lized. The crude yield was quantitative. The solid was recrystallized from Skellysolve C and melted at 108–110°.

6-Dimethylamino-4-cyclohexyl-4-phenyl-3-hexanol.—Ten grams (0.03 mole) of Amidone was dissolved in 60 ml. of glacial acetic acid and 1 g. of platinum oxide catalyst added. This mixture was shaken at 50–60° with an initial hydrogen pressure of 55 lb. During a seventy-two-hour period, the amount of hydrogen absorbed was somewhat more than that calculated for the complete hydrogenation of one benzene ring and reduction of the ketone to the carbinol. At this stage addition of fresh catalyst caused no additional absorption of hydrogen. The catalyst was filtered, and the filtrate concentrated under reduced pressure. The residue was made basic and extracted into ether. The solvent was removed from the dried extract and the residue distilled; b. p. 150–153° (1 mm.). Although a crystalline phosphate was obtained, all other salts prepared were oils.

6-Dimethylamino-4,4-diphenyl-3-acetoxyheptane Hydrochloride.—A mixture of 19 g. (0.061 mole) of Amidone carbinol, 250 ml. of anhydrous ethyl acetate and 7.8 g. (0.100 mole) of acetyl chloride was refluxed for two hours, and then cooled in an ice-bath. The precipitated crystals were recrystallized from ethyl acetate; yield 21.5 g. (90%), m. p. 213–214°.

6-Dimethylamino-4,4-diphenyl-3-(N-phenylcarbamyloxy)-heptane Hydrochloride—Ten g. (0.033 mole) of Amidone carbinol was dissolved in ether and 6.7 g. (0.06 mole) of phenyl isocyanate added. After four hours a small quantity of diphenylurea had separated from the reaction mixture. The ether solution was decanted, and the diphenylurea recrystallized from ethanol; mixed m. p. 238–239°. The ether solution was extracted with 300 ml. of 4 *N* hydrochloric acid. After some time the crystalline hydrochloride separated from the extract, m. p. 150–151° after recrystallization from equal parts of methanol and hydrochloric acid.

Summary

1. Data on a number of ketones related to Amidone are presented.

2. The reduction of the ketones with lithium aluminum hydride and by catalytic hydrogenation is described.

3. Esters, carbonates and carbamates prepared from the carbinols are presented.

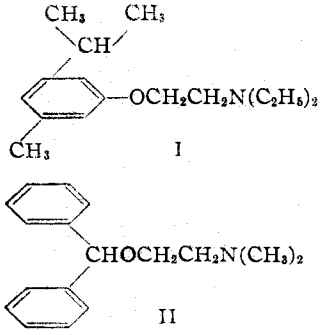
SYRACUSE, NEW YORK RECEIVED JUNE 3, 1948

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Alkylaminoalkyl Ethers of the Benzylphenols

BY L. C. CHENEY, RICHARD R. SMITH AND S. B. BINKLEY

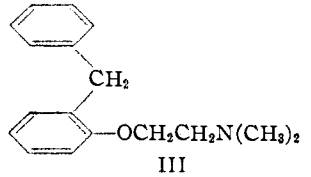
In 1937 Bovet and Staub reported that a series of phenol ethers synthesized by E. Fourneau exerted a protective action against histamine intoxication[1] and anaphylactic shock[2] in guinea pigs. This discovery initiated the ensuing numerous pharmacological investigations of synthetic compounds which have been admirably reviewed by Loew.[3] The more extensive work of Staub[4] suggested that in general the ortho-substituted phenol ethers manifested higher antihistaminic activity than their para and meta isomers. Although the thymol derivative 929F (I) was selected as the most promising compound of this class, toxicity and untoward side-effects militated against its clinical usefulness.



I

II

(1) Bovet and Staub, *Compt. rend. soc. biol.*, **124**, 547 (1937).
(2) Staub and Bovet, *ibid.*, **125**, 818 (1937).
(3) Loew, *Physiol. Revs.*, **27**, 542 (1947).
(4) Staub, *Ann. inst. Pasteur*, **63**, 400 (1939).



