gum which hardened on rubbing and gave colourless prisms of the *triazine* from benzene, m. p. 164—166° (Found : N, 22·5; Cl, 23·2. $C_{12}H_{13}N_5Cl_2$ requires N, 23·5; Cl, 23·8%).

2-*Amino*-4-*anilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3559).—2-Chloro-4-anilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (5 g.) and alcoholic ammonia (40 c.c.) were heated at 120—140° in a sealed tube for 5 hours. Dilution with water (100 c.c.) gave colourless crystals of the *triazine*, m. p. 128—129°, unchanged after crystallisation from benzene (Found : C, 59·0; H, 7·6; N, 32·5. $C_{15}H_{23}N_7$ requires C, 59·7; H, 7·65; N, 32·5%).

2-*Amino*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (V; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$) (3667).—Similarly prepared, the *triazine* formed micro-crystals from light petroleum (b. p. 100—120°), m. p. 136—137° (Found : C, 54·0; H, 6·7; N, 28·1. $C_{15}H_{22}N_7Cl$ requires C, 53·6; H, 6·55; N, 29·2%).

2-*Amino*-4-p-*chloroanilino*-6-*αγ*-*bisdiethylamino*iso*propylamino*-1 : 3 : 5-*triazine* [V; R = H, R′ = $CH(CH_2{\cdot}NEt_2)_2$] (5237).—Similarly prepared, the *triazine* formed colourless crystals from benzene–ligroin, m. p. 132° (Found : C, 57·3; H, 7·8; N, 26·3. $C_{20}H_{33}N_8Cl$ requires C, 57·0; H, 7·85; N, 26·6%).

2-*Amino*-4-p-*chloroanilino*-6-iso*propylamino*-1 : 3 : 5-*triazine* (V; R = H, R′ = Pr*β*) (5228).—Similarly prepared, this thiazine gave the *hydrochloride* from water, m. p. 232—234° (Found : N, 25·3; Cl, 21·0. $C_{12}H_{15}N_6Cl,HCl,H_2O$ requires N, 25·2; Cl, 21·35%).

2-p-*Chloroanilino*-4-*β*-*diethylaminoethylamino*-6-*hydroxy*-1 : 3 : 5-*triazine* (XXII) (3689).—2-Chloro-4-*p*-chloroanilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (5 g.) and 4N-hydrochloric acid (30 c.c.) were refluxed for 4 hours and then filtered. Cooling gave the *dihydrochloride* in needles, m. p. 262—264° (Found : C, 40·2; H, 6·0; N, 19·9; Cl, 23·9. $C_{15}H_{21}ON_6Cl,2HCl,2H_2O$ requires C, 40·3; H, 6·05; N, 18·85; Cl, 23·9%).

2 : 4-*Di*-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (VI; R = R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$) (5354).—2-Chloro-4-*p*-chloroanilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (4 g.), *p*-chloroaniline (1·3 g.), water (20 c.c.), and concentrated hydrochloric acid (0·1 c.c.) were refluxed for 90 minutes. The precipitate of *dihydrochloride* which formed gave colourless crystals from water, m. p. 116—119° (after drying at 100° in vacuum, m. p. 150—154°) (Found : Cl, 26·1; Cl′, 12·7; H_2O, 6·6. $C_{21}H_{25}N_7Cl_2,2HCl,H_2O$ requires Cl, 25·55; Cl′, 12·8; H_2O, 6·5%).

2-*Amino*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine* (VI; R = R′ = Cl, R″ = H) (3875).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (10 g.), *p*-chloroaniline (9 g.), and benzene (350 c.c.) were refluxed for 3 hours. The precipitate of 2-*chloro*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine* (XXIII, R = R′ = Cl) which formed on cooling was lixiviated with dilute hydrochloric acid to remove *p*-chloroaniline. The residue gave colourless prisms from benzene, m. p. 223° (Found : Cl, 27·7. $C_{15}H_{10}N_5Cl_3$ requires Cl, 29·0%). The product (3·7 g.) without further purification, and alcoholic ammonia (25 c.c.) were heated at 120—140° for 3 hours. The precipitate, water washed, dissolved in boiling ethanol (250 c.c.), and treated with charcoal gave on addition of concentrated hydrochloric acid 2-*amino*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine hydrochloride*, m. p. 276—279° (Found : N, 21·6; Cl, 27·8. $C_{15}H_{12}N_6Cl_2,HCl$ requires N, 21·9; Cl, 27·8%).

