

1,3,5-Trisubstituted Hexahydrotriazines as Mannich Reagents. III.
Preparation and Cleavage of 3,4-Dihydro-6-hydroxy-3-substituted-
2H-1,3-benzoxazine Hydrochlorides

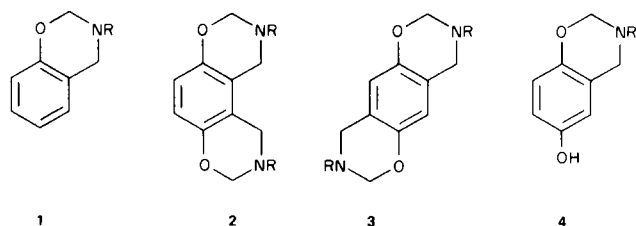
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3,4-Dihydro-6-hydroxy-3-substituted-2H-1,3-benzoxazine hydrochlorides have been prepared by the reaction of hydroquinones with novel aminomethylating reagents prepared from 1,3,5-trisubstituted hexahydrotriazines. With these monooxazine hydrochlorides is formed an equal molar amount of an amine hydrochloride. Purification leads to low yields. This difficulty has been circumvented by the use of bis(alkoxymethyl)amines in the presence of anhydrous hydrogen chlorides. The monooxazines have been hydrolyzed to yield *ortho*-secondary aminomethylhydroquinone derivatives.

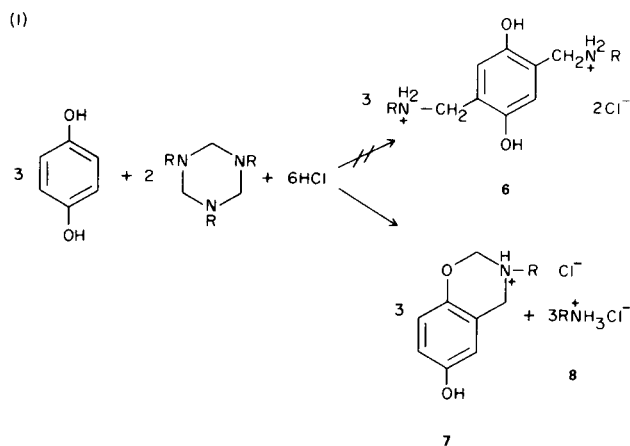
The reaction of phenols with primary amines and formaldehyde to form 3,4-dihydro-3-substituted-2H-1,3-benzoxazines (**1**) has been described by Burke and Stephens (1). Subsequent hydrolysis of the oxazines by dilute hydrochloric acid gave high yields of the *ortho*-secondary aminomethylphenol hydrochlorides. These were converted to the free bases by potassium carbonate. In 1962, a publication from our Laboratory (2) disclosed the results of a similar study involving the condensation of hydroquinone with formaldehyde and primary amines. The products obtained by us were mixtures of the bisoxazine (**3**) derivatives **2** and **3**. We made numerous attempts to prepare the monooxazines (**4**), but the products were again mixtures **2** and **3**. After our experimental work had been completed, two closely related papers (4,5) were published. In neither instance were the monooxazines (**4**) described. The only monooxazines of hydroquinone derivatives that have been



reported (**6**) are those prepared from *t*-butylhydroquinone. The failure of these monooxazines to form the bis derivatives has been attributed to steric factors. A continuation of our investigations of aminomethylation has resulted in two general methods for preparing the monooxazine hydrochloride of hydroquinone and some of its derivatives **7**. Hydroquinone, toluhydroquinone and *t*-butylhydroquinone

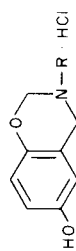
have been used in the present work to illustrate these methods.

In the first two papers of this series (7,8) we described the preparation of a new Mannich reagent and its use in preparing secondary aminomethyl derivatives of mercaptans, hydrogen sulfide and phenols. When this reagent was used in an attempt to prepare 2,5-bis(aminomethyl)hydroquinones **6**, the monooxazine hydrochlorides **7** were obtained quite unexpectedly (eq. 1). The yields of com-



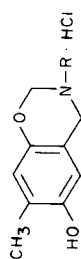
pounds **7** were very good but, as is indicated by eq. 1, the stoichiometric relationship is such that the desired product is accompanied by an equal molar amount of amine hydrochloride **8**. Purification of **7** leads to diminished yields, as indicated under Procedure A, Table II. This difficulty has been circumvented by using the bis(alkoxymethyl)amines **9** in place of the 1,3,5-trisubstituted hexahydrotriazines **5** (eq. 2) (Procedure B).

