ALKYLAMINOMETHYL HYDROQUINONES AND RELATED COMPOUNDS

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Introduction

Von Braun and Rover (1903: 1196) reported the condensation of dibenzylamine and formaldehyde resulted in the formation of tetrabenzyldiaminomethane.

Clarke, Gillespie, and Weishauss (1933:4571) found that tetrabenzyldiaminomethane was reduced to some tertiary amines with formic acid. They also indicated that methylenedipiperdine was reduced under similar conditions to give 45.3% methylpiperdine and 52.7% piperdine isolated as the benzenesulfonyl piperdine. They reported that secondary amines, excepting dimethylamine, were converted to the N-methyl derivatives in the presence of formaldehyde and formic acid.

Burke (1949:609), Burke and Weatherbee (1950:4691), Burke, Hammer, and Weatherbee (1961: 4403), reported on reactions of phenols with N-methylol derivatives obtained by condensing primary amines and formaldehyde. Bruson and MacMullen (1941:270), and Caldwell and Thompson (1939:765), reported similar condensations involving phenolic compounds with secondary amines.

Discussion

In view of the work of Clarke and his co-workers, in this investigation experiments were undertaken to determine if dibenzylamine and formaldehyde react to form N-methyloldibenzylamine which would further condense with dibenzylamine to form the tetrabenzyldiaminomethane. In view of the reduction of the latter compound with formic acid, investigations were carried out to determine if it would dissociate in solution to dibenzyl amine and its N-methylol derivative.

Condensations under a variety of experimental conditions of dibenzyl amine, formaldehyde, and parabenzyloxphenol resulted in the good recovery of the phenol and in the isolation of over 96% yield of tetrabenzyldiaminomethane. Refluxing of the latter compound with formaldehyde and parabenzyloxyphenol gave similar results. This indicated that the postulated N-methyloldibenzylamine reacted with dibenzylamine easier than with the phenol.

Condensations of benzyl amine, formaldehyde, and para-benzyloxyphenol in a 1:2:1 mole ratio under a variety of experimental conditions gave good yields of 3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine. Similar results were obtained at room temperature, refluxing in methanol solution, or refluxing in dioxane solution. However, similar condensations of benzylamine, formaldehyde, and para-benzyloxy-

phenol in a 1:1:1 mole ratio respectively, failed to undergo a condensation; the para-benzyloxyphenol and the benzyl amine as its hydrochloride salt were recovered nearly quantitatively.

Previous investigations by Burke, Hammer, and Weatherbee (1961: 4403), indicated that benzylamine readily condensed with hydroquinone and formaldehyde. The benzylamine and formaldehyde were interacted in the mole ratio of 1:2 respectively and N,N-dimethylolbenzylamine was postulated as the intermediate. The N,N-dimethylolbenzylamine then reacted with hydroquinone in a 2:1 mole ratio respectively to give two isomeric benzoxazines, 3,8-dibenzyl-2, 3,4,7,8,9-hexahydrobenzo 1,2-e,4,5-e′ bis-m-oxazine (compound No.1) and 2,9-dibenzyl1,2,3,8,9,10-hexahydrobenzo 2,1-e,3,4-e′ bis-m-oxazine (compound No. 2).

In this investigation condensation of benzylamine, formaldehyde, and hydroquinone in a 1:1:1 mole ratio failed to give 2-benzylaminomethylhydroquinone, the expected product if N-methylolbenzylamine were postulated as an intermediate. Similar condensations involving benzylamine, formaldehyde, and hydroquinone in a 2:2:1 mole ratio likewise failed to give the expected 2,5-bis(benzylaminomethyl)hydroquinone. Condensations of benzylamine, formaldehyde, and hydroquinone in a 1:2:1 mole ratio with view of securing the monobenzoxazine 3,4-dihydro-3benzyl-6-hydroxy-1,3,2H-benzoxazine resulted in the isolation of the two isomeric bis-benzoxazines (Compounds No. 1 and No. 2) previously mentioned above.

An indirect approach to the preparation of 3,4-dihydro-3-benzyl-6-hydroxy-1,3,2H-benzoxazine was investigated. It was found convenient to prepare 2-benzylaminomethyl-6-benzyloxyphenol hydrochloride by warming 3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine with alcoholic hydrochloric acid. The resulting hydrochloride salt was neutralized with sodium bicarbonate, or an aqueous solution was treated with monoethanolamine, to give the free Mannich base. Treatment of the free base with formaldehyde readily converted it in high yield to the starting oxazine indicating that the benzoloxy group was not cleaved by the alcoholic hydrochloric acid.

