Syntheses from 4-Chlorotetrahydropyran

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Received August 3, 1970

The utilization of 4-chlorotetrahydropyran (**1**), which has recently become readily available, as a starting material in organic synthesis was investigated. Nucleophilic displacement of the chlorine atom is difficult, but moderate yields of 4-aminotetrahydropyran (**4**), 4-piperidinotetrahydropyran (**6**), and 4-morpholinotetrahydropyran (**7**) were obtained by treatment with the appropriate amine at 200°. Sodium sulfide gave a low yield of 4-tetrahydropyranyl sulfide (**8**). A Grignard reagent prepared from **1** in tetrahydrofuran reacted normally with cyclohexanone, and Friedel–Crafts alkylation of benzene or toluene with **1** gave 4-phenyltetrahydropyran (**13a**) and 4-tolyltetrahydropyran (**13b**) (as a mixture of isomers) in good yields. Ring cleavage with hydrobromic acid provided 1,5-dibromo-3-chloropentane (**14**) and treatment with acid chlorides gave esters of 3,5-dichloro-1-pentanol (**15**). Synthesis of 3-chloroglutaric acid (**17**) by nitric acid oxidation of **1** was found to be feasible in high yield at low temperature.

The condensation of 1-olefins, paraformaldehyde, and hydrogen halides has provided a convenient one-step synthesis of 3-alkyl-4-halotetrahydropyrans in good yields from readily available starting materials.[1] In view of the ease of preparation of the 4-chloro compounds, the synthetic utility of those compounds was studied with particular emphasis on syntheses based on the parent 4-chlorotetrahydropyran (**1**).

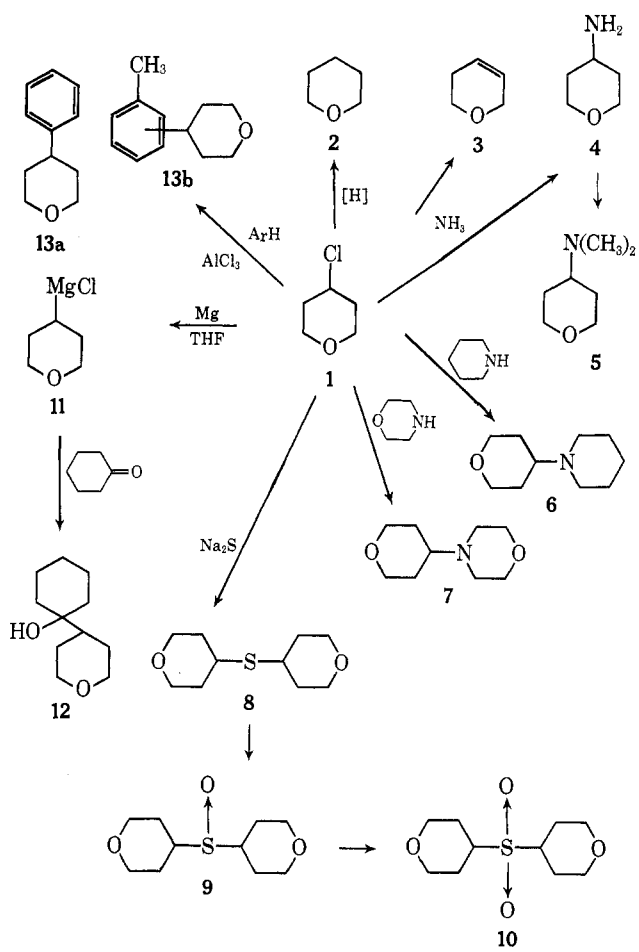
4-Chlorotetrahydropyran is only slightly soluble in water but miscible in all proportions with ether, aliphatic hydrocarbons, aromatic hydrocarbons, and chlorinated solvents. Also soluble in concentrated hydrochloric acid and concentrated sulfuric acid, it can be recovered unchanged upon dilution. Lewis acids such as aluminum chloride, zinc chloride, phosphorus pentachloride, boron fluoride, and stannic chloride dissolve readily in **1** to give deeply colored solutions from which **1** can be recovered on treatment with water. Sulfur trioxide forms stable complexes with both **1** and the 3-alkyl-4-chlorotetrahydropyrans; these may be of particular utility as sulfonating agents since, unlike the sulfur trioxide complexes with dimethylformamide and dioxane, the complexing agent can be readily recovered from aqueous solutions.

