

[CONTRIBUTION NO. 157 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Keto Ethers Derived from *s*-Butyl α -Chloroethyl Ether^{1,2}

BY ROBERT J. SPEER WITH HENRY R. HENZE

We have been interested in the synthesis of keto ethers for attempted conversion subsequently into heterocyclic compounds of possible value as medicinals. Among the alkyl groups to which are ascribed desirable pharmacological properties as producers of narcosis are ethyl and *s*-butyl. It seemed desirable to link together these two in an alkoxyalkyl grouping and to prepare ketones containing the latter.

The synthesis of *s*-butyl α -chloroethyl ether has not been reported previously. From this compound, utilizing the procedures described in earlier papers of this series, there has been obtained α -(*s*-butoxy)-propionitrile, and from the latter nine new keto ethers containing this *s*-butoxyethyl grouping. Despite the proximity of the branched alkoxyalkyl configuration, most of the butoxyethyl alkyl ketones contain a reactive group as evidenced by the ease with which semicarbazones can be obtained from all these keto ethers except the two in which the alkyl group contains a branching in the position α - to the carbonyl group, namely, the *s*-propyl and *s*-butyl members. It was rather surprising therefore to find that not even the *s*-butoxyethyl *n*-alkyl ketones could be condensed with isatin by means of aqueous or alcoholic solutions of potassium hydroxide, by diethylamine, or by anhydrous sodium acetate in glacial acetic acid.

Experimental

Preparation of *s*-Butyl α -Chloroethyl Ether.—This compound was obtained readily through utilization of Henry's³ procedure, but could be purified only with considerable difficulty. From saturation of a mixture of 66 g. of paraldehyde (1.5 moles calculated as CH_2CHO) and 74 g. (1.0 mole) of *s*-butyl alcohol with dry hydrogen chloride and subsequent fractional distillation there was secured approximately 114 g. (83% yield) of α -chloroethyl *s*-butyl ether: b. p. 109° (741 mm.) (profound decomposition) and b. p. 38–39° (20 mm.) (slight decomposition); d^{20}_4 0.9392; n^{20}_D 1.4149; γ^{20} 23.66 dynes/cm.; M_R calcd., 36.42; M_R found, 36.42; P calcd., 325.4; P found, 320.8; molal free surface energy 653.7 ergs.

(1) Preceding paper in this series, Spurlock with Henze, *J. Org. Chem.*, **4**, in press (1939).

(2) Presented before the Division of Organic Chemistry at the 97th meeting of the American Chemical Society at Baltimore, Maryland, April 3–7, 1939.

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

Anal. Calcd. for $\text{C}_8\text{H}_{15}\text{ClO}$: Cl, 25.96. Found: Cl, 25.97.

Preparation of *s*-Butyl α -Cyanoethyl Ether.—The method of Gauthier⁴ served to produce this compound in 77.7% yield, from interaction of 110.0 g. (0.81 mole) of *s*-butyl α -chloroethyl ether and 120 g. (0.9 mole) of silver cyanide in the presence of dry benzene. This nitrile was obtained also by the use of mercuric cyanide but in only 23.4% of the theoretical yield. The cyano ether boiled at 162° (744 mm.), d^{20}_4 0.8594; n^{20}_D 1.4030; γ^{20} 25.22 dynes/cm.; M_R calcd., 35.99; M_R found, 36.11; P calcd., 335.0; P found, 331.7; molal free surface energy 705.1 ergs.

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}$: C, 66.01; H, 10.30; N, 11.01. Found: C, 66.02; H, 10.22; N, 11.09.

Preparation of Keto Ethers.—The method of Sommelet⁵ was again used successfully in the synthesis of the alkyl α -(*s*-butoxy)-ethyl ketones. The appropriate Grignard reagent was prepared under anhydrous conditions and treated with the cyano ether. The ether-soluble reaction product was allowed to stand for eight to twelve hours before being decomposed by addition of ice and dilute hydrochloric acid. The keto ether, usually canary-yellow in color, was extracted with ethyl ether, washed with sodium bicarbonate solution and dried over anhydrous calcium chloride. The residual yellow colored liquid was fractionated under reduced pressure. When freshly distilled the keto ethers are colorless liquids which acquire a yellowish tint on standing. They all possess a slight rancid or pungent odor which becomes more pronounced with passage of time. These compounds are practically insoluble in water but are completely miscible with organic solvents such as the alcohols, ether, benzene, chloroform, and acetone.

Boiling points of the keto ethers were taken with short accurately calibrated Anschütz thermometers, and properly corrected values are reported. Surface tensions of the liquids were measured by means of a Cassel⁶ precision capillarimeter at 20°. Densities were determined by means of a small pycnometer containing 0.9041 g. of water at 20°. The data resulting from the measurement of physical properties, the values for molecular refraction, parachor,⁷ and molal free surface energy derived from these data by calculation, and the information obtained through analysis of the keto ethers are collected in Table I.

