Triazines and Related Products. Part VI.[1] Synthesis and Properties of 4-Amino-2(2*H*)-imino-*s*-triazino[1,2-*c*][1,2,3]-benzotriazines

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2,4-Diamino-6-aryl-*s*-triazines (III) have been prepared for examination as potential tumour-inhibitory agents. 2,4-Diamino-6-(2-aminophenyl)-*s*-triazines (IV) react with formic acid and triethyl orthoformate to form the formylaminophenyl- and ethoxymethyleneaminophenyl-*s*-triazines respectively, but in formamide 4-aminoquinazolines are produced. Diazotisation of the amines (IV) afforded in certain instances stable diazonium salts (X) which cyclised in base to derivatives of *s*-triazino[1,2-*c*][1,2,3]benzotriazine (XI). Replacement of the diazo-group in the *s*-triazinobenzotriazines (XI) by hydrogen, and by amino-, chloro-, hydroxy- and azonaphthol substituents demonstrates the similarity between the chemical properties of 1,2,3-benzotriazines and diazonium compounds. Reduction of the *s*-triazinobenzotriazines with stannous chloride in ethanol yielded *s*-triazino-[1,2-*b*]indazoles (XIV), which were also formed by cyclo-deamination of the hydrazines (XV) and by thermolysis of the azides (XVII). The *s*-triazinobenzotriazenes decompose homolytically in boiling nitrobenzene to afford a mixture of isomeric nitrobiphenyls: the mass spectra of the isomers are discussed.

DIAZO- AND DIAZONIUM COMPOUNDS have found wide applicability in many industrial processes,[2] but their biological properties have been little studied. Although the great chemical reactivity of diazonium compounds would appear to give them the potentiality for versatile interactions with biological substrates, their associated instability could create formidable toxicity and formulation problems. Such disadvantages can be partially overcome in the triazene and 1,2,3-benzotriazine series, since it is well known that these compounds behave as 'masked' diazonium compounds and undergo many of the heterolytic and homolytic decompositions charac-

[1] Part V, H. N. E. Stevens and M. F. G. Stevens, preceding paper.

[2] H. Zollinger, 'Diazo and Azo Chemistry,' Interscience, New York, 1961; M. S. Dinaburg, 'Photosensitive Diazo Compounds,' Focal Press, London, 1964; K. H. Saunders, 'The Aromatic Diazo Compounds,' Edward Arnold, London, 1947.

teristic of diazonium compounds.[3-6] Recently the cytotoxicity of triazenes and fused 1,2,3-triazines has attracted interest.[7]

Certain 2,4-diaminopyrimidine [8-10] and 2,4-diamino-*s*-triazine [11] derivatives exhibit selective toxicity to micro-organisms and proliferating cells which reflect their ability to complex reversibly with the enzyme dihydrofolate reductase. Baker [10] has delineated the extent of a hydrophobic bonding region in or near the active site of this enzyme which is important in substrate–enzyme association. Derivatives of the hitherto unknown ring-system *s*-triazino[1,2-*c*][1,2,3]benzotriazine are of interest since they could complex reversibly to the active site of dihydrofolate reductase both at the ionic or H-bonding locus and at the hydrophobic region (possibly as depicted in Figure 1). Although it has been shown that 2,4-diamino-6-phenyl-*s*-triazine is a much poorer reversible inhibitor of the enzyme than the

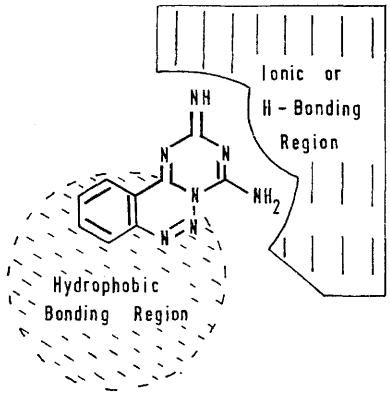
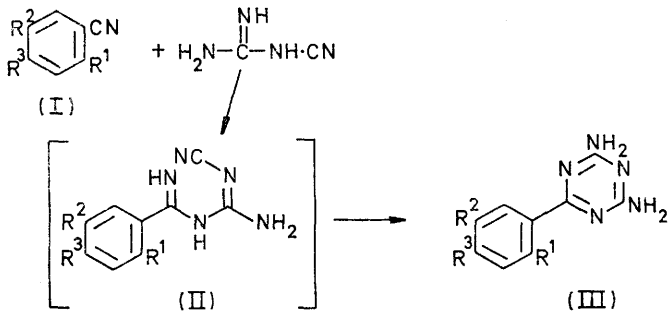


FIGURE 1 Possible mode of binding between the active site of dihydrofolate reductase and 4-amino-2(2*H*)-imino-*s*-triazino-[1,2-*c*][1,2,3]benzotriazine.

corresponding 2,4-diamino-6-phenylpyrimidine,[11] weak hydrophobic bonding in the 1,2,3-benzotriazine could be augmented by covalent interaction between the ' masked diazonium ' group and a suitably reactive site on the enzyme surface; this site could be hydrophilic or hydrophobic in character because 1,2,3-benzotriazines decompose to give diazonium or carbonium ions *or* radicals depending on the nature of the substrate.

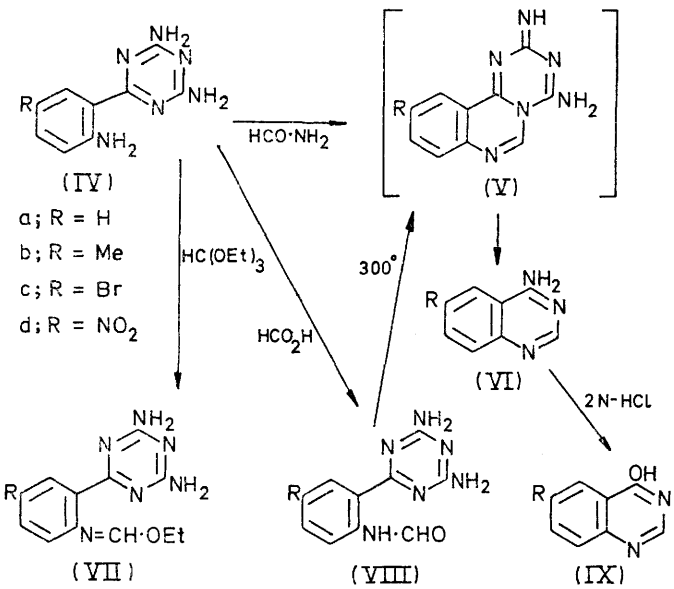
Here we describe the synthesis and properties of some *s*-triazino[1,2-*c*][1,2,3]benzotriazine derivatives which



SCHEME 1

were required for examination of their tumour-inhibitory properties.

The 2,4-diamino-6-(2-aminophenyl)-*s*-triazines required for this work were readily prepared from the



SCHEME 2

corresponding anthranilonitriles (I; $R^1 = NH_2$, R^2 = H, Me, Br, or NO_2, R^3 = H) and cyanoguanidine in boiling 2-ethoxyethanol containing potassium hydroxide (Scheme 1).[12] This route has wide applicability in the synthesis of 2,4-diamino-6-aryl-*s*-triazines, and the compounds prepared by this route are listed in the Table; none of the intermediate guanidines (II) were isolated.

[3] J. G. Erickson, ' The 1,2,3-Triazines ' in ' The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, 1956, vol. 10.

[4] M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1967, 1096.

[5] M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1968, 348.

[6] H. N. E. Stevens and M. F. G. Stevens, Part III, *J. Chem. Soc.* (*C*), 1970, 765.

[7] D. A. Clarke, R. K. Barclay, C. C. Stock, and C. S. Rondestvedt, *Proc. Soc. Exp. Biol. Med.*, 1955, **90**, 484; J. H. Burchenal, M. K. Dagg, M. Beyer, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, 1956, **91**, 398; C. S. Rondestvedt and S. J. Davis, *J. Org. Chem.*, 1957, **22**, 200; G. A. Usbeck, J. W. Jones, and R. K. Robins, *J. Amer. Chem. Soc.*, 1961, **83**, 1113; C. C. Cheng, R. K. Robins, K. C. Cheng, and D. C. Lin, *J. Pharm. Sci.*, 1968, **57**, 1044; Y. F. Shealy, C. A. Krauth, S. J. Clayton, A. T. Shortnacy, and W. R. Laster, *ibid.*, p. 1562, and references therein; T. L. Loo, B. B. Tanner, G. E. Housholder, and B. J. Shepard, *ibid.*, p. 2126; T. L. Loo, J. K. Luce, J. H. Jardine, and E. Frei, *Cancer Research*, 1968, **28**, 2448; C. W. Noell and C. C. Cheng, *J. Medicin. Chem.*, 1969, **12**, 545; R. Preussmann, A. von Hodenberg, and H. Hengy, *Biochem. Pharmacol.*, 1969, **18**, 1; J. A. Montgomery and H. J. Thomas, *Chem. Comm.*, 1969, 458.

[8] G. H. Hitchings and J. J. Burchall, *Adv. Enzymol.*, 1965, **27**, 417.

