305. *Quaternisation of Some* 1,2,4-*Triazines.*

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Quaternary salts of a number of 1,2,4-triazines have been prepared and screened for biological activity. 5,6-Diphenyl-1,2,4-triazine and the 3-methyl derivative each gave a mixture of a colourless and a red methiodide. Evidence is presented which suggests that the colourless isomers are quaternised on N-2 and that the red salts, like other red methiodides prepared, are quaternised on N-1. Attempts to confirm this hypothesis have been inconclusive.

The 1,2,4-triazines are weak bases, as demonstrated by their inability to form salts with dilute mineral acids [1] and the difficulty with which they form quaternary salts. Quaternary salts of 1,2,4-triazines with a fully aromatic structure have not been reported, although those of dihydrotriazines have been prepared.[2,3]

We have obtained poor yields of triaryltriazine methiodides in methanol with methyl iodide or in methyl iodide alone, but the rates of reaction and yields were increased in nitromethane or acetonitrile. The best results were obtained by quaternisation in nitromethane for eight hours and the methiodides were usually red crystalline solids which decomposed at their melting points. Quaternary salts of 3-*m*(or *p*)-nitrophenyl-5,6-diphenyl-1,2,4-triazines could not be prepared, even in nitromethane, and the methiodide of 3-*p*-acetamidophenyl-1,2,4-triazine was not stable enough to be purified. The methiodides of 5,6-diphenyl-3-3′-pyridyl- and -3-4′-pyridyl-1,2,4-triazines were yellow crystalline solids, and this, their ease of formation in methanol, and the fact that the bases did not give a red coloration with concentrated sulphuric acid,[1,4] suggested that quaternisation had occurred on the nitrogen atom of the pyridine ring. The high yield of methiodide given by 5,6-diphenyl-3-(2-phenyl-4-quinolyl)-1,2,4-triazine in methanol also suggested that this quaternisation had not occurred in the triazine ring.

When the triazine carried a methyl group in place of a phenyl substituent, quaternisation

[1] Metze, *Chem. Ber.*, 1954, **87**, 1540.
[2] Grundman and Ratz, *Chem. Ber.*, 1958, **91**, 1766.
[3] Metze and Scherowsky, *Chem. Ber.*, 1959, **92**, 2481.
[4] Laakso, Robinson, and Vandrewala, *Tetrahedron*, 1957, **1**, 103.

occurred more readily. 3-Methyl-5,6-diphenyl-1,2,4-triazine gave a good yield of a colourless monomethiodide, together with a small quantity of a red isomer, when quaternised in methanol. A red isomer was not isolated in the case of 5,6-diphenyl-1,2,4-triazine although the colour of the reaction mixture indicated its presence. Quaternisation of 3,5-diaryl-6-methyl-1,2,4-triazines in methanol gave a moderate yield of a red methiodide

TABLE 1.

Quaternisation of substituted 1,2,4-triazines.

Substituents	Time (hr.) under reflux	Yield (%), and colour of salt	Substituents	Time (hr.) under reflux	Yield (%), and colour of salt
3,5,6-Triphenyl	144	16 (red)	5-Methyl-3,6-diphenyl	24	26 (red)
,,	24	6 (red)	6-Methyl-3,5-diphenyl	24	51 (red)
3-Methyl-5,6-diphenyl	8	56 (colourless)			
,,		1 (red)			

but 3,6-diaryl-5-methyl-1,2,4-triazines gave only a small yield, and attempts to increase this yield by carrying out the reaction in nitromethane led to the isolation of uncrystallisable oils. In the case of 3,6-diphenyl-1,2,4-triazine no reaction occurred in methanol, and in nitromethane a green uncrystallisable oil was obtained. Table 1 shows the effect of the position of the methyl group, when it replaces a phenyl substituent in triphenyltriazine, on the rate of quaternisation with methyl iodide in methanol.

TABLE 2.

Ultraviolet spectra of 1,2,4-triazine methiodides.

