A similar treatment yields the further relationship

$$(18)\quad \sum_{n=1}^{\infty} P^{n-1} S_{2n+1} = -\frac{1}{P} - \frac{2}{\sqrt{P}(1-P)^2}\sinh 2\sqrt{P} + \frac{1+P}{P(1-P)^2}\cosh 2\sqrt{P}$$

Substituting the results of (17), and (18) in (16) and making use of the relations

$$P_{11} + P_{12} = 1$$
$$P_{21} + P_{22} = 1$$

we have

$$(19)\quad f = \frac{P_{12} - P_{21}}{2P_{12}} + \frac{P_{12} + P_{21}}{2P_{12}}\cosh 2\sqrt{P_{12}P_{21}} - \sqrt{\frac{P_{21}}{P_{12}}}\sinh 2\sqrt{P_{12}P_{21}}$$

which may be rearranged to the form

$$(20)\quad f = \left(\cosh\sqrt{P_{12}P_{21}} - \sqrt{\frac{P_{21}}{P_{12}}}\sinh\sqrt{P_{12}P_{21}}\right)^2$$

It is desirable to be able to express f as a function of the polymer composition rather than the propagation probabilities used in equation (20). This may be accomplished by making use of the relations[9]

$$\frac{P_{21}}{P_{12}} = \frac{m_1}{m_2}$$
$$\sqrt{P_{12}P_{21}} = \frac{1 - \sqrt{1 - 4m_1m_2(1 - r_1r_2)}}{2(1 - r_1r_2)\sqrt{m_1m_2}}$$

Thus we see that f is expressible in terms of the copolymer composition m_2 and the quantity $(1 - r_1r_2)$ which is a measure of the alternation tendency in copolymerization. It is possible, therefore, to plot a family of curves of f against m_2 with (r_1r_2) as parameter (see Fig. 1). In the case $r_2 = 0$ that portion of the curve for m_2 greater than 0.5 is unattainable in practice, as is that portion of the curve for m_2 less than 0.5 in the case $r_1 = 0$. The curve drawn for $r_1r_2 = 0$ may therefore be regarded as a composite of the two extreme cases.

(9) r_1 and r_2 are relative rates of propagation and are characteristic of the monomer pair used. See the references given under (8)

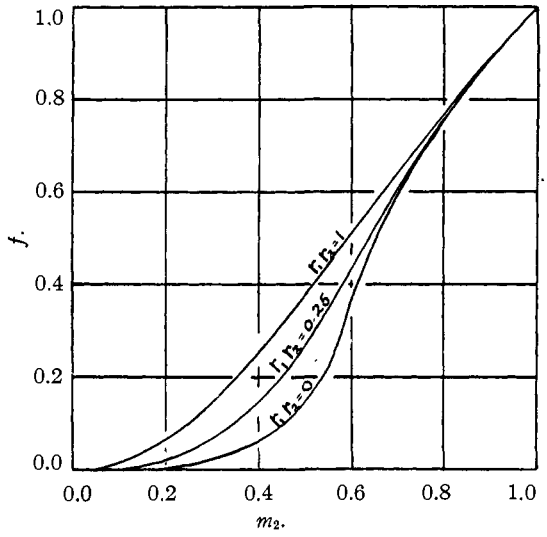

Fig. 1.—Fraction of acid remaining unlactonized as a function of mole fraction of acid in copolymer.

Summary

An expression has been derived for the amount of lactonization to be expected in a copolymer containing hydroxyl and carboxyl groups.

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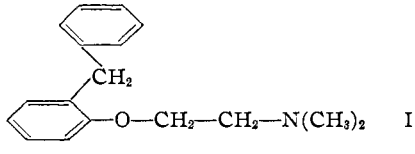
2-Benzylphenol Derivatives. III.[1] Basic Ethers

BY WILLIAM B. WHEATLEY, LEE C. CHENEY AND S. B. BINKLEY

In previous communications the antihistaminic action of 2-benzylphenyl β-dimethylaminoethyl ether (I) and some of its analogs was reported.[1]



I

A number of other β-dimethylaminoethyl ethers related to I have been prepared in this Laboratory and submitted for pharmacological evaluation. More analogs of I are in preparation and will be the subject of a future communication.

