Oxidation of Aldehyde N,N-Dialkylhydrazones with Hydrogen Peroxide. A New Nitrile Synthesis

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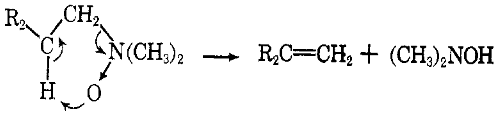
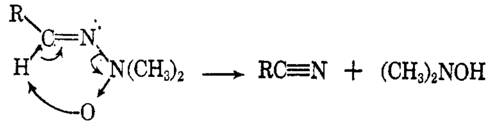
The hydrogen peroxide oxidation of the N,N-dimethylhydrazones of cinnamaldehyde, benzaldehyde, and alkoxy-substituted benzaldehydes gave the corresponding nitriles in good yields. Good yields of nitriles were also obtained by the oxidation of 1-benzalaminopiperidine and 1-(4-methoxybenzalamino)piperidine. Oxidation of the N,N-dimethylhydrazones of *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, *n*-valeraldehyde, and *n*-octanal gave mixtures of nitrile-containing products.

The thermolysis of tertiary amine oxides (the Cope reaction[3]) is a well-established route to olefins that proceeds *via* a cyclic transition state (I). As an outgrowth of earlier work[4] on the synthesis of nitriles, we have attempted the synthesis of N,N-dialkylhydrazone oxides (II), an unknown class of compounds, with the objective of their subsequent conversion to nitriles by a Cope-type elimination reaction.

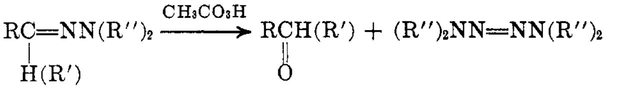


I



II

The most straightforward synthesis of compounds of type II seemed to be mild oxidation of the corresponding dialkylhydrazones. Horner and Fernekess[5] have previously reported that peracetic acid oxidation of dialkylhydrazones results in the formation of the carbonyl compound and the corresponding 2-tetrazenes.



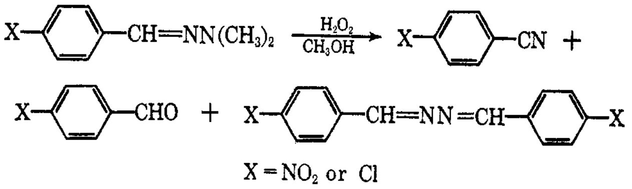
$$\underset{\mathrm{H(R')}}{\mathrm{RC}}{=}\mathrm{NN(R'')_2} \xrightarrow{\mathrm{CH_3CO_3H}} \underset{\mathrm{O}}{\mathrm{RCH(R')}} + \mathrm{(R'')_2NN{=}NN(R'')_2}$$

Benzaldehyde N,N-dimethylhydrazone was oxidized with cold methanolic hydrogen peroxide (the recommended conditions for oxidation of tertiary amines[3]). Under these conditions, a mixture of benzaldehyde and benzonitrile was obtained and none of the anticipated hydrazone oxide could be isolated. When a large excess of hydrogen peroxide and ambient temperatures were employed, benzonitrile was obtained in 54% yield.

$$\mathrm{C_6H_5CH{=}NN(CH_3)_2} \xrightarrow[\mathrm{CH_3OH}]{\mathrm{H_2O_2}} \mathrm{C_6H_5CN} + ?$$

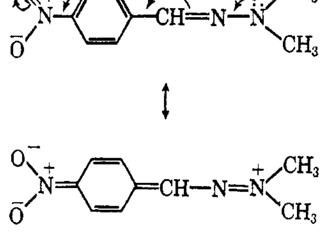
In a "one flask" procedure, benzonitrile and *p*-methoxybenzonitrile were obtained in 50 and 70% yields, respectively, by reaction of the aldehydes with N,N-dimethylhydrazine in methanol, followed by addition of hydrogen peroxide.

Good yields of nitriles (Table II) were also obtained by oxidation of the dimethylhydrazones of piperonal, veratric aldehyde, and cinnamaldehyde. However, the oxidation of the dimethylhydrazones of *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde required forcing conditions and resulted in a mixture of products containing nitrile, aldehyde, and small amounts of the corresponding azine. Starting material was also recovered from the oxidation of the *p*-nitro compound.

