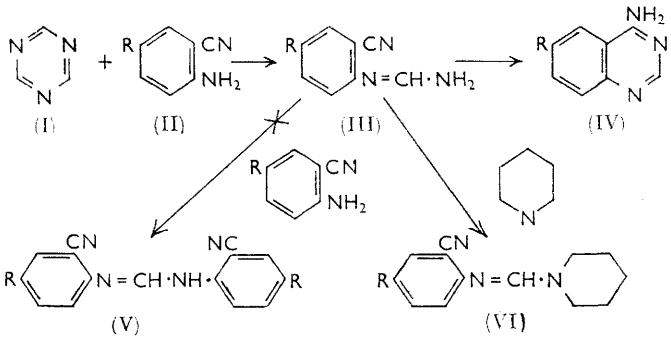
Aminomethinylation of Aromatic Amines

By **A. Kreutzberger**, Institut für pharmaceutische Chemie der Westfälischen Wilhelms-Universität, 44 Münster/W
M. F. G. Stevens,* Department of Pharmacy, Heriot-Watt University, Edinburgh 1

Anthranilonitriles react with *s*-triazine or formamide to give 4-aminoquinazolines. In the presence of secondary alkylamines the intermediate aminomethinylated amines formed with *s*-triazine can be trapped, and aryldialkylformamidines result. The scope of this formamidine synthesis has been investigated.

s-TRIAZINE (I) has been shown to readily undergo ring-cleavage in the presence of nucleophiles,[1] and its use as an aminomethinylating agent has been exploited in the synthesis of formamidines and formazans,[1] heterocyclic systems,[1-3] and polymethine dyes.[4] We have re-examined the interaction of *s*-triazine and some primary arylamines.

Substituted *o*-cyanophenyltriazenes readily cyclise to 3,4-dihydro-4-imino-1,2,3-benzotriazines,[5,6] and analogous syntheses of 4-iminotetrahydroquinazolines have been effected by cyclisation of *o*-cyanophenyl-ureas and -thioureas;[7] the facility of these reactions may be attributed to a favourable juxtaposition of substituents for intramolecular amine–nitrile addition. It was of interest therefore to attempt the synthesis of formamidines of type (V) from anthranilonitriles and *s*-triazine, since the formamidines could undergo analogous cyclisation to 4-iminoquinazolines; such cyclisations could be base-catalysed in the presence of *s*-triazine.



As an introduction to this work the reactions of 4-aminobenzonitrile with formic acid, triethyl orthoformate, and *s*-triazine were examined. The previously reported formation of 4-formylaminobenzonitrile,[8] and *NN'*-di-(4-cyanophenyl)formamidine[9] from the amine and formic acid and triethyl orthoformate respectively was confirmed. The formamidine was also formed less efficiently from the amine and *s*-triazine.

2-Aminobenzonitrile (II; R = H) in boiling 98—100% formic acid afforded 4-hydroxyquinazoline; in triethyl orthoformate at 100° there was no reaction, but with *s*-triazine in anhydrous ethanol 4-aminoquinazoline (IV; R = H) was formed in good yield. Evidently the intermediate product of aminomethinylation (III; R = H), which could not be isolated, undergoes preferential intramolecular amine–nitrile addition to afford the aminoquinazoline; none of the formamidine (V; R = H) or its subsequent cyclisation products was detected. The same intermediate (III; R = H) is probably involved in the cyclisation of the aminonitrile (II; R = H) to the quinazoline (IV; R = H) in boiling formamide. The quinazolines (IV; R = Me or Br) were similarly prepared with *s*-triazine and formamide.

The inability of 2-amino-5-nitrobenzonitrile (II; R = NO_2) to react with *s*-triazine in boiling ethanol or pyridine may be attributed to the weakly basic nature of the amino-group: a similar base-weakening influence of the bromo-substituent in the bromoamino-nitrile (II; R = Br) could explain the low yield (relative to unsubstituted aminoquinazoline) of the bromoaminoquinazoline (IV; R = Br). The poor yields of formamidines from the reaction of 4-nitro- and 4-cyano-anilines with *s*-triazine compared with the high yields from more basic amines [2] afford additional illustrations of the importance of the basicity of the participating amine.

