[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Use of Substituted Phenols in the Mannich Reaction and the Dehalogenation of Aminomethylhalophenols

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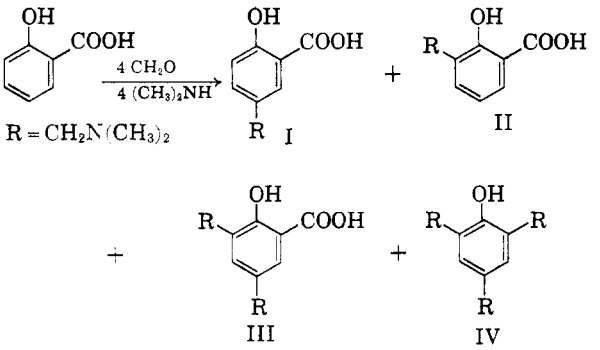
Twenty-two phenols which contained as substituents chlorine, bromine, hydroxyl, methyl, carboxyl, benzyloxy, benzoyloxy, or chlorohydroxybenzyl were condensed with formaldehyde and methylamine, dimethylamine, or morpholine. The aminomethylhalophenols prepared can be dehalogenated with hydrogen and platinum dioxide; in some instances, prolonged hydrogenation yielded aminomethylcyclohexanols.

A Mannich product prepared from a halophenol, during this investigation, proved to be very useful for the structure determination of a bis(aminomethyl)cyclohexanone.[3] This circumstance prompted us to make an extensive study of Mannich reactions in which a number of halophenols, as well as other types of substituted phenols, were employed. Twenty-two phenols which contained as substituents chlorine, bromine, hydroxyl, methyl, carboxyl, benzyloxy, benzoyloxy, or chlorohydroxybenzyl were condensed with formaldehyde and methylamine, dimethylamine, or morpholine. All of the aminomethyl derivatives which were prepared have been numbered and listed in Table II.

It was found that salicylic acid reacted with formalin and dimethylamine to yield a mixture of four products: 4-(dimethylaminomethyl)-2-carboxyphenol (I, 49C), 6-(dimethylaminomethyl)-2-carboxyphenol (II), 4,6-bis(dimethylaminomethyl)-2-carboxyphenol (III), and 2,4,6-tris(dimethylaminomethyl)phenol (IV). Compounds II and III were isolated as hydrochlorides (54C and 56C, respectively). The structures of I and II were



determined by hydrogenolysis with hydrogen and Raney nickel, I yielded 4-methyl-2-carboxyphenol and from II, 6-methyl-2-carboxyphenol (*o*-cresotinic acid) was obtained. The analytical data furnished proof for the structure of III. The liquid base IV is a known compound[4]; it was isolated and characterized as the trihydrochloride.

In order for IV to have been formed, one or more of the compounds—salicylic acid, I, II, or III—in the form of the dimethylamine salt or as a zwitter ion must have undergone decarboxylation during the reaction.

It was found that III, in the form of the dihydrochloride, like salicylic acid and under the same conditions, reacted with formaldehyde and dimethylamine to form a product which was isolated as the trihydrochloride and found to be identical with the trihydrochloride of IV.

Interaction of 5-chloro-2-carboxyphenol (4-chlorosalicylic acid) with formaldehyde and dimethylamine, at steam-bath temperature, produced 4-(dimethylaminomethyl)-5-chloro-2-carboxyphenol (45C) and 2,4,6-tris-(dimethylaminomethyl)-3-chlorophenol. The latter was identified in the form of its trihydrochloride by comparison with an authentic sample (43C). By removal of the chlorine atom from 45C with hydrogen and platinum dioxide, 4-(dimethylaminomethyl)-2-carboxyphenol hydrochloride was formed. The picrate of this substance was identical with the picrate of I.

When 4-chloro-2-carboxyphenol (5-chlorosalicylic acid) was allowed to react with formaldehyde and dimethylamine at 60°, 92% of the original phenol was recovered from the reaction mixture. When the reaction was carried out at steam-bath temperature, the only product which could be isolated, in 20% yield, was 2,6-bis(dimethylaminomethyl)-4-chlorophenol. This substance was found to be identical with the product (6A) obtained by the use of 4-chlorophenol in a Mannich reaction; the two compounds were compared in the form of their dihydrochlorides (7A and 8A).

4-Methyl-2-carboxyphenol reacted with formaldehyde and dimethylamine, at steam bath temperature, to yield 6-(dimethylaminomethyl)-4-methyl-2-carboxyphenol (64C) and 2,6-bis(dimethylaminomethyl)-4-methylphenol.[5] The latter compound was isolated as the dihydrochloride

(1) This paper represents part of a dissertation submitted by F. J. McCarty for the Ph.D. degree in the University of Michigan.

(2) Sterling-Winthrop Fellow.

(3) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).

(4) H. A. Bruson and C. W. MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).

(5) J. Décombe, *Compt. rend.*, **196**, 866 (1933).

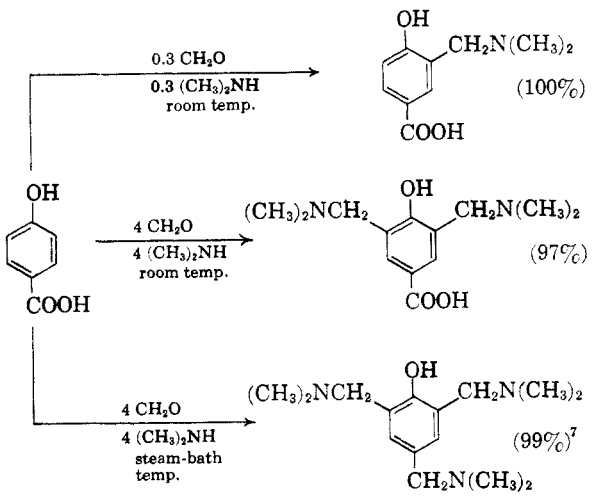
(66C). When 6-methyl-2-carboxyphenol was treated in the same manner, 4-(dimethylaminomethyl)-6-methyl-2-carboxyphenol (67C) and 2,4-bis(dimethylaminomethyl)-6-methylphenol were formed. The last mentioned phenol was identified as the dihydrochloride (69C).

From 2,4-dicarboxyphenol (4-hydroxyisophthalic acid),[6] at steam-bath temperature, 6-(dimethylaminomethyl)-2,4-dicarboxyphenol (62C) was produced.

6-(Dimethylaminomethyl)-4-bromo-5-hydroxy-2-carboxyphenol could not be synthesized from 4-bromo-5-hydroxy-2-carboxyphenol, formaldehyde and dimethylamine; the reaction product was a resin. However, it was possible to prepare the corresponding 6-(morpholinomethyl) compound (47C).

