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The Reaction of α Olefins with Paraformaldehyde and Hydrogen Halides. A Novel Tetrahydropyran Synthesis

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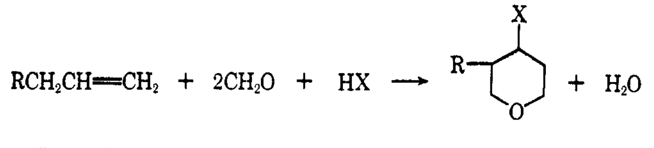
A new reaction has been discovered in which α olefins are condensed with paraformaldehyde and hydrogen halides to give 3-alkyl-4-halotetrahydropyrans. The best yields using hydrogen chloride as the halide component were obtained at −60 to −70°. Isolation of an intermediate homoallylic alcohol provides substantiation of a proposed mechanism.

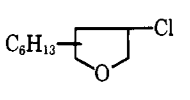
The condensation of olefins with formaldehyde, known as the Prins reaction, was discovered in 1899, and several excellent reviews have been published on the subject.[1] Much of the early work on the condensation of formaldehyde with olefins has been carried out in either water or acetic acid solution using mineral acids as catalysts and, depending on such factors as olefin structure, ratios of reactants, temperature, etc., a variety of compounds can be produced. The primary products are normally 1,3-dioxanes, 1,3-glycols, unsaturated alcohols, and alcohols derived from hydration of the olefin, as well as products obtained either from acid-catalyzed polymerization of the olefin or higher formaldehyde derived condensation products. In the considerable volume of literature on the Prins reaction it is readily apparent, with certain exceptions, that the use of aqueous systems and mineral acid catalysts for the condensation of olefins with formaldehyde leads to complex mixtures. Study of modifications of the Prins reaction in substantially anhydrous media has led to the development of a new reaction in which 1-olefins are condensed with paraformaldehyde and hydrogen halides to give 3-alkyl-4-halotetrahydropyrans.

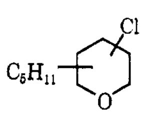


Reaction of gaseous hydrogen chloride with a suspension of paraformaldehyde in 1-octene at 0° gave a major product which showed no hydroxyl adsorption in the infrared spectrum, and upon elemental analysis and molecular weight determination was found to have the empirical formula $C_{10}H_{19}ClO$. Small quantities of water were also formed, presumably *via* the reaction

$$C_8H_{16} + 2CH_2O + HCl \longrightarrow C_{10}H_{19}ClO + H_2O$$

A substantial high boiling residue was also obtained along with considerable quantities of unchanged 1-octene, and small amounts of 2-chlorooctane and a chloro alcohol. Glpc analysis of the major product showed it to be a mixture of two isomers and the infared spectrum showed a strong ether adsorption at 9.15 μ, with no other functional group present. The chlorine in this isomer mixture was not reactive to alcoholic silver nitrate and the nmr spectrum indicated four methylene protons adjacent to an ether linkage, $-CH_2OCH_2-$, and confirmed the absence of a chlorine α to an ether function. These data, along with previous reports[2] of isolation of tetrahydrofuran and tetrahydropyran derivatives from conventional Prins reactions, made it seem likely that this major product was a mixture of *cis/trans* isomers of either a chlorohexyltetrahydrofuran or a chloroamyltetrahydropyran with the chlorine atom occupying a nonreactive β (or γ) position. Confirmation of this reaction product as





being a *cis/trans* isomer mixture was afforded by reduction with sodium and methanol to a single homo-

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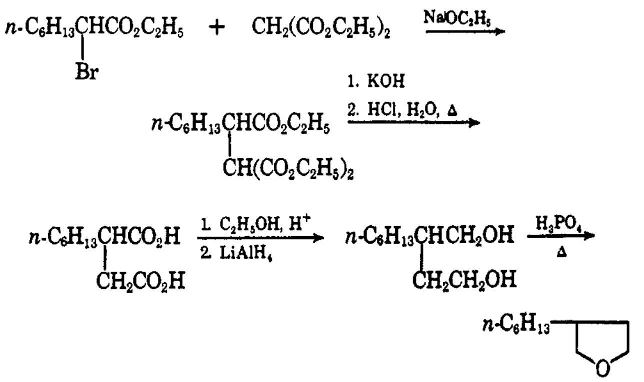
[1] (a) E. Arundale and L. A. Mikesaka, *Chem. Rev.*, **51**, 505 (1952); (b) B. T. Brooks, "The Chemistry of Petroleum Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1955, p 455; (c) C. W. Roberts in "Friedel-Crafts and Related Reactions," G. A. Olah, Ed., Vol. II, Interscience Publishers, New York, N. Y., 1964, p 1175; (d) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1964, p 415.

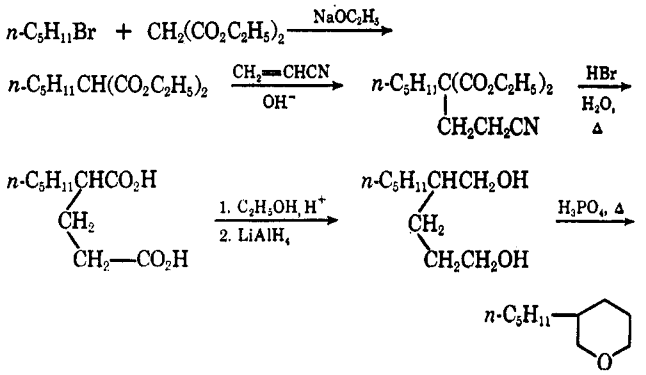
[2] (a) N. A. LeBel, R. N. Liesemer, and E. Mehmedbasich, *J. Org. Chem.*, **28**, 615 (1963); (b) L. Heslinga and M. von Gorkom, *Rec. Trav. Chim.*, **85**, 293 (1966).

geneous product, having an empirical formula $C_{10}H_{20}O$. Neither the nmr spectrum nor the mass cracking pattern of this reduction product was definitive enough to distinguish between a tetrahydrofuran or tetrahydropyran; therefore, authentic samples of 3-*n*-hexyltetrahydrofuran (Scheme I) and 3-*n*-amyltetrahydropyran (Scheme II) were synthesized for direct comparison. Infrared and nmr spectra, mass cracking patterns and glpc retention times of 3-*n*-amyltetrahydropyran and the reduction product from 1-octene were identical in every respect and indicated the chlorinated product to be a *cis/trans*-3-*n*-amylchlorotetrahydropyran.[3]

