A Facile Hydrazone Cleavage

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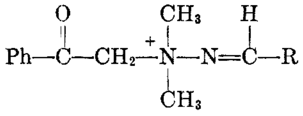
It had been found in these laboratories that the reaction of N,N-dimethylhydrazine with phenacyl halides led to the formation of quaternary compounds. These quaternaries were moderately stable in the solid form but decomposed in hydroxylic solvents.

In an extension of this work we attempted to prepare phenacyl quaternary compounds of type I. The two

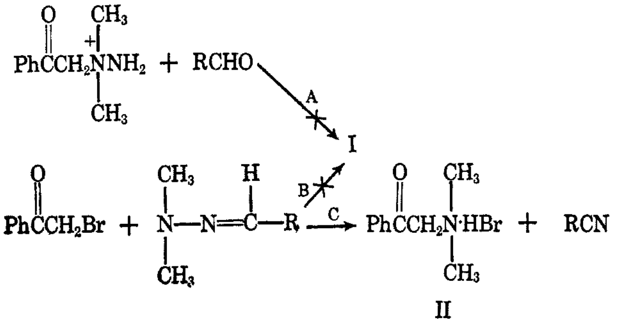


$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{\overset{+}{N}}}{-}N{=}\overset{\overset{H}{|}}{C}{-}R}$$

I

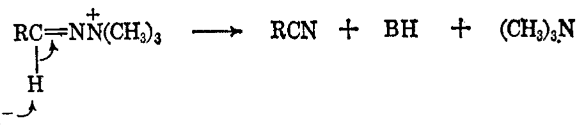
routes which were tried are shown in Scheme I below.

SCHEME I



Route A failed, probably owing to the instability of the quaternary phenacyl compound and low nucleophilicity of the terminal nitrogen. Route B, which consisted of mixing equimolar amounts of the two reactants in acetonitrile at room temperature, also failed. Instead, a good yield of II and the corresponding nitrile was obtained. When ketonic hydrazones were used, the reaction mixture became dark and no identifiable materials were isolated. Apparently the elimination of hydrogen with subsequent formation of a nitrile facilitates pathway C.

Previous workers have reported that quaternary hydrazones, obtained by reaction of acetophenone dimethylhydrazone with methyl iodide, are quite stable, being unchanged on refluxing in ethanol.[1] However, upon addition of sodium ethoxide to the refluxing solution, these authors obtained phenacylamine and trimethylamine. A more recent paper[2] reports on the reaction of N,N,N-trimethylhydrazonium salts derived from aldehydes, which, on treatment with methanolic sodium methoxide, gave the corresponding nitrile and trimethylamine. A mechanism for this β elimination was given by the authors.

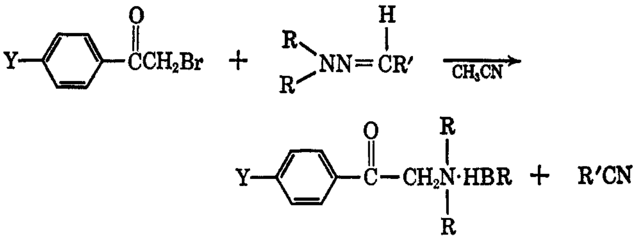


$$\mathrm{R\underset{\underset{\underset{B^-}{H}}{|}}{C}{=}N\overset{+}{N}(CH_3)_3 \longrightarrow RCN + BH + (CH_3)_3N}$$

In both of these cases addition of a strong base or heat was required to effect rearrangement. In our case, if we assume that I is an intermediate, the decomposition is rapid and requires no added base. A summary of our results is given in Table I.

TABLE I

REACTIONS OF HYDRAZONES



No.	R	R	R'	Y	Yield,[a] %
1	CH_3	CH_3	C_3H_7	Br	90 (15 min)
2	CH_3	CH_3	C_6H_{11}	Br	96 (15 min)
3	$(CH_2)_5$		C_3H_7	Br	88 (15 min)
4	CH_3	CH_3	C_6H_5	Br	74 (4 hr) 95.5 (24 hr)
5	CH_3	CH_3	C_3H_7	NO_2	85 (15 min) 93 (24 hr)
5a	Same as 5, but in benzene				17 (15 min) 76 (24 hr)
6	CH_3	CH_3	C_3H_7	H	68 (15 min) 92.5 (24 hr)
7	CH_3	CH_3	o-$NO_2C_6H_4$	Br	36 (24 hr)
8	CH_3	CH_3	p-$NO_2C_6H_4$	Br	0 (2 hr) 21 (24 hr)
9	CH_3	CH_3	b	Br	0

[a] Yields are for the phenacyldialkylamine hydrobromide.

