Mono-1,3-benzoxazines from Hydroquinone[1]

W. J. BURKE, CARL WEATHERBEE, HOWARD LAU, GEORGE VAN LEAR, AND GAROLD GOKEN

Departments of Chemistry of the University of Utah, Salt Lake City, Utah, University of Hawaii, Honolulu, Hawaii, and Millikin University, Decatur, Illinois

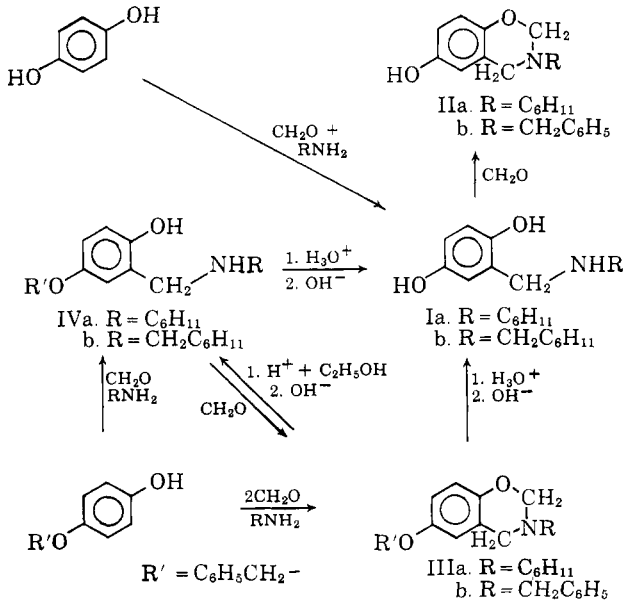
Received August 9, 1962

Mono-1,3-benzoxazines of hydroquinone were prepared by the reaction of 2-substituted aminomethylhydroquinones (I) with formaldehyde. An alternate synthesis involved the preparation of 3-substituted 6-benzyloxy-2*H*-1,3-benzoxazines. The oxazine ring was selectively cleaved to the corresponding Mannich base, which upon treatment with hot aqueous hydrochloric acid gave I.

In connection with a study of the synthesis of benzoxazines from polyhydric phenols,[2,3] it was found that condensation of hydroquinone with formaldehyde and primary amines led to bis- rather than mono-1,3-benzoxazines when the molar ratio of the reactants was that required for the latter or even in the presence of a tenfold excess of hydroquinone.

These results along with the current interest in 1,3-benzoxazines[3-5] and the related hydroquinone nitrogen mustards[6] as potential anti-cancer agents stimulated further work directed toward a feasible synthesis of monobenzoxazines from hydroquinone.

In contrast to results obtained when the amine and formaldehyde were used in a 1:2 molar ratio, reaction of equimolar quantities of hydroquinone, formaldehyde, and cyclohexylamine led to attack at a single position on the aromatic nucleus with the resulting formation of 2-cyclohexylaminomethylhydroquinone (Ia) in 88% yield. Condensation of Ia with formaldehyde occurred readily to give the desired 3,4-dihydro-3-cyclohexyl-6-hydroxy-1,3-2*H*-benzoxazine (IIa) in high yield (90%).



The latter (IIa) was converted to the known[7] 3,4,7,8,9,10-hexahydro-3,8-dicyclohexylbenzo[1,2-*e*,4,5-*e'*]bis-1,3-oxazine (Va).

The analogous substituted 2-aminomethylhydroquinone Mannich bases and corresponding monobenzoxazines were prepared in a similar manner from isopropyl-, *t*-butyl-, α-methylbenzyl-, and *sec*-butylamine. However, the yield of Mannich base with the last compound was very poor and efforts to adapt this synthesis to benzylamine were not successful. These data are summarized in Tables I and II.