III

In 1945 Loew and his colleagues[5] announced their discovery of the potent antihistaminic action of benzohydryl β-dimethylaminoethyl ether (Benadryl) (II) synthesized by Rieveschl and Huber.[6]

Inasmuch as none of the Fourneau phenoxyethylamines investigated,[1,2,4] were substituted by a benzyl group, it was considered of interest to prepare 2-benzylphenyl β-dimethylaminoethyl ether (III) for pharmacological evaluation, especially since III is an isomer and vinylog of Benadryl (II). The present paper describes the preparation of II, its 4-isomer, certain homologs and salts thereof.

Pharmacological assays which will be reported elsewhere indicate that III (C-5581H) is to date more promising medicinally than any of the tabulated homologs. Its water-soluble hydrochloride is relatively non-toxic and it elicits a high order of antihistaminic and local anesthetic activity in animals. Clinical tests are in progress.

With the exception of the two hydrogenated derivatives (489-1 and 489-2), all of the com-

(5) Loew, Kaiser and Moore, *J. Pharmacol.*, **83**, 120 (1945).
(6) Wilson Frederick Huber, Doctoral Dissertation, University of Cincinnati, 1943. Rieveschl, U. S. Patent 2,421,714 (1947).

pounds in Table I were prepared by two general procedures. Method A consisted in condensing sodium benzylphenate with the appropriate aminoalkyl chloride. It is of interest that method A gave a low yield of 518-14 owing to the formation of considerable quantities of low-boiling material which was not investigated. Consequently method B, wherein an ω-bromoalkyl ether of a benzylphenol is caused to react with a particular amine, proved to be the procedure of choice for the synthesis of an ether bearing a secondary amino group.

Because of the marked tendency of the free dialkylaminoalkyl chlorides to polymerize when heated in the presence of polar solvents, the method developed by Dalgliesh[7] for the synthesis of 929F (I) proved less satisfactory than the use of toluene as a solvent. For the same reason sodium or sodium hydride was selected instead of sodium alkoxides for preparing the sodium salts of the phenols. A nitrogen atmosphere guarded against oxidation.

Experimental[8]

The Benzylphenols.—Pure 2-benzylphenol required for this series was first prepared by the method of Claisen[9] in yields ranging from 25 to 35%, a procedure advantageous in the sense that practically none of the 4-isomer is produced. The residues did contain, however, appreciable amounts of the strongly cryptophenolic 2,6-dibenzylphenol,[9,10] which served for the preparation of compound 489-27 (Table I). When larger quantities of 2-benzylphenol were required it proved advantageous to separate the isomeric benzylphenols in commercially available "Santophen 7"[11] by utilizing the marked difference in the water solubility of their barium salts. The procedure is based on a Bayer patent.[12] Another patented method of separating the isomers was not thoroughly investigated. It takes advantage of the remarkably high solubility of the alkali salts of 2-benzylphenol in an inert, non-aqueous organic solvent such as xylene.[13]

Separation of 2-Benzylphenol from 4-Benzylphenol in "Santophen 7."[11,12]—To a boiling solution of 1950 g. of technical grade barium hydroxide octahydrate in 7.5 liters of water contained in a 12-l. round-bottom flask was added 1500 g. of molten "Santophen 7." The mixture was boiled for ten to twelve minutes and then cooled to 10–12°. The insoluble barium 4-benzylphenate was collected in a large Büchner funnel and sucked as dry as possible by the use of a rubber dam. The cake was broken up and digested with occasional stirring on the steam-bath for at least two hours with sufficient 6 *N* hydrochloric acid (*ca.* 1300 ml.) to render the medium strongly acidic (*p*H 2). Crude 4-benzylphenol, m. p. 81–84°, crystallized on cooling and stirring. One crystallization from carbon tetrachloride afforded pure 4-benzylphenol, m. p. 84°.

