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The Preparation and Properties of Certain 1,3-Dichlorobutyl Ethers

BY CLARENCE T. MASON, CLARENCE W. R. WADE[1] AND HILLARD W. POUNCY, JR.[1]

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Gaseous hydrogen chloride reacts with β-hydroxybutyraldehyde (aldol) and an alcohol to give the corresponding 1-alkoxy-1,3-dichlorobutane in yields varying from 33 to 62%. A similar reaction occurs when α-methyl-β-hydroxybutyraldehyde is used, but with slightly lower yields. The chlorine atom in the 1-position is replaced by reaction with sodium alkoxide, sodium acetate, Grignard reagent, malonic ester and cuprous cyanide to give new series of compounds.

Literature references to the preparation and properties of the monohalo- and 1,2-dihaloalkyl-1-alkoxides are fairly abundant, and their application to organic synthesis is well established. With the exception of the work of Duliere[2] and Pineau,[3] however, little attention has been paid to the 1,3-dichloroalkyl-1-alkoxides. Duliere adapted the Henry synthesis[4] to the preparation of 1,3-dichloropropyl-1-alkoxides by saturating an acrolein–alcohol mixture with dry hydrogen chloride, and he prepared the acetals of the resulting halogenated ethers. In a subsequent paper[5] he described the treatment of aliphatic and aromatic Grignard reagents with 1,3-dichloropropyl-1-alkoxides and showed that, as in the case of the 1,2-dihaloalkyl-1-alkoxides, the α-halogen is the more reactive, and thus prepared a number of 1-alkyl and -aryl derivatives of 3-chloropropyl-1-alkoxides. Pineau[3] extended the knowledge of the properties of these 1,3-dihalopropyl ethers by treating them with a number of various reagents.

In view of (1) the possible importance of the 1,3-dichloro-1-alkoxyalkanes as organic intermediates, and (2) the fact that aldol compounds (from which are prepared the raw materials in the Duliere and Pineau methods) are easily accessible, it seems important to investigate these aldols in reactions similar to the Henry synthesis, and in addition, to investigate further the reactions of the 1,3-dichloro-1-alkoxyalkanes thus prepared.

In a cold mixture of aldol, excess hydrochloric acid and an alcohol, the carbonyl should react in the usual way to form an α-chlorinated ether, and also a chlorine atom should be substituted for the hydroxyl group, to give the dichloroalkoxy product. This has been verified experimentally, and the presence of the dichloroalkoxy compound has been demonstrated by analysis. The well-known reaction of the product with sodium alkoxide to give the acetal proved definitely that one of the halogen atoms was in the α-position.

The position of the other chlorine was demonstrated by nitric acid oxidation of the dimethyl acetal to a product identified as 3-chlorobutanoic acid. The reactions of 3-hydroxybutanal (aldol) and of 3-hydroxy-2-methylbutanal proceed normally with acceptable yields. The resulting 1,3-dichlorobutyl ethers are water-clear liquids which possess lachrymatory properties, fume in moist air and turn dark on standing. As indicated by Duliere and Pineau (refs. 2, 3), the γ-chlorine atom is relatively stable, while the α can react with sodium acetate, Grignard reagent, sodiomalonic ester, metal cyanides and sodium alkoxides.

Experimental

3-Hydroxybutanal.—Technical aldol (Matheson) was purified by washing an ethereal solution with a saturated solution of sodium bicarbonate and with water, the non-aqueous layer dried over anhydrous calcium chloride and distilled, the fraction b.p. 80–81° (20 mm.) being used immediately. The technical aldol can be used in the preparation of the chlorinated ether, but the yields are lower and the product more difficult to purify.

2-Methyl-3-hydroxybutanal.—The method of Kyriakides[6] gave good yields when freshly distilled propanal and ethanal were used. The portion b.p. 91–93° (20 mm.) was used immediately.

1,3-Dichloro-1-alkoxybutanes.—Gaseous hydrogen chloride was passed into a mixture of 0.5 mole of aldol and 0.5 mole of alcohol at 2° until the hydrogen chloride ceased to be absorbed. The non-aqueous layer was dried over calcium chloride, a stream of dry air bubbled through to remove excess hydrogen chloride and the liquid vacuum distilled. Several distillations were necessary for purification, the difficulty of purification increasing with the complexity of the alcohol. When possible, the ethers were used immediately after distillation, as they became dark on standing even for short periods. The properties of the halogenated ethers are given in Table I.

TABLE I

1,3-DICHLOROBUTYL ALKOXIDES—$CH_3CHClCH_2CHClOR$

R	B.p. °C.	Mm.	Yield, %	n^{25}_D	d^{20}_4	Cl Analysis, %[a] Calcd.	Found
CH_3	41–42	9	59	1.4399	1.1126	45.17	45.20
C_2H_5	49–50	6	60	1.4409	1.0832	41.44	41.24
C_3H_7	66–67	7	62	1.4400	1.0447	38.31	38.40
C_4H_9	85–86	7	46	1.4318	1.0253	35.62	35.76
i-C_3H_7	61–62	6	33	1.4380	1.0432	38.31	38.45

[a] All halogen analyses were made by macro Parr bomb.