In view of these results and the particular interest in benzoxazines derived from benzylamine,[3,4] an alternative route to monobenzoxazines was sought. In exploratory work it was found that the benzyloxy group could be removed easily from 4-benzyloxyphenol by treatment with concentrated hydrochloric acid. Accordingly, a study of the reaction of cyclohexylamine with formaldehyde and *p*-benzyloxyphenol was initiated and led to a high yield (82%) of 3,4-dihydro-3-cyclohexyl-6-benzyloxy-1,3-2*H*-benzoxazine (IIIa). Treatment of IIIa with alcoholic hydrochloric acid, however, gave the salt of 4-benzyloxy-2-cyclohexylaminomethylphenol (IVa), thus showing that under these conditions the oxazine ring was more readily cleaved than the benzyloxy group. It was also found possible to prepare IVa directly from equimolar quantities of 4-benzyloxyphenol, formaldehyde, and cyclohexylamine.

Removal of the benzyloxy group from IVa was readily effected by warming in concentrated hydrochloric acid. The Mannich base (Ia) also was obtained directly from the benzoxazine (IIIa) by a treatment involving heating with concentrated hydrochloric acid in the presence of phenylhydrazine, which removed formaldehyde as it was formed.

The above procedure was also adaptable to the synthesis of the monobenzoxazine from benzylamine. Although other work in the laboratory had shown that benzoxazines derived from benzylamine were appreciably more resistant to acid hydrolysis than those from cyclohexylamine, treatment of 3,4-dihydro-3-benzyl-6-benzyloxy-1,3-2*H*-benzoxazine (IIIb) with alcoholic hydrochloric acid again resulted in the selected cleavage of the oxazine ring rather than the benzyloxy group. The 2-benzylaminomethylhydroquinone (IVb), obtained by removal of the benzyloxy group with hot aqueous hydrochloric acid, was converted into the desired mono-1,3-benzoxazine (IIb) in 92% yield by reac-

(1) This research was facilitated by grants from the Research Corporation, the National Science Foundation, and the National Cancer Institute of the Public Health Service (grant CY-5211).

(2) W. J. Burke and C. Weatherbee, *J. Am. Chem. Soc.*, **72**, 4691 (1950).

(3) W. J. Burke, C. R. Hammer, and C. Weatherbee, *J. Org. Chem.*, **26**, 4403 (1961).

(4) M. E. Kuehne and E. A. Konopka, *J. Med. Pharm. Chem.*, **5**, 257 (1962).

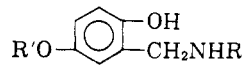
(5) T. Urbanski, Cz. Radrikowski, Z. Ledochowski, and W. Czarnocki, *Nature*, **178**, 1351 (1956).

(6) C. Weatherbee, R. Temple, and W. J. Burke, *J. Org. Chem.*, **21**, 1138 (1956).

(7) Since this work was completed Kuehne and Konopka[4] showed that cyclohexylamine, formaldehyde, and hydroquinone form in addition to Va an isomeric bisbenzoxazine (VIa) in 11% yield. None of the latter was isolated in our work but the 83% yield of Va would preclude the formation of any appreciable amount of VIa.

