Synthetic Uses of Polyphosphoric Acid. Part III.[1] A Ready Synthesis of Aromatic Aldazines and Ketazines

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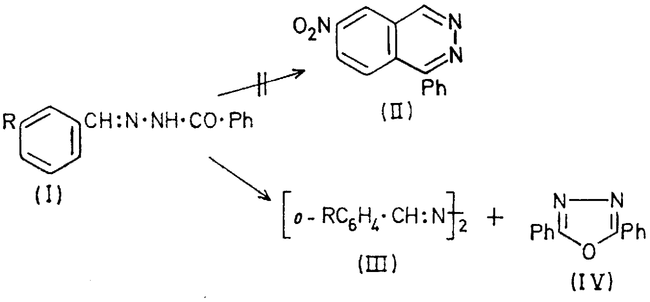
Azines are prepared conveniently by heating aromatic aldehydes or ketones with various carbonyl reagents (hydrazine and its salts, semicarbazide and toluene-*p*-sulphonohydrazide) in polyphosphoric acid at 100° for a few minutes. Various dialkylaminophenylazines have been made by this route.

GENERALLY azines are obtained by condensation of the required carbonyl compound (2 mol.) and hydrazine (1 mol.) which is usually liberated *in situ* from its salt by addition of ammonia or potassium acetate.[2] This method works well for aliphatic and non-sterically hindered aromatic carbonyl compounds such as benzaldehyde which is converted into its azine by this procedure within 7 hr. Acetophenone on the other hand has to be heated in a sealed tube with hydrazine at 100° for 12 hr. The best way of making ketazines appears to be to prepare the hydrazone first and cause it to react with an excess of ketone for 12—15 hr., as for instance in the case of benzophenone.[3] In other less convenient routes it is recommended that either the appropriate nitrile is heated with hydrazine hydrate and Raney nickel[4] under reflux for 40 hr. or a diazoalkane ($R_2{=}CN_2$) is boiled in xylene to bring about liberation of, and reaction with, the derived carbene (R_2C:) to give the azine[5] ($R_2C{=}N{\cdot}N{=}CR_2$). Though yields in the last procedure may be reasonable the disadvantages of a multi-stage reaction involving potentially unstable diazoalkanes are obvious. The use of sulphuric acid as catalyst in azine preparations has been reported in a patent[6] but we find that reaction time and temperature as well as acid concentration are critical if sulphonated and tarry products are to be avoided.

We have now found that at *ca.* 100° polyphosphoric acid (PPA) is an excellent catalyst and solvent for the production of azines from aromatic aldehydes and ketones in presence of various carbonyl reagents, *viz.* hydrazine, its salts, semicarbazide hydrochloride, toluene-p-sulphonohydrazide and acid hydrazides. The reaction is usually complete within 15 min. Phenyl hydrazine was unsuitable since it led to indole formation as expected.[7,8]

Azine formation in PPA has been noted before inadvertently, but has not been assessed for its synthetic value. Thus, quantitative but undesired production of the azine (III; $R = NO_2$) was observed on treating the hydrazone (I; $R = NO_2$) with PPA for 6 hr. at 140° in an unsuccessful attempt to cyclise it to the phthalazine (II).[9] Other workers,[10] however, report that acyl hydrazones (I; R = H) in PPA give a mixture of azines (III; R = H) and oxadiazoles (IV). In an extension of the latter reaction Popp[11] used 1,2-dibenzoylhydrazines and obtained oxadiazole nearly quantitatively at the expense of azine formation.



