A Procedure for Purification of Steam-Volatile Ketones. 2,4-Dinitrophenylhydrazone Cleavage

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Received October 8, 1965

Steam-volatile ketones may be purified through their bisulfite addition products, semicarbazones, hydrazones of *p*-hydrazinobenzenesulfonic acid,[2] or 2,4-dinitrophenylhydrazones. If the bisulfite addition product or semicarbazone forms in good yield and is easily recrystallized, these are the preferred derivatives since their cleavage to ketone may be readily accomplished. Semicarbazones are easily hydrolyzed by steam distillation in the presence of oxalic acid[3] or by exchange with pyruvic acid.[4] Bisulfite addition products are readily cleaved with dilute alkali or acid.[5] Unfortunately, these latter derivatives are restricted to aldehydes and methyl ketones.

2,4-Dinitrophenylhydrazones are excellent derivatives of ketones since they are formed quantitatively and are readily purified by recrystallization. However, their hydrolysis is impractical since the equilibrium strongly favors the 2,4-dinitrophenylhydrazone.

Procedures have been reported in which 2,4-dinitrophenylhydrazones are cleaved. These procedures are dependent on the presence of an acceptor molecule such as pyruvic acid[6,7] or levulinic acid[8] to aid in reversal to the starting ketone and 2,4-dinitrophenylhydrazine.

We have devised a procedure specifically designed for steam-volatile ketones employing α-ketoglutaric acid as the acceptor for 2,4-dinitrophenylhydrazine. α-Ketoglutaric acid serves admirably for this purpose and is preferred over pyruvic or levulinic acid since the latter are steam volatile. It has been pointed out that a γ-keto acid (levulinic acid or, in this case, α-ketoglutaric acid) is especially effective in the decomposition of 2,4-dinitrophenylhydrazones because it possesses a structure permitting internal hydrogen bonding through a cyclic intermediate.[8]

The procedure, which consists of steam distilling the 2,4-dinitrophenylhydrazone in the presence of an equivalent amount of α-ketoglutaric acid and an excess of 30–50% sulfuric acid, has been applied to several steam-volatile ketones. The results of these cleavages are summarized in Table I.

TABLE I

CLEAVAGE OF 2,4-DINITROPHENYLHYDRAZONES

	Mp[b] of 2,4-DNP, °C	Yield,[c] %
Saturated Ketones[a]		
Acetophenone	247–248[e]	87
4-*t*-Butylcyclohexanone	152–154[f]	88
(+)-Camphor	176–178[e]	82
Cyclohexanone	159–161[e]	95
Cyclooctanone	171–173[g]	94
Cyclopentanone	144–146[e]	80
2-Heptanone	72–74[h]	64
2-Methylcyclohexanone	139–141[e]	67
(+)-3-Methylcyclohexanone	138–139[i]	95
3,3,5-Trimethylcyclohexanone	132–134[j]	73
α,β-Unsaturated Ketones[a]		
3-Methyl-2-cyclohexen-1-one	178–179[k]	47
(+)-Pulegone	149–150[e]	5[d]
Hydroaromatic Ketones		
1-Indanone	259–260[e]	61
4,7-Dimethyl-1-indanone	278–279[i]	51
5,7-Dimethyl-1-indanone	277–278[i]	44[l]
3,4-Dihydro-2,5,8-trimethyl-1(2H)-naphthalenone	184–185[i]	53
3,4-Dihydro-3,5,8-trimethyl-1(2H)-naphthalenone	249–250[i]	64[m]
3,4-Dihydro-4,5,8-trimethyl-1(2H)-naphthalenone	226–227[i]	45[n]