TABLE I

SUBSTITUTED 2-AMINOMETHYLPHENOLS AND HYDROCHLORIDES



A·HCl
B

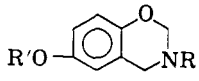
A

Structure	R	R′	Method[a]	M.p., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
A	C_6H_{11}	H	A	172–173[b]	88	$C_{13}H_{19}NO_2$	70.56	70.59	8.65	8.83	6.33	6.17
A	$(CH_3)_2CH$	H	A	160–162[c]	77	$C_{10}H_{15}NO_2$	66.27	66.41	8.34	8.26	7.73	7.94
A	$C_2H_5CHCH_3$	H	A	115–116[d]	2	$C_{11}H_{17}NO_2$	67.66	67.56	8.78	8.35	7.17	7.16
A	$C_6H_5CHCH_3$	H	A	153–153.5[e]	33	$C_{15}H_{17}NO_2$	74.04	74.19	7.04	7.11	5.76	5.50
A	*t*-Octyl	H	A	125–126[f]	67	$C_{15}H_{25}NO_2$	71.65	71.78	10.03	9.96	...	...
A	$C_6H_5CH_2$	H	B	120–121[f]	75	$C_{14}H_{15}NO_2$	73.34	73.53	6.59	6.52	6.11	6.11
A	C_6H_{11}	$C_6H_5CH_2$	B	85–86[g]	81	$C_{20}H_{25}NO_2$	77.13	76.90	8.09	8.03	4.50	4.35
A	$(CH_3)_3C$	$C_6H_5CH_2$	B	70–71[c]	77	$C_{18}H_{23}NO_2$	75.75	75.76	8.12	8.06	...	...
A	$C_6H_5CH_2$	$C_6H_5CH_2$	B	90–91[c]	90	$C_{21}H_{21}NO_2$	78.78	78.71	6.62	6.69	...	...
B	$(CH_3)_3C$	H	C	213–214[h]	61	$C_{11}H_{18}ClNO_2$	57.02	57.31	7.83	7.71	...	...
B	*t*-Octyl	H	A	242–244[i]	35	$C_{15}H_{26}ClNO_2$	62.60	62.66	9.10	8.94	...	...
B	$C_6H_5CH_2$	H	B	176–177[j]	75	$C_{14}H_{16}ClNO_2$	63.27	63.49	6.06	5.90	...	...
B	C_6H_{11}	$C_6H_5CH_2$	B	203–205[k]	98	$C_{20}H_{26}ClNO_2$	69.04	68.60	7.53	7.72	4.03	3.85
B	$(CH_3)_3C$	$C_6H_5CH_2$	B	233–234[k]	65	$C_{18}H_{24}ClNO_2$	67.17	67.11	7.52	7.34	...	...
B	$C_6H_5CH_2$	$C_6H_5CH_2$	B	170–171[c]	90	$C_{21}H_{22}ClNO_2$[l]	70.87	70.46	6.23	6.44	3.94	4.02

[a] Method of preparation: A, directly from condensation of 4-substituted phenol with equimolar quantities of amine and formaldehyde; B, by hydrolysis of corresponding oxazine; C, by hydrolysis of corresponding 4-benzyloxy Mannich base. [b] Recrystallized from 1,4-dioxane–ethanol (1:1). [c] Recrystallized from methanol. [d] Recrystallized from chloroform. [e] Recrystallized from toluene. [f] Recrystallized from benzene. [g] Recrystallized from *t*-butyl alcohol. [h] Recrystallized from ethyl acetate. [i] Recrystallized from ethyl acetate–ethanol (6:1). [j] Recrystallized from *i*-propyl alcohol. [k] Recrystallized from ethanol. [l] Calcd.: Cl, 9.97. Found: Cl, 9.95.

TABLE II

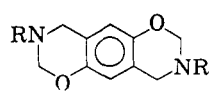
3,4-DIHYDRO-3-ALKYL-6-SUBSTITUTED 2*H*-1,3-BENZOXAZINES



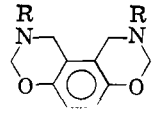
R	R′	M.p., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
C_6H_{11}	H	133–134[a]	90	$C_{14}H_{19}NO_2$	72.07	72.03	8.21	7.97	...	...
$(CH_3)_2CH$	H	145–146[b]	34	$C_{11}H_{15}NO_2$	68.37	68.15	7.82	7.79	7.25	.10
$C_6H_5CHCH_3$	H	143–144[c]	53	$C_{16}H_{17}NO_2$	75.27	74.57	6.71	6.57	...	...
$CH_3CHC_2H_5$	H	64–65[d]	12	$C_{12}H_{17}NO_2$	...	...	...	...	6.76	6.80
$(CH_3)_3C$	H	127–128[e]	51	$C_{12}H_{17}NO_2$	69.54	69.85	8.27	8.12	...	...
$C_6H_5CH_2$	H	105–106[f]	92	$C_{15}H_{15}NO_2$	74.66	75.04	6.26	6.44	5.80	5.79
C_6H_{11}	$C_6H_5CH_2$	69–70[b]	82	$C_{21}H_{25}NO_2$	77.98	77.79	7.79	7.79	4.33	4.49
$(CH_3)_3C$	$C_6H_5CH_2$	59–60[g]	59	$C_{19}H_{23}NO_2$	76.73	76.88	7.80	7.85	...	...
$C_6H_5CH_2$	$C_6H_5CH_2$	86–87[h]	61	$C_{22}H_{21}NO_2$	79.73	79.68	6.39	6.29	4.22	4.11