TABLE I

3,4-Dihydro-6-hydroxy-3-substituted-2*H*-1,3-benzoxazine Hydrochlorides (Procedure B)

-R	M.p., °C	Yield %	Calcd.			Found			Chemical shifts (δ) of oxazine ring protons -ArCH ₂ N-	
			C	H	N	C	H	N	-ArOCH ₂ -	-ArCH ₂ N-
-CH ₃	158-159	66	53.6	6.0	17.6	53.5	5.9	17.4	5.23 (S, 2H)	4.55 (S, 2H)
-C ₂ H ₅	174-175	87	55.7	6.5	16.4	55.5	6.5	16.4	5.13 (S, 2H)	4.46 (S, 2H)
-CH ₂ CH ₂ CH ₃	152-153	70	57.5	7.0	15.4	57.6	6.8	15.5	5.16 (S, 2H)	4.48 (S, 2H)
-C ₄ H ₉ - <i>n</i>	137-138	77	59.1	7.4	14.5	58.9	7.3	14.2	5.20 (S, 2H)	4.51 (S, 2H)
-CH ₂	172-173	73	64.9	5.8	12.8	64.8	5.6	12.7	5.16 (S, 2H)	4.41 (S, 2H)


TABLE II

3,4-Dihydro-6-hydroxy-7-methyl-3-substituted-2*H*-1,3-benzoxazine Hydrochlorides (a)

-R	M.p., °C	Yield, % Procedure	Calcd.			Found			Chemical shifts (δ) of oxazine ring protons -ArCH ₂ N-	
			C	H	N	C	H	N	-ArOCH ₂ -	-ArCH ₂ N-
-CH ₃	192-193 (b)	83	55.7	6.5	16.4	55.7	6.2	16.3	5.13 (S, 2H)	4.43 (S, 2H)
-CH ₂ CH ₃	182-183 (b)	67	57.5	7.0	15.4	57.5	7.0	15.4	5.15 (S, 2H)	4.41 (S, 2H)
-CH ₂ CH ₂ CH ₃	182-183 (b)	53	59.1	7.4	14.5	59.5	7.5	14.2	5.10 (S, 2H)	4.43 (S, 2H)
-CH ₂ CH ₂ CH ₂ CH ₃	166-167 (c)	66	60.6	7.8	13.8	60.6	7.9	13.5	5.18 (S, 2H)	4.46 (S, 2H)
-CH(CH ₃) ₂	177-178 (b)	75	59.1	7.4	14.5	59.2	7.5	14.3	5.13 (S, 2H)	4.45 (S, 2H)
-CH ₂ CH=CH ₂	172-173 (b)	82	59.6	6.7	14.7	59.4	6.8	15.1	5.18 (S, 2H)	4.41 (S, 2H)
-CH ₂	188-190 (b)	98	65.9	6.2	12.2	65.5	6.3	12.1	5.11 (S, 2H)	4.35 (S, 2H)

(a) Tabulated data obtained from compounds prepared by procedure B. Yields obtained by procedure A included for comparison. Recrystallized from (b) acetonitrile-methanol mixture; (c) acetone.

TABLE III
7-*t*-Butyl-3,4-dihydro-6-hydroxy-3-substituted-2*H*-1,3-benzoxazine Hydrochlorides (Procedure B)

