[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE SYNTHESIS OF BETA-BROMO-ALKYL ETHERS AND THEIR USE IN FURTHER SYNTHESES[1,2]

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RECEIVED JULY 1, 1929 PUBLISHED FEBRUARY 6, 1930

Introduction

The remarkable difference in the reactivity of halogen when substituted in the alpha- or beta-position of an aliphatic ether makes it seem desirable to investigate further these derivatives. The present paper describes the preparation of several β-bromo-alkyl ethyl ethers and their use in further syntheses. An adaptation of the method of Houben and Führer[3] was selected as having the most general application. The synthesis consists of a three-stage process, as indicated by the following reactions

$$CH_3CHO + C_2H_5OH + HCl = CH_3CHClOC_2H_5 + H_2O \qquad (1)$$
$$CH_3CHClOC_2H_5 + Br_2 = CH_2BrCHBrOC_2H_5 + HCl \qquad (2)$$
$$CH_2BrCHBrOC_2H_5 + RMgBr = CH_2BrCHROC_2H_5 + MgBr_2 \qquad (3)$$

The initial step was first described by Wurtz and Frapoli[4] and later improved by Gauthier.[5] The second step consists in the bromination of α-chloro-ethyl ethyl ether. The bromination of this compound has been described by Madinaveitia and Puyal[6] as yielding the α-chloro-β-bromo-ethyl ether. The present authors do not obtain the same results. Carefully repeated analyses of the product and a study of the yield values show our product to be the dibromo derivative. The final step is an adaptation of the method used by Houben and Führer[3] for the synthesis of β-chloro ethers applied to the preparation of the corresponding bromo derivatives. The yields are good.

The Synthesis of β-Ethoxy-alkyl Mercaptans.[7]—The β-halogenated ethers are remarkable for their lack of chemical reactivity toward some reagents. The β-bromo ethers herein described may be distilled over solid caustic soda without appreciable decomposition. They do, however, react readily with the alkali metal hydrosulfides, forming the corresponding mercaptans. The β-ethoxy-alkyl mercaptans when freshly pre-

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[1] Presented before the Organic Division of the American Chemical Society, in Philadelphia, September 7, 1926.

[2] This paper is abstracted from the Dissertation presented by Lloyd C. Swallen in partial fulfilment of the requirements for the degree of Doctor of Philosophy, to the Faculty of the Graduate School of Ohio State University, June, 1926.

[3] Houben and Führer, *Ber.*, **40**, 4993 (1907).

[4] Wurtz and Frapoli, *Ann.*, **108**, 226 (1858).

[5] Gauthier, *Ann. chim. phys.*, [8] **16**, 311 (1909).

[6] Madinaveitia and Puyal, *Anales soc. españ. fis. quim.*, **16**, 329–337 (1918).

[7] While this work was in progress two of the compounds herein described were also prepared by Rojahn and Lemme, *Arch. Pharm.*, **263**, 612 (1925).

pared have a not unpleasant odor closely resembling that of the corresponding chloro ethers. Upon standing they develop the usual mercaptan characteristics as to odor but are quite stable. They are easily converted into the corresponding disulfides and mercaptide chloride derivatives by the usual methods. Ethoxy-ethyl mercaptan readily condenses with acetone to form the corresponding mercaptol and is easily oxidized to ethoxy-ethylsulfonic acid. The latter compound has been converted into the corresponding sulfochloride and sulfonamide.

β-Bromo Ethers in the Malonic Ester Synthesis.—β-Ethoxy-ethylmalonic ester has been previously described by Byk,[8] who obtained it by the action of β-iodo-ethyl ethyl ether upon malonic ester. It is now shown that an appreciable yield of the same product results even when the β-chloro ether is used. β-Ethoxy-*n*-butyl bromide also reacts readily with malonic ester to form β-ethoxy-*n*-butylmalonic ester in good yield. The latter compound readily yields γ-ethoxy-*n*-caproic acid.

β-Bromo Ethers in the Williamson Reaction.—The β-ethoxyphenetole formed by the action of sodium phenolate upon β-chloro-ethyl ethyl ether is identical in every respect with the product described by Henry[9] as having been derived by the action of sodium alcoholate upon β-chlorophenetole.