The method of synthesis of these ethers is essentially that reported previously.[1b] The C-alkylation of phenols by halides of the benzyl type, according to the method of Claisen,[2] has been extended to heterocyclic systems. Phenol has been alkylated with 2-thenyl and 5-chloro-2-thenyl chloride to give 2-(2′-thenyl)-phenol, and 2-(5′-chloro-2′-thenyl)-phenol, respectively. In the case of alkylation of phenol with 2-thenyl chloride, the isomeric 4-(2′-thenyl)-phenol has been isolated and characterized. Alkylation of 8-hydroxyquinoline with benzyl chloride gave a compound believed to be 7-benzyl-8-hydroxyquinoline. Conversion of the various substituted phenols to the β-dimethylaminoethyl ethers proceeded smoothly via the Williamson ether synthesis.

(1) For preceding papers in this series, see (a) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949); (b) Wheatley, Cheney and Binkley, *ibid.*, **71**, 64 (1949).

(2) Claisen, *Ann.*, **420**, 210 (1925).

Experimental[3]

Several previously reported alkylated phenols were prepared: 4-bromo-2-benzylphenol,[4] 2-methoxy-6-benzylphenol,[2] 2-cinnamylphenol,[2] 1-benzyl-2-naphthol,[2] 2-benzyl-1-naphthol,[2] 1-allyl-2-naphthol,[5] and 2-allyl-1-naphthol.[6]

2-(4'-Fluorobenzyl)-phenol.—Alkylation of phenol with 4-fluorobenzyl chloride[7] in the manner described previously[1b] gave 2-(4'-fluorobenzyl)-phenol in 41% yield, b. p. 136–141° (3 mm.), $n^{26}D$ – 1.5728.

Anal. Calcd. for $C_{13}H_{11}OF$: C, 77.2; H, 5.5. Found: C, 76.5; H, 5.5.[8]

4-Fluoro-2-benzylphenol.—Alkylation of 4-fluorophenol (prepared by demethylation of 4-fluoroanisole with aluminum chloride according to the method described by Suter, Lawson and Smith[9]) with benzyl chloride gave 4-fluoro-2-benzylphenol in 41% yield, b. p. 117–123° (1 mm.), $n^{26}D$ – 1.5720.

Anal. Calcd. for $C_{13}H_{11}OF$: C, 77.2; H, 5.5. Found: C, 75.7, 75.7; H, 5.6, 5.5.

4-Dimethylamino-2-benzylphenol.—One hundred grams (0.268 mole) of 4-dimethylaminophenol sulfate was shaken with 500 ml. of saturated sodium bicarbonate solution and 200 ml. of chloroform until complete solution was attained. The lower layer was drawn off and the aqueous portion extracted twice with fresh chloroform. The combined extracts were dried with Drierite, an equal volume of toluene added and the solvent distilled until practically all of the chloroform was removed. Gradual addition of this solution to a stirred suspension of 12 g. (0.5 mole) of sodium hydride in 300 ml. of toluene gave a blue-green insoluble sodium salt. After refluxing for an hour to insure complete reaction, 62 g. (0.5 mole) of benzyl chloride was added dropwise over a period of two hours. Following one and one-half hours of additional refluxing, the mixture was hydrolyzed with water. The toluene layer was removed and filtered to remove a small amount of tarry material. The aqueous layer was extracted three times with chloroform and the extracts added to the toluene solution. This solution was dried, stripped and distilled *in vacuo*, the entire distillate boiling between 120 and 210° at 2–3 mm. being retained (69 g.). The distillate was then taken up in 200 ml. of Claisen alkali and extracted twice with Skellysolve D. Addition of sufficient concentrated hydrochloric acid to bring the *p*H of the aqueous solution down to 8 caused an oil to separate. It was taken into ether and the ether extracts dried and stripped. Distillation of the residue at 1 mm. gave three main fractions: (1) 7.9 g., b. p. 111–141°; (2) 16.4 g., b. p. 165–180°, $n^{25}D$ 1.6030; (3) 24.3 g., b. p. 180–217°, $n^{25}D$ 1.6194. Fraction (1) was mainly recovered starting material, (2) was assumed to be the desired 4-dimethylamino-2-benzylphenol and used as such immediately, and (3) was assumed to be 4-dimethylamino-2,6-dibenzylphenol.