Solid semicarbazones could be obtained from all the butoxyethyl alkyl ketones synthesized except those two in which the alkyl group contained a branching in the position α - to the carbonyl group; namely, the *s*-propyl and *s*-butyl members. The

(4) Gauthier, *Compt. rend.*, **143**, 831 (1906).

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

(6) Cassel, *Chem.-Zig.*, **53**, 479 (1929).

(7) Sugden, *J. Chem. Soc.*, **126**, 1180 (1924).

TABLE I
 ALKYL α -(*s*-BUTOXY)-ETHYL KETONES, R—CO—CH(CH₃)—O—CH(CH₃)CH₂CH₃

	—R	°C.	B. p.	Mm.	d_{20}^4	n_{20}^D	γ_{20}^{20} dynes/cm.	Yield, %	Free surface energy, ergs
1	Methyl	162-163		750	0.8707	1.4080	24.40	68.5	735.8
2	Ethyl	174		747	.8700	1.4123	25.11	57.0	805.9
3	<i>n</i> -Propyl	189		750	.8658	1.4153	24.99	53.8	851.8
4	<i>s</i> -Propyl	186		751	.8656	1.4159	24.65	36.5	840.4
5	<i>n</i> -Butyl	212		750	.8640	1.4210	25.47	61.7	915.6
6	Isobutyl	202		747	.8594	1.4179	24.31	63.4	877.2
7	<i>s</i> -Butyl	206		751	.8654	1.4209	25.18	35.7	904.5
8	<i>n</i> -Amyl	226		745	.8621	1.4246	25.93	62.5	980.0
9	Isoamyl	221		747	.8592	1.4237	25.56	67.7	968.2

—R	M. R.		Parachor		Carbon, %		Hydrogen, %	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	40.80	40.84	375.2	368.1	66.62	66.43	11.19	11.10
2	45.42	45.36	414.2	407.1	68.31	68.05	11.46	11.35
3	50.03	49.85	453.2	444.8	69.72	69.67	11.70	11.70
4	50.03	49.95	453.2	443.5	69.72	69.56	11.70	11.77
5	54.65	54.67	492.2	484.4	70.92	70.91	11.91	11.79
6	54.65	54.64	492.2	481.3	70.92	70.80	11.91	11.89
7	54.65	54.58	492.2	482.2	70.92	70.73	11.91	11.70
8	59.27	59.45	531.2	524.3	71.94	71.87	12.08	11.97
9	59.27	59.50	531.2	524.2	71.94	72.09	12.08	11.98

semicarbazones usually crystallize as long needles from diluted methanol (40-50% solution). The melting points reported are corrected values and are tabulated, together with the data for nitrogen analysis of these derivatives, in Table II.

ethers with isatin in alcoholic solution by means of diethylamine. Finally, the ketones were recovered unchanged subsequent to being heated with isatin in glacial acetic acid in which anhydrous sodium acetate had been dissolved.

 TABLE II
 SEMICARBAZONES, C₂H₅CH(CH₃)OCH(CH₃)C(R)=NNH—CONH₂

—R	M. p., °C. (corr.)	Nitrogen, %	
		Calcd.	Found
Methyl	117-118	20.88	20.73
Ethyl	126-127	19.53	19.78
<i>n</i> -Propyl	116	18.33	18.36
<i>n</i> -Butyl	106-107	17.27	17.14
Isobutyl	100	17.27	17.10
<i>n</i> -Amyl	78	16.33	16.20
Isoamyl	104	16.33	16.15

The ketones which readily had formed semicarbazones were warmed with an equivalent quantity of isatin dissolved in a 33% aqueous solution of potassium hydroxide and sufficient alcohol to produce a homogeneous solution, but no evidence of reaction was obtained. Likewise failure attended attempts to condense these keto

Summary

1. *s*-Butyl α -chloroethyl ether has been prepared and converted into α -(*s*-butoxy)-propionitrile. The latter, in turn, has been utilized to obtain nine examples of a new type of keto ether.

2. The carbonyl group in these keto ethers has been shown to be reactive in semicarbazone formation except in those members of the series in which the carbonyl group is linked to two tertiary carbon atoms.

3. Condensation of the ketones which do form semicarbazones could not be effected with isatin by means of aqueous alcoholic potassium hydroxide solution, by an alcoholic solution of diethylamine, or by anhydrous sodium acetate in glacial acetic acid solution.

AUSTIN, TEXAS

RECEIVED MARCH 13, 1939