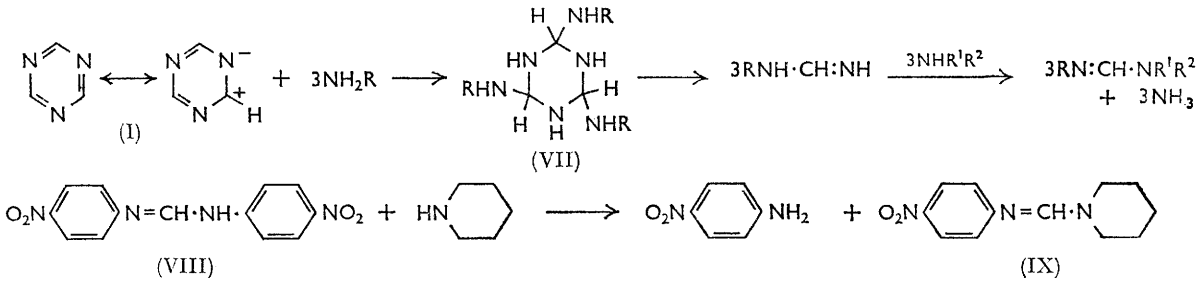
However, a vigorous evolution of ammonia resulted when the aminonitrobenzonitrile (II; R = NO_2) was boiled with *s*-triazine in anhydrous piperidine. The product differed from the previously reported quinazoline [10] (IV; R = NO_2) or the dimer of 2-amino-5-nitrobenzonitrile which is readily prepared from the amino-nitro-nitrile under basic conditions.[11] The i.r. spectrum of this compound showed the presence of a CN group (2222 cm.$^{-1}$), strong aliphatic CH absorption (2860—2950 cm.$^{-1}$), but no NH absorption. Structure (VI; R = NO_2) was confirmed by the mass spectrum which showed the expected molecular ion (*m/e* 258), a base peak (*m/e* 84), and subsequent major fragmentations at *m/e* 69, 56, 41, 30, and 28. Analogous fragmentation patterns have been observed in piperidine alkaloids [12,13] and other formimidoylpiperidines.[3] 2-Aminobenzonitrile (II; R = H) and *s*-triazine reacted in piperidine to give

[1] A. Kreutzberger, *Fortschr. Chem. Forsch.*, 1963, **4**, 273.
[2] C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.*, 1955, **77**, 6559; A. Kreutzberger and C. Grundmann, *J. Org. Chem.*, 1961, **26**, 1121.
[3] A. Kreutzberger and D. Abel, *Arch. Pharm.*, in the press.
[4] A. Kreutzberger, *Arch. Pharm.*, 1966, **299**, 897, 984.
[5] M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc.*, 1964, 3663.
[6] M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1967, 1096; 1968, 348.
[7] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, 1962, **27**, 2622.
[8] M. T. Bogert and L. E. Wise, *J. Amer. Chem. Soc.*, 1910, **32**, 1496.
[9] E. Crundwell, *J. Chem. Soc.*, 1956, 368.
[10] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1948, 360.
[11] E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Amer. Chem. Soc.*, 1960, **82**, 3152.
[12] N. Neuner-Jehle, H. Nesvadba, and G. Spiteller, *Monatsh.*, 1964, **95**, 687.
[13] M. Spiteller-Friedmann and G. Spiteller, *Monatsh.*, 1965, **96**, 104.

predominantly the substituted formamidine (VI; R = H) with similar spectroscopic properties and a trace of the intramolecular cyclisation product (IV; R = H); the bromo-nitrile (II; R = Br) under the same conditions gave an analogous mixture of the formamidine (VI; R = Br) and aminobromoquinazoline (IV; R = Br).

The reasons why the reaction course in the presence of piperidine deviates from aminoquinazoline formation are obscure. If this is a base-catalysis phenomenon then it would be expected that interaction of the weakly basic 2-amino-5-bromobenzonitrile with *s*-triazine in basic, but chemically inert, solvents would give an increased yield of the aminobromoquinazoline (IV; R = Br) relative to the yield in ethanol. However no such increase was found when the reaction was carried out in boiling pyridine, 2,4,6-trimethylpyridine, or triethylamine. Similarly, interaction of 4-nitro- and 4-cyanoanilines with *s*-triazine in boiling triethylamine gave similarly poor yields of formamidines as were obtained when ethanol was employed as solvent. Although previous work [2] has indicated that secondary amines are alkyl groups or part of a heterocyclic ring. A selection of arylamines with electron-attracting and -donating substituents affords substituted formamidines in high yields (see Table). The synthesis is not limited to piperidine derivatives: thus, 4-nitroaniline and *s*-triazine in morpholine, diethylamine, and piperazine give the corresponding formamidines, the absence of NH absorption in the i.r. spectrum of the derivative with piperazine indicating that both NH groups are involved in the reaction. *o*-Phenylenediamine with *s*-triazine in piperidine gave a high yield of benzimidazole. Evidently the intermediate aminomethinylated amine (in contrast to that from 2-aminobenzonitrile) undergoes preferential intramolecular cyclisation. This has been observed also in the absence of piperidine.[2]