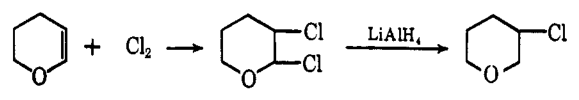
SCHEME I

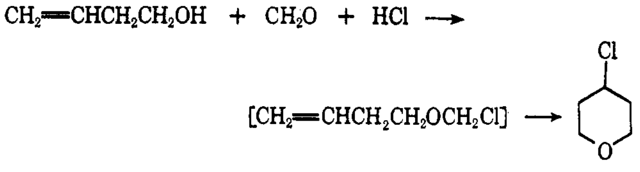


SCHEME II

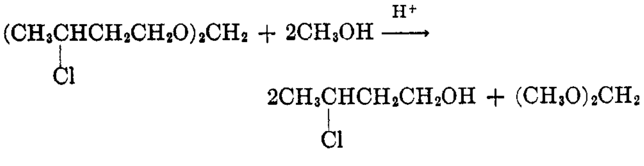


Attention was next turned to the simpler olefin, propylene, in order to facilitate identification of the position of the chlorine substituent. Propylene was condensed into a suspension of paraformaldehyde in methylene chloride at Dry Ice–acetone temperature and an excess of hydrogen chloride was introduced through a dispersion tube at atmospheric pressure. Uptake was rapid, and after work-up and fractionation, an approximately 50% yield of a compound having an empirical formula C_5H_9ClO was obtained. This compound was a single isomer by glpc and the infrared spectrum was very similar to the product derived from 1-octene. Nmr and alcoholic silver nitrate again indicated that the product was not an α-chloro ether and reduction with sodium and amyl alcohol or catalytic hydrogenation over palladium on carbon gave a single compound whose physical properties and infrared spectrum were identical with an authentic sample of tetrahydropyran. With the structure of the major propylene condensation product now established as a chlorotetrahydropyran, the position of the chlorine was determined by synthesis of authentic samples of 3- and 4-chlorotetrahydropyran for comparison since the nmr spectrum and lack of reactivity had eliminated 2-chlorotetrahydropyran from consideration. 3-Chlorotetrahydropyran was prepared as outlined[4] and 4-chlorotetrahydropyran was synthesized by condensation of 3-buten-1-ol with formaldehyde and hydrogen chloride to the unstable chloromethyl ether which cyclized spontaneously.[5] Comparison of physical properties, glpc retention times, and infrared, nmr, and mass spectra unequivocally established that the product from propylene was 4-chlorotetrahydropyran.





In the condensation of propylene with paraformaldehyde and hydrogen chloride, a number of other products were identified in addition to 4-chlorotetrahydropyran. A small quantity (less than 5%) of 4-methyl-1,3-dioxane was inferred to be present by comparison of glpc retention times with an authentic sample, and distillation of the heavy residue gave a 20–25% yield of a high boiling product having an empirical formula $C_9H_{18}Cl_2O_2$. The latter compound was tentatively assigned the structure bis(3-chloro-1-butoxy)methane on the basis of the mass spectrum and nmr spectrum (see Experimental Section). Confirmation was afforded by methanolysis to the known[6] 3-chloro-1-butanol and characterization as the 3,5-dinitrobenzoate ester. Subsequent experiments established that, if the reaction was conducted using lower mole ratios of formaldehyde to propylene, free 3-chloro-1-butanol was formed at the expense of the formal. In summary, the



$$(\mathrm{CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_2O})_2\mathrm{CH_2} + 2\mathrm{CH_3OH} \xrightarrow{\mathrm{H^+}} 2\mathrm{CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_2OH} + (\mathrm{CH_3O})_2\mathrm{CH_2}$$

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[3] Throughout this work 3-alkyl-4-halotetrahydropyrans are *cis/trans* isomer mixtures. In most cases, the mixtures were resolvable into two components on a nonpolar Ucon chromatographic column with the first peak comprising 60–85% of the total. If the assumption is made that the lower boiling isomer elutes first on this column, it seems probable that the major constituent is the *trans* isomer: see L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950).

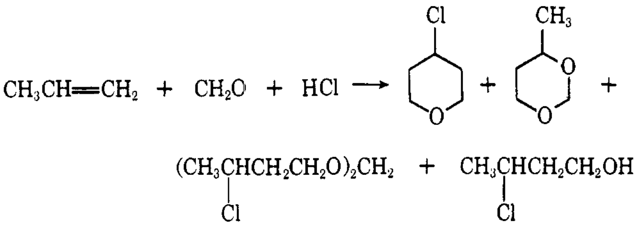
[4] L. Crombie, J. Gold, S. H. Harper, and B. J. Stokes, *ibid.*, 136 (1956).

[5] J. Colonge and P. Boisde, *Bull. Soc. Chim. Fr.*, **23**, 824 (1956).

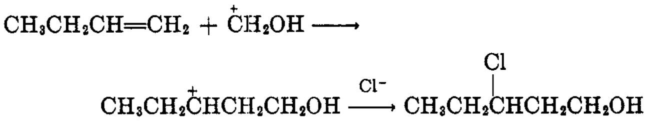
[6] S. Searles, Jr., K. A. Pollart, and F. Block, *J. Amer. Chem. Soc.*, **79**, 952 (1957).

products shown in Scheme III were observed in the reaction of propylene with paraformaldehyde and hydrogen chloride at −65°.

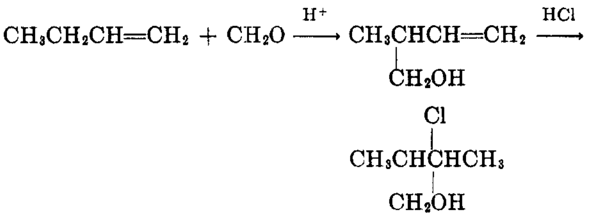
SCHEME III



At this point one element of structural uncertainty remained to be cleared up. Disregarding for the moment the mechanism of formation of 3-alkyl-4-chlorotetrahydropyrans from 1-olefins, there still remained the question of the structure of the by-product 3-chloro-1-alkanols from olefins other than propylene. Using 1-butene as an example, if the adduct were formed by initial addition of a protonated formaldehyde to the double bond, followed by capture of a chloride ion, the resulting product would be 3-chloro-1-pentanol (or the formal). However, if condensation of formaldehyde occurred at an allylic position, followed by simple Markovnikov addition of hydrogen chloride to the double bond, the alcohol would have the structure 3-chloro-2-methyl-1-butanol. Methanolysis of the by-product formal from a 1-butene reaction gave essentially pure 3-chloro-1-pentanol whose structure was established conclusively by its nmr spectrum (see Experimental Section).



