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SYNTHESES AND SPECTRAL CHARACTERISTICS OF 6-MONO-, 3,6-DI- AND 3,5,6-TRISUBSTITUTED-1,2,4-TRIAZINES

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Abstract—The reaction of acidhydrazides with α-substituted carbonyl compounds in the presence of metal acetates gives substituted 1,2,4-triazines. These cyclisations could be effected without any added acetate by refluxing in dimethyl formamide, pyridine/acetic acid or dimethyl sulfoxide. Sixty-five 3,5,6-tri-, 3,6-di- and 6-monosubstituted-1,2,4-triazines (in 50–90% yields) with a wide variation in the C_3-substituent (alkyl, aryl or heteryl) and the C_6-substituent (aryl or heteryl) are reported. The mechanistic path followed in the formation of these compounds is discussed.

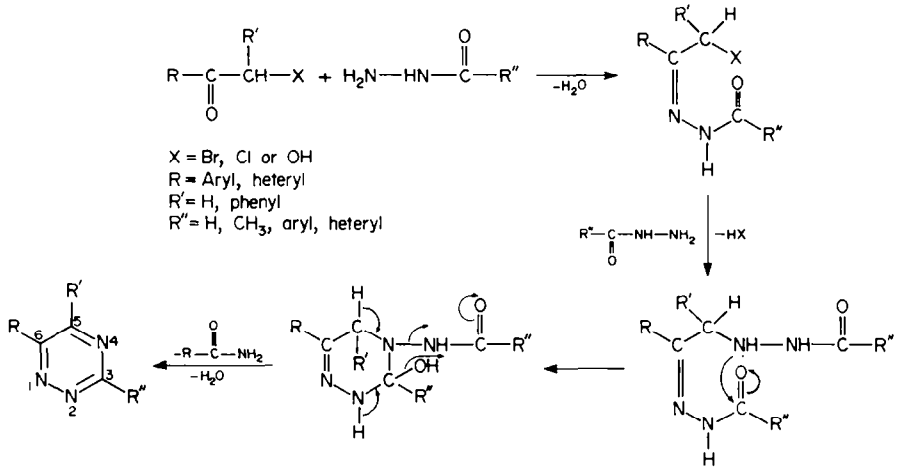
Although a number of functionally-substituted 1,2,4-triazines have been prepared, few reports on the synthesis of non-functionally substituted 1,2,4-triazines and their applications are available. Two general routes for non-functionally substituted 1,2,4-triazines make use of the condensation of α-diketones with hydrazides[1-7] or hydrazidines[8-10] which do not lead to straightforward products. A third method involves the cyclisation with hydrazine of α-acylaminoketones[11-13] which themselves are prepared by multistep sequences in poor overall yields. All these methods afford the 5,6-diaryl- or dialkyl triazines with anomalous results, poor overall yields and mixtures of isomers. Only two 3,6 - disubstituted - 1,2,4 - triazines, 3,6-diphenyl-[11,13] and 3-methyl-6-phenyl-[11] 1,2,4-triazines have been reported thus far.

We had reported earlier[14] a facile procedure for the synthesis of 6-mono- and 3,6-disubstituted 1,2,4-triazines by the reaction of acidhydrazides with a halomethylketone.† The rationale for this reaction was based on the use of an excess of acid hydrazide, which would provide in addition to the contiguous nitrogen atoms, the third nitrogen of the heterocycle through a concomitant or a subsequent N–N fission of the intermediate with the extruded amide anion abstracting a proton from the carbon at the potential 5-position of the final product, the whole sequence being driven to completion by the aromatisation realised as a result of these transformations (Scheme 1).

This paper reports full details on the application of this procedure for the synthesis of a variety of non-functionally substituted 1,2,4-triazines.

In the initial stages of this work when an acid hydrazide and an α-halomethylketone were taken in 2:1 molecular proportion in the minimum quantity of ethanol and left aside overnight, slow precipitation of high melting, poorly soluble crystalline products took place. The IR spectra of several compounds prepared in this way revealed the presence of carbonyl groups indicating that the reaction had not proceeded in the anticipated direction and suggested that the products obtained could be the uncyclised hydrazones. Thus, the crystalline product (Fig. 1, R = R″ = Ph) obtained by the reaction of phenacyl bromide and benzhydrazide analysed for $C_{22}H_{20}N_4O_2$, melted at 232°C, was poorly soluble in a variety of organic solvents, with its IR spectrum revealing the presence of $\diagdown C{=}O$ group. Its NMR spectrum (determined in DMSO-d_6), showed the presence of two methylene protons at 3.40 ppm as a broad singlet and complex peaks ranging

†Only two instances[15-18] of the use of an α-halomethylketone in the synthesis of 1,2,4-triazines are known.



Scheme 1.

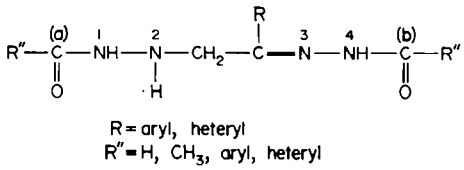


Fig. 1.

from 7.41–8.50 ppm integrating for 15 protons. Two sharp singlets at 8.80 and 12.40 ppm and a broad peak at 14.60 ppm in the spectrum each integrating for one proton were assignable to the three different-NH-protons. While the absorption at 14.40 ppm may be due to the most deshielded N_4 proton, the 12.33 ppm absorption to the slightly less deshielded N_1 proton and the 8.65 ppm absorption to the least deshielded N_2 proton, the possibility exists of the N_2 proton involving itself in hydrogen bonding with the carbonyl group (a). How this will affect the spectrum is still not clear.†

Its gross structure thus became evident as (Fig. 1, R = R'' = Ph). Products similar in properties to this were formed by the reaction of other α-halomethylketones with various carboxylic acid hydrazides. Twenty of these carboxylic acid 2,2'-(2-substituted-1-ethanyl-2-ylidene)dihydrazines (Fig. 1) were prepared and characterised by their high m.ps and poor solubility. M.ps, yields, IR data and other relevant data on these are collected in Table 4.

Attempts to cyclise the benzoic acid 2,2'-(2-phenyl-1-ethanyl-2-ylidene) dihydrazide (Fig. 1, R = R'' = Ph) under a variety of reaction conditions using different reagents did not effect any change. On this basis, it is presumed that the product, once formed, is stable and does not allow of cyclisation and this is, perhaps, the case with other members of this series.