[9] B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings, M. Barnett, and S. R. M. Bushby, *J. Medicin. Chem.*, 1968, **11**, 711.

[10] B. R. Baker, ' Design of Active-Site-Directed Irreversible Enzyme Inhibitors,' John Wiley, New York, 1967.

[11] B. R. Baker and Beng-Thong Ho, *J. Heterocyclic. Chem.*, 1965, **2**, 340.

[12] B. P. 908,301/1962.

However with certain nitriles this procedure failed to realise the expected *s*-triazine derivatives. For example the chloronitronitrile (I; $R^1 = Cl$, $R^2 = NO_2$, $R^3 = H$) was recovered unchanged when boiled with cyanoguanidine and potassium hydroxide in 2-ethoxyethanol, ethylene glycol, or dimethyl sulphoxide; the use of piperidine as solvent and base similarly failed to effect cyclisation. No recognisable products could be isolated from the nitromethylnitrile (I; $R^1 = NO_2$, $R^2 = Me$, $R^3 = H$) or the azidonitrile (I; $R^1 = N_3$, $R^2 = R^3 = H$) under the general reaction conditions; in the latter example this was due presumably to decomposition of the azidonitrile in the basic conditions.[13] Although the (IVa—d) to the *s*-triazino[1,2-*c*]quinazolines (Va—d) by conventional agents were unsuccessful. *s*-Triazine has been used as an agent in related heterocyclic syntheses,[15] but the aminophenyl-*s*-triazines were unreactive towards this reagent. The ethoxymethylene derivatives (VIIa and b) were formed from the amines (IVa and b) and triethyl orthoformate, but the amines (IVc and d) were recovered unchanged after being boiled for a prolonged period in this reagent. The formylamines (VIIIa and c) were formed in good yields from the amines (IVa and c) respectively and boiling 100% formic acid. Surprisingly, vacuum sublimation (300° at 5 mmHg) of the formylamines (VIIIa and c) yielded the aminoquinazolines

Preparation of 6-aryl-2,4-diamino-*s*-triazines (III)

Compound (III)						Found (Required)		
R^1	R^2	R^3	Yield	M.p.	Molecular formula	C	H	N
H	H	H	95	230—232° [a]				
NO_2	H	H	70	233—236 [b]				
H	NO_2	H	45	322—323 [c]				
H	H	NO_2	65	341—342 [d]				
H	H	NH_2	55	185—187 [e]				
H	Me	H	80	246—247 [f]				
H	Br	H	95	233—235 [g]	$C_9H_8BrN_5$	40·8 (40·6)	3·3 (3·0)	29·8 (30·0)
Cl	H	H	90	225—227 [g]	$C_9H_8ClN_5$	49·2 (48·8)	4·0 (3·6)	31·9 (31·6)
CN	H	H	95	228—230 [h]				
$C_6H_4{\cdot}NO_2$-*o*	H	H	75	198—200(eff.) [i]	$C_{15}H_{12}N_6O_2$	58·5 [j,k] (58·4)	4·2 (3·9)	27·1(27·3)
$C_6H_4{\cdot}NO_2$-*m*	H	H	60	218—220(eff.) [g]	$C_{15}H_{12}N_6O_2$	*k*, *l*		
$C_6H_4{\cdot}NO_2$-*p*	H	H	85	204—205 [m]	$C_{15}H_{12}N_6O_2$	*k*, *l*		
2,4-Diamino-*s*-triazin-6-yl	H	H	70	350—360 [n]				
NH_2	Me	H	63	233—236 [p]	$C_{10}H_{12}N_6$	55·3 (55·5)	5·9 (5·6)	39·0 (38·9)
NH_2	Br	H	60	281—283 [q]	$C_9H_9BrN_6$	38·8 (38·4)	3·6 (3·2)	30·0 (29·9)
Dihydrochloride [r]			95	288—292 [s]	$C_9H_9BrN_6,2HCl$	30·8 (30·5)	3·4 (3·1)	23·9 (23·7)
NH_2	NO_2	H	82	over 350 [t]	$C_9H_9N_7O_2$	*l*		

[a] U.S.P. 2,302,162/1942, m.p. 222°. [b] V. A. Titkov and I. D. Pletnev, *Zhur. obshchei Khim.*, 1963, **33**, 1983, m.p. 234—236°. G.P. 1,151,613 (*Chem. Abs.*, 1964, **60**, 6963), m.p. 315—318°. [c] See footnote (*b*), m.p. 330—331°. [d] Ref. 12, m.p. 185—187°. [e] A. Ostrogovich and G. Gheorghiu, *Gazzetta*, 1930, **60**, 648 (*Chem. Abs.*, 1931, **25**, 957), M.p. 239—240°. [f] From aqueous ethanol. [g] B.P. 642,409/1947, m.p. 229—230°. [h] Compd. crystallised from benzene with benzene of crystallisation and sintered at 85°. [i] Desolvated for analysis *in vacuo* at 135° (12 h). [j] *M* (mass spec.) 308 (required 308). [k] No consistent microanalyses obtained. [l] Crystallised with chloroform. Melted with effervescence and resolidification at 160—165°, finally completely melted at 205°. [m] B.P. 685,840/1950, m.p. 359°. [n] From water. [p] From ethanol. [q] Dissociated to yield the free base when crystallised from water. [r] From 5N-hydrochloric acid. [s] Purified by sublimation. I.r. spectrum of sublimate showed presence of 2-amino-5-nitrobenzonitrile ($\nu_{max.}$ 2221 cm.$^{-1}$).

nitrophenyl-*s*-triazine (III; $R^1 = NO_2$, $R^2 = R^3 = H$) underwent reduction with stannous chloride or hydrazine–Raney nickel, these routes to the aminophenyl-*s*-triazine (III; $R^1 = NH_2$, $R_2 = R^3 = H$) were less efficient than direct formation from anthranilonitrile and cyanoguanidine.

The amine (III; $R^1 = NH_2$, $R^2 = R^3 = H$) formed a pale yellow dihydrochloride in 5N-hydrochloric acid which dissociated when crystallised from water to afford the orange monohydrochloride monohydrate [*cf.* 2,4-diamino-6-phenyl-*s*-triazine (III; $R^1 = R^2 = R^3 = H$) forms a monohydrochloride monohydrate].[14] A deep yellow monoformate was also prepared from the amine and cold 100% formic acid. In contrast, the dihydrochloride from the bromoaminotriazine (III; $R^1 = NH_2$, $R^2 = Br$, $R^3 = H$) dissociated to yield the free base on being crystallised from water.

All attempts to cyclise the aminophenyl-*s*-triazines (VIa and c) in moderate yields. Similarly interaction of the amines (IVa, b, and c) with boiling formamide afforded the corresponding aminoquinazolines (VIa, b, and c) in 75, 90, and 100% yields respectively. The unreactivity of the nitroamino-*s*-triazine (IVd) in boiling formamide or triethyl orthoformate may be attributed to the weakly basic nature of the amino-group; a similar base-weakening influence of the bromo-substituent could explain the unreactivity of the bromoamino-*s*-triazine (IVc) in triethyl orthoformate. It seems certain that formation of the aminoquinazolines (VIa and c) by sublimation of the corresponding formylamines (VIIIa and c) involves participation of the intermediate *s*-triazino[1,2-*c*]quinazolines (Va and c) which subsequently undergo fission of the *s*-triazine ring at the temperature of the reaction. However, to invoke the same intermediates (V) in the conversion of the amines (IVa, b, and c) into the aminoquinazolines

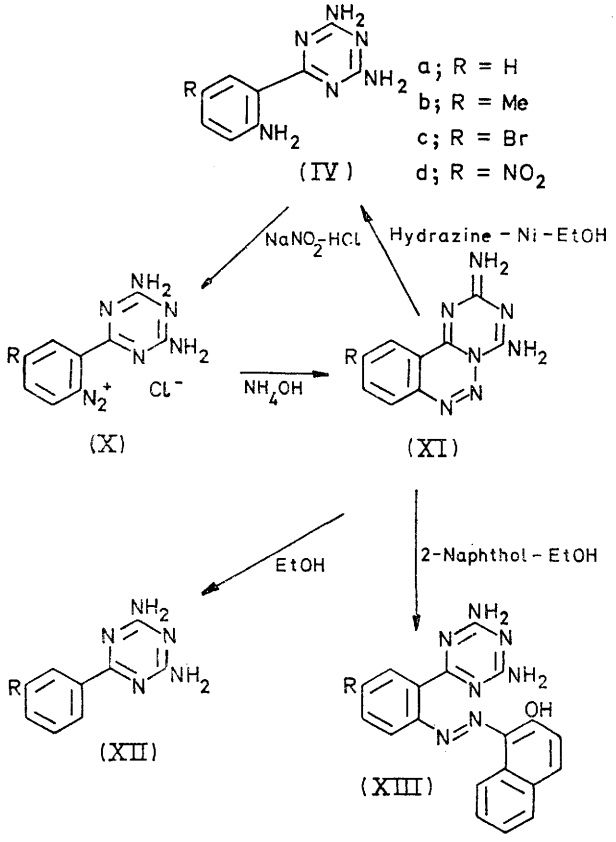
[13] M. O. Forster and H. M. Judd, *J. Chem. Soc.*, 1910, 254.
[14] F. C. Nachod and E. A. Steck, *J. Amer. Chem. Soc.*, 1948, **70**, 2818.
[15] A. Kreutzberger and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1969, 1282; M. F. G. Stevens and A. Kreutzberger, *Angew. Chem.*, 1969, **81**, 84.

