[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

Bis-*m*-oxazines from Hydroquinone[1]

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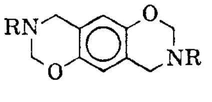
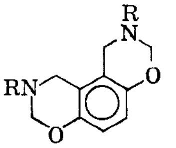
Several new bis-*m*-oxazines were prepared by the condensation of hydroquinone, formaldehyde, and representative primary amines in a molar ratio of 1:4:2. With benzylamine two isomeric products, 3,8-dibenzyl-2,3,4,7,8,9-hexahydrobenzo[1,2-*e*,4,5-*e'*]bis-*m*-oxazine (Ic) and 2,9-dibenzyl-1,2,3,8,9,10-hexahydrobenzo[2,1-*e*,3,4-*e'*]bis-*m*-oxazine (IIa), were obtained. Analogous results were obtained with α-methylbenzylamine but only one product, corresponding to Ic, was isolated when other amines were employed. The bis-*m*-oxazines were characterized and converted to the corresponding Mannich bases.

Phenolic compounds having at least one free *ortho* position have been shown to react with formaldehyde and primary amines to yield *m*-benzoxazines, bis(2-hydroxybenzyl)amines or Mannich bases depending upon condensation conditions and the specific reactants employed.[2] Poly- but not mono-*m*-benzoxazines were readily obtained when compounds having more than one phenolic group on a single benzene ring were employed.[3]

In a study utilizing hydroquinone in this type of condensation, the possibility of obtaining two isomeric bis-*m*-benzoxazines was pointed out.[3] The single benzoxazine isolated with methylamine was shown to correspond to the structure Ia. Since only one product was isolated when cyclohexylamine was used, it was presumed to have an analogous structure (Ib).



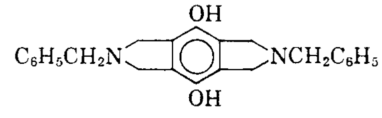
Ia. R = CH_3
b. R = C_6H_{11}
c. R = $C_6H_5CH_2$
d. R = $C_6H_5(CH_3)CH$
e. R = $CH_2{=}CHCH_2$
f. R = $HOCH_2CH_2$
g. R = $(CH_3)_3C$



IIa. R = $C_6H_5CH_2$
b. R = $C_6H_5(CH_3)CH$

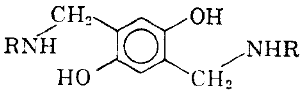
Further work in this laboratory showed that reaction of hydroquinone with formaldehyde and benzylamine in a molar ratio of 1:4:2 yielded two isomeric products, one of which melted at 143–144° and the other at 202–203°. The present study was undertaken to elucidate the structure of these compounds and to determine the effect of utilizing other amines in the reaction.

In addition to the benzoxazine structures Ic and IIa, the isomeric benzodipyrrole (III) was also considered as a possible product. The formation of III with a primary amine would be analogous to the well known synthesis of phenolic Mannich bases from secondary amines. Neither of the two isomers from benzylamine gave positive tests with ferric chloride or with Tollen's reagent. Moreover, treatment of an alcoholic solution of either of the two isomers with 2,4-dinitrophenylhydrazine sulfate quantitatively removed, as the corresponding 2,4-dinitrophenylhydrazone, two moles of formaldehyde from each mole of the original compound. This behavior is consistent with a bis-*m*-oxazine but not with a benzopyrrole type of structure.



III

Reaction of the two isomers from the benzylamine reaction with aqueous hydrochloric acid resulted in the elimination of formaldehyde and the formation of isomeric hydrochlorides in high yields. The free bases were obtained by treatment with sodium bicarbonate. The compound (86% yield) derived in this manner from the higher melting benzoxazine was shown to be identical with the Mannich base (IVa) obtained from the amine exchange reaction[4] (72% yield) of 2,5-bis(dimethylaminomethyl)hydroquinone[5] with benzylamine. Accordingly, the higher melting benzoxazine is 3,8-dibenzyl-2,3,4, 7, 8, 9-hexahydrobenzo[1,2-*e*, 4, 5-*e'*]-bis-*m*-benzoxazine (Ic).