Reaction with Aniline.—Cretcher and Pittenger[10] have shown that morpholines are formed by the action of β,β′-dichloro-diethyl ether upon aniline. In an analogous way the monoethoxy-alkylanilines are now produced by the action of aniline upon the β-halogenated alkyl ethyl ethers.

Reaction with Metals.—The most interesting reaction and one which promises to be of great value in synthesis is the decomposition of the β-halogenated ethers in the presence of metals.

Wislicenus[11] observed that β-chloro-acetal reacts with sodium above its melting point to form ethyl vinyl ether as one of the principal products. Wohl and Berthold[12] have also shown that metallic sodium reacts with β-chlorophenetole to form chiefly sodium phenolate and ethylene. Grignard[13] found that β-bromophenetole formed an alkylmagnesium bromide which rapidly decomposed to give phenoxy magnesium bromide and ethylene. In agreement with these facts it is now found that the β-bromo-alkyl ethyl ethers react with magnesium to form olefins as the principal product. In the experimental part of this paper it will be

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[8] Byk, German Patent 285,636; *Chem. Zentr.*, II, 639 (1915).

[9] Henry, *Bull. soc. chim.*, **40**, 324 (1883); *Compt. rend.*, **96**, 1233 (1883).

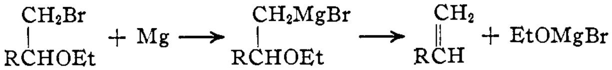
[10] Cretcher and Pittenger, THIS JOURNAL, **47**, 163 (1925); Cretcher, Koch and Pittenger, *ibid.*, **47**, 1173 (1925).

[11] Wislicenus, *Ann.*, **192**, 106 (1878).

[12] Wohl and Berthold, *Ber.*, **43**, 2177 (1910).

[13] Grignard, *Compt. rend.*, **138**, 1048 (1904).

shown that β-ethoxy-*iso*heptyl bromide reacts with magnesium in the presence of anhydrous ether to yield α-*iso*heptene. The course of the reaction can be easily understood upon the basis of the following mechanism



$$\underset{\text{RCHOEt}}{\overset{\text{CH}_2\text{Br}}{|}} + \text{Mg} \longrightarrow \underset{\text{RCHOEt}}{\overset{\text{CH}_2\text{MgBr}}{|}} \longrightarrow \underset{\text{RCH}}{\overset{\text{CH}_2}{\|}} + \text{EtOMgBr}$$

The significance of this decomposition lies in the fact that the β-bromoalkyl ethyl ethers may be synthesized readily as indicated above. The yields are good and the reaction seems to be of quite general application. The process promises well as a method for the synthesis of olefins with a definite constitution. The application to the synthesis of olefins has been further developed and will be offered for publication at an early date.

Experimental Part

Preparation of β-Chloro Ethers.—Several previously described β-chloro ethers were prepared by new or modified methods. The yields and physical constants of these products are shown in Table I.

TABLE I

β-CHLORO ETHERS

Formula	Yield, %	B. p., °C.	d_{20}^{20}
$CH_3—O—CH—CH_2Cl$[14,15]	27	89.5–90.5	1.0659
$C_2H_5—O—CH_2—CH_2Cl$[15,16]	61.7–66	108–109	1.0210
$C_2H_5—O—CHCH_3—CH_2Cl$[17]	54	116–118	0.9798
$C_2H_5—O—CHC_2H_5—CH_2Cl$[17,3]	84	138–139	0.9547
$C_2H_5—O—CHC_6H_5—CH_2Cl$[3]	53	100–105	1.1035

β-Chloro-ethyl methyl ether was prepared by heating a mixture of 80 g. of ethylene chlorohydrin and 120 g. of dimethyl sulfate in a distilling flask over an oil-bath at 145–165° as long as any product distilled. The crude distillate was washed, dried and fractionated.

β-Chloro-ethyl ethyl ether was prepared by dropping slowly a mixture of 175 g. of ethylene chlorohydrin and 350 g. of alcohol into a mixture of 50 cc. of concd. sulfuric acid and 50 cc. of alcohol kept at a temperature of 145–150°. The crude distillate was dried and fractionated using an efficient column, the major portion distilling between 106–110°.

The other three β-chloro ethers of the general type $C_2H_5—O—CHR—CH_2Cl$ were prepared by the method of Houben and Führer. This method consists in adding an ether solution of the appropriate alkylmagnesium bromide to an ether solution of α,β-dichloro-ethyl ethyl ether. Purification was effected in the usual manner.

