Anal. Calcd. for $C_{10}H_{16}O_2$: Carbonyl oxygen, 9.5%, bromine number, 94; hydroxyl, 10.10. Found: Carbonyl oxygen, 8.6; bromine number, 102.8; hydroxyl, 10.25%.

Infrared evidence indicated the presence of an α-hydroxy ketone.

Dehydration of the keto alcohol. The keto alcohol was converted to the semicarbazone which could not be crystallized. The semicarbazone was steam-distilled, the *p*H being kept at 0.9 to 1.0 by the addition of 25% sulfuric acid. The product was isolated from the distillate and purified by conversion to the sodium sulfite derivative. A 15% yield of oil having a spearmint-like odor was obtained.

Anal. Calcd. for $C_{10}H_{14}O$: Carbonyl oxygen, 10.7%; bromine number, 211. Found: Carbonyl oxygen, 10.3%; bromine number, 210.8.

The keto alcohol was converted to the oxime which could not be crystallized. The oxime was refluxed for an hour with 5% oxalic acid, then the mixture was steam-distilled. The product which was isolated from the distillate in 20% yield was shown by infrared analysis to consist of approximately 50% carvone.

Preparation of limonene glycol monoacetate. A solution of 463.7 g. of limonene monoxide in 1400 ml. of acetic acid was refluxed for 4 hr. and allowed to stand at room temperature for 72 hr. On removal of the acetic acid, 561.5 g. (93%) of oil was obtained which had an ester value of 275.2. A sample was steam-distilled.

Anal. Calcd. for $C_{12}H_{20}O_3$: Ester value, 264; bromine number, 75.5; carbonyl, 0. Found: Ester value, 274.9; bromine number, 76.8; carbonyl, 17.4% as dihydrocarvone.

Preparation of limonene glycol diacetate. A solution of 633.8 g. of limonene glycol monoacetate in 1265 ml. of acetic anhydride was refluxed for 7 hr. and allowed to stand at room temperature for 50 hr. On removal of the acetic anhydride and acetic acid, 688 g. (88.4%) of oil was obtained. A steam-distilled sample was submitted for analysis.

Anal. Calcd. for $C_{14}H_{22}O_4$: Ester value, 442; bromine number, 63; carbonyl, 0. Found: Ester value, 413.4; bromine number, 64.7; carbonyl, 6.6% as dihydrocarvone.

A solution of 50 g. of anhydrous limonene glycol in 250 ml. of acetic anhydride was refluxed for 2.5 hr., then poured into water. After the acetic anhydride had hydrolyzed, the product was isolated by extraction with ether. On removal of the ether, a residue of 69 g. (92.5%) of oil was obtained.

Anal. Found: Ester value, 420.7; bromine number, 65.2.

Pyrolysis of limonene glycol diacetate. The pyrolysis was conducted by dropping 544 g. of limonene glycol diacetate (77% pure by ester value, 10% dihydrocarvone) through an electrically-heated column packed with glass helices. It was run at 347–361° over a period of 2.5 hr., being preheated to 190°. The material which came through the column was treated with sodium bicarbonate solution to remove the acid, a yield of 318 g. of oil being obtained.

Anal. Calcd. for $C_{12}H_{18}O_2$: Ester value, 290; bromine number, 164; carbonyl, 0. Found: Ester value, 244.2; bromine number, 118.1; carbonyl, 16.4% as dihydrocarvone.

After two treatments with sodium bisulfite, 257.2 g. of material, which was free of carbonyl was obtained.

Anal. Found: Ester value, 249.0; bromine number, 117.0; glycol, 9.12% as limonene glycol.

The product resulting was distilled *in vacuo*, the main fraction, 92 g., boiling at 83–90°/3.5 mm.

Anal. Found: Ester value, 275.3; bromine number, 145.1; glycol, 5.48% as limonene glycol; carbonyl, 2.45% as dihydrocarvone.

Saponification of carveol acetate to carveol. A solution of 29.1 g. (0.15 mole) of carveol acetate (distilled) in a solution of 20 g. potassium hydroxide (100% excess) in 300 ml. of methanol was refluxed for 1.5 hr. After neutralization of the excess alkali and removal of the solvents and salts, 12 g. of oil was obtained. Infrared evidence indicated that it contained a high concentration of carveol. It contained 32% of dihydrocarvone as an impurity.

Preparation of limonene chlorohydrin. To 550 ml. of 1.9*N* hydrogen chloride in ether was added slowly 150 g. of limonene monoxide (92% pure) and the mixture allowed to stand at room temperature for 3 hr. The solution was then washed with water and dried over anhydrous magnesium sulfate. After removal of the ether, 170 g. (91%) of oil was obtained.

