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ZINC CHLORIDE-CATALYZED BENZYLATIONS OF PHENOLS AND NAPHTHOLS

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In the framework of a general study of the alkylation and arylalkylation of phenols and naphthols (1), the behavior of benzyl chloride and its nuclear-halogenated derivatives has been investigated. This research was further prompted by the fact that benzylation of mono- and di-hydric phenols has often led to compounds of pharmacological interest. 2- and 4-Benzylphenol and 4-phenyl-3-methylphenol, for instance, are anthelmintics (2), and similar substituted diphenylmethanes show specific antiseptic properties (3).

The methods most frequently employed for the benzylation of phenolic compounds are: (a) reaction with benzyl chloride in the presence of metallic zinc (4) or zinc chloride (5) without solvent, or rearrangement of benzyl ethers with zinc chloride and hydrogen chloride at high temperatures (6); (b) Friedel-Crafts reaction of benzyl chloride in the presence of aluminum chloride (7); and (c) condensation of benzyl chloride with the sodio-derivatives of the phenolic compound in a non-ionizing solvent (8). The first two methods have the drawback of giving low yields of condensation products, and the last method is known to bring about *o*-substitution exclusively. We have found the best procedure for benzylations to be the reaction of benzyl chlorides on the phenol in chloroform solution and in the presence of catalytic amounts of zinc chloride (9). Mono- and di-benzylation were thus effected with good yields, and the reaction could be extended on the one hand, to more complex phenolic compounds, and on the other hand, to naphthalene analogs of benzyl chloride. The new compounds obtained are listed in Table I.

With regard to the site of substitution, it is known that Friedel-Crafts type benzylations occur at the position *para* to the phenolic group whenever that position is free (although slight *ortho*-substitution is probable) or otherwise at the *ortho* position (10). The present work upholds these earlier findings, and it was further found that the formation of benzyl ethers was unimportant in every instance.

Apart from their anthelmintic properties, several arylalkylation products described herein are convenient intermediates for the synthesis of various compounds of possible practical interest. Thus, the β-N-diethylaminoethyl ether (I) of 4-methyl-2-*p*-chlorobenzylphenol and similar compounds were prepared for pharmacological testing. From the known methyl 5-benzylsalicylate and methyl 5-(*p*-chlorobenzylsalicylate (11), 5-benzyl- (II) and 5-(*p*-chlorobenzyl)-salicylhydrazide (III) were prepared for testing as potential bacteriostatic agents, in connection with their metal-chelating properties (12); arylalkylation of methyl salicylate with *p*-methylbenzyl and 1-naphthylmethyl chloride yielded methyl 5-(*p*-methylbenzyl)salicylate and methyl 5-(1-naphthylmethyl)salicylate (V), which similarly reacted with hydrazine hydrate to give 5-(*p*-methylbenzyl)-