In a study of compounds available from **1**, two types of reactions were available, *i.e.*, syntheses based on replacement of the chlorine atom, and sequences based on the cleavage of the tetrahydropyran ring. Outlined in Scheme I are a number of compounds prepared which retained the tetrahydropyran ring.

Sodium and methanol reduction of the halotetrahydropyrans to the tetrahydropyran was described previously.[1] In addition, catalytic hydrogenation over palladium on carbon at 1000 psig and 175° provided good yields of tetrahydropyran (**2**) from **1** and 3-methyltetrahydropyran from 4-chloro-3-methyltetrahydropyran. Dehydrochlorination of **1** to 3,6-dihydro-2*H*-pyran (**3**) in nearly quantitative yields was readily effected with alcoholic potassium hydroxide, by distillation from potassium fluoride in ethylene glycol, or catalytically over sodium borate on Celite[2] at 430°. Pyrolysis of **1** in a quartz reactor in a flow system at 500° also provided good yields of **3** at *ca.* 20% conversion levels. At 400° **1** was thermally stable; under identical conditions cyclohexyl chloride was nearly completely dehydrochlorinated.

Nucleophilic displacement reactions of **1** were also

SCHEME I



studied, and, as expected, rather stringent conditions were required and considerable dehydrochlorination occurred as a side reaction. 4-Aminotetrahydropyran (**4**) was formed in 33% yield by treatment with a large excess of ammonia in 85% aqueous isopropyl alcohol at 200° in an autoclave. The use of pure isopropyl alcohol gave a low conversion and reaction in ether solution in the presence of potassium hydroxide gave almost exclusively dihydropyran (**3**). Methylation of **4** using the Eschweiler–Clarke procedure[3] provided 4-dimethylaminotetrahydropyran (**5**). Displacement of the chlorine in **1** was also effected by treatment with piperidine or morpholine at 200° in ethanol solution in an autoclave to provide 4-piperidino-

(1) P. R. Stapp, *J. Org. Chem.*, **34**, 479 (1969).

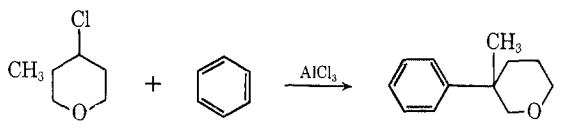
(2) We wish to thank Mr. V. C. Vives for carrying out this experiment.

(3) M. L. Moore, *Org. React.*, **5**, 301 (1949).

tetrahydropyran (6) and 4-morpholinotetrahydropyran (7), respectively, in moderate yields. Reaction of 1 with sodium sulfide in boiling ethanol was slow; in the higher boiling methoxyethanol, however, a low yield of 4-tetrahydropyranyl sulfide (8) was obtained. No improvement in yield was noted when *N*-methylpyrrolidone was used as solvent. The sulfide was oxidized to the sulfoxide (9) and the sulfone (10) in high yield with hydrogen peroxide in acetic acid.[4]

Formation of Grignard reagents from 1 is useful in the introduction of the 4-tetrahydropyranyl moiety into various substrates. The use of 1 and magnesium in tetrahydrofuran led to the formation of 4-tetrahydropyranylmagnesium chloride (11), which, after reaction with cyclohexanone and hydrolysis, led to the crystalline product 12. While formation of Grignard reagents from 3-alkyl-4-chlorotetrahydropyrans was not investigated, it is assumed that suitable conditions would lead to analogous reagents.

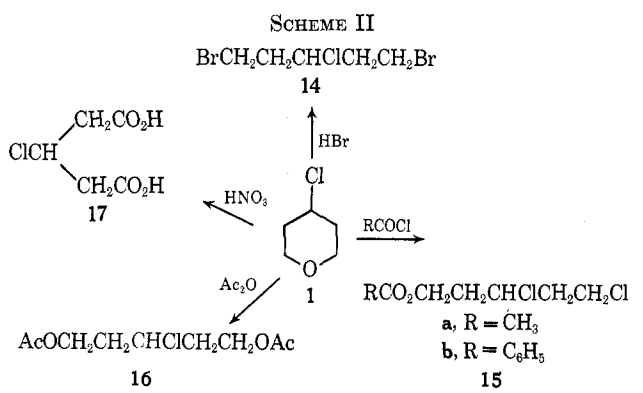
The behavior of 1 in Friedel–Crafts reactions was also examined. With aluminum chloride as the catalyst, benzene and toluene were smoothly alkylated to give 91 and 76% yields of 4-phenyltetrahydropyran (13a) and 4-tolyltetrahydropyran (13b) as a mixture of ortho, meta, and para isomers. A similar alkylation of benzene with *cis,trans*-4-chloro-3-methyltetrahydropyran, under conditions chosen to give about a 50% conversion, gave the rearranged product, 3-methyl-3-phenyltetrahydropyran. The recovered 4-chloro-3-