Anal. Calcd. for $C_{10}H_{17}OCl$: Cl, 18.83; bromine number, 85; sapon. number, 282; glycol, 0; oxirane oxygen, 0. Found: Cl, 17.81; bromine number, 80.5; sapon. number, 274; glycol, 0; oxirane oxygen, 0.

Analytical methods. 1. Bromine number: W. W. Scott and N. H. Furman, *Standard Methods of Chemical Analysis*, Fifth Edition, Vol. 2, p. 1770, Van Nostrand Co., Inc., New York, 1944. 2. Epoxy (ether HCl Method): D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947). 3. Hydroxyl (acetic anhydride-pyridine): C. L. Ogg, W. L. Porter, and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945). 4. Carbonyl (hydroxylamine hydrochloride-pyridine): W. M. D. Bryant and D. M. Smith, *J. Am. Chem. Soc.*, **57**, 57 (1935). 5. Glycol (periodic acid): W. D. Pohle, V. C. Mehlenbacher, and J. H. Cook, *Oil and Soap*, **22**, 115 (1945), or S. Siggia, *Quantitative Organic Analysis via Functional Groups*, First Edition, John Wiley & Sons, New York, 1949, p. 8.

BUFFALO 7, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE HEYDEN NEWPORT CHEMICAL CORP.]

Local Anesthetics. I. Dialkylaminoalkyl Ethers of Benzaldoximes and Benzophenone Oximes

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A number of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes have been prepared and characterized. In preliminary physiological screening studies the β-diethylaminoethyl ether of α-benzaldoxime (as the hydrochloride) appeared to be the most interesting of all the compounds tested for local anesthetic activity; it offered good anesthetic action and was the least irritating.

As part of a synthetic medicinals program started in these laboratories several years ago a search was made for new and improved local anesthetics. In these studies attention was focused on the dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes, two previously unreported types

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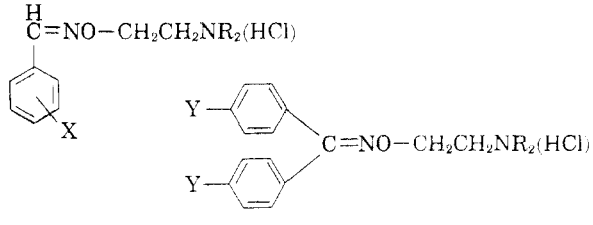
TABLE I

DIALKYLAMINOALKYL ETHERS OF OXIMES (HYDROCHLORIDES)

No.	Oxime	Dialkylaminoalkyl Radical	Yield, %	Solvents Used for Crystallization	M.P., °C. (Corrected)	Formula	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
VI	α-Benzaldoxime	β-Diethylaminoethyl	56.8	Chloroform-Ether; Acetone	124–126	$C_{13}H_{21}ClN_2O$	10.9	10.9	13.9	14.3
VII	α-Benzaldoxime	β-Dimethylaminoethyl	49.3	Ethanol-Ether	123–126.1	$C_{11}H_{17}ClN_2O$	12.3	12.2	15.5	15.6
VIII	α-Anisaldoxime	β-Diethylaminoethyl	73	Ether	142–146	$C_{14}H_{23}ClN_2O_2$	9.8	9.6	12.4	12.7
IX	3,4-Dichlorobenzaldoxime	β-Diethylaminoethyl	66.8	Chloroform-Ether	159.9–162	$C_{13}H_{19}Cl_3N_2O$	8.6	8.5	10.9[a]	11.2[a]
X	3,4-Dichlorobenzaldoxime	β-Dimethylaminoethyl	62.2	Chloroform-Ether	156–158.8	$C_{11}H_{15}Cl_3N_2O$	9.2	9.1	11.9[a]	12.2[a]
XI	Benzophenone oxime	β-Diethylaminoethyl	36.6	Chloroform-Ether	132.1–133.8	$C_{19}H_{25}ClN_2O$	8.4	8.2	10.7[a]	10.8[a]
XII	p,p′-Dichlorobenzophenone oxime	β-Diethylaminoethyl	62.2	Chloroform-Ether	156.5–158.5	$C_{19}H_{24}Cl_3N_2O$	7.0	7.1	26.4	26.6
XIII	p,p′-Dichlorobenzophenone oxime	β-Dimethylaminoethyl	32.8	Chloroform-Ether	188.1–191	$C_{17}H_{19}Cl_3N_2O$	7.7	7.6	9.8[a]	10.1[a]

[a] Ionizable chlorine only.

of compounds represented by formulas A and B, which were found to possess significant anesthetic activity.