Triazine	λ_{max} (mμ) (log ε)
3,5,6-Triphenyl	219 (4·48), 278 (4·47)
3-*p*-Methoxyphenyl-5,6-diphenyl	219 (4·47), 329 (4·47)
3-Methyl-5,6-diphenyl (colourless)	219 (4·40), 302 (3·98)
,, (red)	218 (4·38), 308—312 (3·81)
5,6-Diphenyl (colourless)	222 (4·37), 312 (3·92)
6-Methyl-3,5-diphenyl	220—221 (4·37), 273—275 (4·38)
5-Methyl-3,6-diphenyl	216—217 (4·39), 270 (4·36)
3-*p*-Methoxyphenyl-6-methyl-5-phenyl	223 (4·42), 316 (4·41)
3-*p*-Methoxyphenyl-5-methyl-6-phenyl	220—221 (4·39), 316—317 (4·36)

The methiodides of the triaryl-, 3,5-diaryl-, and 3,6-diaryl-triazines have closely similar ultraviolet spectra (Table 2), which suggests the same site of quaternisation. The red methiodide of 3-methyl-5,6-diphenyl-1,2,4-triazine has a different ultraviolet spectrum from the red methiodides of the other three types, but this is not surprising in view of the distinct pattern of the spectrum of the parent base compared with those of the other three bases.[5] The colourless methiodide of 3-methyl-5,6-diphenyl-1,2,4-triazine is clearly quaternised at a different nitrogen atom and its ultraviolet spectrum is totally different from that of any of the red methiodides.

These results indicate that the factors influencing the site or extent of quaternisation are: (a) the size of the substituents and the relative ease of access of the quaternising agent to a particular nitrogen atom, and (b) changes in the relative basicity of the ring nitrogen atoms which accompany the interchange of groups of different electronic character.

Considering factor (a) in relation to the quaternisation of 3-methyl-5,6-diphenyl-1,2,4-triazine compared with triphenyltriazine, the only alteration which has been made to the steric arrangement is that nitrogen-2 and nitrogen-4 have been made less hindered and therefore more readily accessible to quaternisation. Therefore, if nitrogen-1 had been quaternised in 3,5,6-triphenyltriazine, the change of site in 3-methyl-5,6-diphenyl-1,2,4-triazine would be to the more accessible nitrogen-2 or nitrogen-4. If, however, nitrogen-1 was not quaternised in triphenyl-1,2,4-triazine it is unlikely to be the basic centre in

[5] Atkinson and Cossey, *J.*, 1962, 1805.

3-methyl-5,6-diphenyl-1,2,4-triazine as the steric environment of nitrogen-1 has not been altered. The colourless methiodide of the 3-methyl-1,2,4-triazine can therefore be considered to be quaternised at nitrogen-2 or -4. If nitrogen-4 was the case, it would be expected that 5-methyl-3,6-diphenyl-1,2,4-triazine would be quaternised at the same nitrogen atom since the change in the steric arrangement from the triphenyl-1,2,4-triazine, in this case, is the same as for the 3-methyl isomer: however, only a red methiodide was obtained from the 5-methyl isomer and it therefore seems unlikely that nitrogen-4 is the basic centre for the colourless methiodide. It therefore leaves nitrogen-2 as the most likely centre of quaternisation for the colourless methiodide of 3-methyl-5,6-diphenyl-1,2,4-triazine and of the analogous 5,6-diphenyl-1,2,4-triazine.

The basic centre for the red methiodides is therefore probably nitrogen-1 or -4. If nitrogen-4 is the centre, by substituting a methyl group for phenyl in the 3- or the 5-position of triphenyl-1,2,4-triazine, the accessibility of nitrogen-4 would increase and there would be no change in the centre of quaternisation for the 3-methyl compound. In the case of the 3-methyl isomer, the accessibility of nitrogen-2 has also been increased but if nitrogen-4 is quaternised preferentially to nitrogen-2 in the triphenyl-1,2,4-triazine it would still be quaternised in the 3-methyl compound. It therefore seems likely that nitrogen-1 is the basic centre of the red methiodides since it accounts for the change of site on quaternisation of the 3-methyl isomer, and for the fact that when a methyl group is in the 6-position the yield of methiodide is greater than from triphenyl or 5-methyl-3,6-diphenyl-1,2,4-triazine (Table 1).

If now the effect of (b) is considered, that is, the electronic influence of the substituent groups, no change in the foregoing argument occurs. The effect of replacing a 3- or a 5-phenyl group by methyl in triphenyltriazine should have the same effect on nitrogen-2 and -4 in increasing their basicity, and the influence on nitrogen-1 would be small in both cases. The increased yield of the methiodide of 6-methyl-3,5-diphenyl-1,2,4-triazine (Table 1) is evidence of quaternisation at nitrogen-1, the only ring nitrogen atom to be greatly affected by a methyl group at position-6.