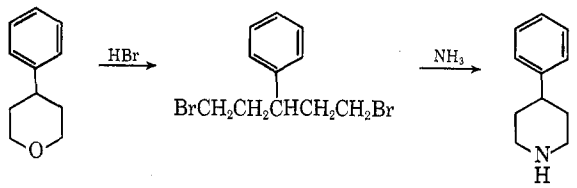
methyltetrahydropyran had the same cis/trans ratio as the starting material.

Investigation of ring opening with chemical reagents to provide polyfunctional intermediates also appeared to present possibilities for the utilization of 1 in synthesis. Scheme II illustrates a number of reactions of this type.

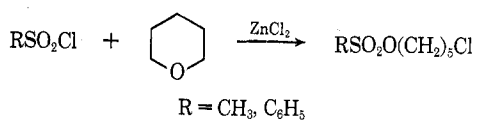
SCHEME II



Reaction of 1 with a 48% hydrobromic acid–concentrated sulfuric acid mixture[5] at reflux for 2.5 hr gave a 72% yield of 1,5-dibromo-3-chloropentane (14). The use of constant-boiling hydrobromic acid alone gave low conversions under the same conditions. The analogous cleavage with hydrochloric acid or zinc chloride–hydrochloric acid gave only very small amounts of 1,3,5-trichloropentane even after extended reaction times. Similar cleavage of 4-phenyltetrahydropyran (13a) with 48% hydrobromic acid gave 64% of 1,5-dibromo-3-phenylpentane which, upon treatment with a 100 mol excess of ammonia, gave the expected 4-phenylpiperidine. The conversion of tetrahydropyran



to 5-chloropentyl esters by reaction with acid chlorides in the presence of zinc chloride has been previously reported.[6] This reaction was extended to include the preparation of 3,5-dichloro-1-pentyl acetate (15a) and 3,5-dichloro-1-pentyl benzoate (15b) from 1 and acetyl chloride or benzoyl chloride in good yields. A related reaction, which has apparently not been previously described, is the conversion of tetrahydropyran to the corresponding 5-chloropentyl sulfonates upon treatment with either methanesulfonyl chloride or benzenesulfonyl chloride and zinc chloride. 5-Chloropentyl methanesulfonate was obtained as a rather unstable yellow oil and characterized by its nmr spectrum but decomposition of the benzenesulfonate occurred on attempted distillation. Although this procedure was



not applied to 1, there seems little doubt that the corresponding 3,5-dichloropentyl sulfonates could be prepared in a similar fashion.

Acetic anhydride reacted with 1 in the presence of zinc chloride at elevated temperature with either an excess of anhydride or 1 as solvent, to give 20 to 40% yields of 1,5-diacetoxy-3-chloropentane (16). The diacetate (16) was always contaminated with 15a (by glpc).

Nitric acid oxidation of 1 according to a procedure for the oxidation of tetrahydropyran to glutaric acid gave only 30% of the known 3-chloroglutaric acid (17). A more detailed study developed conditions (extended reaction time, low temperature) which raised the yield to 95%.

In summary, synthetic procedures were developed to convert 4-chlorotetrahydropyran to a variety of previously rather inaccessible compounds. In most cases, more detailed study of the individual synthesis to optimize conditions, should also result in increased yields. Although most of these experiments were conducted using only 1 as the starting material, these synthetic procedures should be equally adaptable to the entire family of 3-alkyl-4-halotetrahydropyrans.

Experimental Section

4-Aminotetrahydropyran (4).—A mixture of 150 g (1.25 mol) of 1, 45 ml of water, 255 ml of isopropyl alcohol, and 178.1 g (10.5 mol) of ammonia was heated 5 hr at 200° in a stirred, stainless

(4) D. Swern, *Chem. Rev.*, **45**, 33 (1949).