R is methyl or ethyl
X is H, methoxy, dichloro, β-diethylaminoethoxy

A

R is methyl or ethyl
Y is hydrogen, chloro

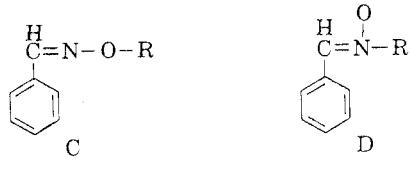
B

Inspection of these general formulas, A and B, will readily suggest structural similarities found in portions of well known physiologically and chemotherapeutically active compounds such as Procaine, Tetracaine, Benadryl, Trasentine, 929F of Forneau and Bovet, Tibione, and the like.

The synthesis of these dialkylaminoalkyl ethers was accomplished by a modification of a method described by Cheney, Smith, and Binkley[2] for preparing dialkylaminoalkyl ethers of benzylphenols. A toluene suspension of the sodium salt of the oxime was treated with a toluene solution of the free base of the various dialkylaminoalkyl chlorides to yield the dialkylaminoalkyl ethers.

(2) Cheney, Smith, and Binkley, *J. Am. Chem. Soc.*, **71**, 60 (1949).

The benzaldoximes (I, II, III) reported in this paper are the anti (α) oximes, which are more stable than the syn (β) forms.[3,4,5] The dialkylaminoalkyl ethers of the benzaldoximes have been assigned the benzaldoxime-*O*-ether structure, C, in preference to the isomeric benzaldoxime-*N*-ether,



C D

D. Although both oxygen and nitrogen ethers are theoretically possible reaction products, the *O*-ethers are much more likely to be the main products and very little of the *N*-ethers is obtained.[2]

In preliminary studies it was observed that in general representative compounds of the series of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes (as hydrochloride salts) tested in the cornea of a rabbit produced a marked anesthesia but in some cases also caused irritation. Compound VI, the β-diethylaminoethyl ether of α-benzaldoxime, was found to be the most promising local anesthetic of the compounds tested, showing the greatest degree of activity and the least irritation. It appears that the presence of halogen

(3) Beckmann, *Ber.*, **23**, 1684 (1890).
(4) Bamberger and Scheutz, *Ber.*, **34**, 2024 (1901).
(5) Hodgson and Beard, *J. Chem. Soc.*, 25 (1927).

substituents in the nuclei of these compounds enhances the irritation effect.

In general representative types of the dialkylaminoalkyl ethers in series A and B showed very little antibacterial or antifungal activity in preliminary *in vitro* tests. Benzaldoxime, anisaldoxime, benzophenone oxime, and *p,p'*-dichlorobenzophenone oxime (compounds I, II, IV, and V) failed to show any significant bacteriological activity, while compound III, the 3,4-dichlorobenzaldoxime, demonstrated sufficient activity to warrant further testing.

EXPERIMENTAL

Synthesis of benzaldehyde and benzophenone oximes. α-Benzaldoxime, sodium salt (I).[6] To 140 g. (3.5 moles) of sodium hydroxide dissolved in 400 ml. of water was added 210 g. (1.98 moles) of benzaldehyde. To this mixture was added, while stirring, 150 g. (2.16 moles) of hydroxylamine hydrochloride. During the mixing the mixture became warm and the oily layer dissolved to form a homogeneous yellow solution which crystallized on cooling. Sufficient water (*ca.* 300 ml.) was added with stirring to form a clear solution. Sufficient carbon dioxide gas was then passed through the solution to cause a colorless emulsion of the *anti*-benzaldoxime to separate on the surface of the solution. The insoluble oil was extracted with two 1-l. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was distilled off leaving an oily residue, the crude α-benzaldoxime. The crude product was treated with 700 ml. of a solution of sodium methoxide [235 g. (4.37 moles) in 1500 ml. of anhydrous alcohol] to form its sodium salt. The mixture was stirred well, filtered, and washed with alcoholic sodium methoxide solution and dried.[8] It was then triturated and washed with three 500-ml. portions of benzene, refiltered and dried at 70°. Weight, 125 g. An additional 62 g. of product was obtained by concentration of the filtrate plus washes. Total yield, 187 g. (65.8%).

The other benzaldoximes were prepared by similar methods. α-Anisaldehyde (II) was obtained in a 45% yield by the procedure of Bamberger and Scheutz[4]; m.p. 60°. The oxime of 3,4-dichlorobenzaldehyde (III) was isolated in an 86.5% yield by the method of Hodgson and Beard[5]; m.p. 116.3–119°.

