Iminophosphorane-mediated Synthesis of Fused [1,2,4]Triazines: Preparation of [1,2,4]Triazolo[5,1-*c*][1,2,4]triazine and [1,2,4]Triazino[4,3-*b*][1,2,4,5]tetrazine Derivatives

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A number of [1,2,4]triazolo[5,1-*c*][1,2,4]triazine and [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives have been prepared. 3-(2-Benzylidene-1-methylhydrazino)-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazine (**3**), available from the iminophosphorane (**2**) and benzaldehyde, reacts with aliphatic isocyanates at room temperature to give the corresponding 8*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazinones (**6**)—(**12**). On the other hand, iminophosphorane (**2**) reacts with acyl chlorides at room temperature to give 3-(2-acyl-1-methylhydrazino)-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazines (**13**)—(**15**), which react with isocyanates at room temperature to give 2*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines (**17**)—(**24**).

Adjacent amino and hydrazino functional groups in a heterocyclic system provide many opportunities for the elaboration of additional ring systems. This synthetic strategy provides a route to ring-fused systems containing a bridgehead nitrogen atom when an *N*-aminoheterocycle is utilized. In this context, the preparation of pyrimido[1,2-*b*][1,2,4,5]tetrazines and [1,2,4]triazolo[4,3-*a*]pyrimidines from 3-amino-2-hydrazino-4(3*H*)-pyrimidones has been reported.[1] Following our work on the preparation of fused triazines we have recently described[2] the synthesis of the novel [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine ring system from 4-amino-3-(1-methylhydrazino)-1,2,4-triazines and carbonyl compounds.

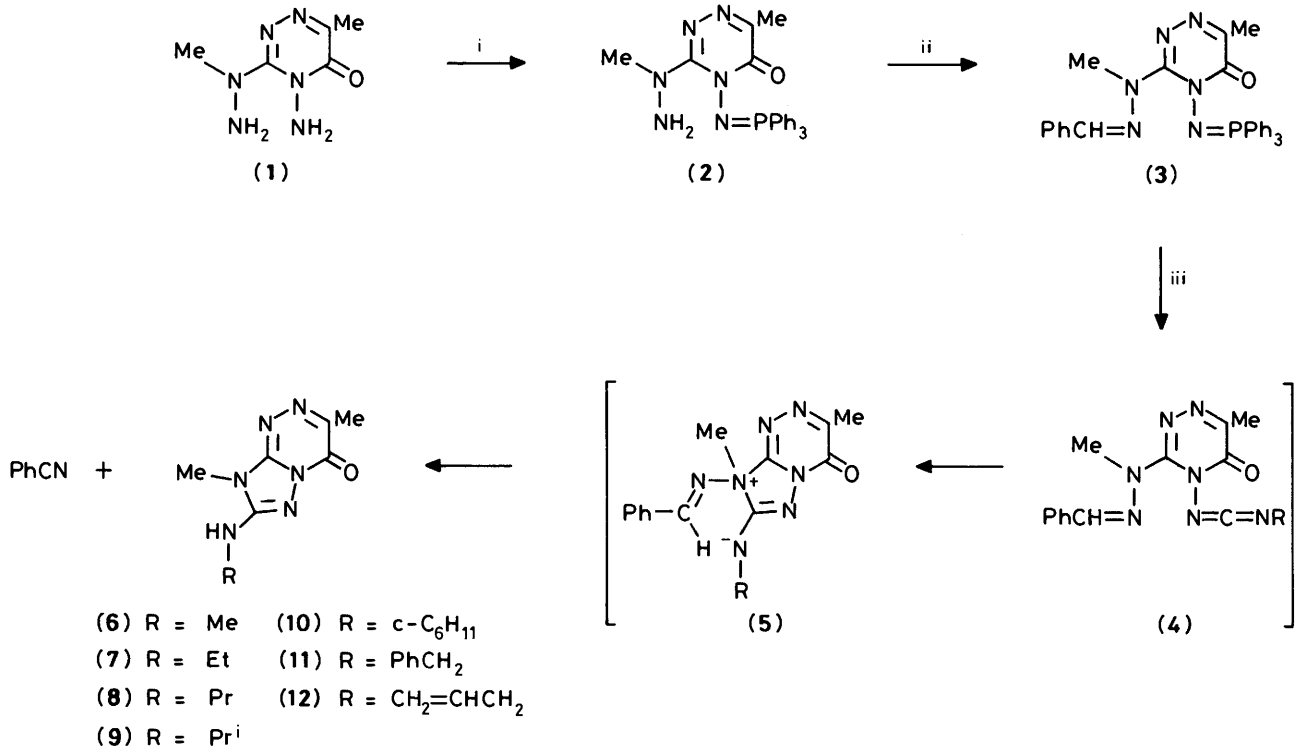
We now describe two general methods for the preparation of some derivatives of the [1,2,4]triazolo[5,1-*c*][1,2,4]triazine and [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine ring systems. Our approach is based on the ready synthesis and subsequent aza-Wittig reaction of iminophosphoranes derived from 4-amino-1,2,4-triazines bearing a hydrazino moiety at position 3. Annulation occurs *via* a carbodi-imide, available from the reaction of the iminophosphorane and an isocyanate, which undergoes ring closure to give the new five- or six-membered heterocyclic ring.

