[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Keto Ethers. II. α-1,3-Dichloroisopropoxyethyl Alkyl Ketones[1]

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Continuing the investigation in this Laboratory on aliphatic compounds of bifunctional type,[2] we have now studied the utilization of glycerol 1,3-dichlorohydrin in the preparation of chlorinated keto ethers. With but very few exceptions, only the simpler, monohydric alcohols have been condensed with the unsubstituted aliphatic aldehydes of low molecular weight, or with trichloroacetaldehyde, according to Henry's[3] method for synthesizing α-chloro ethers. The first successful utilization of a substituted alcohol in this chloro ether synthesis was that of Stappers,[4] in 1905, who effected the condensation of propylene chlorohydrin with formaldehyde, even though aqueous formalin solution was used as a source of the aldehyde. Somewhat later, Grignard and Purdy,[5] using ethylene chlorohydrin and paraldehyde, were able to produce α-chloroethyl β′-chloroethyl ether. However, the attempts of Farren, Fife, Clark and Garland[6] to cause trioxymethylene to interact with glycol and glycerol, respectively, led to no satisfactory results. Although these investigators were convinced that condensation had occurred, they were unable to isolate any pure products from the reaction mixtures. Finally, Blanchard[7] has reported the only other attempt at reaction of an aldehyde with a chlorohydrin, he having obtained 1,3-dichloroisopropyl chloromethyl ether by the action of hydrogen chloride on a mixture of trioxymethylene and glycerol 1,3-dichlorohydrin.

Following the work of Gauthier,[8] by which it was possible to convert α-chloro ethers into the corresponding alkoxy nitriles by heating the former with either cuprous or mercuric cyanides, there have been, from time to time, numerous references made to the preparation and characterization of compounds of this type. Apparently, however, no attempts have been made to apply this reaction to the synthesis of substituted alkoxy nitriles, *e. g.*, chloroalkoxy nitriles from polyhalogenated ethers. Likewise, since chloroalkoxy nitriles were unknown prior to this investigation, there necessarily have been no chloroalkoxy ketones obtained by the procedure of Béhal and Sommelet,[9] in which they found it possible to adapt Blaise's[10] modification of the Grignard reaction in the formation of keto ethers from alkoxy nitriles.

Glycerol 1,3-dichlorohydrin has now been caused to react with paraldehyde to form 1,3-dichloroisopropyl α-chloroethyl ether. This new trichloro ether has been converted into α-1,3-dichloroisopropoxypropionitrile, the latter representing the first example of a chloroalkoxy nitrile to be prepared. From this nitrile there has been obtained, by means of the Grignard reaction, a series of dichloroalkoxy alkyl ketones.

The Hoesch[11] test, as modified by Howells and Little,[12] has been proposed as a micro method for the identification of alkyl nitriles. The condensation of α-1,3-dichloroisopropoxypropionitrile with phloroglucinol has been investigated, with the result that the proposed test appears to be of no value for the recognition of chloroalkoxy nitriles.

Experimental

1,3-Dichloroisopropyl α-Chloroethyl Ether.—Dry hydrogen chloride was passed into a well-stirred mixture of 973 g. (7.55 moles) of glycerol 1,3-dichlorohydrin, prepared by the method of Conant and Quayle,[13] and 502 g. (3.8 moles) of paraldehyde contained in a flask cooled by an ice–salt bath. Saturation was attained in five hours, the mixture separating into two layers. The crude chloro ether layer, weighing 1646 g., was dried over calcium chloride and distilled under diminished pressure. Redistillation at 18 mm. pressure yielded 1142 g. (79.2% of the theoretical) of 1,3-dichloroisopropyl α-chloroethyl ether boiling at 89–90° (corr.). The colorless, oily liquid has a pleasant odor and in contact with air undergoes rather rapid decomposition with the evolution of hydrogen chloride and the deposition of a black, gummy mass: d^{20}_4 1.2864; n^{20}_D 1.4711; M_R calcd., 41.53; M_R found, 41.60; γ^{20} 34.44 dynes/cm.; P calcd., (Sugden's atomic constants) 360.8;

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[1] From the thesis of Bruce B. Allen for the M.A. degree, August, 1936.

[2] Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934).