(VIa, b, and c) in boiling formamide may be a simplification. Vacuum-sublimation of the nitroamine (IVd) at 300°/5 mm. led to the formation of a small yield of 5-nitroanthranilonitrile, and other 2,4-diamino-6-aryl-*s*-triazines on sublimation slowly decompose to give mixtures in which cyano-groups were detected. It seems possible therefore that in boiling formamide the amines (IVa, b, and c) initially undergo fragmentation of the *s*-triazine ring; the anthranilonitriles thus formed could subsequently react with formamide to yield the aminoquinazolines (VIa, b, and c). Perhaps significantly, anthranilonitriles have recently been shown to afford aminoquinazolines in boiling formamide in high yields.[15] The reactions between methinylating agents and 2,4-diamino-6-(2-aminophenyl)-*s*-triazines (IV) are summarised in Scheme 2.

We experienced considerable difficulty in obtaining correct microanalyses for some of the compounds discussed in this paper (*cf.* pteridine derivatives [16]). The aminoquinazolines (VIa, b, and c) were purified by sublimation and identified by comparison (electronic absorption spectra) with authentic samples,[15] and by hydrolysis to the 4-hydroxyquinazolines (IXa, b, and c) in boiling 2N-hydrochloric acid. Sublimation was less successful as a purification technique in many of the *s*-triazine derivatives because of the aforementioned triazine ring-fission. Interestingly, similar ring-fission occurs in the electron-impact promoted fragmentation of *s*-triazines.[17]

Diazotisation of the aminophenyl-*s*-triazines (IVa, b, or c) in 2N-hydrochloric acid gave the diazonium chlorides (X) which on basification yielded the *s*-triazino[1,2-*c*]-[1,2,3]benzotriazines (XIa, b, or c; Scheme 3). Attempted diazotisation of the nitro-*s*-triazine (IVd) in 2N-hydrochloric acid, acetic acid, or with nitrosylsulphuric–phosphoric acid led only to the recovery of starting material, further evidence of the weakly basic nature of this amine. The *s*-triazinobenzotriazines (XIa, b, and c) decomposed vigorously at their melting points, and in one instance (XIa) a slight explosion occurred when the compound was being gently powdered in a glass mortar. However the solid-phase i.r. spectra of the compounds showed no change during storage at 4° (12 months). All attempts to crystallise these compounds were unsuccessful: they were only sparingly soluble in nonpolar solvents, and decomposed rapidly in polar solvents (ethanol, acetic acid, dioxan, dimethylformamide or dimethyl sulphoxide): the compounds failed to afford crystalline hydrochlorides, picrates, or toluene-*p*-sulphonates.

During diazotisation of the amino-*s*-triazines (IVa or c) in 2N-hydrochloric acid crystalline solids were precipitated. The presence of bands at 2263 and 2268 cm^{-1} respectively in their i.r. spectra confirmed that these products were the diazonium chlorides (Xa or c). They crystallised unchanged from ether–methanol, and on basification cyclised to the *s*-triazinobenzotriazines (XIa or c). Product (Xa) analysed as a monohydrochloride monohydrate [*cf.* the amine (IVa) forms a monohydrochloride monohydrate] and the product (Xc) had an analysis consistent with it being the free



SCHEME 3

diazonium chloride [*cf.* dissociation of the dihydrochloride of the bromo-*s*-triazine (IVc) in water]. Both diazonium chlorides were stable for at least 12 months at 4° and 24 hours at 60° (solid phase i.r. spectra).

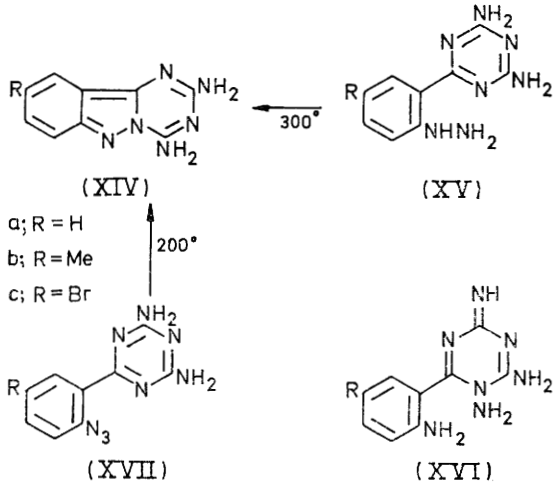
The *s*-triazinobenzotriazines (XIa—c) underwent reductive decomposition in ethanol, evolving nitrogen and yielding the phenyltriazines (XIIa—c); the phenyltriazine (XIIa) was also formed from the benzotriazine (XIa) in boiling dioxan. Hydrazine and Raney nickel in ethanol has previously been used to effect reductive fission of the triazine ring in 1,2,3-benzotriazines: [1,4] the *s*-triazinobenzotriazines (XIa—c) were efficiently degraded by this reagent to the amines (IVa—c). In spite of the competing decomposition reaction, the *s*-triazinobenzotriazines afforded the azo-naphthol derivatives (XIIIa—c) with 2-naphthol in ethanol. The 'masked diazonium' character of the 1,2,3-benzotriazine ring is vividly illustrated by the instantaneous development of a red colour when a mixture of dry powders of the *s*-triazinobenzotriazine (XIa) and 2-naphthol are gently shaken in a dry flask. Although

[16] J. E. Fildes in 'Pteridine Chemistry,' eds. W. Pfleiderer and E. C. Taylor, Pergamon Press, 1964, p. 507.

[17] P. N. Preston, W. Steedman, M. H. Palmer, S. M. Mackenzie, and M. F. G. Stevens, *Organic Mass Spectroscopy*, 1970, **3**, 863.

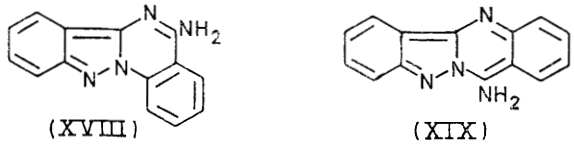
the diazonium chloride (Xc) decomposed in ethanol alone, or in ethanol containing 2-naphthol to the expected products (XIIc) and (XIIIc) respectively, a shaken mixture of the dry diazonium chloride and dry 2-naphthol failed to develop any red colour: the mechanistic implications of these observations are not obvious.

Reduction of the *s*-triazinobenzotriazines (XIa—c) with stannous chloride in ethanol took a different course to the reduction with hydrazine–nickel, and the products were the *s*-triazinoindazoles (XIVa—c). The formation of the *s*-triazinoindazoles may involve either of the hydrazine series (XV) or (XVI) as intermediates, which either cyclise during the reaction or during the subsequent purification. The hydrazines (XVa—c) were readily prepared by reduction of the corresponding diazonium chlorides with stannous chloride in 10N-hydrochloric acid, and melted with evolution of ammonia and resolidification; sublimation of the products yielded the same *s*-triazinoindazoles (XIVa—c). *s*-Triazinoindazoles were also formed by thermolysis of the azides (XVIIa and c), either through the intermediacy of nitrenes or by a concerted neighbouring-group elimination of nitrogen:[18] the former route seems unlikely since attempted de-oxygenation of the *o*-nitrophenyltriazine (III; $R^1 = NO_2$, $R^2 = R^3 = H$) with triethyl phosphite (a reagent known to produce nitrenes[19]) failed to realise any recognisable products.



SCHEME 4

The N–N bond of the *s*-triazinoindazole (XIVa) resembled that in the related indazoloquinazoline (XVIII) in being



stable to reductive conditions (Raney nickel–hydrazine): this contrasts with the reductive cleavage of the N–N bond in the isomeric indazoloquinazoline (XIX).[4]

[18] T. L. Gilchrist and C. W. Rees, 'Carbenes, Nitrenes and Arynes,' Thomas Nelson, London, 1969.
[19] J. I. G. Cadogan, *Quart. Rev.*, 1968, **22**, 222.

In the mass spectrum of the azide (XVIIa), the molecular ion (*m/e* 228) has an abundance of less than 0·1%. The base peak (*m/e* 200, $M - N_2$) presumably corresponds to the *s*-triazinoindazole (XIVa). The electronic absorption properties of the *s*-triazinoindazoles are consistent with their assigned structures (Figure 2).