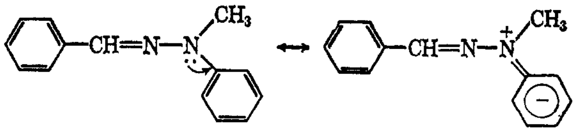


$X = NO_2$ or Cl

The above results seem to indicate that the unshared pair of electrons on the dialkylated nitrogen is initially attacked by the oxidizing agent. The availability of the unshared pair on nitrogen may be decreased by an electron-withdrawing substituent in the *para* position as exemplified by the dimethylhydrazone of *p*-nitrobenzaldehyde (a bright orange, acid-insoluble compound) in which the unshared pair may be delocalized by resonance of the following type.



Further support for this postulate is gained from the fact that benzaldehyde methylphenylhydrazone (III) was recovered unchanged from an attempted oxidation conducted under forcing conditions. Again, extensive delocalization of the electron pair on nitrogen could account for the reluctance of III to undergo the nitrile-forming reaction.



III

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[1] Present address, Department of Chemistry, State University College at Geneseo, Geneseo, N. Y. 14454.

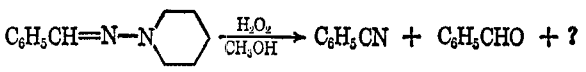
[2] National Science Foundation Undergraduate Research Participant, State University of New York at Albany, 1964-1965.

[3] A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 374 (1960).

[4] R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962).

[5] L. Horner and Fernekess, *Chem. Ber.*, **94**, 723 (1961).

Several unsuccessful attempts were made to determine the fate of the dialkylamino group in the dimethylhydrazone oxidations. Attempted high-vacuum distillation of the tarry nitrile distillation residues, column chromatography, and attempted distillation and derivative preparation of acid-soluble material did not yield identifiable products. Trace amounts of benzamide and benzoic acid were obtained from the benzaldehyde dimethylhydrazone oxidations. It was felt that "larger" dialkylamino groups may facilitate determination of the fate of the dialkylamino group. Accordingly, it was found that 1-benzalaminopiperidine (IV) could be oxidized to a mixture of benzonitrile and benzaldehyde but efforts to obtain other products from the reaction failed. The *p*-methoxy analog of IV afforded the corresponding nitrile in good yields.



IV

Although the results of this study preclude any definitive statements regarding mechanism, it is conceivable that the reaction may proceed *via* the formation of the hydrazone oxides (II). If N,N-dialkylhydroxylamines are formed by elimination, they would undoubtedly be further oxidized in the presence of excess hydrogen peroxide to aliphatic nitrones which are known to be unstable.[6] Isolation of azines from the *p*-nitro- and *p*-chlorobenzaldehyde dimethylhydrazone oxidations suggests that a free-radical mechanism is involved in their formation.

The reaction does not seem well suited for the preparation of simple aliphatic nitriles. The oxidation of N,N-dimethylhydrazones of *n*-valeraldehyde and *n*-octanal afforded complex mixtures which could not be fractionated. Glpc analysis revealed several components including the corresponding nitriles and aldehydes.

Oxidation of cyclohexanone dimethylhydrazone afforded cyclohexanone and unidentified tars.

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. The infrared spectra were determined with a Perkin-Elmer spectrophotometer, Model 21. Spectra of solids were obtained by the use of potassium bromide disks. Analyses are by Mr. Kenneth Fleischer and his staff of the Sterling-Winthrop Research Institute. Gas-liquid partition chromatography (glpc) was conducted on an F and M Model 720 instrument.

Preparation of Dialkylhydrazones.—The dialkylhydrazones were prepared in benzene by the previously described procedure.[4] The properties of the new compounds are described in Table I. The dimethylhydrazones of *n*-octanal and 4-methoxy-, 2,4-dimethoxy-, 4-chloro-, and 4-nitrobenzaldehyde prepared by this method had melting points or boiling points corresponding to literature values.[7]

General Procedure for the Oxidation of Dialkylhydrazones.—Eighty milliliters of 30% hydrogen peroxide was cautiously added to a solution of 20 g of the hydrazone in 180 ml of methanol. Exothermic reactions (frequently requiring external cooling) were observed with the exception of 1-benzalaminopiperidine and the dimethylhydrazones of *p*-nitro- and *p*-chlorobenzaldehyde. The reactions were conducted under the conditions described in Table II. The reaction mixtures were diluted with three volumes of water and the products were isolated by filtration or extraction with ether. The ether extracts were washed with 3 *N* hydrochloric acid and dried over magnesium sulfate. Liquid products were fractionated through a 12-in. Vigreux column. The infrared spectra of the nitriles were compared with those of authentic samples.