The reduction of these salts appeared to offer a method of testing this hypothesis. Reduction of 1,2,4-triazines to imidazoles with zinc and acid has been studied by Laakso *et al.*[4] who obtained a quantitative yield of 2,4,5-triphenylimidazole from 3,5,6-triphenyl-1,2,4-triazine by boiling it for five minutes with zinc and acetic acid, and by Metze and Scherowsky[3] who isolated a mixture of the imidazole and a dihydrotriazine from a variety of 1,2,4-triazines after reduction in 50% ethanol–acetic acid for four hours. A summary of our results of reduction under a variety of conditions, including those of Robinson and Metze, are given in Table 5 (Experimental). By using Metze's method, lower yields of the two products were obtained but the dihydrotriazine could not be isolated by the method described. Repetition of the experiment using acetic acid gave similar results but, with a larger excess of zinc, no dihydrotriazine was obtained. Robinson's method gave similar results but the highest yield of the imidazole was only 45%. Estimation of the ammonia evolved during the reaction by passing nitrogen through the alkaline solution gave a value higher than that expected by simple ring-opening followed by closure to the imidazole by elimination of nitrogen-1 or -2; it appears that substantial side reactions occur.

Notwithstanding these unsatisfactory quantitative results we attempted the reduction of 3,5,6-triphenyl-1,2,4-triazine methiodide with zinc and acetic acid. Only about 35% of lophine was isolated and 20% of methylamine (determined as usual[6]) was detected. It is considered that the methylamine is produced by elimination of nitrogen-1 or -2, the low yields being due to decomposition of the methiodide before reduction; the methiodide readily yields the base when boiled with acetic acid. In spite of the low yields obtained, this evidence supports the hypothesis of quaternisation at nitrogen-1 in 3,5,6-triphenyl-1,2,4-triazine.

[6] Atkinson and Taylor, *J.*, 1955, 4236.

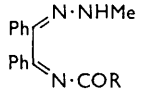
Information on the structure of the quaternary salts was also sought by their conversion into pseudo-bases by treatment with cold dilute alkali. 3,5,6-Triphenyl-1,2,4-triazine methiodide gave a green oil from which only the parent base (20%) was isolated; treatment of the methiodide with boiling water gave 45% of the base. 5-Methyl-3,6-diphenyl- and 6-methyl-3,5-diphenyl-1,2,4-triazine methiodides gave intractable oils. The colourless methiodides of 3-methyl-5,6-diphenyl- and 5,6-diphenyl-1,2,4-triazine gave two isomeric compounds (A and B) and (C and D), respectively, which gave analyses for the corresponding pseudo-bases (α-methylamino-alcohols). One of each pair of isomers has the hydroxyl group attached to a carbon atom also carrying a methyl group (in A or B) or hydrogen (in C or D). However, attempts to dehydrate A or B to an anhydrobase or to oxidise C or D to a ketone were unsuccessful, although a variety of reagents was employed. This apparent absence of a hydroxyl group was supported by the infrared spectra of these compounds (Table 3) whilst such a formulation is not contradicted by the

TABLE 3.

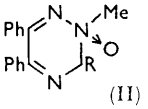
Infrared spectra of products from the action of alkali on 5,6-diphenyl- and 3-methyl-5,6-diphenyl-1,2,4-triazine methiodides.

Compound	Wave number ($cm.^{-1}$) in chloroform
A	3564w, 3274w, 2948m, 2842w, 1618s, 1560w, 1490m, 1385s, 1355m, 1308s, 1177m, 1122m, 1074s, 1071m, 974 m, 924w, 909w.
B	3580w, 3325w, 3020w, 2938w, 1618s, 1560w, 1490m, 1443m, 1385m, 1312s, 1172m, 1100m, 1004m, 968w.
C	3536w, 3272w, 2956m, 2842w, 1624s, 1581w, 1550m, 1490m, 1466m, 1447m, 1324m, 1299s, 1177m, 1117m, 1073s, 1021m, 969m, 914w, 862w.
D	3425w, 3245m, 3040m, 1624s, 1557w, 1540w, 1490m, 1474m, 1450m, 1302s, 1180m, 1121m, 1100m, 1069m, 1005w, 972m, 914w.