[3] Henry, *Bull. soc. chim.*, [2] **44**, 458 (1885).

[4] Stappers, *Rec. trav. chim.*, **24**, 256 (1905).

[5] Grignard and Purdy, *Bull. soc. chim.*, **31**, 982 (1922).

[6] Farren, Fife, Clark and Garland, THIS JOURNAL, **47**, 2412 (1925).

[7] Blanchard, *Bull. soc. chim.*, **39**, 1119 (1926).

[8] Gauthier, *Compt. rend.*, **143**, 831 (1906).

[9] Béhal and Sommelet, *ibid.*, **138**, 89 (1904).

[10] Blaise, *ibid.*, **132**, 38 (1901).

[11] Hoesch, *Ber.*, **48**, 1122 (1915).

[12] Howells and Little, THIS JOURNAL, **54**, 2451 (1932).

[13] Conant and Quayle, "Organic Syntheses," John Wiley & Sons, Inc., New York, Vol. II, 1922, p. 29.

TABLE I

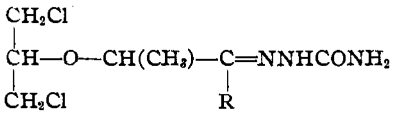
KETO ETHERS DERIVED FROM GLYCEROL 1,3-DICHLOROHYDRIN

Formula	B. p. °C.	B. p. Mm.	Density d^{20}_4	Refractive index, $n^{20}\text{D}$	Surface tension γ^{20}, dynes	Free surface energy $\gamma\ (m/d)^{2/3}$ ergs	Yield, %
$(CH_2Cl)_2CHOCH(CH_3)COCH_3$	105–106	5	1.1986	1.4640	35.81	1086.5	51.4
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_3$	117	7–7.5	1.1691	1.4636	34.97	1139.7	79.5
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_3$	127.5	5	1.1381	1.4627	33.85	1169.2	66.1
$(CH_2Cl)_2CHOCH(CH_3)COCH(CH_3)_2$	124–125.5	12	1.1359	1.4613	33.66	1163.1	47.4
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_2CH_3$	136–136.5	6	1.1140	1.4625	32.90	1205.4	62.7
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH(CH_3)_2$	127–128	5–6	1.1096	1.4608	31.75	1166.4	53.3
$(CH_2Cl)_2CHOCH(CH_3)COCH(CH_3)CH_2CH_3$	129–130	5	1.1167	1.4624	32.90	1203.5	19.9
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_2CH_2CH_3$	148.5–149	5–5.5	1.0932	1.4630	32.59	1260.9	75.9
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH(CH_3)_2$	143–144	5	1.0926	1.4627	31.89	1234.2	44.0
$(CH_2Cl)_2CHOCH(CH_3)COC_6H_2(OH)_3$	175.5	(m. p.)	....	....	...	....	32.5

Formula	Chlorine, % Calcd.	Chlorine, % Found	Molecular refraction Calcd.	Molecular refraction Found	ΔM_R	Parachor Calcd.	Parachor Found	ΔP
$(CH_2Cl)_2CHOCH(CH_3)COCH_3$	35.63	35.56	45.91	45.82	−0.09	410.6	406.2	− 4.4
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_3$	33.30	33.18	50.53	50.24	− .29	449.6	443.1	− 6.5
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_3$	31.23	31.24	55.15	54.92	− .22	488.6	481.2	− 7.4
$(CH_2Cl)_2CHOCH(CH_3)COCH(CH_3)_2$	31.23	31.49	55.15	54.87	− .28	488.6	481.6	− 7.0
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_2CH_3$	29.42	29.27	59.77	59.55	− .22	527.6	518.3	− 9.3
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH(CH_3)_2$	29.42	29.38	59.77	59.59	− .18	527.6	515.7	−11.9
$(CH_2Cl)_2CHOCH(CH_3)COCH(CH_3)CH_2CH_3$	29.42	29.57	59.77	59.39	− .38	527.6	517.0	−10.6
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH_2CH_2$-$CH_3$	27.80	27.63	64.39	64.26	− .13	566.6	557.5	− 9.1
$(CH_2Cl)_2CHOCH(CH_3)COCH_2CH_2CH(CH_3)_2$	27.80	27.79	64.39	64.26	− .13	566.6	554.8	−11.8
$(CH_2Cl)_2CHOCH(CH_3)COC_6H_2(OH)_3$	22.95	23.20	...	...	....	...	...	....

