797. *Aminophenyl-1,2,4-triazines and Analogues and their Orientation by Proton Magnetic Resonance Spectroscopy.*

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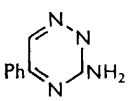
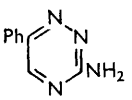
Preparations of the 3-amino-5- and 3-amino-6-phenyl-1,2,4-triazines (I) and (II), have been repeated and the orientations of the products investigated by proton magnetic resonance measurements. Previous work by others is thereby corrected. The proton resonance spectra of pyrazine and pyridazine were measured to provide comparative data.

Several other 1,2,4-triazines have been examined and it is shown that the orientation of alkyl derivatives can also be determined by proton resonance.

Interaction of phenylglyoxal hydrate, A, with aminoguanidine hydrochloride, B, has been claimed [1] to yield either the monoguanylhydrazone (IV) or one of the 1,2,4-triazines (I), (II), and (III), depending on the conditions as listed *a*–*e* in Table 1. The triazine


(I)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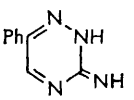
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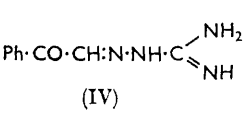
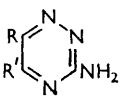

(IV)


(V)

structure (I) was certain, this compound having been deaminated to a product identical with that [2] from the unambiguous cyclisation of carbamylazoacetophenone. The structure of the triazine (II) required confirmation whilst that of the tautomeride (III) appeared

[1] Ekely, Carlson, and Ronzio, *Rec. Trav. chim.*, 1940, **59**, 496.
[2] Wolff, *Annalen*, 1902, **325**, 129.

suspect because this product was stated to yield a hydrochloride and an acetyl derivative distinct from the corresponding derivatives of the triazine (II).

We find that the true situation is as indicated in the last column of Table 1.

TABLE 1.

Literature method	Product claimed	Lit. m. p.	Our m. p.	Acetyl deriv. Lit. m. p.	Acetyl deriv. Our m. p.	Actual product
a. A + B, heated in H_2O cooled and made slightly alkaline	(IV)	183° decomp.	183° decomp.			(IV)
b. (IV) heated to 183°	(I)	233—235	235	182—184°	184°	(I)
c. A + B, boiled in H_2O, excess of NaOH added	(I)	233—235	235	182—184°	184°	(I)
d. A + B, in H_2O, excess of NaOH added	(II)	175	170—174	219—225	*ca.* 218	(I) + (II)
e. A in H_2O, excess of NaOH added, then B	(III)	192—193	197	219—221	227	(II)

A = phenylglyoxal hydrate. B = aminoguanidine hydrochloride.

Support for structure (IV) of the monoguanylhydrazone was provided by the lack in the infrared spectrum of C–H and C=O bands characteristic of an aldehyde function. Cyclisation of this guanylhydrazone at its melting point (method *b*) necessarily provided 3-amino-5-phenyl-1,2,4-triazine (I), identical with the triazine obtained from method *c*, and having the properties previously described.

Preparations *d* and *e* were repeated, and it was confirmed that the products (m. p.s given in Table 1) had the same elementary composition as the triazine (I). (The acetyl derivatives were also prepared.) The infrared absorption spectrum of the product from method *e* was distinct from that of the triazine (I), but the spectrum of the product from *d* showed that this was a mixture of the triazine (I) with the compound from *e*. The last compound evidently had an aminotriazine structure similar to (I), judging from the infrared and ultraviolet absorptions.

It appeared from these several observations that the preparations *b*—*e* provided only two triazines and a mixture of the two, and that the second triazine was not a tautomeride but the positional isomer of (I). An attempt to prove its structure by a synthesis from the guanylhydrazone of phenylglyoxal oxime was abandoned because of difficulty in deoximating this compound. However the constitution of the second triazine as 3-amino-6-phenyl-1,2,4-triazine (II) was demonstrated by proton magnetic resonance spectroscopy (see below). The actual products from the preparations were then as indicated in the last column of Table 1. Construction of a melting point–composition diagram for the triazines (I) and (II) indicated that the mixture from method *d* consisted of about 34% of (I) with 66% of (II).

Whilst the earlier conclusion [1] that one of the products was the tautomeride (III) is incorrect [as also was the identification of (II)], the comments on the course of the cyclisation reactions are reasonable. Reaction *c* gives (I) as expected. Addition of alkali to aqueous phenylglyoxal hydrate (as in method *e*) yields the anion $Ph{\cdot}CO{\cdot}CH\langle^{O^-}_{OH}$ so that condensation with aminoguanidine should then occur at the ketonic carbonyl, leading to the isomeric triazine (II), as we now find.