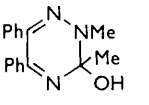
infrared evidence, in which the strong absorption at 1308, 1312, 1299, and 1308 $cm.^{-1}$ in A, B, C, and D, respectively, may be tentatively ascribed to the N ⟶ O frequency: Janda and Haszeldine [7] associate strong absorption at 1270 $cm.^{-1}$ in hexafluoroazoxymethane with the *N*-oxide group, but other workers [7] have assigned to this group absorption at 1350—1390 and 1230—1325 $cm.^{-1}$ which, in chloroform and Nujol mull, showed only very weak absorption in the 3700—3500 $cm.^{-1}$ region. Absorption in the 1650 $cm.^{-1}$ region, characteristic of the carbonyl group, was not observed, thus eliminating an open-chain structure of type (I). Alternatives which agree with the analytical data are amine



(I)



(II)



(III)

oxides of type (II) (or isomers having N^1 ⟶ O or N^4 ⟶ O groups in the structure). The migration of oxygen from nitrogen-2 to nitrogen-1 in the benzotriazine series has been demonstrated by Robbins and Schofield [8] and migration could account for our isolation of pairs of isomers. Further, the reduction of compound D with sodium borohydride gave tetrahydromethyl-5,6-diphenyl-1,2,4-triazine which was also obtained by direct reduction of the methiodide with this reagent. The reduction of an alcoholic group, as in the pseudo-base, to the paraffin seems unlikely, whereas an *N*-oxide is readily reduced to the parent base.

Attempts were made to prepare authentic reference alcohols similar to, if not identical with, the pseudo-bases. 2,3-Dihydro-2-methyl-3-oxo-5,6-diphenyl-1,2,4-triazine [9] did not react with methylmagnesium iodide in diethyl ether, but in boiling tetrahydrofuran

[7] Jander and Haszeldine, *J.*, 1954, 919; Clemo and Daglish, *J.*, 1950, 1481; Koelsch and Gumprecht, *J. Org. Chem.*, 1958, **23**, 1603.
[8] Robbins and Schofield, *J.*, 1957, 3186.
[9] Biltz, Arnd, and Stellbaum, *Annalen*, 1905, **339**, 275.

a product was formed which analysed for the expected compound (III): however, the infrared spectrum showed no absorption for a hydroxyl group, but a strong absorption at 1675 cm.$^{-1}$ characteristic of the stretching frequency of a cyclic amide. In another attempt, the use of methylamine acetate in place of ammonium acetate in the Robinson [4] triazine synthesis of 3,5,6-triphenyl-1,2,4-triazine was expected to yield 3,4(or 4,5)-dihydro-3(or 5)-hydroxy-4-methyl-3,5,6-triphenyl-1,2,4-triazine, but neither of these was obtained.

It has been shown [10,11] that the reduction of quaternary salts by sodium borohydride either reduces the double bond adjacent to the quaternary centre or causes further reduction to a tetrahydro-compound. 5,6-Diphenyl-1,2,4-triazine methiodide gave a tetrahydrotriazine which formed a monoacetyl derivative. An attempt to prepare 2,3-dihydro-2-methyl-5,6-diphenyl-1,2,4-triazine by reduction of the 3-oxo-derivative with sodium borohydride resulted only in reduction of the 4,5-double bond; use of lithium aluminium hydride gave the same product. Further reaction yielded, depending on the conditions, an unidentified nitrogen-free compound or an uncrystallisable product which gave benzaldehyde and some basic material on acid hydrolysis.

Experimental

Melting points are uncorrected. The ultraviolet absorption spectra refer to solutions in absolute methanol. Light petroleum had b. p. 60—80°.

Quaternisation of 1,2,4-*Triazines.*—A solution of the base (x g.) in the solvent (y c.c.) was heated under reflux with methyl iodide (x c.c., or $y/10$ in experiments where $y > 50x$) for the period specified in Table 4. The salt usually crystallised directly from the reaction mixture and was recrystallised for analysis.

Reduction of 3,5,6-*Triphenyl*-1,2,4-*triazine.*—(*a*)The triazine was dissolved in acetic acid and heated under reflux with zinc dust for 5 min. The solution was decanted into an excess of 40% sodium hydroxide solution and ice, the zinc was washed by decantation with acetic acid and the washings were added to the alkaline solution.

