A New Aminoalkylation Reaction. Condensation of Phenols with Dihydro-1,3-aroxazines[1]

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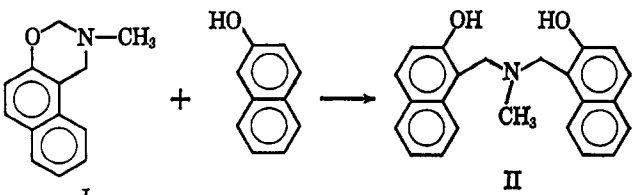
Received May 4, 1965

A number of phenolic compounds were readily aminoalkylated at room temperature by reaction with dihydro-2H-1,3-benzoxazines to give high yields of tertiary amines having two hydroxybenzyl groups attached to nitrogen. This novel aminoalkylation reaction occurred preferentially at the *ortho* position of phenols containing both free *ortho* and *para* positions. Major differences were observed in the behavior of benzoxazines and analogous naphthoxazines in the reaction.

The Mannich reaction has been widely used[4,5] to introduce substituted aminomethyl groups into a variety of organic compounds, and many examples of transaminomethylation with Mannich bases have been observed. Mason and Zief[6] found that N-alkoxymethylamines can also function as aminoalkylating agents as shown below. In a related type of condensation in which the N–C–O linkage was part of a heterocyclic ring structure, it was shown[7] that 1-dibenzylaminomethyl-2-naphthol resulted from the reaction of 2,3-dihydro-2-benzyl-1H-naphth[1,2-*e*][1,3]oxazine with phenylmagnesium bromide. The use of Mannich bases as C-alkylating agents is well known and has been reviewed by Brewster and Eliel[8] and by Hellmann and Opitz.[5]

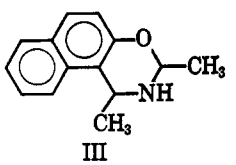
$$R_2NCH_2OC_2H_5 + C_6H_5CH_2MgI \longrightarrow R_2NCH_2CH_2C_6H_5 + C_2H_5MgOI$$

During the course of a study involving the Mannich condensation of phenols with formaldehyde and primary amines, it was found that 2,3-dihydro-2-methyl-1H-naphth[1,2-*e*][1,3]oxazine (I) reacted readily with 2-naphthol at room temperature to give an essentially quantitative yield of N,N-bis(2-hydroxy-1-naphthylmethyl)methylamine (II).



I

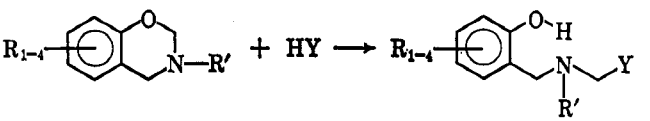
II



III

This novel aminoalkylation reaction was rather unexpected in view of the earlier finding[9] that the related 2,3-dihydro-1,3-dimethyl-1H-naphth[1,2-*e*][1,3]oxazine (III) reacted with 2-naphthol to form a secondary valence addition compound of considerable stability.

Although the present study is concerned with the reaction of dihydro-1,3-benzoxazines with phenols, it was found in exploratory work that the latter could be replaced with a number of different types of compounds (HY) characterized by the presence of a highly nucleophilic carbon or nitrogen atom. These included indoles, carbazole, imides, and aliphatic nitro compounds. The general reaction is shown below.



When a dihydro-1,3-benzoxazine is treated with the phenol from which the benzoxazine was derived, a symmetrical product is obtained as illustrated above in the aminoalkylation of 2-naphthol to give N,N-bis-(2-hydroxy-1-naphthylmethyl)methylamine (II). In all other cases, however, the aminoalkylation of phenols with 1,3-benzoxazines provides an elegant route to tertiary amines having two different hydroxybenzyl substituents.

The study of the aminoalkylation of *o*-cresol was of particular interest since this phenol contains both a free *ortho* and a free *para* position. Reaction of equimolar quantities of 6-chloro-3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (IV) and *o*-cresol led to the isolation of a single aminoalkylation product (V) in 60% yield (Chart I, reaction 10). The same compound was obtained by an alternate aminoalkylation reaction (18) involving the condensation of 3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI) with 4-chloro-2-methylphenol, which has a free *ortho* position but no free *para* position. This indicated that *o*-cresol was aminoalkylated in the *ortho* position. *ortho* aminoalkylation also took place preferentially when 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine (VII) or 3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI) reacted with *o*-cresol (reactions 27 and 19). The alternate syntheses shown in Chart I demonstrate the structure of the products (VIII and IX). Dehalogenation of N,N-bis(5-chloro-2-hydroxy-3-methylbenzyl)methylamine (X) was readily effected with sodium in liquid ammonia to give the desired product (IX) in 88% yield.