-R	M.p., °C	Yield %	Calcd.			Found			Analyses		Chemical shifts (δ) of oxazine ring protons	
			C	H	Cl	C	H	Cl	N	C	N	-ArCH ₂ N-
-CH ₃	210-211	80	60.6	7.8	13.8	5.4	60.2	7.8	13.7	5.7	5.10 (S, 2H)	4.38 (S, 2H)
-C ₂ H ₅	204-205	89	61.9	8.2	13.1	5.2	61.7	8.1	13.5	5.4	5.15 (S, 2H)	4.41 (S, 2H)
-CH ₂ CH ₂ CH ₃	153-154	87	63.0	8.5	12.4	4.9	62.6	8.4	12.5	5.2	5.11 (S, 2H)	4.38 (S, 2H)
-CH ₂ CH ₂ CH ₂ CH ₃	154-155	90	64.1	8.7	11.8	4.8	64.1	8.8	11.7	4.7	5.13 (S, 2H)	4.45 (S, 2H)
-CH(CH ₃) ₂	195-197	92	63.0	8.5	12.4	4.9	62.8	8.5	12.3	4.9	5.16 (S, 2H)	4.40 (S, 2H)
-CH ₂ CH=CH ₂	197-199	67	63.5	7.8	12.5	4.9	63.4	8.0	12.6	5.1	5.13 (S, 2H)	4.38 (S, 2H)
-CH ₂ - 	207-208	88	68.4	7.2	10.6	4.2	68.4	7.3	10.4	4.4	5.06 (S, 2H)	4.41 (S, 2H)

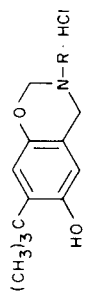



TABLE IV
2-Substituted Aminomethyl-5-methylhydroquinone Hydrochlorides

-R	M.p., °C	Yield %	Calcd.			Found			Analyses		Chemical shift (δ) for -CH ₂ N-
			C	H	Cl	C	H	Cl	N	C	
-CH ₃	198-200	74	53.1	6.9	17.4	6.9	53.1	6.9	17.6	7.0	3.95 (S, 2H)
-C ₂ H ₅	171-172	51	55.2	7.4	16.3	6.4	55.0	7.2	16.2	6.6	3.91 (S, 2H)
-CH ₂ CH ₂ CH ₃	168-170	52	57.0	7.8	15.3	6.1	57.2	8.0	15.0	5.9	3.88 (S, 2H)
-CH(CH ₃) ₂	178-180	59	57.0	7.8	-	6.1	57.3	7.6	-	6.3	3.88 (S, 2H)
-C ₄ H _{9-n}	167-168	49	58.6	8.2	14.4	5.7	58.7	7.9	14.2	5.8	3.91 (S, 2H)
-CH ₂ - 	207-209	71	64.4	6.5	12.8	5.0	64.4	6.5	12.3	5.2	3.91 (S, 2H)

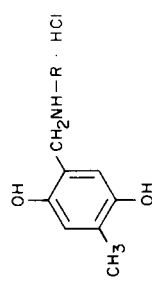

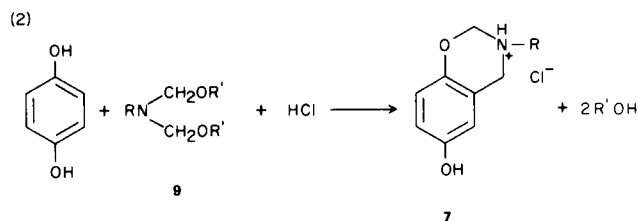
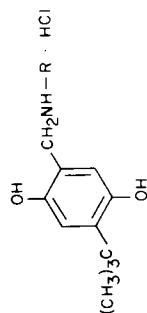


TABLE V
5-*t*-Butyl-2-substituted Aminomethylhydroquinone Hydrochlorides

-R	M.p., °C	Yield %	Analyses				Found			Chemical shift (δ) for $-\text{CH}_2\text{N}-$	
			Calcd.	N			H	Cl	N		
$-\text{C}_2\text{H}_5$	186-187	46	60.1	8.5	13.7	5.4	60.1	8.5	13.6	5.5	3.90 (S, 2H)
$-\text{CH}_2\text{CH}_2\text{CH}_3$	218-220	48	61.4	8.8	13.0	5.1	61.8	8.6	12.5	5.1	3.90 (S, 2H)
$-\text{CH}(\text{CH}_3)_2$	228-230	30	61.4	8.8	13.0	5.1	61.2	9.1	13.1	5.4	3.90 (S, 2H)
$-\text{C}_4\text{H}_9-n$	191-192	42	62.6	9.1	12.3	4.9	62.3	8.9	12.1	5.0	3.91 (S, 2H)
$-\text{CH}_2\text{CH}=\text{CH}_2$	170-171	44	61.9	8.2	13.1	5.2	62.2	8.3	12.9	5.2	3.88 (S, 2H)
	225-227	53	67.2	7.5	11.0	4.4	67.0	7.5	10.9	4.5	3.88 (S, 2H)



The compounds prepared by this method are shown in Tables I-III. A comparison of the two procedures is illustrated by the yields shown in Table II.

