[CONTRIBUTION FROM THE BIOLOGICAL LABORATORIES OF AMHERST COLLEGE]

Reaction of Benzyl Methyl Ethers with Bromine and *N*-Bromosuccinimide[1]

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Various substituted benzyl methyl ethers were subjected to reactions with brominating agents. Elementary bromine in carbon tetrachloride led to a cleavage of the ethers with formation of aldehydes or ketones. On the other hand, *N*-bromosuccinimide reacting with *p*-nitrobenzyl methyl ether gave DL-*N*-α-methoxy-*p*-nitrobenzylsuccinimide (I). The structure of this compound was determined.

The reaction of benzyl methyl ether with chlorine, which produces benzaldehyde, methyl chloride, and hydrochloric acid has been described in the literature.[2]

$$C_6H_5CH_2OCH_3 \xrightarrow{Cl_2} C_6H_5CHO + CH_3Cl + HCl$$

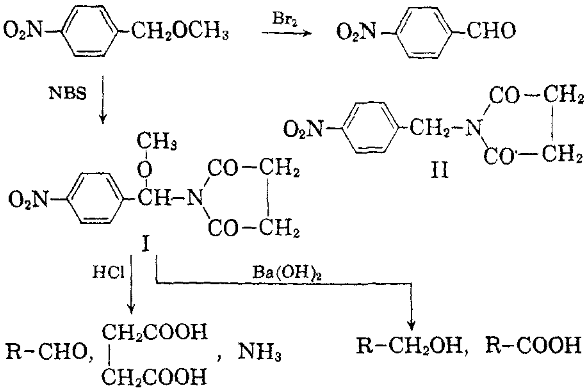
It also has been reported that benzyl ethyl ether reacts in an analogous manner when treated with bromine.[3] No intermediates have been isolated from these reactions, although it seems probable that α-haloethers are formed as primary products. The decomposition of this type of compound to produce aldehydes has been observed on other occasions.[4]

The present investigation was carried out in order to study the possibility of the preparation of oxo compounds by bromination of a variety of benzyl ethers. Furthermore, an attempt was made to prepare the hypothetical brominated intermediate by application of the Wohl-Ziegler reaction using *p*-nitrobenzyl methyl ether as model compound.

The reaction of bromine was carried out with (1) benzyl methyl ether and a number of its ring-substituted derivatives, (2) α,α'-dimethoxy-*p*-xylene, (3) 1-bromo-2-methoxymethylnaphthalene, and (4) benzyl methyl ethers with phenyl-, benzoyl- and carbomethoxy groups on the α-carbon. As expected, the primary ethers furnished aldehydes while from the secondary ones ketones were obtained.

The experimental procedure is exceedingly simple and in most cases the yields of oxo compounds are good, although it is somewhat difficult to obtain the products absolutely free of halogen. It is interesting to note that the bromination of *p*-methylbenzyl methyl ether furnished smoothly *p*-tolualdehyde, indicating the preferential reaction of the methylene group. α,α'-Dimethoxy-*p*-xylene was treated with two equivalents of bromine to give terephthalaldehyde. The physical constants, yields and methods of identification of all reaction products are summarized in Table I in the experimental part.

The reaction of *p*-nitrobenzyl methyl ether with *N*-bromosuccinimide (NBS) took an unexpected course. In *diffuse light*, a lively reaction with evolution of hydrogen bromide and bromine took place and a halogen-free, neutral compound was isolated, which was found to have the empirical formula $C_{12}H_{12}N_2O_5$. On hydrolysis of this product in hydrochloric acid *p*-nitrobenzaldehyde, succinic acid, and ammonia were obtained. Alkaline hydrolysis with barium hydroxide gave *p*-nitrobenzyl alcohol and *p*-nitrobenzoic acid. In this reaction the aldehyde, which was presumably formed, underwent a Cannizzaro reaction. On the basis of the empirical formula and the results of the hydrolytic cleavages, the structure of DL-*N*-α-methoxy-*p*-nitrobenzylsuccinimide (I) is indicated for this product. This is supported by the fact that the ultraviolet absorption spectra of this compound and of *N*-*p*-nitrobenzylsuccinimide (II) are almost identical.



R: *p*-nitrophenyl

In view of this result the bromination of *p*-nitrobenzaldehyde dimethyl acetal with NBS was investigated. In this reaction, however, methyl *p*-nitrobenzoate was obtained, which is in agreement

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(1) This investigation was supported by a grant (CY-2924) from the National Institutes of Health, U. S. Public Health Service to Prof. G. W. Kidder whom the author wishes to thank for his continued interest in this work.

