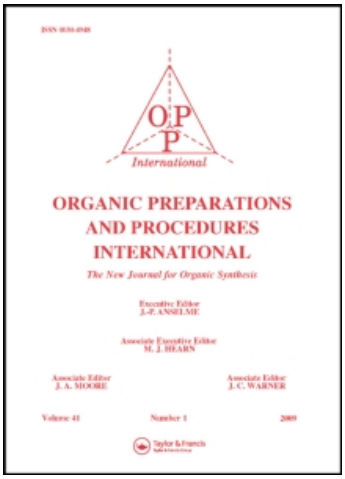

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REACTION OF DIAZOMETHANE WITH N-NITROSO-4-PIPERIDINONES

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did not change the melting point. Structure IV was supported by elemental analysis and IR and NMR spectra. A mixture melting point with the starting material (III) occurred at 45-50°.

Amine IV after treatment with formic acid in the same manner was recovered in an 88% yield.

REFERENCES

1. M. Senkus, J. Am. Chem. Soc., 67, 1515 (1945).

2. T. Clarke, B. Gillespie, and Z. Weisshaus, J. Am. Chem. Soc., 55, 4571 (1933).

REACTION OF DIAZOMETHANE WITH N-NITROSO-4-PIPERIDINONES

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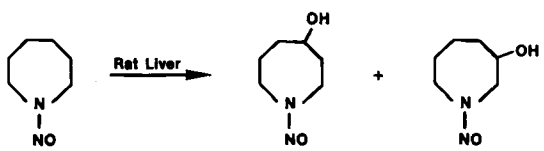
N-Nitrosohexahydroazepine 1 is a powerful liver and esophageal carcinogen in rats[1] and initial biochemical studies indicated that γ-hydroxylation to 2 and β-hydroxylation to 3 are major metabolic pathways (Scheme 1).

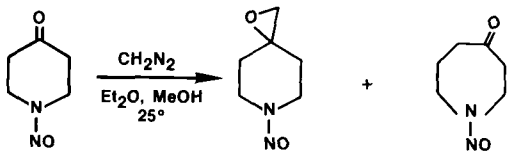


1 2 3

Scheme 1

In order to prepare metabolites 2 and 3 for use as synthetic standards,[2] we explored the ring expansion of some N-

substituted 3- and 4-piperidinones. The reaction of diazomethane with N-nitroso-4-oxopiperidine 4 afforded two new cyclic nitrosamines. The highly electronegative nitroso group favors epoxide formation over ring expansion resulting in a 62% yield of 6-nitroso-1-oxa-6-azaspiro[5.2]octane 5 and only a 17% yield of N-nitroso hexahydroazepine-4-one(6).



4 5 Major 6 Minor

The reaction of diazomethane with several N-substituted 4-oxopiperidines[3-5] indicated that the ratio of ring-expanded ketone to epoxide varied according to the substituent on the ring nitrogen. However, in most cases the ring-expanded ketone was the major product. In the case of N-benzoyl-4-oxopiperidine, our results did not agree with those of Favre et al.[4] They reported a 40% yield of the epoxide and a 26% yield of the ring-expanded ketone (as its phenylhydrazone). Our experiments consistently gave the ring-expanded product in 52% yield, and the epoxide in 23% yield.[2] The yields were quantified by GLC analysis as well as by isolation of the compounds.

The infrared spectrum of compound 4 shows the C=O stretching frequency at 1738 cm^{-1} which is high compared with that of N-benzoyl-4-piperidone (1725 cm^{-1}), of N-methyl and N-acetyl-4-piperidones[6] (1724 cm^{-1} and 1730 cm^{-1} respectively). The experimental results indicate that the nitroso function has a pronounced effect on the nature of the carbonyl group

and the migratory aptitudes of the methylene carbons. This supports the findings of Hirsch et al.[6] that the hybridization at nitrogen affects the electron density at each ring carbon in a six-membered nitrogen heterocycle, the strongest effect being a carbonyl group at the γ-position.

EXPERIMENTAL

Proton magnetic resonance spectra were measured on a Varian XL-100 spectrometer using $CDCl_3$ as solvent containing 0.5% tetramethylsilane as the internal standard. The IR spectra were obtained on a Perkin-Elmer 180 spectrometer. Mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame-ionization detector. A 2.5 m, 8% HI-EFF-1BP coated on Gas Chrom Q column was used (Applied Science Laboratories, Inc., State College, PA). The starting materials used were obtained from Aldrich Chemical Co., Mulwaukee, WI. Elemental analyses were done at Galbraith Laboratories, Inc., Knoxville, TN.

N-Nitroso-4-oxopiperidine(4) was prepared in 75% yield as described by Lijinsky and Taylor,[7] mp. 68-69°, lit.[7] 65-67°; IR ($CHCl_3$): 2925, 1738, 1440, 1365, 1145, 980 cm^{-1}; NMR ($CDCl_3$): δ 2.65 (quintet, 4H), 4.0 (t, 2H), 4.66 (t, 2H).

Reaction of 4 with Diazomethane.- Diazomethane (0.014 mol) in 80 ml of ether, generated by the method of deBoer and Backer[8] was added dropwise to a solution of 1.22 g (0.0095 mol) of N-nitroso-4-oxopiperidine in 30 ml of methanol at 5°. The ice-bath was removed and the solution stirred at 25° for 8 hrs. Excess diazomethane was destroyed by adding a few drops of aqueous acetic acid. The solution was then washed with 5% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 1.15 g

of a yellow oil. GLC analysis of the oil at 190° indicated that the epoxide 5 and the enlarged ketone 6 were present in 81% and 19% relative yields respectively.

