dine. The resulting material was distilled, giving a green-yellow liquid, 17.9 g., b.p. 51–53° (0.9 mm.). The residue was tarry. The distillate appears to be a mixture of nitrobenzene and N-isopropylmaleimide, judging from analysis and refractive index.

A similar experiment with maleimide also failed.

α-*p*-Chlorophenylmaleic Hydrazide.—Since maleic hydrazide was insoluble in aqueous acetone, dimethyl sulfoxide was used as the organic solvent.[19] The mixture obtained from 0.15 mole of each reagent was treated with 0.3 mole of 2,6-lutidine, but no lutidine hydrochloride separated. The only product isolated was a small amount of unreacted maleic hydrazide.

α-(2,4-Dichlorophenyl)-β-chlorosuccinimide.—The reaction of 0.1 mole each of amine and maleimide yielded 11.5 g. of white product, m.p. 196–198° dec. Recrystallization from alcohol gave pure material, m.p. 200–202° dec. The mother liquor yielded 3.2 g., m.p. 173–185° dec., of a mixture of this product and 2,4-dichlorophenylmaleimide (see below), which mixture could be dehydrohalogenated readily to the pure material.

α-2,4-Dichlorophenylmaleimide.—Treatment of the above chlorosuccinimide (1 g.) with 10 ml. of 2,6-lutidine with gentle warming gave a quantitative yield of α-2,4-dichlorophenylmaleimide.

***o*-Methoxyphenylmaleic Anhydride.**—The crude product from maleimide and *o*-anisidine was hydrolyzed directly with aqueous alkali, and the arylmaleic acid was cyclized thermally.[2] The *o*-methoxyphenylmaleic anhydride was isolated by distillation, b.p. 140° (0.2 mm.), and purified by crystallization from methylene chloride, m.p. 135–136°.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.61; H, 4.13.

***m*-Methoxyphenylmaleic Anhydride.**—A similar procedure with *m*-anisidine gave *m*-methoxyphenylmaleic anhydride, m.p. 146–147°.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 65.04; H, 3.88.

Ultraviolet Spectra.—All spectra were measured on a Cary recording spectrophotometer at approximately 10^{-4} *M* concentration. The maleimides and nitriles were dissolved in 95% ethanol, the anhydrides in Phillips Spectro Grade isooctane. The extinction coefficients calculated by Beer's law are believed accurate to within 5%.

Acknowledgments.—Part of this work was supported by the United States Rubber Company. We would like to express our appreciation for this assistance. We are grateful to Dr. D. W. Hein for samples of phenylmaleo- and phenylfumaronitrile and to Prof. L. E. Miller for samples of *p*-methoxyphenylmaleo- and *p*-methoxyphenylfumaronitrile.

ANN ARBOR, MICHIGAN

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[19] Unpublished experiments have shown that the *p*-nitrophenylation of coumarin proceeded in 26% yield with dimethyl sulfoxide solvent, compared to 40–45% in acetone. Hence dimethyl sulfoxide may prove to be a useful solvent for Meerwein reactions in some cases.

[CONTRIBUTION FROM ORGANIC CHEMISTRY SECTION, BALLISTIC RESEARCH LABORATORIES]

Further Studies of the Cleavage of 3-Alkoxypropionitriles with Lithium Aluminum Hydride[1]

BY LOUIS M. SOFFER, MANFRED KATZ AND ELIZABETH W. PARROTTA

RECEIVED JULY 23, 1956

The direct addition reduction of 3-alkoxypropionitriles by lithium aluminum hydride in ether results in 5–10% cleavage at high hydride concentrations (molar ratio of hydride to nitrile, MRHN $\geqslant$ 1) and 52–66% cleavage at low concentrations (MRHN < 1). Reduction in ether by reverse addition, as well as reductions in tetrahydrofuran by both direct and reverse addition lead to high cleavage over a wide MRHN range. Explanations are offered for the varying amounts of hydrogen and parent alcohol produced.