[b] $=\overset{\overset{H}{|}}{C}R$, replaced by $=C_6H_{10}$.

Reactions 1–3 were rapid and nonexothermic, and maximum yields were obtained in 15 min. Reactions 5 and 6 were exothermic; however, maximum yields were obtained only after 24 hr. Electron-withdrawing groups at R' such as phenyl, *o*-, and *p*-nitrophenyl (**4**, **7**, **8**) significantly reduced the rate of the reaction. This may be due to the slower combination of hydrazone and phenacyl bromide. The lower yield (21 *vs.* 36%) from the *p*-nitrophenyl compared with the *o*-nitrophenyl compound is indicative of an electronic rather than a steric effect. Also, the lower yield when the reaction was run in benzene (**5**, **5a**) as compared with acetonitrile would indicate the presence of a polar intermediate or transition state. The use of a ketonic hydrazone **9** gave no product.

Attempts to extend this reaction to other "active" halogen compounds were unsuccessful. With benzyl bromide and butyraldehyde dimethylhydrazone, a quaternary was obtained which decomposed on heating to 100°, or in refluxing acetonitrile. The nature of the products formed was not determined; however, no evidence of benzyldimethylamine or of a nitrile was found. Reaction of ethyl 2-bromoacetate, 2-bromopropiophenone, or acetyl chloride with dimethylhy-

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

(2) R. F. Smith and L. E. Walker, *ibid.*, **27**, 4372 (1962).

drazones resulted in dark reaction mixtures from which no isolable products were obtained.

A reasonable assumption to explain the course of the successful reactions is initial formation of a quaternary intermediate (I) followed by scission at the N-N bond. The higher rate in the more polar solvent tends to support this view. In expt 5 and 6 the reactions were exothermic with maximum yields not obtained until 24 hr. Presumably the intermediates in these reactions have a lower ground state energy and greater stability. However, all attempts to isolate the postulated quaternary intermediate were unsuccessful.

A mechanism similar to that proposed by Smith and Walker[2] in which the solvent assumes the role of the base may be operating.

Experimental Section[3]

Preparation of Hydrazones.—Hydrazones were prepared in the usual manner by allowing equimolar amounts of the unsymmetrical dialkylhydrazine to react with an aldehyde or ketone in a benzene solution. The formed water was removed and the product distilled *in vacuo*. The products are described in Table II. Compounds **2**, **3**, and **5** have not been previously reported in the literature.

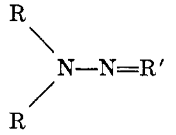
4-Bromophenacyltrimethylhydrazinium Bromide.—To 20.0 g (0.072 mole) of 2,4′-dibromoacetophenone in 190 ml of dry acetonitrile was added 4.4 g (0.073 mole) of N,N-dimethylhydrazine. After 1 hr the colorless solid was filtered and dried *in vacuo* to yield 24.0 g, mp 141–143° dec (99%). The analysis was performed on the crude material since recrystallization and heat resulted in partial decomposition.

Anal. Calcd for $C_{10}H_{14}Br_2N_2O$: C, 35.53; H, 4.17; Br, 47.28; N, 8.29. Found: C, 35.66; H, 4.44; Br, 47.43; N, 8.31.

Reaction of Benzaldehyde Dimethylhydrazone with 2,4′-Dibromoacetophenone.—To a slurry of 18.6 g (0.0675 mole) of 2,4′-dibromoacetophenone in 100 ml of acetonitrile was added 10.0 g (0.0675 mole) of benzaldehyde dimethylhydrazone. The mixture was stirred for 15 min during which the solution became homogeneous and a solid had precipitated. The mixture was allowed to stand for 24 hr and filtered; the precipitate was washed with ether to yield 20.8 g of 2-dimethylamino-4′-bromoacetophenone, mp 190–192°.

