

sufficiently volatile it is best purified by liberation with alkali and distillation with steam. The small amounts of secondary and tertiary amines present are thereby almost completely left behind. The distilled amine is extracted with benzene, dried, and redistilled as usual. When the amine is not very volatile it may often be obtained directly from the acid solution by fractional crystallization of the hydrochloride or may be purified in other ways.

Notes and Modifications.—The above procedure was not satisfactory with camphor because the sublimate rapidly clogged the apparatus. This difficulty was readily overcome by adding to the camphor about one-half its weight of nitrobenzene. The latter is unaffected by heating with formamide and serves to liquefy the camphor in both the reaction mixture and the distillate. The nitrobenzene and unchanged camphor are removed by steam distillation following the hydrolysis of the amine.

A similar procedure was fairly successful when applied to pinacolone. The nitrobenzene in this case appeared to diminish the distillation of the rather volatile ketone (b. p. 106°) and also served to extract it from the aqueous portion of the distillate. However, the general procedure described above is not regarded as suitable for the more volatile and water-soluble ketones. With such ketones it would appear better to start with substantially pure for-

mamide and carry out the reaction entirely by refluxing. The small amount of water formed in the reaction causes no difficulty. In comparative experiments upon acetophenone and fenchone the yield was 4–6% better with pure formamide (4 moles) than with the usual reagent. With cheap ketones, however, the use of formamide is not justified, because of the extra cost.

In a series of experiments with acetophenone the percentage yields of amine were 53, 62, 72 and 72, respectively, when the molar ratios of reagent to ketone were 3.0, 3.5, 4.0 and 5.0. In experiments with 2:1 and 4:1 ratios of pure formamide the yields were 23 and 78%, respectively.

Runs were made with from 0.1 mole to 4.0 moles of ketone without important variations in yield. There is no apparent reason why the scale may not be as large as desired.

Summary

1. The Leuckart synthesis of amines from ketones has been improved and adapted to large scale use. A general procedure is described.

2. Eight new amines have been prepared and described.

NASHVILLE, TENNESSEE

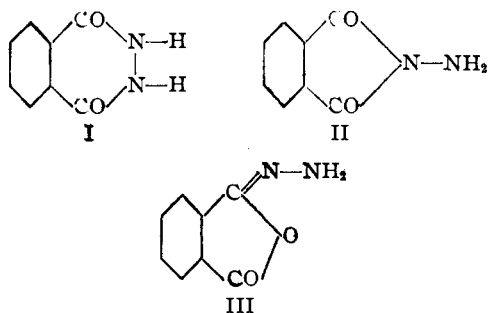
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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

The Methyl and Phenyl Derivatives of the Nitrophthalhydrazides

BY C. N. ZELLNER AND GREGG DOUGHERTY

The brilliant chemiluminescence of some of the phthalhydrazide derivatives has created an interest in the chemistry and structure of these compounds. Of the three structures which have been proposed for phthalhydrazide



I and II have received the most serious consideration. The work of Radulescu and Georgescu,¹ Moyer,² and Rowe and Peters³ on the various methylated and acetylated phthalhydrazides has indicated that structure I or a tautomeric modification of it is preferable to structure II. These

workers confined their efforts to phthalhydrazide which was not substituted in the benzene ring.

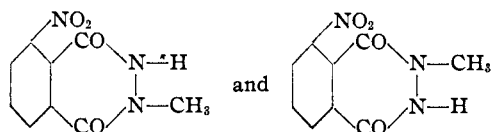
It is obvious that, if the hydrazide structure I is correct, the presence of a substituent in the aromatic nucleus would make possible the existence of various isomeric non-nuclear alkyl or aryl derivatives not capable of existence on the basis of the aminophthalimide formula II. Also the study of a nuclear substituted hydrazide should give some indication of the normal tautomeric condition of the molecule. In order to test these points the present work with the nitrophthalhydrazides was undertaken.

The reaction of 3-nitrophthalic anhydride with methylhydrazine acetate gave two isomeric monomethyl derivatives which were produced in almost equal proportions, one melting at 305°, and the other at 273°. Both were readily acetylated, the two monomethyl monoacetyl derivatives melting at 211 and 144°, respectively. (All melting points have been corrected.) The existence of two *n*-methyl compounds is easily accounted for on the basis of the hydrazide structure

(1) Radulescu and Georgescu, *Bull. soc. chim.*, **37**, 881 (1925).

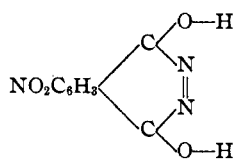
(2) Moyer, private communication.

(3) Rowe and Peters, *J. Chem. Soc.*, 1331 (1933).