1,3-Dichloro-2-methyl-1-alkoxybutanes.—The method above was used in the preparation of these compounds. They required repeated distillations for purification, and were relatively more unstable than the ethers without branching. Properties are given in Table II.

TABLE II

1,3-DICHLORO-2-METHYLBUTYL-1-ALKOXIDES—
$CH_3CHClCH(CH_3)CHClOR$

R	B.p. °C.	Mm.	Yield, %	n^{25}_D	d^{20}_4	Cl, Analyses, %[a] Calcd.	Found
CH_3	67–68	10	55	1.4468	1.0807	41.44	41.40
C_2H_5	77–78	11	54	1.4478	1.0648	38.31	38.23
C_3H_7	83–84	11	43	1.4460	0.9910	35.62	35.56
C_4H_9	95–96	11	33	1.4400	1.0080	33.27	33.33

[a] All halogen analyses were made by macro Parr bomb.

Acetals from the Ethers.—Molar quantities of the α halogenated ether dropped slowly into cold equimolar amounts

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(2) W. Duliere, *Bull. soc. chim.*, **33**, 1647 (1923).

(3) R. J. Pineau, *J. recherches centre natl. recherche sci.*, 292 (1951) [*C. A.*, **46**, 416i (1952)].

(4) L. Henry, *Bull. acad. roy. Belg.*, [3] **25**, 439 (1893).

(5) W. Duliere, *Bull. soc. chim.*, **35**, 584 (1924).

(6) L. P. Kyriakides, THIS JOURNAL, **36**, 530 (1914).

of the appropriate sodium alkoxide, the products filtered, dried over calcium chloride and vacuum distilled give the acetals in Table III.

Table III

3-Chlorobutyl-1,1-dialkoxides—$CH_3CHClCH_2CH(OR)_2$

R	B.p.		Yield,			Cl, Analyses, %	
	°C.	Mm.	%	$n^{25}D$	d^{20}_4	Calcd.	Found
CH_3	40–41	7	63	1.4160	1.0024	23.23	23.31
C_2H_5	68–69	11	61	1.4195	0.9709	19.63	19.78
C_3H_7	87–88	6	61	1.4250	.9335	16.98	17.18
C_4H_9	124–125	13	62	1.4262	.9025	14.97	15.18

3-Chloro-2-Methylbutyl-1,1-dialkoxides—
$CH_3CHClCH(CH_3)CH(OR)_2$

R	°C.	Mm.	%	$n^{25}D$	d^{20}_4	Calcd.	Found
CH_3	67–68	10	60	1.4275	0.9979	21.28	21.21
C_2H_5	79–80	10	60	1.4365	.9658	18.21	18.16
C_3H_7	100–101	11	61	1.4367	.9564	15.92	15.80
C_4H_9	133–134	13	59	1.4377	.9279	14.14	14.32

Identification of 3-Chloro-1,1-dimethoxybutane.—One-half mole of the acetal was dropped, over two hours, into 220 g. of concentrated nitric acid at 25–30°. After standing overnight the reaction mixture was distilled. The fraction of b.p. 108–109° (16 mm.) was identified as β-chlorobutyric acid by its anilide and toluidide melting 89–90° and 114–115°, respectively (lit. values[7] 90° and 114°).

Reaction with Sodium Acetate.—The method of Henze[8] was used. A mixture of 35 g. (0.42 mole) of fused sodium acetate, 150 ml. of sodium-dried benzene and 70 g. (0.38 mole) of 1,3-dichloro-1-propoxybutane was heated at 40–60° with vigorous stirring for 15 minutes. After being stirred 10–14 hours at room temperature the mixture was filtered, dried over calcium chloride for one hour and fractionated at reduced pressure to give 46 g. (58%) of 1-acetoxy-3-chloro-1-propoxybutane; b.p. 88–90° (3 mm.), d^{25}_4 0.9850, $n^{25}D$ 1.4302.

Anal. Calcd. for $C_9H_{17}ClO_3$: Cl, 16.99. Found: Cl, 17.01.

Similarly prepared was 1-acetoxy-3-chloro-1-butoxybutane (yield 78%); b.p. 104–105° (6 mm.), d^{26}_4 1.0083, $n^{25}D$ 1.4394.

Anal. Calcd. for $C_{10}H_{19}ClO_3$: Cl, 15.92. Found: Cl, 15.85.

Reaction with Butylmagnesium Chloride.—To approximately 0.3 mole of butylmagnesium chloride in ether was added gradually with cooling 31.4 g. (0.2 mole) of 1,3-dichloro-1-methoxybutane in an equal volume of sodium-dried ether. At the end of the addition period the mixture was refluxed one hour, cooled and hydrolyzed with 1:4 sulfuric acid and ice. The organic layer was separated, washed with water, neutralized with a saturated sodium bicarbonate solution, washed with water, dried overnight with magnesium sulfate, and fractionated to give 24 g. (67%) of 2-chloro-4-methoxyoctane; b.p. 69–71° (6 mm.), d^{20}_4 0.9158, $n^{20}D$ 1.4300.

