

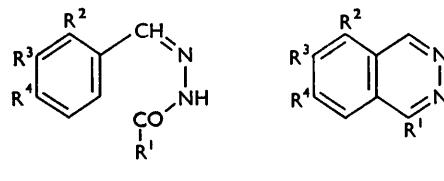
763. Phthalazines. Part I. Re-investigation of the Preparation of Phthalazines by Cyclodehydration of Acylhydrazones.

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The preparation of substituted phthalazines by Aggarwal's method,^{3,4} involving cyclodehydration of acylhydrazones, has been critically examined. This method does not in fact lead to the formation of phthalazines; the products are azines resulting from fragmentation of the starting materials.

As part of an investigation of phthalazines we have been interested in the preparation of 1-alkyl- and 1-aryl-phthalazines. Difficulties associated with the preparation of *o*-formyl-aryl ketones, which could be condensed with hydrazine or substituted hydrazines to yield phthalazines, limit the use of this method, and two alternative procedures have been developed.

The known 1-alkylphthalazines¹ have been prepared exclusively by reduction of the corresponding 1-alkyl-4-chlorophthalazines. With the exception of 1-phenylphthalazine,² 1-arylphtalazines have been prepared by the cyclodehydration, in acid medium, of



(I) — XI) (Ia — XIa)

Formula	R¹	R²	R³	R⁴	Formula	R¹	R²	R³	R⁴
I, Ia	Ph	H	H	H	VII, VIIa	CH ₂ Ph	H	MeO	MeO
II, IIa	"	"	"	MeO	VIII, VIIIa	"	"	O·CH ₂ ·O	"
III, IIIa	"	MeO	"	H	IX, IXa	3 : 4-(MeO) ₂ C ₆ H ₃ ·CH ₂ ·"	"	MeO	MeO
IV, IVa	"	H	MeO	MeO	X, Xa	3 : 4-(MeO) ₂ C ₆ H ₃ ·"	"	"	"
V, Va	"	O·CH ₂ ·O	"	"	XI, XIa	3 : 4-CH ₂ <O ₂ >C ₆ H ₃ ·"	"	O·CH ₂ ·O	"
VI, VIa	CH ₂ Ph	"	H	MeO					

acylhydrazones by Aggarwal's method.^{3,4} Thus the acylhydrazones (I—IX) were reported to yield the phthalazines (Ia—IXa), respectively. In the only independent application of the method, Wilson⁵ reported the successful preparation of 1-(3 : 4-dimethoxyphenyl)-6 : 7-dimethoxyphthalazine (X) and 6 : 7-methylenedioxy-1-(3 : 4-methylenedioxyphenyl)-phthalazine (IXa) from (X) and (XI), respectively. It has now been shown that the procedure does not in fact lead to phthalazines.

As a modification of Aggarwal's method, which involves pentyl alcohol-hydrochloric acid as cyclodehydrating reagent, polyphosphoric acid was used in an attempt to cyclise *o*-nitro- and *m*-nitro-benzaldehyde benzoylhydrazone. The products isolated were *o*-nitro- and *m*-nitrobenzaldazines resulting from hydrolysis of the acylhydrazone and subsequent reaction of the hydrolysis products; we were unable to detect phthalazines in the reaction products. The same compounds resulted when either pentyl alcohol-hydrochloric acid or phosphoric oxide in xylene was used to effect ring-closure, and we were led to re-examine the compounds prepared by Aggarwal *et al.* and by Wilson. One peculiarity was immediately apparent; the compounds (IVa), (VIIa), (IXa), (Xa), described as phthalazines and resulting from various 3 : 4-dimethoxybenzaldehyde acylhydrazones, were all recorded as having m. p. within the range 191—194°; 3 : 4 : 3' : 4'-tetramethoxybenzaldazine⁶ has

¹ Simpson, "The Chemistry of Heterocyclic Compounds," Interscience Publishers, Ltd., London, 1953, Vol. 5, p. 72.

² Lieck, Ber., 1905, **38**, 3918.

³ Aggarwal, Darbari, and Ray, J., 1929, 1941.

⁴ Aggarwal, das Khera, and Ray, J., 1930, 2354.

⁵ Wilson, J. Amer. Chem. Soc., 1948, **70**, 1901.

⁶ Vorlander, Ber., 1906, **39**, 809.

m. p. 191°. The so-called phthalazines (Va), (VIIIa), and (XIa), derived from piperonaldehyde acylhydrazone, had m. p. 200—204°; piperonaldehyde⁶ has m. p. 203°. Similarly, the compounds to which structures (IIa) and (VIa) had been assigned had m. p. 167° and 168—169°, respectively, which are in good agreement with m. p. 168° of 4 : 4'-dimethoxybenzaldehyde.⁷

We have repeated the reaction of these acylhydrazone with pentyl alcohol-hydrochloric acid and with polyphosphoric acid and have shown that in each case the product is the azine, identified by m. p. and mixed m. p. with authentic specimens.

