[CONTRIBUTION FROM THE CANCER CHEMOTHERAPY LABORATORIES, DEPARTMENT OF PHARMACOLOGY, STANFORD UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SAN FRANCISCO]

# Reductions with Hydrazine Hydrate Catalyzed by Raney Nickel. II. Aromatic Nitro Compounds to Intermediate Products[1]

BY ARTHUR FURST AND RICHARD E. MOORE[2]

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Azoxybenzenes and hydrazobenzenes have now been prepared by the hydrazine–Raney nickel reduction method. By varying the concentration of the hydrazine these intermediate reduction products rather than the amines can be obtained.

Hydrazine hydrate in the presence of Raney nickel has been found to reduce alcoholic solutions of aromatic nitro compounds to the corresponding amines in good yield.[3] The method has been applied successfully to the reduction of 6-nitroindole to 6-aminoindole[4] and to the conversion of a nitrostyrylcolchicine ester to the corresponding amine.[5] Application of the method to nitro-[6] or nitrosopyrimidines[7] gave anomalous products not readily characterized.

It is apparent that the nature of the catalyst is not critical to the course of the reaction. Uniformly good yields of amines have been obtained using palladized charcoal[8,9] or platinum[10] as the catalyst. Iron or copper powder also has been used, but the yields were inferior.[11] The catalytic effect may be merely the provision of a surface for reduction, since reduction products have been obtained using only porous tile as the catalyst.[12] However, no reduction took place without a catalyst at room or steam-bath temperatures.[3,10,13]

The concentration of hydrazine appears to be the main factor controlling the nature and yields of reduction products. If large volumes of alcohol and hence small concentrations of hydrazine hydrate were used, amines were the sole products. If the hydrazine hydrate concentration was increased, good yields of intermediate products resulted; the reaction could either be stopped at the azoxybenzene stage or allowed to proceed to hydrazobenzene. Under these conditions both azoxybenzene and azobenzene were smoothly reduced to hydrazobenzene. It was not found possible, however, to isolate azobenzene from any of the reaction mixtures.[14] The rate of reduction of the azo compounds to the hydrazos far exceeds that of the nitro compounds to the azos. Nitrosobenzene was reduced readily to aniline by hydrazine hydrate alone. It is possible that phenyltriazine is an intermediate; this compound has not yet been isolated.

The mechanism of this reduction is now being investigated.

## Experimental

**Hydrazobenzene.**—For each procedure, 9 ml. of hydrazine hydrate 100% (0.18 mole) was added to 0.081 mole of the nitrogen compound dissolved in 15 ml. of 95% ethanol. A small amount of Raney nickel catalyst was introduced,[15] and the flask was shaken vigorously. The temperature was kept just below 35° by external cooling. As the reaction slowed, more catalyst was added.

(a) **From Nitrobenzene.**—Upon addition of the catalyst there was much effervescence and the mixture first turned green, then slightly brownish and finally yellow, whereupon a yellow oil appeared becoming orange as the reaction proceeded. The flask was allowed to stand at room temperature until the dark orange oil had changed to a grayish-white solid. This required 1–3 hr. Water was added to quench the reaction and the solid product immediately filtered, washed with water and recrystallized from alcohol. The yield was 5.6 g. (75%), m.p. 125–127°.

(b) **From 8.1 g. of Azoxybenzene.**—There was considerable effervescence but not much color change when the catalyst was first introduced. The solid azoxybenzene melted to a yellow oil which gradually turned orange. After approximately 15 minutes hydrazobenzene precipitated. Reduction was continued until the yellow color was discharged. The precipitate was collected by filtration and recrystallized from alcohol. The yield was 6.8 g. (90%), m.p. 125–127°.

(c) **From 7.4 g. of Azobenzene.**—The dark orange-red color disappeared almost immediately when the catalyst was added, and hydrazobenzene precipitated. The reaction was complete in about 10 minutes. The precipitate was collected by filtration and recrystallized from alcohol. The yield was 7.5 g. (100%), m.p. 125–127°.

**Aniline Hydrochloride from Nitrosobenzene.**—A solution of 1 g. (0.0093 mole) of nitrosobenzene in 25 ml. of 95% ethanol was treated with 0.5 ml. of 100% hydrazine hydrate. The initial blue color of the solution changed to dark green.