(2) F. Sintenis, *Ann.*, **161**, 330 (1872).

(3) H. Schiff, *Ber.*, **5**, 287 (1872), work done by E. Paternò (Palermo).

(4) M. F. Shostakovsky and A. V. Bogdanova, *Zhur. Obshchei Khim.*, **21**, 388, 429 (1951).

TABLE I

Reaction of Benzyl Methyl Ethers with Bromine

$$\mathrm{RCHR'{-}O{-}CH_3} \xrightarrow{\mathrm{Br_2}} \mathrm{R{-}CO{-}R'}$$

R	R′	Yield of Oxo Compd.[a]	M.P. or B.P. Found,[b] °C.	M.P. or B.P. Lit.,[d] °C.	Derivatives[f]
C_6H_5	H	77%	179–183	179.5	Phenylhydrazone, m.p. 157–158° (Lit. 158°)
4-Cl-C_6H_4	H	70%	48–49	47.5	Phenylhydrazone, m.p. 125–127° (Lit. 127°)
2-NO_2-C_6H_4	H	45%	40–41[c]	40	Phenylhydrazone, m.p. 155–156° (Lit. 153°)
4-NO_2-C_6H_4	H	82%	106[e]	106.5	Phenylhydrazone, m.p. 158–159° (Lit. 155°)
4-CH_3-C_6H_4	H	71%	118–120/ 66 mm.	204	Phenylhydrazone, m.p. 109–111° (Lit. 113°)
4-CH_3OCH_2-C_6H_4	H	73%	114–116[m]	116	Tetraacetate, m.p. 165–166° (Lit. 164°)[g]
2-Br-$C_{10}H_6$	H	87%	116–118	118[h]	Phenylhydrazone, m.p. 201–203°[i] Oxime, m.p. 166.5–168.5° (Lit. 164–166°)[h]
C_6H_5	C_6H_5	36%	48–49[c]	49	Phenylhydrazone, m.p. 137–138° (Lit. 138°)
C_6H_5	C_6H_5CO	96%	94–95[c]	95	Quinoxaline, m.p. 125° (Lit. 124°)[j]
C_6H_5	$COOCH_3$	70%	93–94/ 1.2 mm.	136.8–137.2/ 14 mm.[e]	Quinoxalone, m.p. 245° (Lit. 247°)[k] Oxime, m.p. 137–138° (Lit. 138–139°)[l]

[a] After one recrystallization. [b] After two recrystallizations. [c] No m.p. depression when mixed with an authentic sample. [d] See Ref. 12. [e] Th. Posner and G. Aschermann, *Ber.*, **53**, 1933 (1920). [f] All phenylhydrazones and oximes were prepared according to the general directions given in Ref. 12. The m.p. data were taken from the same source, unless stated otherwise. [g] J. Thiele and E. Winter, *Ann.*, **311**, 353 (1900). [h] F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922). [i] *Anal.* Calcd. for $C_{17}H_{13}BrN_2$: N, 8.62. Found: N, 8.66. [j] O. Hinsberg and F. Koenig, *Ber.*, **27**, 2181 (1894). [k] J. Buraczewski and L. Marchlewski, *Ber.*, **34**, 4008 (1901). [l] Ad. Müller, *Ber.*, **16**, 2987 (1883). [m] Terephthalaldehyde.

with the finding that benzaldehyde diethyl acetal reacts with NBS with formation of ethyl benzoate.[5]

EXPERIMENTAL[6]

Starting materials. The various benzyl methyl ethers including α,α'-dimethoxy-*p*-xylene and 1-bromo-2-methoxymethylnaphthalene were prepared by the reaction of an appropriate halide with sodium methoxide.[7] Benzhydryl methyl ether[8] and benzoin methyl ether[9] were obtained by known procedures; methyl DL-α-methoxyphenylacetate was obtained by treating DL-mandelic acid methyl ether with diazomethane.

p-Methylbenzyl methyl ether. A solution of 11.0 g. of *p*-methylbenzyl bromide in 15 ml. of methanol was added to a solution of 2.0 g. of sodium in 50 ml. of methanol. The mixture was refluxed for 1 hr., poured into water, neutralized with acetic acid, and the product extracted into ether. On distillation *in vacuo* 8.8 g. (82%) of a colorless oil of b.p. 116–117°/74 mm. was obtained. Repeated distillation gave the analytical sample of b.p. 196°.