Results and Discussion

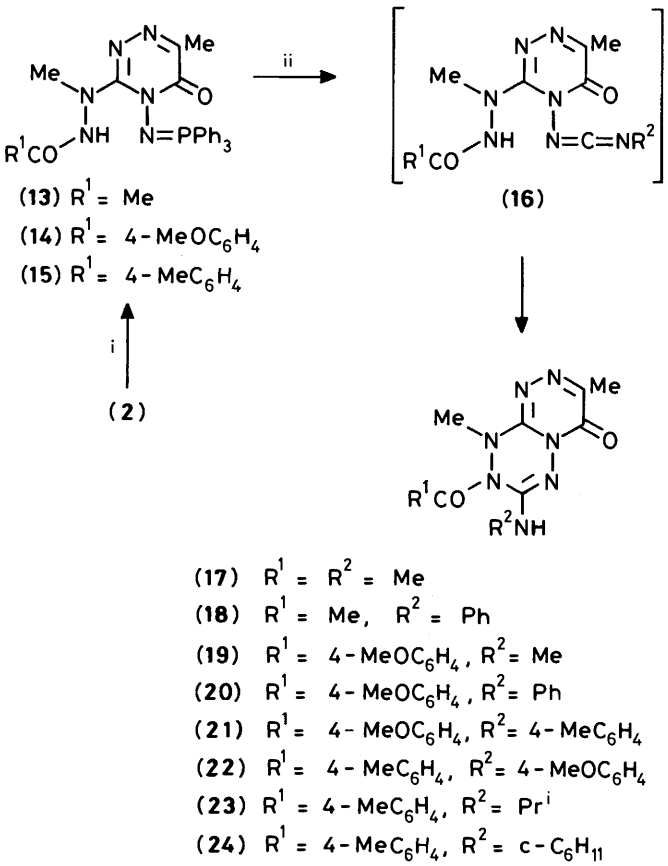
The primary amino function of the hydrazino substituent of the starting 6-methyl-3-(1-methylhydrazino)-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro[1,2,4]triazine (**2**) is found to be more reactive than the iminophosphorane moiety. This compound, available from 4-amino-6-methyl-3-(1-methylhydrazino)-5-oxo-4,5-dihydro[1,2,4]triazine (**1**) and triphenylphosphine dibromide,[2] reacts with benzaldehyde in dry benzene at reflux temperature in the presence of molecular sieves 4 Å to give the iminophosphorane (**3**) in 50% yield. Iminophosphorane (**3**) reacts with allyl, benzyl, and aliphatic isocyanates in dry benzene at room temperature to give the corresponding 7-alkylamino-3,8-dimethyl-4-oxo-4,8-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazines (**6**)—(**12**) (Scheme 1) as crystalline solids in moderate to good yields. The i.r. spectra of the [1,2,4]triazolo[5,1-*c*][1,2,4]triazines (**6**)—(**12**) show absorption due to N–H stretching at 3 307—3 296 cm^{-1} and to the carbonly group at 1 676—1 659 cm^{-1}. In their ^1H n.m.r. spectra the *C*-methyl and *N*-methyl groups appear characteristically as singlets at δ 2.30—2.45 and δ 3.53—3.63 respectively. For compound (**6**) the NH signal appears as a narrow quartet and is as equally well resolved as the singlet due to the methyl group linked to the amino substituent. Electron-impact mass spectra show the expected molecular ion peaks in very high intensity and the fragmentation pattern is in agreement with the proposed structures.