Other 3-amino-1,2,4-triazines (V) substituted in the 5- and/or 6-positions were prepared from aminoguanidine hydrochloride and the appropriate vic.-dicarbonyl compound.

Benzil and furil slowly gave the 5,6-disubstituted products. In contrast to phenylglyoxal hydrate, t-butylglyoxal afforded a single triazine shown to be the 5-t-butyl compound by proton resonance spectroscopy.

Biacetyl and bibutyryl reacted best with an aqueous suspension of aminoguanidine hydrogen carbonate. The sparing solubility of this salt evidently reduces osazone formation, so that cyclisation of the monoguanylhydrazone suffers little competition.[3]

[3] Erickson, *J. Amer. Chem. Soc.*, 1952, **74**, 4706.

The proton magnetic resonance spectrum of the established 5-phenyltriazine (I) showed expected features (Table 2). There was a slightly broadened signal (of intensity two) from the amino group, and a sharp singlet from the 6-proton. The latter signal was at τ 0·87, a position comparable to that of the α-protons in pyridazine (0·76). The five protons of the phenyl substituent gave two bands, of intensity two and three, the former being at the lower field. This suggested that the phenyl ring was more or less coplanar with the triazine ring, the two *ortho*-protons thereby being relatively deshielded (cf. refs. 4*a*, 5). Consistent with this was the fact that 3-amino-5,6-diphenyl-1,2,4-triazine, in which the phenyl groups could not approach coplanarity with the triazine ring, gave a compact signal from the ten phenyl-protons. Any difference in shielding between the phenyl groups, arising from their attachment to different positions of the triazine ring, was evidently no more than 0·1—0·2 p.p.m. A similar conclusion was drawn from the spectrum of the 5,6-di-2′-furyl analogue.

The spectrum of the second monophenyltriazine, m. p. 197°, resembled that of the triazine (I), except that the signals were displaced. The various shifts were indicative of the positionally isomeric structure (II). Thus the singlet signal was at τ 1·40 (Table 2), a

TABLE 2.

Proton magnetic resonance results for 5—10% solutions in (*a*) dioxan, (*b*) $CDCl_3$, and (*c*) Me_2SO, containing 0·2% $SiMe_4$.

Compound	τ	Intensity	Multiplicity	Assignment
(I) *a*	3·65	2	broadened	NH_2
	2·49	3	complex	Ph
	1·88	2	complex	Ph
	0·87	1	singlet	6-H
(II) *a*	3·55	2	broadened	NH_2
	2·59	3	complex	Ph
	2·04	2	complex	Ph
	1·40	1	singlet	5-H
Pyrazine * *b*	1·50	4	singlet	all ring H's
Pyridazine * *b*	2·50	2	triplet } *J* 3·45 c./sec.	4,5-H's
	0·76	2	triplet } *J* 3·45 c./sec.	3,6-H's
(V; R = R′ = Ph) *a*	3·60	2	broadened	NH_2
	ca. 2·67	10	compact band	5,6-Ph's
(V; R = R′ = 2′-furyl) *c*	3·53	1	doublet *J* 3·8 c./sec.	5(?)-furyl-3′-H
	ca. 3·27	3	complex	furyl H's
	2·44	2	broadened	NH_2
	2·14	1	narrow multiplet	5(?)-furyl-5′-H
	2·05	1	narrow multiplet	6(?)-furyl-5′-H
(V; R = H, R′ = t-Bu) *a*	8·71	9	singlet	Me_3C
	3·72	2	broadened	NH_2
	1·25	1	singlet	6-H
(V; R = R′ = Me) *c*	7·70	3	singlet	5-Me
	7·60	3	singlet	6-Me
	3·35	2	broadened	NH_2
(V; R = R′ = Pr) *b*	8·98	6	triplet, *J* 7 c./sec.	two CH_3'S
	ca. 8·26	4	ragged sextuplet	" middle " CH_2's
	7·38	2	*ca.* triplet	5-CH_2
	7·20	2	*ca.* triplet	6-CH_2
	3·10	2	broadened	NH_2

* Commercial specimens with correct physical constants: the spectra were consistent with the compounds' being pure (pyridazine constitutes an A_2X_2 spin system).

position close to that of the α-protons of pyridine [4b] and the protons of pyrazine (1·50), showing that the proton on the 1,2,4-triazine ring was now at the 5-position. As in compound (I), the phenyl group was evidently effectively coplanar with the triazine ring, the two *ortho*-protons giving a multiplet signal separate from, and at lower field than, the other three. The two bands were shifted up-field slightly, consequent upon the phenyl group in

[4] Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, (*a*) p. 126, (*b*) p. 64, (*c*) p. 63, (*d*) pp. 126, 128.
[5] Butt and Elvidge, *J.*, 1963, 4483.