However, a mixture of an acid hydrazide and an ω-haloacetophenone (2:1), in AcOH when heated on a boiling water-bath in the presence of molar quantities of AgOAc for a few minutes, resulted in 3,6-disubstituted 1,2,4-triazines in excellent yields. That the product from benzhydrazide and phenacyl bromide is indeed 3,6-diphenyl-1,2,4-triazine was proved by its m.p.,[11,13] by authentication[11] and by several other spectral features discussed in the following paragraphs. Following such a procedure, twenty-two 3,6-diaryl-1,2,4-triazines were prepared in 60–80% yields (Table 5). Extending this procedure, three 3-methyl-6-aryl-1,2,4-triazines were also obtained by reaction of acethydrazide with different phenacyl bromides. The products had to be purified by column chromatography and were obtained in about 50% yield (Table 6). The need to use formhydrazide, incompatible with AgOAc and which would have to be used for the synthesis of 6-monosubstituted 1,2,4-triazines, necessitated reaction in the presence of NaOAc or KOAc and even these acetates are effective in this reaction. Three 6-monosubstituted-1,2,4-triazines‡ were prepared by using NaOAc (Table 6). The products are obtained by diluting the reaction mixture and were purified by crystallisation or through chromatography. Apart from aromatic acid hydrazides, heterocyclic acid hydrazides such as nicotinic, isonicotinic, 2-furoic and 2-thenoic acid hydrazides also reacted not only with aromatic α-bromomethylketones but also with heterocyclic α-bromomethylketones to yield the corresponding 3,6-disubstituted 1,2,4-triazines. These products could be isolated only through column chromatography in 60–80% yield (Table 6). The reaction proceeded equally well with NH_4OAc in boiling EtOH. The role of the added acetate has not been still clearly understood, but it can be stated that without added acetates the reaction between acid hydrazides and α-bromomethyl ketones in AcOH or EtOH leads only to uncyclised products (Fig. 1). The postulated mechanistic steps indicated were confirmed by the isolation in four cases of the elimination product, the amide, corresponding to the acid hydrazide.

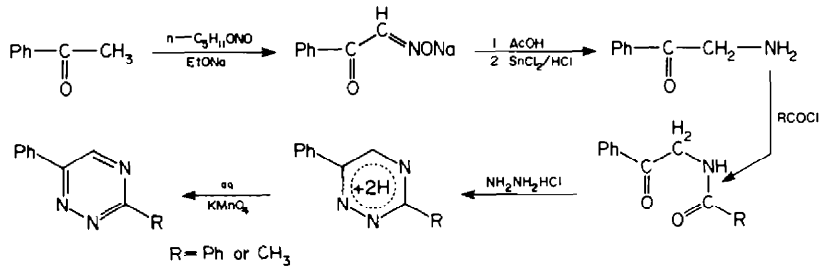
Furthermore, it has also been possible to effect these cyclisations without any added acetates, by a mixture of pyridine-acetic acid (2:3) on a boiling water-bath (1 hr) or dimethyl sulfoxide on a boiling water-bath (15 min) or in dimethyl formamide on an oil-bath at 120°C (1 hr). The conditions under which this facile one-step reaction proceeded prompted an extension of this reaction to the synthesis of 3,5,6-trisubstituted 1,2,4-triazines. When aromatic acid hydrazides were heated with benzoin in 2:1 proportion in acetic acid in the presence of three molar proportions of NaOAc and the reaction product chromatographed on neutral alumina, benzil (formed by oxidation of the unreacted benzoin on the surface of the adsorbent[20]) and the expected trisubstituted 1,2,4-triazines were obtained. A number of 3-aryl- or heteroaryl-5,6-diphenyl-1,2,4-triazines have been obtained thus in 50–60% yields and data are included in Table 6. 3,5,6-Triphenyl-1,2,4-triazine was also prepared by using desyl chloride and benzhydrazide in acetic acid and AgOAc and also by refluxing in dimethylformamide. The product was purified by column chromatography and was obtained in 60% yield, m.p. 148°C.[1,13,20]

Attempts to synthesise the parent heterocycle, by reaction of bromacetal with formhydrazide, and 3-substituted 6-methyl-1,2,4-triazines using suitable hydrazides and chloroacetone resulted only in formation of unidentifiable products. The failure of alkyl-α-halomethyl ketones or α-halomethyl aldehydes to react with acid hydrazides forming 1,2,4-triazines is understandable on the basis of the lack of an electron withdrawing group on the relevant carbon atom.

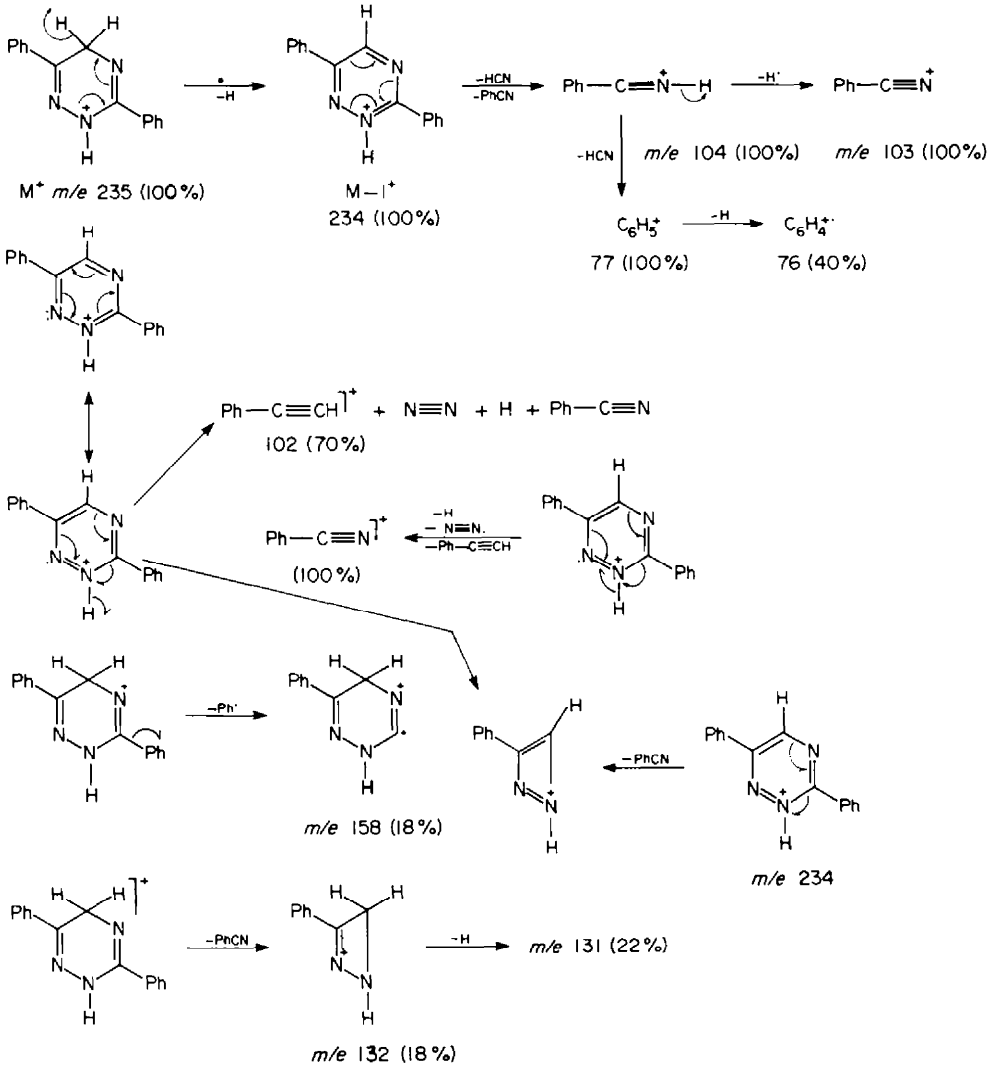
Two compounds were authenticated by an unambiguous synthesis as shown in Scheme 2. The penultimate stage in this synthesis is the formation of dihydrotriazines whose structures have not been established so far. A 1,2-,[11] 2,5- or 4,5-[12] dihydro-structure has been proposed for these intermediates. However, the 1,2-, 2,3- or 5,6-dihydrostructures were excluded by IR studies by Atkinson and Cossey.[13] Attempted methylation by these authors[13] to differentiate between the 2,5- or 4,5-dihydrostructures failed. Our study of the NMR spectrum of the 3,6-diphenyl-dihydro-1,2,4-triazine obtained (Scheme 2; R = Ph) during the authentication of the reaction product from benzhydrazide and phenacyl bromide clearly indicates that this dihyuro compound has a 2,5-dihydro structure and not the alternative 4,5-dihydro structure because of the clear methylene peak appearing as a singlet at 4.55 ppm. The 4,5-dihydro structure would show a doublet for the methylene due to coupling with the -NH-proton. This aspect was also confirmed by the mass spectrum (Scheme 3) of this compound, which does not