Previous investigations [1,2] have suggested that all three methine groups in the *s*-triazine ring participate in its aminomethinylating action, and the formation and decomposition of an intermediate hexahydro-*s*-triazine (VII) in the presence of a secondary alkylamine may be represented by the stoicheiometric reaction shown in



SCHEME

unreactive to *s*-triazine, the possibility that piperidine and not the aromatic amine might be the attacking species in the initial breakdown of *s*-triazine was re-investigated. When carefully fractionated, anhydrous piperidine was mixed with *s*-triazine heat was evolved and a clear solution was formed. This solution was boiled for 2 hr.: fractional distillation afforded an almost quantitative recovery of starting materials, and it must be concluded that there is no chemical reaction between piperidine and *s*-triazine under the reaction conditions employed. However, the heat evolved upon dissolving *s*-triazine in piperidine may be interpreted as a solvation effect between the two components, and to this solvate-formation may be attributed the observed reactivity: a parallel solvent-effect influences the reactivity of Grignard reagents when dissolved in ethers.

The reaction of arylamines with *s*-triazine in the presence of piperidine was found to have wide applicability in the synthesis of formamidines of type RN=CH–NR^{1}R^2, where R is aryl and R^1 and R^2 are the Scheme; the only by-product is ammonia. However, the possible intermediate formation of an *NN'*-diarylformamidine [2] cannot be excluded since the formamidine (VIII) in boiling piperidine affords 4-nitroaniline and *N*-(4-nitrophenyliminomethyl)piperidine (IX) in high yield. This latter reaction may account for the absence of di-arylformamidines in the reaction products. Analogous ammonolyses are well known in the amidine series.[14]

This new route to aryldialkylformamidines which have demonstrated activity against bacterial, protozoal, viral, and helmintic infections,[15] represents a useful addition to conventional syntheses of this type.[15–17]

EXPERIMENTAL

Interaction of Amines and Methinylating Agents.

4-Nitroaniline.—The nitroaniline (2·76 g.) and *s*-triazine (0·5 g.) were boiled in absolute ethanol (8 hr.). *NN'*-Di-(4-nitrophenyl)formamidine (0·29 g., 10%), m.p. 240—242° was separated from unchanged starting material by its insolubility in boiling water. The product was identical

[14] R. L. Shriner and F. W. Neumann, *Chem. Rev.*, 1944, **35**, 351.

[15] U.S.P. 3,073,851/1963, 3,133,078/1964, 3,135,755/1964, 3,153,033/1964, 3,182,053/1965, 3,184,482/1965, 3,189,648/1965; B.P. 969,342/1964.

[16] G. Mandel and A. J. Hill, *J. Amer. Chem. Soc.*, 1954, **76**, 3978.

[17] A. Larizza, G. Brancaccio, and G. Lettieri, *J. Org. Chem.*, 1964, **29**, 3697.

Compound	Yield (%)	M.p.	Formula	Found (%) C	H	N	Required (%) C	H	N
N-(Phenyliminomethyl)piperidine	95	Oil							
toluene-*p*-sulphonate		182—183° [a,b]							
N-(2-*Nitrophenyliminomethyl*)*piperidine*	84	62—63 [c]	$C_{12}H_{15}N_3O_2$	61·5	6·5	17·6	61·8	6·4	18·0
N-(3-*Nitrophenyliminomethyl*)*piperidine*	80	57—58 [c]	$C_{12}H_{15}N_3O_2$	62·0	6·3	17·9	61·8	6·4	18·0
N-(4-*Nitrophenyliminomethyl*)*piperidine*	75	79—80 [c]	$C_{12}H_{15}N_3O_2$	61·4	6·5	18·0	61·8	6·4	18·0
N-(2,4-*Dinitrophenyliminomethyl*)*piperidine*	79	108—110 [d]	$C_{12}H_{14}N_4O_4$	52·0	5·0	20·1	51·8	5·0	20·2
N-(4-*Hydroxyphenyliminomethyl*)*piperidine*	70	176—178 [e]	$C_{12}H_{16}N_2O$	70·2	8·0	13·9	70·6	7·9	13·7
N-(4-*Chlorophenyliminomethyl*)*piperidine*	90	Oil							
picrate		193—194 [e]	$C_{18}H_{18}ClN_5O_7$	47·8	4·2	15·6	47·8	4·0	15·5
toluene-p-*sulphonate*		208—209 [b]	$C_{19}H_{23}ClN_2O_3S$	57·7	6·0	7·0	57·7	5·8	7·0
N-(4-*Cyanophenyliminomethyl*)*piperidine*	88	53—54 [c]	$C_{13}H_{15}N_3$	73·1	7·2	19·8	73·2	7·1	19·7
N-(2-*Cyano*-4-*nitrophenyliminomethyl*)*piperidine*	90	136—137 [d]	$C_{13}H_{14}N_4O_2$	60·5	5·3	21·5	60·5	5·4	21·7
N-(4-Nitrophenyliminomethyl)morpholine	85	112—113 [c,f]							
N-(4-Nitrophenyliminomethyl)diethylamine	75	61—62 [c,g]							
1,4-*Di*-(4-*Nitrophenyliminomethyl*)*piperazine*	30 [h]	214—216 [i]	$C_{18}H_{18}N_6O_4$	56·4	4·8	21·9	56·6	4·7	22·0

