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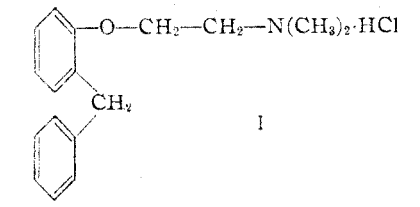
[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

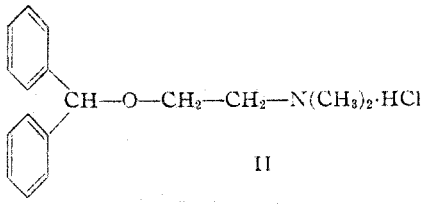
β-Dimethylaminoethyl Ethers of Substituted 2-Benzylphenols

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).

(5) (a) Kropp, Schranz and Schuleman, U. S. Patent 1,580,053, April 6, 1926; (b) Akimoff, U. S. Patent 2,016,848, Oct. 8, 1945.

TABLE I

SUBSTITUTED 2-BENZYLPHENOLS

No.	Phenol	Yield, %	B. p., °C.	Mm.	M. p., °C. or $n^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	4-*t*-Butyl-2-benzyl-	40	157–160	2.5	1.5624	$C_{17}H_{20}O$	84.9	85.0	8.4	8.8
IV	4-Cyclohexyl-2-benzyl-	55	188–196	2	87.5–89.0[b]	$C_{19}H_{22}O$	85.7	85.7	8.3	8.2
V	4-Methoxy-2-benzyl-	46	198–212	7	103.5–104.5[c]	$C_{14}H_{14}O_2$	78.5	78.5	6.6	6.4
VI	4-Ethoxy-2-benzyl-	42	165–167	1	1.5820	$C_{15}H_{16}O_2$	78.9	79.1	7.1	7.3
VII	2-(4′-Isopropylbenzyl)-	38[a]	134–137	1	1.5722	$C_{16}H_{18}O$	84.9	84.6	8.0	7.9
VIII	2-(4′-Methoxybenzyl)-	36[a]	154–157	1	80.0–81.5[b]	$C_{14}H_{14}O_2$	78.5	78.3	6.6	6.6
IX	2-(2′,3′-Dimethoxybenzyl)-	49[a]	148–154	1	125.5–127.0[b]	$C_{15}H_{16}O_3$	73.8	73.8	6.6	6.8
X	2-(α-Methylbenzyl)-	37	122–126	1.5	1.5904	$C_{14}H_{14}O$	84.8	84.8	7.1	7.5
XI	2-(2′,4′-Dichlorobenzyl)	29	142–147	1	1.6124	$C_{13}H_{10}OCl_2$	61.7	61.8	4.0	4.0

[a] The yields in the table represent the once-distilled products, which were treated as described in the experimental reaction to remove any 4-isomer which may have been present. [b] Recrystallized from cyclohexane. [c] Recrystallized from benzene–Skellysolve B.

Pharmacology.—Preliminary pharmacological data indicate that none of the compounds herein reported is as active against histamine-induced spasm in guinea pigs as I. A more complete report of the pharmacology of these compounds will be published elsewhere.

Experimental[6]

Preparation of Substituted 2-Benzylphenols.—In a typical experiment, a solution of 138 g. (1.0 mole) of *p*-ethoxyphenol in 250 cc. of warm toluene was added gradually to a stirred suspension of 24 g. (1.0 mole) of sodium hydride in 150 cc. of toluene, under a nitrogen atmosphere. To the resulting suspension, stirred and maintained at gentle reflux, was added dropwise 140 g. (1.1 moles) of benzyl chloride. After five hours of vigorous refluxing, the reaction mixture was cooled and hydrolyzed with dilute hydrochloric acid. The aqueous layer was discarded and the toluene layer washed in turn with water and saturated sodium bicarbonate solution. The toluene solution was then extracted several times with Claisen alkali; the basic extracts acidified with hydrochloric acid and the liberated phenolic material taken up in ether. Evaporation of the ether left an oil which was distilled *in vacuo*, giving a forerun of recovered *p*-ethoxyphenol, followed by 95.8 g. (42%) of 4-ethoxy-2-benzylphenol, a light yellow oil boiling at 165–167° (1 mm.). In an alternative method of working up the reaction, the toluene solution obtained following hydrolysis was stripped of solvent and the residue taken up in approximately four times its volume of Claisen alkali. The neutral material was removed by extraction with Skellysolve C; acidification of the basic solution gave the phenolic fraction, which was extracted and distilled as described above.

Compounds III–VI, X and XI (Table I) were used in the next step without further purification while VII, VIII and IX were treated with barium hydroxide as described below. In order to separate a mixture of 2- and 4-benzylphenols, one mole of the mixture is dissolved in a boiling solution of 0.75 mole of barium hydroxide octahydrate in 900 cc. of water, boiled ten minutes, then cooled and filtered.[5a] Acidification of the filtrate gives the 2-isomer, which may be distilled or recrystallized. It was found that with substituted 2-benzylphenols, the separation of the insoluble barium salt is best carried out at different temperatures, depending on the particular compound. The temperatures at which the separations were done are as follows: VIII, 50°; IX, 10°. The solution of barium salt of VII formed two layers at 80°; the small lower layer was removed and acidified to give the 2-isomer.