†High resolution NMR studies through the use of model compounds are in progress to confirm the structure and geometry of these compounds.

‡Only one instance° of a 6-monosubstituted-1,2,4-triazine—6-phenyl-1,2,4-triazine (formed along with 5-phenyltriazine) is known. This is obtained by reaction of phenyl glyoxal and formimidic acid hydrozone hydrochloride.



Scheme 2.



Scheme 3.

show a nitrogen loss (M-28' ion peak is absent) as the first change on electron impact. The absence of M-28' ion therefore rules out the 4,5-dihydro structure. It is interesting to note the M^+ ion (100%) losing a H° to give the $(M-1)^+$ ion (also 100%), a transformation supported by the presence of a metastable peak. Degradation under electron impact (shown in the scheme) fits in only with the 2,5-dihydro structure. When these dihydro compounds were dehydrogenated with neutral $KMnO_4$, products identical with the corresponding ones obtained in the reaction between benzhydrazide and phenacyl bromide and acethydrazide and phenacyl bromide resulted.

Atkinson and Cossey[13] reported an absorption of 283–285 nm ($\log \epsilon$ 4.45) for 3,6-diphenyl-1,2,4-triazine. Some of the compounds presently prepared absorb in the 283–311 nm region with $\log \epsilon_{max}$ around 4.45–4.60. In the compounds where the 3-substituent is 3,4,5-trimethoxyphenyl or is a p- or m-substituted phenyl group there is an additional maximum in the 242–256 nm region. The absorption at around 283–311 nm can be assigned to the

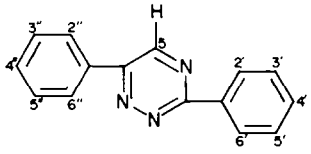
3,6-diaryl-1,2,4-triazine chromophore which exhibits continuous conjugation spread over three ring systems. Chang[21] ascribed a band of medium intensity at 730–750 cm^{-1} to the 1,2,4-triazine ring. Loving *et al.*[22] ascribed four medium to strong bands around 1200, 1160, 1070 and 1045 cm^{-1} to the 1,2,4-triazine ring. The IR spectra of a series of five compounds prepared now (Table 5) are in consonance with the above data.[21,22]

Only one earlier reference[8] is available on the NMR spectra of 1,2,4-triazines, Tables 1–3 report the NMR data obtained now.

In all the 3,6-diaryl triazines the C_5 proton is the most deshielded one and appears around 8.86–9.16 ppm consistent with its position, but in 6-phenyl-1,2,4-triazine the C_5 proton is more deshielded (9.45 ppm) as it is subjected to the N-anisotropic effects of N_2 and N_4. In 3-(3'-pyridyl)-6-phenyl-1,2,4-triazine the 6'-proton of the pyridine ring absorbs at 9.83 ppm due to its siting at a position where the normal deshielding effects of the N_2 and N_4 atoms are intensified by the deshielding effects of the N_1' of the pyridine ring (Table 3).

The 2',6' protons, 2'',6'' protons, 3',4',5' protons and the 3'',4'',5'' protons absorb from low to high field in this order. The absorptions of the 2',6' protons and 2'',6'' protons appear as multiplets when the phenyl rings are unsubstituted, as doublets (with J value of 9 Hz) when the para position is substituted and as singlets (compounds 7, 9 and 10, Table 1) when the 3',4',5' positions are substituted. The assignments of the various absorptions are confirmed because the 2',6', 3',5', 2'',6'' and 3'',5'' absorptions are all doublets with exact J values when the 4' and 4'' positions carry substituents. The doublets are all half the AB quartet pattern, easily recognisible even with absorptions of other protons in between the AB quartets. A nitro group (compounds **9** and **10**, Table 1) at 3'' and 4'' positions shifts the C_6 phenyl protons absorptions to lower fields. The three methoxy groups (compounds **7**, **9** and **10**, Table 1) shield the 2',6' protons so much as to shift the absorption diamagnetically. That this absorption (7.86 ppm) is due to the 2',6' protons is also confirmed by the fact that it is a sharp singlet. The C_3'',C_5'' furan ring protons absorb along with the 3',4',5' protons. The most shielded C_4'' proton of the furan ring appears as a quartet (Table 2).

Table 1.



