[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WEST VIRGINIA UNIVERSITY]

Preparation of Nitro Compounds from Oximes. II. The Improved Synthesis of Nitrocycloalkanes[1]

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The use of N-bromosuccinimide as a brominating agent for cycloketoximes produces α-bromonitroso compounds which are easily oxidized to α-bromonitrocycloalkanes. Subsequent reduction with sodium borohydride provides a practical synthesis of nitrocycloalkanes.

The synthesis of nitro compounds by the sodium hypobromite oxidation of oximes to bromonitro compounds followed by potassium hydroxide–ethanol reduction to the nitro compounds has been recently examined.[2] This sequence was found to yield nitro compounds only in the alicyclic series and then in poor yields. In the present paper, studies employing other reagents for these two steps are described. It has now been found possible to effect these conversions in yields which are in most instances superior to those obtainable by existing syntheses of nitrocycloalkanes.

The initial attempt to improve the first step of the sequence involved re-examination of the use of pyridine in water plus methanol.[3] Difficulty was experienced in isolating the low molecular weight liquid products from the pyridine solutions. The use of bromine with aqueous sodium bicarbonate or sodium carbonate also resulted in no improvement over the hypobromite procedure. Attention was then turned to the reaction of oximes with N-bromosuccinimide, a reaction which apparently has not been studied previously.[4]

It has been found that the reaction of NBS with alicyclic ketoximes in aqueous sodium bicarbonate produces the blue bromonitroso compounds which upon nitric acid oxidation afford bromonitrocycloalkanes in 40 to 70% yields (Table I). This is clearly superior to the yields obtained by the sodium hypobromite procedure. In addition to the improved yield of bromonitro compounds, the greater simplicity of procedure and ease of control due to the only mildly exothermic nature makes the NBS procedure much preferred to the sodium hypobromite method.

TABLE I

BROMONITRO CYCLOALKANES FROM KETOXIMES VIA NBS METHOD

Compound, oxime	Yield, %
Cyclobutanone[a]	69
Cyclopentanone[b]	72
Cyclohexanone	63
2-Methylcyclohexanone	44
4-Methylcyclohexanone	42
Cycloheptanone	38

[a] Ratio NBS to oxime was 2.5:1. [b] When NBS to oxime ratio is 1.1:1 yield is 22%; with ratio of 2:1, yield is 58%.

As noted earlier[2] the formation of nitro compounds occurs in very poor yields, if at all, when α-bromonitro compounds are treated with alcoholic potassium hydroxide. Other reagents which have been employed for this purpose from time to time include potassium iodide,[5,6] potassium cyanide,[5] hydrazine[7] and sodium thiosulfate[6]; these studies have usually been made with polyhalonitro compounds such as chloropicrin or dibromodinitromethane.

Because of its apparent simplicity, the potassium iodide–methanol procedure of Kohler was examined and extended to bromonitrocycloalkanes with the results summarized in Table II. Although nitrocycloalkanes were obtained in every case the yields were poor. The yield of nitrocyclobutane was much superior to the original ethanol–potassium hydroxide procedure.[2] After an unsuccessful attempted reduction of 3-bromo-3-nitropentane using potassium cyanide and methanol according to Kohler no further examination of this combination was made.

TABLE II

YIELD OF NITROCYCLOALKANES FROM BROMONITROCYCLOALKANES

Product	C_2H_5OH–KOH procedure[a] %	CH_3OH–KI procedure %	$NaBH_4$ procedure %	
Nitrocyclobutane	2	22	15	33[b]
Nitrocyclopentane	32	22	60	76[b] 63[c]
Nitrocyclohexane	28	48	80	
2-Nitro-1-methylcyclohexane	..	13	63	
4-Nitro-1-methylcyclohexane	..	11	53	
Nitrocycloheptane	..	2	76	

[a] Ref. 2. [b] Ratio $NaBH_4$ to bromonitro compound was 8:1. [c] Reaction temperature was 0–5°.