(II) being *para* to an (electron-donating) amino-group (cf. ref. 4*c*). A further consequence of the new positions of the substituents was the small down-field shift of the amino-group signal (resulting from electron-withdrawal at the *para*-position). These various observations together made the structure (II) certain.

The " third triazine," from method *d* (above), gave a proton resonance spectrum in agreement with its being a mixture of compounds (I) and (II) in the proportions found from the m. p.–composition diagram.

With the reference data provided by the two monophenyltriazines (I) and (II), orientation of the mono-t-butyl compound was readily achieved. It was clear that hypothetical replacement of the phenyl by a t-butyl substituent in either compound (I) or (II) could not shift the resonance position of the triazine-ring proton paramagnetically. Indeed a diamagnetic shift of about 0·3 p.p.m. is predicted from the data for *o*-phenyl [4d] and *o*-alkyl [4c] substituent shifts. The above replacement in structure (I) (with τ_{6H} 0·87) would then lead to a ring-proton signal near τ 1·17, whereas the replacement in structure (II) (with τ_{5H} 1·40) would lead to a signal near τ 1·70. The observed value of τ 1·25 thus unambiguously indicated that the proton responsible was at the 6-position. The compound was therefore the 3-amino-5-t-butyl-1,2,4-triazine (V: R = H, R′ = t-Bu).

The proton resonance spectra of the 5,6-dimethyl and -dipropyl compounds (V) reflected the difference in shielding at the 5- and the 6-position of the 3-amino-1,2,4-triazine ring. Thus the signals from the side-chain protons α to these ring-positions were 0·1—0·2 p.p.m. apart (Table 2). Hence it would be possible to determine the orientation of many unsymmetrical 5,6-dialkyl analogues by proton resonance spectroscopy.

Finally, some comments concerning the basis of our spectral deductions should perhaps be made. The line-positions of the *ortho* (and other) protons of a phenyl substituent do not reflect the overall shielding at the point of attachment to another aryl-type ring because they are too far removed. They reflect the inductive and mesomeric influences operative there provided the substituent and parent rings are sufficiently coplanar for through-conjugation. In contrast, the chemical shift of the protons of a methyl substituent does give a measure of the total shielding at the point of attachment. Methyl shifts vary in the same sense as ring-proton shifts, though to a smaller extent (cf. ref. 6). This is because they are relatively insensitive to the mesomeric and inductive contributions to the local magnetic shielding.

Experimental

Ultraviolet and infrared absorptions were measured, respectively, with a Unicam S.P. 500 spectrophotometer, and a Grubb-Parsons S.4. double-beam spectrometer with NaCl optics.

Phenylglyoxal,[7] b. p. 101°/27 mm., $\nu_{max.}$ (liquid film) 3067, 2956, 2838 (CH); 1723s (CHO), 1694s (CO), 1603s, 1582, 1453s, 1429, 1320, 1283s, 1229, 1183w, 1124sb, 1073w, 1000sb, 871wb, 770, 718, 691s, cm.$^{-1}$, with warm water gave the hydrate, m. p. 72°, $\nu_{max.}$ ($CHCl_3$) 3478 (OH), 3037 (CH), 1693s (CO), 1604, 1584w, 1449, 1426sh, 1335w, 1310sh, 1279s, 1201sh, 1120, 1092s, 1070, 1003, 972s, 929w, 901w, cm.$^{-1}$, from which the monoguanylhydrazone [1] was prepared as golden plates, m. p. 183°, from water (Found: C, 57·3; H, 5·5; N, 29·3. Calc. for $C_9H_{10}N_4O$: C, 56·8; H, 5·3; N, 29·5%). $\nu_{max.}$ (Nujol Mull) 3493, 3407, 3323 (NH); 3051 (NH or CH), 1662s (CO), 1612s, 1581s, 1493w, 1345s, 1279s, 1185w, 1163sb, 1079w, 1060sb, 1020, 986b, 892, 786, 770w, 758w, 734w, 708, 702w cm.$^{-1}$