(5) D. W. Andrus, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., 1955, p 692.

(6) D. G. Jones and A. W. C. Taylor, *Quart. Rev., Chem. Soc.*, **4**, 195 (1950).

steel autoclave. The autoclave was vented and the reaction mixture was treated with 75 g of solid sodium hydroxide, stirred for 1 hr, filtered, and fractionated. There was obtained 41.1 g (33%) of **4**, bp 148–151° [lit.[7] bp 52–53° (13 mm)].

4-Dimethylaminotetrahydropyran (5).—A mixture of 10.1 g (0.1 mol) of **4**, 23 g of 97% formic acid, and 18 g of 36.6% formalin was refluxed for 12 hr, cooled, treated with 10 ml of concentrated hydrochloric acid, and evaporated to dryness. The residue was dissolved in water, made strongly alkaline with 50% potassium hydroxide solution, and saturated with potassium carbonate. The product was extracted into ether and dried over KOH pellets, the ether was removed, and the product was distilled to give 11.4 g (89%) of colorless oil, bp 71–72° (26 mm) [lit.[8] bp 58–59° (12 mm)].

4-Piperidinotetrahydropyran (6).—A mixture of 115 g (0.95 mol) of **1**, 300 ml of 95% ethanol, 128 g (1.5 mol) of piperidine, and 83.8 g (0.6 mol) of anhydrous potassium carbonate was heated at 200° for 24 hr in the autoclave. The reaction mixture was filtered and distilled to a head temperature of 110° to remove solvent and excess piperidine. The residue was taken up in ether and filtered again, the ether was removed, and the residue was distilled under reduced pressure. There was obtained 43.2 g (27%) of colorless liquid, bp 111–115° (12 mm), n^{20}D 1.4864.

Anal. Calcd for $C_{10}H_{19}NO$: C, 71.0; H, 11.2; N, 8.3. Found: C, 70.9; H, 11.5; N, 8.5.

4-Morpholinotetrahydropyran (7).—The reaction was carried out as for the piperidino compound using 130 g (1.5 mol) of morpholine in lieu of the piperidine. After work-up and removal of solvent and excess morpholine, the residue crystallized. Recrystallization from ether–pentane gave 46.2 g (27%) of colorless, dense needles, mp 62–64°.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.2; H, 10.0; N, 8.2. Found: C, 62.9; H, 9.9; N, 7.9.

4-Tetrahydropyranyl Sulfide (8).—A mixture of 60 g (0.5 mol) of **1**, 60 g (0.25 mol) of sodium sulfide nonahydrate, and 300 ml of methoxyethanol was refluxed with stirring for 24 hr. The reaction mixture was filtered and the inorganic salts were washed thoroughly with dry ether. Removal of the solvents gave 13.3 g of oil which was distilled, bp 99–101° (0.5 mm), and 10.8 g was recovered.

Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.4; H, 8.9; S, 15.8. Found: C, 59.4; H, 9.1; S, 15.5.

4-Tetrahydropyranyl Sulfoxide (9).—To a warm solution of 10 g (0.05 mol) of **8** in 100 ml of glacial acetic acid was added 6.6 ml of 30% hydrogen peroxide over 30 min. The acetic acid was removed on a rotary evaporator and the residue was recrystallized from methanol to give 8.7 g (80%) of **10**, as colorless platelets, mp 140–142°.

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.0; H, 8.3; S, 14.7. Found: C, 54.8; H, 8.0; S, 14.6.

4-Tetrahydropyranyl sulfone (10) was prepared similarly using 13 ml of 30% hydrogen peroxide. The product was recrystallized from 95% ethanol to give 11.1 g of colorless crystals, mp 156–157°.

Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.2; H, 7.7; S, 13.7. Found: C, 50.9; H, 7.8; S, 14.0.

