The correlation of various monosubstituted benzpyrenes was rendered difficult by the unusual properties encountered in compounds of this series. Of special note is the conversion of the 5-amino and 5-hydroxy derivatives into the 5,10-quinone on treatment with nitrous acid.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 23, 1939

Substituted Ethers Derived from Ethylene Chlorohydrin[1,2]

BY SHIRLEY POWELL LINGO WITH HENRY R. HENZE

The chief interest in chloro ethers lies in the ease with which the halogen linked in the α-position can be replaced by other atoms or groups, leading particularly to the formation of cyano ethers, ether amides, ether thioamides, alkoxy acids, alkoxy esters, branched chain aldehydes, alkoxy tertiary alcohols, and keto ethers; the last-mentioned type being capable of conversion into heterocyclic compounds of varying degree of physiological activity and toxicity.

Apparently little consideration has been paid to the feasibility of condensing bifunctional alcohols into substituted α-chloro ethers.[3] In this investigation, ethylene chlorohydrin has been condensed, by means of dry hydrogen chloride, with formaldehyde, paraldehyde, propionaldehyde, and n-butyraldehyde, respectively. Subsequently, the conversion of these chloro ethers into ether nitriles, and of several of the latter type into keto ethers, has been studied.

The conversion of α-chloro ethers into α-cyano ethers is of considerable interest in that sodium or potassium cyanide, which reacts readily with alkyl halides to form nitriles, are ineffectual and cuprous, mercuric or silver cyanide[4] must be used; in the latter instance, no isonitrile is formed despite the fact that a carbylamine is usually the chief product of the interaction of silver cyanide and an alkyl halide. As far as we are aware, but one halogenated α-chloro ether has been converted previously into the corresponding halogenated α-cyano ether, the example being α-1,3-dichloroisopropoxypropionitrile.[3] This very considerable difference in the reactivity of the chlorine atoms linked α- or β- to the oxygen atom in

this chloro ether is characteristic also of the four examples of the new type of monochloroalkoxy nitrile produced in this study.

The ability of the chloroalkoxy nitrile to enter into reaction with Grignard reagents has been tested in the instances of β-chloroethoxyacetonitrile and α-(β-chloroethoxy)-propionitrile. In general, the halogen atom shows no tendency to react and ten β-chloroethoxy ketones have been obtained; the one exception was found in the reaction with methylmagnesium iodide, when partial replacement of chlorine by iodine was observed.[5]

These ketones were prepared in the hope that they might serve as intermediates in the synthesis of substituted hydantoins and of quinoline carboxylic acid derivatives. It was disappointing to find that the carbonyl group in this series of keto ethers seems to be not very reactive, and only the 5-isoamyl- and 5-phenyl-5-(2-chloroethoxy)-methylhydantoins and the 5-ethyl- and 5-n-propyl-5-[1-(2-chloroethoxy)-ethyl]-hydantoins were obtained readily.

Experimental

Synthesis of the α-Chloro Ethers.—Utilizing the procedure of Henry,[3] ethylene chlorohydrin and the appropriate aldehyde were mixed in equimolecular quantities, cooled in an ice–salt bath, and saturated with dry hydrogen chloride. The ether layer was separated, dried over anhydrous calcium chloride; unless the concentration of hydrogen chloride in the chloro ether was maintained, the latter became discolored and partially decomposed. The dried material was freed of dissolved gas by aeration under a partial vacuum of 30–40 mm. All distillations of these compounds were accomplished under diminished pressure, since the chloro ethers exhibit a pronounced tendency to decomposition and formation of resinous products at the temperature of their boiling points at atmospheric pressure.

These chloro ethers are colorless liquids possessed of a faint, pleasant odor when carefully purified, but tend to

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

(2) Preceding paper in series, Speer with Henze, THIS JOURNAL, 61, 1226 (1939).

(3) Allen with Henze, ibid., 59, 540 (1937).

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

(5) Cf. ref. 3, page 542, and ref. 2, page 511.

TABLE I
α-CHLORO ETHERS DERIVED FROM ETHYLENE CHLOROHYDRIN

Formula	Yield, %	B. p., °C.	Mm.	d^{20}_4	n^{20}D	Mol. refr. Calcd.	Mol. refr. Found	ΔMR	Chlorine, % Calcd.	Chlorine, % Found
ClCH₂CH₂OCH₂Cl	55	46	10	1.2814	1.4578[a]	27.43	27.49	+0.06	54.96	55.17
ClCH₂CH₂OCHClCH₃	60	51	10	1.1867	1.4473[b]	32.05	32.20	+ .15	49.62	49.45
ClCH₂CH₂OCHClCH₂CH₃	51	60	10	1.1399	1.4496	36.67	36.89	+ .22	45.17	44.83
ClCH₂CH₂OCHClCH₂CH₂CH₃	70	71	10	1.1009	1.4471	41.29	41.51	+ .22	41.47	43.31

[a] Farren, Fife, Clark and Garland, ref. 3, reported: d^{20}_4 1.2817; n^{20}D 1.4952; it must be obvious that the value for index of refraction represents a typographical error, namely, a transposition of 1.4592.

