1,3,5-Trisubstituted Hexahydrotriazines as Mannich Reagents. II. Preparation of *p*-Secondary Aminomethylphenols.

Delbert D. Reynolds and Bernard C. Cossar

Research Laboratories, Eastman Kodak Company
Rochester, N. Y. 14650

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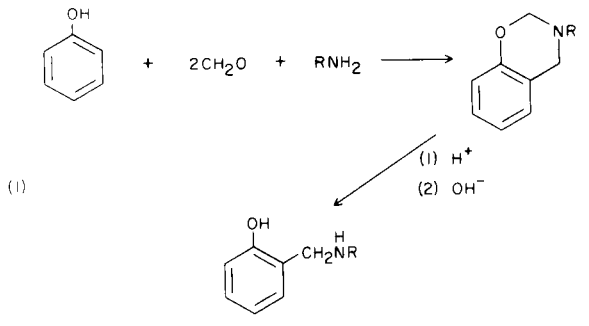
Phenol and a variety of substituted phenols have been aminomethylated by new Mannich reagents prepared from 1,3,5-trisubstituted hexahydrotriazines. In contrast to the conventional aminomethylating agents, which react preferentially in the *ortho* position, the new reagents favor *para* substitution. A variety of new *para* secondary aminomethylphenols have been prepared.

The Mannich reaction has been used extensively for the preparation of aminomethylphenols, which have important pharmaceutical applications. Experimental facts concerning these preparations which have evolved during the last seventy years have been summarized by Reichert (1) and by Hellmann and Opitz (2), along with comprehensive tabulations of the compounds which have been reported. At least three generalizations can be drawn from these summaries and tabulations. These are as follows: (a) there are relatively few instances where primary amines have been used successfully as one of the reactants, (b) *ortho*- is favored over *para*-substitution, and (c) most of the syntheses have been made in the absence of strong acids.

Primary amines and many phenols are bifunctional with respect to the Mannich reaction and for this reason they often form resins in the presence of formaldehyde. In fact, the reaction of phenol with formaldehyde and methylamine has been suggested for the preparation of basic resins (3). Burke and co-workers (4) have broadened the applicability of primary amines in the aminomethylation of phenols by allowing the phenol, formaldehyde and an amine to react in a ratio of 1:2:1. The dihydrobenzoxazines thus formed can be subsequently hydrolyzed to *ortho*-secondary aminomethylphenols (eq. 1).



(1)

With few exceptions (5) phenols are aminomethylated in the available *ortho*-position. Phenol itself reacts sequentially to form 2-, 2,6-, and finally the 2,4,6-trisubstituted aminomethyl derivative. The statement has been made (2) that it has not been possible to selectively aminomethylate phenols in the *para*-position.

In most instances the free amines are preferred over their salts for use in the aminomethylation of phenols. In instances where acidic conditions have been used, acetic acid has been favored since in more strongly acidic media the aminomethylation reaction is completely suppressed in favor of phenol-formaldehyde condensation (6).

In the first paper of this series (7) we described the preparation of secondary aminomethyl sulfide hydrochlorides by the reaction of mercaptans and hydrogen sulfide with Mannich reagents formed by the reaction of hydrogen chloride with 1,3,5-trisubstituted hexahydrotriazines. We have extended the use of this reagent to the aminomethylation of phenol and a number of substituted phenols. The results reported in this paper differ in a number of ways from those obtained with the more conventional reagents.

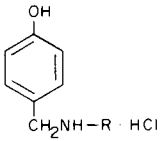
Of foremost importance, this new reagent provides an improved method for direct introduction of the secondary aminomethyl group, $RNHCH_2$-, into an aromatic nucleus. No attempts have been made to optimize yields. Those reported in the tables were the results after several recrystallizations to obtain analytical samples.

Although our reactions are run under acidic conditions there has been no evidence that the aminomethylation has been suppressed by phenol-formaldehyde condensations, or resin formation.