The original filtrate containing the soluble barium 2-benzylphenate was promptly acidified to *p*H 2 (to avoid the formation of purple oxidation products) with about 650 ml. of concentrated hydrochloric acid while cooling and stirring the mixture. It was found expedient to seed the oily product to induce crystallization. When the temperature sank below 8°, the light-brown crystals were collected by suction and dissolved in two liters of hot benzene. The solution was then transferred to a separatory funnel, the water was withdrawn and the benzene layer was washed with two 500-ml. portions of water for the removal of residual inorganic salt. Azeotropic distillation of the water and benzene was then continued until approximately 375 ml. of benzene remained in the flask, whereupon the warm benzene solution was poured into 1500 ml. of petroleum ether (b. p. 77–115°). Cooling and filtration yielded 582 to 654 g. of practically colorless 2-benzylphenol, m. p. 51.5–53°.

The Dialkylaminoalkyl Chlorides.—Treatment of the commercially available amino alcohols with thionyl chloride in benzene solution[14] afforded practically quantitative yields of the corresponding chloride hydrochlorides. In general the free bases were not distilled, but rather prepared from a 20 or 30% excess of the salt shortly before use. Dry toluene solutions of the bases appear to be quite stable at room temperature. The Amidone intermediates, 1-dimethylamino-2-propanol and 1-dimethylamino-2-chloropropane, required for 338-19A and B were prepared satisfactorily as originally described[15]; also the I. G. Farbenindustrie procedures[16] for the preparation of β-1-piperidylethyl chloride and the corresponding alcohol produced excellent results.

β-Cyclohexylaminoethyl chloride hydrochloride, m. p. 219–219.5°, an intermediate for 518-14, was prepared in 97.5% yield by Dr. W. B. Wheatley from N-cyclohexylethanolamine.[17] *Anal.* Calcd. for $C_8H_{17}NCl_2$: C, 48.5; H, 8.7; N, 7.1. Found: C, 48.7; H, 8.7; N, 7.0.

Method A. 2-Benzylphenyl β-Dimethylaminoethyl Ether (C-5581H) (III) Hydrochloride.—Twelve hundred and ten grams (8.4 moles) of β-dimethylaminoethyl chloride hydrochloride[14] was covered with 1 liter of toluene and cooled in an ice-bath. Into the well-stirred suspension was slowly added a cold solution of 400 g. (10 moles) of sodium hydroxide dissolved in 400 ml. of water. The toluene solution of the base was decanted and the aqueous mixture was extracted further by decantation with 1 liter of toluene divided into five portions. (In the event an emulsion forms at this point, the addition of a relatively large quantity of anhydrous potassium carbonate permits filtration.) The combined extracts were dried overnight (or at least two hours on the mechanical shaker) over anhydrous potassium carbonate. Into a twelve-liter three-neck flask equipped with a sealed stirrer, dropping funnel and reflux condenser were placed 1 liter of dry toluene and 138 g. (6.0 moles) of sodium, and a dry nitrogen atmosphere was provided. A Glas-Col heating mantle was utilized to heat the toluene to boiling. When the sodium had melted the stirrer was started and a solution of 1159 g. (6.3 moles) of 2-benzylphenol (dried over phosphorus pentoxide) in 2360 ml. of dry toluene was added *via* dropping funnel at such a rate as to maintain vigorous boiling without external heating. After the addition was complete the mixture was refluxed and stirred until all of the sodium had dissolved. The previously prepared toluene solution of β-dimethylaminoethyl chloride was then added rapidly through the dropping funnel and the stirred mixture was boiled under reflux for seventeen hours. Steam distillation then served to remove the toluene and to volatilize or polymerize excess β-dimethylaminoethyl chloride. The oily product was extracted from the cooled aqueous phase with approximately 3 liters of ether. Combined ether extracts were washed with 20% sodium hydroxide solution, then with a saturated solution of sodium chloride and dried over anhydrous potassium carbonate. Distillation of the product through a twelve-inch Vigreux column afforded 1444 g. (94.3%

(7) Dalgliesh, *J. Chem. Soc.*, 677 (1944).

(8) All melting points are uncorrected.

(9) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

(10) Short and Stewart, *J. Chem. Soc.*, 556 (1929).

(11) "Santophen 7" is a mixture of 2- and 4-benzylphenol supplied by Monsanto Chemical Company. It is evidently produced by the condensation of benzyl chloride with a large excess of phenol at 150° [McMaster and Bruner, *Ind. Eng. Chem.*, **28**, 505 (1936)].