Our PPA preparation of azines has the advantage that the intermediate carbonyl derivatives do not have to be isolated. No difference in yield was observed whether the intermediate hydrazone was preformed or prepared *in situ*, provided that the carbonyl/hydrazine ratio was at least 2·1 and excess of PPA (*ca.* 10 × by wt. based on the carbonyl compound) was present. Excess of hydrazine does not affect the yield. If a hydrazine derivative such as toluene-*p*-sulphonohydrazide is used (*cf.* above), hydrolysis presumably liberates hydrazine which then reacts in the usual way with the carbonyl compound. This idea was supported by heating a solution of 5-nitro-2-piperidinobenzaldehyde toluene-*p*-sulphonylhydrazone (VI; $X = [CH_2]_5R = H$) in PPA. The reaction mixture contained toluene-*p*-sulphonic acid and half the theoretical amount of hydrazine as established by titration under Andrew's conditions,[12] while the other half had been consumed in azine formation which was practically quantitative. The reaction in PPA proceeds smoothly at 100° and is usually complete within 5—10 min. regardless of the steric features of the reactants or the electronic nature of their substituents.

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The short reaction time is in favourable contrast to the prolonged period usually required to form azines from carbonyl compounds with bulky substituents. At temperatures up to 150° no significant decrease in yield was observed since the azomethine linkage of the azine is quite stable to PPA. Above this temperature tar formation occurs progressively with deterioration in the yields. It is noteworthy that no unsymmetrical azines were obtained when two different carbonyl compounds were heated with hydrazine in PPA or two different toluene-*p*-sulphonylhydrazones were pyrolysed in PPA. For instance, benzaldehyde and 5-nitro-2-piperidinobenzaldehyde when treated in admixture with hydrazine gave only the corresponding azines. It has been noticed that unsymmetrical azines are less stable than symmetrical ones and in time tend to revert to their symmetrical analogues.[13] Such a rearrangement is quite feasible in our case under the reaction conditions. This 'symmetry stability' has been previously observed by us in the preparation of γ-pyrones from carboxylic acids and PPA.[14]

TABLE 1

Dialkylamino-substituted aldehydes and ketones (V)

X	R	M.p.	Yield (%)	Found (%) C	Found (%) H	Molecular formula	Required (%) C	Required (%) H
$[CH_2]_4$	H	136°	88	60·0	5·5	$C_{11}H_{12}N_2O_3$	59·7	5·6
$[CH_2]_5$	H	118	90	61·4	5·9	$C_{12}H_{14}N_2O_3$	61·5	5·9
$[CH_2]_6$	H	73	95	62·6	6·3	$C_{13}H_{16}N_2O_3$	62·9	6·5
$[CH_2]_2\cdot O\cdot[CH_2]_2$	H	111	82	55·9	4·9	$C_{11}H_{12}N_2O_4$	55·9	5·1
$[CH_2]_2\cdot NMe\cdot[CH_2]_2$	H	158	78	57·5	6·1	$C_{12}H_{15}N_3O_3$	57·8	6·1
$[CH_2]_5$	Me	50	90	63·1	6·7	$C_{13}H_{16}N_2O_3$	62·9	6·5

TABLE 2

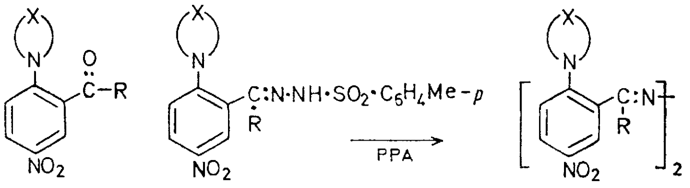
Dialkylamino-substituted aldehyde and ketone toluene-*p*-sulphonylhydrazones (VI)

X	R	M.p.	Yield (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
$[CH_2]_4$	H	189°	Quant.	55·1	5·5	$C_{18}H_{20}N_4O_4S$	55·5	5·2
$[CH_2]_5$	H	179	85	56·6	5·7	$C_{19}H_{22}N_4O_4S$	56·7	5·5
$[CH_2]_6$	H	151	85	57·5	5·5	$C_{20}H_{24}N_4O_4S$	57·3	5·4
$[CH_2]_2O[CH_2]_2$	H	203	70	53·1	4·7	$C_{18}H_{20}N_4O_5S$	53·5	5·0
$[CH_2]_2NMe_1[CH_2]_2$	H	185	80	49·5	5·1	$C_{19}H_{24}ClN_5O_4S$ [a]	50·0	5·3
$[CH_2]_5$	Me	180	90	57·6	6·0	$C_{20}H_{24}N_4O_4S$	57·6	5·8

[a] Precipitates as the hydrochloride by addition of hydrochloric acid (d 1·15) to the reaction mixture.