IVa. R = $C_6H_5CH_2$
b. R = $C_6H_5(CH_3)CH$
c. R = C_6H_{11}

When the Mannich base hydrochloride derived from the lower melting benzoxazine was treated with morpholine, the product (90% yield) gave an

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[1] This investigation was supported in part by a research grant CY-5211 from the National Cancer Institute of the Public Health Service.

[2] W. J. Burke, *J. Am. Chem. Soc.*, **71**, 609 (1949); W. J. Burke, R. P. Smith, and C. Weatherbee, *J. Am. Chem. Soc.*, **74**, 602 (1952); W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *J. Am. Chem. Soc.*, **74**, 3601 (1952).

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

[4] H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948) and **71**, 1058 (1949).

[5] W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

analysis required for a bis(morpholinomethyl)hydroquinone but differed from that of the known 2,5-bis(morpholinomethyl) compound.[6] Hydrogenolysis of the amine exchange product with copper-chromium oxide followed by oxidation gave 2,3-dimethylbenzoquinone. The latter was further characterized by reduction to 2,3-dimethylhydroquinone. Thus the isomer melting at 143–144° was 2,9-dibenzyl-1,2,3,8,9,10-hexahydrobenzo[2,1-*e*,3,4-*e*′]bis-*m*-oxazine (IIa).

The effect of reaction conditions on the yield of the bis-*m*-oxazines (Ic and IIa) was studied. When an aqueous dioxane solution containing hydroquinone, formaldehyde, and benzylamine in a molar ratio of 1:4:2 was heated under reflux for two hours a 72% yield of Ic and 12% of IIa were obtained. Reduction of the reflux time to thirty minutes lowered the yield of Ic to 12% but the yield of the lower melting product (IIa) remained about constant (11%). When the reaction mixture was kept at room temperature for nineteen days relatively low yields of Ic (42%) and IIa (5%) were obtained. Use of 1,3,5-tribenzylhexahydro-*s*-triazine as a source of benzylamine and part of the formaldehyde resulted in a 72% yield of Ic and 11% of IIa.

When α-methylbenzylamine reacted with hydroquinone and formaldehyde in proportions calculated for bisbenzoxazine formation, two products were also obtained. Both of these had analyses for bis-*m*-oxazines (83% over-all yield). Hydrolysis of the higher melting isomer (191–192°) gave the corresponding Mannich base (IVb) hydrochloride (94% yield). This was converted by amine interchange to 2,5-bis(morpholinomethyl)hydroquinone. Accordingly, the higher melting product obtained in 31% yield is 3,8-di-α-methylbenzyl-2,3,4,7,8,9-hexahydrobenzo[1,2-*e*,4,5-*e*′]bis-*m*-oxazine (Id). In an analogous manner the lower melting (176–177°) benzoxazine was converted to 2,3-bis(morpholinomethyl)hydroquinone and thus shown to be 2,9-di - α - methylbenzyl - 1,2,3,8,9,10 - hexahydrobenzo[2,1-*e*,3,4-*e*′]bis-*m*-oxazine (IIb).

Further study of the hydroquinone-formaldehyde-cyclohexylamine condensation (molar ratio 1:4:2) confirmed earlier[3] findings in that only one bis-*m*-oxazine was isolated. Acidic hydrolysis of this compound gave a Mannich base[3] (94% yield) which was shown to be identical with that (IVc) obtained by the amine exchange reaction of cyclohexylamine with 2,5-bis(dimethylaminomethyl)hydroquinone. In addition, the Mannich base IVc was converted to 2,5-bis(morpholinomethyl)hydroquinone (74% yield) by amine interchange with morpholine. This work, accordingly, confirmed the earlier tentatively assigned structure (Ib) for the bis-*m*-oxazine.

Additional evidence for the structure Ib was obtained by reaction of the bis-*m*-oxazine from cyclohexylamine with formic acid in a modification of the method of Icke and Wisegarver[7] for the methylation of primary and secondary amines with formic acid and formaldehyde. In this way the oxazine ring was cleaved to yield the formaldehyde required for the methylation step. The product (80% yield) was identical with the 2,5-bis(*N*-cyclohexyl - *N* - methylaminomethyl)hydroquinone obtained in 76% yield by amine interchange of 2,5 - (dimethylaminomethyl)hydroquinone with *N*-methylcyclohexylamine. The same compound (66% yield) resulted from the direct condensation of hydroquinone, formaldehyde and *N*-methylcyclohexylamine in a molar ratio of 1:2:2.