[b] Grignard and Purdy, ref. 3, reported: d^{19} 1.1823; n^{16}D 1.4497; Cl, 49.0.

TABLE II
α-CYANO ETHERS DERIVED FROM ETHYLENE CHLOROHYDRIN, ClCH₂CH₂—O—CHCN—R

—R	Yield, %	B. p. °C.	Mm.	d^{20}_4	n^{20}D	Mol. refr. Calcd.	Mol. refr. Found	ΔMR	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	50	109–110	27.5	1.1846	1.4459	27.00	26.90	−0.10	29.67	29.78	11.72	11.63
CH₃	41	91	10.0	1.1028	1.4358	31.62	31.64	+ .02	26.55	26.23	10.49	10.21
CH₂CH₃	38	97.5	6.0	1.0944	1.4538	36.24	36.50	+ .26	24.03	23.62	9.49	9.17
CH₂CH₂CH₃	35	105.5	4.5	1.0562	1.4513	40.85	41.21	+ .36	21.95	20.87	8.68	8.01

TABLE III
CHLORO KETO ETHERS DERIVED FROM ETHYLENE CHLOROHYDRIN, ClCH₂CH₂—O—CH(R)—CO—R'

—R	—R'	Yield, %	B. p. °C. (corr.)	Mm.	d^{20}_4	n^{20}D	Mol. refr. Calcd.	Mol. refr. Found	ΔMR	Chlorine, % Calcd.	Chlorine, % Found
H	CH₃	58	72–73	8	1.1405	1.4449	31.81	31.94	+0.13	25.96	26.27
H	C₂H₅	40	82	5	1.1245	1.4468	36.43	35.76	− .67	23.55	25.71
H	n-C₃H₇	55	88.5–90.0	4	1.0817	1.4470	41.05	40.67	− .38	21.54	21.69
H	n-C₄H₉	67	88.2–89.0	2	1.0490	1.4486	45.67	45.65	− .02	19.86	19.95
H	n-C₅H₁₁	50	96.2–97.0	2.5	1.0330	1.4503	50.28	50.16	− .12	18.40	18.34
H	i-C₅H₁₁	53	99.5–100.5	2.5	1.0283	1.4490	50.28	50.26	− .02	18.40	18.45
H	C₆H₅[a]	69	152–155	4.5	1.1989	1.5440	51.30	50.97	− .33	17.15	17.41
CH₃	CH₃	17	70.0–72.0	4	1.0977	1.4398	36.43	36.14	− .29	23.55	23.14
CH₃	C₂H₅	76	71.0	3.5	1.0658	1.4410	41.05	40.75	− .30	21.54	22.55
CH₃	n-C₃H₇	80	87.5–88.3	3	1.0363	1.4409	45.67	45.52	− .12	19.86	20.01
CH₃	CH₃ iodo	34	90–92	4	1.5473	1.4953	44.36	45.65	+1.29	52.43[b]	54.69[b]

[a] For ClCH₂CH₂OCH₂COC₆H₅: m. p. 26.1°.   [b] For iodine content in ICH₂CH₂OCH₂COCH₃.

become discolored on standing, even when sealed in a container with a desiccant. Boiling points, or decomposition points, were determined at diminished pressures with calibrated thermometers; boiling points were also obtained under reduced pressures by use of the capillary tube method of Siwoloboff.[6] Densities were obtained with precision pycnometers of very light weight and relatively large volume. The data resulting from determination of physical constants, the values derived from these data by calculation, and such information as was obtained through analysis of these chloro ethers have been collected in Table I.

Synthesis of α-(β-Chloroethoxy)-nitriles.—The nitriles, representing a new type, were prepared by mixing a molar quantity of dry cuprous cyanide with enough dry benzene to form a paste and adding dropwise a molar amount of the appropriate chloro ether diluted with 100 g. of dry benzene, the mixture being stirred and warmed on a steam-bath for three to four hours. After removal of the mixed cuprous salts by filtration, the benzene was distilled and the residual liquid fractionated under diminished pressure. No evidence could be found for the production of any dinitrile in this preparation. The chloroethoxy nitriles are colorless liquids of faint, pleasant

odor, are but slightly decomposed by distillation at atmospheric pressure and remain uncolored for long periods when sealed in a container. The nitriles are insoluble in water but are miscible with the usual organic solvents. Data for certain physical properties and analytical results are shown in Table II.