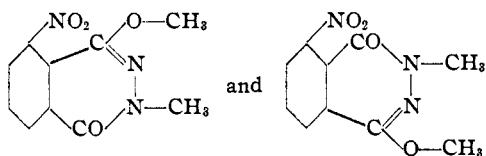


It is not yet possible to say which of the structures should be assigned to which isomer. On the basis of Mihailescu's aminophthalimide structure II,⁴ this type of isomerism would not be possible.

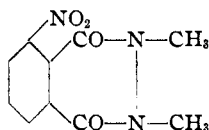
The same two *n*-methyl-3-nitrophthalhydrazides were obtained by treating 3-nitrophthalhydrazide with dimethyl sulfate in alkaline solution. This is an indication that the double enolic form, *i. e.*,



does not occur to any extent at least in alkaline solution, otherwise an *o*-methyl derivative would have been obtained. With excess dimethyl sulfate two dimethylnitrophthalhydrazides were obtained, melting at 207 and 138–139°, respectively. The derivative of m. p. 207° was also prepared by reaction of the higher melting *n*-methyl-3-nitrophthalhydrazide with dimethyl sulfate in alkaline solution, whereas the lower melting dimethyl derivative was obtained from the lower melting mono-methyl compound. Again, the existence of the isomeric dimethyl derivatives is evidence against Mihailescu's formula. The fact that the two were obtained by the methods outlined indicates strongly that they are *n*-methyl *o*-methyl derivatives

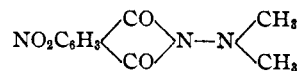


This was further substantiated by the preparation of a third dimethyl derivative from 3-nitrophthalic anhydride and symmetrical dimethyl hydrazine. In this case there is little doubt but that both methyl groups are attached to nitrogen:



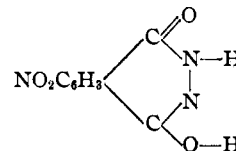
(4) Mihailescu and Protopopescu, *Chem. Zentr.*, **101**, 11, 3021 (1930); *Bulet. Soc. Chim. Romania*, **12**, 95 (1930).

A fourth dimethyl derivative was obtained from the anhydride and unsymmetrical dimethyl hydrazine to which the aminophthalimide structure,



must be assigned. The remaining structurally possible dimethyl derivative in which both methyl groups are attached to oxygen is apparently not formed by any of the ordinary methods of methylation.

Since in the alkylation of 3-nitrophthalhydrazide in alkaline solution, the first methyl group goes to the nitrogen and the second to oxygen, it appears that the lactam-lactim form of the compound, is present and most reactive under the conditions. This conclusion, also arrived at by Rowe and Peters,³ is important when considering the mechanism



of the oxy-luminescence of phthalhydrazide derivatives, always carried out in alkaline solution.

Using 4-nitrophthalic anhydride and the hydrazide, a set of monomethyl and dimethyl derivatives was prepared similar to those obtained from the 3-nitro compounds. These are described in the experimental part. The reaction between phenylhydrazine and the 3 and 4-nitrophthalic anhydrides was studied. In this case only one of the two possible *n*-phenylhydrazides was formed in sufficient quantity to permit isolation and purification. A second compound was formed of the anilino-phthalimide type, $\text{NO}_2\text{-C}_6\text{H}_4\text{-}$ so that methylhydrazine and phenylhydrazine do not behave in quite

the same way in this reaction. The anilino-phthalimide type is insoluble in alkalis which differentiates it sharply from the *n*-phenyl derivatives of the nitrophthalhydrazides.

Experimental

α -3-Nitro-*N*-methyl Phthalhydrazide.—9.6 g. (0.05 mole) of 3-nitrophthalic anhydride was dissolved in 50 cc. of acetic acid. To the hot solution, a 20-cc. aqueous solution of 7.2 g. (0.05 mole) of mono-methylhydrazine sulfate and 6.8 g. of sodium acetate crystals, was added. The reaction mixture was heated to boiling, using an air condenser, until all the acetic acid was driven off. The residue was washed in portions of warm water and the two isomers were fractionally recrystallized from alcohol, until constant melting points were obtained. The more insoluble isomer melted at 305° (cor.).

Anal. Calcd. for $C_9H_7O_4N_3$: C, 48.86; H, 3.19. Found: C, 48.62; H, 3.09.

Boiled in acetic anhydride, it yielded a mono-acetyl derivative which when recrystallized from alcohol melted at 211° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 50.18; H, 3.45. Found: C, 50.52; H, 3.72.

β -3-Nitro-N-methyl Phthalhydrazide.—The more soluble β -compound melted at 273° (cor.).