(12) Kropp, Schranz and Schulemann, U. S. Patent 1,580,052 (1926); [*C. A.*, **20**, 1631 (1926)].

(13) Akimoff, U. S. Patent 2,016,848 (1935); [*C. A.*, **29**, 8008 (1935)].

(14) Slotta and Behnisch, *Ber.*, **65**, 754 (1935).

(15) O. P. B. 981, U. S. Department of Commerce, July, 1945, p. 96.

(16) *Ibid.*, page 41.

(17) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

TABLE I

ALKAMINE ETHERS OF BENZYLPHENOLS AND THEIR HYDROCHLORIDES

No.	R	R-O-R¹ — R¹	Method of prepn.	Yield %
C-5581H	2-Benzylphenyl	$-CH_2CH_2-N(CH_3)_2$	A	94.3
338-20	4-Benzylphenyl	$-CH_2CH_2-N(CH_3)_2$	A	64.5
338-19A	2-Benzylphenyl	$-CH(CH_3)-CH_2-N(CH_3)_2$	A	58.1
338-19B	2-Benzylphenyl	$-CH_2-CH(CH_3)-N(CH_3)_2$	A	
338-22	2-Benzylphenyl	$-CH_2CH_2-N(C_2H_5)_2$	A	76.8
546-1	2-Benzylphenyl	$-CH_2CH_2CH_2-N(CH_2CH_2)_2CH_2$	B	68.3
546-2	2-Benzylphenyl	$-CH_2CH_2CH_2-N(CH_2CH_2)(CH-CH_2)CH_2$, CH_3	B	66.2
546-3	2-Benzylphenyl	$-CH_2CH_2CH_2-N(CH_3)_2$	B	86.6
546-13	2-Benzylphenyl	$-CH_2CH_2CH_2-N(C_4H_9\text{-}n)_2$	A	98.2
546-14	4-Benzylphenyl	$-CH_2CH_2CH_2-N(C_4H_9\text{-}n)_2$	A	75
612-9	2-Benzylphenyl	$-CH_2CH_2-N(CH_2CH_2)_2$	B	73.5
612-10	2-Benzylphenyl	$-CH_2CH_2-N(CH_2CH_2)(CH-CH_2)CH_2$, CH_3	B	75.5
380-1	2-Benzylphenyl	$-CH_2CH_2-N(CH_2CH_2)_2O$	A	85.5[a]
380-3	2-Benzylphenyl	$-CH_2CH_2-N(CH_2CH_2)_2CH_2$	A	55.3[a]
489-27	2,6-Dibenzylphenyl	$-CH_2CH_2-N(CH_3)_2$	A	31.5[a]
489-2	Hexahydro-2-benzylphenyl[b,c]	$-CH_2CH_2-N(CH_3)_2$	Hydrogenation	25.7[a]
489-1	2-Cyclohexylmethyl-cyclohexyl[c]	$-CH_2CH_2-N(CH_3)_2$	Hydrogenation	38[a]
489-9	2-Benzylphenyl	$-CH_2CH_2-NH-CH(CH_3)_2$	B	81.2[a]
489-10	2-Benzylphenyl	$-CH_2CH_2-NH-CH_3$	B	22.3[a,d]
518-14	2-Benzylphenyl	$-CH_2CH_2-NH-CH(CH_2CH_2)_2CH_2$	A	34.8

[a] Yield of pure hydrochloride. [b] The structure of the selective hydrogenation product was not established. [c] Geometrical isomers were not isolated. [d] The low yield is ascribed to the escape of methylamine from the pressure bottle.

yield based on the sodium) of colorless oil, b. p. 141–144° at less than 1 mm.

The hydrochloride was precipitated quantitatively from ether solution by means of commercial hydrogen chloride. Recrystallization from methyl isobutyl ketone produced 1457 g. (88.3% yield) of colorless crystals, m. p. 119–120°.