The Preparation of β-Bromo Ethers.—All attempts to prepare β-bromo ethers by the action of the alkyl hypobromite upon ethylene or of the sodium alcoholate upon ethylene bromide were unsuccessful. A very

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[14] Fileti and Gaspari, *Gazz. chim. ital.*, **27**, II, 293 (1897).

[15] Karvonen, *Ann. acad. sci. Fennicae*, **3A**, 1–103 (1913).

[16] Henry, *Compt. rend.*, **100**, 1007 (1885).

[17] Lieben and Bauer, *Ann.*, **123**, 130–136 (1862).

satisfactory general method for their preparation was found in an adaptation of the method used by Houben and Führer for the preparation of the β-chloro derivatives. The yield values, analyses and physical constants of six β-bromo ethers prepared by this method are given in Table II.

A. Preparation of α-Chloro-ethyl Ethyl Ether,[4,5] $CH_3—CHCl—O—C_2H_5$.—A mixture of 100 g. of paraldehyde and 100 g. of ethyl alcohol was cooled in a freezing mixture and treated with 100 g. of dry hydrogen chloride. The reaction mixture separated into two layers. The upper layer was dried over calcium chloride and fractionally distilled. The portion boiling at 93–96° weighed 162 g., corresponding to a 69% yield. A second run using 200 g. of paraldehyde, 210 g. of alcohol and 226 g. of hydrogen chloride yielded 297 g. (64%).

B. Preparation of α,β-Dibromo-ethyl Ethyl Ether,[18] $C_2H_5—O—CHBr—CH_2Br$. Bromination of α-Chloro-ethyl Ethyl Ether.—The α-chloro-ethyl ether, prepared as described above, was cooled in an ice-bath and the theoretical amount of bromine added in small portions. The reaction mixture was allowed to become decolorized or nearly so, after each addition. The reaction proceeded rapidly at first, but quite slowly toward the end. The gas evolved proved to be almost wholly hydrogen chloride. The crude reaction product was submitted directly to distillation at diminished pressure. Almost the entire product distilled between 92 and 95° (17 mm.). The yields from two successive runs were 91 and 88.4%. Further fractionation yielded a product boiling at 90–91° (20 mm.); d_{20}^{20} 1.7350.

Anal. Calcd. for $C_4H_8OBr_2$: Br, 68.93. Found: Br, 69.08.

The Bromination Reaction.—The yield and analysis as given above leave no doubt as to the identity of the product as α,β-dibromo-ethyl ethyl ether. These results, however, do not correspond to those obtained by Madinaveitia and Puyal,[6] who have described the bromination product of α-chloro-ethyl ether as the α-chloro-β-bromo derivative. In order to secure additional evidence for the correctness of our conclusions the following experiment[19] was made to determine whether the hydrogen halide was hydrogen chloride.

A portion of α-chloro-ethyl ethyl ether was carefully brominated by the procedure described. The gases evolved were absorbed in water. Twenty cc. of the solution thus obtained was treated with an excess of standard silver nitrate solution. The precipitated silver halides were filtered through a Gooch crucible, washed, dried and weighed. The excess silver nitrate in the filtrate was determined by titration with standard ammonium thiocyanate using ferric ammonium alum as an indicator. From these data the relative amounts of silver bromide and silver chloride in the precipitate were calculated. The results were as follows: *Anal.* AgX, 0.2837, 0.2909; cc. of 0.09976 *N* $AgNO_3$, 23.82, 23.88; cc. of 0.1197 *N* NH_4CNS, 3.32, 3.26; AgCl, calcd., 0.2835, 0.2855; AgBr, calcd., 0.0002, 0.00054. These results indicate that the hydrogen halide evolved is almost quantitatively hydrogen chloride and support the view that the bromination product is a dibromo derivative.

C. Preparation of β-Bromo Ethers. Condensation of α,β-Dibromo-ethyl Ether with an Alkylmagnesium Halide.—The Grignard reagents were prepared in the usual

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[18] Wislicenus, *Ann.*, **192**, 111 (1878).