A similar formic acid treatment of the symmetrical bis-*m*-oxazine from benzylamine (Ic) led to the corresponding 2,5-bis-(*N*-benzyl-*N*-methylaminomethyl)hydroquinone in 94% yield. Hydrogenolysis of this product in the presence of copper–chromium oxide followed by oxidation gave 2,5-dimethylbenzoquinone (7% yield). The very low yield of this compound might be explained on the basis of studies by Baltzly and Buck.[8] They found that in the competitive hydrogenolysis of tertiary dibenzylamines with only one substituted benzyl group, the unsubstituted benzyl moiety was generally eliminated from the remainder of the molecule. They also showed that benzyl groups were not generally removed from secondary amines under conditions normally employed in hydrogenolysis reactions.

It was noted that benzyl- and α-methylbenzylamines, each of which gave two bis-*m*-oxazines with hydroquinone and formaldehyde, are appreciably less basic than methyl- or cyclohexylamines, from which only the symmetrical bis-*m*-oxazine was isolated. This was of interest since work in progress in this laboratory indicates the importance of the basic strength of the amine in determining the course of related condensations. Accordingly, it appeared desirable to study reactions employing allylamine and 2-aminoethanol since they are comparable to benzylamine in basicity.

Use of allylamine led to an 82% yield of the symmetrical bis-*m*-oxazine (Ie) as the sole product isolated. The structure of this compound was deduced by its conversion to 2,5-bis(morpholinomethyl)hydroquinone by hydrolysis to the Mannich base followed by amine exchange with morpholine. In the same manner it was shown the only product (53% yield) isolated from the condensation involving 2-aminoethanol was the symmetrical bis-*m*-oxazine (If).

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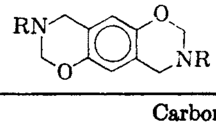
[6] W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 2354 (1939).

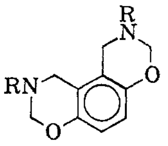
[7] R. N. Icke and B. B. Wisegarver, *Org. Syntheses*, **25**, 89 (1945).

[8] R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **65**, 1984 (1943).

TABLE I

3,8-DISUBSTITUTED 2,3,4,7,8,9-HEXAHYDROBENZO[1,2-*e*,4,5-*e'*]BIS-*m*-OXAZINES

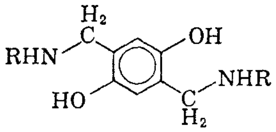


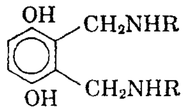
R	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_6H_5CH_2$	72[a]	202–203	$C_{24}H_{24}N_2O_2$	77.39	77.41	6.49	6.42	7.52	7.36
$C_6H_5(CH_3)CH$	31[b]	191–192	$C_{26}H_{28}N_2O_2$	77.97	78.49	7.05	6.77		
$CH_2{=}CHCH_2$	82	139–140	$C_{16}H_{20}N_2O_2$	70.56	70.61	7.40	7.10		
$HOCH_2CH_2$	53	159–160	$C_{14}H_{20}N_2O_4$	59.98	59.94	7.19	7.17		
$(CH_3)_3C$	76	173–174	$C_{18}H_{28}N_2O_2$	71.02	71.58	9.27	9.43		
2,9-DISUBSTITUTED 1,2,3,8,9,10-HEXAHYDROBENZO[2,1-*e*,3,4-*e'*]BIS-*m*-OXAZINES 									
$C_6H_5CH_2$	12[a]	143–144	$C_{24}H_{24}N_2O_2$	77.39	77.56	6.49	6.25	7.52	7.42
$C_6H_5(CH_3)CH$	27[b]	176–177	$C_{26}H_{28}N_2O_2$	77.97	78.03	7.05	6.99		

[a] The combined yield of the two isomers was 93%. [b] 83%.