Method B. 2-Benzylphenyl β-Isopropylaminoethyl Ether Hydrochloride (489-9).—Under an atmosphere of dry nitrogen a solution of 193.4 g. (1.05 moles) of 2-benzylphenol in 200 ml. of dry toluene was added dropwise to a stirred, boiling suspension of 24.0 g. (1.0 mole) of sodium hydride (du Pont) in 100 ml. of dry toluene. After all of the sodium hydride had reacted, 563.6 g. (3 moles) of ethylene bromide was added and the mixture was refluxed for sixty hours. The reaction product, which was still strongly alkaline, was washed successively with water, 20% sodium hydroxide solution, saturated salt solution and then dried over anhydrous magnesium sulfate. After nearly all of the toluene had been distilled under reduced pressure the product crystallized. Recrystallization from isopropyl alcohol produced 142.4 g. (48.8% yield) of crude 2-benzylphenyl β-bromoethyl ether, m. p. 82–85°, which contained a high carbon impurity.

Anal. Calcd. for $C_{15}H_{15}BrO$: C, 62.0; H, 5.20. Found: C, 64.4; H, 5.23.

Into a well-cooled solution of 56.3 g. (0.193 mole) of the above crude bromo ether in 80 ml. of dioxane contained in a pressure bottle was slowly poured 34.2 g. (0.58 mole) of isopropylamine. The bottle was sealed and heated in the steam cone overnight (seventeen hours). The light yellow solid which remained after removal of the solvent and excess isopropylamine under reduced pressure was treated with an excess of sodium hydroxide and the liberated base was taken up in ether. Upon shaking the ether extract with 6 *N* hydrochloric acid, the hydrochloride precipitated. After recrystallization from water 47.7 g. (81.2% yield based on the crude bromoethyl ether) of white crystals, m. p. 174–175°, were obtained.

Crude 2-benzylphenyl γ-bromopropyl ether, m. p. 137–163°, was prepared in a 60% yield by the method described for the above β-bromoethyl homolog. For those syntheses involving amines boiling above 100° the use of a pressure bottle was not required. The bromo ether was refluxed overnight with a large excess of the appropriate amine.

TABLE I (*Continued*)

B. p., °C at 1 mm.	HCl M. p., °C.	Recryst. from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
141–144	119–120	MeCOBu-*i*	$C_{17}H_{21}NO\cdot HCl$	70.1	70.0	7.6	7.7
152–153	179–182	*i*-PrOH	$C_{17}H_{21}NO\cdot HCl$	70.1	70.2	7.6	7.6
148–152	75–80	EtOAc	$C_{18}H_{23}NO\cdot HCl$	70.7	70.8	7.9	8.3
152–157	170–171.5	Me_2CO	$C_{18}H_{23}NO\cdot HCl$	70.7	70.7	7.9	7.9
160–164	158–159	*i*-PrOH	$C_{19}H_{25}NO\cdot HCl$	71.5	71.4	8.2	8.1
192–198	167–168	*i*-PrOH	$C_{21}H_{27}NO\cdot HCl$	73.0	72.9	8.2	8.3
194.5–197	149–150	*i*-PrOH	$C_{22}H_{29}NO\cdot HCl$	73.6	73.7	8.4	8.5
149–153	159–160	*i*-PrOH	$C_{18}H_{23}NO\cdot HCl$	70.8	70.6	7.9	7.8
174–176	86–89	EtOAc	$C_{24}H_{35}NO\cdot HCl$	74.1	74.2	9.3	9.5
197–200	96–98	EtOAc	$C_{24}H_{35}NO\cdot HCl$	74.1	73.6	9.3	9.4
152–163	140–141.5	Me_2CO	$C_{19}H_{23}NO\cdot HCl$	72.1	72.1	7.6	7.7
151–167	139.5–142	MeCOBu-*i*	$C_{21}H_{28}NO\cdot HCl$	72.8	73.3	8.4	8.3
.....	184–185	MeOH	$C_{19}H_{23}NO_2\cdot HCl$	68.5	68.5	7.3	7.2
180–183	139–141	Me_2CO	$C_{20}H_{25}NO\cdot HCl$	73.0	72.4	7.9	7.8
.....	143–144.5	MeCOBu-*i*	$C_{24}H_{27}NO\cdot HCl$	75.6	75.5	7.4	7.3
.....	170	Me_2CO	$C_{17}H_{27}NO\cdot HCl$	68.7	68.6	9.5	9.2
.....	128.5–129	EtOAc	$C_{17}H_{33}NO\cdot HCl$	67.0	67.1	11.6	11.1
.....	174–175	H_2O	$C_{18}H_{23}NO\cdot HCl$	70.8	70.8	7.9	7.9
.....	178.5–179.5	Abs. EtOH	$C_{16}H_{19}NO\cdot HCl$	69.3	69.5	7.2	7.1
165–171	182–183.5	*i*-PrOH	$C_{21}H_{27}NO\cdot HCl$	72.9	73.3	8.2	8.3