6-Nitroso-1-oxa-6-azaspiro[5.2]octane(5).- A solution of 1.15 g of product obtained above in 5 ml of glacial acetic acid and 50 ml of 95% ethanol was refluxed for 30 min with 2 g (0.011 mol) of 1-(carboxymethyl)-pyridinium chloride hydrazide (Girard's Reagent P). The reaction mixture was cooled to 25°, and the ethanol removed on a rotary evaporator. Then 25 ml water was added and the non-ketonic components were extracted into methylene chloride. The aqueous layer was saved for the isolation of 6 (see below). The organic layer was washed with 5% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under vacuum. The residue was chromatographed on neutral alumina using methylene chloride as the eluent, and gave 837 mg (62%) of 5 as an oil which crystallized on standing. Although vacuum distillation can also be used to purify the compound, the recovery is lower than with chromatography; bp 78°/0.2 mm Hg; mp. 42-43°; IR (film): 2970, 2925, 1430, 1370, 1150, 1060, 980, cm^{-1}; NMR ($CDCl_3$): δ 1.57 (s, 2H), 1.5-2.3 (m, 4H), 2.8 (s, 2H), 3.35 (m, 1H *syn* axial), 4.20 (m, 1H *anti* axial), 4.60 (m, 1H *anti* equatorial), δ 4.71 (m, 1H *syn* equatorial); MS: m/e (%), 142 (66.6, M^+), 112 (9.7), 96 (4.1), 83 (12.1), 65 (16), 55 (32.6), 42 (100).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69%; H, 7.09%; N, 19.71%

Found: C, 50.48%; N, 7.17%; N, 19.76%

N-Nitrosohexahydroazepine-4-one(6).- The aqueous layer containing 6 was acidified with 6N HCl to pH 2. After the solu-

tion had been heated to 60° for 30 min, it was cooled to 25° and extracted with methylene chloride. The organic layer was dried over anhydrous potassium carbonate and filtered through a layer of anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator, and the residue chromatographed through neutral alumina using 10% acetone in methylene chloride as the eluting solvent to give 229 mg (17%) of 6, bp. 160°/ 0.05 mm Hg (distillation of this compound is not recommended since it decomposes); IR (film); 2960, 1700, 1462, 1420, 1360, 1105, 895 cm^{-1}; NMR ($CDCl_3$): δ 1.82-2.2 (m, 2H), 2.5-3.0 (m, 4H), 4.96 (m, 2H), 5.51 (m, 2H); MS: m/e (%), 142 (49, M^+), 125 (12), 112 (45), 98 (4), 84 (9), 69 (17), 56 (26), 42 (100).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69%; H, 7.09%; N, 19.70%

Found: C, 50.40%; H, 7.22%; N, 19.54%.

Acknowledgement.- The NMR spectra were recorded by Dr. D. Wilbur, and the mass spectra were run by Mr. S. S. Huang. This work was supported by Contract No. Nol-CO-75380 with the National Cancer Institute, NIH, Bethesda, MD 20205.

REFERENCES

1. C. Goodall, W. Lijinsky and R. Tomatis, Cancer Res., 28, 1217 (1968).
2. L. I. Hecker and J. E. Saavedra, Carcinogenesis, 1, 1017 (1980).
3. A. Casy and H. Birnbaum, J. Chem. Soc., 5130 (1964).
4. H. Favre, Z. Hamlet, R. Lanthier and M. Menard, Can. J. Chem., 49, 3078 (1971).
5. R. Johnson, M. Herr, H. Murray and G. Funken, J. Org.

Chem., 33, 3187 (1968).

6. a) J. Hirsch and A. A. Jarmas, ibid., 43, 4106 (1978); b) J. Hirsch, ibid., 44, 3225 (1979); c) J. Hirsch and E. Havinga, ibid., 41, 455 (1980).
7. W. Lijinsky and W. Taylor, J. Nat. Cancer Inst., 55, 705 (1975).
8. T. J. deBoer, H. J. Backer, Org. Syn., Coll. Vol. 4, John Wiley and Sons, New York, N.Y., 1963, p. 250.

LEWIS ACID CATALYZED PREPARATION OF TETRAMETHYLHEXATHIOADAMANTANE

Submitted by C. S. Giam*, R. L. Tabor and T. E. Goodwin†
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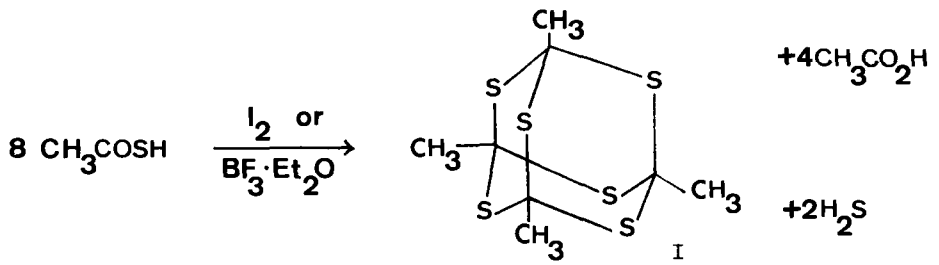
We have utilized two new and convenient processes for the synthesis of tetramethylhexathioadamantane (I)[1,2] from thiolacetic acid. The compound is useful both as a lubricant addi-



tive,[3] and as a thermal stabilizer in poly(methylmethacrylate)[4] where it promotes antiseize properties and confers oxidative