Substitution takes place predominantly in the position *para* to the hydroxyl. This has been ascertained by a study of the aromatic region of the nmr spectra, as indicated in the footnotes of Tables I-VII. In a study in which phenol was converted to its allylaminomethyl derivatives

TABLE I

4-Aminomethylphenol Hydrochlorides

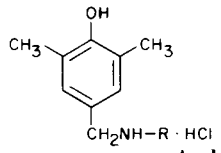


-R	M.p., °C	Yield %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_2-H_6	H_3-H_5
$-C_2H_5$	180-181	33 (a)	57.6	7.5	18.9	7.5	57.6	7.6	18.8	7.7	6.82 (D)	7.38 (D)
$-C_3H_7$-*n*	128-130	32 (b)	59.5	8.0	17.6	7.0	59.3	8.2	17.8	7.4	6.80 (D)	7.38 (D)
$-C_3H_7$-*i*	208-209	42 (c)	59.5	8.0	17.6	7.0	59.3	8.0	17.5	6.9	6.81 (D)	7.41 (D)
$-C_4H_9$	124-125	22 (a)	61.2	8.4	16.4	6.5	61.2	8.3	16.4	6.6	6.82 (D)	7.37 (D)
$-CH_2CH=CH_2$	162-163	38 (a)	60.2	7.1	17.8	7.0	59.9	7.2	17.8	7.4	6.82 (D)	7.38 (D)
$-CH_2$-C$_6$H$_5$	224-225	33 (d)	67.3	6.5	14.2	5.6	67.3	6.5	14.1	5.6	6.88 (D)	–

The aromatic absorption appears as the typical AA'BB' spectrum of a *p*-disubstituted benzene.
Recrystallized from (a) methanol-methyl ethyl ketone; (b) acetonitrile; (c) methanol-acetonitrile; (d) 2-propanol-methyl ethyl ketone.

TABLE II

2,6-Dimethyl-4-aminomethylphenol Hydrochlorides

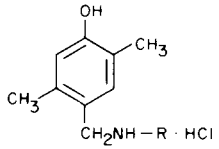


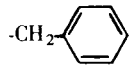
-R	M.p., °C	Yield %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_3	H_5
$-C_2H_5$	194-196	31 (a)	61.2	8.4	16.4	6.5	61.4	8.3	16.2	6.6	6.33 (S)	6.33 (S)
$-C_3H_7$-*n*	167-169	38 (b)	62.7	8.8	15.4	6.1	62.2	8.7	15.2	5.9	7.18 (S)	7.18 (S)
$-CH_2CH=CH_2$	149-150	37 (c)	63.3	8.0	15.6	6.2	63.6	8.0	16.0	6.4	7.13 (S)	7.13 (S)
$-CH_2$-C$_6$H$_5$	211-212	48 (c)	69.2	7.3	12.8	5.0	69.6	7.2	12.7	5.0	6.73 (S)	6.73 (S)

The chemical shift equivalence of the aromatic protons is a consequnce of the symmetry arising from substitution in the 4-position.
Recrystallized from (a) 2-propanol-methyl ethyl ketone; (b) 2-propanol; (c) methanol-methyl ethyl ketone.

TABLE III

2,5-Dimethyl-4-aminomethylphenol Hydrochlorides

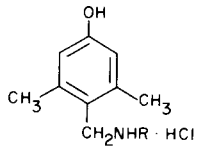


-R	M.p., °C	Yield (a) %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_3	H_6
$-C_2H_5$	195-196	32	61.2	8.4	16.4	6.5	61.3	8.4	16.0	6.1	7.25 (S)	6.76 (S)
$-C_3H_7$-*n*	206-207	38	62.7	8.8	15.4	6.1	62.6	8.3	15.3	6.1	7.23 (S)	6.75 (S)
$-C_3H_7$-*i*	230-232	38	62.7	8.8	15.4	6.1	62.8	8.6	15.8	6.1	7.25 (S)	6.71 (S)
$-CH_2CH=CH_2$	186-187	17	63.3	8.0	15.6	6.2	62.9	8.0	15.8	6.3	7.17 (S)	6.70 (S)
	211-212	48	69.2	7.3	12.8	5.0	69.2	7.4	12.9	5.0	7.21 (S)	6.71 (S)