2-Benzylphenyl β-Dimethylaminoisopropyl Ether (339-19A) and 2-Benzylphenyl β-Dimethylaminopropyl Ether (338-19B).—To a solution of sodium methoxide prepared from 6.9 g. (0.3 mole) of sodium and 117 ml. of absolute methanol was added 55.2 g. (0.3 mole) of 2-benzylphenol. Following removal of excess methanol under reduced pressure, the sodium 2-benzylphenate was dissolved in 180 ml. of dry toluene and refluxed with a large excess (59.5 g.) of freshly distilled 1-dimethylamino-2-chloropropane[15] under an atmosphere of nitrogen for five and one-half hours. The basic material was extracted with dilute hydrochloric acid. Combined acid extracts were made strongly basic with alkali and extracted with ether. The ether solution was washed thoroughly with water, dried over potassium carbonate and distilled through a twelve-inch Vigreux column to obtain two fractions: F_1, b. p. 148–152°, (27.5 g.) and F_2, b. p. 152.5–157°, (19.4 g.) at less than 1 mm. Both fractions were dissolved in ether and precipitated with dry hydrogen chloride. F_1 yielded 33.5 g. of hydrochloride, m. p. 80–132°, which afforded 7.4 g. of product, m. p. 168–169°, on recrystallization from acetone. The hydrochloride from F_2 weighed 23.5 g. and melted at 73–84°. Treatment with hot acetone produced 5.4 g. of material, m. p. 161–164°. On boiling the two fractions with a large volume of acetone 10.4 g. of the less soluble isomer, m. p. 170–171.5°, was obtained in pure form. The acetone mother liquors were concentrated to dryness and the gummy residue (29.6 g.) was recrystallized twice from ethyl acetate to obtain 23.0 g. of the lower melting isomer, m. p. 75–80°. The structures of these anticipated isomers derived from the halide utilized in the original synthesis of Amidone[16] have been assigned by analogy with the physical properties of Amidone and Isoamidone.[18]

2-Cyclohexylmethylcyclohexyl β-Dimethylaminoethyl Ether (489-1) Hydrochloride.—Twenty-five and five-tenths grams (0.10 mole) of 2-benzylphenyl β-dimethylaminoethyl ether was dissolved in 100 ml. of glacial acetic acid. One gram of Adams platinum catalyst and 6 ml. of concentrated sulfuric acid were added and the compound was hydrogenated under a gage pressure of 50 lb. of hydrogen and a temperature of 60° until 0.6 mole of hydrogen was taken up. The catalyst was filtered off and the filtrate was allowed to stand until a duplicate preparation was carried out. After removing the acetic acid from the combined filtrates under reduced pressure, the residue was taken up in 150 ml. of water, made alkaline with 20% sodium hydroxide solution, and extracted into ether. The

(18) For pertinent references see Cheney, Smith and Binkley, THIS JOURNAL, 71, 53 (1949).

ether solution was washed with water and then dried over anhydrous potassium carbonate. The hydrochloride was precipitated with dry hydrogen chloride to obtain 7.1 g. of product, m. p. 128–129°, which afforded 6.6 g. of material which melted at 128.5–129° after recrystallization from ethyl acetate. On concentrating the ether solution and recrystallizing the residue from ethyl acetate 4.9 g. of additional material was obtained. The over-all yield therefore was 31.5%.