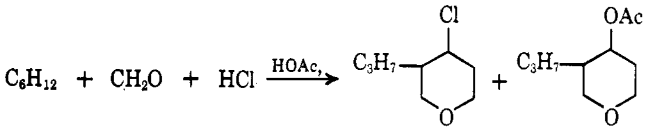
$$CH_3CH_2CH{=}CH_2 + \overset{+}{C}H_2OH \longrightarrow CH_3CH_2\overset{+}{C}HCH_2CH_2OH \xrightarrow{Cl^-} CH_3CH_2\overset{Cl}{\overset{|}{C}}HCH_2CH_2OH$$



$$CH_3CH_2CH{=}CH_2 + CH_2O \xrightarrow{H^+} CH_3\underset{CH_2OH}{\underset{|}{C}}HCH{=}CH_2 \xrightarrow{HCl} CH_3CH\underset{\underset{CH_2OH}{|}}{\overset{\overset{Cl}{|}}{C}}HCH_3$$

Concurrent with the structure determinations outlined above, a brief survey of the effect of temperature on the yield of 4-chloro-3-propyltetrahydropyran from 1-hexene was conducted. For comparison a series of three runs was made using methylene chloride as solvent at different temperatures under otherwise identical conditions and yields of the pyran (in parentheses) were determined by glpc: 0–5° (18%), −20 to −30° (57%), −60 to −70° (90%).

The facile reaction at low temperatures in this modification was quite unexpected in view of the relatively vigorous conditions necessary for 1-olefin condensation in conventional Prins reactions.[1a] Isolated yields of 70–80% of 3-alkyl-4-chlorotetrahydropyrans from the olefins 1-butene, 1-hexene, 1-octene, 1-decene, and 1-dodecene were obtained from reactions carried out by simply passing hydrogen chloride into a stirred mixture of olefin, paraformaldehyde and methylene chloride at −60 to −70°. Lower yields, 45–55%, of 4-chlorotetrahydropyran were obtained from propylene under the same conditions. At higher temperatures, *i.e.*, 0°, reaction rates were slower, conversions were lower, and work-up was complicated by formaldehyde sublimation upon attempted distillation. Variations in solvent among benzene, methylene chloride, chloroform, pentane, or using no solvent gave essentially no change in either products or yields. Pronounced improvement was noted, however, in the preparation of 4-chloro-3-propyltetrahydropyran from 1-hexene, paraformaldehyde, and hydrogen chloride in the more polar solvents such as liquid sulfur dioxide and sulfolane (55% at −10° and 50% at +10°, respectively). A modification using acetic acid solvent gave difficultly resolvable mixtures of the 4-chloro and 4-acetoxy compounds with the relative proportions of the two being somewhat temperature dependent; at a temperature of 50° production of the acetate was favored while at 0° the chloride was predominant.



Attempted preparation of 4-chlorotetrahydropyran from propylene under pressure in an autoclave gave low yields (15–25%); the principal products at 0° were bis(3-chloro-1-butoxy)methane and isopropyl chloride.

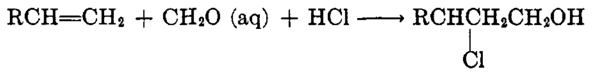
This modification of the Prins reaction was also extended to include anhydrous hydrogen fluoride and hydrogen bromide to prepare the corresponding 4-fluoro- and 4-bromo-3-propyltetrahydropyrans from 1-hexene. Addition of 1-octene to a suspension of paraformaldehyde in anhydrous liquid hydrogen fluoride at 0° gave an inseparable mixture. Slow addition of hydrogen fluoride to a mixture of 1-hexene, paraformaldehyde, and methylene chloride at −65° gave a violently exothermic reaction from which a 30% yield of the tetrahydropyran was isolated. Hydrogen bromide reacted smoothly at 20–30° to give a good yield of the corresponding bromo compound accompanied by small amounts of the formal of the bromo alcohol.

In addition to simple 1-olefins, a variety of other olefin types have also been treated with paraformaldehyde and hydrogen chloride at low temperature. The reaction of internal olefins is the subject of a separate publication. Styrene reacted rapidly to give chiefly the hydrogen chloride adduct α-phenethyl chloride along with a lesser amount of uncharacterized product. Incorporating formaldehyde with butadiene gave an extremely complicated mixture which could not be resolved. Allyl alcohol and crotyl alcohol gave the corresponding chloromethyl ethers. Ethylene, allyl

$$RCH{=}CHCH_2OH + CH_2O + HCl \longrightarrow RCH{=}CHCH_2OCH_2Cl$$

chloride, and sulfolene did not react with paraformaldehyde and hydrogen chloride under these conditions, but functioned as catalysts for the production of bis(chloromethoxy)methane as described in the accompanying note.[7]

In addition to variations in the olefin, some modifications of the carbonyl component were also surveyed. Treatment of propylene with trioxane, the cyclic trimer of formaldehyde, and hydrogen chloride at −65° gave no reaction, and acetaldehyde as the carbonyl component gave only a complex mixture of aldol-type condensation products under identical conditions. Attempted reaction of propylene with acetone gave only the bimolecular acetone condensation product, mesityl oxide. Substitution of aqueous formalin for paraformaldehyde in the preparation of 4-chloro-3-propyltetrahydropyran from 1-hexene and hydrogen chloride at 0° was found to be feasible giving 35–45% yields (by glpc) but purification was difficult and the low-temperature reactions afford much better preparatory procedures. Attempts to define optimum reaction conditions were plagued with difficulty in obtaining reproducible results in the heterogeneous system, but it was found that added salts such as lithium or sodium chloride gave a faster reaction rate. Simultaneous introduction of hydrogen chloride and propylene into formalin at 5–10° was found to give, in addition to small amounts of 4-methyl-1,3-dioxane and 4-chlorotetrahydropyran, moderate yields of an approximately equimolar mixture of 3-chlorobutyl chloromethyl ether, $CH_3CH(Cl)CH_2CH_2OCH_2Cl$, and bis(3-chloro-1-butoxy)methane. Modification of the earlier procedure to permit dropwise addition of 1-hexene to an excess of formalin saturated with hydrogen chloride at 15–25° gave a 27% yield of 3-chloro-1-heptanol. Despite the modest yield, this probably represents the most convenient method of conversion of a 1-olefin to the corresponding 3-chloro-1-alkanol.