Anal. Calcd. for $C_9H_7O_4N_3$: C, 48.86; H, 3.19. Found: C, 48.56; H, 3.19. Its acetyl derivative melted at 144° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 50.18; H, 3.45. Found: C, 50.17; H, 3.71.

3-Nitro-N,N'-dimethyl Phthalhydrazide.—In like manner, from 3-nitro phthalic anhydride and symmetrical dimethylhydrazine hydrochloride and sodium acetate; m. p. 203° (cor.).

Anal. Calcd. for $C_{10}H_9O_4N_3$: C, 51.05; H, 3.86. Found: C, 50.89; H, 4.06.

3-Nitro-N-dimethylamino Phthalimide.—From 3-nitro-phthalic anhydride and *unsym.*-dimethylhydrazine hydrochloride and sodium acetate; m. p. 200 – 201° (cor.).

Anal. Calcd. for $C_{10}H_9O_4N_3$: C, 51.05; H, 3.86. Found: C, 50.93; H, 4.08.

3-Nitro-N-methyl *o*-Methyl Phthalhydrazides.—Prepared by the action of excess dimethyl sulfate, in a dilute alkaline solution, on 3-nitrophthalhydrazide. The two isomers are separated by fractional crystallization from alcohol; the α -derivative melted at 207° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 51.05; H, 3.86. Found: C, 51.31; H, 3.97. The β -derivative melted at 138 – 139° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 51.05; H, 3.86. Found: C, 51.20; H, 3.69.

The former was also obtained from α -3-nitro-N-methyl-phthalhydrazide with dimethyl sulfate, in alkaline solution, and the latter from the β -derivative.

In like manner from 4-nitrophthalic anhydride and the corresponding hydrazines the following were obtained:

α -4-Nitro-N-methyl Phthalhydrazide and β -4-Nitro N-methyl Phthalhydrazide separated by fractional crystallization from alcohol. The α -compound melted at 310 – 311° (cor.).

Anal. Calcd. for $C_9H_7O_4N_3$: C, 48.86; H, 3.19. Found: C, 48.89; H, 3.11.

Its acetyl derivative melted at 213 – 214° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 50.18; H, 3.45. Found: C, 50.23; H, 3.50.

The β -compound melted at 271 – 272° (cor.). Upon acetylation it yields an acetyl derivative melting at 170 – 171° (cor.).

Anal. Calcd. for $C_{11}H_9O_5N_3$: C, 50.18; H, 3.45. Found: C, 49.93; H, 3.36.

4-Nitro-N,N'-dimethyl Phthalhydrazide.—M. p. 203.5° (cor.).

Anal. Calcd. for $C_{10}H_9O_4N_3$: C, 51.05; H, 3.86. Found: C, 51.03; H, 3.86.

4-Nitro-N-dimethylamino Phthalimide.—M. p. 202° (cor.). A mixed melting point determination with the preceding compound showed a large depression.

4-Nitro-anilino Phthalimide.—Prepared by refluxing 4-nitrophthalic anhydride and phenylhydrazine in HOAc for two and a half hours. On cooling, the crystals were filtered and treated with sodium carbonate solution. The insoluble product, recrystallized from alcohol several times, melted at 182° (cor.).

Anal. Calcd. for $C_{14}H_9O_4N_3$: C, 59.31; H, 3.21. Found: C, 59.54; H, 3.26.

4-Nitro-N-phenyl Phthalhydrazide.—Was obtained on acidifying the above sodium carbonate solution. After three recrystallizations from alcohol, it melted at 253° (cor.).

Anal. Calcd. for $C_{14}H_9O_4N_3$: C, 59.31; H, 3.21. Found: C, 59.24; H, 3.33; C, 59.38; H, 3.33.

Its acetyl derivative melted at 186° (cor.).

Anal. Calcd. for $C_{16}H_{11}O_5N_3$: C, 59.08; H, 3.38. Found: C, 58.81; H, 3.31.

3-Nitroanilino Phthalimide.—From 3-nitrophthalic anhydride and phenylhydrazine, after washing in dilute sodium hydroxide solution, and recrystallization from alcohol: m. p. 198 – 199° (cor.).

Anal. Calcd. for $C_{14}H_9O_4N_3$: C, 59.31; H, 3.21. Found: C, 59.39; H, 3.18.

Summary

Evidence has been obtained in favor of the hydrazide structure as opposed to the amino-imide structure for substituted phthalhydrazides. It has been shown that in the methylation of the nitrophthalhydrazides in alkaline solution, the compounds behave as if they possessed the lactam-lactim structure.

The preparation of various methylated and phenylated nitrophthalhydrazides has been described and some of their properties noted.

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