Reaction of 3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI) with phenol gave in 69% yield the same product (XI, reaction 17) as that obtained in 96% yield by the dehalogenation of XII showing that amino-

(1) This investigation was supported by Public Health Service Research Grant No. CA-07108-02 from the National Cancer Institution and by Research Grant No. G13120 from the National Science Foundation.

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(4) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959.

(5) H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960.

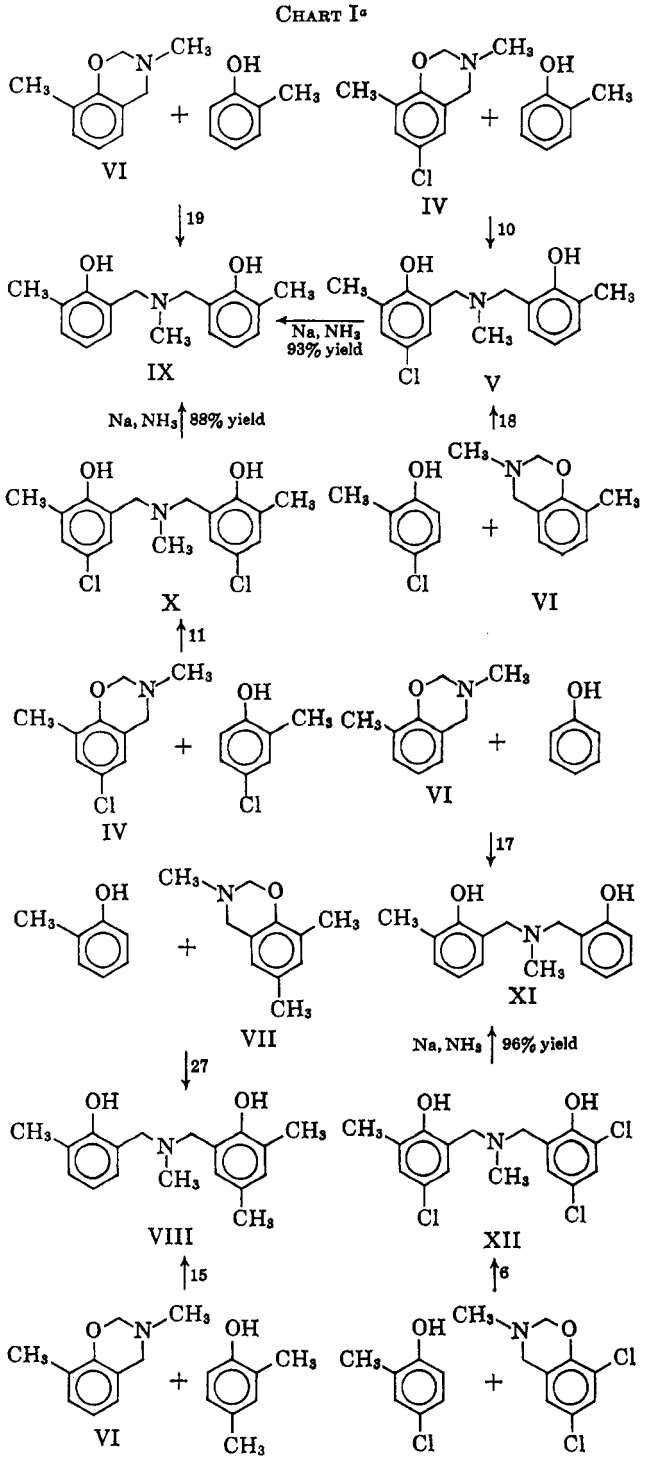
(6) J. P. Mason and M. Zief, *J. Am. Chem. Soc.*, **62**, 1450 (1940).

(7) W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *ibid.*, **74**, 3601 (1952).

(8) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

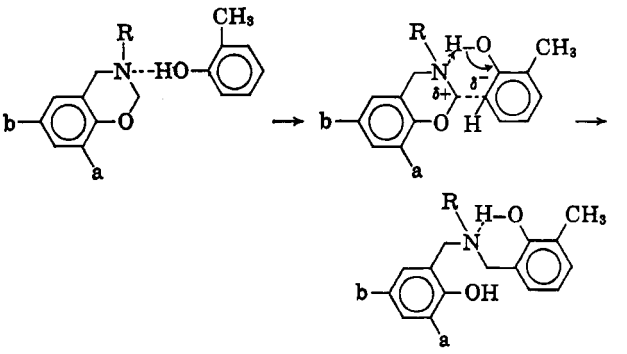
(9) W. J. Burke and R. J. Reynolds, *J. Am. Chem. Soc.*, **76**, 1291 (1954).