[a] Lit.,[15,17] m.p. 178—179°. [b] Crystallised from ethanol–ether. [c] From light petroleum–ether. [d] From benzene–light petroleum. [e] From ethanol. [f] Lit.,[15] m.p. 112·5—114°. [g] Lit.,[15] m.p. 59—60°. [h] Reactants heated on an oil-bath at 120°. The low yield may be attributed to the high volatility of piperazine and *s*-triazine at this temperature. [i] From ethanol–dimethylformamide

to a sample prepared from 4-nitroaniline and triethyl orthoformate.[18]

4-*Aminobenzonitrile*.—Interaction of the amine (2·36 g.) and *s*-triazine (0·5 g.) in boiling absolute ethanol (8 hr.) yielded *NN'*-di-(4-cyanophenyl)formamidine (0·6 g., 25%), m.p. 216—217° (from ethanol), identical to a sample prepared from the amino-nitrile and triethyl orthoformate.[9] 4-Formylaminobenzonitrile (75%) was prepared from 4-aminobenzonitrile and formic acid by the method of Bogert and Wise.[8]

2-*Aminobenzonitrile*.—No changes in the i.r. and u.v. spectra were observed when samples were removed at intervals of 2 hr. from a mixture of 2-aminobenzonitrile and triethyl orthoformate at 100° (total reaction time 10 hr.). Interaction of the amino-nitrile (1·2 g.) and boiling 98—100% formic acid (10 ml.) for 1·5 hr. gave a cream solid when excess of formic acid was evaporated. Crystallisation from benzene afforded 4-hydroxyquinazoline (0·5 g.), m.p. 210—212° with an i.r. spectrum identical with that of an authentic sample.[19]

Synthesis of 4-*Aminoquinazolines*.—(a) A mixture of 2-aminobenzonitrile (1·18 g.) and *s*-triazine (0·35 g.) in absolute ethanol (4 ml.) deposited 4-aminoquinazoline (0·93 g., 64%) when the solution was boiled (8 hr.). The product had m.p. 266—268° (after sublimation) (lit.,[20] 268—269°) and $\lambda_{max.}$ (EtOH) 277infl., 284, 302infl., 312, and 324 mμ (log ε 3·78, 3·81, 3·66, 3·76, and 3·64). The same amine (60%) was formed when 2-aminobenzonitrile (1·18 g.) was boiled in formamide (5 ml.) for 2 hr. and the mixture was poured into water.

(b) Analogous interaction of 2-amino-5-methylbenzonitrile with either *s*-triazine in ethanol, or formamide, afforded 4-amino-6-methylquinazoline in 63 and 65% yields respectively. The products had m.p. 275—277° (lit.[21] 275°) after crystallisation from water, and $\lambda_{max.}$ (EtOH) 278, 285, 306infl., 317, and 330 mμ (log ε 3·65, 3·80, 3·56, 3·73, and 3·61).

(c) 2-Amino-5-bromobenzonitrile (0·8 g.) and *s*-triazine (0·15 g.) were boiled in absolute ethanol (3 ml.) and the mixture was evaporated. Crystallisation of the residue from ethanol gave 4-*amino*-6-*bromoquinazoline* (75 mg., 7%), which was further purified by sublimation (220°/10 mm.), and had m.p. 330—340° (with sublimation). The concentrated ethanolic mother liquors afforded unchanged nitrile. No improvement in the yield of bromoquinazoline was observed when pyridine, 2,4,6-trimethylpyridine, or triethylamine were employed as solvents for the same reaction time (8 hr.), but the same bromoquinazoline [(80%), m.p. and mixed m.p. 330—340° and identical i.r. spectrum] was prepared when the aminobromo-nitrile was boiled alone in formamide (2 hr.). Satisfactory elemental analyses could not be obtained for this compound. It was identified as an aminobromoquinazoline by the close similarity of its characteristic u.v. spectrum with the spectra of the aforementioned aminoquinazolines, *i.e.*, $\lambda_{max.}$ (EtOH) 283infl., 291, 313infl., 323, and 336 mμ (log ε 3·88, 3·92, 3·62, 3·73, and 3·60).