From 3-hydroxybenzoic acid, formaldehyde, and dimethylamine, 2,4,6-tris(dimethylaminomethyl)-3-carboxyphenol (57C) was obtained.

When 4-hydroxybenzoic acid was allowed to react with formaldehyde and dimethylamine at room temperature, either 2-(dimethylaminomethyl)-4-carboxyphenol (58C) or 2,6-bis(dimethylaminomethyl)-4-carboxyphenol (60C) could be isolated depending on the amounts of formaldehyde and dimethylamine employed. When the reaction was carried out at steam bath temperature, the reaction product was 2,4,6-tris(dimethylaminomethyl)phenol.



When attempts were made to introduce two dimethylaminomethyl groups into 4-benzoyloxyphenol, and three dimethylaminomethyl groups into resorcinol and into phloroglucinol, only resinous products could be isolated. However, by the use of formaldehyde and morpholine, under the same conditions, the crystalline products 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol (isolated as the dihydrochloride, 74C, 50% yield), 2,4,6-tris(morpholinomethyl)-3-hydroxyphenol (70C, 100% yield) and 2,4,6-tris(morpholinomethyl)-3,5-dihydroxyphenol (78, 98% yield) were obtained.

By hydrolysis of 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol dihydrochloride (74C) it was possible to obtain 2,6-bis(morpholinomethyl)-4-hydroxyphenol dihydrochloride (77C) in 91% yield. Reaction between hydroquinone, formaldehyde, and morpholine has been shown to yield 2,5-bis(morpholinomethyl)-4-hydroxyphenol.[8]

4-Benzyloxyphenol was converted into 2,6-bis(dimethylaminomethyl)-4-benzyloxyphenol dihydrochloride (73C) which, after hydrogenolysis, yielded 2,6-bis(dimethylaminomethyl)-4-hydroxyphenol dihydrochloride (76C). 2,5-Bis(dimethylaminomethyl)-4-hydroxyphenol has been obtained from hydroquinone, formaldehyde and dimethylamine.[9]

The removal of chlorine or bromine from an aminomethylhalophenol has been described by other investigators [10–12] but platinum dioxide has not been employed as a catalyst as far as we are aware.

Several halophenols were aminomethylated and the aminomethylhalophenols were dehalogenated with hydrogen and platinum dioxide. It was found that in all cases dehalogenation could be effected easily and conveniently. For example, 4,6-bis(dimethylaminomethyl)-2-chlorophenol dihydrochloride (2A) can be dehalogenated in fifteen minutes with the formation of 2,4-bis(dimethylaminomethyl)phenol dihydrochloride (5A) in 90% yield.

The halophenol employed, the aminomethylhalophenol obtained by a Mannich reaction and the aminomethylphenol prepared by dehalogenation are shown in Table I. The aminomethylhalophenols were isolated as bases and, with one exception, were used as hydrochlorides in the dehalogenation process; compound 45C was dehalogenated in the form of the base. In most instances the aminomethylphenol could be obtained as a hydrochloride. In other cases it was necessary to isolate the product as the base or picrate.

When 2-bromophenol was allowed to react with equimolar amounts of formaldehyde and dimethylamine, two mono(dimethylaminomethyl) derivatives were obtained which, in the form of their hydrochlorides, were separated by fractional recrystallization. One of the derivatives, after dehalogenation and treatment with picric acid, yielded 2-(dimethylaminomethyl)-phenol picrate, hence the

(6) This acid was obtained from the Aldrich Chemical Company.

(7) The yield is that of the trihydrochloride (35A), the form in which this substance was isolated.

(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 2354 (1939).

(9) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

(10) J. H. Burckhalter, *J. Am. Chem. Soc.*, **72**, 5309 (1950).

(11) W. T. Burke and C. W. Stephens, *J. Am. Chem. Soc.*, **74**, 1518 (1952).

(12) A. Cohen, R. A. Hall, B. Heath-Brown, M. W. Parkes, and A. H. Rees, *Brit. J. Pharmacol.*, **12**, 194 (1957); *Chem. Abstr.*, **52**, 7310 (1958).

TABLE I

Halophenol	Aminomethylhalophenol	Aminomethylphenol
2-Chlorophenol	4,6-Bis(dimethylaminomethyl)-2-chlorophenol.2HCl (2A)	2,4-Bis(dimethylaminomethyl)-phenol.2HCl (5A)
3-Chlorophenol	2,4,6-Tris(dimethylaminomethyl)-3-chlorophenol.3HCl (43C)	2,4,6-Tris(dimethylaminomethyl)phenol.3HCl (34A)
4-Chlorophenol	2,6-Bis(dimethylaminomethyl)-4-chlorophenol.2HCl (7A)	2,6-Bis(dimethylaminomethyl)-phenol.2HCl (9A)
2,4-Dichlorophenol	6-(Methylaminomethyl)-2,4-dichlorophenol.HCl (16A)	2-(Methylaminomethyl)phenol.-HCl (17A)
2,4-Dichlorophenol	6-(Dimethylaminomethyl)-2,4-dichlorophenol.HCl (20A)	2-(Dimethylaminomethyl)phenol base (21A)
2,6-Dichlorophenol	4-(Dimethylaminomethyl)-2,6-dichlorophenol.HCl (25A)	4-(Dimethylaminomethyl)-phenol.HCl (30A)
5-Chloro-2-carboxyphenol	4-(Dimethylaminomethyl)-5-chloro-2-carboxyphenol base (45C)	4-(Dimethylaminomethyl)-2-carboxyphenol.picrate (52C)
2-(2-Hydroxy-5-chlorobenzyl)-4-chlorophenol	2-(Dimethylaminomethyl)-4-chloro-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol.2HCl (11A)	2-(Dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-2-hydroxybenzyl]phenol.2HCl (14A) 2-(Dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]-phenol.2HCl (12A)
2-Bromophenol	4-(Dimethylaminomethyl)-2-bromophenol.HCl (27A) 6-(Dimethylaminomethyl)-2-bromophenol.HCl (26A)	4-(Dimethylaminomethyl)-phenol.picrate (31A) 2-(Dimethylaminomethyl)-phenol.picrate (23A)

original compound must have been 6-(dimethylaminomethyl)-2-bromophenol. The other derivative, after dehalogenation and treatment with picric acid, yielded 4-(dimethylaminomethyl)phenol picrate, consequently this derivative must have been 4-(dimethylaminomethyl)-2-bromophenol.

Two products, 2-(dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-2-hydroxybenzyl]phenol dihydrochloride (14A) and 2-(dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol dihydrochloride (12A), were obtained when 2-(dimethylaminomethyl)-4-chloro-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol dihydrochloride (11A) was hydrogenated by the general procedure.

