

alcohol containing a few drops of concentrated hydrochloric acid. The solution was heated for fifteen minutes, cooled, neutralized with sodium carbonate, and the semicarbazone prepared *in situ* in the usual manner; m. p. 190–191°; literature, 192°.<sup>5</sup> Other acyloin semicarbazone melting points were as follows: from (VIII) and (XII), 184–186°; from (IX) and (XVII), 193°; from (XIII), 161–162°; from (XIV) and (XVIII), 202–203°.

(5) Hoogenen and Jansen, *Rec. trav. chim.*, **51**, 260 (1932).

### Summary

1. Acetylenic carbinols have been condensed with methanol to produce a number of substituted dioxanes and with ethylene glycol to form various dioxolanes.

2. Similar reactions with acetic acid yield acyloin acetates.

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

## Keto Ethers. IX. Propoxymethyl Alkyl (or Phenyl) Ketones<sup>1</sup>

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During the past decade much attention has been directed in this Laboratory to a study of bifunctional compounds. The keto ethers have proved to be of special interest because of their value as intermediates in further synthesis, for example, of 5,5-disubstituted hydantoins and substituted cinchoninic acids. The latter contain structures favorable to exhibition of pharmacological activities of widely varying types.

In the present study the two isomeric chloromethyl propyl ethers have been prepared and converted into the corresponding propoxyacetonitriles. The latter, in turn, have been caused to react with suitable Grignard reagents to yield fourteen new examples of *n*- or isopropoxymethyl alkyl ketones and of two analogous phenyl ketones.

### Experimental

**Chloromethyl Propyl Ethers.**—Three moles (180 g.) of *n*-propyl alcohol and one equivalent (90 g.) of trioxymethylene were mixed, cooled, and saturated with dry hydrogen chloride during a period of four hours; during the reaction the trioxymethylene dissolved slowly and two layers formed. The upper, ethereal layer was separated, dried and fractionated; yield, 210 g. (64%) of chloromethyl *n*-propyl ether<sup>3</sup> boiling at 26–28° (32 mm.), 110° (755 mm.),  $n^{20}_D$  1.4106,  $d^{20}$ , 0.9894, *MR* calcd. 27.18, *MR* found 27.21. The chloro ether was prepared also in about 60% yield from commercial formalin solution. This chloro ether is very susceptible to hydrolysis and should be used as quickly as possible in further synthesis.

*Anal.* Calcd. for  $C_3H_7ClO$ : Cl, 32.66. Found: Cl, 32.95.

(1) Previous paper in this series, Henze and Wilson, *This Journal*, **63**, 2112 (1941).

(2) Constructed in part from the M.A. theses of the four junior collaborators.

(3) L. Henry, *Bull. soc. chim.*, [2] **44**, 458 (1835); Favre, *ibid.*, [3] **11**, 1095 (1894); Karvonen, *Am. Acad. sci. Fennicae*, **A3**, 1 (1941).

For the preparation of the isopropyl analog, 540 g. (9 moles) of isopropyl alcohol and 750 g. of 36% formalin solution (equivalent to 9 moles of formaldehyde) were utilized. There was obtained 480 g. (49% yield) of isopropyl chloromethyl ether<sup>4</sup> boiling at 36° (45 mm.), 101° (750 mm.),  $n^{20}_D$  1.4095,  $d^{20}$ , 0.9843, *MR* calcd. 27.18, *MR* found 27.30.

*Anal.* Calcd. for  $C_3H_7ClO$ : Cl, 32.66. Found: Cl, 33.01.

The chloro ethers are relatively unstable, especially upon exposure to atmospheric moisture, and were converted at once into the corresponding nitriles.

**Propoxyacetonitriles.**—By heating a well-stirred mixture of 230 g. of dry cuprous cyanide and an equal volume of anhydrous ether to gentle refluxing and slowly adding 212 g. of chloromethyl *n*-propyl ether, diluted with an equal volume of ether, through a period of two hours, filtering from cuprous salts, and fractionation there was obtained 164 g. (55% yield) of *n*-propoxyacetonitrile boiling at 56° (40 mm.), 152° (751 mm.),  $n^{20}_D$  1.4001,  $d^{20}$ , 0.8971, *MR* calcd. 26.75, *MR* found 26.75.