2-(2'-Thenyl)-phenol and 4-(2'-Thenyl)-phenol.—A solution of 390 g. (4.16 moles) of phenol in 800 ml. of xylene was added to 90.9 g. (3.85 moles) of molten sodium under 1100 ml. of hot xylene at a rate such that refluxing was maintained. After the addition was complete, the mixture was refluxed for three hours. To the hot suspension of sodium phenolate was added over a period of thirty minutes 523 g. (3.95 moles) of 2-thenyl chloride.[10] The reaction mixture was refluxed for eighteen hours, acidified with concentrated hydrochloric acid and steam distilled until about four liters of distillate was collected. The two-phase residue was transferred to a separatory funnel and the aqueous layer withdrawn. It was extracted with 300 ml. of ether, the ether stripped and the residual oil added to the original organic layer. This material was taken up in one liter of Claisen alkali and washed three times with Skellysolve C. Acidification of the aqueous layer liberated the phenolic material, which was extracted into ether. The combined ether extracts were dried over anhydrous magnesium sulfate and stripped. Distillation of the residue gave 290 g. (39% yield) of mixed 2-thenylphenols, b. p. 137° (1.5 mm.)–190° (10 mm.). (Considerable decomposition occurred toward the end of the distillation.) The entire distillate was poured into a boiling solution of 365 g. of barium hydroxide octahydrate in 1.4 l. of water. After ten minutes of boiling, the solution was placed in the cold room. The following day the insoluble barium salt was removed by filtration, acidified and the crude 4-(2'-thenyl)-phenol recrystallized from carbon tetrachloride to give 36 g. of pure product (5% yield). An analytical sample melted sharply at 65°.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.4; H, 5.3. Found: C, 69.6; H, 5.5.

The original aqueous filtrate containing the soluble barium salt was acidified at once, and on cooling the oily 2-(2'-thenyl)-phenol crystallized. Since this compound is easily oxidized by atmospheric oxygen, it is necessary to work rapidly to avoid undue loss during manipulations. The crude phenol was collected by filtration and the wet material dissolved in 200 ml. of hot benzene. The aqueous layer was withdrawn and benzene distilled until no more water appeared in the distillate. The solution was then diluted with one liter of Skellysolve D, cooled and seeded. The crystals were collected and recrystallized from cyclohexane. There was obtained 183 g. (24% yield) of pure 2-(2'-thenyl)-phenol, m. p. 50.0–52.0°.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.4; H, 5.3. Found: C, 68.9; H, 5.4.

2-(5'-Chloro-2'-thenyl)-phenol.—Phenol (45.2 g., 0.482 mole) was alkylated with 85.2 g. (0.482 mole) of 5-chloro-2-thenyl chloride[11] according to the previously described procedure,[1b] giving 50.7 g. of crude product, b. p. 165–175° (5 mm.). Continued slight decomposition during distillation prevented attainment of a good vacuum, and the distillate rapidly became discolored. The distillate was therefore added to a hot solution of 53.5 g. of barium hydroxide octahydrate in 210 ml. of water and boiled ten minutes. The hot solution was cooled rapidly to 20° and filtered. Acidification of the filtrate liberated the phenol, which was removed by extraction with ether. The combined extracts were dried, stripped and the residue distilled at 1 mm. to yield 39.5 g. (39%) of 2-(5'-chloro-2'-thenyl)-phenol, b. p. 135–139°.