The monobenzoxazine hydrochlorides **7** have been converted to the corresponding 2-*sec*-aminomethylhydroquinone hydrochlorides by acid hydrolysis by a method similar to that used by Burke and Stephens (1). Representative examples are shown in Tables IV and V.

The oxazines can be converted to their free-base form by treatment with weak bases such as sodium bicarbonate solution. Stronger bases cleave the oxazine ring rapidly.

EXPERIMENTAL

The 1,3,5-trisubstituted hexahydrotriazines were prepared as described earlier (7). The bis(isobutoxymethyl)amines were prepared according to known procedures (2). Melting points are uncorrected. The nmr determinations were made on a Varian A-60 spectrometer. DMSO- d_6 was the solvent and tetramethylsilane was used as an internal standard.

General Procedure A (Table II) (Eq. 1).

A solution of 0.133 mole of the 1,3,5-trisubstituted hexahydrotriazine in 300 ml. of anhydrous acetonitrile was cooled to -30° in a Dry Ice-acetone bath. This temperature was maintained while 16.0 g. of anhydrous hydrogen chloride was introduced. A crystalline product often separated at this point. The hydroquinone (0.2 mole) was then added and the loosely stoppered reaction flask placed on a mechanical shaker. After a few minutes the temperature rose to -10° to 0° and the solution became homogeneous. Then within another 5-10 minutes the monooxazine hydrochloride began to separate as a white crystalline product. After four hours the product was separated by filtration, washed with ether, and dried. The apparent yields were greater than 100% because of the parent amine hydrochloride which was formed as a by-product. Recrystallization solvents are indicated in Table II.

General Procedure B (Tables I-III) (Eq. 2).

To anhydrous acetonitrile (300 ml.) was added 0.2 mole of the hydroquinone and the mixture cooled to -30° in a Dry Ice-acetone bath. This temperature was maintained while 8.0 g. of dry hydrogen chloride gas was absorbed. The bis(isobutoxymethyl)amine (0.2 mole) was added and the solution allowed to warm to room temperature. After about 4 hours the reaction mixture was chilled and the product separated by filtration. Analytical samples were crystallized from acetonitrile-methanol solutions.

The following example is representative of the preparations recorded in Tables IV and V.

2-Methylaminomethyl-5-methylhydroquinone Hydrochloride.

To an ethanol solution of 21.5 g. (0.1 mole) of 3,4-dihydro-3,7-dimethyl-6-hydroxy-2*H*-1,3-benzoxazine hydrochloride was ad-

ded 10.0 ml. of concentrated hydrochloric acid. The mixture was refluxed for 16 hours, the ethanol removed under vacuum, and the residue triturated in dry acetonitrile. The precipitated product, which was collected by filtration and dried, gave 15.0 g. (74%). An analytically pure sample was obtained by dissolving the product in a minimum of methanol and adding acetonitrile, m.p. 198-200°. Nmr absorption at δ 6.86 (S, 1H, ArH); 3.95 (S, 2H, ArCH₂N); 2.51 (S, 3H, N-CH₃); and 2.09 ppm (S, 3H, ArCH₃).

Anal. Calcd. for C₉H₁₄ClNO₂: C, 53.1; H, 6.9; Cl, 17.4; N, 6.9. Found: C, 53.1; H, 6.9; Cl, 17.6; N, 7.0.

3,4-Dihydro-3,7-dimethyl-6-hydroxy-2H-1,3-benzoxazine (free base).

A cold water (250 ml.) solution of 3,4-dihydro-3,7-dimethyl-6-hydroxy-2H-1,3-benzoxazine hydrochloride (Table II) was stirred rapidly with an aqueous solution of 15.0 g. of sodium bicarbonate in 500 ml. of water. The oxazine free base separated immediately as a white crystalline product. (Yield, 17.0 g.) One recrystallization from ethanol gave 11.5 g., m.p. 157-158°. The nmr structure was in complete agreement with the monooxazine structure.

Anal. Calcd. for C₁₀H₁₃NO₂: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.2; N, 8.0.

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