"One Flask" Procedure for the Preparation of Benzonitrile and 4-Methoxybenzonitrile. A. Benzonitrile.—A solution containing 26.5 g (0.25 mole) of benzaldehyde, 19 ml (0.25 mole) of N,N-dimethylhydrazine, and 170 ml of methanol was heated under reflux for 5.5 hr. After the addition of 70 ml of methanol, 148 ml of 30% hydrogen peroxide was slowly added. After an initial exothermic reaction, the reaction mixture was allowed to remain at room temperature overnight and was then diluted with 700 ml of water. The product was extracted with three 200-ml portions of ether and the combined ether extracts were washed with two 100-ml portions of 3 *N* hydrochloric acid. The ether extracts were dried over magnesium sulfate and concentrated, and the residue was distilled to give 12.1 g (50%) of benzonitrile, bp 77–81° (18 mm). The infrared spectrum of the product was identical with that of an authentic sample.

B. *p*-Methoxybenzonitrile.—The reaction was conducted in a manner analogous to procedure described above except that the product was isolated by filtration after dilution with water. Further details of this experiment are given in Table II.

Oxidation of *p*-Chlorobenzaldehyde N,N-Dimethylhydrazone.—A solution containing 30 g of the hydrazone, 350 ml of methanol, and 120 ml of 30% hydrogen peroxide was heated under reflux for 3 hr. No reaction occurred at room temperature. The yellow solution was poured into 1400 ml of water to give 11.3 g of solid material, mp 42–50°. The infrared spectrum of a chloroform solution of the crude mixture revealed the presence of *p*-chlorobenzonitrile and *p*-chlorobenzaldehyde (C≡N band at 2220 and >C=O at 1700 cm^{-1}).

The crude material (0.20 g) was converted to 0.30 g of *p*-chlorobenzaldehyde 2,4-dinitrophenylhydrazone, mp 270–271° (corresponding to a 31% yield of aldehyde). On recrystallization from ethanol, a few milligrams of *p*-chlorobenzaldazine, mp 210–211° (lit.[8] mp 211°) was obtained. Identity of the azine was established by mixture melting point and comparison of the infrared spectrum with that of an authentic sample.

The material remaining from the azine isolation was recrystallized several times from ethanol to give *p*-chlorobenzonitrile, mp 88–89°, which was identified by its infrared spectrum.

Oxidation of *p*-Nitrobenzaldehyde N,N-Dimethylhydrazone.—Attempted reaction at room temperature resulted in recovery of starting material. A refluxing solution of 5.00 g of the hydrazone in 100 ml of methanol was treated with 15 ml of 30% hydrogen peroxide over 15 min. The reaction mixture was heated under reflux for 12 hr. Dilution with water afforded 2.6 g of an orange solid which was suspended in 100 ml of boiling ethanol. Filtration of the hot suspension afforded 0.11 g of *p*-nitrobenzaldazine, mp 305–306° (lit.[9] mp 304.5°). Identity of the azine was established by mixture melting point and comparison of the infrared spectrum with that of an authentic sample. The cooled, ethanolic filtrate deposited 0.25 g of starting material, mp 100–105°. Evaporation of the ethanol afforded a mixture of aldehyde and nitrile, mp 75–110° (C≡N at 2240 and >C=O at 1670 cm^{-1}). A 0.5-g sample of the mixture afforded 0.3 g of *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone, mp 308–312°.

Oxidation of the N,N-Dimethylhydrazones of *n*-Valeraldehyde and *n*-Octanal. A. *n*-Valeraldehyde Dimethylhydrazone.—A vigorous exothermic reaction occurred when 80 ml of 30% hydrogen peroxide was added to 20 g of the hydrazone in 180 ml of methanol. The reaction was moderated by external cooling in an ice bath. After 24 hr at room temperature, the reaction mixture was diluted with water and extracted with ether and the combined extracts were dried over magnesium sulfate. Evaporation of the ether left an oil that was distilled at atmospheric pressure to give 3.3 g of clear liquid, bp 74–98°. Vacuum distillation of the residue afforded several fractions with a boiling point range of 45–112° (20 mm). The mixture with bp 74–98° was found to contain seven compounds by glpc using a 10% silicon rubber Diataport W 60–80 mesh column. The presence of *n*-valeronitrile and *n*-valeraldehyde was established from the infrared spectrum and glpc retention times. Peak heights indicated an aldehyde/nitrile ratio of approximately 1:2.

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(6) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1963).

(7) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 240 (1957).

(8) P. Pascal and L. Normand, *Bull. Soc. Chim. France*, [4] **9**, 1061 (1911).

(9) T. Curtis and A. Lublin, *Chem. Ber.*, **33**, 2464 (1900).