It was found, however, that treatment of alicylic bromonitro compounds with an aqueous methanolic solution of sodium borohydride[8] gave excellent yields of nitrocycloalkanes. A ratio of sodium borohydride to bromonitro compound of 4.5 to 1 usually gave the optimum yield of nitro compound except in the reduction of bromonitrocyclobutane where the yield was improved by a ratio of 8 to 1. The yields of nitrocycloalkanes obtained by the sodium borohydride reductions are shown in Table II.

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September 17, 1952.

(2) D. C. Iffland, G. X. Criner, F. J. Lotspeich, M. Koral, Z. B. Papanastassiou and S. M. White, THIS JOURNAL, **75**, 4044 (1953).

(3) O. Piloty and H. Steinbock, *Ber.*, **31**, 452 (1898).

(4) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(5) E. P. Kohler, THIS JOURNAL, **38**, 887 (1916).

(6) R. A. Gotts and L. Hunter, *J. Chem. Soc.*, **125**, 442 (1925).

(7) A. K. Macbeth and D. D. Pratt, *ibid.*, **120**, 1356 (1921); T. Henderson and A. K. Macbeth, *ibid.*, **121**, 892 (1922); E. Downing and W. B. Orr, *ibid.*, 1671 (1934).

(8) We are indebted to Dr. Harold Shechter, The Ohio State University, for suggesting this use of sodium borohydride.

The extension of these improvements to aliphatic ketoximes is in progress.

Experimental

The preparation of the alicyclic ketoximes has been described.[2] Eastman practical quality N-bromosuccinimide was used. Sodium borohydride was procured from Metal Hydrides, Inc. The preparation of 1-bromo-1-nitrocyclohexane and nitrocyclohexane are representative of the methods used. Physical constants and analyses of the compounds prepared have been tabulated previously.[2]

Preparation of 1-Bromo-1-nitrocyclohexane by the NBS Procedure.—A solution was prepared by mixing 11.3 g. (0.1 mole) of cyclohexanone oxime[9] with 25.3 g. (0.3 mole) of sodium bicarbonate in 150 ml. of water. This solution was added as rapidly as possible to a vigorously stirred suspension of 54.5 g. (0.30 mole) of N-bromosuccinimide in 150 ml. of water cooled to 10° with an ice-bath. The addition required *ca.* 15 min. and the temperature remained about 10°. Stirring was continued an additional 15 min. The reaction product was extracted by stirring with four 50-ml. portions of 35–37° petroleum ether and each decanted from the aqueous solution and suspended solids. The combined extracts (lachrymatory) were concentrated by distillation until about 30–50 ml. of blue solution remained.[10] This solution was shaken with *ca.* 100 ml. of nitric acid (sp. gr. 1.42) until free of the blue color. After dilution with about 100 ml. of water the organic material was extracted with 35–37° petroleum ether. The extract was washed successively with water, 5% aqueous sodium hydroxide and water. After drying over anhydrous sodium sulfate and concentration of the extract, the 1-bromo-1-nitrocyclohexane was distilled, 7.9 g., b.p. 116–117° at 20 mm.

Preparation of Nitrocyclohexane. A. Methanol–Potassium Hydroxide Procedure.—A solution was prepared from 9.0 g. (0.043 mole) of 1-bromo-1-nitrocyclohexane and 30 ml. of methanol. This was mixed with 21.6 g. (0.13 mole) of potassium iodide and refluxed for 24 hours. The reaction mixture was cooled and the iodine formed was reduced with concentrated sodium bisulfite solution. The solution was made distinctly alkaline by adding dilute potassium hydroxide[11] and was then carefully extracted with petroleum ether. The aqueous portion was acidified with 15% aqueous hydroxylamine hydrochloride and after the nitro compound separated it was collected with the aid of petroleum ether. The petroleum ether solution was washed with 85% phosphoric acid and water. After drying over anhydrous sodium sulfate and concentration, the nitrocyclohexane was distilled, 2.7 g., b.p. 108–110° at 40 mm.