The synthesis is not so successful with aliphatic carbonyl compounds whose azines are in any case available by a direct route. We find that complications are due to condensation of the aldehydes and ketones for which PPA is a good reagent. Apart from exploring the scope of the method with various aldehydes and ketones a series of *o*-dialkylamino-substituted arylazines needed for other work was also prepared by this new procedure for which details are listed (*cf.* Table 5). Since azines have found various uses which have been the subject of several patents[15] the ready synthesis of this class of compounds with PPA is of wider than academic interest.

The recently described ethyl ester of PPA (PPEt)[1] did not bring about azine formation as the reagent was ineffective in generating hydrazine from toluene-*p*-sulphonohydrazides and other hydrazine derivatives.



(V) (VI) (VII)

EXPERIMENTAL

Polyphosphoric acid was commercial tetraphosphoric acid (Albright and Wilson) containing *ca.* 85% of phosphorus pentoxide.

Dialkylamino-substituted Aldehydes and Ketones.—2-Chloro-5-nitrobenzaldehyde[16] (1 mol.) sodium hydrogen carbonate (1 mol.) and the appropriate heterocyclic base (1·1 mol.) were heated under reflux in ethanol for 4 hr.[17] When the reaction mixtures were poured into water the dialkylaminoaldehydes separated as yellow solids which were filtered off, dried *in vacuo*, and recrystallised from ethanol. 2-Chloro-5-nitroacetophenone[1] was made to react in a similar way to give dialkylaminoketones. Details of the compounds are given in Table 1.

Dialkylamino-aldehyde- and -ketone Hydrazones.—(a) *Toluene-*p*-sulphonylhydrazones.* In a typical preparation 5-nitro-2-piperidinobenzaldehyde (1 mol.) (V; R = H; $[CH_2]_5$) and toluene-*p*-sulphonohydrazide (1 mol.) were made to react in boiling ethanol for 10 min. The toluene-*p*-sulphonylhydrazone crystallised almost immediately as an orange solid from the reaction mixture. The products

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TABLE 3

Effect of change in the medium and temperature on the yield of azine from the thermolysis of 5-nitro-2-piperidinobenzaldehyde toluene-*p*-sulphonylhydrazone (VI; R = H, X = $[CH_2]_5$)

Reagent	Reaction temp.	Reaction time (min.)	Product	Yield of Azine
PPA	165°	60	Tar	
	150	30	Tar	
	100	60	Azine	Quant.
	100	15	Azine	Quant.
	100	5	Azine	Quant.
	60	60	Azine and starting material	60%
PPEt	150	60	Tar	
	100	60	Starting material	
H_2SO_4 (*d* 1·84)	100	60	Azine	65%

TABLE 4

Yields of azine from the thermolysis of various carbonyl derivatives of 5-nitro-2-piperidinobenzaldehyde in PPA

Derivative	M.p. of deriv.	Reaction temp.	Reaction time (min.)	Product	Yields
Toluene-p-sulphonyl hydrazone	179°	150°	60	Tar	
	179	100	15	Azine	Quant.
Hydrazone	*	100	15	Azine	Quant.
Acethydrazone	125	100	15	Azine	85%
Semicarbazone	262	100	51	Azine	Quant.

* Not isolated. The theoretical quantity of reagent was added to 2·0 g of aldehyde in 20 g. of PPA.

were filtered off and recrystallised from ethanol. Details of yields and m.p.s' are given in Table 2.