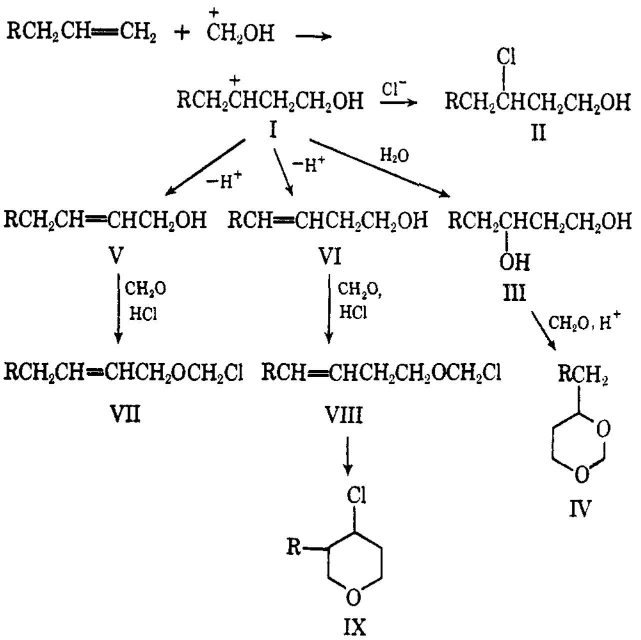
$$RCH{=}CH_2 + CH_2O\ (aq) + HCl \longrightarrow R\underset{\displaystyle Cl}{C}HCH_2CH_2OH$$

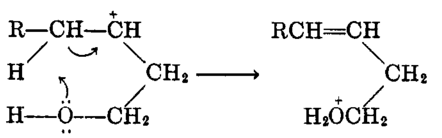
Mechanism

Tetrahydropyran derivatives have been reported, usually as by-products, in a number of examples of conventional Prins reactions involving aqueous solutions or solutions in acetic acid or concentrated sulfuric acid.[2,8–11] Although extrapolation of reaction mechanisms from these conventional Prins reaction to include the reaction of 1-olefins with paraformaldehyde and hydrogen chloride at low temperatures may lack rigor, the proposal that it is unlikely that acids in different media catalyze the Prins condensation by different mechanisms[12] seems warranted. In general, it is accepted that Prins reactions proceed *via* initial electrophilic attack of a protonated formaldehyde upon a double bond[2a,12] to give an intermediate which has been described as either a free carbonium ion[13] or a solvated trimethylene oxide.[14] More recent work[2a,15] suggests that neither intermediate can be conclusively ruled out.

A convenient mechanism (Scheme IV) can be used to rationalize reaction products from either conventional Prins reaction or the low-temperature modification reported here. For simplicity, the reaction mechanism depicted is written with "free" carbonium ions, but there can be little doubt that the charged intermediates are associated. In consideration of the formation of the major products, adduct I of the protonated formaldehyde and olefin may undergo reaction with chloride to give chloro alcohol II, or with water to give glycol III, and ultimately dioxane IV. Proton abstraction from I would give unsaturated alcohols V and VI. It is known that homoallylic alcohols VI cyclize to 4-tetrahydropyranols upon treatment with formaldehyde and sulfuric acid[16] and to 4-chlorotetrahydropyrans on reaction with paraformaldehyde and hydrogen chloride.[17] The analogous cyclization of allyl chloromethyl ethers VII to tetrahydrofuran derivatives is known not to occur readily[5] and neither allyl chloromethyl ethers nor tetrahydrofurans were detected in this work. The most serious objection to the entire scheme is that deprotonation of I to VI would not seem to be thermodynamically greatly favored over V; it may be, however, that deprotonation to give the homoallylic alcohol is greatly facilitated via a cyclic process. In support of this scheme, reaction of a large excess of propylene with paraformaldehyde and hydrogen chloride in liquid sulfur

SCHEME IV





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(7) P. R. Stapp, *J. Org. Chem.*, in press.

(8) J. W. Baker, *J. Chem. Soc.*, 296 (1944).

(9) Netherlands Patent 6,405,236; *Chem. Abstr.*, **62**, 11688*d* (1965).

(10) E. Hanschke, *Chem. Ber.*, **88**, 1048 (1955).

(11) E. Steininger, U. S. Patent 3,154,566; *Chem. Abstr.*, **62**, 4010*a* (1965).

(12) N. C. Yang, D. H. Yang, and C. B. Ross, *J. Amer. Chem. Soc.*, **81**, 133 (1959).

(13) (a) C. C. Price and M. L. Dickman, *Ind. Eng. Chem.*, **40**, 257 (1948); (b) C. Agami and C. Prevost, *C. R. Acad. Sci., Paris*, **263**, 153 (1966).

(14) (a) H. E. Zimmerman and J. English, *J. Amer. Chem. Soc.*, **75**, 2367 (1953); (b) A. T. Blomquist and J. Wolinsky, *ibid.*, **79**, 6025 (1957).

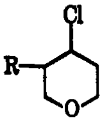
(15) F. A. Meneghini, *Dissertation Abstr.*, **27**, 2299B (1967).

(16) E. Hanschke, *Chem. Ber.*, **88**, 1053 (1955).

(17) J. Colonge, *C. R. Acad. Sci., Paris*, **240**, 1552 (1955).