The mixture was distilled into standard hydrochloric acid until the distillate was no longer alkaline, and the percentage of volatile basic material was calculated: this " ammonia figure " was 125% of that theoretically possible. The precipitate, recrystallised from ethanol, formed needles of 2,4,5-triphenylimidazole, m. p. 267—270°. Crystalline material could not be isolated from the ethanolic liquors or from a chloroform extract of the aqueous alkaline solution.

(*b*) The triazine, dissolved in acetic acid, was heated under reflux with zinc dust for 5 min. The solution was decanted from the excess of zinc dust, the zinc was washed by decantation with acetic acid, and the combined solution evaporated. The oily residue was triturated with hot water until it solidified. The residue, recrystallised from ethanol, formed needles, m. p. 237—240°, of the dihydrotriazine. Concentration of the alcoholic mother-liquors gave 2,4,5-triphenylimidazole, m. p. 267—270°, as needles. Further crystalline products could not be isolated from the alcoholic liquors or by chloroform extraction of the buffered (sodium acetate) or basified (ammonia) solution.

Reduction of 3,5,6-*Triphenyl*-1,2,4-*triazine Methiodide.*—(*a*) The methiodide (4·5 g.) and " AnalaR " zinc dust (18 g.) were heated under reflux in acetic acid (100 ml.) for 2 hr. The cooled mixture was decanted into an excess of 6N-sodium hydroxide and ice. The precipitate was crystallised from ethanol to give needles (30—36%), m. p. 275—276° alone or on admixture with 2,4,5-triphenylimidazole. The mother liquors, on evaporation, gave a yellow oil which could not be recrystallised. The alkaline filtrate was distilled into 0·1N-hydrochloric acid (100 ml.) until the distillate was no longer alkaline and methylamine was estimated as usual. Yellow prisms of methylamine picrate, m. p. and mixed m. p. 206—207°, were isolated.

(*b*) Sodium borohydride (1 g.) was added portionwise to a suspension of the methiodide (1 g.) in methanol (25 ml.). Crystals (0·61 g.), m. p. 142—144°, gradually separated and after 2 hr. the excess of borohydride was destroyed with acetic acid. The crystals provided *dihydro-methyl*-3,5,6-*triphenyl*-1,2,4-*triazine* as yellow needles (0·53 g.), m. p. 143—144° (from ethanol)

[10] Panause, *Compt. rend.*, 1951, **233**, 260, 1200.
[11] Torrossain, *Compt. rend.*, 1952, **235**, 1312.

TABLE 4.

Quaternary salts of substituted 1,2,4-triazines.

No.	Solvent for reaction *	Substituents	Time under reflux (hr.)	Yield (%)	M. p.† (decomp.)	Solvent for recryst.
1	a	3,5,6-Triphenyl	8	53	184°	a
	b	,,	8	27	181	c
	d	,,	144	16	181	c
	—	,,	4	9	181	c
2	a	3-*p*-Methoxyphenyl-5,6-diphenyl	8	25	198	e
	d	,, ,,	72	9	191	c
3	a	3-*p*-Chlorophenyl-5,6-diphenyl	4	20	200	a
4	a	3-*p*-Bromophenyl-5,6-diphenyl	8	27	203—204	a
5	a	3-*p*-Hydroxyphenyl-5,6-diphenyl	8	24	230	e
6	d	5,6-Diphenyl-3-3′-pyridyl	24	73	255—256	e
7	d	5,6-Diphenyl-3-4′-pyridyl	24	65	261—262	b
8	a	3-*p*-Acetamidophenyl-5,6-diphenyl	8	56 [a]	203—204	—
9	d	5,6-Diphenyl-3-(2-phenyl-4-quinolyl)	48	58 [a]	236—237	—
10	d	3-Methyl-5,6-diphenyl	8	56 [b]	168—169	f
				1 [c]	165	f
11	d	5,6-Diphenyl	8	61 [d]	150—152	f
12	d	6-Methyl-3,5-diphenyl	24	51	188	f
13	d	5-Methyl-3,6-diphenyl	24	26	173—174	f
14	d	3-*p*-Methoxyphenyl-6-methyl-5-phenyl	8	28	171—172	f
15	d	3-*p*-Methoxyphenyl-5-methyl-6-phenyl	8	11	181—182	f