The formation of the [1,2,4]triazolo[5,1-*c*][1,2,4]triazines (**6**)—(**12**) presumably involves an initial aza-Wittig reaction between the iminophosphorane (**2**) and the isocyanate to give a carbodi-imide as intermediate which undergoes nucleophilic attack by one nitrogen atom of the hydrazone moeity to give the zwitterionic bicyclic intermediate (**5**), which by an internal proton abstraction undergoes fragmentation to give benzonitrile and the [1,2,4]triazolo[5,1-*c*][1,2,4]triazine. This assumption is supported by the isolation and characterization of the carbodi-imide (**4**) in one case (R = t-butyl); attempts to cyclize this intermediate (**4**) failed to give the bicyclic heterocycle, probably due to the sterically hindered 'aliphatic' substituted C=N double bond. It is worth noting that no reaction between carbodi-imides and *N*,*N*-disubstituted hydrazones has hitherto been reported.[3] The last step of this conversion is conceptually similar to the previously reported fragmentation of *N*,*N*-dialkylhydrazone *N*-oxides to give nitriles through a Cope-type elimination reaction.[4]

On the other hand, we have previously reported[2] that iminophosphorane (**2**) reacts with acyl chlorides in the presence of triethylamine in benzene at reflux temperature to give the corresponding 3-aryl-1,4-dihydro-1,7-dimethyl-6-oxo-4*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines. We now report that the reaction of iminophosphorane (**2**) with acyl chlorides in benzene at room temperature leads to acyl iminophosphoranes (**13**)—(**15**) instead of the expected imidoyl chlorides.[5] As indicated earlier, this conversion shows the preferential reactivity of the hydrazino group of compound (**2**) with respect to the iminophosphorane moiety towards electrophilic reagents. Iminophosphoranes (**13**)—(**15**) react with aliphatic and aromatic isocyanates in dry dichloromethane at room temperature to give 2*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives (**17**)—(**24**) as crystalline solids in moderate to good yields (Scheme 2). The i.r. spectra of compounds (**17**)—(**24**) show absorptions in the region 3 422—3 140 cm^{-1} due to the N–H stretching and two strong absorption bands at 1 693—1 669 and 1 661—1 619 cm^{-1} attributable to the two carbonyl groups. Salient features of the ^1H n.m.r. spectra are given in Table 3. The mass spectra show the expected molecular ion peaks and the fragmentation pattern is in accord with the proposed structures. We believe that the conversion (**13**)—(**15**) into (**17**)—(**24**) involves initial aza-Wittig reaction between the iminophos-



Scheme 1. *Reagents:* i, Ph_3PBr_2; ii, PhCHO; iii, RNCO



Scheme 2. *Reagents and conditions:* i, R^{1}COCl, Et_3N, room temperature; ii, R^{2}NCO, CH_2Cl_2, room temperature

phorane and the isocyanate to give a carbodi-imide (**16**) as highly reactive intermediate which undergoes cyclization by nucleophilic attack of the amino group of the hydrazide moiety to give the corresponding 2*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]-tetrazine derivative. Although reaction of carbodi-imides with hydrazines,[6] carbonohydrazide,[7] and thiocarbonohydrazide[8] have been reported, to our knowledge this is the first example reported of heterocyclization based on the reaction of carbodi-imides with hydrazides.

Experimental

M.p.s were recorded on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Nicolet FT-5DX spectrometer. ^{1}H N.m.r. spectra were recorded on a Varian FT-80 (80 MHz) spectrometer with Me_4Si as internal standard. Electron-impact mass spectra were carried out on a Hewlett-Packard 5993C spectrometer at an ionization potential of 70 eV. Elemental analyses were performed with a Perkin-Elmer 240C instrument.

Reagents.—All solvents were dried according to standard procedures, distilled, and stored over activated molecular sieves 4 Å. 4-Amino-6-methyl-3-(1-methylhydrazino)-5-oxo-4,5-dihydro-1,2,4-triazine[2] (**1**) and 6-methyl-3-(1-methylhydrazino)-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazine[2] (**2**) were prepared following the methods described in the literature.