TABLE I

3-ALKYL-4-CHLOROTETRAHYDROPYANS



Compd no.	R[a]	Yield, %	Bp, °C	Pressure, mm	Formula	Calcd, %			Found, %		
						C	H	Cl	C	H	Cl
1	H	50	70–71	50.0	C_5H_9ClO	49.8	7.5	29.5	49.9	7.5	29.7
2	CH_3	78	80–84	40.0	$C_6H_{11}ClO$	53.5	8.2	26.4	53.3	8.0	26.5
3	n-C_3H_7	80	91–95	15.0	$C_8H_{15}ClO$	59.1	9.2	21.9	58.9	9.0	22.0
4	n-C_5H_{11}	75	77–81	0.5	$C_{10}H_{19}ClO$	63.0	10.0	18.6	63.2	10.0	18.9
5	n-C_7H_{15}	72	95–99	0.8	$C_{12}H_{23}ClO$	65.9	10.6	16.2	65.5	10.7	15.9
6	n-C_9H_{19}	77	115–120	0.5	$C_{14}H_{27}ClO$	68.1	11.0	14.4	68.2	11.0	14.4

[a] Registry numbers are as follows: 1, 1768-64-5; 2, (*cis*) 18755-76-5, (*trans*) 18755-77-6; 3, (*cis*) 18755-78-7, (*trans*) 18755-79-8; 4, (*cis*) 18764-70-0, (*trans*) 18764-71-1; 5, (*cis*) 18755-80-0, (*trans*) 18755-81-2; 6, (*cis*) 18755-82-3, (*trans*) 18755-83-4.

dioxide at −65° led to the isolation of a 34% yield of the intermediate homoallylic alcohol, 3-buten-1-ol, along with small quantities of the normal products 4-chlorotetrahydropyran and 3-chloro-1-butanol.

Reaction of 1-hexene with paraformaldehyde and hydrogen chloride in the presence of large quantities of chloride ion (as tetramethylammonium chloride) at 0° gave a 55% yield of 4-chloro-3-propyltetrahydropyran. The contrast between a similar reaction which gave only 18% in the absence of added chloride, as well as higher yields in the polar solvents such as liquid sulfur dioxide and sulfolane, indicates that the Hughes-Ingold[18] generalization holds true for this particular system.

Experimental Section[19]

Preparation of 3-Alkyl-4-chlorotetrahydropyrans.—Only the most convenient general procedure is given. A four-necked flask with a sealed stirrer, Dry Ice–acetone condenser connected to an exit bubbler, low-temperature thermometer, and dispersion tube was charged with 200–500 ml of methylene chloride and 3.0 mol of 92% paraformaldehyde. Then 2.0 mol of 1-olefin was added, the flask was cooled in Dry Ice–acetone (gaseous olefins were condensed in from weighed cylinders at this point) and hydrogen chloride was passed in with rapid stirring until uptake ceased (about 2–4 hr on this scale). The reaction mixture was allowed to warm to room temperature (usually overnight), washed with water, then with sodium carbonate solution, and dried ($MgSO_4$). After filtration, the solvent was distilled at atmospheric pressure, and the residue was fractionated under reduced pressure. The 3-alkyl-4-chlorotetrahydropyrans listed in Table I were prepared by this procedure.

Sodium and Methanol Reduction of $C_{10}H_{19}ClO$ from 1-Octene.—A 500-ml round-bottomed flask fitted with a reflux condenser was charged with 200 ml of methanol and 23 g of the $C_{10}H_{19}OCl$ product. Over a period of 20 min, with occasional shaking, 13.8 g (0.6 g-atom) of clean sodium was added in pieces through the reflux condenser at such a rate as to maintain reflux. After the reaction was complete, the mixture was cooled, poured into water, dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled at atmospheric pressure. Glpc of the residue indicated that the reaction was about 65% complete so the reduction was repeated using 200 ml of methanol and 13.8 g of sodium. After isolation as before, the reduction product was fractionated through a 0.5 × 18 in. column packed with 6-mm Raschig rings to give 9.2 g (49%) of colorless liquid, bp 85–87° (15 mm), $n^{20}D$ 1.4421.

Anal. Calcd for $C_{10}H_{20}O$: C, 76.9: H, 12.8: mol wt, 156. Found: C, 76.8; H, 12.7; mol wt, 156 (mass spectrometer).

Preparation of Diethyl α-Carbethoxy-*n*-heptylmalonate.—Sodium ethoxide was prepared from 26.5 g (1.15 g-atom) of clean sodium in 1 l. of absolute ethanol in a 2-l. three-necked flask. Then 200 g (1.25 mol) of diethylmalonate was added over 20 min, followed by 270 g (1.08 mol) of ethyl α-bromocaprylate which was added dropwise over a period of 0.75 hr (slightly exothermic). The reaction mixture (with precipitated solid) was refluxed for 4 hr with stirring, and the inorganic salts were dissolved by the addition of 150 ml of water. The layers were separated, the aqueous layer was extracted twice with ether, and the combined organic material was dried over $MgSO_4$, filtered, and the solvents were removed on a rotary evaporator. The residue was distilled under reduced pressure to give 231.6 g (65%) of product, bp 126–129° (0.2 mm), $n^{20}D$ 1.4360.

Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.8; H, 9.1. Found: C, 61.7; H, 9.1.

Preparation of *n*-Hexylsuccinic Acid.—A 2-l. three-necked flask was equipped with a stirrer and reflux condenser. The flask was charged with 230 g (0.696 mol) of diethyl α-carbethoxy-*n*-heptylmalonate, and 260 g (4.0 mol) of 85% potassium hydroxide in 1 l. of absolute ethanol. After refluxing for 8 hr, most of the ethanol was removed by distillation, 1 l. of water was added and the solution was concentrated to 250 ml by distillation. The hot solution was neutralized with concentrated HCl (CO_2 evolution) with stirring and was then refluxed with stirring for 6 hr (CO_2 evolution had ceased at this time). The layers were separated, and the aqueous layer was extracted several times with ether. The combined organic solution was evaporated on a rotary evaporator to yield crude *n*-hexylsuccinic acid which was not further purified but used directly for conversion to the diester.

Preparation of Diethyl *n*-Hexylsuccinate.—The crude acid was esterified by refluxing with 200 ml of 95% ethanol, 400 ml of benzene, and 15 ml of methanesulfonic acid with constant water separation for 3 days. The product was fractionated to give 136.2 g (50.5%) of the diester, bp 102–105° (0.5 mm).

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.1; H, 10.1. Found: C, 65.1; H, 10.3.

Preparation of 2-*n*-Hexyl-1,4-butanediol.—A 1-l. three-necked flask with stirrer, condenser, and dropping funnel (under nitrogen) was charged with 15.2 g (0.4 mol) of lithium aluminum

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[18] (a) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935); (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 83.