Table II

Hydrazones



No.	R	R	R′	Mp or bp, °C (mm)	n^{20}_{D}
1	CH_3	CH_3	CHC_3H_7	134 (760)[a]	1.4420
2	$(CH_2)_5$		CHC_3H_7	70–74 (8)[b]	1.4791
3	CH_3	CH_3	CHC_6H_{11}	124–128 (50)[c]	1.4821
4	CH_3	CH_3	CHC_6H_5	144–146 (35)[d]	1.5988
5	CH_3	CH_3	$CH(o\text{-}NO_2C_6H_4)$	104–105 (0·04)[e]	
6	CH_3	CH_3	$CH(p\text{-}NO_2C_6H_4)$	110–112[f]	
7	CH_3	CH_3	C_6H_{10}[g]	62–64 (10)[h]	1.4740

[a] Lit. bp 136–140°, n^{24}_{D} 1.4390. R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957). [b] Picrate, mp 103–104°. *Anal.* Calcd for $C_9H_{18}N_2$ (base): C, 70.07; H, 11.76; N, 18.16. Found: C, 70.23; H, 11.40; N, 17.88. [c] Picrate, mp 156–158°. *Anal.* Calcd for $C_{15}H_{21}N_5O_7$ (picrate): C, 46.99; H, 5.52; N, 18.27. Found: C, 47.27; H, 5.76; N, 18.28. [d] Lit. bp 127–128° (20 mm), n^{29}_{D} 1.5920. D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949). [e] *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.22; H, 5.85; N, 21.81. [f] Lit. mp 111°. O. L. Brady and G. P. McHugh, *J. Chem. Soc.*, **121**, 1651 (1922). [g] Cyclohexylidene. [h] Lit. bp 177–180°, n^{27}_{D} 1.4697. See footnote *d*.

Anal. Calcd for $C_{10}H_{13}Br_2N_2O$: C, 37.18; H, 4.05; Br, 49.53; N, 4.34. Found: C, 37.48; H, 3.99; Br, 49.28; N, 4.28.

The filtrate was evaporated *in vacuo* to yield 6.0 g of a brown liquid which was distilled to yield 4.9 g (71%) of benzonitrile of boiling point 190°. The infrared spectra and refractive index were identical with those of an authentic sample of benzonitrile.

N-Benzyl-N,N-dimethyl-N′-butylidene Hydrazonium Bromide.—To a solution of 6.7 g (0.0584 mole) of butyraldehyde dimethylhydrazone in 40 ml of acetonitrile was added 10.0 g (0.0584 mole) of benzyl bromide. After 16 hr the solvent was removed *in vacuo* and the colorless solid residue was recrystallized from benzene–hexane to give 13 g (78%). Recrystallization from benzene gave a product with a melting point of 82–86° dec.

Anal. Calcd for $C_{13}H_{21}BrN_2$: C, 54.73; H, 7.42; N, 9.82. Found: C, 54.33; H, 7.58; N, 9.40.

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[3] Melting points were determined on a calibrated Fisher-Johns apparatus. Elemental analysis were performed by Midwest Microlab, Inc., Indianapolis, Ind. 46226.

Alkaline Hydrogen Peroxide Oxidation of a Steroidal α,β-Unsaturated Ketone. A Baeyer–Villiger Product[1]

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The alkaline hydrogen peroxide oxidation of A-nortestosterone gives rise to a mixture of products which includes the epoxy lactone, 2-oxa-4β,5β-oxido-17β-hydroxyandrostan-3-one. The structure, stereochemistry, and mode of formation of this Baeyer–Villiger product are discussed.

The oxidation of α,β-unsaturated ketones with alkaline hydrogen peroxide has been observed to lead to the exclusive formation of epoxy ketones (**1**), without any evidence of Baeyer–Villiger products.[2] This is in sharp contrast to the oxidation of Δ^4-3-keto steroids with various peracids, in which an enol lactone (**2**) has been isolated[3] or postulated[4–6] as the initial Baeyer–Villiger product. A similar enol lactone has also been suggested as an intermediate in the oxidation of a Δ^4-3-keto steroid with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide[7] (Scheme I). During the course of the alkaline hydrogen peroxide

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[1] A preliminary account of this material has appeared: S. D. Levine, *Tetrahedron Letters*, 2233 (1965).

[2] C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).

[3] E. Caspi, Y. M. Chang, and R. I. Dorfman, *J. Med. Pharm. Chem.*, **5**, 714 (1962).

[4] G. Pettit and T. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

[5] A. Salamon, *Z. Physiol. Chem.*, **272**, 71 (1941).

[6] J. T. Pinhey and K. Schaffner, *Tetrahedron Letters*, 601 (1965).

[7] E. Caspi and S. N. Balasubrahmanyam, *Experientia*, **19**, 396 (1963).