CHART I[a]



[a] The reaction numbers refer to those listed in Table I.

alkylation had again occurred at the *ortho* position. In the reaction of a 1,3-dihydrobenzoxazine with a phenol having both a free *ortho* and a free *para* position, it was found in all cases studied that aminoalkylation occurred preferentially at the free *ortho* position. A possible explanation for these results may be related to the fact that the position of the phenolic hydroxyl group to the free *ortho* position puts the latter in a favorable position for reaction as a result of intermolecular hydrogen bonding in the initial step as shown below with *o*-cresol as an example.



Although no *p*-aminoalkylation products were isolated in the examples just given, reaction at the *para* position may have occurred to a small degree since small amounts of unidentified material were isolated in certain instances. Burckhalter and Leib[10] proposed a similar mechanism involving a hydrogen-bonded intermediate as a possible explanation of the preponderant but not exclusive *ortho* substitution of phenols in the Mannich reaction.

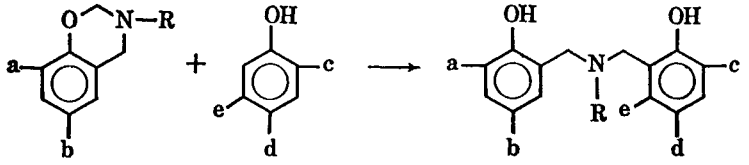
Reaction of 2,4-dimethylphenol with 6,8-dibromo- or 6,8-dichloro-3,4-dihydro-3-methyl-2H-1,3-benzoxazine occurred readily to give good yields (68–93%) of the anticipated *ortho* aminomethylation products. However, replacement of 2,4-dimethylphenol with 2,6-dimethylphenol in the reactions under comparable conditions resulted only in the isolation of starting material and the corresponding 2,6-dihalo-6-methylaminomethylphenols, which resulted from the opening of the benzoxazine ring. However, aminoalkylation in the *para* position was effected in 76% yield by reaction of the N-methylnaphthoxazine (I) with 2,6-dimethylphenol at room temperature over a period of several months. For shorter periods of time extending over several days the recovery of starting material was high. A 39% yield of aminoalkylation product was obtained when the reaction mixture was kept at 80° for 6 days. Substitution of 2,6-dimethylphenol at the 4 position in the condensation was confirmed by 60 Mc./sec. p.m.r. spectra taken during the course of the reaction in $CDCl_3$. As the characteristic NCH_2O methylene absorption at δ 4.78 disappeared, the typical splitting pattern (δ 6.5 to 7.2 centered at 6.90) caused by three adjacent nuclear hydrogens of the 2,6-dimethylphenol became a single peak (δ 6.90) as expected for the equivalent hydrogens remaining at positions 3 and 5.

The behavior of the N-methylnaphthoxazine (I) was also quite different from that encountered with 1,3-benzoxazines of mononuclear phenols in reactions involving mononuclear phenols with a free *ortho* position. In all such instances *ortho* aminomethylation of the phenol did not occur, but, instead, high yields of N,-N-bis(2-hydroxy-1-naphthylmethyl)methylamine (II) were obtained. In view of the results of recent studies[11] on Mannich bases of 2-naphthol, it is presumed that the phenol brought about ring opening of the naphthoxazine to form the corresponding Mannich base which then underwent self condensation to form II.

The possibility of introducing a second substituted-aminomethyl group into a mononuclear phenol was realized in the reaction of 3,4-dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine with *p*-cresol. In this case both

(10) J. H. Burckhalter and R. I. Leib, *J. Org. Chem.*, **26**, 4078 (1961).
(11) W. J. Burke, W. A. Nasutavicus, and C. Weatherbee, *ibid.*, **29**, 407 (1964).