[a] Recrystallized from ethyl acetate–ethanol (1:1). [b] Recrystallized from ethanol. [c] Recrystallized from chloroform. [d] Recrystallized from *t*-butyl alcohol. [e] Recrystallized from benzene. [f] Recrystallized from carbon tetrachloride. [g] Recrystallized from methanol. [h] Recrystallized from methanol–ethanol (2:5).

tion with formaldehyde. Reaction of the monobenzoxazine (IIb) with benzylamine and formaldehyde gave the two isomeric bis-1,3-benzoxazines (Vb and VIb) reported earlier[3] by direct synthesis from hydroquinone.



Va. R = C_6H_{11}
b. R = $CH_2C_6H_5$



VIa. R = C_6H_{11}
b. R = $CH_2C_6H_5$

Experimental[8]

2-Cyclohexylaminomethylhydroquinone (Ia) from Hydroquinone.—To a cooled solution of 9.9 g. (0.1 mole) of cyclohexylamine in 50 ml. of methanol was added dropwise with shaking 7.5 ml. of 37% formaldehyde (0.1 mole). Then 11 g. (0.1 mole) of hydroquinone dissolved in 50 ml. of methanol was added and the mixture kept at room temperature for 24 hr. The solvents from the dark reaction mixture were removed by vacuum distillation. The resulting brownish-white solid was treated with 40 ml. of water and 10 ml. of concentrated hydrochloric acid (0.12 mole) and extracted with one 40-ml. portion and three 25-ml. portions of ethyl ether. The combined ether extracts were washed with 5 ml. of water. Upon evaporation of the ether 0.76 g. of solid was recovered; m.p. and m.m.p. with hydroquinone, 170–171°. The aqueous extract was treated with 12 ml. of 2-aminoethanol (0.2 mole) and upon standing a brown solid separated (18.1 g., 88% yield); m.p. 172–173° after two recrystallizations from a 1:1 mixture of 1,4-dioxane–ethanol.

3,4-Dihydro-3-cyclohexyl-6-hydroxy-2*H*-1,3-benzoxazine (IIa).—To a solution of 6.63 g. (0.03 mole) of cyclohexylaminomethylhydroquinone in 35 ml. of cold methanol was added 2.25 ml. of 37% aqueous formaldehyde (0.03 mole) in 10 ml. of methanol. The mixture was shaken for 20 min. and then allowed to stand at room temperature for 48 hr. The solvents were removed by vacuum distillation. The resulting brownish-white solid was recrystallized from ethyl acetate; 5.7 g. (81% yield), m.p. 133–134°.

3,8-Dicyclohexyl-2,3,4,7,8,9-hexahydrobenzo[1,2-*e*,4,5-*e*′]bis-1,3-oxazine (Va). To 1.5 ml. of 37% aqueous formaldehyde (0.02 mole) in 20 ml. of cooled methanol was added dropwise 1.15 ml. (0.01 mole) of cyclohexylamine dissolved in 10 ml. of methanol. Then 2.33 g. (0.01 mole) of IIa dissolved in 30 ml. of methanol

(8) All melting points are uncorrected.

was added. The flask was stoppered, shaken well for several minutes, and kept at room temperature for 24 hr. The solvents were removed by vacuum distillation. The remaining dark liquid was dissolved in 20 ml. of hot ethanol. Upon cooling 2.97 g. (83% yield) of a white solid was obtained, m.p. 158–160°. Upon recrystallization from ethyl acetate, the m.p. was 161–162° (lit.,[2] m.p. 161–162°).