TABLE II

2,5-BIS(SUBSTITUTED AMINOMETHYL)HYDROQUINONES



R	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$C_6H_5CH_2$	86	160–161	$C_{22}H_{24}N_2O_2$	75.83	75.94	6.94	6.87		
$C_6H_5(CH_3)CH$	94	224–225	$C_{24}H_{30}Cl_2N_2O_2$[a]					15.78	15.83
$CH_2{=}CHCH_2$	93	211–213	$C_{14}H_{22}Cl_2N_2O_2$[a]					22.07	22.16
$HOCH_2CH_2$	87	208–209	$C_{12}H_{22}Cl_2N_2O_4$[a]					21.54	21.11
$(CH_3)_3C$	84	171–172	$C_{16}H_{28}N_2O_2$[b]	68.53	68.33	10.06	9.79		
C_6H_{11}	95	284–285	$C_{20}H_{34}Cl_2N_2O_2$[a]					17.49	17.53
2,3-BIS(SUBSTITUTED AMINOMETHYL)HYDROQUINONES 									
$C_6H_5CH_2$	83	132–133	$C_{22}H_{24}N_2O_2$	75.83	76.37	6.94	7.35		
$C_6H_5(CH_3)CH$	89	182–184	$C_{24}H_{30}Cl_2N_2O_2$[a]					15.78	15.52

[a] Isolated and characterized as the dihydrochloride. [b] The hydrochloride melted at 252–256°. *Anal.* Calcd. for $C_{16}H_{30}Cl_2N_2O_2$: Cl, 20.07. Found: Cl, 20.14.

A consideration of steric factors made it of interest to study the condensation of *t*-butylamine with formaldehyde and hydroquinone under conditions favorable to bis-*m*-oxazine formation. Again the only product (76% yield) isolated was the symmetrical bis-*m*-oxazine (Ig). This structure was assigned on the basis of the conversion of the product to the Mannich base, which then yielded 2,5-bis(morpholinomethyl)hydroquinone by reaction with morpholine.

It is, of course, possible that minor amounts of the unsymmetrical bis-*m*-oxazines were formed in those condensations in which only the symmetrical isomer was isolated. In the two instances in which the two isomeric pairs of bis-*m*-oxazines were obtained, the symmetrical product was higher melting and less soluble and thus more readily isolable.

Several of the bis-*m*-oxazines and Mannich bases reported in this study are being evaluated as potential anticancer agents at the Cancer Chemotherapy Center of the National Institutes of Health.

EXPERIMENTAL[9]

3,8-Dibenzyl-2,3,4,7,8,9-hexahydrobenzo[1,2-e,4,5-e']bis-m-oxazine (Ic) *and 2,9-dibenzyl-1,2,3,8,9,10-hexahydrobenzo-[2,1-e,3,4-e']bis-m-oxazine* (IIa). Benzylamine (24.0 ml., 0.22 mole) was added dropwise to a cooled solution of 33.0 ml. of 37% aqueous formaldehyde (0.44 mole) in 50 ml. of dioxane. Hydroquinone (11.0 g., 0.10 mole) was added, and the resulting solution refluxed for 2 hr., during which time a product separated. The mixture was cooled and the solid (34.6 g., 93% total yield) removed by filtration. The product was placed in 400 ml. of boiling methanol and the mixture filtered. The residue Ic (26.8 g., 72% yield) melted at 194–199°; m.p. 202–203° after recrystallization from benzene. The filtrate was cooled and the crystals of IIa (4.5 g., 12% yield, m.p. 135–138°) removed by filtration; m.p. 143–144° after recrystallization from methanol.

In another experiment hydroquinone (11.0 g., 0.10 mole) and 23.4 g. of 1,3,5-tribenzylhexahydro-*s*-triazine (0.067 mole) were dissolved in a solution of 15 ml. of 37% aqueous formaldehyde (0.20 mole) in 40 ml. of dioxane. The solution was refluxed for 2 hr. and cooled. The solid (36.6 g., 98% total yield) was removed by filtration. The product was placed in 400 ml. of boiling methanol, and the mixture was filtered. The residue (26.6 g., 72% yield, m.p. 197–200°) was recrystallized from benzene; m.p. 202–203°. The melting point of the product was not depressed when mixed with compound Ic from the above procedure. The filtrate was cooled and the crystals IIa (3.9 g., 11% yield, m.p. 137–140°) removed by filtration; m.p. 143–144° after recrystallization from methanol. The melting point of the product was not depressed when mixed with compound IIa from the above procedure.