TABLE I

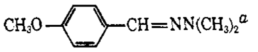
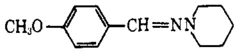
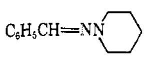
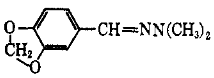
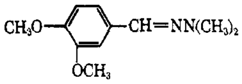
N,N-DIALKYLHDRAZONES OF ALDEHYDES

Aldehyde	Yield, %	Bp (mm) or mp, °C	C, %		H, %		N, %	
			Calcd	Found	Calcd	Found	Calcd	Found
From 1,1-Dimethylhydrazine								
n-Valeraldehyde	47	55–56 (13)	65.57	65.70	12.58	12.84	10.94[c]	10.69
Piperonaldehyde	90	188–189 (31)[a]	62.48	62.70	6.30	6.24	14.58	14.37
trans-Cinnamaldehyde	73	172–173 (28)	75.82	75.63	8.09	8.21	16.07	15.82
From 1-Aminopiperidine								
4-Methoxybenzaldehyde	83	47.5–49[b]	71.52	71.82	8.31	8.53	12.84	12.67

[a] Mp 49–51°. [b] Recrystallized from methanol–water. [c] Basic nitrogen determined by titration with perchloric acid in acetic acid.

TABLE II

NITRILES BY OXIDATION OF N,N-DIALKYLHYDRAZONES

Hydrazone	Conditions	Crude yield, %	Crude mp or bp (mm), °C	
			Found	Lit.
$C_6H_5CH{=}NN(CH_3)_2$[a]	Ambient temp, 24 hr	50	77–81 (18)[c]	
	Ambient temp, 24 hr	70	56–59	61–62[e]
	Reflux, 3 hr	85	50–52[d]	
	Reflux, 5 hr	50[b]		
$C_6H_5CH{=}CHCH{=}NN(CH_3)_2$	Reflux, 3 hr	92[c]		
	Reflux, 0.5 hr	85	76–78	94–95[f]
	Ambient temp, 24 hr	68	56–58	67[g]

[a] Prepared *in situ* (see the Experimental Section). [b] A mixture, bp 86–96° (28 mm), was obtained which contained benzaldehyde and benzonitrile by analysis of the infrared spectrum. Separation of benzaldehyde and benzonitrile was possible by glpc utilizing a 6-ft, 10% Lac 728 on 60–80 mesh Diataport W column with programming at 15°/min from 100 to 220°. The yield of 13% benzaldehyde and 50% benzonitrile was estimated from peak heights. [c] The infrared spectrum of the undistilled product was identical with that of an authentic sample. [d] The infrared spectrum of the product was identical with that of an authentic sample with the exception of a very weak carbonyl band at 1680 cm^{-1} (aldehyde?). [e] "Dictionary of Organic Compounds," Revised, I. M. Heilbron, Ed., 1st ed, Oxford University Press, London, 1965, p 178. [f] E. Marcus, *Ber.*, **24**, 3656 (1891). One recrystallization of the crude product from water gave mp 89–90°. [g] R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 620.

B. ***n*-Octanal Dimethylhydrazone.**—Oxidation of 30 g of the hydrazone was carried out by the procedure described in the preceding section. Five fractions were collected ranging in boiling point from 33 to 175° (26 mm). The infrared spectrum of a 2.1-g fraction with bp 73–86° (26 mm) indicated the presence of aldehyde and nitrile. Glpc analysis of this fraction (conducted as in the preceding section) confirmed the presence of *n*-octanal and *n*-octanonitrile in an approximate ratio of 1:10. Five other minor components were also present.

Attempted Oxidation of Benzaldehyde N-Methyl-N-phenylhydrazone.—A solution containing 3.0 g of the hydrazone,[10] 54 ml of methanol, and 12 ml of 30% hydrogen peroxide was heated under reflux for 3 days. Starting material (2.2 g, mp 99–102°) crystallized from the cooled reaction mixture.

Oxidation of Cyclohexanone N,N-Dimethylhydrazone.—Addition of 40 ml of 30% hydrogen peroxide to 10 g (0.072 mole) of the hydrazone[11] in 90 ml of methanol resulted in an exothermic reaction that was moderated by external cooling. After 24 hr at room temperature, the reaction mixture was diluted with 300 ml of water and extracted with three 150-ml portions of chloroform. The dried chloroform extracts were evaporated and distillation of the residue afforded 4.5 g (70%) of cyclohexanone, bp 90–93° (45 mm), which was identified by its infrared spectrum. The dark distillation residue formed a gummy picrate that could not be induced to crystallize.

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[10] A. Elberg, *Ann.*, **227**, 352 (1885).

[11] P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).