Anal. Calcd. for $C_9H_{12}O$: C, 79.36; H, 8.88. Found: C, 79.20; H, 8.83.

α,α'-Dimethoxy-p-xylene. This product was obtained similarly from 10.5 g. of α,α'-dibromo-*p*-xylene suspended in 30 ml. of methanol and 2.5 g. of sodium dissolved in 50 ml. of the same alcohol. The yield of crude material of boiling range 97–100°/8 mm. was 5.0 g. (76%). Redistillation gave the analytical sample, b.p. 96°/3.5 mm.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.49.

1-Bromo-2-methoxymethylnaphthalene. A mixture of 15.0 g. of 1-bromo-2-bromomethylnaphthalene and 200 ml. of methanol was added to a solution of 1.8 g. of sodium in 50 ml. of methanol. The reaction mixture was worked up as above giving 9.9 g. (79%) of material of boiling range 138–146°/1.0 mm. Redistillation gave the analytical sample of b.p. 140–142°/1.6 mm.

Anal. Calcd. for $C_{12}H_{11}BrO$: C, 57.39; H, 4.42. Found: C, 57.33; H, 4.34.

Reaction of benzyl ethers with bromine. An equimolecular amount of bromine dissolved in carbon tetrachloride was added dropwise to a boiling solution of the ether in the same solvent. The reaction mixture was illuminated by a 150-watt bulb. Usually the color of the bromine disappeared instantaneously. After the reaction was complete the volatile materials were evaporated and the residue was purified by distillation or recrystallization. The yields, physical properties, and the methods of identification of the products are given in Table I.

DL-N-α-Methoxy-p-nitrobenzylsuccinimide (I). A mixture of 5.0 g. of *p*-nitrobenzyl methyl ether, 5.0 g. of NBS, and 50 ml. of carbon tetrachloride was heated to gentle reflux. After approximately 20 min. a lively reaction took place with the liberation of hydrogen bromide and bromine. When all the NBS had been consumed the mixture was filtered hot and 2.3 g. (29%) of crude DL-*N*-α-methoxy-*p*-nitrobenzylsuccinimide (I) crystallized on cooling. Recrystallization from ethanol gave the colorless analytical sample, m.p. 152–153°; λ_{max} in absolute ethanol 267–268 mμ; log ϵ, 4.05.

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(5) E. N. Marvell and M. J. Joncich, *J. Am. Chem. Soc.*, **73**, 973 (1951).

(6) All melting points were determined on a Fisher-Johns apparatus and are corrected. The boiling points are not corrected.

(7) J. Thiele and O. Dimroth, *Ann.*, **305**, 108 (1899).

(8) St. v. Kostanecki and V. Lampe, *Ber.*, **39**, 4014 (1906).

(9) E. Fischer, *Ber.*, **26**, 2412 (1893).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.6. Found: C, 54.72, 54.40; H, 4.46, 4.59; N, 10.5, 10.8.

For comparison *N-p-nitrobenzylsuccinimide* (II) was prepared according to a known procedure.[10] Its m.p. was 152–154° (lit. 150–152°)[10]; λ_{max} in absolute ethanol 266 mμ; log ϵ, 4.01. The m.p. of a mixture of I and II was 120–125°.

Hydrolysis of DL-*N-α-methoxy-p-nitrobenzylsuccinimide.* (*a*) A 1.0-g. sample of I was heated briefly with 20 ml. of saturated aqueous barium hydroxide. The dark alkaline solution was extracted with ether after cooling, the extract dried with sodium sulfate and evaporated to give 0.2 g. (69%) of *p-nitrobenzyl alcohol*, m.p. 92–93° (lit. 93°)[11] which was converted to *p-nitrobenzyl acetate*, m.p. 76–78° (lit. 78°).[12] The basic mother liquor was acidified with hydrochloric acid and yielded 0.2 g. (63%) of *p-nitrobenzoic acid*, m.p. 239–240° (lit. 242.4°)[11] after recrystallization from water.