Anal. Calcd. for $C_{11}H_9OSCl$: C, 58.8; H, 4.0. Found: C, 58.5; H, 4.2. The phenol was immediately converted to the basic ether, which proved to be a fortunate procedure, since the next day the remainder of the analytical sample, originally a colorless liquid, had become a black solid with a strong odor of hydrogen chloride. The basic ether appeared to be perfectly stable at room temperature.

Two attempts to prepare the bromo analog from phenol and 5-bromo-2-thenyl chloride[11] were unsuccessful, as the reaction products decomposed rapidly, in one case with explosive violence.

7-Benzyl-8-hydroxyquinoline.—A solution of 100 g. (0.69 mole) of 8-hydroxyquinoline in 250 ml. of toluene was added slowly to a stirred suspension of 16.5 g. (0.69 mole) of sodium hydride in 750 ml. of toluene. A bright, yellow insoluble sodium salt formed. The reaction mixture was refluxed for thirty minutes, then, while refluxing was maintained, 79 ml. (87 g., 0.69 mole) of benzyl chloride were added dropwise over a period of five hours. The mixture was then stirred and refluxed overnight and finally hydrolyzed with dilute hydrochloric acid. Addition of sodium bicarbonate brought the *p*H of the aqueous layer up to 8. The toluene layer was removed and stripped

(3) All melting points are uncorrected.

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

(5) Claisen, *Ber.*, **45**, 3157 (1912).

(6) Claisen and Eisleb, *Ann.*, **401**, 61 (1913).

(7) Bennett and Jones, *J. Chem. Soc.*, 1815 (1935).

(8) The fluorine-containing phenols consistently gave low carbon analyses, but in each case the final compound gave a satisfactory analysis.

(9) Suter, Lawson and Smith, THIS JOURNAL, **61**, 161 (1939).

(10) Blicke and Leonard, *ibid.*, **68**, 1934 (1946).

(11) Clapp, *et al.*, *ibid.*, **69**, 1549 (1947).

TABLE I

$R—O—CH_2—CH_2—N(CH_3)_2$

R	Yield, %	B. p. °C.	Mm.	Hydrochlorides M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Methoxy-6-benzylphenyl	83	144–148	1	92.5– 94.0[f]	$C_{18}H_{24}O_5N_2$[b]	62.1	61.8	6.9	7.1		
4-Bromo-2-benzylphenyl	89	164–167	1.5	179.5–181.0[f]	$C_{17}H_{21}ONBrCl$	55.1	55.7	5.7	5.7	3.8	3.8
4-Iodo-2-benzylphenyl[a]	73[a]	.....	...	167.0–170.0[g]	$C_{17}H_{21}ONICl$	48.9	49.1	5.1	5.1		
4-Fluoro-2-benzylphenyl	89	131–134	1	124.5–125.5[f]	$C_{17}H_{21}ONFCl$	65.9	65.7	6.8	6.8	4.5	4.9
4-Dimethylamino-2-benzylphenyl	73	171–186	1	154.0–156.0[h]	$C_{19}H_{27}ON_2Cl$	68.1	67.9	8.1	8.1	8.4	8.8
2-(4′-Fluorobenzyl)-phenyl	72	140–146	2	131.0–132.5[f]	$C_{17}H_{21}ONFCl$	65.9	65.7	6.8	6.9		
2-Cinnamylphenyl	82	137–141	1	154.0–156.5[f]	$C_{19}H_{24}ONCl$	71.8	71.9	7.6	7.8	4.4	4.6
2-(2′-Thenyl)-phenyl	76	159–160	1	129.0–130.0[k]	$C_{15}H_{19}ONS$[d]	68.9	68.2	7.3	6.8		
2-(5′-Chloro-2′-thenyl)-phenyl	86	149–150	1	103.0–106.0[f]	$C_{15}H_{19}ONSCl_2$	54.2	54.3	5.8	5.7	4.2	4.1
1-Benzyl-2-naphthyl	88	184–192	1.5	178.0–181.0[i]	$C_{21}H_{24}ONCl$	73.8	73.8	7.1	7.1		
2-Benzyl-1-naphthyl	79	200–207	2	183.5–185.5[f]	$C_{21}H_{24}ONCl$	73.8	73.6	7.1	7.4		
1-Allyl-2-naphthyl	87	139–143	1	151.0–152.5[f]	$C_{17}H_{22}ONCl$	70.0	70.2	7.6	7.9		
2-Allyl-1-naphthyl	79	136–145	1	.....[c]							
7-Benzyl-8-quinolyl	86	190–197	1	205.0–207.0[j]	$C_{20}H_{24}ON_2Cl_2$[e]	63.3	63.0	6.4	6.2	7.4	7.4