Lack of coupling between the aromatic hydrogens shows their *para* relationship.
(a) Recrystallized from methanol-methyl ethyl ketone mixture

TABLE IV

3,5-Dimethyl-4-aminomethylphenyl Hydrochlorides

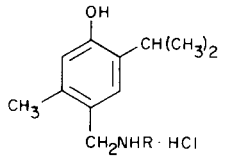


-R	M.p., °C	Yield %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_2	H_6
$-C_2H_5$	231-232	31 (a)	61.2	8.4	16.4	6.5	60.8	8.3	16.1	6.2	6.65 (S)	6.65 (S)
$-C_3H_7$-*n*	216-217	17 (b)	62.7	8.8	15.4	6.1	62.6	8.7	15.0	6.1	6.53 (S)	6.53 (S)
$-C_3H_7$-*i*	241-242	23 (b)	62.7	8.8	15.4	6.1	62.9	8.7	15.4	6.1	6.61 (S)	6.61 (S)

The chemical shift equivalence of the aromatic protons is a consequence of the symmetry arising from substitution in the *para*-position.
Recrystallized from (a) 2-propanol; (b) methanol-methyl ethyl ketone.

TABLE V

2-Isopropyl-5-methyl-4-aminomethylphenol Hydrochlorides

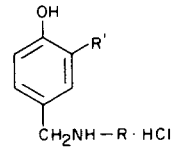


-R	M.p., °C	Yield (a) %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_3	H_6
$-C_2H_5$	194-195	29	64.0	9.1	14.5	5.7	64.2	9.0	14.4	5.7	7.37 (S)	6.78 (S)
$-C_3H_7$-*n*	204-205	36	65.2	9.4	13.8	5.4	65.2	9.4	13.4	5.1	7.33 (S)	6.73 (S)
$-C_3H_7$-*i*	235-236	26	65.2	9.4	13.8	5.4	64.7	9.4	13.5	5.4	7.35 (S)	6.71 (S)
$-CH_2CH=CH_2$	205-206	42	65.7	8.7	–	5.5	65.5	8.7	–	5.6	7.31 (S)	6.75 (S)
$-CH_2$-C6H5	219-220	39	70.7	7.9	11.6	4.4	70.7	7.5	11.3	4.6	–	6.78 (S)

Lack of coupling between the aromatic hydrogens shows their *para* relationship.
(a) Recrystallized from methanol-methyl ethyl ketone mixture.

TABLE VI

2-Substituted 4-Aminomethylphenol Hydrochlorides

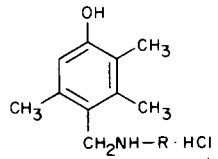


-R	-R'	M.p., °C	Yield (a) %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons Range
$-C_2H_5$	$-CH_3$	161-162	33	59.5	8.0	17.6	7.0	59.3	8.0	17.3	6.7	6.83-7.31 (b)
$-CH_2CH=CH_2$	$-CH_3$	163-164	16	61.8	7.6	16.6	6.6	61.6	7.2	16.7	6.5	6.88-7.28 (b)
$-C_2H_5$		201-202	48	68.3	6.9	13.4	5.3	68.2	6.7	13.1	4.9	7.05-7.58 (c)
$-CH_2CH=CH_2$		191-192	12	69.7	6.6	12.9	5.1	69.6	6.5	12.9	5.0	7.01-7.70 (c)
$-C_3H_7$-*i*	$-OC_2H_5$	187-188	20	58.6	8.2	14.4	5.7	58.6	8.6	14.1	5.6	6.86-7.35 (b)

(a) Recrystallized from methanol-methyl ethyl ketone mixture. (b) The aromatic absorption shows typical, though partially unresolved, ABX absorption where J_{AX} is small and $J_{BX} \cong 0$, indicating the 1,2,4-relationship of these protons. (c) The phenol aromatic absorption is obscured by the phenyl proton absorption.