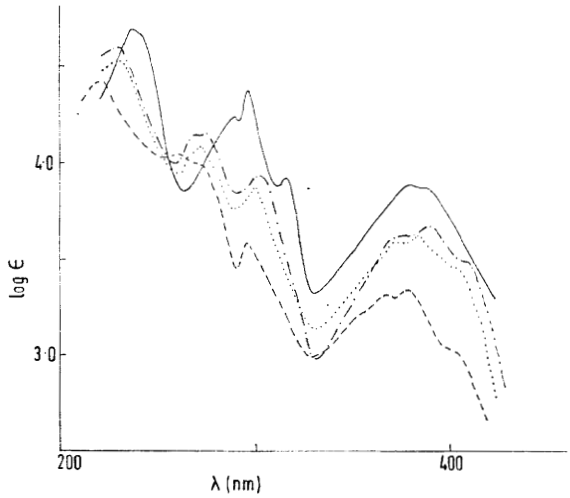
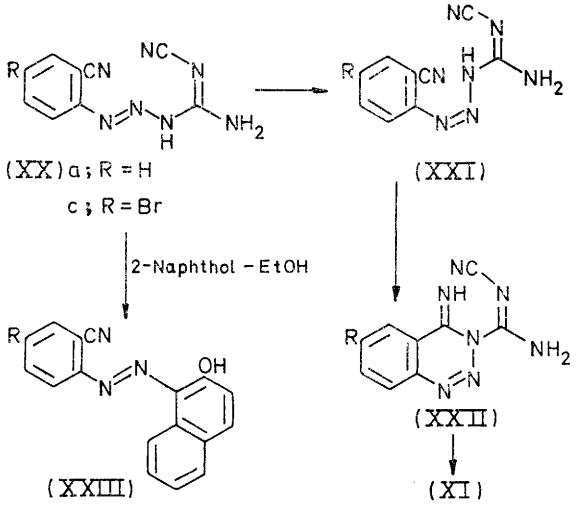


FIGURE 2 Electronic absorption spectra (in ethanol) of 2,4-diamino-*s*-triazino[1,2-*b*]indazole (XIVa – – – – –), 2,4-diamino-9-methyl-*s*-triazino[1,2-*b*]indazole (XIVb ·····), 9-bromo-2,4-diamino-*s*-triazino[1,2-*b*]indazole (XIVc —·—·—), and 5-aminoindazolo[2,3-*a*]quinazoline (XVIII ————).

Walther and Grieshammer[20] coupled diazotised arylamines with cyanoguanidine and obtained triazenoguanidines which decompose in the presence of concentrated hydrochloric acid and protic solvents to afford arylcyanoguanidines.[21] It appeared possible that triazenoguanidines (XX) from diazotised anthranilonitriles and cyanoguanidine could cyclise to benzotriazine derivatives because the amino- and cyano-groups in the proposed intermediates (XXI) and (XXII) are in favourable orientation for successive nucleophilic amine–nitrile addition reactions.[4-6,15] This approach could provide an attractive alternative route to the *s*-triazino-[1,2-*c*][1,2,3]benzotriazine ring-system [(XI) Scheme 5]. Accordingly, diazotised anthranilonitrile and 5-bromoanthranilonitrile were coupled with cyanoguanidine in basic media (no reaction occurred under neutral or acid conditions). The products (XXa and c) could not be crystallised from the usual solvents, decomposed explosively when dry, and were conveniently used as wet pastes.[21] Cyclisations of type (XX) ⟶ (XI) are known to be promoted by water or base,[6] but no identifiable products were obtained when the *o*-cyanophenyltriazenes (XXa and c) were boiled with piperidine in absolute ethanol or anhydrous benzene. The triazene (XXa) effervesced vigorously in boiling aqueous ethanol. If the *s*-triazinobenzotriazine (XIa) participates as an

[20] R. von Walther and W. Grieshammer, *J. prakt. Chem.*, 1915, **92**, 209.
[21] B.P. 576,401/1946.

intermediate in this reaction, the product would be 2,4-diamino-6-phenyl-*s*-triazine (XIIa): however this compound was not detected (t.l.c.). Similarly reduction of



SCHEME 5

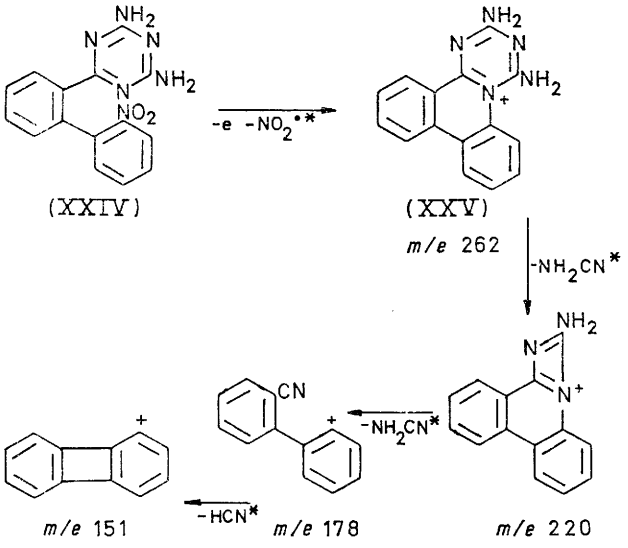
the triazene (XXa) with Raney nickel–hydrazine in ethanol yielded none of the amine (IVa) or anthranilonitrile, and reaction with 2-naphthol in ethanol afforded none of the azonaphthol-triazine (XIIIa). The only product isolated in the latter reaction was the cyanoazonaphthol (XXIIIa). No recognisable products were identified (t.l.c.) when the bromotriazene (XXc) was boiled in aqueous ethanol, or reduced with Raney nickel–hydrazine. However, the bromotriazene in ethanol containing 2-naphthol gave, in addition to the cyanoazonaphthol (XXIIIc) traces of the azonaphthol-triazine (XIIIc) and the bromophenyltriazine (XIIc): it appears therefore that although the bromotriazene (XXc) does partially decompose by the route shown in Scheme 5, this route is inapplicable to the efficient preparation of the *s*-triazino[1,2-*c*][1,2,3]benzotriazine ring-system.

Interaction of a solution of the diazonium chloride (Xa) and sodium arsenite yielded, not the expected arsonic acid (Bart reaction), but 2,4-diamino-6-(2-hydroxyphenyl)-*s*-triazine (III; $R^1 = OH$, $R^2 = R^3 = H$) which was also prepared independently from methyl salicylate and biguanide.[22] Replacement of amino-groups by hydroxy groups proceeded smoothly in boiling 2N-hydrochloric acid to afford 2,4-dihydroxy-6-(2-hydroxyphenyl)-*s*-triazine. This same trihydroxy-compound (65%) was also formed directly from the *s*-triazinobenzotriazine (XIa) in boiling 2N-hydrochloric acid, replacement of the 'diazo-' group of the 1,2,3-benzotriazine by a hydroxy group presumably involving a heterolytic mechanism. Similarly, replacement of a diazo-group by a chloro-group was readily effected by cuprous chloride to yield the chlorophenyl-*s*-triazine (III; $R^1 = Cl$, $R^2 = R^3 = H$). However, interaction of the *s*-triazinobenzotriazine (XIa) or a solution of the diazonium chloride (Xa) with cuprous cyanide in hydrochloric acid led to the formation, not of the cyanophenyl-*s*-triazine (III; $R^1 = CN$, $R^2 = R^3 = H$) but a mixture of the aforementioned chlorophenyl-*s*-triazine and what appeared to be a cuprous cyanide complex of the chlorophenyl-*s*-triazine. This high-melting, insoluble complex was also formed simply by mixing an acid solution of the chlorophenyl-*s*-triazine with cuprous cyanide solution. The i.r. spectrum of the complex showed the absence of aromatic cyano-absorption (over 2200 cm^{-1}) and was very similar to that of the chlorophenyl-*s*-triazine with an additional absorption at 2170 cm^{-1} (inorganic cyanide). Surprisingly, pyrolysis of the cuprous cyanide complex of the chlorophenyl-*s*-triazine afforded phthalodinitrile, probably by nucleophilic substitution of a chloro- by a cyano-group associated with the pyrolytic fragmentation of the *s*-triazine ring. All attempts to cyclise the cyanophenyl-*s*-triazine (III; $R^1 = CN$, $R^2 = R^3 = H$) (prepared from phthalodinitrile and cyanoguanidine) either thermally, or under acid or basic conditions were unsuccessful: in boiling 2N-hydrochloric acid hydrolysis of the nitrile was effected and the product was the corresponding acid (III; $R^1 = CO_2H$, $R^2 = R^3 = H$), which was identical to the same acid unequivocally prepared from biguanide and phthalic anhydride.[23]

In contrast to the aforementioned heterolytic reactions, decomposition of the *s*-triazinobenzotriazine (XIa) in boiling nitrobenzene is undoubtedly homolytic in character since the products are the 2,2′-disubstituted biphenyl (XXIV) and its *m*- and *p*-nitro-analogues (total yield 65%). We were unable to separate the three isomers by t.l.c. or g.l.c. and the mixture could not be analysed by the spectroscopic technique used for related biphenyl mixtures.[5] The i.r. spectrum of the mixture accorded well with the spectra of the three isomers which were independently prepared from the corresponding cyanobiphenyls[5] and cyanoguanidine: no additional peaks were present. We experienced difficulty with the microanalyses of the three isomers. The *o*-nitrobiphenyl (XXIV) crystallised from benzene with solvent of crystallisation which could only be removed by prolonged evacuation at 130°. No consistent analyses for the *m*- and *p*-nitrophenyl isomers could be obtained. However the mass spectra of the nitrobiphenyls confirmed the correct molecular weights (308) and demonstrated an interesting steric effect. The molecular ion from the *ortho*-isomer (XXIV) is very weak, and the spectrum shows a base peak at *m/e* 262 ($M - NO_2$): possibly an intramolecular arylation is involved yielding the ion (XXV) since related cyclisations in 2,2′-disubstituted biphenyls are well known.[5,24] Subsequent major ions occur at *m/e* 220, 178, and 151 (Scheme 6).