Warming of the 2-benzylaminomethyl-6-benzyloxyphenol with 37% aqueous hydrochloric acid for ½ hour readily cleaved the ether and 2-benzylaminomethyl hydroquinone hydrochloride was isolated in good yield. The corresponding free base was secured by neutralization with potassium bicarbonate. Upon warming the 2-benzylaminomethyl hydroquinone with a methanol solution of formaldehyde in a 1:1 mole ratio gave good yields of 3,4-dihydro-3-benzyl-6-hydroxy-1,3,2H-benzoxazine. Upon reaction of the latter compound with a dioxane solution of formaldehyde and benzyl amine in a 1:2:1 mole ratio resulted in the isolation of the two isomeric bis benzoxazines (compounds No. 1 and No. 2).

Considerable time was spent investigating methods of converting 2-benzylaminomethyl-6-benzyloxyphenol to 2-benzylaminomethylhydroquinone. The conventional use of hydroiodic acid, and other methods of splitting ethers failed to give good

results. The use of 37% hydrochloric acid under relatively mild conditions was found to be a convenient method. Splitting of other benzyl ethers was studied. Para-benzyloxyphenol was readily converted in high yields to hydroquinone.

Condensations of other primary amines or secondary amines, formaldehyde, and para-benzyloxyphenol, hydroquinone, or other phenolic compounds were investigated. Although dibenzylamine, formaldehyde, and hydroquinone in a 2:2:1 mole ratio respectively failed to yield the expected 2,5-bis(dibenzylaminomethyl)-hydroquinone, yields in excess of 75% of 2,5-bis(dimethylaminomethyl)-hydroquinone were readily secured. Reactions of dimethylamine, formaldehyde, and hydroquinone in a 1:1:1 mole ratio respectively resulted in the isolation of 2,5-bis(dimethylaminomethyl)-hydroquinone and not the expected mono derivative, 2-demethylaminomethylhydroquinone.

Experimental

3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine. To 30.6 ml. of 40% formaldehyde (0.4 mole) in 1-propanol dissolved in 50 ml. of dioxane at 10 to 15°C. was added 22 ml. (0.2 mole) of benzyl amine with stirring over a period of 3 to 4 minutes. To the resulting solution was added 40 grams of para-benzyloxyphenol (0.2 mole). After adding an additional 25 ml. of dioxane, the flask was stoppered and stirred with a mag-mix stirrer until a complete solution resulted. The solution was warmed to gentle refluxing for 2 hours and then allowed to stand at 25°C. for 22 hours. The solvents were removed by evaporation under a hood. The white solid was dissolved in 300 ml. of ether and 150 ml. of water containing 11 grams of sodium hydroxide. The ether layer was separated and the aqueous layer further extracted with two-100 ml. and one-50 ml. portions of ether. Removal of the ether gave 57 grams (86% crude yield) of white solid m.p. 73 to 77°C. Upon recrystallization from 210 ml. of a methanol-ethanol (2 parts methanol and 5 parts ethanol by volume) solution, the compound melted at 86 to 87°C. The aqueous layer was acidified with hydrochloric acid. Upon extraction with ether, 6 grams of para-benzyloxyphenol was recovered. (Analysis of the oxazine: $C_{22}H_{21}NO_2$: Calculated: C 79.73, H 6.39, N 4.22. Found: C 79.68, H 6.29, N, 4.11).

The condensation was repeated under a variety of experimental conditions. The reaction mixture was allowed to stand at room temperature for 40 hours, it was refluxed in dioxane for 3 hours, it was gently refluxed in methanol using 37% aqueous formaldehyde, etc.; in most cases the yields were somewhat lower than the above example.

2-benzylaminomethyl-4-benzyloxyphenol hydrochloride. A 3.6 gram sample of 3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine was dissolved in 25 ml. of 95% ethyl alcohol and placed in a round bottom flask equipped with a claissen flask, dropping funnel, and condenser for distillation. After cooling on an ice bath, 2 ml. of 37% aqueous hydrochloric acid was added dropwise through the dropping funnel with shaking. The flask was

gradually warmed until 5 ml. of alcohol distilled over into an alcoholic solution of 2,4-dinitrophenylhydrazine. The distilling flask was cooled and an additional 1 ml. of hydrochloric acid was added. Distillation was repeated until 10 ml. of alcohol distilled over. The residue in the distilling flask was decanted to a beaker, cooled on an ice bath, and approximately 20 ml. of acetone was added. A white solid, 3.4 grams, melting point 168-169°C. was secured. Upon two recrystallizations from 95% ethanol the melting point was 170-171°C. (Analysis: $C_{21}H_{22}ClNO_2$: Calculated: C 70.87, H 6.23, Cl 9.97, N 3.94. Found: C 70.46, H 6.44, Cl 9.95, N 4.02).