Hexahydro-2-benzylphenyl β-Dimethylaminoethyl Ether (489-2) Hydrochloride.—The same quantities and procedure were used as described for 489-1 with the exception that the hydrogenation was interrupted when only one-half as much hydrogen had been taken up. From the partial reduction of 51 g. (0.2 mole) of C-5581H there was obtained 41.9 g. of material melting over the range 117–150°. Two recrystallizations from acetone led to the isolation of 15.3 g. (25.7% yield) of white crystals melting at 169–170°.

Acknowledgment.—The authors wish to thank Mr. Richard M. Downing for the microanalyses and the assistance of Messrs. L. E. Lorensen and H. J. Reiche and Dr. W. B. Wheatley is gratefully acknowledged.

Summary

1. The preparation of 2-benzylphenol and 4-benzylphenol is described.

2. Twenty dialkylaminoalkyl ethers of the benzylphenols and their hydrochlorides are reported.

3. 2-Benzylphenyl β-dimethylaminoethyl ether hydrochloride manifests potent antihistaminic and local anesthetic activity.

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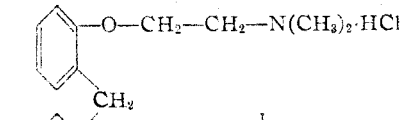
[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

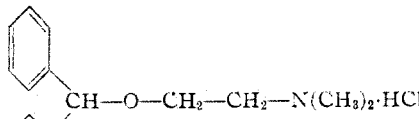
β-Dimethylaminoethyl Ethers of Substituted 2-Benzylphenols

BY W. B. WHEATLEY, L. C. CHENEY AND S. B. BINKLEY

It has been observed that 2-benzylphenyl β-dimethylaminoethyl ether hydrochloride (I) possesses greater antihistaminic activity when tested



I



II

in guinea pigs than Benadryl (II).[1] Therefore the synthesis of β-dimethylaminoethyl ethers of various substituted 2-benzylphenols was undertaken in order to ascertain whether substitution enhances the antihistaminic activity of the parent compound. In this paper is described a number of new basic ethers related to I, all incorporating the β-dimethylaminoethyl group, but with substitutions in the 2-benzylphenyl portion of the molecule.

In general the basic ethers were prepared by heating together the substituted sodium 2-benzylphenolate and β-dimethylaminoethyl chloride in an inert solvent such as toluene. The products were isolated by standard procedures and converted to the hydrochlorides by saturation of the ether solution of the amines with dry hydrogen chloride. These hydrochlorides are white crystalline compounds, most of which are quite soluble in water.

A survey of the literature reveals that 2-benzylphenol may be prepared in a number of ways. Phenol may be condensed with benzyl chloride alone[2] or with either benzyl chloride or the alcohol in the presence of a variety of catalysts[3] to yield a mixture of 2- and 4-benzylphenols together with traces of benzyl phenyl ether. On the other hand, the use of sodium phenolate and benzyl chloride yields the 2-isomer almost exclusively.[4] A considerable amount of ether is formed, but it can be removed easily by extraction, whereas the separation of 2- and 4-benzylphenols requires more involved procedures.[2,5] For this reason, the method of Claisen, *et al.*,[4] was used to prepare the intermediate substituted 2-benzylphenols (see Table I). Several of those prepared from sodium phenolate and a substituted benzyl chloride were treated with barium hydroxide[5a] in order to insure complete removal of the 4-isomer, but as the amount of 4-isomers appeared to be negligible, this treatment was omitted in later preparations. Sodium hydride, which has recently become available commercially, was employed exclusively to prepare the sodium phenolates, both in the Claisen reaction and in the Williamson ether synthesis. It was found that in the quantities used in the laboratory, sodium hydride is more conveniently handled than sodium, and reacts rapidly and completely with phenolic compounds.

(1) Cheney, Smith and Binkley, THIS JOURNAL, 71, 60 (1949).

(2) McMaster and Bruner, *Ind. Eng. Chem.*, **28**, 505 (1936).

(3) (a) Rennie, *J. Chem. Soc.*, **49**, 406 (1886); (b) Huston, THIS JOURNAL, **46**, 2275 (1924); (c) Meyer and Bernhauer, *Monatsh.*, **53 and 54**, 721 (1929); (d) Andrianov, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 846 (1936).

(4) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

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