*Anal.* Calcd. for  $C_3H_7NO$ : N, 14.13. Found: N, 13.99.

**Isopropoxyacetonitrile** was obtained in 56% yield from interaction of 480 g. of chloromethyl isopropyl ether and 520 g. of dry cuprous chloride suspended in 1000 g. of anhydrous ether; b. p. 74° (53 mm.), 145–146° (748 mm.);  $n^{20}_D$  1.3960,  $d^{20}$ , 0.8918, *MR* calcd. 26.75, *MR* found, 26.69.

*Anal.* Calcd. for  $C_3H_7NO$ : N, 14.13. Found: N, 13.93.

**Preparation of Keto Ethers.**—The appropriate Grignard reagent, prepared in the usual manner from an alkyl or phenyl halide, was treated with slightly less than the equivalent amount of a propoxyacetonitrile (using 0.4 to 1.0 molar quantities); usually reaction was vigorous and more ether had to be added to permit stirring of the

(4) Litterschied, *Ann.*, **330**, 108 (1903); Stappers, *Chem. Zentr.*, **76**, 921 (1905); Farren, Fife, Clark and Garland, [*This Journal*, **47**, 2419 (1925)] reported  $n^{18}$  1.4592,  $d^{20}$ , 0.9790, *MR* obs. 26.85. Actually, from this index of refraction, the calculated *MR* is 30.33, whereas an index of refraction of 1.3994 is required to yield the calculated *MR* of 26.85.

TABLE I  
 PROPOXYMETHYL ALKYL (OR PHENYL) KETONES, C<sub>4</sub>H<sub>7</sub>OCH<sub>2</sub>COR      2,4-DINITROPHENYLHYDRAZONES

C <sub>6</sub> H <sub>7</sub>	R	Yield, %	B. p., (cor.) mm.	n <sub>D</sub> <sup>20</sup>	d <sub>4</sub> <sup>20</sup>	Molec. refract.		Carbon, %		Hydrogen, %		M. p., °C. (cor.)	Nitrogen, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found		Calcd.	Found
n-	-CH <sub>3</sub>	52	49 <sup>a</sup>	6	1.4052	0.9020	31.56	31.55	62.04	61.88	10.41	10.36		
i-	-CH <sub>3</sub>	48	35	10	1.4004	.8918	31.56	31.59	62.04	62.11	10.41	10.40	144	18.92 10.03
n-	-C <sub>2</sub> H <sub>5</sub>	46	56	4	1.4122	.8940	36.18	36.17	64.57	64.26	10.84	10.68		
i-	-C <sub>2</sub> H <sub>5</sub>	41	47	11	1.4082	.8875	36.18	36.18	64.57	64.24	10.84	10.98	103	18.06 18.16
n-	n-C <sub>3</sub> H <sub>7</sub>	64	64	4	1.4155	.8858	40.80	40.80	66.62	66.42	11.18	11.02		
i-	n-C <sub>3</sub> H <sub>7</sub>	42	56	8	1.4120	.8786	40.80	40.82	66.62	66.72	11.18	11.20	98	17.28 17.39
n-	i-C <sub>3</sub> H <sub>7</sub>	35	79	60	1.4147	.8847	40.80	40.80	66.62	66.49	11.18	11.19		
i-	i-C <sub>3</sub> H <sub>7</sub>	8	42	6	1.4095	.8790	40.80	40.56	66.62	65.86	11.18	11.02	89	17.28 17.43
n-	n-C <sub>4</sub> H <sub>9</sub>	51	81	12	1.4210	.8815	45.42	45.44	68.31	68.02	11.47	11.36		
i-	n-C <sub>4</sub> H <sub>9</sub>	37	63	7	1.4196	.8761	45.42	45.38	68.31	68.03	11.47	11.51	78	16.57 16.66
i-	i-C <sub>4</sub> H <sub>9</sub>	25	56	5	1.4138	.8674	45.42	45.54	68.31	68.01	11.47	11.67	95	16.57 16.65
i-	s-C <sub>4</sub> H <sub>9</sub>	11	50	5	1.4165	.8763	45.42	45.33	68.31	67.70	11.47	11.17	61	16.57 16.72
n-	n-C <sub>5</sub> H <sub>11</sub>	48	120	45	1.4240	.8783	50.03	50.04	69.72	69.47	11.70	11.49	73	15.91 16.08
i-	n-C <sub>5</sub> H <sub>11</sub>	45	83	8	1.4209	.8709	50.03	50.12	69.72	69.83	11.70	11.89	77	15.91 16.07
n-	i-C <sub>5</sub> H <sub>11</sub>	46	111	26	1.4230	.8726	50.03	50.02	69.72	69.43	11.70	11.56	79	15.91 16.36
i-	i-C <sub>5</sub> H <sub>11</sub>	30	83	9	1.4189	.8691	50.03	50.02	69.72	69.36	11.70	11.78	82	15.91 16.03
n-	-C <sub>6</sub> H <sub>5</sub>	37	118	6	1.5150	1.0333	51.71 <sup>b</sup>	51.94	74.13	73.87	7.92	7.87		
i-	-C <sub>6</sub> H <sub>5</sub>	40	112	6	1.5129	1.0290	51.71 <sup>b</sup>	51.97	74.13	74.01	7.92	7.77		

