CCCIV.—*Phthalazines. Part II.*

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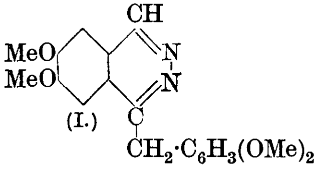
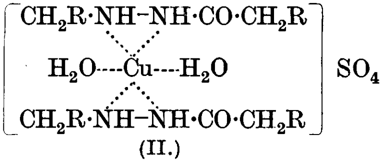
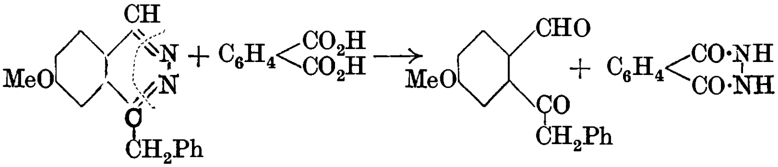
Benzoylhydrazine condenses with aromatic aldehydes to give arylidenebenzoylhydrazines, which can be dehydrated to phthalazines (Aggarwal, Darbari, and Rây, J., 1929, 1941). It seemed to the present authors that an extension of this method would lead to the synthesis of substances analogous to papaverine if phenylacetylhydrazine (or a derivative) were substituted for benzoylhydrazine in the above reaction; *e.g.*, 3 : 4-dimethoxyphenylacetylhydrazine on condensation with veratraldehyde and subsequent dehydration should give (I). A large number of these substances, which are now described, have been synthesised. For their pharmacological investigation we are indebted to Professor E. Hesse, of Breslau, who informs us that the substance (I) is without action on tubercle bacilli.


(I.)


(II.)

The alkylacylhydrazines formed by reduction of the condensation products of aldehydes and acylhydrazines give with salts of copper complexes of the type (II). Aggarwal, Darbari, and Rây (*loc. cit.*) proposed the utilisation of the similar complexes obtained from benzoylhydrazine for the rapid evaluation of copper. It has now been found, however, that the acylhydrazines of both types do not precipitate the metal quantitatively from solutions containing less than 0·5% of copper.

The hydrolysis of the phthalazines has been accomplished by heating them with a trace of hydrochloric acid in presence of phthalic acid. The hydrazine formed reacts with the phthalic acid to give insoluble phthaloylhydrazine and the aldehydo-ketone is isolated from the solution in the form of its diphenylhydrazone. The yield is only moderate.



EXPERIMENTAL.

α-Phenylacetyl-β-veratrylidenehydrazine, $C_6H_3(OMe)_2 \cdot CH \colon N \cdot NH \cdot CO \cdot CH_2Ph$. —Equimolecular quantities of veratraldehyde and phenylacetylhydrazine were heated together for 3 hours in absolute alcohol containing a few drops of 20% sodium hydroxide solution. The *product*, separated from the cooled mixture, crystallised from alcohol in plates, m. p. 171—172° (yield, theoretical) (Found: N, 9·3. $C_{17}H_{18}O_3N_2$ requires N, 9·4%).

6 : 7-*Dimethoxy*-1-*benzylphthalazine*.—(*a*) A solution of phenylacetylveratrylidenehydrazine (6 g.) in 60 c.c. of amyl alcohol (saturated with dry hydrogen chloride at 0°) was heated on the steam-bath for 1 hour and then under reflux for 1½ hours. The yellowish-brown mass obtained on cooling, after being ground with dilute sodium hydroxide solution and washed with water, was thrice crystallised from benzene, giving yellowish needles (3 g.), m. p. 191—192° (Found: N, 10·2. $C_{17}H_{16}O_2N_2$ requires N, 10·0%).

(*b*) Phenylacetylveratrylidenehydrazine in chloroform solution (1 : 10) was treated with phosphoryl chloride (1 : 5) on the steam-bath for 3 hours, the product poured on ice, and the chloroform layer dried over sodium sulphate and freed from solvent, finally in a vacuum. The residue, on treatment as under (*a*), gave a very poor yield of crystals, m. p. 191°, mixed m. p. 191—192°.

α-Phenylacetyl-β-4 : 5-*dimethoxybenzylhydrazine* was prepared by reduction of α-phenylacetyl-β-4 : 5-dimethoxybenzylidenehydrazine with 3% sodium amalgam in the usual way; m. p. 129—130° (Found: N, 9·5. $C_{17}H_{20}O_3N_2$ requires N, 9·3%).