[22] U.S.P. 2,386,517/1945.
[23] U.S.P. 2,446,980/1948.
[24] D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1962, 4579.

In marked contrast to the behaviour of the *ortho*-isomer, the *meta*- and *para*-nitro-biphenyls form intense molecular ions: the *para*-isomer loses nitric oxide from the molecular ion consistent with the known behaviour of



* Denotes transition supported by metastable peak.

SCHEME 6

nitroaromatics.[25] An ion at *m/e* 261 is prominent in the spectrum of the *meta*-nitro-isomer, present in the *para*-nitro-isomer but absent in (XXIV); possibly in the former cases the stereochemical disposition of the nitro-group and the amino- (or imino-) groups of the heterocyclic ring are favourable for nitrous acid elimination. In this respect it is interesting to note that all three isomers effervesce at their melting points (the *para*-nitro-isomer with resolidification); we propose to investigate the thermolysis of these unusual 2,2′-disubstituted biphenyls.

Many of the 2,4-diamino-6-aryl-*s*-triazines and *s*-triazinobenzotriazines discussed here were screened for tumour-inhibitory activity in mice inoculated with L-1210 lymphoid leukaemia; these results will be published in full elsewhere. Preliminary findings indicate that none of the compounds show appreciable biological activity, which appears to confirm the conclusions of Baker [11] that this class of compounds are 'unlikely candidates for construction of active-site-directed irreversible inhibitors'.

EXPERIMENTAL

Preparation of Nitriles.—(i) 2-Aminobenzonitrile was prepared by reduction of 2-nitrobenzonitrile with iron powder in ethanol and 10N-hydrochloric acid (1 : 1) at 50—55°.

(ii) 2-Amino-5-methylbenzonitrile was prepared (75%) by reduction of the nitro-analogue with stannous chloride,[26] or by pyrolysis of 5-methylisatin 3-oxime.[27]

(iii) 2-Aminobenzonitrile (21 g) in acetic acid (250 ml) at 15° was treated with bromine (29·4 g) at a rate sufficient to keep the temperature from rising. The product, 2-amino-5-bromobenzonitrile hydrobromide, was collected and basified with ammonia; the aminobromonitrile (80%) crystallised from carbon tetrachloride as flakes, m.p. 93—95° (lit.,[28] m.p. 96—97°). Hydrolysis of the nitrile in boiling 3N-sodium hydroxide yielded 2-amino-5-bromobenzoic acid (60%), m.p. 281—283°, identical to the product formed on brominating anthranilic acid.[29]

Other aryl nitriles required in this work were prepared by published routes.

2,4-*Diamino*-6-(2-*aminophenyl*)-s-*triazine*.— 2-Aminobenzonitrile (16 g), cyanoguanidine (11·2 g), and potassium hydroxide (1·2 g) were boiled (4 h) in 2-ethoxyethanol (60 ml). The cooled mixture was poured into water (1 l) to give a gum which rapidly solidified to give an off-white solid (15·5 g.); this crystallised from water as needles, m.p. 179—181° (lit.,[12] m.p. 165—168°). The same aminotriazine (45 and 40% yields respectively) was formed by reduction of 2,4-diamino-6-(2-nitrophenyl)-*s*-triazine with either Raney nickel–hydrazine in ethanol, or by stannous chloride in hydrochloric acid.

A solution of the aminophenyltriazine in 5N-hydrochloric acid deposited the *dihydrochloride* (95%) which crystallised from 5N-hydrochloric acid as cream needles, m.p. 268—272° (Found: C, 39·6; H, 4·8; N, 30·7; Cl, 26·1. $C_9H_{10}N_6$,2HCl requires C, 39·6; H, 4·4; N, 30·6; Cl, 25·8%). The dihydrochloride dissociated when crystallised from water to afford yellow needles of the *monohydrochloride monohydrate*, m.p. 265—270° (Found: C, 42·3; H, 5·5; N, 32·8. $C_9H_{10}N_6$,HCl,H_2O requires C, 42·0; H, 5·1; N, 32·8%).

The aminophenyltriazine and cold 100% formic acid (1 mol equiv.) gave the yellow *monoformate* which crystallised from water as yellow needles, m.p. 132—134° (Found: N, 33·7. $C_9H_{10}N_6$,HCO_2H requires N, 33·9%). Basification of the monoformate with aqueous ammonia gave the aminophenyltriazine.

In the Table are recorded 6-aryl-2,4-diamino-*s*-triazines prepared from aryl nitriles, cyanoguanidine, and potassium hydroxide in 2-ethoxyethanol.

2,4-*Diamino*-6-(2-*ethoxymethyleneaminophenyl*)-s-*triazine* (VIIa).—Triethyl orthoformate (20 ml) and 2,4-diamino-6-(2-aminophenyl)-*s*-triazine (1·0 g) were boiled (1 h) after which excess of solvent was removed under reduced pressure. The residue was extracted into anhydrous toluene from which the *ethoxymethyleneamino-derivative* (80%) was deposited as a cream, amorphous solid, m.p. 235—240° (Found: C, 55·5; H, 5·0; N, 32·5. $C_{12}H_{14}N_6O$ requires C, 55·8; H, 5·4; N, 32·6%).

2,4-*Diamino*-6-(2-*ethoxymethyleneamino*-5-*methylphenyl*)-s-*triazine* (VIIb).—The aminomethylphenyltriazine (IVb) with triethyl orthoformate similarly gave an *ethoxymethyleneamino-derivative*, m.p. 172—175° (Found: C, 57·4; H, 5·5; N, 31·2. $C_{14}H_{16}N_6O$ requires C, 57·4; H, 5·9; N, 30·9%).

The triazines (IVc and d) were recovered unchanged after being boiled for a prolonged period in triethyl orthoformate.

[25] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, 1967, p. 515.
[26] W. Findeklee, *Chem. Ber.*, 1905, **38**, 3542.
[27] G. R. Bedford and M. W. Partridge, *J. Chem. Soc.*, 1959, 1633.
[28] E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Amer. Chem. Soc.*, 1960, **82**, 3152.
[29] A. S. Wheeler, *J. Amer. Chem. Soc.*, 1909, **31**, 565.

2,4-*Diamino*-6-(2-*formylaminophenyl*)-s-*triazine* (VIIIa).—The amine (IVa) (2·0 g) was boiled in 100% formic acid (20 ml) for 1 h after which the excess of solvent was evaporated off. The *formyltriazine* (90%) crystallised from ethanol as cream rosettes, m.p. 233—235° (Found: C, 52·5; H, 4·3; N, 36·5. $C_{10}H_{10}N_6O$ requires C, 52·2; H, 4·3; N, 36·5%).

2,4-*Diamino*-6-(5-*bromo*-2-*formylaminophenyl*)-s-*triazine* (VIIIc).—This compound was prepared similarly from the amine (IVc); it was purified by extraction into anhydrous toluene and had m.p. 280—282° (eff.) (Found: C, 39·9; H, 3·0; N, 27·2. $C_{10}H_9BrN_6O$ requires C, 39·7; H, 2·9; N, 27·2%).

2,4-Diamino-6-(2-amino-5-nitrophenyl)-*s*-triazine was recovered unchanged from boiling formic acid.

4-*Aminoquinazoline* (VIa).—(i) The solution formed when 2,4-diamino-6-(2-aminophenyl)-*s*-triazine (2·0 g) was boiled in formamide (5 ml) was cooled and triturated with water (20 ml). The product, 4-aminoquinazoline (1·1 g, 75%) was purified by sublimation and had m.p. 266—268° with identical spectroscopic properties to an authentic sample.[15]

(ii) 2,4-Diamino-6-(2-formylaminophenyl)-*s*-triazine (0·2 g) sublimed when heated at 300° at 5 mmHg. The colourless sublimate (0·05 g) had identical m.p. and spectroscopic properties to the foregoing sample.

4-Hydroxyquinazoline (0·25 g, 50%) was deposited when 4-aminoquinazoline (0·5 g) was boiled in 2N-hydrochloric acid for 1 h and then the solution was cooled.