Those compounds with substituents in the phenol ring were prepared from the substituted sodium phenolate and benzyl chloride; the others from sodium phenolate and the substituted benzyl chloride (α-bromoethylbenzene was used to synthesize X). In addition to those phenols listed in Table I, there was prepared a number of other substituted 2-benzylphenols, which have been described in the literature: 2-benzyl-4-cresol,[4] 2-benzohydrylphenol,[4] 2-benzoylphenol,[7] 2-(4′-bromobenzyl)-phenol,[8] 4-chloro-2-benzylphenol,[9] 6-chloro-2-benzylphenol,[9] 4-chloro-2-(4′-chlorobenzyl)-phenol,[9] 4,6-dichloro-2-benzylphenol[10] and 2-(2′,3′ and 4′-chlorobenzyl)-phenols.[3]

In one case it was shown that an increase in reaction temperature increased the yield of benzylated phenol. The reaction of 4-chlorobenzyl chloride with sodium phenolate in toluene gave the desired 2-(4′-chlorobenzyl)-phenol in 29% yield; in xylene, 40% yield.

Preparation of Substituted 2-Benzylphenyl β-Dimethylaminoethyl Ethers.—The following is a typical example. To a well-stirred, ice-cold suspension of 37 g. (0.26 mole) of β-dimethylaminoethyl chloride hydrochloride[11] in 50 cc. of toluene were added slowly 30 cc. of a 56% potassium hydroxide solution; the mixture was stirred for about fifteen minutes, then the toluene layer decanted. The aqueous sludge was stirred with two successive 50-cc. of portions of toluene and the combined toluene decantates dried by shaking over anhydrous potassium carbonate for four hours. To a suspension of 4.8 g. (0.2 mole) of sodium hydride in 200 cc. of toluene, under a nitrogen atmosphere, was added gradually a solution of 39.6 g. (0.2 mole) of 2-benzyl-4-cresol in 100 cc. of toluene. After completion of the addition, the mixture was refluxed for thirty minutes. To the resulting clear yellow solution, maintained at gentle reflux, was added dropwise the above-described toluene solution of β-dimethylaminoethyl chloride. Precipitation of sodium chloride began almost immediately. After seven hours of refluxing, the mixture was cooled and water added. The toluene layer was washed with 10% potassium hydroxide solution, dried, stripped and the residue distilled *in vacuo*, giving 47.8 g. (89% yield) of 2-benzyl-4-tolyl β-dimethylaminoethyl ether, b. p. 168–174° (3 mm.). The basic ether was converted to its hydrochloride by saturating an ice-cold ether solution of the amine with dry hydrogen chloride. The insoluble hydrochloride was collected by filtration, and recrystallized from isopropyl alcohol–Skellysolve B.

Since crystalline hydrochlorides of 518–19 and 551–43 (Table II) could not be obtained readily, the basic ethers were dissolved in cold 95% ethanol and ethyl acetate, respectively, and the calculated amount of concentrated nitric acid added. Dilution with ether caused precipitation of the crystalline nitrates, which were collected and recrystallized.

(6) All melting points are uncorrected.

(7) Morgan and Plummer, *Rec. trav. chim.*, **56**, 629 (1937).

(8) Huston, *et al.*, THIS JOURNAL, **55**, 2146 (1933).

(9) Huston, *et al.*, *ibid.*, **55**, 4639 (1933).

(10) Huston and Eldridge, *ibid.*, **53**, 2260 (1931).