TABLE I

New Arylalkylation Products of Phenols and Naphthols

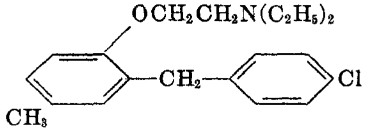
Substance[a]	Formula	B.P., °C./mm.	M.P., °C.	n_D(°C.)	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
2-Benzyl-4-*tert*-octylphenol	$C_{21}H_{28}O$	192/0.4		1.5548(19)	85.1	9.5	85.2	9.6
x-Benzyl-*tert*-octyl-*m*-cresol[b]	$C_{22}H_{30}O$	218–220/14		1.5675(24)	85.2	9.7	85.3	10.0
2-(*p*-Chlorobenzyl)-4-*tert*-octylphenol	$C_{21}H_{27}ClO$	190/0.2	64		76.3	8.2	76.1	8.5
2-(*p*-Chlorobenzyl)-4-*tert*-butylphenol	$C_{17}H_{19}ClO$	179–180/0.4	87		74.3	6.9	74.0	7.0
2-Benzyl-4-chloro-5-methylphenol	$C_{14}H_{13}ClO$	200–205/15		1.6043(15)	72.3	5.6	72.2	5.5
2-Chloro-4-(*o*-chlorobenzyl)phenol	$C_{13}H_{10}Cl_2O$	195–196/12		1.6143(24)	61.7	4.0	61.4	4.0
2-Chloro-4-(2,4-dichlorobenzyl)phenol	$C_{13}H_9Cl_3O$	215–216/13		1.6203(24)	54.3	3.1	54.2	3.2
2-(*o*-Chlorobenzyl)-4-chlorophenol	$C_{13}H_{10}Cl_2O$	212–214/16		1.6153(23)	61.7	4.0	61.8	4.2
2-(2,4-Dichlorobenzyl)-4-chlorophenol	$C_{13}H_9Cl_3O$	221–223/12	55	1.6212(25)	54.3	3.1	54.0	3.2
2-(*o*-Chlorobenzyl)-4-chloro-5-methylphenol	$C_{14}H_{12}Cl_2O$	224–225/14	92		62.9	4.5	62.8	4.8
2-(*p*-Chlorobenzyl)-4-chloro-5-methylphenol	$C_{14}H_{12}Cl_2O$	226–228/13	108		62.9	4.5	62.8	4.7
2-(2,4-Dichlorobenzyl)-4-chloro-5-methylphenol	$C_{14}H_{11}Cl_3O$	265–266/30	108		55.7	3.6	55.5	3.9
3-Methyl-4-(*p*-chlorobenzyl)-6-isopropylphenol[c]	$C_{17}H_{19}ClO$	220–224/15			74.3	6.9	74.1	7.1
2-Methyl-4-(*o*-chlorobenzyl)-5-isopropylphenol	$C_{17}H_{19}ClO$	242–244/29		1.5864(21)	74.3	6.9	74.1	6.8
2-Methyl-4-(*p*-chlorobenzyl)-5-isopropylphenol	$C_{17}H_{19}ClO$	215–216/12		1.5855(21)	74.3	6.9	74.0	7.1
2-Methyl-4-(2,4-dichlorobenzyl)-5-isopropylphenol	$C_{17}H_{18}Cl_2O$	222–226/12		1.5930(19)	66.0	5.8	65.9	5.6
2-Benzyl-3-methyl-4-chloro-6-isopropylphenol	$C_{17}H_{19}ClO$	219–220/18		1.5861(24)	74.3	6.9	74.5	6.8
x-Benzyl-*o*-hydroxybiphenyl		245–246/16		1.6358(28)	87.7	6.2	87.9	6.5
x-(*p*-Chlorobenzyl)-*o*-hydroxybiphenyl	$C_{19}H_{16}O$	264–268/17		1.6376(23)	77.4	5.1	77.5	5.0
x-(*p*-Chlorobenzyl)-1-naphthol	$C_{17}H_{13}ClO$	260–262/12	119		76.0	4.8	76.2	5.0

TABLE I—(*Concluded*)

Substance[a]	Formula	B.P., °C./mm.	M.P., °C.	n_D(°C.)	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
1-(*p*-Chlorobenzyl)-2-naphthol	$C_{17}H_{13}ClO$	264–265/15	106		76.0	4.8	76.1	5.1
x-Benzyl-5-hydroxyhydrindene	$C_{16}H_{16}O$	221–223/20	60		85.7	7.1	85.4	7.2
4-Methyl-2-(1-naphthomethyl)phenol	$C_{18}H_{16}O$	246–248/15			87.1	6.5	87.0	6.3
x-(*p*-Chlorobenzyl)-guaiacol	$C_{14}H_{13}ClO_2$	174–175/0.2		1.5992(19)	67.6	5.2	67.5	5.5
x-(*p*-Chlorobenzyl)-4-methoxyphenol	$C_{14}H_{13}ClO_2$	195–198/1.5	80		67.6	5.2	67.3	5.3
x,*x*′-Dibenzyl-*o*-cresol[d]	$C_{21}H_{20}O$	260–265/15		1.6177(24)	87.5	7.0	87.2	7.3
2,4-Di-(*p*-chlorobenzyl)-3-methyl-6-isopropylphenol	$C_{24}H_{24}Cl_2O$	249–250/0.6	105		72.2	6.0	72.0	6.1
x,*x*′-Di-(*p*-chlorobenzyl)-*o*-cresol	$C_{21}H_{18}Cl_2O$	280–284/14			70.6	5.0	70.4	5.4
x,*x*′-Di-(*o*-chlorobenzyl)-4-chlorophenol	$C_{20}H_{15}Cl_3O$	290–292/13		1.6351(21)	63.6	4.0	63.9	4.3
x,*x*′-Dibenzylguaiacol	$C_{21}H_{20}O_2$	230–232/0.5	108		82.9	6.6	82.6	6.5
x,*x*′-Di-(*p*-chlorobenzyl)guaiacol	$C_{21}H_{18}Cl_2O_2$	238–240/0.2	133		67.4	4.8	67.3	5.0
2,6-Di-(*p*-chlorobenzyl)-4-*tert*-butylphenol	$C_{24}H_{24}Cl_2O$	239–240/0.8	79		72.2	6.0	72.5	6.1
4,6-Dibenzyl-5-hydroxyhydrindene	$C_{23}H_{22}O$	278–280/20	77		87.9	7.0	87.6	7.3
2,4-Di-(*p*-chlorobenzyl)-1-naphthol	$C_{24}H_{18}Cl_2O$	315–318/12	133		73.4	4.6	73.2	4.6
x,*x*′-Dibenzyl-*o*-hydroxybiphenyl	$C_{26}H_{22}O$	302–305/15		1.6438(25)	89.1	6.3	89.2	6.5