Benzophenone oxime IV. Starting with 100 g. (0.55 mole) of benzophenone, the oxime was prepared essentially by the method described by Lachman and Noller[9] with the exception that powdered potassium hydroxide was used in place of sodium hydroxide. The crude product was recrystallized from methanol to give 90 g. (83% yield) of product melting at 143–144°.

p,p'-Dichlorobenzophenone oxime V. The oxime of *p,p'*-dichlorobenzophenone was prepared starting with 138 g. (0.55 mole) of the ketone by the method used for benzophenone oxime. Yield, 110 g. (75.3%); m.p. 135.2–136.9°. Newton and Groggins[10] reported 136° as the melting point for this compound.

Synthesis of dialkylaminoalkyl chlorides. Most of the required β-dialkylaminoalkyl chlorides were commercially available as the hydrochloride salts. The preparation of the unavailable β-dialkylaminoalkyl chlorides was effected by the method of Slotta and Benisch.[11]

Synthesis of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes. Procedure A. This procedure is illustrated by the synthesis of compound VI. *β-Diethylaminoethyl ether of α-benzaldoxime (hydrochloride)* (VI). A suspension of 42.9 g. (0.3 mole) of the sodium salt of α-benzaldoxime in 1 l. of toluene was stirred while a dried toluene solution of the free base of β-diethylaminoethyl chloride was slowly added by means of a dropping funnel. When the addition was complete, stirring was continued for 1 hr. without any external heating. The mixture was then heated at reflux temperature (*ca.* 71–92°) for 12 hr. At the end of this period the reaction mixture was cooled to room temperature and filtered to remove salt and insoluble impurities. The filtrate was distilled *in vacuo* to remove excess free amine chloride and toluene.

To the residue was added 2 l. of dry ether, and after filtration the ethereal solution was treated with dry hydrogen chloride until precipitation of a crude oily hydrochloride salt was complete. The gummy precipitate was purified by dissolving it in 200 ml. of chloroform, filtering to remove cloudiness, and then slowly pouring the filtrate into an excess of fresh, dry ether (1500 ml.). The product, which separated as a pale yellowish oil that crystallized on standing, was filtered, washed with two 100-ml. portions of fresh, dry ether, and dried. The dried material was ground, triturated well with 500 ml. of dry ether, filtered, and redried to rid it of a benzaldehyde-like odor. The weight of this product melting at 120 to 125° was 46.4 g. (60.3% yield). Further purification was effected by recrystallization from dry acetone. The pure product melted at 124–126° and weighed 43.8 g. (56.8% yield). Analytical data are given in the table.

Procedure B. This procedure is illustrated with the synthesis of compound IX. *β-Diethylaminoethyl ether of 3,4-dichlorobenzaldoxime (hydrochloride)* (IX). To a freshly prepared sodium methoxide solution obtained by dissolving 7 g. (0.3 mole) of sodium in 120 ml. of dry methanol was added 57 g. (0.3 mole) of 3,4-dichlorobenzaldoxime. After the mixture had been stirred 1 hr. to effect solution, the excess methanol was removed by vacuum distillation. The residual mass, the sodium salt of the oxime, was suspended in 1 l. of toluene. To the toluene suspension of the sodium salt of 3,4-dichlorobenzaldoxime was added about 1 l. of dried toluene solution of the free base of β-diethylaminoethyl chloride prepared from 72.2 g. (0.42 mole) of the corresponding hydrochloride salt. The mixture was heated at reflux temperature (95–97°) for 12 hr. and then worked up as described in Procedure A. The crude hydrochloride salt was purified by recrystallizing it from chloroform by the addition of dry ether. The white crystalline product melting 159.9–162° weighed 65 g. (66.8% yield). Analytical data are given in the table.

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(6) Procedures used for alkylating the α-oximes were essentially the same as those reported in the literature to give the *O*-ethers.[7] Studies of the ultraviolet spectra of *N*- and *O*-methyl and *N*- and *O*-benzyl ethers of benzaldoxime [Meisenheimer and Dorner, *Ann.*, **499**, 161 (1933) and Ramart-Lucus and Martynoff, *Bull. soc. chim.*, 916 (1949)] have shown that the *O*-ethers have spectra similar to that of the parent oxime, whereas the spectra of the *N*-ethers are quite different. The similarity between the ultraviolet absorption curves of the diethylaminoethyl ethers of 3,4-dichlorobenzaldoxime and *p,p'*-dichlorobenzophenoneoxime and those of the parent oxime offered confirmation that these compounds are *O*-ethers.