3-*Amino*-5-*phenyl*-1,2,4-*triazine* (I).—(i) At 183° the monoguanylhydrazone gave the triazine, m. p. 232°. (ii) The same product (mixed m. p. undepressed; identical i.r. spectrum) was obtained by adding phenylglyoxal hydrate (4·56 g.) to a slightly acid solution of aminoguanidine [from 4·14 g. (an excess) of the hydrogen carbonate [8] and 2N-hydrochloric acid], heating to the b. p., adding an excess of 30% sodium hydroxide (5 c.c.), and cooling. From ethanol, the triazine (3·5 g.) formed pale yellow laths, m. p. 235° (Found: C, 63·0; H, 4·9; N, 32·3. Calc. for $C_9H_8N_4$: C, 62·8; H, 4·7; N, 32·5%), $\lambda_{max.}$ (in EtOH) 272, 333 mμ (10^{-3}

[6] Elvidge and Jackman, *J.*, 1961, 859.
[7] Riley and Gray, *Org. Synth.*, Coll. Vol. p, II, 509.
[8] Shriner and Neumann, *Org. Synth.*, Coll. Vol. III, p, 73.

ε 11·2, 8·1), $\nu_{max.}$ (Nujol Mull) 3265, 3085 (NH_2); 1654s (NH_2 def.), 1584w, 1531s, 1310, 1288w, 1214w, 1163w, 1129s, 1073w, 1049, 1025, 1015w, 916, 862, 849w, 770s, 747, 696s cm.$^{-1}$.

The acetyl derivative, m. p. 184°, from aqueous ethanol, had $\nu_{max.}$ (Nujol mull) 3152 (NH), 1713s (CO), 1589w, 1574 (amide-II), 1540, 1507s, 1491w, 1445 (C–CH_3as.), 1396s (C–CH_3 sym.), 1314, 1283, 1245s, 1179w, 1159, 1107, 1077, 1037, 1014, 1002w, 993, 890, 795b, 774s, 700s cm.$^{-1}$.

3-*Amino*-6-*phenyl*-1,2,4-*triazine* (II).—(i) A cold solution of phenylglyoxal hydrate (4·56 g.) in water was treated with 30% sodium hydroxide (3 c.c.) and then aqueous aminoguanidinium chloride (from 1·36 g. of the hydrogen carbonate). The precipitate was washed with water to remove a purple colour, and crystallised 4 times from ethanol to give pale straw-coloured needles (0·8 g.), m. p. 197°, of 3-*amino*-6-*phenyl*-1,2,4-*triazine* (Found: C, 62·8; H, 4·7, N, 32·0%), $\lambda_{max.}$ (in EtOH) 266, 343 mμ (10^{-3} ε 27·0, 4·2), $\nu_{max.}$ (Nujol mull) 3316, 3139 (NH_2); 1662s (NH def.), 1625, 1574s, 1512, 1310w, 1270w, 1178w. 1122, 1078, 1050s, 1033, 953w, 867, 807s, 762s, 756, 691s cm.$^{-1}$.

(ii) To a stirred solution of phenylglyoxal hydrate (4·55 g.) in water, 30% sodium hydroxide (3 c.c.) was added, followed (dropwise) by aqueous aminoguanidinium chloride (from 4 g. of the hydrogen carbonate). After 1 hour's stirring, the purple precipitate was chromatographed in chloroform on alkaline alumina (Spence, type H) to afford, after evaporation of the first clear yellow runnings, substantially pure 3-amino-6-phenyl-1,2,4-triazine which crystallised from methanol as straw-coloured needles (3 g., 58%), m. p. 191—193°.

The acetyl derivative, m. p. 277°, from aqueous ethanol, had $\nu_{max.}$ (Nujol mull) 3158 (NH), 1713s (CO), 1585 (amide-II), 1542, 1508, 1486, 1446 (C–CH_3 as.), 1405 (C–CH_3 sym.), 1329, 1235s, 1192w, 1109, 1079w, 1059, 1038w, 1022w, 1007, 953w, 922w, 810s, 773sh, 761s, 690s cm.$^{-1}$.

Mixture of Triazine (I) *and* (II).—Phenylglyoxal hydrate (4·56 g.) in water was added to aqueous aminoguanidinium chloride (from 4·14 g. of the hydrogen carbonate) and then 50% potassium hydroxide was added in drops until the solution was just alkaline (to thymol blue). Crystallisation of the greenish-blue precipitate 3 times from ethanol afforded pale straw crystals (1·2 g.), m. p. 170—174° (Found: C, 62·9; H, 4·8; N, 32·45%). Under the microscope the substance appeared as a mixture of needles and small clusters of plates, and both the u.v. and i.r. absorptions were indicative of a mixture of triazines (I) and (II). Acetylation afforded a product, m. p. *ca.* 218°.