[a] All substances were recrystallized from petroleum ether (b.p. 60–80°) or cyclohexane. Yields of monosubstitution-products ranged from 40% (phenols with *o*- and *p*-positions free) to 85% (phenols with only one *o*-position free). [b] Prepared from technical *tert*-octyl-*m*-cresol, with unspecified position. [c] Substances for which neither m.p. nor refraction index are given were very viscous oils or thick resins. [d] Yields of disubstitution-products ranged from 20 to 45%, and increased with the number of free *ortho* and *para* positions on the phenol molecule.

salicylhydrazide (IV) and 5-(1-naphthylmethyl)salicylhydrazide (VI) respectively.



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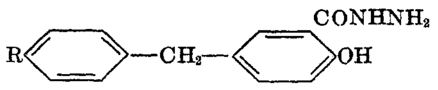
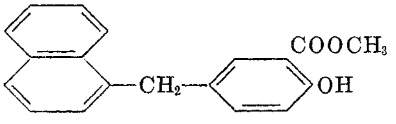


II R = H
III R = Cl
IV R = CH$_3$

Biological tests gave the following results: 5-benzylsalicylhydrazide showed *in vitro* bacteriostatic activity against *Mycobacterium tuberculosis* at a concentration of 10^{-4} (strain H37 Rv and a bovine strain), but no appreciable activity *in vivo* in mice and guinea pig tuberculosis and in tuberculosis meningitis in rabbits; the hydrazides (III), (IV) and (VI) were also inactive *in vivo*. The antibacterial and fungistatic activity of 5-benzylsalicylhydrazide on various other microorganisms is reported in Table II. Estimations of antipyretic activity in rats and anti-inflammatory activity in mice showed that at a dose of 200 mg./kg., 5-benzylsalicylhydrazide is only slightly effective compared with butazolidine.



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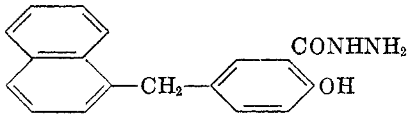

VI

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EXPERIMENTAL

Arylalkylation of phenols and naphthols. The condensation of *p*-chlorobenzyl chloride with *p*-cresol serves as a typical example for such reactions. A solution of 40 g. of *p*-cresol and 40 g. of *p*-chlorobenzyl chloride in 200 ml. of dry chloroform was gently refluxed for 12 hours with 15 g. of finely powdered, freshly fused zinc chloride. After cooling, water was added, and the chloroform layer was washed thoroughly with water to remove the zinc chloride, and dried over sodium sulfate. After evaporation of the solvent, the residue was

TABLE II

ANTIBACTERIAL PROPERTIES OF 5-BENZYLSALICYLHYDRAZIDE

Microorganism	Bacteriostatic Activity at Concentration of	Bactericidal Activity at Concentration of
Staphylococci	10^{-5} to 5×10^{-6}	$< 10^{-3}$
Bac. coli		$< 10^{-3}$
Bac. anthracis		$> 10^{-3}$–$< 10^{-4}$
Pneumococci		$< 10^{-3}$
Streptococci		5×10^{-6}–10^{-6}
Enterococci		$< 10^{-3}$