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

TABLE II

SUBSTITUTED 2-BENZYLPHENYL β-DIMETHYLAMINOETHYL ETHERS, R—O—CH_2—CH_2—$N(CH_3)_2$

No.	R	Yield, %	B. p., °C.	Pressure, mm.	M. p., °C.	Formula	Hydrochlorides: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
446-24	2-Benzyl-4-tolyl	89	168–174	3	126.5–128.0[b]	$C_{24}H_{24}ONCl$	70.7	70.7	7.9	8.2	4.6	4.5
480-6	4-*t*-Butyl-2-benzylphenyl	87	137–140	1	162.5–164.0[b]	$C_{21}H_{28}ONCl$	72.5	72.6	8.7	8.8	4.0	3.8
446-44	4-Cyclohexyl-2-benzylphenyl	87	186–190	1	152.5–154.0[b]	$C_{23}H_{28}ONCl$	73.9	72.8	8.6	8.4	3.7	3.7
446-15	4-Methoxy-2-benzylphenyl	86	174–177	1	131.0–132.0[e]	$C_{14}H_{14}O_2NCl$	67.2	67.3	7.5	7.6	4.4	4.6
446-28	4-Ethoxy-2-benzylphenyl	79	167–171	1	136.0–137.0[b]	$C_{15}H_{16}O_2NCl$	67.9	67.7	7.8	7.6	4.2	4.1
446-21	4-Chloro-2-benzylphenyl	82	172–176	1	173.5–175.5[b,g]	$C_{17}H_{21}ONCl_2$	62.6	62.7	6.5	6.5	4.3	4.4
551-43	6-Chloro-2-benzylphenyl	76	160–164	1	93.0–95.0[e,h]	$C_{17}H_{21}O_4N_2Cl$	57.9	57.9	6.0	6.1	7.9	8.0
480-25	2-(4′-Isopropylbenzyl)-phenyl	90	151–152	1	144.0–145.5[b]	$C_{20}H_{28}ONCl$	71.9	72.1	8.5	8.5	4.2	4.2
446-34	2-(4′-Methoxybenzyl)-phenyl	89	149–152	1	123.0–126.0[b]	$C_{16}H_{18}O_2NCl$	67.2	67.0	7.5	7.5	4.4	4.4
480-38	2-(2′,3′-Dimethoxybenzyl)-phenyl	90	164–166	1	1.5560[f]	$C_{19}H_{25}O_3N$	72.3	72.2	8.0	8.2	4.4	4.3
518-35	2-(2′-Chlorobenzyl)-phenyl	80	155–167	1	139.5–142.5[b]	$C_{17}H_{21}ONCl_2$	62.6	62.5	6.5	6.5	4.3	4.2
551-13	2-(3′-Chlorobenzyl)-phenyl	82	146–152	1	120.0–121.5[b]	$C_{17}H_{21}ONCl_2$	62.6	62.3	6.5	6.6	4.3	4.5
446-48	2-(4′-Chlorobenzyl)-phenyl	81	179–185	3	152.0–153.0[b]	$C_{17}H_{21}ONCl_2$	62.6	62.3	6.5	6.9	4.3	4.2
570-26	2-(4′-Bromobenzyl)-phenyl	92	162–165	1	158.0–160.5[b]	$C_{17}H_{21}ONBrCl$	55.1	55.1	5.7	5.9	3.8	3.8
518-39	4-Chloro-2-(4′-chlorobenzyl)-phenyl	86	177–182	1	150.0–152.0[b]	$C_{17}H_{20}ONCl_3$	56.6	56.6	5.6	5.8	3.9	3.9
570-31	2-(2′,4′-Dichlorobenzyl)-phenyl	91	149–152	1	139.5–141.0[b]	$C_{17}H_{20}ONCl_3$	56.6	56.7	5.6	5.7	3.9	3.8
570-35	4,6-Dichloro-2-benzylphenyl	85	159–163	1	137.5–140.5[b]	$C_{17}H_{20}ONCl_3$	56.6	56.4	5.6	5.6	3.9	3.8
490-12	2-Benzoylphenyl	95	180–181	1	144.0–145.5[b]	$C_{17}H_{20}O_2NCl$	66.8	66.6	6.6	6.8	4.6	4.4
490-15	2-(α-Hydroxybenzyl)-phenyl	70	.....	...	153.0–154.0[d]	$C_{17}H_{22}O_2NCl$	66.3	66.3	7.2	7.4	4.6	4.7
518-49	2-(α-Methylbenzyl)-phenyl	78	142–146	1	141.0–142.5[b]	$C_{18}H_{24}ONCl$	70.7	70.7	7.9	8.1	4.6	4.3
518-19	2-Benzohydrylphenyl	88	189–192	1	184.0–186.5[e,h]	$C_{32}H_{32}O_4N_2$	70.0	70.3	6.6	6.9	7.1	7.0

[a] Recrystallized from isopropyl alcohol–ether. [b] Recrystallized from isopropyl alcohol–Skellysolve B. [c] Recrystallized from ethyl acetate–ether. [d] Recrystallized from isopropyl alcohol–methyl isobutyl ketone. [e] Recrystallized from 95% ethanol. [f] n^{23}, formula and analysis of the free base. [g] A double melting point was observed, the lower at 141.0–143.0°. The lower melting form was converted to the higher by fusion and seeding with a crystal of the higher melting form. [h] Melting point, formula and analysis of the nitrate.

2-(α-Hydroxybenzyl)-phenyl β-Dimethylaminoethyl Ether Hydrochloride.—Twenty grams (0.075 mole) of the hydrochloride of 490-12 was dissolved in 100 cc. of absolute ethanol and hydrogenated over Adams platinum oxide catalyst at three atmospheres pressure. After 2.75 hours, the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, the filtrate diluted with ether and the precipitated amine salt (14.0 g., 70% yield) recrystallized from a mixture of isopropyl alcohol and methyl isobutyl ketone.

Acknowledgment.—Dr. E. C. Horning of the University of Pennsylvania kindly supplied samples of *p*-isopropylbenzyl chloride and 2,3-dimethoxybenzyl alcohol. Microanalyses were performed by Mr. Richard M. Downing. Mr. William E. Fitzgibbon carried out certain reactions reported herein.

Summary

1. The synthesis of a number of new substituted 2-benzylphenols is reported.

2. The synthesis of a series of β-dimethylaminoethyl ethers of substituted 2-benzylphenols is reported.

3. Preliminary pharmacological data indicate that some of these basic ether hydrochlorides prevent histamine-induced asthma in guinea pigs.

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