2-*Amino*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine* (VI; R = R′ = OMe, R″ = H) (3541).—*p*-Anisidine and 2 : 4-dichloro-6-*p*-anisidino-1 : 3 : 5-triazine brought into reaction as above in boiling benzene gave colourless platelets of 2-*chloro*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine* (XXIII; R = R′ = OMe) from benzene, m. p. 197—199° (Found : Cl, 9·5. $C_{17}H_{16}O_2N_5Cl$ requires Cl, 9·95%). This, without further purification, reacted with alcoholic ammonia to give a base, m. p. 202—203° from benzene. The *hydrochloride* crystallised from ethanol–hydrochloric acid, m. p. 277° (Found : C, 52·4; H, 5·3; N, 21·1. $C_{17}H_{18}O_2N_6,HCl,H_2O$ requires C, 51·9; H, 5·35; N, 21·4%).

2-*Amino*-4-p-*chloroanilino*-6-p-*anisidino*-1 : 3 : 5-*triazine* (VI; R = Cl, R′ = OMe, R″ = H) (3874).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (9·2 g.), *p*-anisidine (8·2 g.), and benzene (200 c.c.) were stirred at room temperature for 1·5 hours, then refluxed for 1 hour and filtered hot. 2-*Chloro*-4-p-*chloroanilino*-6-p-*anisidino*-1 : 3 : 5-*triazine* (XXIII; R = Cl, R′ = OMe) crystallised from the filtrate

as colourless prisms, m. p. 186° (Found : Cl, 18·3. $C_{16}H_{13}ON_5Cl_2$ requires Cl, 19·6%). The same substance was obtained from 2 : 4-dichloro-6-*p*-anisidino-1 : 3 : 5-triazine and *p*-chloroaniline. It was used in the next stage without further purification. The material insoluble in hot benzene was lixiviated with dilute hydrochloric acid and the residue of 2-p-*chloroanilino*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine hydrochloride* (VI; R = R′ = OMe, R″ = C_6H_4Cl) (3766) gave colourless crystals from acetic acid, m. p. 261° (Found : C, 54·6; H, 4·6; N, 16·7. $C_{23}H_{21}O_2N_6Cl,HCl,H_2O$ requires C, 54·8; H, 4·65; N, 16·7%). 2-Chloro-4-*p*-chloroanilino-6-*p*-anisidino-1 : 3 : 5-triazine and alcoholic ammonia gave 2-amino-4-*p*-chloroanilino-6-*p*-anisidino-1 : 3 : 5-triazine isolated as the *hydrochloride*, m. p. 259—261° (Found : N, 20·3; Cl, 17·65. $C_{16}H_{15}ON_6Cl,HCl,H_2O$ requires N, 20·3; Cl, 17·1%).

2 : 4-*Di*-p-*anisidino*-6-*ethoxy*-1 : 3 : 5-*triazine* (XXIV; R = OMe, R′ = C_6H_4·OMe).—2-Chloro-4 : 6-di-*p*-anisidino-1 : 3 : 5-triazine (3·6 g.), β-diethylaminoethylamine (1·16 g.), and absolute alcohol (30 c.c.) were heated in a sealed tube at 120—140° for 3 hours. The reaction product gave the *hydrochloride*, m. p. 252—253°, from acetic acid–hydrochloric acid (Found : C, 56·1; H, 5·4; N, 16·4; Cl′, 8·4. $C_{19}H_{21}O_3N_5,HCl$ requires C, 56·5; H, 5·45; N, 17·4; Cl′, 8·8%).

2-p-*Chloroanilino*-4-iso*propylamino*-6-*ethoxy*-1 : 3 : 5-*triazine* (XXIV; R = Cl, R′ = Pr^{β}) (5292).—2-Chloro-4-*p*-chloroanilino-6-*iso*propylamino-1 : 3 : 5-triazine (6 g.), absolute alcohol (20 c.c.), and *iso*propylamine (3·5 c.c.) were heated in a sealed tube at 120—140° for 3 hours. The crystalline precipitate, washed with ethanol and water, gave colourless crystals from benzene–light petroleum or aqueous ethanol, m. p. 163—164° (Found : C, 54·6; H, 6·1; Cl, 11·5. $C_{14}H_{16}ON_5Cl$ requires C, 54·55; H, 5·85; Cl, 11·6%).

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[*Received, June 3rd,* 1946.]