FUNGISTATIC ACTIVITY[a] OF 5-BENZYLSALICYLHYDRAZIDE AND RELATED COMPOUNDS

5-Benzylsalicylhydrazide	10^{-3}
5-(*p*-Methylbenzyl)salicylhydrazide	10^{-3}
5-(*p*-Chlorobenzyl)salicylhydrazide	10^{-2}–5×10^{-3}
5-(1-Naphthylmethyl)salicylhydrazide	10^{-3}

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[a] Determined on a strain of *Trichophyton mentagrophytes* in test-tube cultures. All the substances were found inactive at a concentration of 1% in the hair test.

fractionated twice in a vacuum, to give 48 g. (50% yield) of *4-methyl-2-(p-chlorobenzyl)phenol,* b.p. 210°/16 mm., crystallizing from petroleum ether in long silky needles, m.p. 54°. A higher-boiling portion consisted of a disubstitution product which was a thick oil, b.p. 280–290°/16 mm. A similar reaction performed with *o*-cresol gave *2-methyl-4-(p-chlorobenzyl)-phenol* (52% yield), b.p. 206–208°/14 mm., m.p. 71–72° (after recrystallization from petroleum ether).

β-N-Dimethylaminoethyl ether of 4-methyl-2-p-chlorobenzylphenol. A solution of 20 g. of the phenol and 12 g. of potassium hydroxide in aqueous ethanol was treated with 18 g. of the hydrochloride of β-N-diethylaminoethyl chloride, and the mixture was refluxed for one hour. The ethanol then was evaporated off, and the reaction product was taken up in ether, washed with water, and purified by distillation in a vacuum. Yield: 18 g. of a pale yellow oil, b.p. 182–185°/0.4 mm., n_D^{19} 1.5688, which gave a *hydrochloride* in the form of colorless needles, m.p. 172–173°, extremely soluble in water.

Anal. Calc'd for $C_{20}H_{27}Cl_2NO$: N, 3.8; Cl, 19.3.

Found: N, 3.9; Cl, 19.0.

The β-N-diethylaminoethyl ether of 4-methyl-2-(1-naphthomethyl)phenol, similarly prepared, was a thick, pale yellow oil, b.p. 205–207°/0.2 mm., whose hydrochloride was extremely soluble in water and did not crystallize.

Anal. Calc'd for $C_{24}H_{29}NO$: C, 83.0; H, 8.4.

Found: C, 83.0; H, 8.2.

5-Benzylsalicylhydrazide. A solution of 10 g. of methyl 5-benzylsalicylate and 5 g. of 95% hydrazine hydrate in 50 ml. of ethanol was gently refluxed for 20 hours. On cooling, long colorless needles separated (90% yield), melting at 172° after recrystallization from ethanol.

Anal. Calc'd for $C_{14}H_{14}N_2O_2$: N, 11.6. Found: N, 11.5.

The *4-chlorobenzal derivative* crystallized from toluene in shiny colorless prisms, m.p. 157°.

Anal. Calc'd for $C_{21}H_{17}ClN_2O_2$: N, 7.7. Found: N, 7.5.

The *2-hydroxybenzal derivative* crystallized from *n*-propanol in colorless, sublimable microcrystals, m.p. 277°.

Anal. Calc'd for $C_{21}H_{18}N_2O_3$: N, 8.1. Found: N, 8.0.

5-(p-Chlorobenzyl)salicylhydrazide. This compound crystallized from ethanol in shiny colorless prisms, m.p. 174°.

Anal. Calc'd for $C_{14}H_{13}ClN_2O_2$: C, 60.8; H, 4.7.

Found: C, 60.6; H, 4.6.

The *4-chlorobenzal derivative* crystallized from ethanol in colorless prisms, m.p. 245°.

Anal. Calc'd for $C_{21}H_{16}Cl_2N_2O_2$: N, 7.0. Found: N, 7.0.

The *salicylidene derivative* crystallized from ethanol in pale microcrystals, m.p. 275°.

Anal. Calc'd for $C_{21}H_{17}ClN_2O_3$: N, 7.4. Found: N, 7.1.