No.	3-Substituent	6-Substituent	C_5 H	2',6' H	2'',6'' H	3',4',5' H	3'',4'',5'' H	4'-Substituent	4''-Substituent
1	H(9.45 s)	C_6H_5–	8.96 s	—	7.91 m	—	7.36 m	—	H
2	CH_3(2.86 s)	C_6H_5–	8.86 s	—	8.01 m	—	7.48 m	—	H
3	C_6H_5–	C_6H_5–	8.86 s	8.41 m	8.00 m	7.42 m	7.42 m	H	H
4	4Me–C_6H_4–	C_6H_5–	8.96 s	8.53 d	8.17 m	7.46 d	7.60 m	CH_3 (2.41 s)	H
5	4MeO–C_6H_4–	C_6H_5–	9.00 s	8.58 d	8.15 m	7.12 d	7.57 m	MeO (3.96 s)	H
6	C_6H_5–	4Me–C_6H_4–	8.96 s	8.58 m	8.03 d	7.51 m	7.33 d	H	CH_3 (2.38 s)
7	3,4,5-$(MeO)_3$–C_6H_2–	C_6H_5–	8.96 s	7.86 s	8.13 m	$(MeO)_3$ (3.96 s)	7.55 m	MeO (3.96 s)	H
8	4Me–C_6H_4–	4Me–C_6H_4–	8.95 s	8.48 d	8.03 d	7.33 d	7.33 d	CH_3 (2.41 s)	CH_3 (2.41 s)
9	3,4,5-$(MeO)_3$–C_6H_2–	3NO_2–C_6H_4–	9.08 s	7.86 s	8.50 m	$(MeO)_3$ (4.00 s)	3''NO_2 5''7.80 m	MeO (4.00 s)	H (9.00 m)
10	3,4,5-$(MeO)_3$–C_6H_2–	4NO_2–C_6H_4–	9.16 s	7.96 s	8.45 s	$(MeO)_3$ (4.06 s)	3'',5'' 8.45 s	MeO (4.06 s)	NO_2

s = singlet; d = doublet; m = multiplet; All doublets have a J value of 9 Hz.

Table 2.

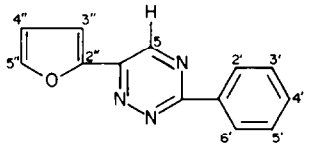
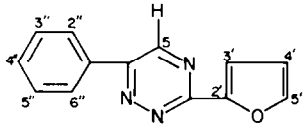
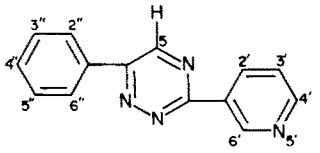
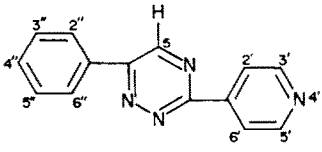
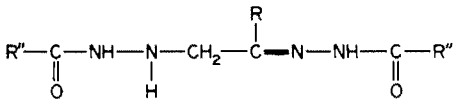
Structure	C_5 H	2',6' H	2'',6'' H	Remaining protons	
	9.00 s	8.56 m	—	7.40–7.71 m (3',4',5',3'',5'' H)	6.65 q (4'' H)
	9.00 s	—	8.10 m	7.50–7.80 m (3'',4'',5'',3',5' H)	6.70 q (4' H)

Table 3.

Structure	6′ H	C_5 H	2′,4′ H	3′,5′ H	2′,6′ H	2″,6″ H	3″,4″,5″ H
	9.83 s	9.11 s	8.88 d (J = 10 Hz)	—	—	8.25 m	7.67 m (&3′ H)
	—	9.16 s	—	8.86 m	8.43 m	8.25 m	7.62 m

d = doublet; q = quartet; m = multiplet; s = singlet.

Table 4.



No.	R	R″	m.p. (°C)	Crystallisation solvent	Yield (%)	$\nu_{C=O}^{Nujol}$ (cm^{-1})	Molecular formula	Nitrogen (%) Found	Calc.
1	C_6H_5–	H–	165	M	60	1610	$C_{10}H_{12}N_4O_2$	25.12	25.44
2	C_6H_5–	CH_3–	172	E	68	1655 1690	$C_{12}H_{16}N_4O_2$	22.81	22.57
3	CH_3–	C_6H_5–	265	E	70	1650	$C_{17}H_{18}N_4O_2$	17.78	18.05
4	C_6H_5–	C_6H_5–	232	E	85	1655 1680	$C_{22}H_{20}N_4O_2$	14.88	15.04
5	C_6H_5–	4Me–C_6H_4–	175	E	80	—	$C_{24}H_{24}N_4O_2$	13.76	13.99
6	C_6H_5–	4MeO–C_6H_4–	225	M:C(1:1)	82	—	$C_{24}H_{24}N_4O_4$	12.71	12.95
7	4Me–C_6H_4–	4Me–C_6H_4–	198	M:C(1:1)	85	1650 1680	$C_{25}H_{26}N_4O_2$	13.19	13.52
8	C_6H_5–	3,4,5-$(MeO)_3$–C_6H_2–	145	E	80	—	$C_{28}H_{32}N_4O_8$	10.29	10.14
9	4Cl–C_6H_4–	C_6H_5–	218	M:C(1:1)	75	—	$C_{22}H_{19}N_4O_2Cl$	13.47	13.80
10	4Br–C_6H_4–	C_6H_5–	220	M:C(1:1)	70	—	$C_{22}H_{19}N_4O_2Br$	12.75	12.42
11	C_6H_5–	3-C_5H_4N	190	E	67	—	$C_{20}H_{18}N_6O_2$	22.63	22.45
12	C_6H_5–	4-C_5H_4N	186	E	70	—	$C_{20}H_{18}N_6O_2$	22.59	22.45
13	4-Cl–C_6H_4–	3-C_5H_4N	220	M:C(1:1)	70	—	$C_{20}H_{17}N_6O_2Cl$	20.24	20.59
14	4-Cl–C_6H_4–	4-C_5H_4N	209	M:C(1:1)	72	1600 1670	$C_{20}H_{17}N_6O_2Cl$	20.10	20.59
15	4Br–C_6H_4–	3-C_5H_4N	235	M:C(1:1)	68	—	$C_{20}H_{17}N_6O_2Br$	18.42	18.55
16	4Br–C_6H_4–	4-C_5H_4N	242	M:C(1:1)	65	—	$C_{20}H_{17}N_6O_2Br$	18.65	18.55
17	$4NO_2$–C_6H_4–	3-C_5H_4N	210	M:C(1:1)	65	—	$C_{20}H_{17}N_7O_4$	23.48	23.39
18	$4NO_2$–C_6H_4–	4-C_5H_4N	236	M:C(1:1)	70	—	$C_{20}H_{17}N_7O_4$	23.19	23.39
19	C_6H_5–	2-C_4H_3O	170	M	60	1660 1680	$C_{18}H_{16}N_4O_4$	15.99	15.90
20	C_6H_5–	2-C_4H_3S	155	E	65	1635 1650	$C_{18}H_{16}N_4O_2S_2$	14.29	14.58

C = Chloroform; E = Ethanol; M = Methanol.