[19] All melting and boiling points are uncorrected. Olefins used were Phillips Petroleum Co. pure grade materials. Hydrogen halides were obtained from the Matheson Co. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Mass Spectra were obtained on a Consolidated Electrodynamics Corp. Model 21-110 spectrometer. Nuclear magnetic resonance data were obtained on a Varian Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as an internal standard. Glpc analyses were carried out on a Perkin-Elmer Model 720 gas chromatograph using 10 ft × 0.25 in. columns of 20% SE-30 silicone oil on Chromosorb P or 20% Ucon LB-550-X on Chromosorb P.

hydride and 550 ml of dry ether. With ice-bath cooling, a solution of 90 g (0.35 mol) of diethyl *n*-hexylsuccinate in 100 ml of dry ether was added dropwise over 1.5 hr. After addition was complete, the reaction mixture was refluxed for 2 hr, cooled, and decomposed with saturated sodium potassium tartrate solution. After extraction into ether, the solution was dried ($MgSO_4$), the ether was removed, and the residue was distilled through a short column under reduced pressure to give 55.2 g (91%) of glycol, bp 118–122° (0.05 mm).

Anal. Calcd for $C_{10}H_{22}O_2$: C, 69.0; H, 12.65. Found: C, 68.8; H, 12.9.

Preparation of 3-*n*-Hexyltetrahydrofuran.—In a 100-ml distilling flask with a thermowell were placed 30 g (0.172 mol) of 2-*n*-hexyl-1,4-butanediol and 35 g of 85% phosphoric acid. The flask was attached to a condenser and heated at 125–130° for 4 hr. After cooling, the reaction mixture was poured into water and extracted into ether. The ether solution was washed with saturated Na_2CO_3 solution and dried over $MgSO_4$. The ether was removed at atmospheric pressure and the residue was distilled (from sodium) to give 21.3 g (80%) of 3-*n*-hexyltetrahydrofuran, bp 85–85.5° (10 mm), $n^{20}D$ 1.4381.

Anal. Calcd for $C_{10}H_{20}O$: C, 76.8; H, 12.8. Found: C, 76.6; H, 12.9.

Preparation of Diethyl *n*-Amyl-2-cyanoethylmalonate.—In a 500-ml erlenmeyer flask with a magnetic stirrer was prepared a solution of 138 g (0.6 mol) of ethyl *n*-amylmalonate[20] and 3.0 g of 30% methanolic potassium hydroxide in 150 g of *t*-butyl alcohol. With ice-bath cooling to maintain a temperature of 30–35°, 31.8 g (0.6 mol) of acrylonitrile was added dropwise over 30 min and the clear solution was stirred an additional 3 hr, was poured into water, and extracted into ether. After drying over $MgSO_4$ the ether was removed and the residue was distilled under reduced pressure to give 147.6 g (87%) of material, bp 121–125° (0.1 mm), $n^{20}D$ 1.4449.

Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.8; N, 5.0. Found: C, 63.5; H, 8.6; N, 5.0.

Preparation of 2-*n*-Amylglutaric Acid.—A 2-l. round-bottomed flask was charged with 132.6 g (0.47 mol) of diethyl *n*-amyl-2-cyanoethylmalonate and 600 ml of 48% hydrobromic acid. The mixture was boiled under reflux for 18 hr, concentrated almost to dryness on a rotary evaporator, diluted with water to dissolve the precipitated salts and then extracted several times with ether. The combined ether extracts were evaporated on a rotary evaporator to leave the crude acid which was used directly in the next step.

Preparation of Diethyl 2-*n*-Amylglutarate.—The crude 2-*n*-amylglutaric acid, 250 ml of absolute ethanol, 500 ml of benzene, and 15 ml of methanesulfonic acid were refluxed with constant water separation for 3 days. There was obtained 93.5 g (77.4%) of diester, bp 112–114° (1.0 mm), $n^{20}D$ 1.4326.

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.1; H, 10.1. Found: C, 64.7; H, 10.1.

Preparation of 2-*n*-Amyl-1,5-pentanediol.—In a 2-l. three-necked flask with stirrer, condenser, and dropping funnel (under nitrogen) was placed 15.2 g (0.4 mol) of lithium aluminum hydride in 500 ml of dry ether. To the stirred suspension, with ice-bath cooling, 84 g (0.326 mol) of diethyl 2-*n*-amylglutarate in 100 ml of dry ether was added dropwise over 1 hr. After work-up, there was obtained 55.8 g (97.4%) of glycol, bp 114–117° (0.1 mm), $n^{20}D$ 1.4584.

Anal. Calcd for $C_{10}H_{22}O_2$: C, 69.0; H, 12.7. Found: C, 68.6; H, 12.7.

Preparation of 3-*n*-Amyltetrahydropyran.—A mixture of 30 g (0.172 mol) of 2-*n*-amyl-1,5-pentanediol and 35 g of 85% phosphoric acid gave, after distillation of the product from sodium, 19.8 g (74%) of the tetrahydropyran, bp 103.5–105° (30 mm), $n^{20}D$ 1.4410. The infrared, nmr, and mass spectra of a center cut were identical with the product from sodium and methanol reduction of the reaction product of 1-octene, paraformaldehyde and hydrogen chloride.

Identification of Products from Reaction of Propylene, Paraformaldehyde, and Hydrogen Chloride.—The reaction of 4.0 mol of paraformaldehyde and 2.6 mol of propylene with hydrogen chloride in 400 ml of methylene chloride was carried out at −60 to 70° according to the general procedure. Fractionation gave 20.8 g of forerun, bp 30–70° (50 mm), 83.7 g of pure 4-chlorotetrahydropyran, bp 70–71° (50 mm), $n^{20}D$ 1.4619, 30.2 g of intermediate fraction, bp 47–119° (15 mm), and 51.8 g of a second product, bp 119–129° (15 mm). The 4-chlorotetrahydropyran was homogeneous by glpc (10-ft Ucon column, 175°) and the infrared, nmr, and mass spectra and glpc retention time were identical with an authentic sample[5] and readily distinguishable from an authentic sample of 3-chlorotetrahydropyran.[4] The forecut was found to consist of a mixture of 4-chlorotetrahydropyran and a compound whose retention time was identical with that of 4-methyl-1,3-dioxane.