The direct addition (DA) reduction[2] of 3-alkoxypropionitriles with excess lithium aluminum hydride in ether results in 5–10% yields of the parent alcohol, whereas 70–95% yields are obtained from an identical reduction in tetrahydrofuran. The agreement in yields of hydrogen and of alcohol in ether was explained in terms of a reaction of hydride with a hydrogen atom from the α-carbon of the alkoxypropionitrile to produce hydrogen gas and an unstable organoaluminohydride species which cleaved to yield alcohol. This sequence was not satisfactory when applied to the results in tetrahydrofuran because of the excess of hydrogen over alcohol obtained in this solvent. This paper describes additional experiments made at various molar ratios of hydride to nitrile (MRHN) and utilizing both DA and RA procedures.

Results and Discussion

As shown in Table I, runs 1–3, essentially the same yields of hydrogen, alcohol and unsplit amine were obtained at MRHN of 1.1 and 2.0. As the MRHN was lowered below 1, however, there was a surprising increase in the yield of alcohol at the expense of unsplit amine, with a much smaller increase in the amount of hydrogen. It is interesting (runs 5 and 6) that nearly identical results were obtained at MRHN of 0.4 and 0.3, with the only difference being in the amount of alkoxypropionitrile undergoing reaction. In these runs the amount of alcohol produced was greater than the amount of hydride initially present. Therefore, under these conditions, alcohol must result from an additional process to that described above; a probable one is the reaction of one or more of the organoaluminohydride species[3] present with alkoxypropionitrile.

In RA reductions (runs 7–12), where alkoxypropionitrile was present in excess for a considerable portion of each reaction, cleavage was dominant with high yields of hydrogen at all MRHN. This may be attributed to the increasing amount of abstraction arising from the more polar environ-

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[1] L. M. Soffer and E. W. Parrotta, THIS JOURNAL, **76**, 3580 (1954).

[2] Direct addition means that the nitrile was added to the hydride solution. Reverse addition (RA) is the opposite procedure: L. M. Soffer and Manfred Katz, *ibid.*, **78**, 1705 (1956).

[3] For example, $ROCH_2C^{\ominus}HC{\equiv}N$-complex (or reduced version), $ROCH_2CH_2CH{=}N$-complex, $ROCH_2CH_2CH_2N$-complex and RO-complex.

TABLE I

LITHIUM ALUMINUM HYDRIDE REDUCTIONS OF 3-ALKOXYPROPIONITRILES IN ETHER (34°)

Run	Alkoxy-propio-nitrile	Method	Moles hydride per mole nitrile (MR-HN)	Mole % H_2	Mole % alcohol	Mole % un-split amine	Recovery of reacn. products, %
1[a]	*n*-Octyl	DA	2.0	5.1	3.2	90.6	93.8
2[a]	*n*-Butyl	DA	1.1	7.7	7.4	90.6	98.0
3	*n*-Octyl	DA	1.1	9.8	2.3	86.2	88.5
4	*n*-Butyl	DA	0.55	19.2	52.2	36.1	88.3
5	*n*-Octyl	DA	.39	13.2	66.0	21.9	87.9
6[b]	*n*-Butyl	DA	.28	13.3	64.0	22.2	89.0[c]
7[a,d]	*n*-Butyl	RA	1.1	87.8	83.3	8.5	91.9
8[a]	*n*-Octyl	RA	0.81	83.8	82.8	9.8	92.6
9[e]	*n*-Octyl	RA	.55	82.4	75.3	8.0	83.3
10[b]	*n*-Butyl	RA	.41	61.4	81.9	5.9	90.5[f]
11[a,b]	*n*-Octyl	RA	.29	59.4	76.1	6.3	85.2[g,h]
12[b,i]	*n*-Octyl	RA	.28	71.4	80.1	3.0	88.2[j]

[a] Performed by E.W.P. All the remaining experiments were by M.K. [b] Yields of products are based on the amount of alkoxypropionitrile which reacted. [c] 19.9% of 3-(*n*-butyloxy)-propionitrile was recovered. [d] An identical run made at 0° gave similar results (M.K.). [e] When attempted at −70° no reaction occurred and the oxynitrile was recovered. In this run decomposition of complexes and excess hydride was effected with methanol. [f] 15.8% of 3-(*n*-octyloxy)-propionitrile was recovered. [g] 22.0% of 3-(*n*-butyloxy)-propionitrile was recovered. [h] In another run omission of the acidification step during hydrolysis had no effect on product yields. [i] Made at 0°. [j] 30.0% of 3-(*n*-butyloxy)-propionitrile was recovered.