The physical constants ascribed by Aggarwal to compounds (Ia) (m. p. 174—175°) and (IIIa) (m. p. 135°) do not agree with the literature values for benzalazine⁸ (m. p. 93°), and 2 : 2'-dimethoxybenzaldehyde⁶ (m. p. 143°) but in our hands the azines have been obtained. It is significant that 1-phenylphthalazine, prepared by the reductive dehalogenation of 4-chloro-1-phenylphthalazine² is described as having m. p. 142—143°.

The formation of azines under the conditions used by Aggarwal is probably the result of alcoholysis with simultaneous formation of pentyl esters, for when polyphosphoric acid [10 g. of phosphoric oxide in 10 c.c. (85%, d 1.75) of phosphoric acid] was used all the N-benzoylhydrazone gave benzoic acid as a by-product. When the proportion of phosphoric oxide was increased the reaction was metathetical, the azine being accompanied by 2 : 5-diphenyl-1 : 3 : 4-oxadiazole, presumably formed by dehydration of the intermediary NN-dibenzoylhydrazine.

It was therefore necessary to reinvestigate the claim that the products of cyclisation of the acylhydrazone (VI) and (VIII) were hydrolysed to the corresponding 2-acetyl-phenylbenzaldehydes by phthalic acid in alcoholic hydrochloric acid,⁴ for it is impossible for such products to arise from the azines. In our hands the azines were partially decomposed to the parent aldehyde when digested with alcoholic hydrochloric acid-phthalic acid and indeed the m. p. quoted⁴ for 4-methoxy- and 3 : 4-methylenedioxy-2-phenyl-acetylbenzaldehyde bisphenylhydrazone (122° and 104°, respectively) correspond to the literature values for the phenylhydrazone of anisaldehyde (120—121°) and piperonaldehyde (103°).

Exploratory experiments have indicated that 1-alkyl- and 1-aryl-phthalazines can be prepared readily by hydrolysis of the corresponding toluene-*p*-sulphonylhydrazine derivatives;^{9,10} the results of this study will be published subsequently.

EXPERIMENTAL

Attempted Cyclodehydration of Acylhydrazone.—*o*-Nitrobenzaldehyde benzoylhydrazone (1 g.) was heated for 6 hr. at 130—140° in polyphosphoric acid [10 g. of phosphoric oxide in 10 c.c. of phosphoric acid (d 1.175)], the mixture was poured into water (400 c.c.), and the aqueous suspension warmed for 30 min. The product was washed, dried, and crystallised from alcohol; it formed pale yellow crystals (0.5 g.), m. p. 209° undepressed by authentic 2 : 2'-dinitrobenzaldehyde (Found: C, 56.4; H, 3.4; N, 18.3. 5-Nitro-1-phenylphthalazine, C₁₄H₉O₂N₃, requires C, 66.9; H, 3.6; N, 16.7. 2 : 2'-Dinitrobenzaldehyde, C₁₄H₁₀O₄N₄, requires C, 56.4; H, 3.4; N, 18.8%). The same product was formed when *o*-nitrobenzaldehyde benzoylhydrazone was refluxed with anhydrous pentyl alcohol-hydrochloric acid or with phosphoric oxide in xylene.

Similarly *m*-nitrobenzaldehyde benzoylhydrazone yielded 3 : 3'-dinitrobenzaldehyde, m. p. and mixed m. p. 198° (Found: C, 56.4; H, 3.4; N, 18.4. 6-Nitro-1-phenylphthalazine, C₁₄H₉O₂N₃, requires C, 66.9; H, 3.6; N, 16.7. 3 : 3'-Dinitrobenzaldehyde requires C, 56.4; H, 3.4; N, 18.8%). The acylhydrazone (IV), (VII), and (IX) yielded 3 : 4 : 3' : 4'-tetramethoxybenzaldehyde, m. p. and mixed m. p. 190—191°, and the hydrazone (V) and (VII), on treatment with any of the cyclodehydrating agents cited above, gave piperonaldehyde, m. p. 203°. The compounds (II) and (VI) yielded 4 : 4'-dimethoxybenzaldehyde, m. p. 168°.

Whenever benzoylhydrazone were treated with polyphosphoric acid small quantities of

⁷ Knopfer, *Monatsh.*, 1909, **30**, 31.

⁸ Curtius and Jay, *J. prakt. Chem.*, 1889, **39**, 44.

⁹ Albert and Royer, *J.*, 1949, 1148.

¹⁰ Osborn and Schofield, *J.*, 1955, 2102.

benzoic acid were isolated. When the proportion of phosphoric oxide in the polyphosphoric acid was doubled there resulted 2 : 5-diphenyl-1 : 3 : 4-oxadiazole, m. p. and mixed m. p. 139°.

Hydrolysis.—4 : 4'-Dimethoxybenzaldazine (0.5 g.) and phthalic acid (0.5 g.) were refluxed in alcoholic hydrochloric acid (15 c.c.) for 8 hr. When the mixture cooled a small quantity of white crystals (phthalhydrazide?) was deposited. The clarified solution was worked up according to Aggarwal⁴ and the resulting material converted into the 2 : 4-dinitrophenylhydrazone. The product, crystallised from alcohol, had m. p. 249°, undepressed by an authentic specimen of *p*-methoxybenzaldehyde 2 : 4-dinitrophenylhydrazone.

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