Synthesis of Chloro Keto Ethers.—These compounds were prepared from either β-chloroethoxyacetonitrile or α-(β-chloroethoxy)propionitrile according to Sommelet's[7] method for producing alkoxynitriles. The appropriate alkyl or phenylmagnesium halide was prepared in anhydrous ether and treated with an ether solution of the chloroethoxy nitrile. The addition product was decomposed with ice and cold, dilute hydrochloric acid and the ether layer separated, dried over calcium chloride and fractionated under about 5 mm. pressure. The ethers are colorless oils when sufficiently purified, otherwise possess a slight yellow tint. All of the liquids are insoluble in water, but readily miscible with the usual organic solvents. The data obtained in characterizing these chloro keto ethers are included in Table III.

From the attempt to condense methylmagnesium iodide and α-(β-chloroethoxy)-propionitrile there was obtained a product in amount such as to represent a

(6) Siwoloboff, *Ber.*, **19**, 795 (1886).

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

yield of about 50% of the theoretical; however, the material contained iodine as well as chlorine. Repeated refractionation indicated that approximately one-third of the product was the anticipated methyl 1-(2-chloroethoxy)-ethyl ketone, while the remainder was the iodo analog; however, the latter was not isolated in a state of analytical purity. This replacement of chlorine (or of bromine) in a reaction with methylmagnesium iodide has been recognized previously in this Laboratory.[5]

In general, the keto ethers prepared and studied in this Laboratory are characterized by the presence of a reactive carbonyl group, as evidenced by the ease with

TABLE IV

SEMICARBAZONES OF CHLORO KETO ETHERS DERIVED FROM ETHYLENE CHLOROHYDRIN

$$ClCH_2CH_2—O—CHRC{=}NNHCONH_2$$
$$\underset{R'}{|}$$

−R	−R'	M. p., °C. (corr.)	Chlorine, % Calcd.	Found
H	CH₃	103	18.31	18.28
H	C₂H₅	92.5	17.08	16.95
H	C₆H₅	119.5–120.0	13.92	13.94
CH₃	C₂H₅	104	15.99	15.96
CH₃	n-C₃H₇	127	15.04	14.93

TABLE V

HYDANTOINS DERIVED FROM β-CHLOROETHOXYALKYL KETONES

$$\begin{array}{c} HN\!\!-\!\!CO \\ | \qquad | \\ OC \qquad | \quad CHR—O—CH_2CH_2Cl \\ | \qquad C{<} \\ NH\!\!-\!\! \qquad R' \end{array}$$

−R	−R'	Yield, %	M. p., °C. (corr.)	Chlorine, % Calcd.	Found
H	i-C₅H₁₁	87	152.5	13.20	13.33
H	C₆H₅	91	159.8	12.81	12.71
CH₃	C₂H₅	85	168.8	15.11	14.99
CH₃	n-C₃H₇	81	140.5	14.26	14.13

which they yield semicarbazones. In the majority of the attempts to prepare semicarbazones of the ketones included in this report, no evidence of reaction was observed and the unchanged ketone was recovered. Likewise, we have never before failed to convert an alkoxy ketone with unbranched alkyls by means of the procedure of Bucherer[8] into the correspondingly substituted hydantoins. It was not possible to produce hydantoins from the majority of the keto ethers prepared in this investigation. Data for the semicarbazones and hydantoins obtained are listed in Tables IV and V.

Summary

1. The utilization of ethylene chlorohydrin in the synthesis of α-chloro ethers has been studied.

2. Four examples of the new type of chloroalkoxy nitriles have been obtained from the dichloro ethers. No evidence of the formation of any dinitrile was observed.

3. From two of the β-chloroethoxy nitriles there have been obtained, by means of the Grignard reaction, ten examples of a new type of monochloro keto ether.

In an attempted preparation of α-(β-chloroethoxy)-ethyl methyl ketone from methylmagnesium iodide, partial replacement of the chlorine by iodine was observed.

4. In these ketones the carbonyl group appears to be less reactive, as judged by the ability of these compounds to yield semicarbazones and hydantoins, than in the analogous keto ethers previously reported.

(8) Bucherer and Lieb, J. prakt. Chem., [2] 141, 5 (1934).

Retention of Configuration in the Reaction of the 3-Bromo-2-butanols with Hydrogen Bromide

BY S. WINSTEIN AND H. J. LUCAS

When 2,3-diacetoxybutane is converted into 2,3-dibromobutane by the action of fuming hydrobromic acid, the transformation appears to be accompanied by an odd number of inversions, for the dl-diacetate gives rise to the meso-dibromide, and the meso-diacetate to the dl-dibromide.[1] Moreover, the purity of the products shows that the various reaction steps proceed with either 100% inversion, or 100% retention of configura-

tion. One would have expected, on the assumption that the reaction proceeds similarly at each asymmetric carbon atom, an even number of inversions. In order to ascertain the number of inversions and the steps at which they take place, it has been necessary to follow the reaction step by step, through the isolation of intermediate products and to study the behavior of each intermediate with hydrobromic acid.

It has been found that 3-bromo-2-butanol is

(1) Wilson and Lucas, THIS JOURNAL, 58, 2396 (1936).