TABLE I.—AMINOALKYLATION OF PHENOLIC COMPOUNDS WITH 3,4-DIHYDRO-2H-1,3-BENZOXAZINES



No.[a]	R	a	b	c	d	e	% yield	Recrystn. solvent	Prod. m.p., °C.	Product formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	% Cl⁻, % N, or neut. equiv. Calcd.	% Cl⁻, % N, or neut. equiv. Found
1	CH_3	Br	Br	H	CH=CH—CH=CH		100	EtOH	174	$C_{19}H_{17}Br_2NO_2$	50.58	50.69	3.79	4.05	450	454
2	CH_3	Br	Br	CH_3	CH_3	H	68[b]	EtOH	140	$C_{17}H_{19}Br_2NO_2$	47.57	47.26	4.46	4.60		
3	CH_3	Cl	Cl	H	CH=CH—CH=CH		88[c]	EtOH	162	$C_{19}H_{17}Cl_2NO_2$	62.99	63.09	4.73	4.66	362	362
3a								MeOH–H_2O	136	$C_{19}H_{17}Cl_2NO_2$·HCl					Cl^-, 8.89	8.41
4	CH_3	Cl	Cl	CH_3	CH_3	CH_3	68[d]	EtOH	145	$C_{18}H_{21}Cl_2NO_2$	61.02	60.71	5.98	5.87	354	353
5	CH_3	Cl	Cl	CH_3	CH_3	H	93	EtOH–H_2O	141	$C_{17}H_{19}Cl_2NO_2$	60.01	59.75	5.63	5.52		
6	CH_3	Cl	Cl	CH_3	Cl	H	97	EtOH	124	$C_{16}H_{16}Cl_3NO_2$	53.28	53.11	4.47	4.51	361	363
7	C_6H_{11}	Cl	Cl	H	CH=CH—CH=CH		90	Diox.–H_2O	154[e]	$C_{24}H_{25}Cl_2NO_2$	66.98	66.76	5.86	6.01		
7a								MeOH–H_2O	205	$C_{24}H_{25}Cl_2NO_2$·HCl					Cl^-, 7.60	7.54
8	$CH_2C_6H_5$	Cl	Cl	H	CH=CH—CH=CH		85	MeOH	141	$C_{25}H_{21}Cl_2NO_2$	68.50	68.41	4.83	4.99		
8a								MeOH–H_2O	145	$C_{25}H_{21}Cl_2NO_2$·HCl					Cl^-, 7.47	7.38
9	CH_3	CH_3	Cl	H	CH=CH—CH=CH		79	EtOH	143	$C_{20}H_{20}ClNO_2$	70.27	70.20	5.90	5.97		
9a								MeOH–H_2O	137	$C_{20}H_{20}ClNO_2$·HCl					Cl^-, 9.37	9.33
10	CH_3	CH_3	Cl	CH_3	H	H	63	EtOH–H_2O	125	$C_{17}H_{20}ClNO_2$	66.76	66.43	6.59	6.59		
11	CH_3	CH_3	Cl	CH_3	Cl	H	29	MeOH	105[f]							
12	C_6H_{11}	CH_3	Cl	H	CH=CH—CH=CH		82	$CHCl_3$	143	$C_{25}H_{28}ClNO_2$	73.24	72.83	6.88	6.64		
12a								MeOH–H_2O	139	$C_{25}H_{28}ClNO_2$·HCl					Cl^-, 7.96	7.97
13	$CH_2C_6H_5$	CH_3	Cl	H	CH=CH—CH=CH		91	EtOH	144	$C_{26}H_{24}ClNO_2$	74.72	74.43	5.79	5.72		
13a								MeOH–H_2O	143	$C_{26}H_{24}ClNO_2$·HCl					Cl^-, 7.80	7.66
14	CH_3	CH_3	H	H	CH=CH—CH=CH		96	EtOH–Me_2CO	146	$C_{20}H_{21}NO_2$	78.14	78.00	6.89	6.89	N, 4.56	4.63
15	CH_3	CH_3	H	CH_3	CH_3	H	87	EtOH	117	$C_{18}H_{23}NO_2$	75.75	75.70	8.12	8.13	285	287
16	CH_3	CH_3	H	H	CH_3	H	85	EtOH–H_2O	110	$C_{17}H_{21}NO_2$	75.24	74.97	7.80	7.70		
17	CH_3	CH_3	H	H	H	H	69	C_6H_6	143	$C_{16}H_{19}NO_2$	74.68	74.90	7.44	7.53	N, 5.44	5.58
18	CH_3	CH_3	H	CH_3	Cl	H	94	EtOH–H_2O	126[g]							
19	CH_3	CH_3	H	CH_3	H	H	60	EtOH	148	$C_{17}H_{21}NO_2$	75.24	74.80	7.80	7.93		
20	CH_3	H	CH_3	H	CH=CH—CH=CH		42	C_6H_6	138	$C_{20}H_{21}NO_2$	78.14	77.87	6.89	6.99	307	308
21	CH_3	H	CH_3	CH_3	CH_3	H	30	*i*-PrOH–H_2O	124[h]							
22	CH_3	H	CH_3	H	CH_3	H	34	EtOH	159	$C_{17}H_{21}NO_2$	75.24	75.05	7.80	7.76	N, 5.17	5.24
23	C_6H_{11}	H	*t*-C_4H_9	H	CH=CH—CH=CH		40	C_6H_6	145	$C_{28}H_{35}NO_2$	80.53	80.86	8.45	8.51		
23a								MeOH–H_2O	135	$C_{28}H_{35}NO_2$·HCl					Cl^-, 7.81	7.56
24	C_6H_{11}	H	*t*-C_4H_9	H	*t*-C_4H_9	H	8[i]	MeOH–C_6H_6	165	$C_{28}H_{41}NO_2$	79.38	79.67	9.76	9.76		
25	CH_3	CH_3	CH_3	H	CH=CH—CH=CH		100[j]	EtOH	134	$C_{21}H_{23}NO_2$	78.47	78.80	7.22	7.52	N, 4.36	4.43
26	CH_3	CH_3	CH_3	CH_3	CH_3	H	97	*i*-PrOH–MeOH	127[k]							
27	CH_3	CH_3	CH_3	CH_3	H	H	43	EtOH	117[l]							
28	CH_3	CH_3	CH_3	H	CH_3	H	72[m]	*i*-PrOH–H_2O	125	$C_{18}H_{23}NO_2$	75.75	75.78	8.12	8.06	N, 4.91	5.10