Bubbles of nitrogen appeared immediately indicating phenyltriazine, unstable in alcohol solution at room temperature, as a probable intermediate, and the solution turned colorless. The mixture was concentrated on the steam-bath to approximately 2 ml., water was added and the oil extracted with ether. After evaporation of the ether on the steam-bath, 1.5 ml. of concd. HCl was added. The resulting aniline hydrochloride was recrystallized from alcohol yielding 0.8 g. (95%), m.p. 196–198°.

**Azoxybenzene.**—To 10 g. of nitrobenzene (0.081 mole) was added 9 ml. of 100% hydrazine hydrate (0.18 mole) and 5 ml. of 95% ethanol. Some Raney nickel catalyst was added. The flask was shaken vigorously,[16] and the

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[2] Abstracted from a report submitted by Richard E. Moore, for the undergraduate research program, U.S.F.

[3] D. Balcom and A. Furst, THIS JOURNAL, **75**, 4334 (1953).

[4] R. K. Brown and N. A. Nelson, *ibid.*, **76**, 5149 (1954).

[5] D. S. Tarbell, R. F. Smith and V. Boekelheide, *ibid.*, **76**, 2470 (1954). In this case the compound first isolated, probably a polyamide, had to be hydrolyzed to the corresponding amine.

[6] P. E. Fanta and E. A. Hedman, *ibid.*, **78**, 1434 (1956).

[7] A. Furst and H. P. Hamlow, unpublished work.

[8] S. Pietra, *Gazz. chim. ital.*, **85**, 850 (1955).

[9] M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 2556 (1956).

[10] L. P. Kuhn, THIS JOURNAL, **73**, 1510 (1951).

[11] S. Kubota, K. Nara and S. Onishi, *J. Pharm. Soc. Japan*, **76**, 801 (1956); *C. A.*, **51**, 1086*h* (1957).

[12] W. H. Stafford, M. Los and N. Thomson, *Chemistry & Industry*, 1277 (1956).

[13] The only exception was the reported reduction of 2,2′-dinitrodiphenyl disulfide by hydrazine in boiling alcohol without a catalyst; R. Mohlau, H. Beyschlag and H. Kohres, *Ber.*, **45**, 131 (1921).

[14] Both azoxybenzene and azobenzene, however, were isolated if alcoholic potassium hydroxide was used as the solvent in a hydrazine–palladized calcium carbonate reduction; M. Busch and K. Schulz, *Ber.*, **62**, 1458 (1929).

[15] If too much catalyst was added all at once, the reaction became extremely violent and exothermic.

[16] Vigorous shaking of the mixture was essential to provide good contact between the nitrobenzene and the hydrazine and to prevent the violent reaction.

temperature was kept under 35° by external cooling. When the reaction became sluggish, more catalyst was added. Reduction was complete when a viscous yellow oil appeared and only a faint odor of nitrobenzene could be detected.[17] Water was added and the mixture placed in an ice–salt-bath. The yellow oil soon crystallized. The crude azoxybenzene was removed by rapid filtration. Some of the impurities oiled out leaving behind a yellow solid. The oil was chilled and the process repeated for an additional yield of crude azobenzene. The azoxybenzene was recrystallized from alcohol, yield 5.5 g. (65%), m.p. 34–35°. On a second recrystallization the product melted at 35–36°.

**2,2'-Dimethylazoxybenzene.**—To 10 g. of *o*-nitrotoluene (0.073 mole) was added 9 ml. of 100% hydrazine hydrate (0.18 mole) and 20 ml. of 95% ethanol. Some Raney nickel catalyst was introduced. There was much effervescence and the mixture turned slightly green, then yellow. The temperature of the reaction was kept under 35°. When the reaction became less vigorous, the solution was orange. More catalyst was added and the mixture allowed to stand at 0° overnight. The resulting orange-yellow crystals of 2,2'-dimethylazoxybenzene were collected by filtration and recrystallized from a mixture of alcohol and water. A second crop was obtained by adding water to the mother liquor, from the original filtration and treating the resulting dark orange-red oil with dil. HCl until it crystallized. The total yield was 3.2 g. (39%), m.p. 57.5–58.5°.[18]

**4,4'-Dimethylazoxybenzene.**—Ten grams of *p*-nitrotoluene (0.073 mole) was suspended in a solution of 9 ml. of 100% hydrazine hydrate (0.18 mole) and 30 ml. of 95% ethanol. Some Raney nickel catalyst was introduced and the mixture stirred for several hours. The *p*-nitrotoluene gradually dissolved and yellow crystals of 4,4'-dimethylazoxybenzene were deposited. When effervescence had ceased, the product was filtered and recrystallized from a mixture of alcohol and water. This yield was 3.4 g. (42%), m.p. 70–71°.[18]

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[17] If the reaction was allowed to proceed too far, an orange oil or a low melting solid was obtained which was impossible to purify by recrystallization.