TABLE II

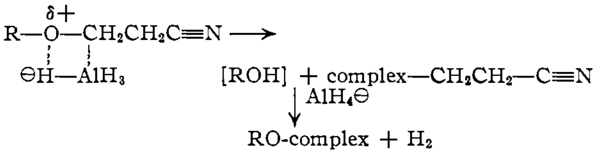
LITHIUM ALUMINUM HYDRIDE REDUCTIONS OF 3-ALKOXYPROPIONITRILES IN TETRAHYDROFURAN (30–35°)

Run	Alkoxy-propio-nitrile	Method	Moles hydride per mole nitrile (MR-HN)	Mole % H_2	Mole % alcohol	Mole % unsplit amine	Recovery of reacn. products, %
1[a]	*n*-Octyl	DA	2.0	102.1	91.3	7.4	98.7
2[a]	*n*-Octyl	DA	1.1	97.9	84.5	4.5	89.0
3	*n*-Butyl	DA	1.1	97.5	68.8	16.8	85.6
4	*n*-Octyl	DA	0.55	64.1	63.0	19.2	82.2
5[b]	*n*-Octyl	DA	0.26	40.8	69.8	14.5	88.4[c]
6	*n*-Octyl	RA	1.1	104.7	85.3	Trace	85.3
7[b]	*n*-Octyl	RA	0.4	59.6	87.4	1.1	88.9[d]
8[b]	*n*-Octyl	RA	0.27	50.5	82.9	0	87.0[e]

[a] Performed by E.W.P. All the remaining experiments were by M.K. [b] Yields of products are based on the amount of alkoxypropionitrile which reacted. [c] 26.2% of 3-(*n*-octyloxy)-propionitrile was recovered. [d] 3.3% of 3-(*n*-octyloxy)-propionitrile was recovered. [e] 24.0% of 3-(*n*-octyloxy)-propionitrile was recovered.

ment than that had in DA reduction.[4] The near equivalence of hydrogen and alcohol at higher MRHN (runs 7–9) supports this view. At lower MRHN (runs 10–12) the yields of alcohol again exceeded that of hydrogen which suggests that some cleavage, without hydrogen production, resulted from the reaction of intermediate species with alkoxypropionitrile. Moderate variations in temperature appear to have little, if any, effect on the course of the reaction. At 1.1 MRHN (run 7) no difference was noted when the reaction was performed at 0°; at 0.3 MRHN (runs 11 and 12) the only significant difference between reaction at 0° and at 34° was in the amount of alkoxypropionitrile consumed. However, at −70° no reaction whatever occurred with 3-(*n*-octyloxy)-propionitrile (run 10), in decided contrast with the successful reduction of simple nitriles to aldehydes (RA, low MRHN, −70°).[5]

The dominant influence of the reaction environment is clearly seen in DA reactions performed in tetrahydrofuran (Table II, runs 1–5) where cleavage was the principal process even though hydride was present in excess for at least a large part of the reduction. However, the excess of hydrogen over alcohol (runs 1–3, 6) is puzzling because it requires that slightly more than one mole of hydrogen be obtained per mole of alkoxypropionitrile cleaved. It is possible that in tetrahydrofuran there is an additional reaction, occurring prior to or simultaneously with abstraction at the α-carbon atom, in which the aluminohydride ion attacks the oxygen atom.[6] A somewhat similar mechanism has been applied to the RA reductions of N,N-disubstituted-α,β-unsaturated amides in ether.[7] At lower MRHN (runs 4 and 5) the yields of hydrogen fell off more rapidly than those of alcohol because hydride was essential for the evolution of hydrogen, whereas alcohol can be produced in an absence of hydride through the reaction of intermediate species with alkoxypropionitrile.



$$\mathrm{R{-}\overset{\delta+}{O}{-}CH_2CH_2C{\equiv}N} \longrightarrow [\mathrm{ROH}] + \mathrm{complex{-}CH_2CH_2{-}C{\equiv}N} \xrightarrow{\mathrm{AlH_4}^{\ominus}} \mathrm{RO\text{-}complex} + \mathrm{H_2}$$

$\ominus\mathrm{H{-}AlH_3}$

In general RA and DA reductions in tetrahydrofuran were quite similar with the possible exception that somewhat more alcohol and less unsplit amine were obtained in RA reduction at a given MRHN (runs 5 and 8).