[a] Numbers followed by "a" (*i.e.*, 3a) designate hydrochlorides of the amines. P.m.r. spectra in trifluoroacetic acid show doublets for the methyl and methylene groups attached to the nitrogen. The free bases show singlets in neutral solvents. [b] Plus 31% starting material. [c] Yield in acetone; 74% yield in methanol 7 times as dilute. [d] Plus 21% starting material. [e] Mixture melting point with neutralization product of 7a was undepressed. [f] Mixture melting point with authentic sample was undepressed.[13] [g] Mixture melting point with product 10 was undepressed. [h] Mixture melting point with product 28 was undepressed. [i] Plus 47% starting material. [j] Yield in methanol after 1 day; yield 99% after 29 days in methanol 10 times as dilute. [k] Mixture melting point with authentic sample was undepressed: W. J. Burke, R. P. Smith, and C. Weatherbee, *J. Am. Chem. Soc.*, **74**, 602 (1952). [l] Mixture melting point with 15 was undepressed. [m] Plus 19% yield of 2,6-bis-substituted product, based on oxazine.

the 2-mono- (72% yield) and the 2,6-diaminoalkylation (19% yield) products were obtained.

Significantly higher yields of *ortho* aminoalkylation products were obtained in the reaction with a given phenolic compound when the dihydro-1,3-benzoxazine was derived from a phenol having an *ortho* substituent. This is shown by a comparison of reactions 20–24 with others in Table I. Under comparable reaction conditions, higher yields of aminoalkylation products were also obtained from mononuclear phenols having one rather than two free active positions (compare reactions 17, 19, and 27 with others in Table I). Benzoxazines with a free *ortho* position and phenols with two free *ortho* positions undergo the aminoalkylation reaction to form tertiary amines still containing free *ortho* positions. Since aminoalkylation has been shown to take place preferentially at the *ortho* position with dihydro-1,3-benzoxazines, the presence of additional highly reactive *ortho* positions in the initial product would possibly lead to a side reaction involving another *ortho* aminoalkylation reaction. Accordingly, this may offer a possible explanation for the above results.

It was apparent from initial studies that the structure of the benzoxazine was an important factor in the condensation. Benzoxazines derived from methylamine were found to be much more reactive than those from benzylamine while those from cyclohexylamine were of intermediate reactivity. For example, under comparable reaction conditions 6-chloro-3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine (IV, Chart I) aminoalkylated 4-chloro-2-methylphenol (reaction 11), while only starting materials were isolated when the analogous benzoxazine derived from cyclohexylamine was employed. As indicated above, 2,3-dihydro-2-methyl-1H-naphth[1,2-*e*][1,3]oxazine (I) reacted with 2-naphthol to give an essentially quantitative yield of the aminoalkylation product II, but with the corresponding naphthoxazines derived from benzylamine, aniline, or *p*-toluidine no aminoalkylation was observed and the starting materials were recovered in high yield. With the naphthoxazine from cyclohexylamine a moderate yield of aminoalkylation product of 2-naphthol was obtained along with recovered starting materials.