When 2,4-dichlorophenol reacted with one half of a molecular equivalent of formaldehyde and the same molecular amount of methylamine, 6-(methylaminomethyl)-2,4-dichlorophenol (15A) was obtained. When the reaction was carried out with one molecular equivalent of formaldehyde and one fourth of a molecular equivalent of methylamine, the reaction product was 6-[methyl(2-hydroxy-3,5-dichlorobenzyl)aminomethyl]-2,4-dichlorophenol which was isolated as the hydrochloride (18A).

2,6-Dibromophenol, formaldehyde, and dimethylamine yielded 4-(dimethylaminomethyl)-2,6-dibromophenol (28A).

Compounds 18A and 28A were not dehalogenated.

It was found that upon prolonged hydrogenation, in the presence of platinum dioxide, 6-(dimethylaminomethyl)-2,4-dichlorophenol hydrochloride (20A) yielded 2-(dimethylaminomethyl)-cyclohexanol hydrochloride (40B). The dihydrochlorides of both 2,6-bis(dimethylaminomethyl)-4-chlorophenol (7A) and 2,6-bis(dimethylaminomethyl)phenol (9A) were converted into 2,6-bis(dimethylaminomethyl)cyclohexanol dihydrochloride; the products obtained from 7A and 9A were isolated as the dihydrochloride (38B) and base (36B), respectively. From 4-(dimethylaminomethyl)-2,6-dichlorophenol hydrochloride (25A), a mixture of the hydrochlorides of 4-(dimethylaminomethyl)cyclohexanol (41B) and dimethylaminomethylcyclohexane[13] was produced.

EXPERIMENTAL

General procedures. The molecular amounts of reactants employed in methods A–E and the structures of the products obtained by these procedures, and by methods F and G, are shown in Table II. The letter after each compound number indicates the general formula (A, B, or C) to which the compound conforms.

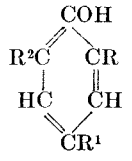
A. Formalin (37%) was added, dropwise, during a 15–30 min. period, to a stirred mixture of the required phenol and 25% aqueous dimethylamine (or morpholine or 40% aqueous methylamine) maintained at 20–25°. The mixture was stirred for 1 hr. at 25° and then for 3 hr. on a steam bath.

(13) H. Heckel and R. Adams [*J. Am. Chem. Soc.*, **47**, 1712 (1925)] hydrogenated 4-dimethylaminophenol hydrochloride in the presence of platinum dioxide and sodium nitrate and obtained a mixture of 4-dimethylaminocyclohexanol, dimethylaminocyclohexane, and cyclohexane after treatment of the reaction mixture with alkali.

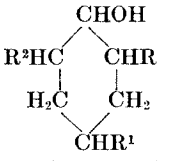
TABLE II

Aminomethyl Derivatives of Phenols and Cyclohexanol

A



(compounds 1–35, incl.)



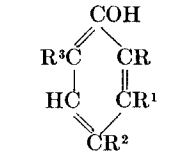
B

(compounds 36–41)

	R	R^1	R^2	Method	Molecular amounts[a]			Yield, %	M.p., °C.
1A	Cl	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	A	0.40	1.20	1.20	77	62–63
2A	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						196–197 (dec.)
3A	Cl	$CH_2N(CH_3)_2$·P[b]	$CH_2N(CH_3)_2$·P						180–181
4A	Cl	$CH_2N(CH_3)_2$·M[c]	$CH_2N(CH_3)_2$·M						113–114
5A	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	F				90	217–218
6A	$CH_2N(CH_3)_2$	Cl	$CH_2N(CH_3)_2$	A	0.40	1.20	1.20	73	103 (0.2 mm.)[d]
7A	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl						233–234 (dec.)
8A	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30	20	231–232 (dec.)
9A	$CH_2N(CH_3)_2$·HCl	H	$CH_2N(CH_3)_2$·HCl	F				77	205–206[e]
10A	[f]	Cl	$CH_2N(CH_3)_2$	A	0.10	0.40	0.40	97	140–141
11A	[f] HCl	Cl	$CH_2N(CH_3)_2$·HCl						158–160 (dec.)
12A	[f] HCl	H	$CH_2N(CH_3)_2$·HCl	F					158–160 (dec.)
13A	[g]	H	$CH_2N(CH_3)_2$						84–85
14A	[g] HCl	H	$CH_2N(CH_3)_2$·HCl	F					156–158 (dec.)
15A	$CH_2NH(CH_3)$	Cl	Cl	B	0.10	0.05	0.05	52	199–200
16A	$CH_2NH(CH_3)$·HCl	Cl	Cl						193–194 (dec.)
17A	$CH_2NH(CH_3)$·HCl	H	H	F				37	146–147[h]
18A	[i]	Cl	Cl	B	0.10	0.10	0.025	37	181–182 (dec.)
19A	$CH_2N(CH_3)_2$	Cl	Cl	A	0.40	0.80	0.80	95[j]	62–63[j]
20A	$CH_2N(CH_3)_2$·HCl	Cl	Cl						189–190[j]
21A	$CH_2N(CH_3)_2$	H	H	F				37	110–112 (10 mm.)[k]
22A	$CH_2N(CH_3)_2$·P	H	H						150–152[l]
23A	$CH_2N(CH_3)_2$·P	H	H	F[m]				42	150–152[l]
24A	Cl	$CH_2N(CH_3)_2$	Cl	A	0.06	0.12	0.12	100	184–185 (dec.)
25A	Cl	$CH_2N(CH_3)_2$·HCl	Cl						242–243 (dec.)
26A	$CH_2N(CH_3)_2$·HCl	H	Br	B	0.30	0.30	0.30	12	181–182
27A	H	$CH_2N(CH_3)_2$·HCl	Br	B	0.30	0.30	0.30	5	236–237 (dec.)
28A	Br	$CH_2N(CH_3)_2$	Br	A	0.16	0.21	0.21	89	179–180
29A	Br	$CH_2N(CH_3)_2$·HCl	Br						243–244 (dec.)
30A	H	$CH_2N(CH_3)_2$·HCl	H	F				63	184–185[n]
31A	H	$CH_2N(CH_3)_2$·P	H	F[o]				67	170–171
32A	H	$CH_2N(CH_3)_2$·P	H						170–171
33A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	[p]					277–278 (dec.)
34A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	F				81	275–276 (dec.)
35A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.40	0.40	99	277–278 (dec.)
36B	$CH_2N(CH_3)_2$	H	$CH_2N(CH_3)_2$	G				40	80–81 (0.1 mm.)
37B	$CH_2N(CH_3)_2$·P	H	$CH_2N(CH_3)_2$·P						198–199
38B	$CH_2N(CH_3)_2$·HCl	H	$CH_2N(CH_3)_2$·HCl	G[q]				34	230–231 (dec.)