Preparation of Iminophosphorane (**3**).—To a solution of 6-methyl-3-(1-methylhydrazino)-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazine (**2**) (0.86 g, 2 mmol) in dry benzene (20 ml) were added benzaldehyde (0.21 g, 2 mmol) and toluene-*p*-sulphonic acid (0.1 g). The resultant solution was heated at reflux temperature in the presence of

Table 1. 7-Alkylamino-3,8-dimethyl-4-oxo-4,8-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazines (**6**)—(**12**)

Compound	Crystal form	Yield (%)	M.p. (°C)[a]	Found (%) [Requires (%)] C	H	N	Formula
(**6**)	Prisms	60	319	43.3 (43.29)	5.3 (5.19)	43.2 (43.27)	$C_7H_{10}N_6O$
(**7**)	Prisms	54	251—253	46.2 (46.14)	5.8 (5.80)	40.4 (40.36)	$C_8H_{12}N_6O$
(**8**)	Prisms	59	267	48.5 (48.64)	6.4 (6.35)	37.9 (37.81)	$C_9H_{14}N_6O$
(**9**)	Prisms	71	241	48.4 (48.64)	6.3 (6.35)	37.7 (37.81)	$C_9H_{14}N_6O$
(**10**)	Prisms	63	274	55.1 (54.94)	6.8 (6.92)	32.1 (32.04)	$C_{12}H_{18}N_6O$
(**11**)	Prisms	52	176—179	57.8 (57.77)	5.3 (5.22)	31.2 (31.09)	$C_{13}H_{14}N_6O$
(**12**)	Prisms	54	237—239	49.1 (49.08)	5.5 (5.49)	38.2 (38.16)	$C_9H_{12}N_6O$

[a] From EtOH

Table 2. 2*H*-[1,2,4]Triazino[4,3-*b*][1,2,4,5]tetrazine derivatives (**17**)—(**24**)

Compound	Crystal form	Yield (%)	M.p. (°C)	Solvent	Found (%) [Requires (%)] C	H	N	Formula
(**17**)	Needles	55	196—198	EtOH	42.9 (43.03)	5.2 (5.22)	39.15 (39.02)	$C_9H_{13}N_7O_2$
(**18**)	Needles	56	217—218	MeOH	53.5 (53.67)	5.0 (4.83)	31.1 (31.29)	$C_{14}H_{15}N_7O_2$
(**19**)	Needles	77	220—222	THF	52.3 (52.47)	5.2 (4.99)	28.4 (28.56)	$C_{15}H_{17}N_7O_3$
(**20**)	Needles	87	265	THF	59.2 (59.25)	4.7 (4.72)	24.3 (24.18)	$C_{20}H_{19}N_7O_3$
(**21**)	Needles	63	270—271	THF	60.2 (60.13)	4.9 (5.05)	23.5 (23.38)	$C_{21}H_{21}N_7O_3$
(**22**)	Needles	57	265—266	EtOH	60.1 (60.13)	5.2 (5.05)	23.2 (23.38)	$C_{21}H_{21}N_7O_3$
(**23**)	Prisms	66	191—193	MeOH	57.35 (57.45)	5.8 (5.96)	27.7 (27.59)	$C_{17}H_{21}N_7O_2$
(**24**)	Prisms	57	251—253	MeOH	60.65 (60.74)	6.2 (6.37)	24.9 (24.79)	$C_{20}H_{25}N_7O_2$

Table 3. ^{1}H N.m.r. data of 2*H*-[1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives (**17**)—(**24**)