The 2,4-dinitrophenylhydrazine solution was acidified with dilute sulfuric acid, warmed to refluxing, and concentrated to one-half volume under the hood. A yellow solid was obtained which did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of formaldehyde.

2-benzylaminomethyl-4-benzyloxyphenol. A 4.95 gram sample of 2-benzylaminomethyl-4-benzyloxyphenol hydrochloride was stirred in 150 ml. of water with a mag-mix stirrer. After adding 1.5 ml. of monoethanolamine, the mixture was vigorously stirred for several minutes. The mixture containing a white solid was extracted with several small portions of ether. Upon evaporation of the ether, 4.16 grams of white solid, melting point 83-88°C. was secured. After two recrystallizations from methanol, the sample melted at 90-91°C. A mixed melting point with 3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine melted at 70 to 73°C. (Analysis: $C_{21}H_{21}NO_2$: Calculated: C 78.78, H 6.62. Found: C 78.71, H 6.69).

Conversion of 2-benzylaminomethyl-4-benzyloxyphenol to 3,4-dihydro-3-benzyl-6-benzyloxy-1,3,2H-benzoxazine. A 6.39 gram sample of 2-benzylaminomethyl-4-benzyloxyphenol was dissolved in 100 ml. of warm methanol. After cooling on an ice bath, 1.5 ml. of 37% aqueous formaldehyde was added. The solution was shaken for several minutes and a white solid separated. The mixture was gradually warmed to gentle refluxing for two hours. After cooling on an ice bath, the resulting 5.3 grams white solid was removed by filtration and recrystallized from methanol. The solid melted at 85-86°C. and did not depress the melting point of an authentic sample of the oxazine.

2-benzylaminomethyl-hydroquinone hydrochloride. An 8.8 gram sample of 2-benzylaminomethyl-4-benzyloxyphenol hydrochloride was placed in a round bottom flask with 15 ml. of 37% aqueous hydrochloric acid. After attaching to a reflux condenser the mixture was warmed on a boiling water bath for 30 minutes. An oil formed. The mixture was cooled on an ice bath. A white solid was removed by filtration and washed with several small portions of ether. After drying, the solid weighed 5.1 grams. It was recrystallized from isopropyl alcohol, melting point 177-178°C. (Analysis: $C_{14}H_{16}ClNO_2$: Calculated: C 63.27, H 6.06. Found: C 63.49, H 5.90).

The ether was separated from the aqueous layer. Upon removal of the ether, 1.1 grams of benzyl chloride,

boiling point 178-180°C. was secured.

2-benzylaminomethyl-hydroquinone. The above experiment was repeated using 21.8 grams of 2-benzylaminomethyl-4-benzyloxyphenol hydrochloride and 25 ml. of aqueous hydrochloric acid. A solid did not form. After extracting the aqueous layer with ether to remove the benzylchloride, it was saturated with potassium bicarbonate and extracted with several small portions of ether. Removal of the ether gave 7.9 grams of the free base, melting point 115-117°C. Upon three recrystallizations from benzene the solid melted at 120-120.5°C. (Analysis: $C_{14}H_{15}NO_2$: Calculated: C 73.34, H 6.59, N 6.11. Found: C 73.53, H 6.52, N 6.11).

Conversion of Hydroquinonemonobenzylether to Hydroquinone. Three grams of hydroquinone monobenzylether was placed in a round bottom flask with 10 ml. concentrated hydrochloric acid and the mixture warmed at 85-90° under a reflux condenser for 45 minutes. The ether gradually changed to a brown oil and finally nearly a clear solution resulted. The flask was cooled and an additional 10 ml. conc. hydrochloric acid was added. The mixture was warmed for 1 hour at 85-90°, cooled to room temperature, made basic with sodium hydroxide, and extracted with one-20 ml. and two-10 ml. portions of ether. The ether was allowed to evaporate leaving a nearly colorless liquid, which was identified as benzyl chloride, boiling point 180-181°C. at 759 mm.; quaternary ammonium salt with N,N-dimethylaniline gave a melting point of 109-111°C.

The aqueous extracts were made acidic with hydrochloric acid and extracted with one-30 ml. and two-20 ml. portions of ether, which upon evaporation gave 170 g. of brownish white solid, m.p. 105-140°. The solid was recrystallized from tertiary butyl alcohol giving 1.5 g. white solid m.p. 165-170°. An additional recrystallization gave m.p. 169-171°; mixed m.p. with hydroquinone showed no depression.