Beyond the work of Paudler and Herbener[23] on the mass spectra of 1,2,4-triazine and its carboxylic acid esters and another one[24] on the mass spectra of some 3-(functionally) substituted 1,2,4-triazines no information is extant on the mass spectra of 1,2,4-triazines. We have observed two general pathways of fragmentation under electron impact† of the compounds prepared now. The molecular ion "A" (Fig. 2) loses nitrogen to give rise to fragment "B" represented as an aromatic azacyclobutadienium ion. The assignment of such a structure to fragment "B" is confirmed by the presence of *a flat topped meta-stable peak*‡ for this transformation (i.e. $M-N_2$) in most of the compounds studied. The four membered ring ion "B" further fragments to an acetylene ion "C" and a nitrile ion "D". The very fact that another ion is present corresponding to the molecular ion of a second nitrile moiety bearing the 6-substituent (Fig. 3)

†A detailed paper on the mass spectra of these compounds is under communication.

‡Recently[25] several decompositions of metastable ions have been reported which do not give rise to peaks of the usual Gaussian shape. Insteak, the peaks are considerably broader than normal and have a flat or concave top. This peak is the result of the release of internal energy of the parent ion as kinetic energy of the fragments.

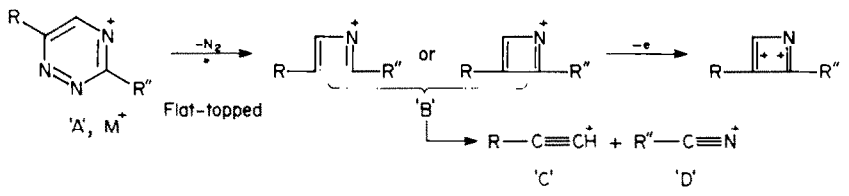


Fig. 2.

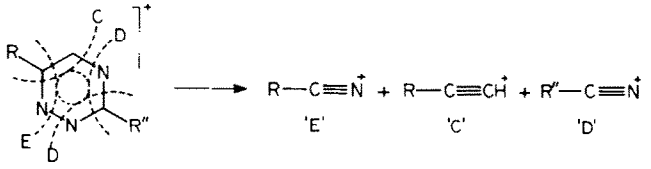


Fig. 3.

Table 5. 3,6-Diaryl-1,2,4-triazines

No.	R (6-substituent)	R' (3-substituent)	m.p. (°C) (crystallisation solvent)	Yield (%)	Molecular formula	Analysis (Calc./found) C	H	N(%)	λ_{max}^{MeOH} nm (log ϵ_{max})	ν_{max}^{Nujol} cm^{-1}
1	C_6H_5–	C_6H_5–	160(E) (156,[11] 156–7[13])	82	—		—		283 (4.48) (283–5, (4.45)[13])	†1210, 1120 1045, 725 ‡755, 685
2	4Cl–C_6H_4–	C_6H_5–	200(E)	60	$C_{15}H_{10}ClN_3$	67.30 67.21	3.17 3.42	15.70 15.81	287 (4.61)	—
3	4Br–C_6H_4–	C_6H_5–	201(E)	65	$C_{15}H_{10}BrN_3$	57.71 57.92	3.23 3.03	13.46 13.58	292 (4.48)	—
4	4Me–C_6H_4–	C_6H_5–	158(E)	85	$C_{16}H_{13}N_3$	77.71 77.90	5.30 5.50	16.99 16.65	291 (4.43)	†1080, 1075 1025, 1020, 725 ‡750, 695
5	4MeO–C_6H_4–	C_6H_5–	170(E)	80	$C_{16}H_{13}N_3O$	72.99 72.63	4.98 4.72	15.96 15.81	—	—
6	4NO_2–C_6H_4–	C_6H_5–	245(M)	75	$C_{15}H_{10}N_4O_2$	64.74 64.59	3.62 3.51	20.13 20.00	—	—
7	3NO_2–C_6H_4–	C_6H_5–	236(E)	70	$C_{15}H_{10}N_4O_2$	64.74 64.59	3.62 3.54	20.13 20.00	—	—
8	C_6H_5–	4Me–C_6H_4–	168(E)	85	$C_{16}H_{13}N_3$	77.71 77.50	5.30 6.41	16.99 16.83	292 (4.50)	†1080, 1035, 720 ‡790, 685
9	4Cl–C_6H_4–	4Me–C_6H_4–	224(M)	60	$C_{16}H_{12}ClN_3$	68.21 68.70	4.29 4.31	14.91 14.82	297 (4.57)	—
10	4Br–C_6H_4	4Me–C_6H_4–	231(E)	65	$C_{16}H_{12}BrN_3$	58.91 58.49	3.71 3.82	12.88 12.76	298 (4.56)	—
11	4Me–C_6H_4–	4Me–C_6H_4–	185(E)	85	$C_{17}H_{15}N_3$	78.13 78.44	5.75 5.49	16.08 16.36	—	†1195, 1090, 1030, 720 ‡820, 785
12	4NO_2–C_6H_4–	4Me–C_6H_4–	255 (B·E, 1:1)	70	$C_{16}H_{12}N_4O_2$	65.75 65.83	4.14 4.27	19.17 19.25	—	—
13	C_6H_5–	4MeO–C_6H_4–	168(E)	85	$C_{16}H_{13}N_3O$	72.99 72.75	4.98 4.77	15.96 15.85	253; 306; (4.23)(4.30)	—
14	4Cl–C_6H_4–	4MeO–C_6H_4–	191 (B·E, 1:1)	60	$C_{16}H_{12}ClN_3O$	64.65 64.99	4.04 4.21	14.14 14.24	—	—
15	4Br–C_6H_4–	4MeO–C_6H_4–	180(E)	65	$C_{16}H_{12}BrN_3O$	56.10 56.45	3.51 3.71	12.27 12.50	—	—
16	4Me–C_6H_4–	4MeO–C_6H_4–	171(E)	80	$C_{17}H_{15}N_3O$	73.63 73.35	5.45 5.65	15.15 15.20	—	—
17	4NO_2–C_6H_4–	4MeO–C_6H_4–	258(M)	65	$C_{16}H_{12}N_4O_3$	62.34 62.15	3.92 3.65	18.17 18.02	—	—
18	C_6H_5–	3,4,5-$(MeO)_3$–C_6H_2–	110(E)	85	$C_{18}H_{17}N_3O_3$	66.86 66.53	5.30 5.45	13.06 13.23	252, 305; (3.92)(4.42)	†1175, 1085, 1035, 1020, 745 ‡760, 685
19	4Cl–C_6H_4–	3,4,5-$(MeO)_3$–C_6H_2–	171(E)	70	$C_{18}H_{16}ClN_3O_3$	60.51 60.75	4.48 5.05	11.75 11.95	256, 311, (3.86)(4.40)	—
20	4Br–C_6H_4–	3,4,5-$(MeO)_3$–C_6H_2–	169(E)	76	$C_{18}H_{16}BrN_3O_3$	53.74 54.05	3.98 4.15	10.45 10.25	256; 310; (3.92)(4.50)	—
21	4Me–C_6H_4–	3,4,5-$(MeO)_3$–C_6H_2–	148(E)	80	$C_{19}H_{19}N_3O_3$	67.64 67.45	5.68 5.28	12.45 12.35	—	—
22	4NO_2–C_6H_4–	3,4,5-$(MeO)_3$–C_6H_2–	210 (M·B, 1:1)	75	$C_{18}H_{16}N_4O_5$	58.69 58.85	4.38 4.08	15.21 15.41	—	—

B = Benzene; E = Ethanol; M = Methanol.
†Absorptions ascribed to the 1,2,4-triazine ring.
‡Absorptions due to monosubstituted phenyl rings.
§Absorption due to disubstituted phenyl rings.

