STEARIC HINDRANCE EFFECTS OF THE TERTIARY BUTYL RADICAL IN SOME MANNICH CONDENSATIONS

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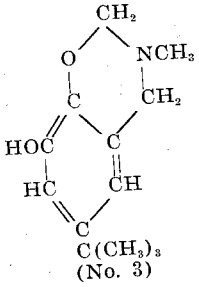
INTRODUCTION

Burke (1949:609) prepared 3,4-dihydro-3-cyclohexyl-6-tertiary-butyl-1,3,2H-benzoxazine in good yield by the interaction of cyclohexylamine, formaldehyde, and para-tertiary-butyl phenol in a 1:2:1 molar basis, respectively. Burke, Smith, and Weatherbee (1952:602) reported that a benzoxazine was not formed when 2,4-di-tertiary-butyl-5-methyl-phenol, formaldehyde, and methylamine were interacted in a 1:2:1 molar basis, but instead a good yield of N,N-bis(3,5-di-tertiary-butyl-2-hydroxy-6-methyl-benzyl)-methyl amine was obtained. The presence of the tertiary butyl group in the ortho position to the phenolic group served as a stearic hindrance and prevented the phenolic hydrogen from entering the reaction.

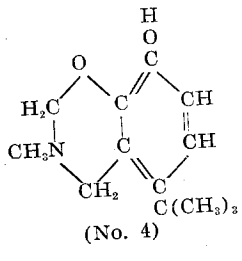
Burke and Weatherbee (1950:4691) found that hydroquinone, formaldehyde, and cyclohexylamine condensed in a 1:4:2 molar basis to give 2,3,4,7,8,9-hexahydro-3,8-dicyclohexylbenzo[1,2-e,4,5-e'] bis-m-oxazine. In unpublished work they found that 2,5-di-tertiary-butyl-hydroquinone failed to undergo a condensation with formaldehyde and primary amines; this indicated that both the phenolic hydrogens and the ortho nuclear hydrogens were inactivated.

DISCUSSION

In this investigation Mannich-type condensations involving para-tertiary-butyl-catechol (No. 1) and tertiary-butyl-hydroquinone (No. 2) were studied. The former condensed with formaldehyde and methyl amine in a 1:2:1 molar ratio to give 3,4-dihydro-3-methyl-6-tertiary-butyl-8-hydroxy-benzoxazine (No. 3). The structure No. 3 is preferred over the possible isomer 3,4-dihydro-3-methyl-5-tertiary-butyl-8-hydroxy-benzoxazine (No. 4) in view of the fact that 2,5-di-tertiary-butyl-hydroquinone failed to undergo a Mannich condensation to give a bis-benzoxazine.



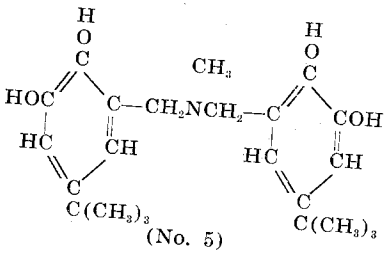
(No. 3)



(No. 4)

Reaction of No. 1 with formaldehyde and methylamine in a 1:4:2 molar ratio did not yield a bis-benzoxazine as did the reaction of catechol, formaldehyde, and methyl amine in work reported by Burke and Weatherbee (1950:469).

Condensation of No. 1 with formaldehyde and methylamine in a 2:2:1 molar ratio led to formation N,N-bis(2,3-dihydroxy-5-tertiary-butyl-benzyl)-methyl amine (No. 5). Structure No. 5 was preferred over the possible isomer N,N-bis(2,3-dihydroxy-6-tertiary-butyl-benzyl)-methylamine (No. 6).



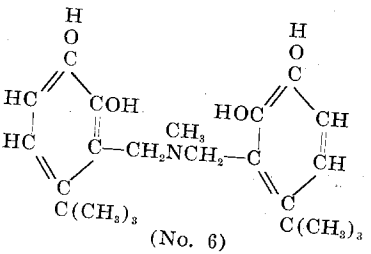
(No. 5)

Thus, the tertiary-butyl group which is meta to one of the phenolic groups in No. 1 prevented the phenolic hydrogen from entering into the Mannich condensations; if structure No. 5 is correct the nuclear hydrogen in the 3-position is inactivated.