TABLE II (*Continued*)

C



(Compounds 42–77)

	R	R¹	R²	R³	Method	Molecular amounts[a]			Yield, %	M.p., °C.
39B	$CH_2N(CH_3)_2$	H	H		G				60	102–104 (10 mm.)[r]
40B	$CH_2N(CH_3)_2$·HCl	H	H							160–161[r]
41B	H	$CH_2N(CH_3)_2$·HCl	H		G					223–224
42C	$CH_2N(CH_3)_2$	Cl	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	A	0.10	0.40	0.40	92	131–132 (0.1 mm.)
43C	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						239–240 (dec.)
44C	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.40	0.40		238–239 (dec.)
45C	H	Cl	$CH_2N(CH_3)_2$	COOH	C	0.10	0.40	0.40		237–239 (dec.)
46C	H	Cl	$CH_2N(CH_3)_2$·HCl	COOH						220–221 (dec.)
47C	$CH_2NC_4H_8O$[s]	OH	Br	COOH	D	0.01	0.02	0.02	21	187–188 (dec.)
48C	$CH_2NC_4H_8O$·HCl	OH	Br	COOH						209–210 (dec.)
49C	COOH	H	$CH_2N(CH_3)_2$	H						235–240 (dec.)
50C	COOH	H	$CH_2N(CH_3)_2$·HCl	H						197–198 (dec.)
51C	COOH	H	$CH_2N(CH_3)_2$·P	H						183–184 (dec.)
52C	COOH	H	$CH_2N(CH_3)_2$·P	H	F[t]				25	183–184 (dec.)
53C	COOH	H	$CH_2N(CH_3)_2$·CH_3Br	H					33	208–209 (dec.)
54C	COOH	H	H	$CH_2N(CH_3)_2$·HCl						203–204 (dec.)
55C	COOH	H	H	$CH_2N(CH_3)_2$·P						167–168
56C	COOH	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						236–237 (dec.)
57C	$CH_2N(CH_3)_2$	COOH	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	C	0.10	0.50	0.50	13	177–180 (dec.)
58C	$CH_2N(CH_3)_2$	H	COOH	H	D	0.21	0.07	0.07	100	196–197 (dec.)
59C	$CH_2N(CH_3)_2$·HCl	H	COOH	H						214–215 (dec.)
60C	$CH_2N(CH_3)_2$	H	COOH	$CH_2N(CH_3)_2$	D	0.10	0.40	0.40	97	203–205 (dec.)
61C	$CH_2N(CH_3)_2$·HCl	H	COOH	$CH_2N(CH_3)_2$·HCl						219–220 (dec.)
62C	COOH	H	COOH	$CH_2N(CH_3)_2$	C	0.03	0.12	0.12	28	Above 360
63C	COOH	H	COOH	$CH_2N(CH_3)_2$·HCl						249–250 (dec.)
64C	COOH	H	CH_3	$CH_2N(CH_3)_2$	C	0.10	0.30	0.30		222–225 (dec.)
65C	COOH	H	CH_3	$CH_2N(CH_3)_2$·HCl						219–224 (dec.)
66C	$CH_2N(CH_3)_2$·HCl	H	CH_3	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30		221–222[e]
67C	COOH	H	$CH_2N(CH_3)_2$	CH_3	C	0.10	0.30	0.30		224–228 (dec.)
68C	COOH	H	$CH_2N(CH_3)_2$·HCl	CH_3						209–211 (dec.)
69C	CH_3	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30		178–179
70C	$CH_2NC_4H_8O$	OH	$CH_2NC_4H_8O$	$CH_2NC_4H_8O$	E	0.03	0.09	0.09	100	138–139
71C	$CH_2NC_4H_8O$·HCl	OH	$CH_2NC_4H_8O$·HCl	$CH_2NC_4H_8O$·HCl						179–180 (dec.)
72C	H	$CH_2N(CH_3)_2$·HCl	OH	$CH_2N(CH_3)_2$·HCl	[u]					270–271 (dec.)
73C	$CH_2N(CH_3)_2$·HCl	H	$OCH_2C_6H_5$	$CH_2N(CH_3)_2$·HCl	B	0.05	0.15	0.15	90	197–198
74C	$CH_2NC_4H_8O$·HCl	H	$OOCC_6H_5$	$CH_2NC_4H_8O$·HCl	B	0.01	0.03	0.03	50	235–236 (dec.)
75C	$CH_2N(CH_3)_2$	H	OH	$CH_2N(CH_3)_2$						129–130
76C	$CH_2N(CH_3)_2$·HCl	H	OH	$CH_2N(CH_3)_2$·HCl					85	205–206
77C	$CH_2NC_4H_8O$·HCl	H	OH	$CH_2NC_4H_8O$·HCl					91	193–194 (dec.)
78	2,4,6-Tris(morpholinomethyl)phloroglucinol				E	0.01	0.03	0.03	98	170–171
79	2,4,6-Tris(morpholinomethyl)phloroglucinol trihydrochloride									193–194 (dec.)