(*b*) An 0.7-g. sample of I was distilled slowly with 25 ml. of 5% hydrochloric acid. *p*-Nitrobenzaldehyde distilled with the steam and the water was replaced in the reaction mixture from time to time. After about 3 hr. a clear solution was obtained. Heating was continued for another hour, then both reaction mixture and distillate were cooled to 5°. The main crop of aldehyde was isolated from the distillate and combined with a small amount filtered from the acidic reaction mixture. The total yield was 0.3 g. (75%), m.p. 105–106° (lit. 106.5°).[11] The acidic solution was then evaporated and the residue was recrystallized from water. A crop of 130 mg. (41%) of succinic acid, m.p. 189–190° [lit. 185° (189–190°)][11] was obtained. When the mother liquor of the succinic acid was made alkaline, the presence of ammonia was detected by its odor and further established with Nessler's reagent. All solid products isolated in the course of these experiments were identified by mixed melting point determinations with authentic samples.

Reaction of p-nitrobenzaldehyde dimethyl acetal with NBS. A mixture of 3.5 g. of *p*-nitrobenzaldehyde dimethyl acetal,[13] 3.5 g. of NBS, and 70 ml. of carbon tetrachloride was refluxed. After about 4 hr. all the NBS had reacted and the mixture was filtered. Most of the product crystallized on cooling but an additional amount was obtained on evaporation of the mother liquor. The two crops were combined and recrystallized from dilute methanol and benzene–petroleum ether respectively to give 3.0 g. (91%) of methyl *p*-nitrobenzoate, m.p. 94–95° (lit. 96°).[11] No depression of this melting point was observed on admixture to an authentic sample.

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[10] S. Hoogewerff and W. A. Van Dorp, *Rec. trav. chim.*, **18**, 358 (1899).

[11] *Handbook of Chemistry and Physics*, 34th edition, The Chemical Rubber Publishing Co., Cleveland, Ohio, 1952.

[12] The staff of Hopkins and William Research Laboratory, *Organic Reagents for Organic Analysis*, Chemical Publishing Co., Inc., Brooklyn, N. Y., 1950.

[13] E. Fischer and G. Giebe, *Ber.*, **30**, 3057 (1897)

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Structure of Succinyl Dichloride and of Certain Other Potentially Cyclic Difunctional Compounds[1]

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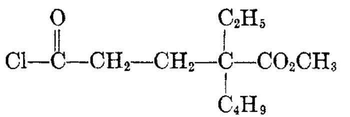
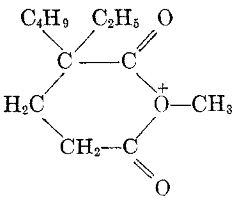
Examination of the infrared absorption by carbonyl in succinyl dichloride furnishes additional evidence that this compound exists in the open chain form. Products of the known reactions of this dichloride may be satisfactorily correlated on the basis of the open chain structure, provided recognition be taken of the fact that γ-keto acid chlorides exist entirely (or almost so) in the cyclic form. δ-Ketoenanthyl chloride is also in the cyclic form. Certain derivatives of α-butyl-α-ethylglutaric acid, other than the ester acid chlorides, are found to exist partly or largely in the cyclic form.

In a previous investigation in this laboratory,[2] data were assembled which demonstrated that the ester acid chlorides (I, or its isomer) of α-butyl-α-ethylglutaric acid exist entirely as open chain structures at room temperatures, and rearrange rather slowly by way of a cyclic structure at temperatures in the range 120–150°. Rearranged products were obtained only in those reactions where a Lewis acid extracts halogen to yield as a reaction intermediate the cyclic oxonium ion, shown in one resonance form in II. In view of the stability of the ester acid chlorides such as I, it was suggested[2] that succinyl dichloride also exists as an open chain compound and that cyclic reaction products are formed from the open chain structure by way of cyclic intermediates such as are shown in two resonance forms in III.

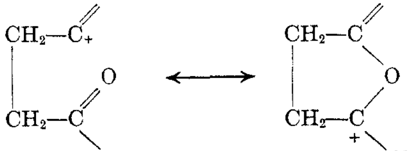


$$Cl-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{C_4H_9}{|}}{\overset{\overset{C_2H_5}{|}}{C}}-CO_2CH_3$$

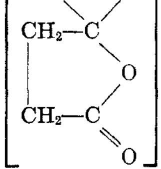
I



II



III



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[1] This investigation was supported in part by a research grant (E-86) from the National Institutes of Health, U. S. Public Health Service. A part of these data was presented at the 127th meeting of the American Chemical Society, Cincinnati, Ohio, March 30, 1955.

[2] J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953).