[19] This experiment is taken from the unpublished work of Dr. Harry B. Dykstra.

manner from the corresponding alkyl bromides. The α,β-dibromo ether was mixed with about twice its volume of anhydrous ether and placed in a two-liter flask surrounded by an ice-bath. The flask was provided with a reflux condenser and the Grignard reagent added dropwise, with constant shaking. The reaction took place instantaneously and with a hissing sound. The rate at which the reagent was added was regulated so as to avoid undue loss of ether by volatilization through the condenser. A slight excess of the alkylmagnesium halide not only served to increase the yield but also to render the product more easily purifiable. The reaction mixture was decomposed by pouring on ice and acidifying with dilute hydrochloric acid. The ether layer was separated, dried over calcium chloride and the ethyl ether removed by distillation. The product was then transferred to a smaller flask, about 5% of its weight of solid sodium hydroxide added and fractionated.

β-Ethoxy-*n*-propyl bromide and β-ethoxy-*n*-butyl bromide were distilled at atmospheric pressure, but the remaining compounds were distilled under diminished pressure. Further purification was effected by refractionation, sometimes over solid alkali, using an efficient column.

The bromine determinations were made by decomposing the compounds by the Bacon–Stephanow procedure and titrating the halogen by the Volhard method, using ferric nitrate as an indicator.

TABLE II

β-BROMO-ALKYL ETHYL ETHERS, $C_2H_5O—CHR—CH_2Br$

β-Ethoxy- ( )-bromide	R-	Yield, %	B. p., °C.	d_{20}^{20}	Bromine, % Found	Calcd.
n-Propyl	CH_3-	77.4	138	1.2706	47.91	47.85
n-Butyl	C_2H_5-	60.5	166	1.2317	44.22	44.15
n-Amyl	*n*-C_3H_7-	66.5	176	1.1929	41.06	40.98
Iso-amyl	*iso*-C_3H_7-	30.0	172	1.2183	40.54	40.98
n-Hexyl	*n*-C_4H_9-	70.0	85–87 (15 mm.)	1.1573	38.22	38.24
*Iso*heptyl	*iso*-C_5H_{11}-	60.0	93–95 (15 mm.)	1.1286	35.67	35.83

Ethyl-β-iodo-ethyl Ether,[20] $C_2H_5—O—CH_2—CH_2I$.—The methods described by Baumstark and by Henry for the preparation of this compound were tried but the following procedure was found to be much superior.

A mixture of 35 g. of anhydrous sodium iodide, 35 cc. of 95% alcohol and 24 g. of β-chloro-ethyl ethyl ether was refluxed on the water-bath for five hours. The reaction mixture was diluted with water, causing the separation of an oily layer. The aqueous layer was extracted with chloroform, the extract added to the oily layer and the solution thus obtained dried and fractionally distilled. Ten g. of the chloro ether was recovered. The yield was 24 g. or 89% of the theoretical based on the amount of chloro ether actually used. After further purification the ethyl β-iodo-ethyl ether boiled at 154.5–155° (corr.); d_{20}^{20} 1.7032. Demole gives the same boiling point. Henry gives the density as d^0 1.6924.

Preparation of β-Ethoxy-alkyl Mercaptans and their Derivatives

β-Ethoxy-alkyl Mercaptans, $C_2H_5—O—CHR—CH_2SH$.—A solution of potassium hydrosulfide was prepared by saturating a solution of potassium hydroxide in methyl alcohol with hydrogen sulfide. The appropriate β-chloro-ether was added to this solution in such amounts as would leave the hydrosulfide in approximatey 100% excess. The combined solutions were placed in pressure bottles in 100–150-cc. por-

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[20] Baumstark, *Ber.*, **7**, 1172 (1874); Demole, *ibid.*, **9**, 746 (1876); Henry, *Bull. soc. chim.*, **44**, 459 (1885); *Compt. rend.*, **100**, 1007 (1885).

tions and heated in a water-bath for the time indicated. The reaction mixture was diluted with water, causing a large part of the product to separate as an oily layer. The aqueous portion was extracted with petroleum ether and the extract added to the main product. Usually it was found advantageous to dissolve the mercaptan in caustic soda solution and reprecipitate with hydrochloric acid. When the reaction had been carried quite to completion this solution and reprecipitation proved unnecessary. The crude mercaptan was finally dried and fractionally distilled. A small amount of the sulfide was always formed as a by-product. The experimental conditions and yield values are shown in Table III.