TABLE II

SEMICARBAZONES OF α-1,3-DICHLOROISOPROPOXYETHYL KETONES



$$\begin{array}{l} CH_2Cl \\ | \\ CH{-}O{-}CH(CH_3){-}\underset{\displaystyle R}{\underset{|}{C}}{=}NNHCONH_2 \\ | \\ CH_2Cl \end{array}$$

α-1,3-Dichloroisopropoxyethyl	R	M. p., °C. (corr.)	Nitrogen, % Calcd.	Nitrogen, % Found
-Methyl ketone	$-CH_3$	110.5	16.41	16.28
-Ethyl ketone	$-CH_2CH_3$	131.5–132	15.56	15.42
-*n*-Propyl ketone	$-CH_2CH_2CH_3$	114.5	14.79	14.71
-*n*-Butyl ketone	$-CH_2CH_2CH_2CH_3$	94.8	14.10	14.16
-*n*-Amyl ketone	$-CH_2CH_2CH_2CH_2CH_3$	108.6	13.46	13.44
-iso-Amyl ketone	$-CH_2CH_2CH(CH_3)_2$	111.5	13.46	13.61
Semicarbazone of α-1-iodo-3-chloroisopropoxyethyl methyl ketone		123–124	12.09	11.96

P found, 360.5. *Anal.* Calcd. for $C_5H_9Cl_3O$: Total Cl, 55.56. Found: Cl, 55.51, 55.07 (by Carius method). α-Cl content calcd., 18.52. Found: Cl, 18.15, 18.29 (by direct determination with aqueous silver nitrate solution).

α-1,3-Dichloroisopropoxypropionitrile.—The method of Gauthier[8] was adapted: 500 g. (2.61 moles) of 1,3-dichloroisopropyl α-chloroethyl ether, diluted with 125 cc. of anhydrous benzene, was added dropwise over a period of one hour to 250 g. of dry cuprous cyanide. Reaction was evidenced by the evolution of sufficient heat to occasion refluxing of the benzene. The mixture was stirred and heated on a steam-bath for three hours. After removal of the mixed cuprous salts by filtration, the benzene was distilled and the residual liquid fractionated under diminished pressure; yield, 232 g. (48.8%); b. p. 99° (corr.)/4 mm.; d^{20}_4 1.2259; $n^{20}\text{D}$ 1.4643; M_R calcd., 41.10; M_R found, 40.99; γ^{20} 37.77 dynes/cm.; P calcd., 370.4; P found, 368.0.

Anal. Calcd. for $C_6H_9Cl_2NO$: Cl, 39.03; N, 7.69. Found: Cl, 39.24; N, 7.64.

Preparation of α-1,3-Dichloroisopropoxyethyl Alkyl Ketones.—Sommelet's[14] method for preparing alkoxy ketones from alkoxy nitriles was applied successfully to the synthesis of dichloroalkoxy ketones, except in the case of the first member of the series. In general, the appropriate alkylmagnesium halide was prepared under anhydrous conditions and treated with the α-1,3-dichloroisopropoxypropionitrile. The reaction product, after standing overnight, was decomposed by addition of ice-cold, dilute hydrochloric acid, and the yellow colored ether solution was separated,

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[14] Sommelet, *Ann. chim. phys.*, [8] 9, 484 (1906).

dried over calcium chloride, and fractionated under a pressure of 5 mm. until sufficiently purified. The keto ethers were obtained as colorless oils having faint, slightly rancid odors which became more intense with age; unless highly purified the compounds darkened to a deep yellow color upon standing in contact with air. All of these oils were found to be insoluble in water, but readily miscible with organic solvents such as alcohol, ether, acetone, chloroform, benzene and petroleum ether.