No.	Found (%) C	H	I	N	Molecular formula	Required (%) C	H	I	N
1	58·25	4·2	28·0	9·3	$C_{22}H_{18}IN_3$	58·5	4·0	28·1	9·3
2	56·8	4·3	27·1	8·45	$C_{23}H_{20}IN_3O$	57·4	4·2	26·4	8·7
3	54·7	3·5	33·0	8·45	$C_{22}H_{17}ClIN_3$	54·4	3·5	33·4	8·65
4	49·25	3·2	39·8	7·8	$C_{22}H_{17}BrIN_3$	49·8	3·2	39·0	7·9
5	56·6	3·8	27·6	8·2	$C_{22}H_{18}IN_3O$	56·6	3·9	27·6	9·0
6	56·5	4·0	27·5	12·1	$C_{21}H_{17}IN_4$	55·8	3·8	28·1	12·4
7	56·0	4·05	27·9	12·6	$C_{21}H_{17}IN_4$	55·8	3·8	28·1	12·4
8	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—
10 white	51·6	5·0	30·0	10·2	$C_{17}H_{16}IN_3$,MeOH	51·2	4·8	30·1	10·0
10 red	52·4	4·5	32·3	10·9	$C_{17}H_{16}IN_3$	52·5	4·1	32·6	10·8
11	49·8	4·3	31·4	10·4	$C_{16}H_{14}IN_3$	50·1	4·5	31·2	10·3
12	52·2	3·8	32·9	10·8	$C_{17}H_{16}IN_3$	52·5	4·1	32·6	10·8
13	52·2	4·1	33·1	10·55	$C_{17}H_{16}IN_3$	52·5	4·1	32·6	10·8
14	50·6	4·7	28·6	9·4	$C_{18}H_{18}IN_3O$,MeOH	50·6	4·9	28·1	9·3
15	51·7	4·5	29·9	10·4	$C_{18}H_{18}IN_3O$	51·55	4·3	30·3	10·05

* a, Nitromethane; b, acetonitrile; c, chloroform–light petroleum; d, methanol; e, ethanol; f, methanol–ether.

† Rapid heating to 10° below the melting point.

[a] Decomposed on recrystallisation; purified by trituration with ether to constant m. p. [b] White needles; separated from reaction mixture on cooling; further yield on concentration. [c] Red needles; precipitated from concentrated reaction mixture on adding ether. [d] White needles as *c*.

TABLE 5.

Reduction of 3,5,6-triphenyl-1,2,4-triazine.

Time under reflux (min.)	Method	Parts of zinc dust	Parts of acetic acid	Lophine (%)	Dihydrotriazine (%)
5	*a*	4	20	29—42 *	0
5	*b*	4	20	31	0
5	*b*	1·5	15	23	14
10, 30, or 120	*a*	4	20	42 ± 3	0
240	*b*	1·5	15 †	30	13
240	*b*	1·5	15	22	14
240	*b*	4	20	17	0

* Variation of yield caused by different samples of zinc dust. † 50% Ethanol–acetic acid used.

(Found: C, 81·2; H, 5·9; N, 12·9. $C_{22}H_{19}N_3$ requires C, 81·2; H, 5·9; N, 12·9%), $\lambda_{max.}$ 273 and 410—420 mμ (ε 29,000 and 4200).

Action of Acetic Acid on 3,5,6-*Triphenyl*-1,2,4-*triazine Methiodide*.—The methiodide (5 g.) in acetic acid (100 ml.) was heated under reflux for 10 min. The cooled mixture was diluted with ether and the red oily solid filtered off. The filtrate was washed successively with sodium carbonate solution, sodium thiosulphate solution, and water. Evaporation of the dried ($MgSO_4$) ethereal layer gave a yellow residue which crystallised from ethanol as yellow needles (2·0 g., 60%), m. p. and mixed m. p. with 3,5,6-triphenyl-1,2,4-triazine 145°.