5-(p-Methylbenzyl)salicylic acid. A solution of 180 g. of methyl salicylate and 140 g. of *p*-methylbenzyl chloride in 300 ml. of dry chloroform was refluxed with 35 g. of fused zinc chloride for 4 hours. The chloroform layer which formed on treatment with water was dried over sodium sulfate. The residue from evaporation of the solvent yielded on fractionation in a vacuum 121 g. of *methyl 5-(p-methylbenzyl)salicylate,* b.p. 220°/15 mm., which crystallized from ethanol in colorless prisms, m.p. 98°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.

Found: C, 75.0; H, 6.5.

5-(p-Methylbenzyl)salicylic acid, obtained on saponification, crystallized from aqueous acetic acid in colorless prisms, m.p. 132–133°.

Anal. Calc'd for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8.

Found: C, 74.1; H, 5.9.

5-(p-Methylbenzyl)salicylhydrazide crystallized from ethanol in silky colorless prisms, m.p. 163°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.9. Found: N, 10.7.

5-(1-Naphthylmethyl)salicylic acid. A solution of 85 g. of methyl salicylate and 83 g. of 1-naphthylmethyl chloride (prepared by chloromethylation of naphthalene) in chloroform was refluxed for 3 hours with 15 g. of zinc chloride, and the reaction mixture was worked up in the usual way. Yield: 26 g. of methyl *5-(1-naphthylmethyl)salicylate,* b.p. 267–270°/3 mm., crystallizing from ethanol in colorless needles, m.p. 113°.

Anal. Calc'd for $C_{19}H_{16}O_3$: C, 78.1; H, 5.5.
Found: C, 78.0; H, 5.4.

5-(1-Naphthylmethyl)salicylic acid crystallized from acetic acid in colorless microcrystals, m.p. 173°.

Anal. Calc'd for $C_{18}H_{14}O_3$: C, 77.7; H, 5.0.
Found: C, 77.9; H, 5.1.

5-(1-Naphthylmethyl)salicylhydrazide crystallized from ethanol in silky colorless needles, m.p. 184°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: N, 9.6. Found: N, 9.5.

SUMMARY

1. The arylalkylation of a wide variety of phenols and naphthols with halogenated compounds of the benzyl chloride type has been investigated. A convenient procedure, using zinc chloride as catalyst, is proposed for such reactions.

2. Several derivatives of these arylalkylated compounds have been prepared for biological testing.

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REFERENCES

(1) Buu-Hoï, Le Bihan, Binon, *et al.*, *J. Org. Chem.*, **15,** 1060 (1950); **16,** 185, 988 (1951); **17,** 243, 1122 (1952); **18,** 4 (1953).
(2) Schulemann, *Deutsch. med. Wochenschr.*, **46,** 1051 (1920).
(3) Klarmann, *J. Am. Chem. Soc.*, **48,** 792 (1926); Klarmann and von Wowern, *J. Am. Chem. Soc.*, **51,** 608 (1929); Huston *et al.*, *J. Am. Chem. Soc.*, **55,** 2146, 4639 (1933); **72,** 4171 (1950); **73,** 2483, 3443 (1951).
(4) Paternò, *Ber.*, **5,** 288 (1872); Fileti, *Ber.*, **6,** 757 (1873).
(5) Liebmann, *Ber.*, **15,** 152 (1882); detailed literature in Price, *Org. Reactions,* **3,** 2 (1946).
(6) Short and Stewart, *J. Chem. Soc.*, **556** (1929).
(7) Huston, *J. Am. Chem. Soc.*, **46,** 2778 (1924).
(8) Claisen, *et al.*, *Ann.*, **442,** 210 (1925).
(9) Dziewoński and Dziecielewski, *Bull. Intern. Acad. Polon.*, [A], 275 (1927); Buu-Hoï and Demerseman, *J. Chem. Soc.*, 4699 (1952).
(10) See for instance Huston and Houk, *J. Am. Chem. Soc.*, **54,** 1506 (1932).
(11) Földi, *Ber.*, **61,** 1614 (1928); Buu-Hoï, Eckert, and Demerseman, *J. Org. Chem.*, **19,** 726 (1954).
(12) See Buu-Hoï, Xuong, Binon, and Nam, *Compt. rend.*, **235,** 329 (1952); **236,** 635 (1953); Duval, Buu-Hoï, Xuong, and Jacquinot, *Microchim. Acta,* **3,** 212 (1953).