4-*Amino*-6-*methylquinazoline* (VIb).—Interaction of 2,4-diamino-6-(2-amino-5-methylphenyl)-*s*-triazine (1·0 g) and boiling formamide (4 ml) gave the aminomethylquinazoline (0·7 g, 90%) when the mixture was diluted with water. After sublimation the product had identical u.v. and i.r. spectra to an authentic sample.[15]

The aminomethylquinazoline (0·2 g) was boiled in 2N-hydrochloric acid (10 ml) for 1 h and the cooled solution was made alkaline with aqueous ammonia. 4-Hydroxy-6-methylquinazoline (0·17 g, 85%) was collected, m.p. 248—250° (lit.,[30] m.p. 250—251°).

4-*Amino*-6-*bromoquinazoline* (VIc).—(i) This quinazoline, prepared from the corresponding amine (IVc) and boiling formamide (95% yield) was identical to a sample previously described.[15] As in this previous work no reliable microanalyses were obtained for this compound. The mass spectrum gave a molecular ion at *m/e* 223 and a large $M + 2$ peak at *m/e* 225 ($C_8H_6BrN_3$ requires *M*, 223·9).

(ii) 2,4-Diamino-6-(5-bromo-2-formylaminophenyl)-*s*-triazine was heated at 300° for 15 min and then sublimed at 300°/5 mm. The sublimate (60%) was identical to the aminobromoquinazoline (above).

Hydrolysis of the aminobromoquinazoline in 2N-hydrochloric acid (4 h) gave (when the solution was cooled) 6-*bromo*-4-*hydroxyquinazoline* (40%), which crystallised from water as pale yellow needles, m.p. indefinite above 230° (Found: C, 43·1; H, 2·4; N, 12·8. $C_8H_5BrN_2O$ requires C, 42·7; H, 2·2; N, 12·4%).

2,4-Diamino-6-(2-amino-5-nitrophenyl)-*s*-triazine was recovered from boiling formamide (1 h).

Diazotisation of 2,4-*Diamino*-6-(2-*aminophenyl*)-s-*triazine*.—(i) A suspension of the amine (5·0 g) in 2N-hydrochloric acid (150 ml) at 0° was stirred with a solution of sodium nitrate (2·0 g) in water (25 ml) for 1 h. The precipitated solid (4·7 g) was dissolved in warm ether–methanol and filtered. Addition of excess ether to the filtrate deposited the *diazonium chloride* (Xa) as its *monohydrochloride monohydrate* (2·6 g; m.p. above 150° with efferv.) (Found: C, 35·2; H, 4·0; N, 32·3. $C_9H_8ClN_7,HCl,H_2O$ requires C, 35·5; H, 3·6; N, 32·2%); $\nu_{max.}$ (KBr) 2263 cm^{-1} (N≡N).

No change in the i.r. spectrum was observed when the diazonium chloride monohydrochloride monohydrate was stored either at 4° (1 year) or at 60° (24 h).

(ii) The amine was diazotised as above, stirred at 0° (30 min) and basified with an excess of aqueous ammonia–ice. 4-*Amino*-2(2H)-*imino*-s-*triazino*[1,2-c][1,2,3]*benzotriazine* (XIa) was deposited (85%) as a cream solid, m.p. indefinite about 200° (with efferv.). The product was thoroughly washed with distilled water, collected, and dried over silica gel (Found: C, 50·4; H, 3·4; N, 46·1. $C_9H_7N_7$ requires C, 50·7; H, 3·3; N, 46·0%). All attempts to crystallise this compound, or convert it into crystalline salts were unsuccessful.

The same benzotriazine was formed when the dry diazonium chloride monohydrochloride monohydrate prepared above was basified with aqueous ammonia.

WARNING: A sample of the *s*-triazinobenzotriazine (XIa) exploded on being powdered in a glass mortar.

No observable change occurred in the i.r. spectrum of the *s*-triazinobenzotriazine (XIa) on storage at 4° (1 year).

Diazotisation of 2,4-*diamino*-6-(2-*amino*-5-*methylphenyl*)-s-*triazine*.—No diazonium chloride precipitated when the amine (5·0 g) in 2N-hydrochloric acid (150 ml) was diazotised with a solution of sodium nitrite (2·0 g) in water (25 ml), and the mixture was stirred at 0° (1 h). Basification with aqueous ammonia–ice deposited 4-*amino*-2(2H)-*imino*-10-*methyl*-s-*triazino*[1,2-c][1,2,3]*benzotriazine* (XIb) (85%) as a cream solid which darkened on exposure to light. The *s*-triazinobenzotriazine melted indefinitely at *ca.* 300° (with efferv.) (Found: N, 43·5. $C_{10}H_9N_7$ requires N, 43·2%). The i.r. spectrum was transparent in the region 2100—2300 cm^{-1} and showed no change when the compound was stored at 4° (1 year).

Diazotisation of 2,4-*diamino*-6-(2-*amino*-5-*bromophenyl*)-s-*triazine*.—(i) The bromotriazine (5·6 g) diazotised as usual in 2N-hydrochloric acid (120 ml) with sodium nitrite (1 mol equiv.) deposited a cream solid (3·3 g), which was dried over silica gel and dissolved in warm ether–methanol. Addition of an excess of ether to the filtered solution precipitated the *diazonium chloride* (Xc), m.p. 161° (efferv.); $\nu_{max.}$ (KBr) 2268 cm^{-1} (N≡N) (Found: C, 33·1; H, 2·5. $C_9H_7BrClN_7$ requires C, 32·9; H, 2·1%). No change in the i.r. spectrum occurred when the compound was heated at 60° (24 h) or stored at 4° (1 year).

(ii) The diazonium suspension prepared as above was basified with ammonia. The precipitated cream solid (90%) of 4-*amino*-10-*bromo*-2(2H)-*imino*-s-*triazino*[1,2-c]-[1,2,3]*benzotriazine* (XIc) rapidly darkened on exposure to light and melted indefinitely at 270° (eff.) (Found: C, 36·3; H, 2·4; N, 33·6. $C_9H_6BrN_7$ requires C, 37·0; H, 2·1; N, 33·6%).

The same compound was obtained when the dry diazonium chloride prepared above was basified with ammonia. The i.r. spectrum of the product showed no absorptions in the diazo-region (2100—2300 cm^{-1}) and the spectrum was unchanged when the *s*-triazinobenzotriazine was stored at 4° (1 year).

Properties of 4-*Amino*-2(2H)-*imino*-s-*triazino*[1,2-c][1,2,3]-*benzotriazine* (XIa).—(i) The *s*-triazinobenzotriazine (0·5 g) effervesced when boiled in 95% ethanol (50 ml) for 2·5 h.

[30] U.S.P. 3,047,462/1962.

The evaporated residue was dissolved in 2N-hydrochloric acid and filtered. 2,4-Diamino-6-phenyl-*s*-triazine (0·45 g), m.p. and mixed m.p. 230—232° (after crystallisation from water) was precipitated from the solution on basification.

The same product (65%) was formed when the *s*-triazinobenzotriazine was boiled in dioxan.

(ii) The triazine (0·6 g) immediately developed a red colour when boiled (0·5 h) in ethanol (20 ml) containing 2-naphthol (0·4 g). The *naphthol-azo-triazine* (XIIIa) crystallised from acetic acid (0·7 g, 70%) as red micro-needles, m.p. 295° (Found: C, 63·5; H, 4·2. $C_{19}H_{15}N_7O$ requires C, 63·9; H, 4·2%).

The same napthol-azo-triazine (70%) was formed when a solution of diazotised 2,4-diamino-6-(2-aminophenyl)-*s*-triazine was coupled with 2-naphthol in aqueous sodium hydroxide solution.

(iii) The *s*-triazinobenzotriazine (0·5 g) in ethanol (20 ml) containing Raney nickel (0·5 g) was treated with 3 × 1 ml portions of hydrazine hydrate (during 1 h) while the temperature was maintained at 60—65°. After further reaction at 60—65° (1 h) the filtered (Kieselguhr) solution was evaporated to dryness. Crystallisation of the residue from water afforded 2,4-diamino-6-(2-aminophenyl)-*s*-triazine (0·3 g, 65%), m.p. 179—181° and identical i.r. spectrum to the sample previously prepared.

(iv) The *s*-triazinobenzotriazine (0·2 g) in boiling 2N-hydrochloric acid (8 h) deposited (when the solution was cooled) a yellow solid. Crystallisation from aqueous ethanol gave 2,4-*dihydroxy*-6-(2-*hydroxyphenyl*)-s-*triazine* (65%), m.p. 308—312° (Found: C, 52·8; H, 3·6; N, 20·1%; *M* (mass spec.), 205. $C_9H_7N_3O_3$ requires C, 52·7; H, 3·4; N, 20·5%; *M*, 205).

Hydrolysis of 2,4-diamino-6-(2-hydroxyphenyl)-*s*-triazine [22] in boiling 2N-hydrochloric acid (8 h) yielded the same trihydroxy-*s*-triazine (65%).