(7) Richter-Anschütz, *The Chemistry of the Carbon Compounds*, Vol. III, 3rd ed., Elsevier, New York, 1946, pp. 273–274.

(8) Beckmann[3] noted that an alkaline wash removes virtually all of the small amount of the β-oxime present.

(9) Lachman and Noller, *Org. Syntheses*, **Coll. Vol. II** 70 (1944).

(10) Newton and Groggins, *Ind. Eng. Chem.*, **27**, 1397 (1935).

(11) Slotta and Benisch, *Ber.*, **68**, 754 (1935).

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GARFIELD, N. J.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. VI.[2] Use of *O*-Benzoyl Blocking Group for Synthesis of 6-Chloropurine Nucleosides

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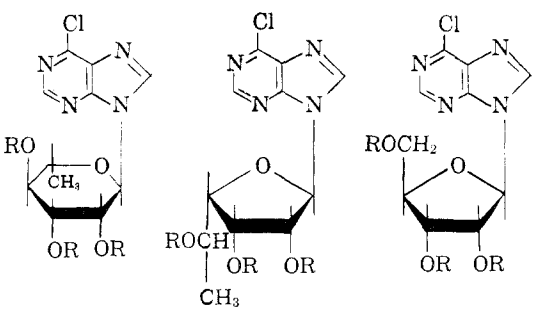
A general method for the synthesis of 6-chloropurine nucleosides, particularly valuable as intermediary nucleosides, is described. Condensation of chloromercuri-6-chloropurine with the proper *O*-benzoylated glycosyl chloride has afforded 9-α-L-rhamnopyranosyl-, 9-α-L-rhamnofuranosyl-, and 9-β-D-ribofuranosyl-6-chloropurines in 28–41% yields.

Since Fischer and Helferich[4] synthesized the first nucleoside, 7-glucopyranosyltheophylline, by condensation of silver theophylline with tetra-*O*-acetyl-α-D-glucopyranosyl bromide there have been only three improvements in the procedure. Davoll, Lythgoe, and Todd[5] observed that tri-*O*-acetylpentofuranosyl chlorides, due to their increased stability, gave higher yields of nucleosides than the corresponding furanosyl bromides. Another major improvement was the introduction of the use of chloromercuri derivatives of purines, rather than silver purines, by Davoll and Lowy.[6] The third major improvement was the introduction of *O*-benzoyl blocking groups, rather than *O*-acetyl for the sugar moiety by Kissman, Pidacks, and Baker[7]; that higher yields are obtained has been verified several times.[8–10] In certain cases, the use of the more hydrolytically stable *O*-benzoyl group is essential for transformation work necessary during synthesis of the blocked sugars.[7,11,12]

The use of *O*-benzoyl blocking groups for the synthesis of nucleosides may have the serious drawback that base-catalyzed removal of the group from base-labile nucleosides, such as those derived from 6-chloropurine, may not be feasible. The finding that 6-chloropurine nucleosides can be made from poly-*O*-benzoyl glycosyl halides in satisfactory yield is the subject of this paper.

The only example of a 6-chloropurine nucleoside described in the literature is the 9-β-D-ribofuranoside (VII). Brown and Weliky[13] synthesized this nucleoside (VII) from 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride and chloromercuri-6-chloropurine. They obtained a 26% yield of crude, colored nucleoside; recrystallization was attended by a considerable loss and the yield of pure material was not specified.



I, R = C_6H_5CO—
II, R = H

III, R = C_6H_5CO—
IV, R = H

V, R = CH_3CO—
VI, R = C_6H_5CO—
VII, R = H

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(1) Affiliated with Sloan-Kettering Institute.

(2) This work was supported in part by the Kettering Foundation and by the Lasker Foundation. For paper V of this series see L. L. Bennett, Jr. and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957).

(3) Present address: Stanford Research Institute, Menlo Park, Calif.

(4) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(5) (a) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948). (b) An apparent exception that furanosyl chlorides can be expected to give higher yields of nucleosides than furanosyl bromides has been observed with the 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl halides.[9]

(6) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(7) H. M. Kissman, C. Pidacks and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

(8) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

(9) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(10) J. A. Johnson and H. J. Thomas, Southern Research Institute, to be published.

(11) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955).

(12) B. R. Baker and K. Hewson, Paper VIII of this series, *J. Org. Chem.*, **22**, 966 (1957).

(13) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).