1-(4-Tetrahydropyranyl)cyclohexanol (12).—A Grignard reagent was prepared in the usual manner from 36 g (0.3 mol) of **1** and 7.3 g (0.3 g-atom) of magnesium turnings in 150 ml of dry tetrahydrofuran. Most of the magnesium was consumed. A solution of 29.4 g (0.3 mol) of cyclohexanone in 50 ml of dry tetrahydrofuran was added dropwise over 30 min, refluxed for 30 min, cooled, and hydrolyzed with saturated ammonium chloride. After extraction into ether and drying, the product was fractionated to give 24.1 g (42%) of material, bp 95–125° (0.2 mm), which crystallized. Recrystallization of an 11-g portion from heptane gave 7.0 g of colorless crystals, mp 68–69°.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.8; H, 10.9. Found: C, 71.7; H, 10.9.

Preparation of 4-Phenyltetrahydropyran (13a).—To 53.4 g (0.4 mol) of anhydrous aluminum chloride and 200 ml of dry benzene was added 42.2 g (0.35 mol) of **1** in 50 ml of dry benzene over a 20-min period. The reaction was moderated from time to time when HCl evolution was too rapid by cooling in an ice bath. After the exothermic reaction had subsided, the reaction was stirred for 1 hr at room temperature and poured over 600 g of crushed ice. The product was extracted into ether and dried, and the ether was removed to leave a crystalline solid which was recrystallized from aqueous ethanol to give 38.5 g of colorless platelets, mp 48–49° (lit.[9] mp 46–47°), and a second crop of 13 g of slightly yellow material, mp 42–46°, or a total yield of 51.5 g (91%).

4-Tolyltetrahydropyran (13b).—Treatment of a toluene suspension of aluminum chloride with **1** using identical conditions and quantities gave, after work-up and distillation, 46.9 g (76.4%) of colorless oil, bp 88–90° (0.6 mm), n^{20}D 1.5295.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 81.8; H, 9.1.

The nmr spectrum of **13b** had methyl resonances at −131 and −133 Hz (relative to TMS) in a ratio of 37:63 ascribed to the para isomer and a mixture of ortho and meta, respectively. The infrared spectrum also was indicative of a mixture with strong adsorption at 695, 720, 749, 781, and 812 cm^{-1}. A similar reaction at 5–10° gave incomplete reaction with recovery of 70% of unreacted **1** after 2 hr. The nmr spectrum indicated the product to contain 44% para and 56% ortho and meta.

3-Methyl-3-phenyltetrahydropyran was prepared by reaction of 67.3 g (0.5 mol) of *cis,trans*-4-chloro-3-methyltetrahydropyran, 300 ml of benzene, and 70 g (0.52 mol) of aluminum chloride at 50–60° for 30 min. Distillation of the products after work-up gave 43.0 g of unreacted *cis,trans*-4-chloro-3-methyltetrahydropyran (*ca.* 55% trans by glpc on a 10 ft × 0.25 in. UCON-LB-550-X on Chromosorb P column), bp 48–51° (10 mm), and 22.4 g (77% based on reacted chloride) of 3-methyl-3-phenyltetrahydropyran: bp 80–81° (0.5 mm); n^{20}D 1.5293; nmr ($CDCl_3$) δ 6.95–7.5 (m, 5, Ar **H**), 3.25–4.0 (m, 4, CH_2O), 1.2–2.2 (m, 4, CH_2), and 1.1 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 81.7; H, 9.0.

1,5-Dibromo-3-chloropentane (14).—To a warm (40°) solution, prepared by addition of 120 ml of concentrated sulfuric acid to 510 ml of 48% hydrobromic acid was added 120.5 g (1.0 mol) of **1**. The mixture became warmer (60°) and was mixed by swirling and refluxed for 2.5 hr. The dark reaction mixture was cooled, poured over 1 kg of crushed ice, and extracted into methylene chloride. After drying and removal of solvent, the product was distilled through a short column and 167.4 g (72%) of crude product, bp 120–151° (30 mm), was obtained. This was refractionated and a center cut, bp 108–110° (5 mm), n^{20}D 1.5363, was analyzed.

Anal. Calcd for $C_5H_9Br_2Cl$: C, 22.7; H, 3.4; Br, 60.5; Cl, 13.4. Found: C, 22.4; H, 3.5; Br, 60.9; Cl, 13.2.

1,5-Dibromo-3-phenylpentane.—A mixture of 500 ml of 48% hydrobromic acid and 90 g (0.55 mol) of **13a** was refluxed with stirring for 17 hr. After work-up and distillation there was obtained 110.1 g (64%) of slightly yellow oil, bp 117–119° (0.5 mm).