2,4-*Diamino*-s-*triazino*[1,2-b]*indazole* (XIVa).—A mixture of the *s*-triazinobenzotriazine (XIa) (2·15 g) and stannous chloride dihydrate (4·5 g) was boiled in ethanol (50 ml) for 1·5 h. The solution was concentrated to 20 ml by distillation, and basified to pH 11 with aqueous 2N-sodium hydroxide. The yellow solid (70%) was sublimed (300° at 5 mmHg) to yield the *triazinoindazole*, as yellow micro-needles, m.p. 313° (Found: C, 53·8; H, 4·1; N, 41·9. $C_9H_8N_6$ requires C, 54·0; H, 4·0; N, 42·0%).

No recognisable products were obtained when a mixture of triethyl phosphite and 2,4-diamino-6-(2-nitrophenyl)-*s*-triazine were heated together at 150° (2 h).

Attempted reduction of the triazinoindazole with Raney nickel and excess hydrazine in ethanol (at 60—65°) or in butanol (at 90—95°) led to the recovery of starting material.

Properties of 4-*Amino*-2(2H)-*imino*-10-*methyl*-s-*triazino*-[1,2-c][1,2,3]*benzotriazine* (XIb).—(i) Decomposition of the methylbenzotriazine in boiling ethanol furnished 2,4-diamino-6-(3-methylphenyl)-*s*-triazine (64%), m.p. and mixed m.p. 246—247°, and identical i.r. spectrum to a sample prepared from 3-methylbenzonitrile and cyanoguanidine (Table 1).

(ii) The methylbenzotriazine (1·15 g) and 2-naphthol (0·8 g) in boiling ethanol (50 ml) deposited a red solid when boiled (0·5 h). The *azonaphthol-methyltriazine* (XIIIb) crystallised from acetic acid as red needles (60%), m.p. 306° (Found: C, 64·7; H, 4·4; N, 26·0. $C_{20}H_{17}N_7O$ requires C, 64·7; H, 4·6; N, 26·4%).

(iii) Reduction of the methylbenzotriazine with Raney nickel in ethanol containing excess hydrazine hydrate (at 60—65°) yielded 2,4-diamino-6-(2-amino-5-methylphenyl)-*s*-triazine (45%), m.p. and mixed m.p. 233—235° (from water).

2,4-*Diamino*-9-*methyl*-s-*triazino*[1,2-b]*indazole* (XIVb).—Stannous chloride dihydrate (2·25 g) and the *s*-triazinobenzotriazine (XIb) (1·15 g) were boiled in ethanol (25 ml) for 1·5 h; 0·5 g of dark material remained undissolved and was filtered off. Solvent was removed from the filtrate which was then basified to pH 11 (aqueous sodium hydroxide); the precipitated yellow solid (0·5 g) was sublimed (300° at 5 mm). Crystallisation of the sublimate from water afforded the *methyltriazinoindazole* as pale yellow needles, m.p. 308—311° (Found: C, 56·3; H, 4·5; N, 39·1. $C_{10}H_{10}N_6$ requires C, 56·1; H, 4·7; N, 39·3%).

Properties of 4-*amino*-10-*bromo*-2(2H)-*imino*-s-*triazino*-[1,2-c][1,2,3]*benzotriazine* (XIc).—(i) The bromobenzotriazine effervesced in boiling ethanol; the product (50%) was identical to an authentic sample of 2,4-diamino-6-(3-bromophenyl)-*s*-triazine (Table).

The same product (50%) was obtained when the dry diazonium chloride (Xc) was boiled in ethanol.

(ii) The bromobenzotriazine (0·6 g) and 2-naphthol (0·3 g) in boiling ethanol (0·5 h) gave the *naphthol-azo-bromotriazine* (XIIIc) (60%) when the solution was cooled. The azo-compound crystallised as red micro-needles from acetic acid with m.p. 330—335° (Found: C, 52·0; H, 3·4; N, 22·8. $C_{19}H_{14}BrN_7O$ requires C, 52·3; H, 3·2; N, 22·5%).

The same naphthol-azo-bromotriazine (40%) was obtained from the diazonium chloride (Xc) and 2-naphthol in ethanol.

(iii) Reduction of the bromobenzotriazine with Raney nickel in ethanol and hydrazine at 60—65° afforded 2,4-diamino-6-(2-amino-5-bromophenyl)-*s*-triazine, m.p. and mixed m.p. 281—283°.

2,4-*Diamino*-9-*bromo*-s-*triazino*[1,2-b]*indazole* (XIVc).—Reduction of the bromobenzotriazine (XIc) (2·95 g) with stannous chloride dihydrate (4·5 g) in boiling ethanol (50 ml) for 1·5 h gave a yellow solid when the concentrated solution was basified to pH 11 (aqueous sodium hydroxide). Sublimation (300° at 55 mm) of the yellow solid yielded the *bromotriazinoindazole*, m.p. 305—312° (Found: C, 39·0; H, 2·9; N, 29·9. $C_9H_7BrN_6$ requires C, 38·7; H, 2·5; N, 30·1%).

2,4-*Diamino*-6-(2-*hydrazinophenyl*)-s-*triazine* (XVa).—2,4-Diamino-6-(2-aminophenyl)-*s*-triazine (10·0 g) was diazotised in 2N-hydrochloric acid (150 ml) with sodium nitrite (1 mol equiv.), and the ice-cold diazonium solution was poured slowly (0·5 h) into 10N-hydrochloric acid (150 ml) containing stannous chloride dihydrate (22·5 g). The mixture was stirred at 0° for 18 h. The precipitated solid was suspended in water and basified to pH 11 with sodium hydroxide. The *hydrazine* (6·0 g) was collected and crystallised from toluene (yellow needles), m.p. 200—202° (with resolidification) (Found: C, 50·2; H, 5·3; N, 44·8. $C_9H_{11}N_7$ requires C, 49·8; H, 5·1; N, 45·2%).

The *benzylidene-derivative*, formed from the hydrazine and benzaldehyde (1 mol equiv.) in acetic acid, had m.p. 110° (from aqueous ethanol) (Found: C, 62·9; H, 5·2; N, 31·7. $C_{16}H_{15}N_7$ requires C, 63·0; H, 4·9; N, 32·1%).

The hydrazine evolved ammonia when heated at 250° (1 h). Sublimation (300° at 5 mmHg) of the solid residue afforded 2,4-diamino-*s*-triazino[1,2-*b*]indazole, m.p. and mixed m.p. 313°.

2,4-*Diamino*-6-(2-*azidophenyl*)-s-*triazine* (XVIIa).—2,4-

Diamino-6-(2-aminophenyl)-*s*-triazine (5·0 g) was diazotised and treated with sodium azide (2·5 g); the mixture was stirred at 0° for 1·5 h. The precipitated solid was collected, suspended in water, and neutralised with sodium acetate. The *azidophenyltriazine hydrate* (4·0 g) crystallised from aqueous ethanol as plates, m.p. 165—170° (with effervescence, resolidification, and final melting at 310—313°) (Found: C, 44·3; H, 4·4; N, 45·1. $C_9H_8N_8,H_2O$ requires C, 43·9; H, 4·1; N, 45·5%); $\nu_{max.}$ (KBr) 2126 and 2080 cm^{-1} (N_3).

Thermolysis of the azide (0·02 g) in sand (0·4 g) at 200° (1 h) followed by sublimation (300° at 5 mmHg) afforded 2,4-diamino-*s*-triazino[1,2-*b*]indazole (70%), m.p. and mixed m.p. 313° and an i.r. spectrum identical to those of the aforementioned samples.

2,4-*Diamino*-6-(2-*hydrazino*-5-*methylphenyl*)-s-*triazine* (XVb).—The diazonium solution prepared from 2,4-diamino-6-(2-amino-5-methylphenyl)-*s*-triazine was reduced with stannous chloride in concentrated hydrochloric acid at 0°. The *hydrazine* thus produced (40%) crystallised from water as yellow needles, m.p. 236—238° (with efferescence, resolidification, and final melting at 308—311° (Found: C, 51·5; H, 5·8. $C_{10}H_{13}N_7$ requires C, 51·9; H, 5·7%).

The *benzylidene-derivative* crystallised from aqueous ethanol as yellow flakes, m.p. 166—168° (Found: C, 64·0; H, 5·5; N, 30·6. $C_{17}H_{17}N_7$ requires C, 64·0; H, 5·3; N, 30·7%).

Pyrolysis of the hydrazine at 250° followed by sublimation (300° at 5 mmHg) afforded 2,4-diamino-9-methyl-*s*-triazino[1,2-*b*]indazole (80%) with an i.r. spectrum identical to that of the compound previously prepared.

2,4-*Diamino*-6-(5-*bromo*-2-*hydrazinophenyl*)-s-*triazine* (XVc).—Reduction of the diazonium chloride (Xc) with stannous chloride in 10N-hydrochloric acid in the manner previously described yielded the *bromohydrazine* (65%), which crystallised from aqueous dimethylformamide as yellow needles, m.p. indefinite over 200° with effervescence and resolidification. No satisfactory analyses for this compound were obtained. Its *benzylidene derivative*, from the hydrazine and benzaldehyde in acetic acid crystallised (60%) from butanol as yellow micro-prisms, m.p. 304—305° (Found: C, 50·4; H, 3·8; N, 25·5. $C_{16}H_{14}BrN_7$ requires C, 50·0; H, 3·6; N, 25·5%).