ANALYSES, %

		Formula	Carbon		Hydrogen		Nitrogen		Halogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1A	A[v]	$C_{12}H_{19}ON_2Cl$	59.36	58.83	7.89	7.85	11.54	11.40		
2A	B	$C_{12}H_{21}ON_2Cl_3$	45.64	45.77	6.71	6.93			22.47	22.15
3A	C	$C_{24}H_{25}O_{15}N_8Cl$	41.13	41.15	3.60	3.66				
4A	D	$C_{20}H_{27}O_9N_2Cl$	50.58	50.49	5.73	5.66				
5A	B	$C_{12}H_{22}ON_2Cl_2$	51.25	51.18	7.89	7.86	9.97	9.92	25.22	25.27
6A		$C_{12}H_{19}ON_2Cl$	59.30	59.08	7.89	8.04				
7A	E	$C_{12}H_{21}ON_2Cl_3$	45.64	45.84	6.71	6.86	8.88	8.66	22.47	22.53
8A	E	$C_{12}H_{21}ON_2Cl_3$					8.88	8.56		
9A	F	$C_{12}H_{22}ON_2Cl_2$	51.25	51.43	7.89	7.87	9.97	9.82	25.22	25.07
10A	G	$C_{19}H_{24}O_2N_2Cl_2$	59.54	59.51	6.31	6.48				
11A	G	$C_{19}H_{26}O_2N_2Cl_4$	50.00	49.77	5.74	6.08			15.54	15.27
12A	E	$C_{19}H_{27}O_2N_2Cl_3$	54.10	53.95	6.45	6.28				
13A	A	$C_{19}H_{26}O_2N_2$	72.59	72.52	8.34	8.34				
14A	E	$C_{19}H_{28}O_2N_2Cl_2$	58.90	58.84	7.29	7.49				
15A	G	$C_8H_9ONCl_2$	46.62	46.89	4.40	4.71	6.80	7.12		
16A	E	$C_8H_{10}ONCl_3$	39.62	39.64	4.16	4.30				
17A	H	$C_8H_{12}ONCl$	55.35	55.40	6.97	7.07			20.43	20.41
18A	H	$C_{15}H_{14}O_2NCl_5$	43.15	43.14	3.38	3.67			8.49	8.42
19A	A	$C_9H_{11}ONCl_2$	49.11	48.82	5.04	5.31				
20A	E	$C_9H_{12}ONCl_3$	42.13	42.00	4.72	4.79	5.46	5.30	13.82	13.72
24A	G	$C_9H_{11}ONCl_2$	49.11	49.11	5.04	5.06				
25A	E	$C_9H_{12}ONCl_3$	42.13	42.20	4.72	4.84	5.46	5.84	13.82	13.93
26A	E	$C_9H_{13}ONBrCl$	40.54	40.56	4.91	4.98			13.30	13.51[w]
27A	E	$C_9H_{13}ONBrCl$	40.54	40.53	4.91	4.99			13.30	13.47[w]
28A	G	$C_9H_{11}ONBr_2$	34.98	34.99	3.59	3.81			51.71	51.69
29A	G	$C_9H_{12}ONBr_2Cl$	31.29	31.34	3.50	3.45			10.27	10.30[w]
31A	F	$C_{15}H_{16}O_8N_4$	47.38	47.41	4.24	4.31				
33A	G	$C_{15}H_{30}ON_3Cl_3$	48.08	47.96	8.07	8.11			28.38	28.02
36B		$C_{12}H_{26}ON_2$	67.25	67.29	12.23	12.21				
37B	C	$C_{24}H_{32}O_{15}N_8$	42.86	42.96	4.80	5.10				
38B	E	$C_{12}H_{28}ON_2Cl_2$	50.16	50.12	9.82	9.85	9.75	9.54	24.68	24.47
41B	E	$C_9H_{20}ONCl$	55.80	55.83	10.41	10.27			18.30	18.31
42C		$C_{15}H_{26}ON_3Cl$	60.07	60.22	8.74	8.83				
43C	E	$C_{15}H_{29}ON_3Cl_4 \cdot H_2O$[x]	42.17	42.53	7.32	7.54				
45C	I	$C_{10}H_{12}O_3NCl$	52.27	52.20	5.27	5.39	6.10	6.36		
46C	E	$C_{10}H_{13}O_3NCl_2$	45.12	45.18	4.92	5.19				
47C	I	$C_{12}H_{14}O_5NBr$	43.38	43.21	4.25	4.28	4.22	4.73		
48C	E	$C_{12}H_{15}O_5NBrCl$	39.10	39.07	4.10	4.28				
49C	J	$C_{10}H_{13}O_3N$	61.53	61.39	6.71	6.68	7.18	7.27		
50C	E	$C_{10}H_{14}O_3NCl$	51.84	51.84	6.09	6.16				
51C	F	$C_{16}H_{16}O_{10}N_4$	45.29	45.38	3.80	3.81				
53C	K	$C_{11}H_{16}O_3NBr$	45.52	45.46	5.56	5.47				
54C	L	$C_{10}H_{14}O_3NCl$	51.84	51.64	6.09	6.14	6.05	6.12		
55C	F	$C_{16}H_{16}O_{10}N_4$	45.29	45.55	3.80	4.09				
56C	E	$C_{13}H_{22}O_3N_2Cl_2$	48.00	47.89	6.82	6.82	8.61	8.75		
57C	E	$C_{16}H_{27}O_3N_3$	62.11	62.27	8.80	8.85	13.58	13.72		
58C	E	$C_{10}H_{13}O_3N$	61.53	61.39	6.71	6.84	7.18	7.49		
59C	B	$C_{10}H_{14}O_3NCl$	51.84	51.63	6.09	6.29				
60C	E	$C_{13}H_{20}O_3N_2$	61.88	62.00	7.99	8.02	11.10	11.30		
61C	E	$C_{13}H_{22}O_3N_2Cl_2$	48.00	47.74	6.82	6.90				
62C	C	$C_{11}H_{13}O_5N$	55.23	54.92	5.48	5.39	5.86	5.61		
63C	E	$C_{11}H_{14}O_5NCl$	47.92	47.72	5.12	5.32				
64C	E	$C_{11}H_{15}O_3N$	63.13	63.13	7.23	7.12	6.69	6.84		
65C	E	$C_{11}H_{16}O_3NCl$	53.76	53.86	6.56	6.48				
66C	E	$C_{13}H_{24}ON_2Cl_2$	52.89	52.85	8.19	8.25			24.02	23.75
67C	E	$C_{11}H_{15}O_3N$	63.13	63.21	7.23	7.37	6.69	6.73		
68C	E	$C_{11}H_{16}O_3NCl$	53.76	53.55	6.56	6.62				
69C	H	$C_{13}H_{24}ON_2Cl_2$	52.89	52.87	8.19	8.29			24.02	23.78
70C	M	$C_{21}H_{33}O_5N_3$	61.90	62.11	8.16	8.11	10.32	10.47		
71C	E	$C_{21}H_{36}O_6N_3Cl_3$	48.79	48.59	7.02	7.18				
72C	G	$C_{12}H_{22}O_2N_2Cl_2$	48.49	48.44	7.46	7.43			23.86	23.52
73C	E	$C_{19}H_{28}O_2N_2Cl_2$	58.90	58.88	7.28	7.23			18.30	18.18
74C	N	$C_{23}H_{30}O_5N_2Cl_2$	56.91	56.71	6.23	6.34			14.61	14.42
75C	A	$C_{12}H_{20}ON_2$	64.26	63.97	8.99	8.76				
76C	E	$C_{12}H_{22}ON_2Cl_2$	48.49	48.49	7.46	7.38			23.86	23.75
77C	E	$C_{16}H_{26}O_4N_2Cl_2$	50.41	50.11	6.88	6.98			18.60	18.73
78	O	$C_{21}H_{33}O_6N_3$	59.57	59.64	7.85	7.82				
79	E	$C_{21}H_{36}O_6N_3Cl_3$	47.33	46.97	6.81	7.04			19.96	20.12