[a] The base was not distilled, but was directly converted to its hydrochloride. The yield is that of crude hydrochloride. [b] Melting point, formula and analysis of the nitrate. [c] A crystalline salt could not be obtained. [d] Formula and analysis of the free base. [e] Dihydrochloride. [f] Recrystallized from isopropyl alcohol–Skellysolve B. [g] Recrystallized from methyl isobutyl ketone. [h] Recrystallized from isopropyl alcohol. [i] Recrystallized from water–isopropyl alcohol. [j] Recrystallized from methanol–ether. [k] Recrystallized from acetone.

under reduced pressure. The residue was taken up in 400 ml. of Claisen alkali and extracted twice with Skellysolve D. On adjustment of the *p*H of the aqueous layer to about 7, a brown semi-solid formed. This mixture was extracted three times with ether containing a little chloroform, the extracts combined, dried and stripped. Distillation of the residue at 3 mm. gave 27 g. of recovered 8-hydroxyquinoline, followed by 93 g. (58% yield) of material boiling at 193–205°. This material solidified in the receiver, and a portion recrystallized four times from cyclohexane melted at 96.5–97.5°. By analogy with the benzylation of α-naphthol,[2] it was assumed that the product was 7-benzyl-8-hydroxyquinoline.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.6. Found: C, 81.7; H, 5.6.

4-Iodo-2-benzylphenol.—Benzylation of 4-iodophenol[12] gave 4-iodo-2-benzylphenol in 44% yield, b. p. 163–167° (1 mm.). Considerable decomposition occurred during distillation, and the product was obtained as a violet oil which could not be crystallized. It was dissolved in toluene, freed of iodine by shaking with saturated sodium bisulfite solution and immediately converted to the β-dimethylaminoethyl ether.

Basic Ethers.—The basic ethers in Table I were prepared except as noted below, as described previously,[1b] using approximately a 30% excess of β-dimethylaminoethyl chloride hydrochloride. In the case of those phenols containing a basic function, 4-dimethylamino-2-benzylphenol and 7-benzyl-8-hydroxyquinoline, only the theoretical amount of β-dimethylaminoethyl chloride hydrochloride was used in order to minimize quaternary formation.

In general the basic ethers were converted to hydrochlorides by passing dry hydrogen chloride into cold ethereal solutions of the free bases. The monohydrochloride of 4-dimethylamino-2-benzylphenyl β-dimethylaminoethyl ether was obtained by dissolving the base in isopropyl alcohol, adding one equivalent of hydrogen chloride in ethanol and diluting with ether. The nitrate of 2-methoxy-6-benzylphenyl β-dimethylaminoethyl ether was prepared by adding one equivalent of concentrated nitric acid to an ethanol solution of the basic ether and precipitating the salt with ether.

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Summary

A number of β-dimethylaminoethyl ethers of various aralkylphenols has been synthesized. The Claisen alkylation of phenols by halides of the benzyl type has been extended to heterocyclic phenols and halides.

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(12) Dains and Everly, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 355.