2,5-Bis(benzylaminomethyl)hydroquinone (IVa). 2,5-Bis-(dimethylaminomethyl)hydroquinone (4.5 g., 0.02 mole) was dissolved in 44 ml. of benzylamine (0.40 mole) and refluxed for 12 hr. The solvents were removed by distillation, and the residue was cooled. The solid (5.0 g., 72% yield, m.p. 147–151°) was removed by filtration; m.p. 159–161° after recrystallization from ethyl acetate.

In an alternate procedure Ic (18.6 g., 0.050 mole) was mixed with a solution of 20 ml. of concd. hydrochloric acid (0.236 mole) and 100 ml. of water. The mixture was heated under reflux on a steam bath for 1 hr., during which time all of the solid dissolved. The solution was cooled and kept at room temperature for 1 day. The *hydrochloride* (19.6 g., 93% yield, m.p. 295–297° dec.) was removed by filtration; m.p. 295–297° dec. after recrystallization from ethanol-water solution (50–50).

Anal. Calcd. for $C_{22}H_{26}Cl_2N_2O_2$: C, 62.71; H, 6.22; Cl, 16.83; neut. equiv., 211. Found: C, 62.72; H, 6.06; Cl, 16.61; neut. equiv., 210.

The *free base* was obtained in 92% yield by treatment of an aqueous solution of the hydrochloride with aqueous sodium bicarbonate; m.p. 160–161° after recrystallization from chloroform–petroleum ether (b.p. 60–110°). The melting point of the product was not depressed when mixed with 2,5-bis(benzylaminomethyl)hydroquinone obtained from 2,5-bis(dimethylaminomethyl)hydroquinone by amine interchange.

Reaction of Ic *with 2,4-dinitrophenylhydrazine sulfate.* Ic (3.7 g., 0.01 mole) was added to a filtered solution of 3.9 g. of 2,4-dinitrophenylhydrazine (0.02 mole), 24 ml. of concd. sulfuric acid, and 35 ml. of water in 100 ml. of 95% ethanol. The solution was kept at room temperature for 70 hr. The solid (4.1 g., 100% yield, m.p. 162–163.5°) was removed by filtration; m.p. 164–165° after recrystallization from ethanol. The melting point of the product was not depressed when mixed with an authentic sample of formaldehyde 2,4-dinitrophenylhydrazone (lit.,[10] m.p., 166°).

Neutralization of the filtrate with aqueous sodium bicarbonate gave the free base (IVa) in 87% yield; m.p. 159–160° after recrystallization from chloroform–petroleum ether (b.p. 60–110°). The melting point of the product was not depressed when mixed with 2,5-bis(benzylaminomethyl)-hydroquinone obtained from 2,5-bis(dimethylaminomethyl)-hydroquinone by amine interchange.

Analogous results were obtained when the isomeric bis-*m*-oxazine (IIa) was used in place of Ic.

Reaction of 2,5-bis(benzylaminomethyl)hydroquinone (IVa) *dihydrochloride with morpholine.* IVa dihydrochloride (4.2 g., 0.010 mole) was dissolved in 20 ml. of morpholine (0.23 mole), and the solution was refluxed for 12 hr. The solvents were removed by distillation under reduced pressure and a solid formed in the reaction mixture. The solid (2.8 g., 91% yield, m.p. 191–196°) was removed by filtration and washed with cold water; m.p. 203–204° after recrystallization from methanol. The melting point of the product was not depressed when mixed with an authentic sample of 2,5-bis(morpholinomethyl)hydroquinone (lit.,[6] m.p. 203–204°).

2,3-Bis(benzylaminomethyl)hydroquinone. IIa (7.4 g., 0.020 mole) was mixed with a solution of 7 ml. of concd. hydrochloric acid (0.083 mole) and 40 ml. of 95% ethanol in 40 ml. of water. The mixture was refluxed on a steam bath for 30 min., during which time the solid dissolved. The solvents were removed by distillation under reduced pressure, and the solution was cooled. The *hydrochloride* (7.8 g., 93% yield, m.p. 198–204°) was removed by filtration. After recrystallization from water-methanol, the product melted at 113–114° with some residue, followed by resolidification, then decomposition at 218–220°.