3,4-Dihydro-3-cyclohexyl-6-benzyloxy-2*H*-1,3-benzoxazine (IIIa).—Cyclohexylamine (11.5 ml., 0.1 mole) was added dropwise with stirring to 15 ml. of 37% aqueous formaldehyde (0.2 mole) dissolved in 100 ml. of methanol at 15 to 18°. 4-Benzyloxyphenol (20 g., 0.1 mole) was added and the resulting solution kept at room temperature for 24 hr. Upon removing the solvents, a sticky white solid remained. It was treated with a mixture of 50 ml. of ether and 40 ml. of water containing 6 g. of sodium hydroxide. The ether layer was separated. The aqueous portion was further extracted with three 20-ml. portions of ether. The ether extracts were combined. The aqueous portion was acidified with dilute hydrochloric acid, and 11.8 g. of white solid, m.p. 119–121°, separated. A mixture melting point with 4-benzyloxyphenol showed no depression. The residue obtained by removal of solvent from the combined ether extracts was dissolved in 25 ml. of hot 95% ethanol. Upon cooling 11.9 g. of white solid, m.p. 66–69°, was obtained. After three recrystallizations from 95% ethanol the product melted at 69–70°; 82% yield, based upon consumed 4-benzyloxyphenol.

2-Cyclohexylaminomethyl-4-benzyloxyphenol (IVa).—To the benzoxazine IIIa (9.69 g., 0.03 mole) in 20 ml. of 95% ethanol was added 3 ml. of concentrated hydrochloric acid. The flask was warmed slowly on a water bath until 5 ml. of ethanol distilled. Then the flask was cooled and an additional 1.5 ml. of concentrated hydrochloric acid was added. The mixture was again distilled until 3 ml. of ethanol passed over. The undistilled solution gradually deposited 9.6 g. of white product, m.p. 190–197°. After three recrystallizations from 95% ethanol the *hydrochloride* melted at 203–205°.

A 4.8-g. sample of the hydrochloride was placed in a separatory funnel with 50 ml. of water. After adding 4 ml. of 2-aminoethanol with shaking, the mixture was extracted with four 25-ml. portions of ether. Evaporation of the ether left 4.6 g. brownish-white solid, m.p. 83–85°; after three recrystallizations from *t*-butyl alcohol, m.p. 85–86°. A mixture melting point with a sample prepared directly by interacting equimolar quantities of cyclohexylamine, formaldehyde, and 4-benzyloxyphenol gave no depression.

2-Cyclohexylaminomethylhydroquinone (Ia) from IVa Hydrochloride.—A 20.4-g. sample of IVa hydrochloride (0.059 mole) in 55 ml. of concentrated hydrochloric acid was refluxed for 1 hr. After cooling, an additional 30 ml. of concentrated hydrochloric acid was added and the mixture warmed under reflux for 2 hr. at 90 to 95°. The resulting light brown solid was removed by filtration, washed with six 20-ml. portions of ether, and dissolved in hot water. After cooling, 2-aminoethanol was added to the aqueous solution until no further solid (7.6 g.) separated; m.p. 169–171° after recrystallization from ethanol–petroleum ether (1:1). The melting point was not depressed by mixing with Ia prepared directly from hydroquinone. An additional 1.3 g. was obtained by adding 2-aminoethanol to the original filtrate after separation of the ether; 68% total yield.

Cyclohexylaminomethylhydroquinone (Ia) from 3-Cyclohexyl-6-benzyloxy-3,4-dihydro-2*H*-1,3-benzoxazine (IIIa).—The benzoxazine IIIa (1.0 g., 0.003 mole) and 0.5 g. of phenylhydrazine were dissolved in 15 ml. of 37% hydrochloric acid and 15 ml. of water. The mixture was heated under reflux at 75° for 5 hr. and then filtered. The resulting filtrate was extracted with ether. Upon evaporation of the ether a clear liquid remained, b.p. 179–181°/754 mm. The b.p. of benzyl chloride taken simultaneously was 180–181°. The aqueous layer was cooled to 0° and 2 ml. of 2-aminoethanol was added dropwise. The cloudy mixture was extracted with ether and upon evaporation of the ether layers 0.4 g. of a white solid was obtained, m.p. 168–170°; yield, 61%. The solid was recrystallized from methanol–benzene (19:1); m.p. and m.m.p. with an authentic sample of Ia, 172–173°.