TABLE VII

2,3,5-Trimethyl-4-aminomethylphenol Hydrochlorides



-R	M.p., °C	Yield %	Analyses Calcd. C	H	Cl	N	Found C	H	Cl	N	Chemical shift (δ) of ring protons H_6
$-C_2H_5$	213-214	24 (a)	62.7	8.8	15.4	6.1	63.1	8.4	15.2	5.9	6.67 (S)
$-C_3H_7$-*n*	213-215	37 (b)	64.1	9.1	14.6	5.8	64.1	9.4	14.1	5.5	6.67 (S)
$-CH_2CH=CH_2$	206-207	28 (a)	64.6	8.3	14.7	5.8	64.8	8.3	14.3	5.8	6.67 (S)
$-CH_2$ 	210-212	31 (a)	70.0	7.6	12.2	4.8	70.0	7.5	12.1	4.8	6.65 (S)

Structure not resolved by nmr and therefore subject to question.

Recrystallized from (a) methanol-2-propanol-methyl ethyl ketone; (b) 2-propanol-methyl ethyl ketone.

the ratio of *ortho* to *para* substitution was approximately 1:4. From a preparative point of view, this new reagent has made the secondary *p*-aminomethylphenols, otherwise difficult to prepare, more readily available.

EXPERIMENTAL

The 1,3,5-trisubstituted hexahydrotriazines were prepared by the reaction of primary amines with formaldehyde according to previously described methods (7). The melting points of the products listed in Tables I-VII are uncorrected. The nmr spectra were determined with a Varian A-60 spectrometer. Tetramethylsilane was used as the reference standard.

A standard procedure has been used for the aminomethylation of the phenols. This procedure is represented by the following preparation of *p*-(*n*-propylaminomethyl)phenol hydrochloride.

A solution of 21.3 g. (0.1 mole) of 1,3,5-tri-*n*-propylhexahydrotriazine in 100 ml. of anhydrous acetonitrile was cooled to -30° in a Dry Ice-acetone bath. This temperature was maintained while 12.0 g. of anhydrous hydrogen chloride was introduced into the reaction mixture. Phenol (9.4 g., 0.1 mole) was dissolved in 50 ml. of acetonitrile and added to the reaction mixture, which was allowed to remain at room condition for 24 hours. After concentration under vacuum, the resulting syrup was crystallized by trituration in methyl ethyl ketone. The product was separated by filtration, washed with ether and dried to give 35.0 g. (56%) of *p*-(*n*-propylaminomethyl)phenol hydrochloride. An analytical sample was prepared by recrystallization from acetonitrile, m.p. 128-130°.

For other examples see Tables I-VII.

Allylaminomethylphenol Hydrochloride.

The following experiment was run in order to learn more about the nature of the reaction products.

An anhydrous acetonitrile solution (500 ml.) of 1,3,5-triallylhexahydrotriazine (62.1 g., 0.3 mole) was cooled to -30° and 36 g. of anhydrous hydrogen chloride was absorbed therein. Phenol (85.2 g., 0.9 mole) was then added. The reaction mixture was shaken mechanically and allowed to warm up to room temperature. The white crystalline salt which formed during this period was separated by filtration, washed with ether and dried to yield 72.0 g. of product (39.2%). An analytical sample was prepared by recrystallization from a methanol-methyl ethyl ketone mixture, m.p. 162-163°.

The filtrate was examined by column chromatography using silica gel. Another 11.7% of *p*-allylaminomethylphenol hydrochloride was isolated in addition to 11.7% of *o*-allylaminomethylphenol hydrochloride. Phenol (25.3%) was recovered unchanged. The percentage yields are based upon the starting phenol. Thus, 87.9% of the starting phenol was accounted for. The *para* and *ortho* isomers are formed in a ratio of 4.4 to 1.0.

Acknowledgment.

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(6) Ref. 2, p. 141.

(7) D. D. Reynolds and B. C. Cossar, *J. Heterocyclic Chem.*, 8, 597 (1971).