Anal. Calcd. for $C_{22}H_{26}Cl_2N_2O_2$; Cl, 16.83; neut. equiv., 211. Found: Cl, 16.72; neut. equiv., 212.

The *free base* was obtained in 89% yield by treatment of an aqueous solution of the hydrochloride with aqueous sodium bicarbonate; m.p. 132–133° after recrystallization from chloroform–petroleum ether (b.p. 60–110°).

2,3-Bis(morpholinomethyl)hydroquinone. 2,3-Bis(benzylaminomethyl)hydroquinone dihydrochloride (5.9 g., 0.014 mole) was dissolved in 25 ml. of morpholine (0.288 mole) and refluxed for 12 hr. The solvents were removed by distillation under reduced pressure, and the brown oil that remained was cooled. Crystals (3.9 g., 90% yield, m.p. 159–173°) were removed by filtration; m.p. 185–186° after two recrystallizations from methanol.

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.31; H, 7.84. Found: C, 62.35; H, 7.83.

2,3-Dimethylbenzoquinone. 2,3-Bis(morpholinomethyl)-hydroquinone (12.3 g., 0.040 mole) and 3.0 g. of copper–chromium oxide catalyst were mixed with 75 ml. of absolute ethanol and added with hydrogen to a high pressure bomb. The reaction mixture was heated at 200° and 3000 p.s.i. pressure for 4 hr. The catalyst was removed by filtration and washed with ether. The ether was added to 20 ml. of water, and the mixture was warmed to 40–45° to remove the ether. The aqueous solution and 25 ml. of 1.5*M* sulfuric acid was added to the reaction mixture filtrate and cooled to 5°. A cooled solution of 9.0 g. of sodium dichromate (0.030 mole) in 120 ml. of 3*M* sulfuric acid was added portionwise with agitation to the cold solution over a period of 12 hr., and the mixture was kept at 5° for 60 hr. The yellow crystalline solid (2.3 g., 42% yield), obtained by ether extraction followed by steam distillation under reduced pressure melted at 56–56.5°, after recrystallization from petroleum ether. The melting point was not depressed when mixed with an authentic sample of 2,3-dimethylbenzoquinone

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(9) All melting points are uncorrected.

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 283.

(m.p. 56–57°) obtained by chromic acid oxidation of 2,3-dimethylaniline hydrochloride.[11]

The 2,3-dimethylbenzoquinone (1.4 g., 0.010 mole) prepared by hydrogenation as described above was mixed with 40 ml. of water, and the mixture warmed as sulfur dioxide was bubbled into the water for 1 hr. White crystals (1.1 g., 77% yield) were removed by filtration; m.p. 220–221°, lit.,[12] m.p. 221°. The melting point of the product was not depressed when mixed with an authentic sample of 2,3-dimethylhydroquinone.

3,8-Di-α-methylbenzyl-2,3,4,7,8,9-hexahydrobenzo[1,2-e,4,5-e′]bis-m-oxazine (Id) *and 2,9-di-α-methylbenzyl-1,2,3,8,9,10-hexahydrobenzo[2,1-e,3,4-e′]bis-m-oxazine* (IIb). To a cooled solution of 30 ml. of 37% aqueous formaldehyde (0.40 mole) in 30 ml. of dioxane was added 25.8 ml. of α-methylbenzylamine (0.20 mole) and 11.0 g. of hydroquinone (0.10 mole) and the resulting solution was refluxed for 4 hr. and cooled. The solid (33.2 g., 83% yield) was removed by filtration. It was placed in 400 ml. of boiling methanol and filtered. The residue (Id; 12.4 g., 31% yield, m.p. 179–182°) melted at 191–192° after recrystallization from benzene–methanol. The filtrate was evaporated and cooled. The solid (IIb; 10.7 g., 27% yield, m.p. 163–167°) melted at 176–177° after three recrystallizations from ethyl acetate.