Table 6. 6-Mono-, 3,6-Di(aryl, heteroaryl)- and 3,5,6-Tri-substituted 1,2,4-Triazines

No	R (6-substituent)	R* (3-substituent)	Eluent (crystallisation solvent)	m.p (°C)	Yield (%)	Molecular formula	Analysis (calc./found) C	H	N(%)	λ_{max}^{MeOH} nm (log ε_{max})
1	C_6H_5–	H–	PE(PE)	102 (103*)	32	—		—		250 (4.23)
2	4Cl–C_6H_4–	H–	PE B(PE) 21 1	120	35	$C_9H_6ClN_3$	56.14 56.02	3.16 3.22	21.93 21.86	—
3	4Br–C_6H_4–	H–	PE B(PE) 20 1	135	31	$C_9H_6BrN_3$	45.79 45.31	2.56 2.49	17.80 17.85	—
4	C_6H_5–	CH_3–	PE(PE 60–80)	108 (106*)	53	—		—		250, 287 (4.25)(4.47)
5	4Cl–C_6H_4–	CH_3–	PE(PE)	164	50	$C_{10}H_8ClN_3$	58.41 57.94	3.92 3.81	20.43 20.19	—
6	4Br–C_6H_4–	CH_3–	PE B(PE) 20·1	148	50	$C_{10}H_8BrN_3$	48.03 47.93	3.22 3.10	16.83 16.47	—
7	C_6H_5–	3-C_5H_4N	B(M)	175	78	$C_{14}H_{10}N_4$	71.78 71.54	4.30 4.10	23.92 23.82	287 (4.56)
8	4Cl–C_6H_4–	3-C_5H_4N	C(B)	216	60	$C_{14}H_9ClN_4$	62.58 62.35	3.38 3.75	20.85 20.52	—
9	4Br–C_6H_4–	3-C_5H_4N	B(M·B. 1.1)	219	60	$C_{14}H_9BrN_4$	53.70 53.25	2.90 2.95	17.89 17.69	291 (4.56)
10	3NO_2–C_6H_4–	3-C_5H_4N	C·B(M) 1·1	231	68	$C_{14}H_9N_5O_2$	60.21 60.35	3.25 3.45	25.08 24.78	—
11	C_6H_5–	4-C_5H_4N	PE.B(M) 1.1	176	75	$C_{14}H_{10}N_4$	71.78 71.95	4.30 4.76	23.92 23.55	285 (4.55)
12	4Cl–C_6H_4–	4-C_5H_4N	C(B)	210	62	$C_{14}H_9ClN_4$	62.58 62.76	3.38 3.74	20.85 20.45	—
13	4Br–C_6H_4–	4-C_5H_4N	PE·B(B) 1.1	223	60	$C_{14}H_9BrN_4$	53.70 53.45	2.90 3.06	17.89 17.54	296 (4.57)
14	4Me–C_6H_4–	4-C_5H_4N	B(M)	200	75	$C_{15}H_{12}N_4$	72.54 72.65	4.84 4.92	22.58 22.38	—
15	3NO_2–C_6H_4–	4-C_5H_4N	B.C(M.B. 5 1, 1 1)	225	70	$C_{14}H_9N_5O_2$	60.21 60.45	3.25 3.05	25.08 24.86	—
16	C_6H_5–	2-C_4H_3O	P B(E) 1·1	165	70	$C_{13}H_9N_3O$	69.95 70.02	4.03 3.86	18.83 18.79	—
17	2-C_4H_3O	C_6H_5–	PE B(PE) 1.1	140	68	$C_{13}H_9N_3O$	69.95 69.65	4.03 4.46	18.83 18.55	—
18	2-C_4H_3O	4Me–C_6H_4–	H:B(PE) 3 1	65	65	$C_{14}H_{11}N_3O$	70.87 70.67	4.67 4.58	17.71 17.95	—
19	2-C_4H_3O	4MeO–C_6H_4–	H.B(E) 5 1	158	75	$C_{14}H_{11}N_3O_2$	66.40 66.25	4.38 4.68	16.59 16.49	—
20	2-C_4H_3O	3,4,5-(MeO)$_3$–C_6H_2–	H.B(E) 5 1	156	70	$C_{16}H_{15}N_3O_4$	61.35 61.16	4.79 4.85	13.42 13.38	—
21	2-C_4H_3O	2-C_4H_3S	H B(E) 10.1	193	60	$C_{11}H_7N_3OS$	57.65 57.85	3.05 3.25	18.34 18.04	—
22	2-C_4H_3O	2-C_4H_3O	H B(E) 10·1	206	60	$C_{11}H_7N_3O_2$	61.97 61.75	3.31 3.52	17.71 19.65	—
23	2-C_4H_3O	3-C_5H_4N	H.B(E) 1 5	176	65	$C_{13}H_8N_4O$	64.28 64.48	3.60 3.45	24.99 24.75	—
24	2-C_4H_3O	4-C_5H_4N	H B(E) 1 2	186	65	$C_{13}H_8N_4O$	64.28 64.52	3.60 3.25	24.99 24.72	—
25	2-C_4H_3O	C_6H_5–	B PE(E)	176	60	$C_{13}H_9N_3S$	65.29 65.19	3.76 3.56	17.57 17.43	—
26	2-C_4H_3S	4Me–C_6H_4–	H(PE)	91	65	$C_{14}H_{11}N_3S$	66.39 66.19	4.34 4.52	16.61 16.52	—
27	2-C_4H_3S	4MeO–C_6H_4–	H·PE(E) 1·1	213	74	$C_{14}H_{11}N_3OS$	62.44 62.65	4.08 4.28	15.61 15.35	—
28	2-C_4H_3S	3,4,5-(MeO)$_3$–C_6H_2–	H B(E) 2 1	163	75	$C_{16}H_{15}N_3O_3S$	58.35 58.65	4.55 4.15	12.76 12.56	—
29	2-C_4H_3S	2-C_4H_3O	H B(E) 2.3	211	70	$C_{11}H_7N_3OS$	57.65 57.95	3.05 2.85	18.34 18.14	—
30	2-C_4H_3S	2-C_4H_3S	PE B(PE) 1 1	213	63	$C_{11}H_7N_3S_2$	53.88 54.05	2.85 3.15	17.14 16.95	—
31	2-C_4H_3S	3-C_5H_4N	PE·B(E) 1·1	210	65	$C_{12}H_8N_4S$	60.01 69.25	3.33 3.45	23.33 23.41	—
32	2-C_4H_3S	4-C_5H_4N	B(E)	211	65	$C_{12}H_8N_4S$	60.01 60.15	3.33 3.25	23.33 23.23	—
33*	C_6H_5–	C_6H_5–	PE:B(E) 5 1	148†	55	—		—		226, 255; (4.30)(4.30) 280‡ (4.45)
34*	C_6H_5–	4Me–C_6H_4–	PE B(E) 5·1	138†	52	—		—		226; 277; (4.34)(4.35)
35*	C_6H_5–	4MeO–C_6H_4–	H.PE(E) 1 1	162†	55	—		—		227, 306; (4.33)(4.55)
36*	C_6H_5–	3,4,5-(MeO)$_3$–C_6H_2–	PE·B(E) 1 1	161†	56	—		—		226, 304, (4.33)(4.54)
37*	C_6H_5–	3-C_5H_4N	B(E)	185†	50	—		—		226; 248; (4.40)(4.35) 275, 316, (4.50)(4.50)
38*	C_6H_5–	4-C_5H_4N	B(E)	170†	50	—		—		226, 248, (4.40)(4.35) 274; 315, (4.50)(4.50)
39*	C_6H_5–	2-C_4H_3O	PE:B(E) 1 1	199†	50	—		—		225, 309, (4.33)(4.51)