Anal. Calcd for $C_{11}H_{14}Br_2$: C, 43.1; H, 4.6; Br, 52.3. Found: C, 43.41; H, 4.6; Br, 51.9.

4-Phenylpiperidine.[10]—A mixture of 10 g (0.033 mol) of 1,5-dibromo-3-phenylpentane, 30 ml of isopropyl alcohol, and 112 g (6.6 mol) of ammonia was heated 5 hr at 110° in a rocking autoclave. The reaction mixture was treated with 100 ml of 5% sodium hydroxide solution and extracted with chloroform. After drying the solvent was removed to leave 4.6 g (87%) of crystalline solid which was recrystallized from pentane to give pale yellow crystals, mp 60–62° (lit.[11] 57–60°).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.9; H, 9.4; N, 8.7; neut equiv, 161. Found: C, 82.0; H, 9.8; N, 8.8; neut equiv, 165.

3,5-Dichloro-1-pentyl Acetate (15a).—A mixture of 60.3 g (0.5 mol) of **1**, 5 g of anhydrous zinc chloride, 100 ml of carbon tetrachloride, and 39.8 g (0.5 mol) of acetyl chloride was refluxed with stirring for 3 hr and allowed to stand overnight. Unreacted acetyl chloride was hydrolyzed with 50 ml of water, the layers were separated, and the organic material was washed with water, sodium bicarbonate solution, and dried. After removal of solvent, the residue was fractionated to give 36.1 g of unreacted **1**, bp 64–66° (38 mm), 3.2 g of an intermediate fraction, bp 56–121° (13 mm), and 27.8 g (78%) of product, bp 122–125° (13 mm): n^{20}D 1.4596; nmr ($CDCl_3$) δ 4.0–4.45 (m, 3, CHCl and CH_2Cl),

(7) V. Prelog, E. Cerkovnikov, and G. Ustricev, *Justus Liebigs Ann. Chem.*, **535**, 37 (1938).

(8) E. Cerkovnikov and V. Prelog, *Chem. Ber.*, **74B**, 1648 (1941).

(9) M. G. J. Beets and H. van Essen, *Recl. Trav. Chim. Pays-Bas*, **76**, 1009 (1957).

(10) We wish to thank Mr. R. P. Williams for carrying out this experiment.

(11) C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 2459 (1943).

3.6–3.85 (t, 2, OCH_2), and 1.85–2.20 (m, 7, CH_2CH_2 overlapping a singlet at 2.05, CH_3).

Anal. Calcd for $C_7H_{12}Cl_2O_2$: C, 42.3; H, 6.0. Found: C, 42.5; H, 6.2.

3,5-Dichloro-1-pentyl benzoate (15b) was prepared similarly in 74% yield, bp 131–135° (0.2 mm), $n^{20}D$ 1.5288.

Anal. Calcd for $C_{12}H_{14}Cl_2O_2$: C, 55.4; H, 5.4; Cl, 26.9. Found: C, 55.2; H, 5.4; Cl, 26.8.

5-Chloropentyl Methanesulfonate.—A mixture of 128 g (1.49 mol) of tetrahydropyran, 114.5 g (1.0 mol) of methanesulfonyl chloride, and 10 g of anhydrous zinc chloride was refluxed under nitrogen for 3 hr. The reaction mixture was taken up in ether, washed with water, and dried, and the ether was removed. The residue was distilled to give 101.4 g (51%) of bright yellow oil, bp 121–124° (0.5 mm), which darkened rapidly: nmr ($CDCl_3$) δ 4.2 (t, 2, $SO_2OCH_2CH_2$), 3.6 (t, 2, $-CH_2Cl$), 3.0 (s, 3, CH_3SO_2O), and 1.3–2.15 (m, 6, $-CH_2CH_2CH_2-$).

3-Chloroglutaric Acid (17).—To 200 ml of concentrated nitric acid at 80° was added a few drops of 1. After the reaction had initiated, the oxidation solution was cooled and 40 g (0.33 mol) of 1 was added dropwise at 30–40° over a 3-hr period. The reaction mixture was stirred an additional 18 hr at 20°, and the excess nitric acid was removed on a rotary evaporator at 20°. The resulting solid was dried over phosphorus pentoxide in a vacuum desiccator to give 52 g (95%) of colorless 3-chloroglutaric acid, mp 125–126° (lit.[12] mp 125–126°).