[a] Molecular amounts of reactants employed: substituted phenol, formaldehyde, and amine, respectively. [b] Picrate. [c] Maleate. [d] Boiling point. [e] J. Decombe [*Compt. rend.*, **196**, 866 (1933)] described the base. [f] 2-Hydroxy-3-(dimethylaminomethyl)-5-chlorobenzyl. [g] 2-Hydroxy-3-(dimethylaminomethyl)benzyl. [h] W. J. Burke and C. W. Stephens [*J. Am. Chem. Soc.*, **74**, 1518 (1952)], m.p. 144–145°. [i] $CH_2N(CH_3)CH_2C_6H_2$(OH-2, Cl-3, Cl-5)·HCl. [j] M. Julia and G. Tchernoff [*Bull. soc. chim. France*, 830 (1955)], m.p. of base, 60°; yield 30%; m.p. of hydrochloride, 185°. [k] German patent 92,309 (*Frdl.*, **4**, 103); footnote [e], b.p. 104–108° (17 mm.). [l] A. Madinaveitia [*Anales soc. espan. fis. quin.*, **19**, 259 (1921); *Chem. Abstr.*, **16**, 1230 (1922)], m.p. 151°. [m] Prepared by dehalogenation of 26A and treatment of the product with picric acid. [n] E. Stedman [*J. Chem. Soc.*, 1902 (1927)], m.p. 185°. [o] Prepared by dehalogenation of 27A and treatment of the product with picric acid. [p] The base of this compound was prepared as described by H. A. Bruson and C. W. Macmullen, *J. Am. Chem. Soc.*, **63**, 270 (1941). [q] In this instance the product was prepared by simultaneous dehalogenation and ring hydrogenation of 7A. [r] C. Mannich and R. Braun [*Ber.*, **53**, 1874 (1920)], b.p. 108° (13 mm.); m.p. of hydrochloride, 160°. [s] Morpholinomethyl. [t] Obtained in dehalogenation of 45C and treatment of the product with picric acid. [u] The base of this compound was prepared as described by W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939). [v] Solvents used in recrystallization: A, petroleum ether (60–75°); B, isopropyl alcohol; C, water; D, acetone; E, methanol-ether; F, ethanol; G, methanol; H, isopropyl alcohol–ether; I, methanol-water; J, 90% methanol; K, ethanol-ether; L, isopropyl alcohol–ethyl acetate; M, petroleum ether (90–100°); N, isopropyl alcohol–ethyl acetate–ether; O, benzene–petroleum ether (90–100°). [w] Chlorine. [x] The water could not be removed by heating the compound at 120° (0.1 mm.) for 24 hr.

The product precipitated as a solid[14] or an oil. In the former case, it was removed by filtration. When the product separated as an oil, the mixture was treated with 160 g. of sodium chloride per mole of phenol employed. The product was extracted with ether, the extract was dried over magnesium sulfate, the solvent was removed, and the residue was distilled.

Compounds 1A and 42C could not be distilled without extensive decomposition. However, 1A crystallized after several weeks, and 42C, in crude form, was satisfactory for the preparation of the trihydrochloride (43C).

B. This procedure was the same as A except for the following variations. Ethanol[15] was used as a solvent and the addition of sodium chloride was omitted. After the heating period was completed, the mixture was concentrated *in vacuo*. The oily residue was dissolved in ether, the solution was dried and treated with hydrogen chloride. The precipitated salt was recrystallized from an appropriate solvent.

Compound 15A separated from the reaction mixture and was removed by filtration.

Compounds 26A and 27A were synthesized from 2-bromophenol. After removal of the ethanol and water *in vacuo*, the residue was distilled; b.p. 107–108° (0.1 mm.). This fraction, which consisted of a mixture of two isomeric bases, was dissolved in ether and the solution was treated with hydrogen chloride. The precipitated hydrochlorides (26A and 27A) were dissolved in methanol and ether was added until the solution became turbid. Compound 27A separated first and was recrystallized four times from methanol-ether. Compound 26A precipitated after the addition of more ether to the solution from which 27A had separated.

Compound 74C was obtained by the use of 4-benzoyloxyphenol.[16]

C. Procedure A was modified in the following manner. The addition of sodium chloride was omitted and the reaction mixture was heated under reduced pressure until all of the water had been removed. The residual oil was crystallized from ethanol or ethanol-ether.

Compound 8A. 4-Chloro-2-carboxyphenol (5-chlorosalicylic acid)[17] was used for the preparation of this product. The oily residue, obtained after removal of the water from the reaction mixture under reduced pressure, was dissolved in ether and the extract was treated with hydrogen chloride whereupon the dihydrochloride precipitated; m.p. and mixed m.p. with an authentic sample prepared by method A, 231–232° (dec.).

Compound 35A. In this instance, 4-hydroxybenzoic acid was the required phenol. The reaction mixture was heated on a steam bath for 7 hr. When the ether solution of the residual oil was treated with hydrogen chloride, the trihydrochloride precipitated; m.p. and mixed[18] m.p. 277–278° (dec.).

Compounds 44C and 45C. These compounds, in the form of a mixture, were obtained from 5-chloro-2-carboxyphenol (4-chlorosalicylic acid).[19] The residual oil was dissolved in ethanol and ether was added to the solution; 45C precipitated in crystalline form (4.6 g.). After filtration, the filtrate was treated with hydrogen chloride. The precipitated oily trihydrochloride (44C) crystallized when it was heated with isopropyl alcohol; yield 5.8 g.; m.p. 238–239° (dec.) after several recrystallizations from methanol-ether and then from methanol–ethyl acetate; mixed m.p. with an authentic sample (43C), 239–240° (dec.).

Compounds 64C and 66C. The required phenol was 4-methyl-2-carboxyphenol.[20] After the residual oil had been dissolved in ethanol and ether had been added, the precipitated crystalline product (64C) (8.0 g.) was filtered and the filtrate was treated with hydrogen chloride. After the addition of ether, the precipitated oily dihydrochloride (66C) was crystallized by heating it with isopropyl alcohol; yield 5 g.

Compounds 67C and 69C. The required phenol was 6-methyl-2-carboxyphenol (*o*-cresotinic acid).[21] The residual oil was dissolved in ethanol and ether was added to the solution. After filtration of the precipitated crystalline product (67C) (10.2 g.), the filtrate was treated with hydrogen chloride. The precipitated oil was separated, dissolved in water, the solution was made alkaline with potassium carbonate, and the oily precipitate was extracted with ether. After removal of the solvent, the product was distilled; b.p. 103–104° (0.6 mm.); yield 1.0 g. The product was converted into the dihydrochloride (69C) with ethereal hydrogen chloride.

D. After the addition of formalin, as in procedure A, the mixture was stirred for 5 hr. at room temperature, then

(14) Compounds 10A, 19A, 24A, and 28A separated as solids. 2-(2-Hydroxy-5-chlorobenzyl)-4-chlorophenol (G-4 brand of dichlorophene), required for the preparation of 10A, was obtained from the Sindar Corporation, New York, N. Y.

