

Reaction of Alkylhydrazines. I.
Reaction of 1,1-Dimethylhydrazine with Alkyl Phthalates (1)

Jay Nematollahi

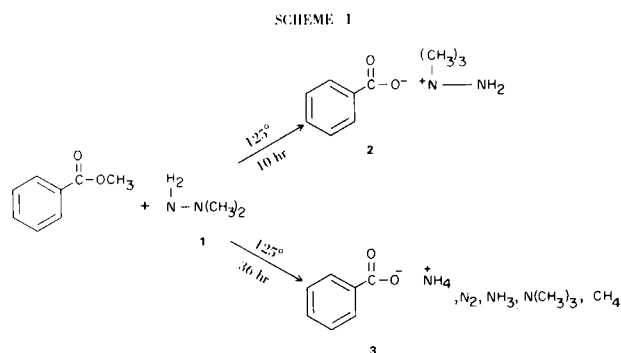
College of Pharmacy, The University of Texas at Austin,
Austin, Texas 78712

Received June 21, 1972—Revised March 2, 1972

Hydrazine and methylhydrazine react readily with both the methyl and ethyl esters of 1-methylimidazole-4-carboxylic acid and imidazole-4,5-dicarboxylic acid to give the expected hydrazides (2). When each ester was heated with 1,1-dimethylhydrazine (1), however, a complex product rather than the expected hydrazide was obtained. A literature survey revealed that **1** reacts with only a few esters such as ethyl formate, methyl acrylate, and methyl benzoate giving 1-formyl-2,2-dimethylhydrazine (3), 1,1-dimethylpyrazolin-3-ium oxide (4) and trimethylhydrazonium benzoate (5) respectively.

Because of the relative simplicity of the reactions of nonheterocyclic aromatic system as compared with those of heterocyclic systems an attempt was made to study the reaction of **1** individually with methyl benzoate, ethyl benzoate, dimethyl phthalate, and diethyl phthalate, and possibly relate these results to the reactions of heterocyclic carboxylic acid esters.

When methyl benzoate was heated with **1** for 10 hours in a sealed tube (helium atmosphere) at 125-130° oil bath the product was trimethylhydrazonium benzoate (**2**). Upon prolonged heating to 36 hours the reaction products were ammonium benzoate (**3**) and a mixture of gases, whose identities were determined by mass spectrometry to be nitrogen, methane, ammonia and trimethylamine.

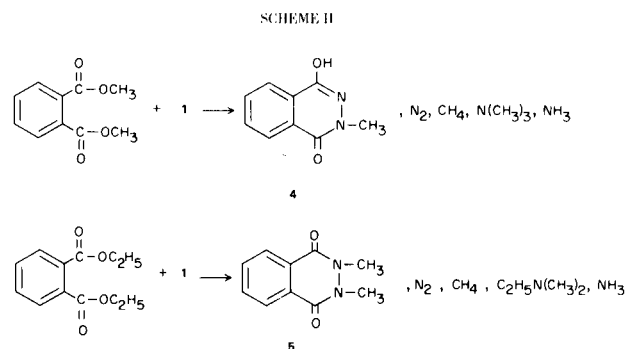


Ethyl benzoate under analogous conditions did not react with **1** even upon prolonging the heating time to 60 hours. Raising the temperature of the oil bath to 160°

caused an explosion after about 50 hours of heating.

In an effort to determine the scope and limitation of these reactions, **1** was allowed to react with dimethyl phthalate (sealed tube, helium, 125°, 12-16 hours). The reaction product, a mixture of a solid and gases, was first analyzed by using mass spectrometry to determine the identity of the gases. They consisted of nitrogen, methane, ammonia and trimethylamine. The structure of the tertiary amine was further identified by its ir spectrum. The solid portion of the product, by using ir, nmr, mass spectrometry and elemental analysis, was identified as 2-methyl-1,4-phthalazinedione (**4**).

When diethyl phthalate was treated with **1** by an analogous procedure the gaseous products were nitrogen, methane, ammonia and ethyldimethylamine. The solid portion consisted roughly of equal quantities of **4** and 2,3-dimethyl-1,4-phthalazinedione (**5**).



That the presence of both the trialkylhydrazonium salt and **1** in the sealed tube was essential for formation gaseous products, was inferred from the observation that heating either compound individually (sealed tube, 125°, 30 hours) did not afford any product.

In an effort to elucidate the mechanism of formation of **4** and **5**, methyl trimethylhydrazonium phthalate (**6**), was synthesized. When **6** was allowed to react with **1** in a sealed tube, similar to the condition described above, **4** was afforded.

Because some phthalic anhydride (**7**) formation results from heating of a dialkyl phthalate, the possibility of **7**

being an intermediate in the formation of **5** was evaluated. Heating **7** with **1** (sealed tube, 125°, 12 hours) gave **5**.

Considering the result of these experiments one can reasonably assume **6** or ethyl ethyldimethylhydrazonium phthalate (**8**) to function as the intermediate in the formation of **4**; and **7** as the intermediate in the formation of **5**.