Experimental[8]

Materials.—The purification of solvents, the preparation of hydride solutions and the properties of 3-alkoxypropionitriles have been described.[1,23]

Reduction of 3-Alkoxypropionitriles.—Experiments were made with 0.10–0.15 mole of alkoxypropionitrile. Identical procedures were used in ether and in tetrahydrofuran, all runs in the latter being made at 30–35°. The RA reduction of 3-(*n*-octyloxy)-propionitrile in ether at 0.29 MRHN follows:

In the apparatus used previously[2] was placed 18.3 g. (0.10 mole) of 3-(*n*-octyloxy)-propionitrile and 150 ml. of anhydrous ether. The dropwise addition of an ether solution containing 0.0287 mole of lithium aluminum hydride resulted in the evolution of 1125 ml. (0.05 mole) of hydrogen. The mixture was carefully decomposed (ice-bath) by the successive additions of 15 ml. of 50% (wt.) sulfuric acid and 50 ml. of water, with an accompanying evolution of 105 ml. of gas. Ether and aqueous phases were separated and the latter was extracted three times with 50-ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. Distillation

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[4] Similar behavior was observed with DA and RA reductions of simple nitriles (reference 3).

[5] L. Friedman, Abstracts, 116th Meeting, American Chemical Society New York, N. Y., Sept., 1949, p. 5M.

[6] It is assumed that the transfer of hydride ion to oxygen is facilitated by a slight positive charge on oxygen induced by the strongly electron-attracting nitrile group.

[7] H. R. Snyder and R. E. Putnam, THIS JOURNAL, **76**, 1894 (1954).

[8] B.p.'s are uncorrected.

yielded 8.35 g. of *n*-octyl alcohol (64.1%, b.p. 48–50° at 0.5 mm., $n^{23}\text{D}$ 1.4288; lit.[9] 98° at 19 mm., $n^{20.5}\text{D}$ 1.4303), 2.9 g. of 3-(*n*-octyloxy)-propionitrile (15.8%, b.p. 84–87° at 0.5 mm., $n^{23}\text{D}$ 1.4329; lit.[1] b.p. 152–153° at 20 mm., $n^{24}\text{D}$ 1.4324) and 0.6 g. of residue.

The aqueous phase from the above separation was made alkaline in the presence of 100 ml. of ether and extracted three times with 50-ml. portions of ether. After drying over sodium sulfate, distillation of the ether extracts yielded 1.0 g. of 3-(*n*-octyloxy)-propylamine (5.3%, 68–70° at 0.5 mm., $n^{24}\text{D}$ 1.4388; lit.[1] 101° at 1 mm., $n^{24}\text{D}$ 1.4383) and 1.4 g. of residue. The recovery of identified products was 85.2%.

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[9] I. Heilbron, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

The Syntheses of Radioactive *o*- and *m*-Chloroacetanilide-Cl^{36}[1]

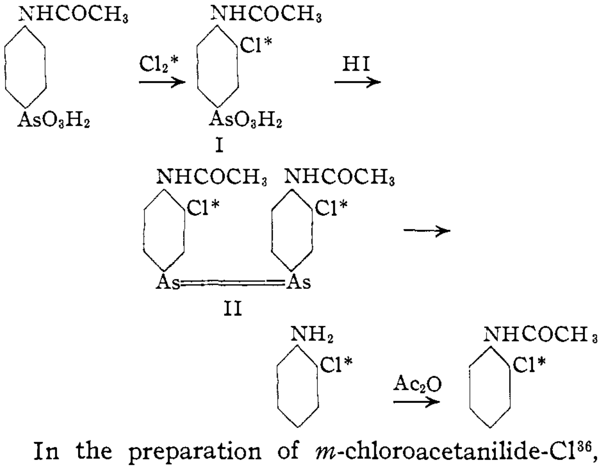
BY MARJORIE P. NEWELL,[2] MARY F. ARGUS AND FRANCIS E. RAY

RECEIVED JULY 13, 1956

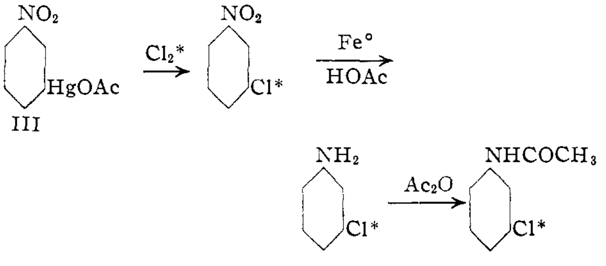
The syntheses of *o*- and *m*-chloroacetanilide-Cl^{36} have been accomplished *via* the chlorination of N-acetylarsanilic acid and *m*-nitrobenzenemercuric acetate, respectively.