Mixtures (10 mg. each) containing the following percentages of pure triazine (I) (m. p. 235°) with pure triazine (II) (m. p. 197°) were melted and allowed to solidify, and the m. p.'s were then determined: 90, 227—232°; 80, 215—223°; 70, 206—215°; 50, 193—197°; 40, 184—186°; 30, 176—184; 20, 184—185°; 10, 192—194°; 5, 194—197°.

Guanylhydrazone of Phenylglyoxal Oxime.—α-Hydroxyimino-β-oxo-β-phenylethane [9] (3·3 g.) in 50% aqueous ethanol was refluxed with aqueous aminoguanidinium chloride (from 3·3 g. of the hydrogen carbonate) for 4 hr. Addition of aqueous ethanolic picric acid gave the *picrate* (4·2 g.), m. p. 208—210°, from aqueous ethanol (Found: C, 41·9; H, 3·5; N, 26·2. $C_{15}H_{14}N_8O_8$ requires C, 41·5; H, 3·2; N, 25·8%).

3-*Amino*-5,6-*diphenyl*-1,2,4-*triazine* [10] was obtained by stirring benzil (21 g.) in ethanol with aqueous aminoguanidinium chloride (from 7·4 g. of the hydrogen carbonate) for 2 days and adding an excess of N-sodium hydroxide. Crystallisation of the product (12 g., 54%) from ethanol–water (charcoal) afforded pale yellow needles, m. p. 176·5—177·5° (Found: C, 72·4; H, 4·95; N, 22·4. Calc. for $C_{15}H_{12}N_4$: C, 72·6; H, 4·9; N, 22·6%).

3-*Amino*-5,6-*di*-2′-*furyl*-1,2,4-*triazine*.—Furil (9·5 g.) was stirred with ethanol (450 c.c.), 25% sodium hydroxide (10 c.c.) was added, and then aqueous aminoguanidinium chloride (from 3·7 g. of the hydrogen carbonate). The solution was kept (14 days) until the product had separated (yield, 5·5 g., 55%). Crystallisation from methanol gave the *triazine* as straw-coloured needles, m. p. 234—235·5° (Found: C, 57·75; H, 3·75; N, 24·3. $C_{11}H_8N_4O_2$ requires C, 57·9; H, 3·5; N, 24·55%).

3-*Amino*-5-t-*butyl*-1,2,4-*triazine*.—Portions (1 c.c.) of aqueous aminoguanidinium chloride (from 17·3 g. of the hydrogen carbonate) were stirred into t-butylglyoxal [11] (14·5 g.) in ethanol (40 c.c.), the solution being adjusted to pH 7 with 5% sodium hydroxide after each addition. The mixture was then shaken for 2 hr., a slight excess of 25% sodium hydroxide was added, and the precipitate collected. From benzene, the *triazine* (5·5 g., 28%) crystallised as needles,

[9] Slater, *J.*, 1920, 587.
[10] Thiele and Bihan, *Annalen*, 1898, **302**, 299.
[11] Fuson, Gray, and Gouza, *J. Amer. Chem. Soc.*, 1939, **61**, 1937.

m. p. 187—189° (Found: C, 55·1; H, 8·0; N, 36·6. $C_7H_{12}N_4$ requires C, 55·2; H, 7·95; N, 36·8%).

3-*Amino*-5,6-*dimethyl*-1,2,4-*triazine* [3] gave pale yellow crystals, m. p. 209·5—211°, from ethanol–toluene.

3-*Amino*-5,6-*dipropyl*-1,2,4-*triazine*.—Bibutyryl (10 g.) made [12] from butyroin, was stirred with powdered aminoguanidinium hydrogen carbonate (5·5 g.) and water (60 c.c.) for 1 day, during which carbon dioxide was evolved. By warming the mixture on the steam-bath for 2 hr., and adding a little ethanol, a clear solution was obtained, from which the product crystallised (4·5 g., 36%). Recrystallisation from ethanol–water gave diamond-shaped crystals of the *triazine*, m. p. 115—117° (Found: C, 59·7; H, 9·0; N, 31·55. $C_9H_{16}N_4$ requires C, 60·0; H, 8·95; N, 31·1%).

We are glad to acknowledge a maintenance grant (to T. G. S.) from the Surrey County Council. One of us (J. A. E.) thanks Professor D. H. R. Barton, F.R.S., for access to a Varian A60 spectrometer on permanent loan to him from the Trustees of the Wellcome Foundation.

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[*Received, January* 21*st*, 1964.]

[12] Bloch, Lehr, Erlenmeyer, and Vogler, *Helv. Chim. Acta*, 1945, **28**, 1410.