(d) Starting material was quantitatively recovered when 2-amino-5-nitrobenzonitrile was boiled with *s*-triazine in anhydrous pyridine or absolute ethanol for 8 hr.

N-(2-*Cyanophenyliminomethyl*)*piperidine*.—A mixture of 2-aminobenzonitrile (2·38 g.) and *s*-triazine (0·7 g.) in anhydrous piperidine (5 ml.) rapidly evolved ammonia when boiled (2 hr.). Excess of piperidine was evaporated off and the residue was stirred with cold benzene (10 ml.). An insoluble solid (30 mg., 1%) was identified as 4-aminoquinazoline, m.p. and mixed m.p. 266—268°. The benzene-soluble material was chromatographed on alumina. Elution (benzene) and evaporation of a pale brown band afforded the *iminomethylpiperidine* (3·97 g., 93%) which crystallised from benzene–light petroleum as cream prisms, m.p. 74—75° (Found: C, 73·1; H, 7·2; N, 19·7. $C_{13}H_{15}N_3$ requires C, 73·1; H, 7·1; N, 19·7%) and $\nu_{max.}$ (KBr) 2940 and 2860 (aliphatic CH), 2220 (CN), 1620, 1584, 1470, 1196, and 760 cm.$^{-1}$. The *picrate* (from ethanol) had m.p. 173—174° (Found: C, 51·9; H, 4·3; N, 19·1. $C_{19}H_{13}N_6O_7$ requires C, 51·6; H, 4·1; N, 19·0%), and the *toluene*-p-*sulphonate* (colourless flakes, from ethanol–ether) had m.p. 179—180° (Found: C, 62·3; H, 6·1; N, 10·8. $C_{20}H_{23}N_3O_3S$ requires C, 62·3; H, 6·0; N, 10·9%). Analogous interaction of 2-amino-5-bromobenzonitrile (1·96 g.) and *s*-triazine (0·35 g.) in anhydrous piperidine (3 ml.) yielded a brown gum following vacuum-evaporation of excess of the piperidine. This was separated into light petroleum-insoluble 4-amino-6-bromoquinazoline (20 mg.) m.p. and mixed m.p. 330—340°, and N-(5-*bromo*-2-*cyanophenyliminomethyl*)*piperidine* (2·0 g., 70%), which crystallised from light petroleum–ether as white needles, m.p.

[18] R. Walther, *J. prakt. Chem.*, 1896, **53**, 475.
[19] St. von Niementowski, *J. prakt. Chem.*, 1895, **51**, 565.
[20] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, 1946, **11**, 341.
[21] V. Oakes, H. N. Rydon, and K. Unheim, *J. Chem. Soc.*, 1962, 4678.

84—85° (Found: C, 53·4; H, 4·8; N, 14·6. $C_{13}H_{14}BrN_3$ requires C, 53·4; H, 4·8; N, 14·4%).

In the Table are recorded analogous formamidines similarly prepared. Unless otherwise stated primary amines were treated with *s*-triazine at the boiling point of the secondary amine (for 2 hr.).

Interaction of NN′-Di-(4-*nitrophenyl*)*formamidine and Piperidine*.—The formamidine (2·86 g.) was boiled in anhydrous piperidine (8 ml.) for 1·5 hr. and excess of solvent was evaporated off. A solution of the residue in hot benzene (10 ml.) deposited 4-nitroaniline (0·9 g.). The benzene-soluble material was chromatographed on alumina in benzene. Evaporation of the solvent from the yellow band afforded *N*-(4-nitrophenyliminomethyl)piperidine (2·0 g., 85%), m.p. and mixed m.p. 79—80° and identical i.r. spectrum to the sample previously prepared (see Table).

Interaction of o-*Phenylenediamine and* s-*Triazine in Piperidine*.—A solution of the diamine (2·16 g.) and *s*-triazine (0·7 g.) in anhydrous piperidine (5 ml.) rapidly evolved ammonia when boiled (2 hr.). Evaporation of the solution afforded benzimidazole (1·9 g., 80%), m.p. 169—170° after crystallisation (benzene) and identical to an authentic sample.[2]

[8/1743 *Received, November 27th*, 1968]