Attempted Preparation of 3,4(*or* 4,5)-*Dihydro*-3(*or* 5)-*hydroxy*-4-*methyl*-3,5,6-*triphenyl*-1,2,4-*triazine*.—Benzil (5 g.) and benzhydrazide (3·2 g.) in acetic acid (25 ml.) were heated under reflux with methylamine hydrochloride (16 g.) and anhydrous sodium acetate (19·5 g.) for 24 hr. The cooled mixture was poured into water and the yellow oily solid was washed with water by decantation, dried (*in vacuo*), and extracted with light petroleum. The residue was recrystallised from ethanol to give needles of benzil bisbenzhydrazone, m. p. and mixed m. p. 204—206°. The light-petroleum extract gave an oil which crystallised from ethanol as yellow needles (0·35 g.), m. p. 144—145° alone or on admixture with 3,5,6-triphenyl-1,2,4-triazine. The ethanolic mother-liquors slowly deposited yellow needles of benzil (0·5 g.), m. p. 90—94°. The original filtrate was made alkaline and the yellow precipitate was washed with water and dried. Sublimation at 140°/0·5 mm. gave a colourless solid (1·2 g.), which crystallised from aqueous ethanol in prisms (0·52 g.), m. p. 157—158° (Found: C, 81·8; H, 5·9; N, 11·55%).

Action of Alkali on 3-*Methyl*-5,6-*diphenyl*-1,2,4-*triazine Methiodide*.—The methiodide (5 g.) was suspended in 2N-sodium hydroxide (50 ml.) and ether (200 ml.) and stirred until it had decomposed. The ether layer was combined with further ether extracts, dried ($MgSO_4$), and concentrated to yield prisms. Recrystallisation from ether gave prisms (A), m. p. 124—125° (decomp., rapid heating to 115°) (Found: C, 73·1; H, 6·1; N, 15·0. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·1%), $\lambda_{max.}$ 312 mμ (ε 7200). The ethereal mother-liquors were left to evaporate at room temperature and yielded a residue; digestion of this with boiling ether left a residue, m. p. 156—158° (decomp.). Concentration of the ethereal digest gave a further yield of (A) (0·25 g.), making the total yield 1·25 g. (30%). The less-soluble residue was recrystallised from ethyl acetate to give needles (B), m. p. 159—160° (decomp., rapid heating to 150°) (Found: C, 72·95; H, 6·2; N, 14·75. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·1%), $\lambda_{max.}$ 307—308 mμ (ε 7700), λ_{infl} 220—223 mμ (ε 14,400). Evaporation of the ethereal mother-liquors and recrystallisation of the residue from ethyl acetate gave a further yield (0·23 g.) of (B), making the total yield 0·46 g. (13%).

Action of Methylmagnesium Iodide on 2,3-*Dihydro*-2-*methyl*-3-*oxo*-5,6-*diphenyl*-1,2,4-*triazine*.—Methyl iodide (6·5 g.) in dry tetrahydrofuran (20 ml.) was added to magnesium turnings (1·1 g.) in tetrahydrofuran (50 ml.) with stirring. After the magnesium disappeared, 2,3-dihydro-2-methyl-3-oxo-5,6-diphenyl-1,2,4-triazine (3 g.) in tetrahydrofuran was added portionwise during 1 hr., and the mixture was heated under reflux for 24 hr. The solution was cooled, poured into ammonium chloride solution, and extracted with chloroform. The extract gave, on evaporation, a residue which was recrystallised from benzene–light petroleum and then aqueous methanol to give needles (0·6 g., 20%), m. p. 172—174° (Found: C, 73·3; H, 6·2; N, 14·8. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·1%), $\lambda_{max.}$ 284—286 mμ (ε 8500).

Action of Alkali on 5,6-*Diphenyl*-1,2,4-*triazine Methiodide*.—(*a*) The methiodide (1 g.) was shaken in 2N-sodium hydroxide (50 ml.) and ether (50 ml.). The ether layer was separated, the alkaline layer was extracted with ether, and the combined extracts dried ($MgSO_4$). After concentration to a small volume and cooling, there separated prisms (C) (0·4 g., 60%), m. p. 116—118°, not changed by recrystallisation from ether (Found: C, 73·2; H, 6·1; N, 15·4. $C_{16}H_{15}N_3O$ requires C, 72·4; H, 5·7; N, 15·8%), $\lambda_{max.}$ 316—317 mμ (ε 7900). The mother-liquors were evaporated and the residue recrystallised from benzene as needles (D) (0·03 g.), m. p. 151—152° (decomp., rapid heating to 141°) (Found: C, 72·2; H, 5·7; N, 14·5. $C_{16}H_{15}N_3O$ requires C, 72·4; H, 5·7; N, 15·8%), $\lambda_{max.}$ 308—309 mμ (ε 6500).