B. **Sodium Borohydride Procedure.**—A solution of 5.20 g. (0.135 mole) of sodium borohydride was prepared in 100 ml. of 75% (volume) aqueous methanol. This solution was contained in a 500-ml. three-neck flask equipped with a high speed Hershberg stirrer with a mercury seal, a reflux condenser and an addition funnel containing 6.24 g. (0.03 mole) of 1-bromo-1-nitrocyclohexane. A few drops of the bromonitro compound were added to the sodium borohydride solution. The reaction started slowly and occasionally required external heating. Only after the reaction had started (rapid evolution of gas) and the solvent was at reflux temperature, the remainder of the bromonitro compound was added as rapidly as possible. After completion of the reduction, aqueous potassium hydroxide was added if the mixture was not already strongly alkaline and the methanol was then separated by steam distillation. The nitrocycloalkane was isolated from the remaining aqueous solution by acidification with 15% aqueous hydroxylamine hydrochloride and extracted with petroleum ether. The extract was treated as in part A to yield 3.1 g. of nitrocyclohexane, b.p. 109–110° at 40 mm.

(9) Whenever solution was not complete the resulting suspension was used or as in the case of the methylcyclohexanone oximes and cycloheptanone oxime, dioxane was added to increase the solubility.

(10) At this point *ca.* 1.5 g. of white bromonitroso dimer separated in the preparation of bromonitrocyclobutane. This solid decomposed when heated to 80° and dissolved in dioxane, methanol or chloroform yielding intensely blue solutions.

(11) It should be emphasized that adequate time must be allowed for the reaction of the nitro compound with base and the regeneration of the nitro compound from the salt. The reaction of 2-nitro-1-methylcyclohexane was particularly slow even when considerable excess base was used. On the other hand nitrocyclobutane, while insoluble in water, very interestingly dissolves rapidly in dilute aqueous alkali to form the non-extractable salt.

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New Methods of Synthesis of β-Aminoethylpyrazoles

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Some new methods of synthesis and some improvements in the known methods of preparation of the powerful gastric secretory stimulants, 3-β-aminoethylpyrazole (I) and 4-β-aminoethylpyrazole (II), are described. A key intermediate, 3-hydroxymethylpyrazole, has been made by lithium aluminum hydride reduction of *n*-butyl 3-pyrazolecarboxylate and also by condensation, under acidic conditions, of hydrazine with the acetylene compounds, 4,4-diethoxy-2-butyne-1-ol and 2-(4′,4′-diethoxy-2′-butynyl)-oxytetrahydropyrane. 3-β-Aminoethylpyrazole was prepared by catalytic hydrogenation of 3-pyrazoleacetaldehyde hydrazone which, in turn, was obtained quantitatively by the reaction of hydrazine with γ-pyrone. 4-β-Aminoethylpyrazole was prepared from 4-β-hydroxyethylpyrazole which was obtained by the reaction of hydrazine with 2-ethoxy-3-tetrahydrofuranaldehyde diethyl acetal. A new method of preparation of ethyl 4-pyrazolecarboxylate and a number of related new pyrazole derivatives are described.

A preceding paper from this Laboratory described the preparation of 3-β-aminoethylpyrazole (I) and 4-β-aminoethylpyrazole (II).[1] These analogs of histamine were tested for their physiological activity and were found to have practically no effect on guinea pig ileum strips or on cat's blood pressure,[2] and were stated to have no other observable physiological activities.[1] Subsequently, they were tested for their effect on gastric secretion and surprisingly were found to possess high stimulatory activity on acid secretion in animals and man.[3] 3-β-Aminoethylpyrazole (I) is particularly interesting in that on a weight basis it is about one-seventieth as active as histamine in stimulating gastric acid secretion[3a] but only very slightly active in causing smooth muscle contractions, and it has no inflammatory action on the skin.[4] Thus, in effect, it possesses only one of the actions of histamine (*i.e.*, stimulation of gastric secretion) and none of the others.

(1) R. G. Jones, THIS JOURNAL, **71**, 3994 (1949).

(2) H. M. Lee and R. G. Jones, *J. Pharmacol.*, **95**, 71 (1949).

(3) (a) C. E. Rosiere and M. I. Grossman, *Science*, **113**, 651 (1951); (b) private communication from Dr. M. I. Grossman.

(4) 3-β-Aminoethylpyrazole is relatively non-toxic (LD_{50} in mice is about 800 mg./kg. i.v.), and it has been used clinically.