Although it is recognized that other factors such as steric effects are involved, the preliminary results obtained indicate a possible correlation between the aminoalkylation aptitude of the benzoxazine, and the basic strength of the amine[12] used in the synthesis of the benzoxazine.

As would be anticipated from the nature of the reaction, the electron density at the active sites on the ring of the phenolic substrate also appeared to be important. For example, 2-naphthol, which is known to have a high electron density at position 1, was readily aminoalkylated by 1,3-benzoxazines derived from mononuclear phenols while 2,4-dichlorophenol was not aminoalkylated under any of the conditions tried. Phenols having only one halogen nuclear substituent did, however, undergo the aminoalkylation reactions. In contrast to the effect of halogen substituents on the phenolic substrate, the 1,3-benzoxazines derived from 2,4-dichloro- and 2,4-dibromophenol were among the most active aminoalkylators uncovered in this work. As was noted earlier,[13] the heterocyclic ring of such benzoxazines is readily cleaved merely by treatment with warm ethanol.

Two new benzoxazines were synthesized for use in this study by the condensation of methylamine and formaldehyde with *o*-cresol and with *p*-cresol.

(12) The following pK_b values were reported by "The Handbook of Chemistry and Physics," 45th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p. D76: methylamine, 3.36; cyclohexylamine, 3.36; benzylamine, 4.63; *p*-toluidine, 8.92; aniline, 9.42. A pK_b value of 4.17 was reported for cyclohexylamine by J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951), and a value of 4.18 by V. Prelog, *Helv. Chim. Acta*, **33**, 365 (1950).

Experimental Section

N,N-Bis(2-hydroxy-1-naphthylmethyl)methylamine (II).—2-Naphthol (1.44 g., 0.01 mole) was added to a solution of 2,3-dihydro-2-methyl-1H-naphth[1,2-*e*][1,3]oxazine (2.00 g., 0.01 mole) in 50 ml. of methanol. After 9 hr. at 25°, the solution was cooled overnight. The resulting solid (2.85 g.) was pulverized, collected, and washed with methanol: m.p. 145–146°. From the filtrate an additional 0.55 g. (m.p. 145–145.5°) was obtained. Yield of product was 99%, m.p. 145–146° after recrystallization from acetone solution by the addition of propanol-2 (lit.[7] m.p. 147–148°); mixture melting point with authentic sample was undepressed.

N,N-Bis(2-hydroxy-1-naphthylmethyl)cyclohexylamine.—The reaction of 2-cyclohexyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine with 2-naphthol in the manner just described for the N-methyl analogy gave a 24% yield of N,N-bis(2-hydroxy-1-naphthylmethyl)cyclohexylamine, m.p. and m.m.p. (with an authentic sample[7]) 120–122°. Starting naphthoxazine was recovered from the filtrate.

N-(2-Hydroxy-3-methylbenzyl)-N-(3,5-dimethyl-2-hydroxybenzyl)methylamine (VIII). A (Table I, 15).—3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI, 1.63 g., 0.01 mole, m.p. 39°) and 2,4-dimethylphenol (1.22 g., 0.01 mole, m.p. 26°) were combined and liquified by slight warming. The mixture, which remained liquid at 25°, became quite viscous within 2 days. Crystallization was induced by addition of 10 ml. of methanol and cooling. To separate unreacted starting material that was present, the product was washed with methanol: m.p. (before and after ethanol recrystallization) and m.m.p. (with product from B) 117°, yield 2.48 g. or 87%.

B (Table I, 27).—3,4-Dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine[14] (VII, 1.77 g., 0.01 mole, m.p. 27°, n^{20} 1.5393) and *o*-cresol (1.08 g., 0.01 mole, m.p. 30°) were liquified and treated as in A at 25° for 2 days. The viscous liquid was crystallized by stirring in methanol, cooling, and seeding. The product was washed with methanol; 0.90 g., m.p. 117°. Ethanol was stirred into the evaporated filtrate to obtain 0.75 g. of additional product, m.p. 118–119°, total yield 1.65 g. or 43%. Starting material was still present in the mother liquor.

N-(2-Hydroxybenzyl)-N-(2-hydroxy-3-methylbenzyl)methylamine (XI). A (Table I, 17).—3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI, 1.63 g., 0.01 mole) and phenol (0.94 g., 0.01 mole) were dissolved in 5 ml. of methanol and left stoppered at 25°. In 15 days crystals had appeared, and the solvent was allowed to evaporate. After being triturated with 5 ml. of methanol and dried, the solid (1.31 g.) melted at 137.5–139°. From the filtrate an additional 0.47 g. of material melting at 130–134° was obtained. The product (69% yield) melted at 141.5–142.5° after recrystallization from benzene.