An attempt to prepare the simplest member of the series by interaction of α-1,3-dichloroisopropoxypropionitrile and methylmagnesium iodide resulted in the formation of a reddish-brown oil which decomposed on distillation below 5 mm. pressure. From this oil there was formed a semicarbazone which melted with decomposition at 123–124° (corr.) after recrystallization from a benzene–petroleum ether mixture. Analysis of the semicarbazone indicated there had been partial replacement of chlorine by iodine during the Grignard reaction, with production of α-1-chloro-3-iodoisopropoxyethyl methyl ketone. Effort was made to regenerate this ketone from its semicarbazone, but the resulting liquid decomposed on attempted distillation under diminished pressure. For this semicarbazone the following data were obtained. *Anal.* Calcd. for $C_8H_{15}ClIN_3O_2$: Cl, 10.20; I, 36.52; N, 12.09. Found: Cl, 9.99; I, 36.30; N, 11.96.

The desired dichloro ketone was secured by utilizing methylmagnesium bromide instead of the iodide. Difficulty was also encountered in endeavors to synthesize the *t*-butyl member of the series. Initial trials were made using *t*-butylmagnesium bromide, but very nearly all of the chloroalkoxy nitrile was recovered unchanged. Following the suggestion of Gilman and Zoellner,[15] that better yields of Grignard reagent are obtained by using *t*-butyl chloride rather than the bromide, renewed attempts were made using the alkylmagnesium chloride, but here, too, no keto ether was obtained.

Semicarbazones, easily prepared and readily purified, useful as a further means of identifying the keto ethers, were formed from all the ketones containing the normal alkyl structure and, also, from α-1,3-dichloroisopropoxyethyl isoamyl ketone. Since these ketones which formed solid semicarbazones did so with such rapidity and in such good yields, failure to obtain such solids in the instances of the isobutyl, *s*-butyl and *s*-propyl α-1,3-dichloroisopropoxyethyl ketones must be attributed to steric hindrance resulting from alkyl substitution in the positions alpha or beta to the carbonyl group.

The Hoesch[11] test, as proposed by Howells and Little[12] as a micro method for identifying alkyl cyanides, was employed in the formation of a new dichloroalkoxyalkyl trihydroxyphenyl ketone. Although the amounts of materials used (0.04 mole) were considerably larger than those deemed adequate by Howells and Little, the yield of purified ketone was scarcely more than enough for simple characterization and analysis.

Boiling points were taken with calibrated thermometers and the properly corrected values are reported for the liquid keto ethers. Likewise, the melting points of the trihydroxyphenyl ketone and of the seven semicarbazones prepared are corrected values. Surface tensions were measured by means of Cassel's[16] precision capillarimeter at 20°. Densities were determined by means of a Sprengel tube weighing 1.2734 g. and calibrated to contain 2.1316 g. of distilled water at 4°. The data resulting from the determination of physical constants, the values derived from these data by calculation, and such information as was obtained through analysis of these keto ethers have been tabulated in Table I. Table II is devoted to the data resulting from the study of the semicarbazones of the dichloroalkoxy ketones.

Summary

1. The series of β′,β″-dichloro-α-chloroalkyl ethers has been extended by the synthesis of 1,3-dichloroisopropyl α-chloroethyl ether. The latter has been converted into α-1,3-dichloroisopropoxypropionitrile, the first chloroalkoxy nitrile yet prepared.

2. Nine examples of a new type of chlorinated keto ether have been obtained. In this series of dichloroisopropoxyethyl alkyl ketones, the normal, iso- and secondary alkyl types are represented; the tertiary alkyl type could not be synthesized by means of the Grignard reaction from the nitrile.

In an attempted preparation of α-1,3-dichloroisopropoxyethyl methyl ketone from methylmagnesium iodide, replacement of chlorine was observed, and the iodochloroalkoxy ketone formed was subsequently identified by means of its semicarbazone.

3. Semicarbazones, useful in the identification of the keto ethers, were obtained from each of the normal alkyl homologs and, as well, from the isoamyl member of the series. Failure of the secondary propyl, secondary butyl, and isobutyl ketones to form solid semicarbazones may be attributed to steric hindrance.

4. The Hoesch test, as modified by Howells and Little, apparently is valueless as a micro method for the identification and recognition of chloroalkoxy nitriles.

5. For the series of compounds included in this investigation, the parachor was found to be less sensitive than the molecular refraction as an index to purity.

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(15) Gilman and Zoellner, THIS JOURNAL, **50**, 425 (1928).

(16) Cassel, *Chem.-Ztg.*, **53**, 479 (1929).