3,4-dihydro-3-benzyl-6-hydroxy-1,3,2H-benzoxazine. The Mannich base 2-benzylaminomethyl-4-hydroxy phenol was readily converted to the oxazine under conditions to those described for conversion of 2-benzylaminomethyl-4-benzyloxyphenol to its corresponding oxazine as indicated above in 91.5% yield, melting point 105-106° after three recrystallizations from carbon tetrachloride. (Analysis: $C_{15}H_{15}NO_2$: Calculated: C 74.66, H 6.26, N 5.80. Found: C 75.04, H 6.44, N 5.79).

Condensation of para-benzyloxyphenol, formaldehyde, and dibenzylamine. To 1.87 ml. of 37% aqueous formaldehyde (0.025 mole) in 50 ml. of methanol was added dropwise with mag-mix stirring and cooling on an ice bath 4.93 grams (0.025 mole) of dibenzylamine. After adding 5 grams (0.025 mole) para-benzyloxyphenol, the solution was refluxed for 3 hours. The solvents were removed under a hood; the residue was dissolved in 100 ml. ether and 100 ml. water containing 5.6 grams (0.1 mole) of potassium hydroxide. The aqueous extract was further extracted with two 35 ml. portions of ether. The combined ether extracts upon evaporation under the hood gave 4.87 grams (96% yield) of tetrabenzyldiaminomethane, melting point 91-93°. Upon recrystallization

from 95% ethanol the melting point was 97-98°C. (literature value 99-101°C.) (Analysis: $C_{29}H_{36}N_2$: Calculated: C 85.70, H 7.44, N 6.90. Found: C 86.04, H 7.25, N 7.07).

Condensation of hydroquinone, formaldehyde, and dibenzylamine. Dibenzylamine (9.86 grams; 0.05 mole), formaldehyde (3.75 ml. 37%; 0.05 mole), and hydroquinone (2.75 grams; 0.025 mole) in 50 ml. of methanol were condensed as for para-benzyloxyphenol above. An essential quantitative yield of tetrabenzyldiaminomethane was isolated.

When dimethylamine was used in lieu of the dibenzylamine, yields in excess of 75% of 2,5-bis(dimethylaminomethyl)hydroquinone (melting point 190-191°; literature value 190°) were readily obtained. Condensation of equal mole quantities of dimethylamine, formaldehyde, and hydroquinone gave a product which did not depress the melting point of the 2,5-derivative.

Condensation of tetrabenzyldiaminomethane with formaldehyde and para-benzyloxyphenol. Tetrabenzyldiamonomethane (10.15 grams, 0.025 mole), formaldehyde (1.87 ml. 37%; 0.025 mole), and para-benzyloxyphenol (10 gram; 0.025 mole) in 50 ml. of methanol was refluxed for 3 hours. The solvents were removed under a hood. The resulting mixture was dissolved in 100 ml. water containing 2.8 gram of potassium hydroxide (0.05 mole) and 100 ml. ether. The ether was removed and the aqueous layer further extracted with two small portions of ether. Removal of the ether under the hood gave a nearly quantitative recovery of the tetrabenzyldiaminomethane. Acidification of the aqueous layer with hydrochloric acid followed by three extractions with small portions of ether gave 10 grams, quantitative recovery of the para-benzyloxyphenol.

Condensation of benzylamine, formaldehyde, and hydroquinone. Benzyl amine (11 ml., 0.1 mole), formaldehyde (7.5 ml., 37%, 0.1 mole), and hydroquinone (11 g., 0.1 mole) in 75 ml. of methanol was refluxed for 2 hours. The solvents were removed under the hood. The resulting mixture was extracted with ether and 100 ml. of water containing 10 grams of sodium hydroxide. The ether extracts were treated with 37% aqueous hydrochloric acid. Upon standing a nearly quantitative recovery of the amine as its hydrochloride salt was secured.

Repetition of the experiment using benzylamine hydrochloride in lieu of the free base gave similar results.

Summary

Dibenzylamine, formaldehyde, and para-benzyloxyphenol or hydroquinone did not undergo a Mannich condensation under conditions similar to the condensation of dimethylamine, formaldehyde, and hydroquinone which gave high yields of 2,5-bis(dimethylaminomethyl)hydroquinone. Benzylamine and formaldehyde in 1:1 mole ratio condensations failed to give Mannich bases with hydroquinone or para-benzyloxyphenol. Condensations of benzylamine and formaldehyde in a 1:2 mole ratio with these phenolic compounds gave 1,3,2H-benzoxazines. Reaction of benzylamine, formaldehyde, and hydroquinone in a 1:2:1 mole ratio gave two isomeric bis benzoxazines instead of the expected mono 3,4-

dihydro-3-benzyl-6-hydroxyl-1,3,2H-benzoxazine. An indirect synthesis of the latter compound was reported.

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