Anal. Calcd for $C_5H_7ClO_4$: C, 36.1; H, 4.2; Cl, 21.3; neut equiv, 83.3. Found: C, 36.2; H, 4.4; Cl, 21.5; neut equiv, 83.4.

Registry No.—**1**, 1768-64-5; **6**, 27070-15-1; **7**, 27070-16-2; **8**, 27070-17-3; **9**, 27070-18-4; **10**, 27070-19-5; **12**, 27070-20-8; **13b**, 27054-52-0; **14**, 27111-66-6; **15a**, 27070-21-9; **15b**, 27070-22-0; 3-methyl-3-phenyltetrahydropyran, 27070-23-1; 1,5-dibromo-3-phenylpentane, 27070-24-2; 5-chloropentyl methanesulfonate, 4337-21-7.

Acknowledgment.—We wish to thank Dr. J. C. Randall and Mrs. Joy Buell for recording the nmr spectra and Messrs. G. R. Herrington and W. F. Bowen for their technical assistance.

(12) W. Triebs and H. Walthee, *Chem. Ber.*, **88B**, 396 (1955).

The Redox Cleavage of the Sulfur–Sulfur Bond and Carbon–Sulfur Bond in Tetramethylthiuram Disulfide by *N*-Benzyl-1,4-dihydronicotinamide

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Received June 17, 1970

The interaction between *N*-benzyl-1,4-dihydronicotinamide and *N,N,N',N'*-tetramethylthiuram disulfide in ethanol at room temperature in the dark has led to the formation of *N*-benzyl-3-carbamylpyridinium *N,N*-dimethyldithiocarbamate, carbon disulfide, and possibly *N,N*-dimethylperthiocarbamate. The mode of formation and the nature of these salts are discussed.

In an earlier study we have proposed[2] that the cleavage of the sulfur–sulfur bond in diphenyl disulfide by *N,N*-dimethylaniline and by ethanolamine may proceed by a one-electron transfer mechanism, analogous to the redox reaction between hydrogen peroxide and ferrous ion.[3] The corresponding thiyl radical, mercaptide ion, and amine cation radical are formed.[2]

$$ArS—SAr + R_3N: \rightleftharpoons R_3N\cdot^+ \cdots ArS^- + ArS\cdot$$

In the extension of this study, we have examined the reactions between *N*-benzyl-1,4-dihydronicotinamide with *N,N,N',N'*-tetramethylthiuram disulfide and monosulfide and wish to report these findings.

The reports by Westheimer and others on the oxidation of 1,4-dihydropyridines by certain carbonyl compounds[4,5] and by olefinic double bonds[6] and further on the oxidation of 1-alkyl-1,4-dihydronicotinamide by malachite green[7] and thiobenzophenone[8] have led to information relevant to the biological oxidation–reduction involving the coenzyme, nicotinamide–adenine nucleotide (NAD) and its reduced form (NADH).

These reactions appear to proceed by an ionic hydride transfer mechanism. However, free-radical mechanisms were not ruled out since *N*-alkyl-1,4-dihydronicotinamide reduces α,α-diphenyl-β-picrylhydrazyl[8] and quinone[9] which are indeed free-radical reactions. The free-radical mechanism has been further enhanced by other findings of Westheimer and coworkers on the photochemical reduction of bromotrichloromethane by derivatives of 1,4-dihydropyridine[10] and the isolation of stable pyridinyl free radicals by Kosower.[11] Another report on the oxidation of 3,5-dimethyl-2,4-dicarbethoxy-1,4-dihydropyridine by 2-mercaptobenzophenone suggests that a thiyl radical intermediate is involved in this transformation.[12]

Results and Discussion

Reduction of Tetramethylthiuram Disulfide (TMTD) with *N*-Benzyl-1,4-dihydronicotinamide.—*N*-Benzyl-1,4-dihydronicotinamide reacts with an equimolar quantity of TMTD in absolute ethanol at room temperature in the dark to afford two products with ultraviolet absorption maxima at 410 and 435 mμ, respectively. A trace amount of carbon disulfide was also

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(4) R. H. Abeles and F. H. Westheimer, *J. Amer. Chem. Soc.*, **80**, 5459 (1958).

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