(15) For 15A and 18A, 50 ml. of 50% ethanol; for 26A (and 27A), 80 ml. of ethanol; for 73C, 40 ml. of ethanol, and for 74C, 25 ml. of ethanol.

(16) F. Kehrmann, M. Sandoz, and R. Monnier, *Helv. Chim. Acta*, **4**, 941 (1921).

(17) Purchased from Distillation Products Industries.

(18) An authentic sample (33A) was obtained by conversion of the base, described previously (ref. 4), into the trihydrochloride.

(19) Purchased from the Aldrich Chemical Company.

(20) Obtained in 43% yield by the method of J. I. Jones [*Chem. & Ind. (London)*, 228 (1958)].

(21) Obtained from Matheson, Coleman, and Bell.

heated on a steam bath under reduced pressure until all of the water had been removed. The oily residue was crystallized from ethanol-ether.

Compound 47C. The required phenol was 4-bromo-5-hydroxy-2-carboxyphenol (5-bromo-2,4-dihydroxybenzoic acid).[6] In this instance, 25 ml. of 50% ethanol was used as a solvent. The product separated from the reaction mixture and was removed by filtration.

Compound 58C. In this case, 50 ml. of ethanol was used as a solvent. After completion of the reaction, the mixture was heated under reduced pressure until all of the water and ethanol had been removed.

E. The required phenol, morpholine, and sufficient ethanol to form a solution were shaken and treated slowly with formalin. The mixture was then allowed to remain at room temperature.

Compound 70C. After 12 hr. most of the ethanol was removed whereupon the product separated in crystalline form. The trihydrochloride (71C) melted at 212–213° (dec.) after recrystallization from methanol-ether. After it had been dried at 110° (0.1 mm.) for 12 hr., it melted at 179–180° (dec.).

Compound 78. This product precipitated after 3 hr. and was removed by filtration.

F. *Conversion of aminomethylhalophenol hydrochlorides into aminomethylphenol hydrochlorides.* A mixture of the required aminomethylhalophenol hydrochloride (0.02 mole), 75 ml. of water, and 0 2 g. of platinum dioxide was hydrogenated under an initial pressure of 55 pounds until the calculated amount of hydrogen had been absorbed (15–30 min.). After filtration, the water was removed under reduced pressure. In some instances (9A, 30A, and 34A), the oily hydrochloride crystallized when cooled. It was then recrystallized from a suitable solvent. Compound 5A was crystallized from isopropyl alcohol–ether.

Compounds 12A and 14A. These products were prepared from 11A. The mixture of oily dihydrochlorides was dissolved in methanol; upon the addition of ether, 14A precipitated in crystalline form; yield 5.5 g. After removal of 14A by filtration, ether was added to the filtrate whereupon 12A (2.0 g.) precipitated.

Compound 21A. This substance was obtained from 20A. Three hours were required for the hydrogenolysis. Since the oily hydrochloride could not be crystallized, it was converted into the base which was then distilled. The picrate was prepared from the oily hydrochloride in ethanol-water solution.

Compound 34A. This product was obtained from 43C. The reaction mixture was heated at 55–60° for 2 hr.

Compound 52C. In order to obtain this substance, 45C (the base) was hydrogenated at 55–60° for 2 hr.

Compounds 5A, 9A, 17A, 23A, 30A, 31A, and 52C were obtained from 2A, 7A, 16A, 26A, 25A, 27A, and 45C, respectively. The hydrochlorides (5A, 9A, 17A, and 30A) were isolated in crystalline form from the reaction mixtures. The picrates (23A, 31A, and 52C) were prepared by addition of picric acid, dissolved in ethanol, to an aqueous solution of the crude hydrochloride. The melting points of 23A, 31A, and 52C and the mixed melting points of each of these compounds with an authentic sample (22A, 32A, and 51C, respectively) were the same.

G. Conversion of an aminomethylphenol hydrochloride and of aminomethylchlorophenol hydrochlorides into aminomethylcyclohexanol hydrochlorides. A mixture of 0.05 mole of the required phenol hydrochloride, 200 ml. of water, and 0.5 g. of platinum dioxide was hydrogenated, at 55–60°, under an initial pressure of 55 pounds until the calculated amount of hydrogen had been absorbed. In the preparation of 39B and 41B, hydrogenation required 6 hours; the latter compound was hydrogenated at room temperature. In order to hydrogenate 7A and 9A, it was necessary to filter the mixture after 15 hr., add 0.5 g. of catalyst and hydrogenate for an additional 15 hr.

After hydrogenation had been completed, the mixture was filtered, most of the water was removed, the residue was made strongly basic, and the product was extracted with ether. The solvent was removed from the dried extract and the product was distilled.

Compound 38B. The dried extract was not distilled but was treated with hydrogen chloride. The precipitated dihydrochloride was recrystallized several times from methanol-ether.

Compound 41B. In the preparation of this substance, the desired base (1.0 g.) distilled at 120–123° (15 mm.). A lower boiling fraction was obtained and identified as dimethylaminomethylcyclohexane; yield 3.2 g.; b.p. 72–73° (15 mm.)[22]; picrate, m.p. 135–137°[22]; hydrochloride, m.p. 249–250°.

Anal. Calcd. for $C_9H_{20}NCl$: Cl, 19.94. Found: Cl, 20.10.

Compounds 36B, 38B, 39B, and 41B were prepared from 9A, 7A, 20A, and 25A, respectively.

2,4,6-Tris(dimethylaminomethyl)phenol trihydrochloride, 4-(dimethylaminomethyl)-2-carboxyphenol (49C), 6-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (54C), and 4,6-bis(dimethylaminomethyl)-2-carboxyphenol dihydrochloride (56C). Salicylic acid (138 g., 1.0 mole) and 25% aqueous dimethylamine (720 g., 4.0 moles) were stirred and maintained at 20–25° while 37% formalin (324 g., 4.0 moles) was added, dropwise, during a 30-min. period. The mixture was stirred for 1 hr. and then stirred and heated for 3 hr. on a steam bath. The oily residue obtained, after removal of the water under reduced pressure, was dissolved in 500 ml. of hot ethanol. When the solution was cooled, 48 g. of 49C precipitated and was removed by filtration. The filtrate was treated with hydrogen chloride and the precipitated 2,4,6-tris(dimethylaminomethyl)phenol trihydrochloride (47 g.) was filtered; m.p. and mixed[18] m.p. 277–278° (dec.). The filtrate was treated with ether until it became turbid. The mixture was cooled and the precipitate, 61 g. of 56C, was removed by filtration. After the solvents had been removed from the filtrate, the oily residue was dissolved in hot isopropyl alcohol and ethyl acetate was added until the solution became cloudy. After 4 weeks, 15 g. of 54C precipitated.