Compound	7-Me	1-Me	R^1	R^2	NH
(**17**)	2.34 (3 H, s)	3.38 (3 H, s)	2.32 (3 H, s)	2.92 (3 H, d, *J* 5.0 Hz)	7.83
(**18**)	2.43 (3 H, s)	3.57 (3 H, s)	2.46 (3 H, s)	8.0—7.1 (5 H, m)	10.89
(**19**)	2.40 (3 H, s)	3.56 (3 H, s)	8.2—7.7 (2 H, d) 7.5—7.2 (2 H, d) 3.95 (3 H, s, MeO)	2.98 (3 H, d, *J* 5.0 Hz)	8.40
(**20**)	2.52 (3 H, s)	3.55 (3 H, s)	8.3—7.2 (9 H, m) 3.92 (3 H, s, MeO)		11.03
(**21**)	2.36 (3 H, s)	3.60 (3 H, s)	8.1—7.1 (8 H, m) 3.92 (3 H, s, MeO)	2.44 (3 H, d, MeAr)	10.72
(**22**)	2.47 (3 H, s)	3.63 (3 H, s)	8.3—7.1 (8 H, m) 2.47 (3 H, s, MeAr)	3.87 (3 H, s, MeO)	10.77
(**23**)	2.45 (3 H, s)	3.67 (3 H, s)	8.1—7.8 (2 H, d) 7.5—7.3 (2 H, d) 2.53 (3 H, s, MeAr)	4.3—3.7 (1 H, m) 1.33 (6 H, d, *J* 6.5 Hz)	6.05
(**24**)	2.40 (3 H, s)	3.62 (3 H, s)	8.3—7.4 (4 H, m) 2.45 (3 H, s, MeAr)	3.5—3.1 (1 H, m) 2.3—0.7 (10 H, m)	8.40

molecular sieves 4 Å for 2 h. After cooling, the solution was filtered, the filtrate was concentrated to dryness under reduced pressure, and the residual material was recrystallized from benzene–hexane (1:1 v/v) to give 3-(2-*benzylidene*-1-*methylhydrazino*)-6-*methyl*-5-*oxo*-4-*triphenylphophoranylideneamino*-4,5-*dihydro*[1,2,4]*triazine* (**3**) (0.52 g, 50%) as prisms, m.p. 175—177 °C (Found: C, 69.3; H, 5.1; N, 16.1. $C_{30}H_{27}N_6OP$ requires C, 69.49; H, 5.25; N, 16.21%); $\nu_{max.}$(Nujol) 1 631vs, 1 438vs,

1 235vs, 1 109vs, 1 042s, 754m, 723s, 695s, and 604s cm^{-1}; $\delta_H(CDCl_3)$ 8.3—7.2 (21 H, m), 3.65 (3 H, s), and 2.35 (3 H, s); *m/z* 518 (M^+, 7%), 441 (16), 414 (5), 304 (32), 190 (16), 277 (27), 276 (93), 262 (35), 198 (13), 184 (20), 183 (100), 152 (14), 125 (10), 108 (72), 107 (18), 104 (14), 83 (12), and 77 (46).

General Procedure for the Preparation of 7-Alkylamino-3,8-dimethyl-4-oxo[1,2,4]triazolo[5,1-c][1,2,4]triazines (**6**)—(**12**).—The appropriate isocyanate (2 mmol) was added dropwise to a stirred solution of iminophosphorane (**3**) (1.04 g, 2 mmol) in dry benzene (20 ml). The resultant solution was stirred at room temperature for 24 h whereupon the precipitated solid was separated by filtration and recrystallized from ethanol to give the corresponding [1,2,4]triazolo[5,1-*c*][1,2,4]triazine (**6**)—(**12**). The solvent was removed from the filtrate under reduced pressure and the residual material was extracted with hexane (2 × 10 ml); elimination of the solvent afforded almost pure benzonitrile. Yields, m.p.s and elemental analyses of the products (**6**)—(**12**) are given in Table 1.

As a typical product of this reaction, *7-methylamino-3,8-dimethyl-4-oxo[1,2,4]triazolo[5,1-c][1,2,4]triazine* (**6**) had $\nu_{max.}$(Nujol) 3 307vs, 1 676vs, 1 647vs, 1 627vs, 1 591vs, 1 415m, 1 353m, 1 233w, 1 218m, 1 148m, 1 097m, 1 072m, 1 006m, and 754m cm^{-1}; $\delta_H[(CD_3)_2SO]$ 7.65 (1 H, q, *J* 5 Hz), 3.53 (3 H, s), 2.96 (3 H, d, *J* 5 Hz), and 2.42 (3 H, s); *m/z* 194 (M^+, 85%), 167 (5), 166 (40), 152 (5), 138 (5), 124 (5), 98 (5), 97 (38), 96 (17), 83 (10), 82 (58), 71 (12), 69 (13), 67 (29), 57 (100), and 55 (35).