PE = Petroleum ether (40–60), B = Benzene; C = Chloroform; E = Ethanol, M = Methanol.

In cases **33–39**, a fast moving yellow band eluted with 40–60 petroleum ether was identified as benzil by comparison with an authentic sample. The next band contained the triazine

*In compounds **33–39**, the 5-substituent is C_6H_5–.

†M.ps in literature are respectively 145,[11,20] 136–7,[1] 159–60,[11] 158–9,[1] 174–5,[11] 161–2,[11] 181–3.[1]

‡Atkinson and Cossey[13] report a maximum at 281 nm (4.45) for this compound.

affords evidence to the second, i.e. direct mode of fragmentation. The mass spectra of these compounds are all dominated by the extremely strong base peak corresponding to the molecular ion of the acetylene.

EXPERIMENTAL

M.ps were determined in capillary tubes and are uncorrected. All reported yields refer to recrystallised material. NMR spectra were recorded on a Varian Analytical NMR Spectrophotometer (60 MHz). All chemical shifts are given in δ ppm relative to TMS as internal standard. UV spectra were measured on Uvispek single beam spectrophotometer (Hilger–Watts). IR spectra were recorded on Perkin–Elmer Model 337 instrument (Grating). Mass spectra were recorded on a Perkin Elmer Hitachi RMU-6L instrument with electron beam energy 70 eV. Brockmann neutral alumina was used for column chromatography. All the 1,2,4-triazines presently described develop a dark-red colour on treatment with a few drops of concentrated sulphuric acid.

General procedure for the preparation of carboxylic acid 2,2'-(2-substituted-1-ethanyl-2-ylidene) dihydrazide

To 0.005 mole of the appropriate α-bromomethylketone in about 20 ml EtOH was added 0.01 mole of the hydrazide and the mixture was warmed for a few min on a boiling water bath until the reactants dissolved, and then set aside at room temp. overnight. The crystalline compounds that separated were recrystallised from a suitable solvent. Data on the compounds prepared thus are collected together in Table 4.

Attempted cyclisation of benzoic acid 2,2'-(2-phenyl-1-ethanyl-(2-ylidene)dihydrazide

(a) *In refluxing acetic acid containing NaOAc.* To 1.86 g (0.005 mole) of the title compound in 15 ml of glacial acetic acid was added 5.0 g (excess) of NaOAc and the mixture refluxed for 2 h in an oil bath. The reaction mixture was poured into water and the pale yellow glistening material was recrystallised from boiling ethanol (1.50 g, 80%), m.p. 232°C, identical with the starting material.

(b) *Under sealed tube conditions in acetic acid containing NaOAc.* The same reaction was carried out in a sealed pressure tube (at 160°C, 2 h). Working out the reaction mixture as above gave 1.55 g (85%) of the starting material.

(c) *In refluxing DMF.* The dihydrazide (0.75 g; 0.002 mole) was dissolved in 10 ml of DMF and refluxed in an oil bath for 1 h. Working out the reaction product as in (a) above gave back the starting material (0.70 g, 92%).

(d) *By heating in DMSO.* The above product 0.75 g (0.002 mole) was dissolved in 10 ml of DMSO and warmed in a boiling water bath for 1 h. Working out the material as in (a) gave 0.72 g, (96%) of the starting material.

Two methods and some variations of one method were adopted in the synthesis of all the triazines reported herein:

Method A and its variations. This involved the reaction of an acid hydrazide with an appropriate α-bromomethylketone with or without an added acetate in a suitable solvent. The products were obtained by diluting the reaction mixture with a large excess of water (until the precipitate clearly separated out) and processing the separated material by neutralisation with sufficient amount of $NaHCO_3$, thorough washing with cold water and recrystallisation from a solvent or a mixture of solvents. The order of addition of reactants is important in order to prevent the formation of the uncyclised material. Suitable working up of the filtrate in some specified cases, as mentioned later, afforded the amide corresponding to the acid hydrazide.

Variation 1. Acid hydrazide 0.01 mole and AgOAc 0.005 mole were dissolved in about 15 ml (the mimimum quantity) of acetic acid on a boiling water bath and the appropriate α-bromomethylketone 0.005 mole was added when the solution turned immediately milky and developed a yellow colour. The heating was continued for 30 min and the product was worked out as mentioned earlier. Compounds **1–22** were prepared by this method in yields mentioned in Table 5.

Variation 2. The change effected here was the replacement of costly AgOAc by crystalline NaOAc, KOAc or NH_4OAc. Compounds **1–22** were prepared by using crystalline NaOAc/AcOH in 55–58% yields, comparable to those obtained in the foregoing variation. Compounds **1**, **8** and **18** were prepared by using KOAc/AcOH in 75–80% yields. Compounds **1** and **4** were prepared by using NH_4OAc/AcOH in 80–85% yields.