2,5-Bis(cyclohexylaminomethyl)hydroquinone (IVc). 2,5-Bis(dimethylaminomethyl)hydroquinone (4.5 g., 0.020 mole) was dissolved in 46 ml. of cyclohexylamine (0.40 mole) and refluxed for 12 hr. The solvents were removed by distillation under reduced pressure, and the residue cooled. The solid (6.3 g., 94% yield, m.p. 158–163°) was removed by filtration; m.p. 170–171° after recrystallization from ethyl acetate. The melting point of the product was not depressed when mixed with a sample of the Mannich base (m.p. 173–174°) obtained by the hydrolysis of the bis-*m*-oxazine (Ib) from cyclohexylamine.[3]

2,5-Bis(N-cyclohexyl-N-methylaminomethyl)hydroquinone. Formic acid (9.2 ml. of 85% aqueous solution, 0.20 mole) was added dropwise with agitation to 3.6 g. of Ib (0.010 mole) at room temperature. The solution was refluxed for 30 min., then cooled and added dropwise to a slurry of 20 g. of sodium bicarbonate (0.25 mole) in 100 ml. of water. The solid (2.9 g., 80% yield, m.p. 186–188°) was removed by filtration and washed with cold water; m.p. 189–190° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{36}N_2O_2$: C, 73.29; H, 10.07. Found: C, 73.13; H, 9.86.

The melting point was not depressed when the product was mixed with a sample (m.p. 190–191°) prepared by reaction of 2,5-bis(dimethylaminomethyl)hydroquinone with *N*-methylcyclohexylamine or when mixed with the product (m.p. 190–191°) from the condensation of hydroquinone, formaldehyde, and *N*-methylcyclohexylamine in a molar ratio of 1:2:2.

2,5-Bis(N-benzyl-N-methylaminomethyl)hydroquinone. Formic acid (25.0 ml. of 85% aqueous solution, 0.55 mole) was added dropwise to 9.3 g. of Ic (0.025 mole), and the resulting solution was kept at room temperature for 2 hr. The temperature was increased to 75° for 1 hr. The solution was cooled, poured into water, and neutralized with a solution of sodium bicarbonate. The solid (8.8 g., 94% yield, m.p. 173–178°) was removed by filtration; m.p. 181–182° after recrystallization from acetone.

Anal. Calcd. for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.72; H, 7.53; N, 7.37.

Hydrogenolysis of 2,5-bis(N-benzyl-N-methylaminomethyl)-hydroquinone. 2,5-Bis(*N*-benzyl-*N*-methylaminomethyl)hydroquinone (7.5 g., 0.020 mole) and 2.0 g. of copper–chromium oxide catalyst were mixed with 100 ml. of absolute ethanol and added with hydrogen to a high pressure bomb. The reaction mixture was heated at 225° and 3200 p.s.i. pressure for 2 hr. The catalyst was removed by filtration and washed with ethanol, which was added to the filtrate. The filtrate was mixed with aqueous ferric chloride, extracted twice with benzene, and discarded. The benzene extract was evaporated to dryness. A yellow crystalline solid (0.2 g., 7% yield, m.p. 120–121°) was removed by sublimation. 2,5-Dimethylbenzoquinone is reported[13] to melt at 123°.

3,8-Diallyl-2,3,4,7,8,9-hexahydrobenzo[1,2-e,4,5-e′]bis-m-oxazine (Ie). Allylamine (7.5 ml., 0.10 mole) was added dropwise with cooling to a solution of 15 ml. of 37% aqueous formaldehyde (0.20 mole) in 20 ml. of dioxane. Hydroquinone (5.5 g., 0.05 mole) was added, and the resulting solution was refluxed for 3 hr. and then cooled. The solid (11.1 g., 82% yield, m.p. 123–128°, was removed by filtration; m.p. 139–140°, after two recrystallizations from acetone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Synthesis of 2,5 Bis(perfluoroalkyl)-1,3,4-oxadiazoles

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2,5-Bis(perfluoroalkyl) 1,3,4-oxadiazoles, in which the perfluoroalkyl groups were CF_3, C_2F_5, C_3F_7, or C_7F_{15}, were prepared by the dehydration of the corresponding *N,N′*-bis(perfluoroacyl)hydrazines. Preparation of the previously unreported intermediate perfluoroalkyl hydrazides and *N,N′*-bis(perfluoroacyl)hydrazines is described.

As a continuation of our interest in the unusual properties of heterocyclic compounds having perfluoroalkyl groups as ring substituents, several 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles have been synthesized. In view of the pronounced differences in reactivity[3,4,5] between the perfluoroalkyl-heterocycles and the nonfluorinated heterocycles, a

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