Compounds (**7**)—(**12**) were similarly prepared. Their i.r., m.s., and ^1H n.m.r. data have been deposited as a Supplementary Publication.*

General Procedure for the Preparation of 3-[2-Aroyl-1-methylhydrazino)-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazines (**13**)—(**15**).—To a solution of 6-methyl-3-(1-methylhydrazino)-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazine (**2**) (0.53 g, 1.2 mmol) in dry benzene (20 ml) were added the appropriate acyl chloride (1.2 mmol) and triethylamine (0.12 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure at 25 °C and the residual material was slurried with cold ethanol (10 ml). The separated solid was collected by filtration, dried, and recrystallized from ethanol.

Thus, *3-(2-acetyl-1-methylhydrazino)-6-methyl-5-oxo-4-triphenylphosphoranylideneamino-4,5-dihydro-1,2,4-triazine* (**13**) was obtained in 45% yield as *prisms*, m.p. 164—165 °C (Found: C, 63.65; H, 5.2; N, 17.6. $C_{25}H_{25}N_6O_2P$ requires C, 63.55; H, 5.33; N, 17.79%); $\nu_{max.}$(Nujol) 3 415s, 1 698vs, 1 625vs, 1 483vs, 1 438vs, 1 398vs, 1 285m, 1 257m, 1 228vs, 1 183m, 1 109vs, 1 058s, 996w, 753s, 725s, and 707vs cm^{-1}; $\delta_H(CDCl_3)$ 8.98 (1 H, s), 8.3—7.4 (15 H, m), 3.53 (3 H, s), 2.22 (3 H, s), and 1.83 (3 H, s); *m/z* 278 (45%), 277 (99), 201 (25), 199 (28), 194 (60), 185 (10), 183 (24), 166 (30), 154 (10), 152 (19), 136 (6), 109 (15), 99 (32), 83 (7), 82 (18), 56 (100), and 55 (22).

Compounds (**14**) and (**15**) were similarly prepared. Compound (**14**) was obtained in 67% as *prisms*, m.p. 187 °C (Found: C, 65.9; H, 5.1; N, 14.8. $C_{31}H_{29}N_6O_3P$ requires C, 65.95; H, 5.18; N, 14.88%); compound (**15**) was obtained in 59% as *prisms*, m.p. 182—184 °C (Found: C, 67.7; H, 5.3; N, 15.4. $C_{31}H_{29}N_6O_2P$ requires C, 67.87; H, 5.33; N, 15.32%). Their i.r., m.s., and ^1H n.m.r. data have been deposited in the supplementary publication.

General Procedure for the Preparation of 2-Acyl-3-alkyl(aryl)-amino-1,7-dimethyl-6-oxo-1,6-dihydro-2H-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazines (**17**)—(**24**).—The appropriate isocyanate (2 mmol) was added dropwise to a well stirred solution of an iminophosphorane (**13**)—(**15**) (2 mmol) in dry dichloromethane (20 ml). The mixture was stirred at room temperature for 24 h whereupon the solvent was removed under reduced pressure and the residual material was slurried with benzene (10 ml) and the separated solid was collected by filtration, dried, and recrystallized from the appropriate solvent. Yields, m.p.s, and elemental analyses of the products (**17**)—(**24**) are given in Table 2, and ^1H n.m.r. data in Table 3.

Thus prepared was *2-acetyl-1,7-dimethyl-3-methylamino-6-oxo-1,6-dihydro-2H-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazine* (**17**) $\nu_{max.}$(Nujol) 3 296w, 3 216w, 1 693vs, 1 661vs, 1 626s, 1 570s, 1 260w, 1 110m, 1 097m, 1 023w, 982w, 883w, 743w, and 708w cm^{-1}; *m/z* 251 (M^+, 35%), 182 (10), 168 (10), 154 (10), 153 (25), 140 (10), 139 (12), 126 (59), 125 (20), 99 (68), 83 (10), 69 (25), 68 (21), and 58 (100).

The i.r. and m.s. data for compounds (**18**)—(**24**) have been deposited in the Supplementary Publication.

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* *Supplementary data available:* (No. SUP 56730, 6 pp). Deposited at the British Library Document Supply Centre. See Instructions for Authors, section 4.0, in the January issue.

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