A sample of 49C, dissolved in absolute ethanol, was heated with excess methyl bromide at 65° for 24 hr. After ether had been added, the methobromide (53C) precipitated.

Preparation of salts. The hydrochlorides, 2A, 7A, 11A, 16A, 20A, 33A, 40B, 41B, 43C, 71C, and 79, precipitated when a solution of the base in ether was treated with hydrogen chloride. In the case of 25A and 29A, absolute methanol was used as the solvent.

Compounds 46C, 48C, 50C, 59C, 61C, 63C, 65C, and 68C precipitated upon the addition of ether to a methanol solution of the base which had been treated with hydrogen chloride. Compound 72C was obtained in the same manner except that ethanol was used as a solvent.

The dipicrate 37B was obtained by addition of picric acid, dissolved in ethanol, to a solution of the base, 36B, in the same solvent. The dipicrate 3A was obtained in the same manner from the dihydrochloride 2A. The picrates 22A, 32A, and 55C were prepared from the oily hydrochloride of 21A and the hydrochlorides 30A and 54C, respectively, by the addition of an ethanol solution of picric acid to a solution of the hydrochloride in water. Compound 51C was prepared by the same process except that an aqueous solution of the base, 49C, was used.

The dimaleate 4A was obtained by mixing methanol solutions of the base, 1A, and maleic acid and then adding ether to precipitate the salt.

Structure proof of 4-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (50C). A solution of 1.5 g. of 50C in 20 ml. of water, which had been made alkaline with potassium car-

(22) M. Mousseron, R. Jacquier, and R. Zagdoun [*Bull. soc. chim. France*, 197 (1952)], b.p. 75–76° (15 mm.); picrate, m.p. 133°.

bonate, was added to 2 g. of wet Raney nickel paste[23] and the mixture was hydrogenated at 55–60° under an initial pressure of 52 pounds until the calculated amount of hydrogen had been absorbed (20 hr.). After removal of the catalyst by filtration, the cooled filtrate was acidified with concentrated hydrochloric acid. The precipitated 4-methyl-2-carboxyphenol weighed 0.75 g. (76%); m.p. 152–153°.

Structure proof of 6-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (54C). This procedure, with the use of 54C, was carried out in the manner mentioned above. The product, 6-methyl-2-carboxyphenol, weighed 0.3 g. (30%); m.p. 165–166°; reported[24] m.p. 167°; mixed m.p. with an authentic sample, 165–166°.

Reaction of 4,6-bis(dimethylaminomethyl)-2-carboxyphenol dihydrochloride (56C) with formaldehyde and dimethylamine. A mixture of 3.3 g. (0.01 mole) of 56C, 5.0 g. (0.06 mole) of formalin and 11.0 g. (0.06 mole) of 25% aqueous dimethylamine was heated on a steam bath for 3 hr. The mixture was made alkaline with potassium carbonate and then concentrated until most of the water had been removed. The residue was extracted with ether and the dried extract was treated with hydrogen chloride. The precipitated 2,4,6-tris(dimethylaminomethyl)phenol trihydrochloride (0.5 g.) was recrystallized from methanol; m.p. 276–277° (dec.); mixed m.p. with an authentic sample (33A), 276–277° (dec.).

2,6-Bis(dimethylaminomethyl)-4-hydroxyphenol dihydrochloride (76C). A mixture of 3.9 g. of 2,6-bis(dimethylaminomethyl)-4-benzyloxyphenol dihydrochloride (73C), 50 ml. of acetic acid and 2.5 g. of palladium on carbon[25] was hydrogenated under an initial pressure of 14 pounds for 15 min. The mixture was filtered and the solvent was removed under reduced pressure. The oily residue was crystallized from hot isopropyl alcohol; yield 2.5 g. (85%); m.p. 205–206° (dec.) after recrystallization from methanol-ether.

2,6-Bis(morpholinomethyl)-4-hydroxyphenol dihydrochloride (77C). A solution of 2.0 g. of 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol dihydrochloride (74C) in 30 ml. of 18% hydrochloric acid was heated for 3 hr. on a steam bath. The mixture was cooled and filtered to remove benzoic acid (0.45 g.). The water and hydrochloric acid were removed under reduced pressure and the residue was recrystallized from methanol-ether; yield 1.4 g. (91%); m.p. 115–116° (dec.). After the product had been dried at 65° (0.1 mm.) for 24 hr., it melted at 193–194° (dec.).

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(23) Sponge Nickel Catalyst which was obtained from the Davison Chemical Company, Division of W. R. Grace and Company, Department T, Baltimore 3, Md.

(24) N. V. Sidgwick, *J. Chem. Soc.*, **117**, 396 (1920).

(25) Obtained from Baker and Company, Newark, N. J.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Disubstitution of Cycloalkanones in the Mannich Reaction

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Ten bis(aminomethyl)cycloalkanones were prepared by the simultaneous introduction of two aminomethyl groups into a cycloalkanone by the use of a Mannich reaction. It was definitely established that the reaction product obtained from cyclohexanone, paraformaldehyde and dimethylamine hydrochloride was 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride and not the salt of the isomeric 2,2-disubstitution product.

The introduction of one aminomethyl group into a ketone by the use of a Mannich reaction has been reported in many instances but only a relatively few examples are known in which two aminomethyl groups have been introduced into a ketone either intentionally or fortuitously.

It was reported that acetone reacts with formaldehyde and dimethylamine[3,4] or diethylamine,[4,5] under certain conditions, with the formation of a 1,1-bis(dialkylaminomethyl)acetone, and the structures of these products have been definitely established.

From acetone, formaldehyde, and hexahydroazepine hydrochloride the disubstituted acetone 2-acetylpropane-1,3-bis(hexahydro-1-azepine) dihydrochloride has been obtained.[6]

1,1,1-Trifluoroacetone reacted with the methylols of piperidine, morpholine, and diisobutylamine to form products which appeared to be hydrates of the bis(aminomethyl)ketone.[7]

A disubstitution product obtained from methyl ethyl ketone, formaldehyde, and dimethylamine hydrochloride has been stated to be either 1-dimethylamino-4-(dimethylaminomethyl)-3-pentanone or 3,3-bis(dimethylaminomethyl)-2-butanone by Cardwell[4] but according to Barrett and Chambers[8] the product is the former compound; Haeussler and Schacht[9] claim that the product is the latter substance.

From propiophenone and from 3-acetylpyridine, β,β'-bis(1-piperidyl)pivalophenone and bis(1-piperidylmethyl)methyl-3-pyridyl ketone, respectively, were obtained by Mannich reactions.[10]

(1) This paper represents part of a dissertation submitted by F. J. McCarty for the Ph.D. degree in the University of Michigan.

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