B.—N-(5-Chloro-2-hydroxy-3-methylbenzyl)-N-(3,5-dichloro-2-hydroxybenzyl)methylamine (XII, 1.25 g., 0.00346 mole) was put in a three-neck 500-ml. flask equipped with stirrer and cooled in a Dry Ice–methanol bath. Anhydrous ammonia and a small steady N_2 stream were passed through until 200 ml. of liquid ammonia solution was present. Sodium was added in small pieces until the blue color of the complex persisted for 5 min. Anhydrous ammonium chloride was added until the blue color left. The solution was stirred overnight as the ammonia was allowed to evaporate slowly in a stream of N_2. Water (100 ml.) was added to the white solid residue, and 6

(13) W. J. Burke, E. L. M. Glennie, and C. Weatherbee, *J. Org. Chem.*, **29**, 909 (1964).

(14) W. H. Massengale, M.S. Thesis, University of Utah, 1961.

N HCl was added until complete solution resulted. Sodium bicarbonate was added to neutralize the hydrochloride salt. The mixture was extracted with two 50-ml. portions of ether and the combined ether layers were dried over $CaCl_2$. The ether was evaporated and the residue was washed with benzene to provide 0.85 g., 96% yield of product, m.p. and m.m.p. (with product from A) 138–139°.

N-(3,5-Dimethyl-4-hydroxybenzyl)-N-(2-hydroxy-1-naphthylmethyl)methylamine. A.—2,3-Dihydro-2-methyl-1H-naphth-[1,2-*e*][1,3]oxazine (I, 2.00 g., 0.01 mole) and 2,6-dimethylphenol (1.23 g., 0.01 mole) were dissolved in 50 ml. of methanol and the solution was left stoppered at room temperature. After several weeks large prisms had grown in clusters. After 8 months they were separated and washed with cold methanol: 1.49 g., m.p. 162.5–163°. The filtrate yielded an additional 0.95 g., m.p. 154–155° undepressed by mixture with first crop, total yield 76%.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.20. Found: C, 78.34; H, 7.04.

B.—The reactants were dissolved in 40 ml. of ethanol in 0.0075 *M* quantities and refluxed gently (80°) for 6 days in a closed system. Evaporation at room temperature gave a thick syrupy residue. This was taken up in ethanol, and water was added nearly to the emulsion point. The crystals which deposited upon stirring were collected and the process was repeated with the filtrate except that methanol was used instead of ethanol. As the methanol was allowed to evaporate, the solid formed slowly in large crystals which were collected and washed with methanol. No more product was obtained from the 1.46 g. of oil remaining. Total product isolated was 0.93 g., 39% yield, m.p. 158–159.5°. Mixture melting point with product from A was undepressed.

N-(2-Hydroxy-5-methylbenzyl)-N-(3,5-dimethyl-2-hydroxybenzyl)methylamine and 2,6-Bis[N-(3,5-dimethyl-2-hydroxybenzyl)-N-methylaminomethyl]-*p*-cresol (Table I, 28).—3,4-Dihydro-3,6,8-trimethyl-2H-1,3-benzoxazine (VII, 1.77 g., 0.01 mole) and *p*-cresol (1.08 g., 0.01 mole) were dissolved in 15 ml. of methanol and left stoppered for 5 days at 25°. Evaporation of the solvent left an oil, which was taken up in 5 ml. of methanol. Addition of a few drops of water led to crystal formation in 4 hr. After 2 weeks from the start of the reaction, the solid was collected and washed with cold methanol to obtain 1.70 g. of material which melted at 85–115°. Fractional recrystallization from methanol separated 0.44 g. which melted at 103–113° and 1.26 g. with m.p. 120–124°. Additional material, 0.79 g., m.p. 122–124°, was obtained from the mother liquor. The fraction melting between 120 and 124° was recrystallized by solution in propanol-2 and addition of water. It showed a correct analysis for N-(2-hydroxy-5-methylbenzy)-N-(3,5-dimethyl-2-hydroxybenzyl)methylamine, 2.05 g., 72% yield, m.p. 124–124.5°.

The 0.44-g. fraction melting between 103 and 113° was recrystallized twice from benzene–methanol: m.p. 121–121.5°. The analysis corresponded to that calculated for the diaminoalkylation product, 2,6-bis[N-(3,5-dimethyl-2-hydroxybenzyl)-N-methylaminomethyl]-*p*-cresol, yield 19% based on the oxazine.