TABLE III

β-ETHOXY-ALKYL MERCAPTANS, $C_2H_5—O—CHR—CH_2SH$

β-Ethoxy-( )-mercaptan	Formula	Chloro ether, g.	Temp., °C.	Time, hours	Yield, % mercaptan	Yield, % sulfide
Ethyl[7]	$C_2H_5OCH_2CH_2SH$	100	65	24	74	13
n-Propyl	$C_2H_5OCH(CH_3)CH_2SH$	25	..	50	36[a]	..
n-Butyl	$C_2H_5OCH(C_2H_5)CH_2SH$	50	90	60	61	14

[a] Eight grams of chloro ether recovered.

The β-ethoxy-alkyl mercaptans are colorless liquids, readily obtained in a high degree of purity. The boiling points are remarkably constant. These ethoxy mercaptans form insoluble salts of both mercury and lead but all attempts to obtain such salts in the crystalline condition failed.

Mercury β-Ethoxy-alkyl Mercaptide Chloride, $C_2H_5—O—CHR—CH_2SHgCl$.—The mercuric chloride derivatives were readily prepared by mixing an alcoholic solution of mercuric chloride with that of the mercaptan. The salt is deposited slowly as a crystalline white powder. These deposits were filtered off, washed first with alcohol and then with ether, dried and submitted directly to analysis.

Bis-(β-ethoxy-alkyl) Disulfide, $(C_2H_5O—CHR—CH_2)_2S_2$.—The ethoxy mercaptans were oxidized quantitatively to the disulfides by shaking with the theoretical amount of iodine in either aqueous or alcoholic solution. The oily products which separated were washed with water, dried over calcium chloride and distilled under diminished pressure.

The physical constants and analyses of the β-ethoxy-alkyl mercaptans and their derivatives are summarized in Table IV.

TABLE IV

PHYSICAL CONSTANTS AND ANALYSES

β-Ethoxy-( ) mercaptan	Formula	B. p., °C. (uncorr.)	d^{20}_{20}	Sulfur, % Calcd.	Sulfur, % Found
Ethyl[7]	$EtOCH_2CH_2SH$	125.5–125.8	0.9479	30.20	30.24
n-Propyl	$EtOCHMeCH_2SH$	134.0–134.5	.9238	26.69	26.88
n-Butyl	$EtOCHEtCH_2SH$	156–157	.9177	23.89	25.95
Bis-(ethoxy-( )-) disulfide					
Ethyl	$(EtOCH_2CH_2)_2S_2$	161 (33 mm.)	1.0510	30.50	30.31
n-Butyl	$(EtOCHEtCH_2)_2S_2$	135 (8 mm.)	1.0013	...	...
Mercury ethoxy-( ) mercaptide chloride		M. p. (dec.)			
Ethyl	$EtOCH_2CH_2SHgCl$	152.0–153.5	....	9.40	9.41
n-Propyl	$EtOCHMeCH_2SHgCl$	121–123	....	9.03	9.14
n-Butyl	$EtOCHEtCH_2SHgCl$	86–87	....	8.68	8.53

Bis-(β-Ethoxy-ethyl) Sulfide, $(C_2H_5O—CH_2—CH_2)_2S$.—A solution of 20 g. of sodium hydroxide in 100 cc. of 70% alcohol was saturated with hydrogen sulfide. To this solution 25 g. of α-ethoxy-ethyl chloride was added and the reaction mixture heated at the boiling point for three hours. As no effort was made to prevent the escape of hydrogen sulfide the active agent was sodium sulfide. After cooling the reaction mixture was diluted with water, causing the product to separate as an oily layer. The aqueous layer was extracted with ether and the extract added to the main product. The ether solution was dried and the product purified by fractional distillation. The yield was 51%; b. p. 229° (corr.); d^{20}_{20} 0.9840.

Anal. Subs., 0.1483: $BaSO_4$, 0.933. Calcd. for $C_8H_{18}O_2S$: S, 17.99. Found: S, 17.90.

Formation of Ethylene Sulfide.—Six g. of β-ethoxy-ethyl mercaptan was heated with 12 g. of 48% hydrobromic acid on a water-bath for three hours. A white solid separated, which was proved to be a mixture of the polymers of ethylene sulfide by complete conversion into diethylene disulfide by depolymerization with phenol.