(b) *Hydrazone.* 5-Nitro-2-piperidinobenzaldehyde (1 mol.) was made to react with hydrazine hydrate (1 mol.) as in (a) to give 5-*nitro*-2-*piperidinobenzaldehyde hydrazone* (85%) as yellow prisms from ethanol, m.p. 95—96° (Found: C, 57·9; H, 6·3; N, 22·5. $C_{12}H_{16}N_4O_2$ requires C, 58·1; H, 6·5; N, 22·6%).

(c) *Semicarbazone.* To a solution of 5-nitro-2-piperidinobenzaldehyde (1 mol.) in hot ethanol was added semicarbazide hydrochloride (1 mol.) and sodium acetate to act as buffer. The semicarbazone precipitated as yellow needles, m.p. 262° (from ethanol) (Found: C, 53·1; H, 5·7; N, 23·8. $C_{12}H_{17}N_5O_3$ requires C, 53·5; H, 5·9; N, 24%).

(d) *Acethydrazone.* 5-Nitro-2-piperidinobenzaldehyde (1 mol.) was made to react with acethydrazide (1 mol.) as in (a) to give 5-*nitro*-2-*piperidinobenzaldehyde acethydrazone* (85%) as yellow needles, m.p. 125° (from ethanol) (Found: C, 57·9; H, 6·1; N, 19·2. $C_{14}H_{18}N_4O_3$ requires C, 58·2; H, 6·2; N, 19·3%).

Preparation of Azines in Polyphosphoric Acid.—(a) *With Preformed Carbonyl Derivatives.* In a typical reaction under optimum conditions (Table 3) the carbonyl derivative (3·0 g.) was mixed with PPA (30 g.) and stirred for 0·25 hr. at 100°. The mixture while still fluid was diluted with ice–water (150 ml.) and the precipitated azine was filtered off, washed with water, and dried *in vacuo*. Results are given in Table 4 for the various carbonyl derivatives.

(b) *Without Preformed Carbonyl Derivatives.* In a typical reaction the aldehyde or ketone (2 mol.) in PPA (10 g. for each 1 g. of carbonyl compound) was mixed with a suitable hydrazine derivatives (1 mol.) and the reaction was carried out as in (a) above. Yields and products were identical in both cases. Results with hydrazine hydrate are given in Table 5 for a wide range of aldehydes and ketones.

A quantitative investigation of the reaction products was carried out from the decomposition of 5-nitro-2-piperidinobenzaldehyde toluene-*p*-sulphonylhydrazone as described in (a) above. The azine (VII; R = H; X

TABLE 5

Reaction of various carbonyl compounds in PPA at 100° for 0·25 hr. with hydrazine hydrate