To extend comparative studies of the distribution and metabolism of carcinogenic and non-carcinogenic amines and the effect of position substitution on this metabolism, the syntheses of radioactive *o*- and *m*-chloroacetanilide-Cl^{36} were undertaken.[3,4] The Sandmeyer reaction, which is the laboratory synthesis of choice for these compounds, was closed to us since this reaction requires a great excess of chloride ions that would dilute the chlorine-36. We sought syntheses, therefore, that gave better yields based on chlorine.

In developing a synthesis for *o*-chloroacetanilide-Cl^{36} we first used the sulfonic acid and nitro groups to block the *para* position. The removal of the sulfonic group was not accomplished easily and the replacement of the nitro group was accompanied by formation of phenols; hence, we prepared *o*-chloroacetanilide-Cl^{36} by direct chlorination of N-acetylarsanilic acid with subsequent reduction of the arsonic group with hydriodic acid.



In the preparation of *m*-chloroacetanilide-Cl^{36}, it was found that direct chlorination of *m*-nitrobenzene required a catalyst and that this catalyst combined with the unexpendable radioactive chloride ions. Replacement of the carboxyl group of the silver salt of *m*-nitrobenzoic acid by chlorine was also attempted unsuccessfully. We found, however, that *m*-chloronitrobenzene-Cl^{36} could be prepared readily by chlorination of *m*-nitrobenzenemercuric acetate. Reduction of the nitro group followed by acetylation of the amine yielded the desired *m*-chloroacetanilide-Cl^{36}.



Experimental[5]

Preparation of *o*-Chloroacetanilide-Cl^{36}. *o*-Chloro-N-acetylarsanilic Acid-Cl^{36} (I).—Five and two-tenths grams of N-acetylarsanilic acid (0.02 mole) was suspended in 70 ml. of glacial acetic acid and heated to boiling in a modification of Bertheim's method[6] of preparing *o*-chloro-N-acetylarsanilic acid. Chlorine gas (0.04 mole) was obtained in the following manner. Two generators were set up in series to provide the best utilization of the radioactive chlorine. The first generator contained 0.02 mole of active hydrochloric acid (200 μc.) plus 0.02 mole of inactive 6 *N* hydrochloric acid. This acid was oxidized to Cl_2^{36} with permanganate as previously described[3] and was conducted through a drying tube into the suspension of N-acetylarsanilic acid. The Cl_2^{36} generator was swept out with 0.02 mole of inactive chlorine gas from the second generator. The entire system was then swept out with carbon dioxide. As gassing proceeded, the suspension of N-acetylarsanilic acid dissolved completely leaving a clear pale amber solution. This solution was evaporated under reduced pressure at 55–60°. The product was washed twice with water and dried overnight.

Anal. Calcd. for $C_8H_9O_4AsClN$: Cl, 12.1. Found: Cl, 12.3.

o-Chloroaniline-Cl^{36}.—Three and nine-tenths gram of *o*-chloro-N-acetylarsanilic acid-Cl^{36} was suspended in 50 ml. of water in a 200-ml. three-necked flask fitted with a thermometer, stirrer, and condenser with gas trap attached. Stirring was begun and eight molar portions (0.104 mole, 13.68 ml.) of 57% HI was added through the reflux con-

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[1] Supported by Contract AT(40-1)1403 with the Atomic Energy Commission.

[2] Part of this paper is from the thesis by Marjorie P. Newell submitted in partial fulfillment of the requirements for the degree of Master of Science, University of Florida, August, 1954.

[3] J. M. Gryder, M. F. Argus, M. P. Newell and F. E. Ray, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 667 (1954).

[4] F. E. Ray, J. M. Gryder and M. F. Argus, *Proc. Am. Assoc. Cancer Research*, **1**, 39 (1954).

[5] All melting points uncorrected.

[6] A. Bertheim, *Ber.*, **43**, 529 (1910).