Substitution in the Hydantoin Ring. III.[1] Halogenation[2]

RENÉE A. CORRAL AND ORFEO O. ORAZI

Facultad de Química y Farmacia, Universidad Nacional de La Plata, La Plata, Argentina

Received July 10, 1962

On the basis of competitive reactions between 1,5,5- and 3,5,5-trimethylhydantoins added to the study of transfer of positive halogen, it has been concluded that halogenation of the hydantoin ring, with several agents, occurs preferentially in position 3. Monohalogenation of nitrogen-unsubstituted hydantoins leads in all cases to the 1-halo derivative as a result of the intermediate formation of the 1,3-dihalo compound (isolated from various reactions) and later transfer of the halogen atom on N_3 position to another hydantoin molecule.

By substitution reactions in the hydantoin itself or in its derivatives, N-mono- and N,N′-dihalogenated compounds have been obtained corresponding to all halogen excepting fluorine.

The N-chloro derivatives, known for some time, have been obtained by utilizing different chlorinating agents: sodium hypochlorite, hypochlorous acid generated in the reaction medium starting from the former, or methyl N,N-dichlorocarbamate[3]; by passing chlorine through a water solution of the hydantoin in either neutral or alkaline medium,[4–6] and finally by transfer of halogen in reactions between hydantoins and their dihalo derivatives.[7]

The preparation and use of the bromo derivatives of a number of hydantoins were more recently described by this laboratory,[8] employing bromine in an alkaline solution of hydantoins for these preparations.

In obtaining the iodinated compounds, which were introduced as halogenating agents for the aromatic nucleus, iodine and the silver derivative of the hydantoins were employed for the N-monoiodo compounds, while for N,N′-diiodo-5,5-dimethylhydantoin, a solution of the hydantoin in alkaline aqueous medium was made to react[9] with iodine monochloride.

As regards the structure of the products which result from monohalogenation, very limited data were available in the literature which could allow a decision as to the possibilities of placing the halogen in position N_1 or N_3. Products from chlorination by means of sodium hypochlorite have been formulated as N_1 compounds, in support of which are their solubility in alkali[3]; as re-

(1) Part II, R. Jeandupeux, O. O. Orazi, and R. A. Corral, *J. Org. Chem.*, **27**, 2520 (1962).

(2) This work was supported by a grant from the Consejo Nacional de Investigaciones Científicas y Técnicas.

(3) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

(4) H. Biltz and K. Slotta, *J. prakt. Chem.*, **113**, 233 (1926).

(5) A. O. Rogers, U.S. Patent 2,392,505; *Chem. Abstr.*, **40**, 2468 (1946).

(6) O. O. Orazi, J. F. Salellas, M. E. Fondovila, R. A. Corral, N. M. Mercere, and E. R. de Alvarez, *Anales asoc. quím. Arg.*, **40**, 61 (1952).

(7) P. La F. Magill, U. S. Patent 2,430,233; *Chem. Abstr.*, **42**, 2278 (1948).

(8)(a) O. O. Orazi and J. Meseri, *Anales asoc. quím. Arg.*, **37**, 192 (1949); (b) O. O. Orazi, M. E. Fondovila, and R. A. Corral, *ibid.*, **40**, 109 (1952); (c) R. A. Corral, O. O. Orazi, and J. D. Bonafede, *ibid.*, **45**, 151 (1957); and references therein quoted.

(9) R. A. Corral and O. O. Orazi, *ibid.*, **44**, 11 (1956).