Carbonyl compd.	Product *	Yield (%)	M.p.	Found (%) C	Found (%) H	Molecular formula	Required (%) C	Required (%) H
2-Nitrobenzaldehyde	2,2′-Dinitrobenzaldehyde azine †	95	204°					
3-Nitrobenzaldehyde	3,3′-Dinitrobenzaldehyde azine †	98	197					
2-Methoxybenzaldehyde	2,2′-Dihydroxybenzaldehyde azine †	95	212					
2-Ethylbenzaldehyde	2,2′-Diethylbenzaldehyde azine	90	66	81·7	7·9	$C_{18}H_{20}N_2$	81·7	7·6
Benzaldehyde	Benzaldehyde azine † [a]	95	93					
4-Dimethylaminobenzaldehyde	4,4′-Dimethylaminobenzaldehyde azine ‡	95	253					
Pyridine-2-carbaldehyde	Pyridine-2-carbaldehyde azine §	48	150					
5-Nitro-2-pyrrolidinobenzaldehyde	Azine (VII; R = H; X = $[CH_2]_4$) [b]	80	265	60·65	5·80	$C_{22}H_{24}N_6O_4$	60·53	5·55
5-Nitro-2-piperidinobenzaldehyde	Azine (VII; R = H; X = $[CH_2]_5$) [b]	98	279	61·65	5·78	$C_{24}H_{28}N_6O_4$	62·06	6·08
2-Morpholino-5-nitrobenzaldehyde	Azine (VII; R = H; X = $[CH]_2{\cdot}O{\cdot}[CH_2]_2$ [b]	95	240	56·05	4·90	$C_{22}H_{24}N_6O_6$	56·40	5·17
5-Nitro-2-perhydroazepinobenzaldehyde	Azine (VII; R = H; X = $[CH_2]_6$ [b]	90	234	63·30	6·30	$C_{26}H_{32}N_6O_4$	63·40	6·55
2-*N*-Methylpiperazino-5-nitrobenzaldehyde	Azine (VII; R = H; X = $[CH_2]_2{\cdot}NMe[CH_2]_2$) [c,d]	90	230	41·53	4·90	$2H_3PO_4$ $C_{24}H_{30}N_8O_4$	41·74	5·25
Acetophenone	Acetophenone azine ¶	90	121					
Benzophenone	Benzophenone azine ¶	68	164					
5-Nitro-2-piperidinoacetophenone	Azine (VII; R = Me; X = $[CH_2]_5$)	92	195	63·40	6·3	$C_{26}H_{32}N_6O_4$	63·40	6·55
2-Benzoylpyridine	2,2′-Dibenzoylpyridine azine	83	114			$C_{24}H_{22}N_4$		

[a] Yellow needles from benzene–light petroleum (b.p. 60—80°). [b] From anisole. [c] From dimethylformamide. [d] Analysed as a diphosphate.

* All azines were recrystallised from ethanol unless otherwise stated. † E. R. Blout and R. M. Gofstein, *J. Amer. Chem. Soc.*, 1945, **67**, 13. ‡ T. Curtius and A. Bertho, *J. prakt. Chem.*, 1930, **125**, 23. § J. D. Bowyer and G. R. Ramage, *J. Chem. Soc.*, 1957, 4506. ¶ E. R. Blout, V. W. Eager, and R. M. Gofstein, *J. Amer. Chem. Soc.*, 1946, **68**, 1983.

= $[CH_2]_5$) was filtered off (95%) and washed thoroughly; the washings were combined with the reaction liquors. The presence of toluene-*p*-sulphonic acid was shown by its u.v. spectrum ($\lambda_{max.}$ 286 nm.) and that of hydrazine by titration using M/40-potassium iodate under Andrews conditions. The liquors contained *ca.* 50% of the hydrazine used.

Attempted Preparation of Mixed Azines.—Benzaldehyde (2·12 g.), 5-nitro-2-piperidinobenzaldehyde (4·68 g.), and hydrazine hydrate (2·0 g.) were heated in PPA (50 g.) at 100° for 0·25 hr. The mixture was diluted with ice–water (200 g.) and the precipitated azines were filtered off and dried *in vacuo*. Extraction of the azines with hot, light petroleum ether (b.p. 60—80°) gave a pale yellow solid (2·0 g., 96%) m.p. 96° identical to an authentic sample of benzaldehyde azine. The residue was found to consist solely of 5,5′-dinitro-2,2′-dipiperidinobenzaldehydeazine, m.p. and mixed m.p. 279°. No evidence of mixed azines was found.

Reactions in PPEt.—5-Nitro-2-piperidinobenzaldehyde toluene-*p*-sulphonylhydrazone (2·0 g.) and PPEt (20 g.) were stirred together (for 0·25 hr. at 100°) as before. Dilution of the mixture with ice–water led to a quantitative recovery of starting material. Similarly the corresponding hydrazone, acethydrazone and semicarbazone failed to yield any azine. Higher temperatures led to extensive tar formation.

We thank the S.R.C. for a grant (to D. B. M.) and Mr. J. S. Millership for additional results to Table 5.

[0/1089 *Received, June 26th,* 1970]