The following substances were prepared by the methods described above: the figures in parentheses are the theoretical percentages for the analyses.

α-Phenylacetyl-β-*piperonylidenehydrazine*, m. p. 210°; N, 9·9 (9·9). 6 : 7-*Methylenedioxy*-1-*benzylphthalazine*, m. p. 203—204°; N, 10·55 (10·6). α-*Phenylacetyl*-β-p-*methoxybenzylidenehydrazine*, m. p. 167°; N, 10·6 (10·4). 7-*Methoxy*-1-*benzylphthalazine*, m. p. 168—169°; N, 11·1 (11·2) : *picrate*, m. p. 208—209° (from hot benzene); N, 14·7 (14·6). α-*Phenylacetyl*-β-p-*methoxybenzylhydrazine*, m. p. 98—99°; N, 10·6 (10·4). α-*Phenylacetyl*-β-m-*methoxybenzylidenehydrazine*, m. p. 107—108°; N, 10·6 (10·4). This substance was not converted into a phthalazine by the usual treatment. α-*Phenylacetyl*-β-m-*methoxybenzylhydrazine*, m. p. 94—95°; N, 10·3 (10·4). α-*Phenylacetyl*-β-o-*methoxybenzylidenehydrazine*, m. p. 141—142°; N, 10·5 (10·4). This did not furnish a phthalazine. α-*Phenylacetyl*-β-o-*methoxybenzylhydrazine*, m. p. 79—80°; N, 10·4 (10·4). α-*Phenylacetyl*-β-*benzylidenehydrazine*, m. p. 148—149°; N, 11·9 (11·8). α-*Phenylacetyl*-β-*benzylhydrazine*, m. p. 113—114°; N, 11·9 (11·7).

3 : 4-*Dimethoxyphenylacetylhydrazine*, prepared by the interaction of ethyl 3 : 4-dimethoxyphenylacetate and hydrazine hydrate on the steam-bath, separated from hot benzene in crystals, m. p. 115—116° (Found : N, 13·45. $C_{10}H_{14}O_3N_2$ requires N, 13·3%). It condensed readily with veratraldehyde. Since the product tended to change into the phthalazine, it was treated with phosphoryl chloride or amyl-alcoholic hydrogen chloride, and 6 : 7 : 3′ : 4′-*tetramethoxy*-1-*benzylphthalazine* (I) isolated and crystallised from hot alcohol; m. p. 192—193° (Found : N, 8·7. $C_{19}H_{20}O_4N_2$ requires N, 8·2%). The *picrate* (from hot benzene) had m. p. 186—187° (Found : N, 13·1. $C_{19}H_{20}O_4N_2,C_6H_3O_7N_3$ requires N, 12·7%).

Compound of Copper Sulphate and α-*Phenylacetyl*-β-4-*methoxybenzylhydrazine* (as II).—The hydrazine (2 g.), dissolved in the minimum of absolute alcohol, was treated with 20% copper sulphate solution (10 c.c.); after a few minutes bluish-green silky needles separated. These were washed with water and with alcohol and dried in a vacuum [Found : N, 7·7; Cu, 8·7; SO_4, 13·4 (estimated by precipitation in hydrochloric acid solution with barium chloride). $C_{32}H_{14}O_{10}N_4SCu$ requires N, 7·6; Cu, 8·6; SO_4, 13·05%].

Hydrolysis of 7-*Methoxy*-1-*benzylphthalazine*.—A solution of the phthalazine (2 g.) and phthalic acid (2 g.) in alcohol containing 1 c.c. of hydrochloric acid (*d* 1·16) was heated in a sealed tube at 100° for 8—10 hours. The insoluble phthaloylhydrazine was then removed, and the filtrate diluted with water and extracted with ether. From the washed (sodium carbonate solution) and dried (sodium sulphate) extract, an oil was obtained which, heated with phenylhydrazine acetate in alcohol, gave 4-*methoxy*-2-*phenylacetylbenzaldehydediphenylhydrazone*; after recrystallisation from alcohol, this had m. p. 122—123° (yield, 1·5 g.) (Found : N, 12·7. $C_{28}H_{26}ON_4$ requires N, 12·9%).

Similarly, 6 : 7-methylenedioxy-1-benzylphthalazine on hydrolysis furnished an oily aldehydo-ketone, which was isolated as its *diphenylhydrazone*, m. p. 104—105° (Found : N, 12·6. $C_{28}H_{24}O_2N_4$ requires N, 12·5%).

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