

Preparation of 3,4-Dihydro-2*H*-1,3-benzoxazines (1)

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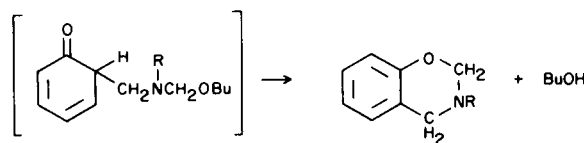
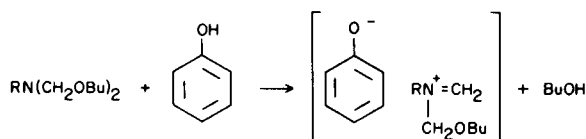
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N,N-Di(butoxymethyl)alkylamines react with phenols under mild conditions to yield substituted 3,4-dihydro-2*H*-1,3-benzoxazines.

The reactions of primary amines and formaldehyde with phenol (3), *p*-substituted phenols (4), and polyhydroxybenzenes (5) were extensively investigated by Burke et al. The procedures of Burke concerning phenol and *p*-substituted phenols led to the formation of substituted 3,4-dihydro-2*H*-1,3-benzoxazines, a new series of compounds. The polyhydroxybenzenes led to poly-*m*-benzoxazines. The possibility that *N,N*-dimethylolamines were the intermediates in these Mannich reactions was suggested by Burke.

Feldman and Wagner (6) utilized preformed methylene-bis-amines in place of formaldehyde and secondary amines in the reaction with 2-naphthol. The formation of piperidylmethyl derivatives of the cresols by the novel condensation of *N*-ethoxypiperidine with *ortho*-, *meta*-, and *para*-cresol was reported by Tseou and Yang (7). This investigation was concerned with the use of preformed *N,N*-di(butoxymethyl)alkylamines in place of primary amines and formaldehyde for the preparation of substituted 3,4-dihydro-2*H*-1,3-benzoxazines.

The mechanism of the hydrolysis of *N*-(alkoxymethyl)-dialkylamines was studied by Stewart and Bradley (8) with the conclusion that it involves the primary formation of a *N,N*-dialkylmethyleniminium ion. Indeed by fortuitous use of the proper amount of hydrochloric acid, the latter investigators were able to isolate *N,N*-diethylmethyleniminium chloride from *N*-(isobutoxymethyl)diethylamine. Similarly Lieberman and Wagner (9) came to the conclusion that the Mannich reaction of 2-naphthol with preformed methylene-bis-amines proceeded *via* a *N,N*-dialkylmethyleniminium ion. The proposed mechanism for the reaction of phenols with *N,N*-di(butoxymethyl)alkylamines is represented by the following equation.

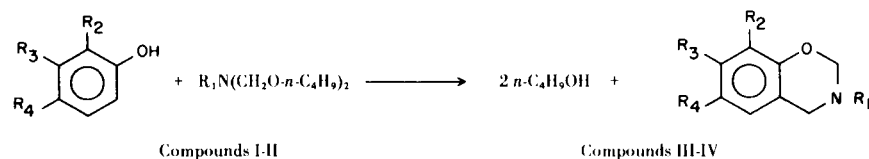


While *N,N*-di(butoxymethyl)methylamine has been known since 1923, no investigations, up to the present, have been made concerning the chemical behavior of these interesting amino ethers. The *N,N*-di(butoxymethyl)-methylamine was prepared by Robinson and Robinson (10) by the reaction of methylamine, formaldehyde and *n*-butyl alcohol in water solution. Through the use of azeotropic removal of water with benzene, the authors were able to obtain higher yields than when the procedure of Robinson and Robinson was used.

The 3,4-dihydro-3,6-disubstituted-2*H*-1,3-benzoxazines are of pharmacological interest, primarily for their antineoplastic activity (11,12). All of the known 3,4-dihydro-2*H*-1,3-benzoxazines show a tuberculostatic action (13), and Rigtterink (14) patented the use of 3,6-dicyclohexyl-3,4-dihydro-2*H*-1,3-benzoxazine as an antibacterial and antifungal agent.

The 1,3-benzoxazines prepared by Burke (4) and all of those prepared and tested pharmacologically were synthesized from *p*-substituted phenols and thus were 3,6-disubstituted. The authors have shown that *ortho*- and *meta*-cresol result in the formation of 3,8- and 3,7-dialkyl substitution, respectively. Only in the case of *m*-cresol would there be possible ambiguity of product structure. As none of the compounds prepared in this investigation have been previously reported in the literature, their structures were assigned by the use of elemental analyses, infrared and nmr spectral studies, and chemical degradation. The physical properties and analytical data are summarized in Tables I and II respectively. It is significant to note that the infrared spectra of the 3-alkyl, 3,6-dialkyl, and 3,7-dialkyl substituted benzoxazines gave two sharp peaks in the 1575-1625 cm^{-1} region, while the 3,8-dialkyl derivatives gave but one at 1597-1600 cm^{-1} .