Reduction of 4-Chlorotetrahydropyran with Sodium and Amyl Alcohol.—The reduction of 24.1 g (0.2 mol) of 4-chlorotetrahydropyran in 200 ml of amyl alcohol was accomplished by addition of 23 g (1.0 g-atom) of sodium portionwise. The reduction product was isolated by room temperature distillation at 15 mm into a trap cooled in a Dry Ice–acetone bath. This was then fractionated at atmospheric pressure to give 15.3 ml of tetrahydropyran, bp 86–89°, whose infrared spectrum and glpc retention time on a 10 ft silicone rubber column operated isothermally at 60° were identical with an authentic sample.

Identification of Bis(3-chloro-1-butoxy)methane.—The high-boiling fraction from preparation of 4-chlorotetrahydropyran above was refractionated and a center cut, bp 129° (15 mm), homogeneous by glpc on a 10-ft silicone rubber column at 175°, was submitted for analysis.

Anal. Calcd for $C_9H_{18}Cl_2O_2$: C, 47.2; H, 7.9; Cl, 31.0. Found: C, 47.4; H, 8.0; Cl, 30.8.

The nmr spectrum supports the assigned structure with adsorption at τ 5.4 (2 H, singlet), 5.85 (2 H, multiplet), 6.38 (4 H, triplet), 8.1 (4 H, multiplet), and 8.5 (6 H, doublet). The mass spectrum exhibits a strong fragment peak at *m/e* 227 which must contain two atoms of chlorine to account for chlorine isotope peaks at *m/e* 229 and 231. The calculated probable intensity ratios are *m/e* 227, 229, 231 = 9.8:6.2:1 and the observed ratios were 10.5:6.0:1 in satisfactory agreement. In addition, an exact mass measurement by high resolution mass spectrometry of the *m/e* 227 peak (m − 1 ion) indicates that it has the composition $C_9H_{17}O_2Cl_2$, mass 227.173 (calcd 227.171).

Methanolysis of Bis(3-chloro-1-butoxy)methane.—In a 250-ml round-bottomed flask with a reflux condenser were placed 25.6 g (0.107 mol) of bis(3-chloro-1-butoxy)methane, 150 ml of methanol, and 10 ml of concentrated hydrochloric acid and the reaction mixture was refluxed for 2.5 hr. The methanol was removed on a rotary evaporator and the residue was taken up in 150 ml of ether, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and the ether was removed. Distillation of the residue through a short column gave 14.2 g (61%) of viscous oil: bp 68–69° (14 mm), $n^{20}D$ 1.4416 [lit.[6] bp 74° (16 mm), $n^{20}D$ 1.4398].

Anal. Calcd for C_4H_9ClO: C, 44.2; H, 8.2. Found: C, 43.8; H, 8.3.

The 3,5-dinitrobenzoate melted at 75–76° (lit.[6] mp 71–72°).

Anal. Calcd for $C_{11}H_{11}ClN_2O_6$: C, 43.6; H, 3.6; N, 9.2. Found: C, 43.4; H, 3.5; N, 8.8.

A phenylurethane was prepared, mp 55–56°, from heptane as fluffy colorless needles.

Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.0; H, 6.15; N, 6.1. Found: C, 58.0; H, 6.3; N, 6.0.

Purification of Formal By-Products from 1-Butene.—The high-boiling fractions from several preparations of 4-chloro-3-methyltetrahydropyran were combined and fractionated to give the *pure formal*, bp 113–115° (0.9 mm), $n^{20}D$ 1.4559. Methanolysis gave a 75% yield of the chloro alcohol, bp 81–85° (15 mm), $n^{20}D$ 1.4480.

Anal. Calcd for $C_5H_{11}ClO$: C, 49.0; H, 9.0. Found: C, 49.3; H, 9.0.

The 3,5-dinitrobenzoate ester after two recrystallizations from absolute ethanol melted at 76–77°.

Anal. Calcd for $C_{12}H_{13}ClN_2O_6$: C, 45.5; H, 4.1; N, 9.0. Found: C, 45.6; H, 4.4; N, 8.8.

The nmr spectrum provided conclusive evidence that the compound had the structure 3-chloro-1-pentanol (I) rather than the isomeric structure, 3-chloro-2-methyl-1-butanol (II). A singlet at τ 5.3 measures one proton and is produced by the hydroxyl group. In the τ 5.7–6.7 region is a multiplet overlapped by a triplet representing three protons. This is the region for $-CH$ adjacent to $-Cl$ and $-CH_2$ α to $-OH$. The multiplet is due to the former and the triplet to the $-CH_2$ α to the $-OH$ coupled with an adjacent methylene group. Isomer II would give a doublet rather than a triplet at this chemical shift position. The complex series of peaks between τ 7.8–8.7 are

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[20] A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 107 (1957).

due to $-CH_2$ β to $-Cl$ and measured four protons. The upfield triplet between γ 8.8 and 9.2 is due to a methyl group and the coupling indicates an adjacent methylene group. Structure II would produce a doublet for this resonance.

Preparation of 4-Fluoro-3-propyltetrahydropyran.—A 400-ml two-necked polyethylene flask was fitted with a Teflon-covered stirring bar, a Weston thermometer, and a polyethylene dispersion tube. The flask was charged with 84 g (1.0 mol) of 1-hexene, 27.6 g (0.92 mol) of paraformaldehyde and 100 ml of methylene chloride. The flask was cooled in Dry Ice–acetone and magnetically stirred while hydrogen fluoride was passed in for 1.3 hr. The reaction was vigorously exothermic and difficulty in keeping the temperature below −20° was noticed. The reaction mixture was allowed to warm to room temperature, poured over ice, and neutralized with concentrated ammonia solution. The methylene chloride layer was separated, dried (Na_2SO_4), filtered, and the solvent was distilled at atmospheric pressure. The residue was fractionated through a 0.75 × 24 in. column packed with 6-mm Raschig rings and 20.7 g (31%) of 4-fluoro-3-propyltetrahydropyran, bp 61–64° (11 mm), was obtained. The nmr, infrared, and mass spectra were consistent with the assigned structure.

Anal. Calcd for $C_8H_{15}FO$: C, 65.7; H, 10.3. Found: C, 65.6; H, 10.3.