[18] L. Zechmeister and P. Ron, *Ann.*, **468**, 117 (1929).

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

# Methylene Derivatives as Intermediates in Polar Reactions. VIII. Difluoromethylene in the Reaction of Chlorodifluoromethane with Sodium Methoxide[1]

BY JACK HINE AND JOHN J. PORTER

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Since chlorodifluoromethane reacts with methanolic sodium methoxide 150 times as fast as chlorofluoromethane does at 35° despite the fact that α-fluorine substituents are known to decrease $S_N2$ reactivity, the reaction of chlorodifluoromethane is very probably not $S_N2$ in character. It is instead believed to involve an initial α-dehydrohalogenation to give difluoromethylene, a reactive intermediate that yields a mixture of methyl difluoromethyl ether and trimethyl orthoformate. The intermediate, methoxyfluoromethylene, appears to be involved in the production of the orthoformate. The α-elimination mechanism is further supported by the observation that while chlorodifluoromethane reacts only very slowly with sodium thiophenoxide alone, in the presence of sodium methoxide the reaction (which yields phenyl difluoromethyl sulfide) is relatively rapid. The thiophenoxide ion is found to be more than one hundred times as effective as methanol at combining with difluoromethylene.

## Introduction

Chloroform and several other haloforms have been shown to undergo basic hydrolysis by the mechanism[2,3]

$$CHX_3 + OH^- \rightleftharpoons CX_3^- + H_2O$$
$$CX_3^- \longrightarrow CX_2 + X^-$$

followed by rapid reactions of the intermediate dihalomethylene. This mechanism represents the principal reaction path only because such possible alternatives as the $S_N2$ mechanism[4] are considerably slower. Since α-fluoroalkyl halides are considerably more reactive by the $S_N2$ mechanism than are the analogous chloro, bromo and iodo derivatives,[5] it was of interest to learn whether the dihalomethylene (or α-elimination) mechanism is operative for such haloforms as chlorodifluoromethane.

## Results and Discussion

**The Reaction of Chlorodifluoromethane with Sodium Methoxide.**—The only organic products observed in the reaction of chlorodifluoromethane and sodium methoxide in methanol were trimethyl orthoformate and methyl difluoromethyl ether. Although the difluoromethyl ether, a new compound, was not analyzed because of its tendency to decompose on standing, the following evidence exists for its structure. Its method of preparation is analogous to that used for ethyl difluoromethyl ether[6] and isopropyl difluoromethyl ether.[7] A survey in Lange's "Handbook of Chemistry" of twenty-seven series of methyl, ethyl and isopropyl compounds showed that the difference in boiling point between the methyl and ethyl compounds was 3.0 to 12.9° (av. 8.7 ± 2.6) greater than between the ethyl and isopropyl compounds. In view of this the boiling point of methyl difluoromethyl ether (−4°) is quite plausible considering the values reported for the ethyl (23.7°) and isopropyl (44.5°) analogs. Since an alkoxy substituent is known to activate a $-CF_2-$ group so that its acid hydrolysis

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[1] Ref. 7 is considered part VII. For part VI under a somewhat different series title see J. Hine, N. W. Burske, M. Hine and P. B. Langford, THIS JOURNAL, **79**, 1406 (1957). Much of the content of parts VIII and IX was presented in a talk at the Sixth Biannual Conference on Reaction Mechanisms, Swarthmore, Pennsylvania, September 13, 1956.

[2] J. Hine, *ibid.*, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).

[3] J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., *ibid.*, **78**, 479 (1956).

[4] For the meaning of the term "$S_N2$" see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, Chap. 5.

[5] J. Hine, C. H. Thomas and S. J. Ehrenson, THIS JOURNAL, **77**, 3886 (1955); J. Hine, S. J. Ehrenson and W. H. Brader, Jr., *ibid.*, **78**, 2282 (1956).

[6] A. L. Henne and M. A. Smook, *ibid.*, **72**, 4378 (1950).

[7] J. Hine and K. Tanabe, *ibid.*, **79**, 2654 (1957).