Anal. Calcd. for $C_9H_{19}ClO$: Cl, 19.84. Found: Cl, 19.50.

Also prepared from 30 g. (0.18 mole) of 1,3-dichloro-1-ethoxybutane and butylmagnesium chloride was 20 g. (59%) 2-chloro-4-ethoxyoctane, b.p. 58–60° (4 mm.) d^{24}_4 0.9041, $n^{24}D$ 1.4294.

Anal. Calcd. for $C_{10}H_{21}ClO$: Cl, 18.40. Found: Cl, 17.97.

Reaction with Malonic Ester.—Forty grams (0.25 mole) of malonic ester was added to 6 g. (0.255 gram-atom) of finely divided sodium in sodium-dried ether and the mixture refluxed and stirred until reaction ceased. To this was gradually added 40 g. (0.255 mole) of 1,3-dichloro-1-methoxybutane, the mixture allowed to stand for 12 hours, refluxed one hour and allowed to stand an additional four hours, filtered, and the solids washed several times with dry ether. The filtrate and washings were combined, dried over magnesium sulfate, and distilled to give 30 g. (43%) of 1,1-dicarbethoxy-2-methoxy-4-chloropentane; b.p. 143–145° (5 mm.), d^{20}_4 1.1053, $n^{20}D$ 1.4471.

Anal. Calcd. for $C_{12}H_{21}ClO_5$: Cl, 12.63. Found: Cl, 12.55.

Similarly prepared from 14 g. (0.08 mole) of 1,3-dichloro-2-methyl-1-methoxybutane was 8 g. (33%) of 1,1-dicarbethoxy-2-methoxy-3-methyl-4-chloropentane; b.p. 138° (3 mm.), d^{20}_4 1.0778, $n^{20}D$ 1.4462.

Anal. Calcd. for $C_{13}H_{23}ClO_5$: Cl, 12.03. Found: Cl, 12.45.

Reaction with Sodium Cyanide.—A modification of the procedure of Henze[8] was used. To 53.9 g. (1.1 moles) of oven-dried sodium cyanide was slowly added 147 g. (1.0 mole) of 1,3-dichloro-1-methoxybutane in 100 ml. of sodium-dried benzene, the mixture stirred and heated at 58–67° for 30 hours, filtered and dried over magnesium sulfate. On fractionation there was obtained 105 g. (72%) of 3-chloro-1-cyano-1-methoxybutane, b.p. 53° (10 mm.), d^{20}_4 1.0386, $n^{20}D$ 1.4298. This compound was identified by conversion to the methyl ester (of the corresponding acid) which was analyzed for chlorine.

Sodium cyanide was found to be superior to cuprous cyanide. Once prepared, the nitrile was extremely stable to hydrolysis. The methods of Henze[8] using barium hydroxide, Krieble and Noll[9] with hydrochloric acid, and Berger and Olivier,[10] using 100% phosphoric acid, and that of Rietz,[11] were all tried, but were unsuccessful in producing identifiable quantities of the acid. In each case the nitrile was decomposed and could not be recovered.

Hydrolysis of the Cyano Derivative to the Methyl Ester.—Twenty-five grams (0.17 mole) of the cyano compound above, 18 g. of methyl alcohol and two drops of water were saturated with hydrogen chloride and refluxed. After one hour the mixture was washed with water, extracted with ether, dried over magnesium sulfate, and fractionated. There was obtained 12 g. (40%) of 1-carbomethoxy-3-chloro-1-methoxybutane; b.p. 45° (5 mm.), d^{20}_4 1.0766, $n^{20}D$ 1.4250.

Anal. Calcd. for $C_7H_{13}ClO_3$: Cl, 19.63. Found: Cl, 19.90.

The ester could not be hydrolyzed to the acid.

Reaction of the Cyano Derivative with Butylmagnesium Chloride.—To approximately one-half mole of butylmagnesium chloride was slowly added 36.7 g. (0.25 mole) of 3-chloro-1-cyano-1-methoxybutane, the mixture stirred at room temperature for 24 hours, the product hydrolyzed with 1:4 sulfuric acid, extracted with ether, washed with saturated sodium bicarbonate solution, washed with water, dried over magnesium sulfate and fractionated. There was obtained 32 g. (68%) of 2-chloro-4-methoxy-5-nonanone; b.p. 75–77° (8 mm.), d^{20}_4 0.9669, $n^{20}D$ 1.4311.

Anal. Calcd. for $C_{10}H_{19}ClO_2$: Cl, 17.17. Found: Cl, 17.49.

This product did not form an oxime, semicarbazone, or 2,4-dinitrophenylhydrazone.

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Tuskegee Institute, Alabama

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