<sup>a</sup> Gauthier [*Ann. chim. phys.*, [8] 16, 289 (1909)] reported b. p. 145° (732 mm.); we record b. p. 150° (763 mm.).

<sup>b</sup> Includes 0.65 for exaltation due to C<sub>6</sub>H<sub>5</sub>CO grouping [*J. prakt. Chem.*, [2] 84, 35 (1911)].

viscous reaction mixture to continue. Hydrolysis of the adduct was accomplished with cold hydrochloric acid, usually yielding a deeply red-colored solution. After repeated fractionation, the ketones are stable, colorless liquids with characteristic odor. They decompose slightly when heated to their respective boiling points at atmospheric pressure.

### Summary

The synthesis is reported of sixteen new keto ethers containing either the normal or isopropoxy grouping.

AUSTIN, TEXAS

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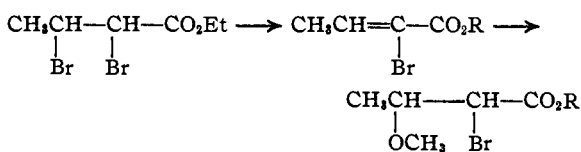
## NOTES

### Synthesis of $\alpha$ -Bromo- $\beta$ -methoxy-*n*-butyric Acid

BY HERBERT E. CARTER AND LUMAN F. NEV

As an intermediate in the synthesis of threonine West and Carter<sup>1</sup> used the mixture of  $\alpha$ -bromo- $\beta$ -methoxy-*n*-butyric acids obtained by brominating a mercuration product of crotonic acid. This mixture of bromomethoxybutyric acids contains approximately 50% of the threonine<sup>2</sup> precursor. Recently Wood and du Vigneaud<sup>3</sup> reported the conversion of ethyl  $\alpha,\beta$ -dibromopropionate to ethyl  $\alpha$ -bromo- $\beta$ -ethoxypropionate by the action of sodium ethylate. It seemed probable that ethyl  $\alpha$ -bromo- $\beta$ -methoxy-

*n*-butyrate might be prepared from ethyl  $\alpha,\beta$ -dibromo-*n*-butyrate in a similar manner. Therefore we have made a study of the reactions



The reaction of ethyl  $\alpha,\beta$ -dibromo-*n*-butyrate with one mole of sodium methylate gives ethyl  $\alpha$ -bromocrotonate together with a small amount of ethyl  $\alpha$ -bromo- $\beta$ -methoxy-*n*-butyrate. However, in the presence of slightly larger quantities of sodium methylate the dibromo ester is converted into the bromomethoxy ester in yields of 80–90%. Ethyl  $\alpha$ -bromocrotonate also gives an excellent yield of bromomethoxy ester when treated with sodium methylate and hence may be considered an intermediate in the above reaction.

(1) West and Carter, *J. Biol. Chem.*, 119, 109 (1937).

(2)  $\alpha$ -Amino- $\beta$ -hydroxy-*n*-butyric acids exist in two racemic forms, *dl*-threonine and *dl*-allo-threonine. Threonine has the same spatial configuration as does threonine, hence the name [Meyer and Rose, *J. Biol. Chem.*, 115, 721 (1936)]. The second form was designated as *allo*-threonine by West and Carter<sup>1</sup> to express its relation to threonine.

(3) Wood and du Vigneaud, *ibid.*, 134, 413 (1940).