[a] These studies were carried out in the Research Laboratories of Aldrich Chemical Co., Milwaukee, Wis. [b] The melting points are not corrected. [c] Yields are based on gas chromatography analyses. [d] An 86% yield of (+)-3-methylcyclohexanone was observed; this product is formed by acid-catalyzed cleavage of (+)-pulegone.[10] [e] See ref 11. [f] E. L. Eliel and M. K. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960). [g] O. L. Brady, *J. Chem. Soc.*, 756 (1931). [h] N. D. Cheronis, J. Entrikin, and E. M. Hodnett, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1965. [i] Unpublished observation from these laboratories. [j] A. E. Braude and E. A. Evens, *J. Chem. Soc.*, 607 (1954). [k] C. D. Hodgman, "Tables for Identification of Organic Compounds, Supplement to Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland 14, Ohio, 1960. [l] Sulfuric acid (50%) was required to effect cleavage. There was no apparent reaction with less concentrated acid. [m] Steam distillation in the presence of α-ketoglutaric acid and 35% sulfuric acid gave an 11% yield of the expected ketone. In the presence of 50% sulfuric acid, the yield rose to a total of 64%. [n] Sulfuric acid (35%) was first used with no apparent cleavage. The reaction mixture was cooled and the 2,4-dinitrophenylhydrazone was recovered by filtration and steam distilled with 500 ml of 50% sulfuric acid in the presence of 1.74 g of γ-ketopimelic acid to give the expected ketone.

In general, the 2,4-dinitrophenylhydrazones of saturated ketones responded to the cleavage reaction in good yield during a convenient period of reaction time. Even the 2,4-dinitrophenylhydrazone of (+)-camphor, which could be expected to be hydrolyzed with difficulty because of steric hindrance, cleaved in good yield with no evidence of skeletal rearrangement[9] despite the strong acidity of the reaction mixture.

We call attention to the cleavage of the 2,4-dinitrophenylhydrazone of 3-methyl-2-cyclohexen-1-one since this ketone, although α,β unsaturated, gave 50% of unaltered 3-methyl-2-cyclohexen-1-one. (+)-Pulegone 2,4-dinitrophenylhydrazone underwent cleavage in 5% yield but was also converted to (+)-3-methylcyclohexanone in 86% yield.[10]

Gas chromatographic curves [15% phenyldiethanolamine succinate (PDEAS) on 60–80 mesh acid-washed

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[1] American Petroleum Institute Research Project 58A Graduate Research Assistant, 1964–.

[2] W. Treibs and H. Rohnert, *Chem. Ber.*, **84**, 433 (1951).

[3] C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 4433 (1961).

[4] E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

[5] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 88.

[6] V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948).

[7] C. Djerassi, *ibid.*, **71**, 1003 (1949).

[8] C. H. DePuy and B. W. Ponder, *ibid.*, **81**, 4629 (1959).

[9] Camphor showed $[\alpha]^{24}\mathrm{D}$ +59.3° (*c* 6.22, ether) for starting material and +56.8° (*c* 4.26, ether) for product.

[10] E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

firebrick; helium flow 80 cc/min] of 2-methylcyclohexanone and (+)-3-methylcyclohexanone showed minor impurities for these substances as starting materials. These impurities were no longer present in the final product.

It is recommended that the product be distilled to remove the yellow color introduced by traces of 2,4-dinitrophenylhydrazine carried over during steam distillation. In each case, gas chromatography of the crude reaction product showed the ketone to be purer than the starting material and to exhibit only a single peak.

Experimental Section

The 2,4-dinitrophenylhydrazones were prepared[11] and purified by recrystallization from ethyl acetate and mixtures of ethyl acetate and methanol.

General Procedure.—A 0.01-mole sample of 2,4-dinitrophenylhydrazone and 1.61 g (0.011 mole) of α-ketoglutaric acid[12] were added to a 1-l. two-necked flask containing 500 ml of warm 35% sulfuric acid[13] and equipped with steam inlet tube and a 12-in. Vigreux column fitted with a splash bulb. An efficient condenser mounted for downward distillation was attached to the splash bulb. The reaction flask was heated with a mantle, and steam[13] was introduced until the condensate no longer gave a positive reaction with 2,4-dinitrophenylhydrazine reagent.[14] The steam distillate was saturated with salt and extracted with 200 ml of ethyl ether in two portions; the ether was washed twice with small portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated by distillation. The concentrate was diluted to 20.0 ml with ether.

Standard solutions of ketone in ether (1, 2, and 4%) were prepared and the gas chromatographic curves (PDEAS column) of the solutions were obtained. The peak areas of these curves were plotted *vs.* concentrations of the standard ether–ketone solutions. The resulting straight-line plot was used to obtain the concentration of the steam-distilled ketone by interpolating from the peak area. The yield was calculated from these data.

Acknowledgment.—We are grateful to the Aldrich Chemical Company, Milwaukee, Wisconsin, for their contribution to this work, and to the American Petroleum Institute for some financial support. We wish to thank Dr. O. C. Dermer for having read the manuscript.