Acetone β-Ethoxy-ethyl Mercaptol, $(CH_3)_2C(SCH_2—CH_2OC_2H_5)_2$.—A mixture of 11 g. of β-ethoxy-ethyl mercaptan and 5 g. of acetone was saturated with dry hydrogen chloride. The reaction mixture became warm and water separated. The mercaptol was washed with water, dried over calcium chloride and distilled *in vacuo*. The yield was 80%; b. p. 134° (7 mm.); d^{20}_{20} 1.0044.

Anal. Subs., 0.2173: $BaSO_4$, 0.4070. Calcd. for $C_{11}H_{24}O_2S_2$: S, 25.41. Found: S, 25.72.

Sodium β-Ethoxy-ethyl Sulfonate,[21] $C_2H_5—O—CH_2—CH_2SO_3Na$.—Fourteen grams of β-ethoxy-ethyl mercaptan was placed in a flask under a reflux condenser. While the contents of the flask was kept at the boiling point, a solution of 30 g. of concd. nitric acid in 100 cc. of water was added in small portions during the course of an hour. The digestion was continued at the boiling point until the reaction mixture became homogeneous. The solution was concentrated on the steam plate, neutralized with sodium hydroxide solution and evaporated to dryness. The sodium sulfonate was extracted with 90% alcohol. Evaporation of the alcoholic extract yielded 21 g. of crude product. Recrystallization from alcohol gave a pure product. The sodium was determined by ashing a weighed sample, treating with sulfuric acid and igniting.

Anal. Calcd. for $C_4H_9O_4SNa$: Na, 13.06. Found: Na, 13.64.

The sodium salt of β-ethoxy-ethyl sulfonic acid is very soluble in water, moderately soluble in 90% alcohol, but only slightly soluble in absolute alcohol. The free acid was not obtained in the pure condition.

β-Ethoxy-ethyl Sulfochloride, $C_2H_5—O—CH_2—CH_2SOCl$.—Twenty-one grams of dry, finely pulverized sodium β-ethoxy-ethyl sulfonate was mixed with 27 g. of phosphorus pentachloride in a round-bottomed flask. The reaction proceeded with the evolution of heat. The flask was arranged for vacuum distillation and heated gently at first but more strongly as the reaction neared completion. The portion distilling above 100° under strongly diminished pressure was washed with water, dried over calcium chloride and twice distilled *in vacuo*. A yield of 8 g. boiling at 118–122° (26 mm.) was obtained. The product was not pure since analysis showed a chlorine content of 21.64% while the calculated value is 20.54%.

A benzene solution of the β-ethoxy-ethyl sulfochloride described above was saturated with dry ammonia gas. The solution was filtered from the ammonium chloride and evaporated. The product obtained was an oil which crystallized after several

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[21] Hübner, *Ann.*, **223**, 218 (1884).

days standing as large colorless crystals, m. p. 41°. This substance, apparently the amide, was not obtained in sufficient purity for analysis.

Use of β-Halogen Ethers in the Malonic Ester Synthesis

β-Ethoxy-ethyl Malonic Ester,[22] $C_2H_5OCH_2—CH_2—CH(COOC_2H_5)_2$.—Seven and one-half grams of sodium was dissolved in 100 cc. of anhydrous alcohol and 50 g. of pure malonic ester added. The flask was shaken vigorously to break up the lumps of the sodium salt and 35 g. of β-chloro-ethyl ethyl ether added with warming and shaking until a clear solution was obtained. The reaction mixture was heated on the water-bath for three hours. The alcohol was distilled off, water added and the product extracted with petroleum ether. Two fractionations under diminished pressure yielded 11.4 g. (14%) of β-ethoxyethylmalonic ester boiling at 134–138° (15 mm.), d^{20}_{20} 1.0430. The boiling point given in the literature is 136° (13 mm.).

β-Ethoxy-*n*-butylmalonic Ester, $C_2H_5O—CHC_2H_5—CH_2—CH(COOC_2H_5)_2$.—A similar reaction was carried out using 50 cc. of anhydrous alcohol, 3 g. of sodium, 22 g. of malonic ester and 18.1 g. of α-bromo-β-ethoxy-*n*-butane. The product boiled at 146–150° (12 mm., uncorr.). Titration of the aqueous solution for ionized halogen showed only 64% of the bromo ether to have been destroyed. The reaction mixture was also quite alkaline, indicating that the heating should have been continued for a longer time. The yield was 58% on the basis of bromo ether actually destroyed. The product was not analyzed but was carried directly to the following preparation.