The crude bromohydrazine was heated (270° for 1 h) and then sublimed (300° at 5 mmHg) to yield 2,4-diamino-9-bromo-*s*-triazino[1,2-*b*]indazole (50%), m.p. and mixed m.p. 305—312°.

2,4-*Diamino*-6-(2-*azido*-5-*bromophenyl*)-s-*triazine* (XVIIc).—Interaction of diazotised 2,4-diamino-6-(2-amino-5-bromophenyl)-*s*-triazine with sodium azide (2 mol equiv.) in 2N-hydrochloric acid afforded a yellow solid which was collected and basified with aqueous ammonia. The *azidobromotriazine* thus formed (85%) crystallised from aqueous dimethylformamide as cream needles, which melted indefinitely above 160° with efferv. and resolidification; the residue eventually melted at 305—310° (Found: C, 35·7; H, 2·7; N, 36·1. $C_9H_7BrN_8$ requires C, 35·3; H, 2·3; N, 36·5%); $\nu_{max.}$ (KBr) 2135 and 2095 cm^{-1} (N_3).

Thermolysis of the azide in sand at 200° afforded a yellow product, which after sublimation was shown to be identical to 2,4-diamino-9-bromo-*s*-triazino[1,2-*b*]indazole (i.r. spectrum).

Interaction between Diazotised Anthranilonitriles and Cyanoguanidine.—(i) Diazotised 2-aminobenzonitrile (2·36 g) was coupled with cyanoguanidine (1 mol.) in the presence of an excess of sodium carbonate according to the established procedure.[21] The product, 2-*cyanophenylazocyanoguanidine* (XXa) (1·1 g) was collected and dried over silica gel: it melted at 62—65° (with efferv.) and could not be crystallised.

WARNING: A dry sample of the product decomposed violently when powdered.

The azocyanoguanidine (0·1 g) in 70% ethanol (10 ml) was boiled (2 h). T.l.c. examination of the mixture on alumina plates, with toluene–ethanol (8 : 2) as solvent showed the presence of at least six compounds; no 2,4-diamino-6-phenyl-*s*-triazine was detected.

Reduction of the azocyanoguanidine with Raney nickel and excess of hydrazine in ethanol at 60—65° afforded no 2-aminobenzonitrile or 2,4-diamino-6-(2-aminophenyl)-*s*-triazine when the products were subjected to t.l.c. examination under the conditions described above.

The azocyanoguanidine (0·43 g) and 2-naphthol (0·29 g) were boiled in ethanol (25 ml) for 2 h; the solvent was evaporated off. The residue in benzene was chromatographically fractionated on an alumina column (15 cm) to give yellow, orange, and red bands. Removal of solvent from the orange band afforded 2-*naphthol*-1-*azo*-(2-*benzonitrile*) (0·02 g), m.p. 188—189° (red needles, from methanol) (Found: C, 74·9; H, 4·2; N, 15·0. $C_{17}H_{11}N_3O$ requires C, 74·7; H, 4·0; N, 15·4%). No other identifiable products were detected. The naphtholazobenzonitrile was identical to the product formed by coupling diazotised 2-aminobenzonitrile with 2-naphthol in sodium hydroxide solution.

(ii) Analogous interaction of diazotised 2-amino-5-bromobenzonitrile (1·96 g) and cyanoguanidine (1 mol equiv.) in the presence of excess sodium carbonate solution yielded 4-*bromo*-2-*cyanophenylazocyanoguanidine* (1·5 g) which was dried over silica gel and could not be crystallised without decomposition.

No identifiable products were detected (t.l.c.) when the crude azocyanoguanidine (XXc) was boiled in ethanol, or reduced with Raney nickel and excess hydrazine in ethanol at 60—65°.

The azocyanoguanidine (XXc) (0·13 g) and 2-naphthol (0·065 g) in ethanol (10 ml) were boiled (2 h). T.l.c. examination of the products on alumina or silica gel with three different solvent systems showed the presence of 2,4-diamino-6-(3-bromophenyl)-*s*-triazine (XIIc), and the azonaphthol-derivative (XIIIc). Chromatographic fractionation of a benzene extract of the reaction mixture on an alumina column gave a red band. Evaporation of the red band afforded 2-*naphthol*-1-*azo*-(4-*bromo*-2-*benzonitrile*) (XXIIIc), which crystallised from ethanol as red needles (0·06 g), m.p. 218—220° (Found: C, 57·8; H, 2·8; N, 11·7. $C_{17}H_{10}BrN_3O$ requires C, 58·0; H, 2·8; N, 11·9%). This azo-compound was also formed (86%) by coupling diazotised 2-amino-5-bromobenzonitrile with 2-naphthol in sodium hydroxide solution.

Bart and Sandmeyer Reactions.—(i) Diazotised 2,4-diamino-6-(2-aminophenyl)-*s*-triazine (2·0 g) was treated with sodium arsenite under the conditions employed for the preparation of phenylarsonic acid without the addition of excess sodium carbonate.[31] The concentrated mixture afforded 2,4-diamino-6-(2-hydroxyphenyl)-*s*-triazine (1·15 g), m.p. 266—268°, identical to a sample prepared from methyl salicylate and biguanide (lit.,[22] m.p. 267°).

[31] C. S. Hamilton and J. F. Morgan, 'Organic Reactions,' John Wiley, New York, vol. II, p. 423.

(ii) 4-Amino-2(2*H*)-imino-*s*-triazino[1,2-*c*][1,2,3]benzotriazine (XIa) (1·42 g) was added in small portions (during 10 min) to a vigorously stirred cuprous chloride solution at *40—50°*. The mixture was boiled to complete the reaction and allowed to cool. The precipitate was collected and basified with aqueous ammonia; the product crystallised from aqueous ethanol to give 2,4-diamino-6-(2-chlorophenyl)-*s*-triazine (0·9 g), m.p. 225—227°; this was identical (i.r. spectrum) to a sample prepared from 2-chlorobenzonitrile and cyanoguanidine (Table 1).

(iii) A cuprous cyanide solution [from copper sulphate (11·6 g) and potassium cyanide (13·4 g) in water (80 ml)] was heated to 60° and treated (during 0·5 h) with a solution prepared by diazotising 2,4-diamino-6-(2-aminophenyl)-*s*-triazine (8·08 g) in 2N-hydrochloric acid (240 ml). The mixture was heated to 90°, allowed to cool, and the brown solid was collected. This solid (unmelted over 350°) may be the cuprous cyanide complex of 2,4-diamino-6-(2-chlorophenyl)-*s*-triazine since its i.r. spectrum was very similar to that of the chlorotriazine with an additional band at 2170 cm^{-1} (inorganic cyanide). The insoluble complex could not be crystallised. The mother-liquors left after collection of the complex were concentrated. Basification (aqueous ammonia) of the white solid thus produced yielded 2,4-diamino-6-(2-chlorophenyl)-*s*-triazine (3·0 g).

(iv) Interaction of the *s*-triazinobenzotriazine (XIa) (2·0 g) suspended in 2N-hydrochloric acid (40 ml) with cuprous cyanide solution (22 ml) at 60—70° similarly gave the brown insoluble complex (1·4 g) and 2,4-diamino-6-(2-chlorophenyl)-*s*-triazine (0·3 g).

(v) 2,4-Diamino-6-(2-chlorophenyl)-*s*-triazine (1·0 g) in 2N-hydrochloric acid (30 ml) was treated with cuprous cyanide solution (10 ml) at 60—70° after which it was heated to 90°. The brown precipitate (1·0 g) was identical to the brown complex prepared previously. The concentrated mother-liquors gave unchanged starting material (0·35 g).

The cuprous cyanide complex (0·5 g) was sublimed at 450° at 5 mmHg. The white sublimate (0·1 g) was identical (m.p. and i.r. spectrum) with phthalodinitrile.

2,4-*Diamino*-6-(2-*carboxyphenyl*)-s-*triazine*.—A solution of 2,4-diamino-6-(2-cyanophenyl)-*s*-triazine (0·5 g) in 2N-hydrochloric acid (35 ml) was boiled (5 min), cooled, neutralised with aqueous ammonia, and concentrated to 10 ml. The carboxylic acid (0·45 g) crystallised on cooling and was identical to an authentic sample prepared from biguanide and phthalic anhydride.[23]

Homolytic Decomposition of 4-*amino*-2(2H)-*imino*-s-*triazino*[1,2-c][1,2,3]*benzotriazine in Nitrobenzene*.—The *s*-triazinobenzotriazine (6·0 g) effervesced vigorously when boiled (1·5 h) in nitrobenzene (50 ml). Most of the nitrobenzene was removed (distilled under reduced pressure), and final traces were steam distilled. A chloroform extract of the residue, when diluted with light petroleum deposited a mixture of 2-(2,4-diamino-*s*-triazin-6-yl)2′-nitrobiphenyl, and its 3′- and 4′-nitro-isomers (total yield 5·5 g), which could not be separated by t.l.c. or g.l.c.

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