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[11] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, Inc., New York, N. Y., 1964.

[12] γ-Ketopimelic acid was also tried and is an excellent substitute.

[13] An earlier experiment using 20% sulfuric acid was not successful since the 2,4-dinitrophenylhydrazone was not completely cleaved. Steam distillation times varied from 20 (300 ml of condensate) to 90 min (1100 ml of condensate). The exchange rate is dependent upon the solubility of the 2,4-dinitrophenylhydrazone in the reaction mixture.

[14] A. L. Wilds, *Org. Reactions*, **2**, 200 (1944).

Ten π Electron Nitrogen Heterocyclic Compounds. V. The Site of Protonation and N-Methylation of Imidazo[1,2-*a*]pyridines and the Planarity of the Ring System

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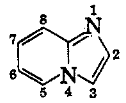
Received September 7, 1965

Recent publications from this laboratory have described some aspects of the chemistry of imidazo[1,2-*a*]pyridines.[1,2a] We now wish to report some studies of the protonation of this ring system and to discuss the question of planarity of the imidazo[1,2-*a*]pyridines (**1**).



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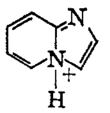
Analysis of the Nmr Spectra.—The nmr spectra of the hydrohalides and of the N-methyl derivatives of the imidazo[1,2-*a*]pyridines are considerably different from those of the free bases[1] and their analyses require some detailed discussion.

The assignment of the chemical shifts of H-2 and H-3 was made by comparing the spectra of 7-methylimidazo[1,2-*a*]pyridine hydrochloride with the 7-methyl-3-deuterioimidazo[1,2-*a*]pyridine hydrochloride (Table I).[2b] From this data it is clear that H-3 (H_E in Table I) is more deshielded than H-2 (H_F in Table I) in these compounds, while the reverse is true in the free bases.[1,2a,3–5] The assignment of the chemical shifts and coupling constants of the remaining protons now becomes relatively straightforward. It is of some interest to note the chemical shift differences between H-7 and H-8. The differences of these protons are of the same order of magnitude as the coupling constants; consequently they no longer appear as an AB pattern since the low-intensity transitions are not visible over the noise level of the instrument. It is, therefore, not possible to assign the chemical shifts of H-7 and H-8 precisely. The value reported for H-7 and H-8 in Table I is simply the center position of the apparent "doublet."

The Site of Protonation and N-Methylation in Imidazo[1,2-*a*]pyridines.—The protonation of these compounds can conceivably occur at either N-1 or N-4 to form salts of structures **2**, **3**, or **4**, or a resonance hybrid of **3** and **4**.[6]



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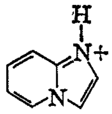

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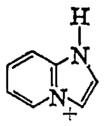

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The most facile way of establishing the position of protonation involves the study of the nmr spectra of the salts and a comparison of these spectra with the corresponding mono-N-methyl derivatives.[7]

The imidazo[1,2-*a*]pyridines can readily be converted to their mono-N-methyl derivatives (**5** or **6**) with methyl iodide. Some studies are reported which favor methylation of N-1 for these compounds.[8]

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[1] W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 353 (1965).

[2] (a) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965). (b) This compound was prepared by reduction of the corresponding 3-bromo compound by the method previously described.[2a]

[3] P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Australian J. Chem.*, **17**, 1128 (1964).

[4] J. G. Lombardino, *J. Org. Chem.*, **30**, 403 (1965).

[5] J. P. Paolini and R. K. Robbins, *J. Heterocyclic Chem.*, **21**, 53 (1965).

[6] Ultraviolet spectral data suggest that protonation occurs on N-1: W. L. F. Armarego, *J. Chem. Soc.*, 4226 (1964); 2778 (1965).

[7] The nmr spectra of the salts were obtained under conditions (approximately 1 *M* solutions) where the concentration of the nonprotonated species is essentially nil; thus, the comparison of the spectra of an equilibrium controlled process (hydrohalide salts in D_2O) with a nonequilibrium process (N-methylated compounds in D_2O) is tenable.

[8] A. E. Tschitschibabin, *Ber.*, **59**, 2048 (1926); *J. Russ. Phys. Chem. Soc.*, **58**, 1159 (1926).