Anal. Calcd. for $C_{29}H_{38}N_2O_3$: C, 75.29; H, 8.28; neut. equiv., 231. Found: C, 75.35; H, 8.42; neut. equiv., 234.

3,4-Dihydro-3,8-dimethyl-2H-1,3-benzoxazine (VI).—Methylamine in 25% aqueous solution (54 ml., 0.40 mole) was added slowly with stirring to a cooled mixture of 37% aqueous formaldehyde (60 ml., 0.80 mole) and 150 ml. of purified 1,4-dioxane. *o*-Cresol (43.2 g., 0.40 mole) in 50 ml. of dioxane was added, and the mixture refluxed for 3 hr. at *ca.* 90°. The solvent was removed under vacuum at 30°, and 35 ml. of 6 *N* NaOH was added to the residue. It was extracted with saturated aqueous Na_2SO_4 *vs.* ether. Removal of the ether in a vacuum rotator left 65.18 g. of liquid product with a characteristic odor. A sample frozen over solid CO_2 melted at 35–38°, m.p. 37.5–38.5° after recrystallization from ethanol. Distillation (b.p. 80–90° at 0.3 mm.) gave 41% recovery.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.59; neut. equiv., 163. Found: C, 73.17; H, 7.99; N, 8.50; neut. equiv., 163.

3,4-Dihydro-3,6-dimethyl-2H-1,3-benzoxazine.—An 80% yield of liquid oxazine was obtained from *p*-cresol and methylamine by reaction under conditions similar to those above, followed by ether–10% KOH extraction. Stirring the liquid with cold propanol-2 induced crystallization. The crystals (m.p. 45–46°) were used to seed the supercooled liquid form. The compound readily sublimed to needles, m.p. 49–49.5°.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; neut. equiv., 163. Found: C, 73.60; H, 7.98; neut. equiv., 163.

The aqueous layer from the KOH extraction was neutralized with $NaHCO_3$. The solid which separated was washed on a filter with several small portions of methanol and then with 1 l. of hot water. The remaining solid (8.48 g., 7% yield, m.p. 156–157.5°) recrystallized from ethanol as prisms, m.p. 159°. It gave an undepressed mixture melting point with an authentic sample of N,N-bis(2-hydroxy-5-methylbenzyl)methylamine (Table I, 22).

Oxaziridines. I. The Irradiation Products of Several Nitrones[1]

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Received April 30, 1965

The properties and reactions of some oxaziridines resulting from the irradiation of the corresponding nitrones are described. The mechanism of the thermal reactions of the oxaziridines as inferred from substituent effects is discussed.

The investigation of the properties and reactions of 2-alkyl-3-aryl- and 2,3-diaryloxaziridines[2] has continued since the publication of the preliminary communication.[3] The N,α-diarylnitrones and corresponding oxaziridines chosen for study include a wide range of substituent effects. In this paper is given a description of the oxaziridines resulting from the irradiation of these nitrones and of end products resulting from further thermal reaction of the unstable 2,3-diaryloxaziridines. In the following papers of this series the photochemical reaction of the nitrones, the kinetics of the oxaziridine thermal reactions, as well as reactions of the oxaziridines with acids, iodine, and light, will be discussed.

The sensitivity of nitrones to light has been known for many years.[4] In 1910, Alessandri[4a] first reported the isolation of benzanilide and hydrolysis products from the irradiation of N,α-diphenylnitrone. During the study of the irradiation products of *o*-nitrostilbenes,[5] several nitrones were prepared and found to be photosensitive in solution. Following the report by

(1) For a short review, see O. Chapman, *Advan. Photochem.*, **1**, 410 (1963).
(2) A review, E. Schmitz, *Advan. Heterocyclic Chem.*, **2**, 83 (1963).
(3) J. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 65 (1958).
(4) (a) L. Alessandri, *Atti accad. nazl. Lincei, Mem. Classe-sci. fis. mat. nat. Sez.*, **19**, **2**, 122 (1910); *Chem. Zentr.*, **2**, 1043 (1910); *Chem. Abstr.*, **5**, 276 (1911); (b) O. Brady and A. McHugh, *J. Chem. Soc.*, **125**, 547 (1924); (c) L. Chardonnens and P. Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949); (d) J. Landquist, *J. Chem. Soc.*, 2830 (1953).
(5) J. Splitter and M. Calvin, *J. Org. Chem.*, **20**, 1086 (1955).