Variation 3. The acid hydrazide (0.01 mole) and crystalline NaOAc (0.015 mole) or AgOAc (0.005 mole) were taken in ethanol (30 ml) and warmed until the hydrazide dissolved; 0.005 mole of the appropriate α-bromomethylketone was added and the mixture refluxed on a boiling water bath for 1 h. The silver residue (when AgOAc was used) was separated by filtration and the liquid concentrated to half its volume under reduced pressure and poured into a large excess of cold water. Compounds **1** and **11** were prepared by using AgOAc/EtOH in 80% yield and compounds **1**, **8**, **11**, **13** and **18** were prepared by using NaOAc/EtOH in 60–80% yields.

Variation 4. Compounds **1**, **4**, **8**, **11**, **13** and **18** were prepared in 80–90% yields by cyclisation in DMF. In these cases the hydrazide (0.01 mole) was dissolved in 15 ml of DMF, to which was added the required α-bromomethylketone (0.005 mole) when a dark colour developed. The reaction mixture was heated at 120°C on an oil bath for 1 h and the product worked out as usual.

Variation 5. Compound **1** was prepared in 60% yield by cyclisation in a mixture of glacial acetic acid/pyridine (3:2) on a boiling water bath for 30 min.

Variation 6. Compound **1** was also prepared in 60% yield by gentle warming on a water bath (75°C) for 15 min in DMSO.

Method B. (Data about these compounds are collected together in Table 6). For the synthesis of 3(6-aryl)heteroaryl-disubstituted-1,2,4-triazines, 6-monosubstituted-, 3-methyl- and 3,5,6-trisubstituted-1,2,4-triazines this procedure had to be adopted.

To 0.01 mole of the hydrazide and 0.015 mole of NaOAc dissolved (by warming if necessary) in the minimum volume of glacial acetic acid (*ca.* 5–10 ml) was added the appropriate α-bromomethylketone or benzoin (0.005 mole) and the mixture heated on a boiling water bath for 30 min (except for compounds **33–39** which could be obtained only after 2 h of refluxing). The reaction mixture was poured into cold water and the product then separated as a semisolid. Nicotinic, isonicotinic and 2-furoic acid hydrazides with aryl α-bromomethylketones gave a solid product directly, but a small quantity of each of which was purified by chromatography for spectral and analytical purposes. After neutralisation of the contents with a sufficient amount of $NaHCO_3$ the material was extracted with suitable solvents (ether, ethylacetate or chloroform), the extracts washed thoroughly with water and dried (Na_2SO_4). The solvents were removed by distillation under reduced pressure and the residual material was subjected to column chromatography.

Compound **33** was also prepared from benzhydrazide (0.02 mole) and desylchloride[7] (0.01 mole) in the presence of AgOAc (0.01 mole) and glacial acetic acid (25 ml) and refluxing the reaction mixture for 2 h in an oil bath. Processing as usual and subjecting the product to column chromatography (elution with PR:B, 2:1) gave 1.6 g (52%) of 3,5,6-triphenyl-1,2,4-triazine. Further elution of the column with B:C, 1:1 afforded a white, crystalline product m.p. 228°C (0.3 g), which was not characterised.

Compound **33** was also prepared in 47% yield by refluxing benzhydrazide and desylchloride in 50 ml of DMF for 2 h in an oil bath and purification through a column.

Isolation of the amides corresponding to acid hydrazides

The filtrate obtained after the removal of 3,6-diphenyl-1,2,4-triazine was extracted thoroughly with ether. The ether was evaporated and the residue treated with aqueous $NaHCO_3$ (5%), filtered and further extracted with hot benzene. The benzene extract was washed with water and dried over Na_2SO_4. Concentration of benzene gave 0.3 g (50%), of benzamide, m.p. 130°C. Benzamide, 0.29 g (47%), was also obtained by working out similarly the aqueous portion decanted from the sticky material produced by the reaction of benzoin and benzhydrazide in NaOAc/AcOH. The aqueous filtrate after the removal of 3-(4-methoxyphenyl)-6-phenyl-1,2,4-triazine prepared under

NaOAc/AcOH conditions was similarly processed to gét 0.38 g (50%) of anisamide, m.p. 163°C. 0.4 g (~50%) of *p*-nitrobenzamide, m.p. 201°C, was isolated by extracting (with ether and hot chloroform) the aqueous filtrate after separation of 3-(4-nitrophenyl)-6-phenyl-1,2,4-triazine.

All the amides were authenticated by comparison with known samples.

Authentication of 3,6-*diphenyl*-1,2,4-*triazine*

The required α-benzamido-acetophenone was prepared from *n*-amylnitrite,[28] through its conversion to isonitroso acetophenone[29] which was reduced and converted to its hydrochloride,[30] followed by its transformation to α-benzamido acetophenone[31] through benzoylation.

3,6-*Diphenyl*-2,5-*dihydro*-1,2,4-*triazine*.[11] The foregoing α-benzamido-acetophenone (4.78 g) in 20 ml ethanol and 1.9 g of hydrazine hydrochloride (prepared by passing gaseous HCl into 95% hydrazine hydrate) in 6 ml of water were gently refluxed for 1 h. The reaction mixture was poured into water (400 ml) and neutralised with 10% NH_4OH solution. The curdy precipitate obtained was washed thoroughly with water and recrystallised from ethanol to obtain white heavy crystals 3.5 g (73%), m.p. 196°C.

Oxidation of the foregoing dihydro compound to 3,6-*diphenyl*-1,2,4-*triazine*. To a gently refluxing solution of the above compound (2.35 g; 0.01 mole) in 200 ml of acetone was added portionwise 120 ml of 5% aqueous $KMnO_4$ during 1 h. After removal of the manganese dioxide, the clear solution was cooled and 1.5 g (65%) of a product melting at 156°C was obtained. Recrystallisation from ethanol raised the m.p. to 160°C. Mixed m.p. with 3,6-diphenyl-1,2,4-triazine prepared herein was undepressed.

Authentication of 3-*methyl*-6-*phenyl*-1,2,4-*triazine*

α-Aminoacetophenone hydrochloride[30] was converted to α-acetamido acetophenone (m.p. 85°C[32]) by acetylation.[31]

3-*Methyl*-6-*phenyl*-2,5-*dihydro*-1,2,4-*triazine*.[11] The above compound (3.54 g, 0.20 mole) in 20 ml of ethanol and 1.9 g of hydrazine hydrochloride in 6 ml of water were refluxed for 1 h. Working out as in the previous case and recrystallisation from hot ethanol gave a white crystalline material, m.p. 134°C, 2.50 g (70%).

The foregoing product (1.73 g, 0.01 mole) was oxidised to 3-methyl-6-phenyl-1,2,4-triazine by following the procedure as in the earlier case. The product on recrystallisation from 50% aqueous ethanol gave fine yellow needles melting at 109°C. Mixed m.p. with the product obtained from acethydrazide and phenacyl bromide was undepressed.

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