Preparation of 4-Bromo-3-propyltetrahydropyran.—The general procedure was followed using 168 g (2.0 mol) of 1-hexene, 90 g (3.0 mol) of paraformaldehyde, and 200 ml of methylene chloride. Hydrogen bromide was passed in for 1.5 hr while maintaining the temperature at 20–30°. (An induction period was noted until the temperature was raised to 30°, the exothermic reaction was moderated by external cooling after initiation.) Isolation and fractionation gave 103 g of 2-bromohexane, bp 55–58° (40 mm), identified by comparison of infrared and nmr spectra with an authentic sample, and 155.2 g (40%) of 4-bromo-3-propyltetrahydropyran, bp 95–99° (10 mm).

Anal. Calcd for $C_8H_{15}BrO$: C, 46.5; H, 7.3. Found: C, 46.9; H, 7.5.

Preparation of 4-Chloro-3-propyltetrahydropyran from Aqueous Formalin.—Hydrogen chloride was passed into a rapidly stirred mixture of 84 g (1.0 mol) of 1-hexene, 20 g of sodium chloride, and 150 g (2.0 mol) of 40% formalin at 0°–15° (ice bath) for 1 hr. After work-up and distillation, 102.5 g of material, bp 85–130° (20 mm), was obtained which by glpc analysis on a 10-ft Ucon column at 225° was found to contain 64% of 4-chloro-3-propyltetrahydropyran.

Reaction of Propylene and Hydrogen Chloride with Aqueous Formalin.—Propylene and hydrogen chloride were passed simultaneously through two dispersion tubes into a rapidly stirred mixture of 1.5 l. of 36.6% formalin and 300 ml of concentrated hydrochloric acid at ice-bath temperature for 8 hr. The organic layer was separated, washed several times with water, dried ($CaCl_2$) and fractionated. The following fractions were collected: fraction A, bp 75–80° (50 mm), 109 g; fraction B, bp 74–105° (26 mm), 223 g; fraction C, bp 100–144° (22 mm), 13.4 g; and fraction D, bp 144–155° (22 mm), 197.2 g. Glpc analysis (5-ft Ucon column, 125°) of fraction A showed it to contain about 70% 4-methyl-1,3-dioxane and 30% 4-chlorotetrahydropyran, fraction B (10-ft silicone rubber, 180°) contained small amounts of 4-methyl-1,3-dioxane and 4-chlorotetrahydropyran but was chiefly a new compound, fraction D was nearly pure bis(3-chloro-1-butoxy)methane, and fraction E was a mixture of B and D. Refractionation of fraction B gave pure 3-chlorobutyl chloromethyl ether, bp 99.5–100° (22 mm).

Anal. Calcd for $C_5H_{10}Cl_2O$: C, 38.3; H, 6.4; Cl, 45.2. Found: C, 38.1; H, 6.6; Cl, 45.5.

The nmr spectrum confirmed the assigned structure with adsorption at τ 4.5 (2 H, singlet), 5.85 (1 H, multiplet), 6.15 (2 H, triplet), 8.0 (2 H, quartet), 8.45 (3 H, doublet).

Preparation of 3-Chloro-1-heptanol.—A 2-l., four-necked flask equipped with a stirrer, thermometer, dropping funnel and dispersion tube was charged with 820 g of 36.6% formalin and 150 ml of concentrated hydrochloric acid. The flask was cooled in an ice bath, saturated with hydrogen chloride, and a slow stream of hydrogen chloride was passed continuously through the rapidly stirred reaction mixture while 353 g (4.2 mol) of 1-hexene was added dropwise over 2.5 hr. The organic material was separated, washed with water, and refluxed for 1 hr with 1 l. of methanol containing 25 ml of concentrated sulfuric acid to hydrolyze any formals. After isolation the product was fractionated through an efficient column. After removal of the lower boiling 4-chloro-3-propyltetrahydropyran and other byproducts there was obtained 170.3 g (27%) of 3-chloro-1-heptanol, bp 121–123° (25 mm).

Anal. Calcd for $C_7H_{15}ClO$: C, 55.8; H, 10.0; Cl, 24.5. Found: C, 55.9; H, 10.2; Cl, 24.2.

Preparation of 3-Buten-1-ol.—A 1-l. four-necked flask was cooled in Dry Ice–acetone and approximately 250 ml of liquid sulfur dioxide was condensed in from a cylinder. Then 60 g (2.0 mol) of paraformaldehyde was added and 193 g (4.6 mol) of propylene was condensed in from a cylinder. Dry hydrogen chloride was passed in for 3 hr and the solvent was allowed to evaporate overnight. Work-up and distillation gave 127.5 g of liquid, bp 40–125° (60 mm), which by glpc analysis had the following composition in order of elution from a 5-ft Ucon column at 125°: 3-buten-1-ol (38.1%), 4-methyl-1,3-dioxane (trace), 4-chlorotetrahydropyran (19%), 3-chloro-1-butanol (36.8%). Redistillation at atmospheric pressure through a packed column gave 39.2 g of 3-buten-1-ol, bp 112–114°, whose infrared spectrum was identical with an authentic sample.

Registry No.—3-*n*-Pentyltetrahydropyran ($C_{10}H_{20}O$), 18755-28-7; diethyl α-carbethoxy-*n*-heptylmalonate, 18755-29-8; diethyl *n*-hexylsuccinate, 18755-30-1; 2-*n*-hexyl-1,4-butanediol, 18755-31-2; 3-*n*-hexyltetrahydrofuran, 18755-32-3; diethyl *n*-amyl-2-cyanoethyl-malonate, 18755-33-4; diethyl 2-*n*-amylglutonate, 18755-34-5; 2-*n*-amyl-1,5-pentanediol, 18755-35-6; bis(3-chloro-1-butoxy)methane, 18755-84-5; 3-chloro-1-pentanal, 18755-85-6; 3-chloro-1-pentanol, 18289-54-8; 3-chloro-1-pentanol 3,5-dinitrobenzoate, 18755-87-8; 4-fluoro-3-propyltetrahydropyran (*cis*), 18755-88-9; 4-fluoro-3-propyltetrahydropyran (*trans*), 18755-99-2; 4-bromo-3-propyltetrahydropyran (*cis*), 18755-89-0; 4-bromo-3-propyltetrahydropyran (*trans*), 18756-00-8; 3-chlorobutyl chloromethyl ether, 18755-90-3; 3-chloro-1-heptanol, 18755-91-4.

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