Calcium β-Ethoxy-*n*-butylmalonate, $C_2H_5O—CHC_2H_5—CH_2—CH(COO)_2Ca$.—The entire product from the preceding preparation was hydrolyzed by heating on the water-bath with a solution of sodium hydroxide (5 g. in 10 cc. of water) until the oily layer had disappeared. The solution was neutralized with concd. hydrochloric acid and the calcium salt precipitated by the addition of a concd. solution of calcium chloride. The salt was filtered off, washed and dried; yield, 6.5 g.

A portion of the salt recrystallized from a mixture of equal parts of methyl alcohol and water was obtained as a white crystalline powder. Calcium was determined by igniting a weighed sample, treating with sulfuric acid and re-igniting.

Anal. Calcd. for $C_9H_{14}O_5Ca$: Ca, 16.54. Found: Ca, 16.33.

γ-Ethoxy-*n*-caproic Acid, $C_2H_5—OCHC_2H_5—CH_2—CH_2—COOH$.—Eight cc. of concd. hydrochloric acid was added to the remainder of the calcium salt obtained in the previous preparation and the free substituted malonic acid extracted with ether. Upon evaporation of the ether, β-ethoxy-*n*-butylmalonic acid was obtained as a thick sirup which could not be induced to crystallize. The product was heated at 180° on an oil-bath as long as any gas was evolved (fifteen minutes); γ-ethoxycaproic acid, b. p. 138–140° (8 mm.) uncorr., d^{20}_{20} 0.9816, was obtained in a yield of 3.3 g.

The barium salt was prepared by neutralizing a solution of barium hydroxide with a slight excess of the acid and carefully evaporating the solution. It is very soluble in water, alcohol and acetone. Barium was determined by ashing a weighed sample and igniting with sulfuric acid.

Anal. Calcd. for $C_{16}H_{30}O_6Ba·H_2O$: Ba, 29.01. Found: Ba, 29.10.

The Williamson Reaction

β-Ethoxyphenetole, $C_6H_5—O—CH_2—CH_2—OC_2H_5$.—Ethyl β-chloro-ethyl ether was heated with an excess of an alcoholic solution of sodium phenolate for ten days. The greater part of the alcohol was removed by distillation and the residue diluted with water. The oily layer which separated was washed with dilute caustic soda solu-

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[22] German Patent 285,636; *Chem. Zentr.*, II, 639 (1915).

tion, dried and fractionally distilled. The product was obtained as a colorless liquid; b. p. 230–232° (corr.); d_{20}^{20} 1.0057.

Bentley, Haworth and Perkin,[23] who obtained the same product by an application of the malonic ester synthesis, give the b. p. as 230°. Henry,[9] who obtained the compound by the action of sodium ethylate upon β-chlorophenetole, gives the boiling point as 230°; *d* 1.018.

Reaction with Aniline

β-Ethoxy-ethylaniline, $C_6H_5NHC_2H_4—O—C_2H_5$.—Fifty grams of ethyl β-chloroethyl ether and an equal weight of aniline were heated at the boiling point for about ten hours. The temperature rose to 180°. The reaction mixture was decomposed by dilute sodium hydroxide solution and the mixture of bases separated, dried and submitted to fractional distillation. Repeated fractionation was necessary to separate the products. Mono-β-ethoxy-ethylaniline was obtained as a colorless liquid, b. p. 262–263° (corr.), d_{20}^{20} 1.0156. It darkens on standing and develops a disagreeable odor.

Anal. Subs., 0.3798: required 22.7 cc. of 0.10006 *N* H_2SO_4. Calcd. for $C_{10}H_{15}ON$: N, 8.49. Found: N, 8.36.

Mono-β-ethoxybutylaniline, $C_6H_5NH—CH(C_2H_5)—CH_2—OC_2H_5$.—This compound was prepared in an analogous manner but with much greater difficulties in purification, due to the formation of tarry substances. The compound boils at 264–269° (corr.) and has a density of d_{20}^{20} 0.9830.