Although proposing an unequivocal mechanism for the formation of **4** and **5** at this stage is somewhat speculative, the result of the experiments and literature survey leads us to assume possible involvement of the intermediates depicted in Scheme III and IV.

Compound **6** was synthesized. Its formation is presumed to proceed in a fashion analogous to that of trimethylhydrazonium iodide which has been prepared

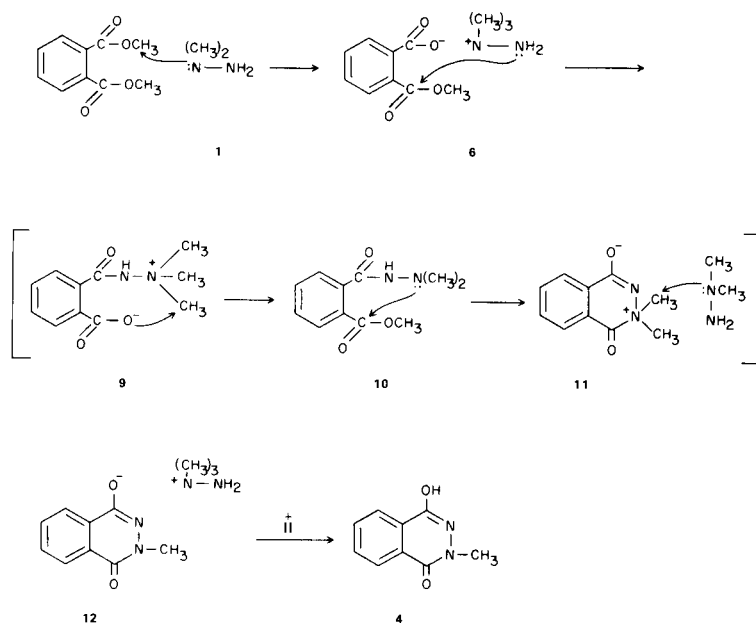
by treating **1** with methyl iodide, and is known to involve SN₂ displacement. Treating **6** with **1** gave **4**. Structures **9**, **10**, and **11** are assumed to be intermediates (6).

In the case of the reaction of diethyl phthalate with **1** phthalic anhydride is produced along with **8** (8,9).

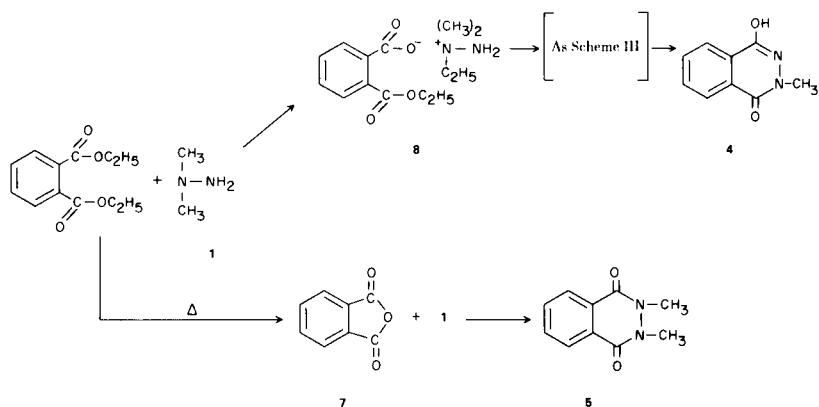
The formation of gaseous substances, whose identities were determined by using mass spectrometry, requires the presence of both **1** and the hydrazonium salt. The involvement of some intermediates in the reaction may be envisaged analogous to those of Wolff-Kishner reduction (10).

The experimental results thus far lead one to conclude that the interaction of 1,1-dimethylhydrazine with an ester of benzoic acid and of phthalic acid is not analogous to those of monosubstituted hydrazines. Vicinal diesters

SCHEME III



SCHEME IV



such as phthalates afford bicyclic systems. This new and facile route of synthesis of bicyclic systems might become applicable for the preparation of a series of novel compounds containing hetero atoms in both rings. The structural similarity of the latter system to purine is a factor which may contribute to manifestation of some significant biologic properties.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The nmr spectra were determined on a Varian A-60. The ir spectra were determined in potassium bromide disks on a Beckman IR-8 spectrometer.

Reaction of 1,1-Dimethylhydrazine with Dimethyl Phthalate (This procedure is representative of the other reactions in the series).

Inside a tube of 25 cm. long, 19 mm. o.d. and 12 mm. i.d. was placed 1.98 g. (0.01 mole) of dimethyl phthalate and 2.4 g. (0.04 mole) of dry 1,1-dimethylhydrazine. About $\frac{3}{4}$ of the tube was immersed in a dry ice-alcohol bath. While introducing a stream of helium gas inside, the tube was sealed. After allowing the tube to come to room temperature, it was immersed in an oil bath 125-130° and heated for 12-24 hours. The tube was then removed from the oil bath, allowed to come to room temperature. The drawn end of the tube was inserted in one end of a 30 cm. long plastic tubing in which had been placed a 10 cm. long by 9 mm. o.d. metal pipe. The other end of the plastic tubing was connected to one arm of a 3-way stopcock whose other two arms were connected to a vacuum pump and a receiver flask equipped with a stopcock. After evacuating the system, the reaction tube was cooled with liquid nitrogen and then opened by means of the pipe. The low boiling gases were collected at about -150 to -35°. The gases boiling at -35° were collected in a second receiver. The content of each receiver was analyzed using mass spectrometry. The content of the second receiver was also analyzed using ir.