(*b*) The methiodide (2 g.) was treated as above and the ethereal solution evaporated to give a residue (1·35 g.), m. p. 110—117°. Recrystallisation from aqueous acetone and then benzene gave needles (0·61 g., 46%), m. p. 151—152° (decomp., rapid heating to 141°) alone or on admixture with (D). No (C) was obtained.

Tetrahydromethyl-5,6-*diphenyl*-1,2,4-*triazine*.—(*a*) Potassium borohydride (2 g.) was added portionwise to a solution of 5,6-diphenyl-1,2,4-triazine methiodide (2 g.) in methanol (50 ml.)

and the solution set aside for 2 hr. The excess of borohydride was destroyed with acetic acid, and the solution made alkaline and diluted to precipitate a solid. Recrystallisation from light petroleum gave yellow prisms (0·71 g., 54%), m. p. 107—108°, of the *tetrahydrotriazine* (Found: C, 76·2; H, 6·6; N, 16·7. $C_{16}H_{16}N_3$ requires C, 76·5; H, 6·8; N, 16·7%), $\lambda_{max.}$ 297 mμ (ε 11,500).

(*b*) Potassium borohydride (0·2 g.) was added portionwise to the product (D) (0·3 g.) in methanol (20 ml.), and the mixture was set aside for 2 hr. and worked up as before. The oily solid was dissolved in ether, the solution dried ($MgSO_4$), and the oil obtained on evaporation was recrystallised from light petroleum to give yellow prisms (0·12 g.), m. p. 107—108° alone or on admixture with the sample above.

Acetyltetrahydromethyl-5,6-diphenyl-1,2,4-triazine.—The preceding tetrahydrotriazine (0·5 g.) was heated under reflux in acetic anhydride (10 ml.) for 2 hr., cooled, poured into water, and made alkaline, and the solid recrystallised from ligroin as prisms of the *acetyltetrahydrotriazine* (0·37 g., 67%), m. p. 143—144° (Found: C, 73·0; H, 6·1; N, 14·1. $C_{18}H_{19}N_3O$ requires C, 73·7; H, 6·5; N, 14·3%), $\lambda_{max.}$ 293—294 mμ (ε 12,100).

Reduction of 2,3-Dihydro-2-methyl-3-oxo-5,6-diphenyl-1,2,4-triazine.—(*a*) Potassium borohydride (1 g.) was added portionwise to the triazine (1 g.) [8] in methanol (50 ml.) and the mixture was set aside for 2 hr. The excess of borohydride was decomposed with acetic acid and water was added. The precipitate was recrystallised from aqueous methanol to give plates of a tetrahydro-derivative (0·8 g., 80%), m. p. and mixed m. p. 197—198° (lit.,[8] m. p. 199°), $\lambda_{max.}$ 297—299 mμ (ε 11,900), λ_{infl} 218 mμ (ε 13,600).

(*b*) Lithium aluminium hydride (1 g.) was added portionwise to the oxotriazine (1 g.) in dry dioxan (25 ml.) and the mixture was heated under reflux for 4 hr. After cooling, the excess of lithium aluminium hydride was destroyed with ethyl acetate, water was added, and the mixture was extracted with chloroform, the insoluble hydroxides being filtered off. The chloroform extract yielded a yellow oil which crystallised from ethanol as plates (35 mg.), m. p. 164—165° (Found: C, 82·3; H, 11·1%). The mother-liquors slowly deposited a solid which crystallised from benzene–light petroleum as plates (0·07 g.), m. p. 197—198° alone or on admixture with tetrahydro-2-methyl-3-oxo-5,6-diphenyl-1,2,4-triazine. Evaporation of the mother-liquors gave an oil which could not be crystallised.

(*c*) The above experiment was repeated with double quantities and heating under reflux for 8 hr. On evaporation of the chloroform, an uncrystallisable yellow oil was obtained which was warmed with 2N-hydrochloric acid for 20 min., cooled, and extracted with ether. The dried ($MgSO_4$) extract yielded a yellow oil which contained benzaldehyde (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 236°).

Biological Tests.—Tests against *P. berghei*, *Babesia rodhaini*, *T. equiperdum*, *T. congolense*, and *T. cruzi* in white mice were kindly carried out by Dr. Hawking at the National Institute for Medical Research using compounds 1—10 (excluding no. 5) listed in Table 4; all were inactive.

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