Reaction with Magnesium

Preparation of 1,2-*Iso*heptene, $(CH_3)_2CH—CH_2—CH_2—CH{=}CH_2$.—Thirty-five grams of β-ethoxy *iso*heptyl bromide was added in small portions to 12 g. of magnesium turnings covered with 75 cc. of dry ether. The magnesium soon became coated with a gummy white substance which rendered it somewhat inactive. After warming for five hours on the water-bath, the ether was distilled off using an efficient column. The remaining liquid was decanted from the residue and distilled until the temperature reached 120°. Further fractionation of the distillate yielded 5 g. of *iso*heptene boiling between 80 and 85°, mainly at 85°. The product was identified by conversion into the dibromide.

1,2-*Iso*heptene Dibromide, $(CH_3)_2CH—CH_2—CH_2—CHBr—CH_2Br$.—The *iso*heptene from the preceding preparation was dissolved in chloroform and treated with a slight excess of bromine. The crude dibromide was washed successively with concd. sulfuric acid, dilute sodium hydroxide and water and then dried. The product which distilled *in vacuo* with slight decomposition was obtained in a yield of 8 g., b. p. 95° (13 mm.), d_{20}^{20} 1.5083.

Anal. Calcd. for $C_7H_{14}Br_2$: Br, 61.96. Found: Br, 60.29.

Summary

The method of Houben and Führer has been adapted to the synthesis of β-bromo-alkyl ethyl ethers and six new compounds of this type are described.

It is shown that, notwithstanding the relatively low chemical reactivity of the β-halogenated ethers in comparison with the α-halogenated derivatives, the β-bromo-alkyl ethers may be used advantageously in certain syntheses. They react readily with the alkali hydrosulfides to form β-ethoxy-alkyl mercaptans, which in turn may be converted into the corre-

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[23] Bentley, Haworth and Perkin, *J. Chem. Soc.*, **69**, 171, 1503 (1896).

sponding disulfides, sulfonic acids and related derivatives. The β-bromo-alkyl ethers may be used in the same way as ordinary alkyl halides in the malonic ester synthesis, Williamson's reaction and in the formation of ethoxy-alkylanilines.

β-Bromo-alkyl ethyl ethers react in ether solution with magnesium to form olefins. *Iso*heptene is prepared in this way.

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PICTET AND GAMS' BERBERINE SYNTHESIS

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RECEIVED JULY 15, 1929 PUBLISHED FEBRUARY 6, 1930

The synthesis of the alkaloid berberine by Pictet and Gams[1a] has long been regarded as classic. Some doubt as to its accuracy has, however, recently arisen.

Buck and Perkin[2] in attempting to synthesize *epi*-berberine (2,3-dimethoxy-9,10-methylenedioxyprotoberberine)[3] by the method of Pictet and Gams[1] obtained only the isomeric pseudo-*epi*-berberine (2,3-dimethoxy-10,11-methylenedioxyprotoberberine). Haworth, Perkin and Rankin[4] in repeating Pictet and Gams' synthesis of berberine (2,3-methylenedioxy-9,10-dimethoxyprotoberberine) obtained exclusively the isomeric pseudoberberine (2,3-methylenedioxy-10,11-dimethoxyprotoberberine), the second ring closure taking place so as to give the 10,11- and not the 9,10-dimethoxy compound. A search of the literature showed that Pictet and Gams' alleged ring closure to give the 9,10 compound is unique, at least when the ring substituents are methoxyl or methylenedioxy groups. Pictet himself expresses astonishment that berberine and not the isomer should be formed. The only departure from the general rule is the formation of both tetrahydropalmatine and nor-coralydine from tetrahydropapaveroline, recorded by Späth and Kruta.[5] Here, however, hydroxyl, not alkoxyl, groups were the substituents.

It therefore appeared necessary to investigate the synthesis further, in order to detect any error, if such were present. The authors believe that they have definitely shown the synthesis to be erroneous.

Pictet and Gams[1] on heating homoveratroylhomopiperonylamine with

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[1] The material presented in this paper is from a dissertation submitted by Rose M. Davis to the Graduate School of Arts and Sciences of Duke University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1929.

[1a] Pictet and Gams, *Ber.*, **44**, 2480 (1911).

[2] Buck and Perkin, *J. Chem. Soc.*, **125**, 1675 (1924).

[3] The nomenclature of Buck, Perkin and Stevens, *ibid.*, **127**, 1462 (1925), is used in the present paper.

[4] Haworth, Perkin and Rankin, *ibid.*, **125**, 1686 (1924).

[5] Späth and Kruta, *Monatsh.*, **50**, 341 (1928).