After collecting the gases the solid residue was washed 3 times with hexane and then with chloroform to give 1 g. (56%) of **4**. The analytical sample, prepared by crystallizing **4** from benzene containing a small quantity of methanol, had a m.p. 240-242° [lit. (7) m.p. 238-240°]; ir 1630, 1570 cm^{-1} ; nmr (DMSO) δ 3.60 (NCH₃, s), ca. 8 (ph, m).

Anal. Calcd. for C₉H₈N₂O₂: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.69; H, 4.74; N, 15.86.

Reaction of **1** with diethyl phthalate under analogous condition gave a mixture consisting of 0.4 g. (22%) of **4** and 0.3 g. (16%) of **5**. The two compounds were separated by heating a suspension of the mixture in hexane in which only **5** was soluble. The analytical sample, prepared by crystallizing **5** from hexane, had a m.p. 172-174° [lit. (7) m.p. 174-175°]; ir 1620, 1600 cm^{-1} ; nmr (DMSO) δ 3.77 (NCH₃, s), ca. (Ph, m).

Anal. Calcd. for C₁₀H₁₀N₂O₂: C, 63.16; H, 5.26; N, 14.73. Found: C, 63.37; H, 5.59; N, 14.55.

Heating 0.9 g. (0.015 mole) of **1** with 1.0 g. (0.006 mole) of phthalic anhydride with a procedure analogous to that for the formation of **4** or **5** gave 0.5 g. (45%) of **5**.

Methyl 1,1,1-Trimethylhydrazonium Phthalate (**6**).

In a 100 ml. flask was placed 3 g. (0.05 mole) of **1** and 1.98 g. (0.01 mole) of dimethyl phthalate. The mixture was heated under reflux for about 20 hours at which time a solid was formed.

The solid was washed several times with hexane and ether and dried in a desiccator to give 2.3 g. (46%) of **6**. The analytical sample, prepared by crystallizing **6** from benzene containing a few drops of methanol, had a m.p. 144°, ir 1700, 1550 cm^{-1} ; nmr (D₂O) δ 3.25 (N(CH₃)₃, s); 3.70 (OCH₃, s) ca. 7.5 (Ph, m). *Anal.* Calcd. for C₁₂H₁₈N₂O₄: C, 56.69; H, 7.08; N, 11.02. Found: C, 56.46; H, 7.34; N, 11.22.

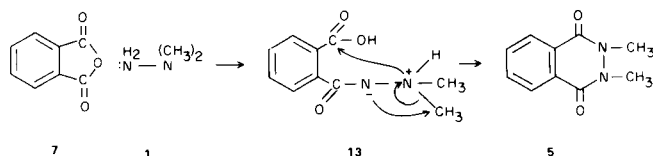
Acknowledgments.

The author wishes to thank Miss Zarine Mehta and Mr. Mikeska for their help. Mr. Maseles and Dr. Cone for mass spectra and Drs. Maness, Monti, Nulu, and Stotter for discussions and suggestions.

This paper was presented in the ACS 27th Southwest Regional meeting December 3, 1971.

REFERENCES

- (1) This investigation was supported in part by Biomedical Sciences Support Grant FR-07091-04 from NIH.
- (2) J. R. Nulu and J. Nematollahi, *J. Med. Chem.*, **12**, 804 (1969); J. Nematollahi, unpublished data.
- (3) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958).
- (4) N. P. Zapevalova, L. A. Ovsyannikova, and T. A. Sokolova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2200 (1966); *Chem. Abstr.*, **66**, 85394s (1967).
- (5) R. F. Smith, A. C. Bates, A. J. Battisti, P. G. Byrnes, C. T. Mroz, T. J. Smearing, and F. X. Albrecht, *J. Org. Chem.*, **33**, 851 (1968).
- (6) Structure **11** is analogous to 1,1-dimethylpyrazolin-3-ium oxide, which has been prepared (4) by reacting methyl acrylate with **1**. This conceivably results from a rapid cyclization of **10** analogous to the formation of 1-methyl-4,7-dihydroxyimidazo[4,5-d]pyridazine reported by Jones (7) and 1,5-dimethyl-7-hydroxyimidazo[4,5-d]pyridazin-4-one, observed by us (2).
- (7) R. G. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
- (8) In comparison with dimethyl phthalate, steric factor may hinder the S_N2 displacement which is assumed to be involved in the formation of the hydrazonium salts. This allows the formation of phthalic anhydride which is known to occur upon heating of alkyl phthalates.
- (9) Treating **7** with **1** gave **5**. As shown below, the course of the reaction may involve **13** as an intermediate whose rearrangement analogous to Stevens rearrangement gives **5**.



- (10) The postulated structure **16** in the following scheme is analogous to hydrazones formed in Wolff-Kishner reduction whose heating gives nitrogen and the respective hydrocarbon, which in this case is methane.