TABLE I
Substituted 3,4-Dihydro-2*H*-1,3-Benzoxazines



Compound	R ₁	R ₂	R ₃	R ₄	B.P. (mm), °C	Yield, %	n _D ²⁵	d ₄ ²⁵
I	<i>i</i> -C ₃ H ₇				126 (15.0)	73	1.4215	0.8568
II	C ₂ H ₅				96 (4.0)	60	1.4195	0.8579
III	<i>i</i> -C ₃ H ₇	H	H	CH ₃	95 (3.0)	75	1.5208	1.0165
IV	<i>i</i> -C ₃ H ₇	H	CH ₃	H	87 (3.5)	73	1.5206	1.0149
V	<i>i</i> -C ₃ H ₇	CH ₃	H	H	82 (3.5)	63	1.5224	1.0197
VI	<i>i</i> -C ₃ H ₇	H	H	H	75 (4.0)	35	1.5246	1.0366
VII	C ₂ H ₅	H	H	CH ₃	78 (3.0)	71	1.5225	1.0273
VIII	C ₂ H ₅	H	CH ₃	H	81 (3.0)	44	1.5245	1.0291
IX	C ₂ H ₅	CH ₃	H	H	73 (3.0)	54	1.5240	1.0322

TABLE II
Analytical Data

Compound	Formula	Eq. Wt.	Calcd., %			Eq. Wt.	Found, %		
			C	H	N		C	H	N
I	C ₁₃ H ₂₉ NO ₂	231.4	67.46	12.63	6.05	230.2	67.47	12.58	6.12
II	C ₁₂ H ₂₇ NO ₂	217.4	66.28	12.52	6.44	216.5	66.25	12.35	6.32
III	C ₁₂ H ₁₇ NO	191.3	75.33	8.96	7.32	192.4	75.44	8.92	7.28
IV	C ₁₂ H ₁₇ NO	191.3	75.33	8.96	7.32	193.1	75.34	8.94	7.25
V	C ₁₂ H ₁₇ NO	191.3	75.33	8.96	7.32	193.9	75.42	8.96	7.34
VI	C ₁₁ H ₁₅ NO	177.2	74.55	8.53	7.91	176.8	74.39	8.49	7.89
VII	C ₁₁ H ₁₅ NO	177.2	74.55	8.53	7.91	178.3	74.61	8.62	8.00
VIII	C ₁₁ H ₁₅ NO	177.2	74.55	8.53	7.91	178.9	74.49	8.55	7.98
IX	C ₁₁ H ₁₅ NO	177.2	74.55	8.53	7.91	178.4	74.25	8.41	8.15

The reaction of *N,N*-di(butoxymethyl)ethylamine with *m*-cresol could yield either 3,4-dihydro-3-ethyl-7-methyl-2*H*-1,3-benzoxazine or the 3-ethyl-5-methyl isomer. The aforementioned infrared data would tend to support the 3,7-isomer, however not conclusively. To solve this ambiguity, the benzoxazine was hydrolyzed by the procedure of Burke (4) to yield a methyl(ethylaminomethyl)phenol. Reduction of this product with hydrogen in the presence of copper chromite according to the procedure of Caldwell and Thompson (15) yielded 2,5-dimethylphenol. Thus the reaction with *m*-cresol yielded the 3,7-isomer.

The nmr spectra (16) supported the structures for both the amino ethers and the benzoxazines. The significant chemical shifts for the amino ethers were: (N-CH₂-O),

4.42-4.46 δ , singlet, 2H; (O-CH₂-Propyl), 3.50-3.56 δ , triplet, 2H. The significant chemical shifts for the benzoxazines were: (N-CH₂-O), 4.78-4.93 δ , singlet, 2H; (N-CH₂-Aryl), 3.83-3.97 δ , singlet, 2H; (CH₃-Aryl), 2.17-2.20 δ , singlet, 3H.

EXPERIMENTAL

N,N-Di(butoxymethyl)isopropylamine (I).

In a 300 ml. two-necked flask provided with a reflux condenser and a dropping funnel were placed 30.0 g. (1.0 mole) of para-formaldehyde, 75.0 g. (1.01 moles) of *n*-butyl alcohol, and 100 ml. of benzene. The mixture was heated to reflux and 29.5 g. (0.5 mole) of isopropyl amine was added over a twenty minute period. A Barrett type water separator was inserted between the

flask and the reflux condenser and refluxing was continued until the theoretical amount of water was removed azeotropically (approximately 4 hours). Vacuum distillation of the products gave 87.5 g. (76%) of the amino ether. The *N,N*-di(butoxymethyl)ethylamine was prepared in a similar manner (17).

3,4-Dihydro-3-isopropyl-6-methyl-2H-1,3-benzoxazine (III).

In a flask which was provided with a reflux condenser and a magnetic stirring bar was placed 27.0 g. (0.25 mole) of *p*-cresol and 58.0 g. (0.25 mole) of *N,N*-di(butoxymethyl)isopropylamine. The flask and its contents were heated to 100° and the solution was stirred for two hours at this temperature. Vacuum distillation of the resulting solution gave 35.8 g. (75%) of a light yellow colored oil. All of the other 1,3-benzoxazines were prepared by this procedure.

Degradation of 3,4-Dihydro-3-ethyl-7-methyl-2H-1,3-benzoxazine (VIII).

The procedure of Burke (5) for the hydrolysis of 3,4-dihydro-3,6-dialkyl-2H-1,3-benzoxazines was followed to yield the intermediate, 2-(ethylaminomethyl)-5-methylphenol. This latter phenol was hydrogenated in the presence of copper chromite (Adkins) at a pressure of 2800 psig and at 160-170° according to the procedure of Caldwell and Thompson (15). The 2,5-dimethylphenol obtained was shown to be identical by mixed melting point and spectral comparisons with a purified commercial sample (Eastman Kodak Co.). The 3,4-dihydro-3-isopropyl-7-methyl-2H-1,3-benzoxazine was similarly degraded to yield 2,5-dimethylphenol.

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- (16) The nmr spectra were run on the pure liquids, using tetramethylsilane as an internal standard. The authors are indebted to Dr. William Wadsworth, South Dakota State University, for these spectra.
- (17) The use of ethyl alcohol led to the formation of the ethyl homologs, however in lower yield.