Tertiary-butyl-hydroquinone (No. 2) reacted readily with cyclohexylamine and formaldehyde to give a mono-benzoxazine, 3,4-dihydro-3-cyclohexyl-6-hydroxy-7-tertiary-butyl-1,3,2H-benzoxazine (No. 7). The latter structure is assigned instead of the isomer 3,4-dihydro-3-cyclohexyl-5-tertiary-butyl-6-hydroxy-1,3,2H-benzoxazine since all attempts to obtain a bis-oxazine have been unsuccessful. When No. 7 was allowed to react with formaldehyde and cyclohexylamine in a 1:2:1 ratio, with a view of obtaining a bis-benzoxazine, an 83% recovery of No. 7 was secured.

Compound No. 2, unlike compound No. 1, did not yield a bis-benzyl-alkylamine similar to No. 5 and No. 6; all condensations of No. 2 with formaldehyde and primary amines carried out to date on a 2:2:1 molar basis yielded mono-benzoxazines.

Compound No. 1 reacted readily with other primary amines and formaldehyde. The following amines have yielded derivatives of No. 3:



(No. 6)

cyclohexylamine, benzylamine, alpha-methylbenzylamine, and tertiary-butylamine. Condensations involving No. 2 gave crystalline products also but they were more difficult to purify.

The type of formaldehyde best suited for these reactions was investigated. Commercially available 37% aqueous solution, paraformaldehyde dissolved in methanol containing a trace of potassium hydroxide, and formaldehyde dissolved in 1-propanol were used. The latter source in most cases in this investigation gave a purer initial crude product.

Experimental

The experimental procedures followed in this investigation are illustrated by the following examples:

3,4-dihydro-3-methyl-6-tertiary-butyl-8-hydroxy-benzoxazine (No. 3).—To 30.6 mls. 40% formaldehyde (0.4 mole) in 1-propanol dissolved in 50 ml. of methanol at 10-15° C.

was added 24.8 gms. 25% methylamine (0.2 mole) dissolved in 50 ml. methanol, with shaking over a period of 3 to 4 minutes. To the resulting solution was added 33.2 gms. of para-tertiary-butyl-catechol (0.2 mole) dissolved in 40 mls. methanol. The solution was shaken for several minutes and then placed in a stoppered flask in the dark at 26-28° C. for 28 hours. The brownish solution was decanted to a beaker and placed under a hood to evaporate the solvents, leaving a crude, brownish solid. One recrystallization from methanol gave 33.55 gms. of product (78% yield), melting point 118-122°. After six recrystallizations from methanol the melting point was raised to 130-131°. (Analysis: $C_{13}H_{19}NO_2$: Calculated: C 70.56, H 8.65. Found: C 70.24, H 8.89).

3,4-dihydro-3-cyclohexyl-6-tertiary-butyl-8-hydroxy-benzoxazine.—Yield 59%; m.p. 87-88.5° C. (Analysis: $C_{18}H_{27}NO_2$: Calculated: C 74.70, H 9.41, N 484. Found: C 74.52, H 9.48, N 4.65).

N,N-bis(2,3-dihydroxy-5-tertiary-butyl-benzyl)-methylamine (No. 5).—Condensation was similar to the preparation of No. 3, excepting that 0.2 mole formaldehyde, 0.1 mole of methylamine, and 0.2 mole of para-tertiary-butyl-catechol, were employed to give a 65% yield of No. 5, m.p. 149-150° C. (Analysis: $C_{23}H_{33}NO_4$: Calculated: C 71.28. H 8.58, N 3.62. Found: C 71.28, H 8.67, N 3.80).

3,4-dihydro-3-cyclohexyl-6-hydroxy-7-tertiary-butyl-1,3,2H-benzoxazine (No. 7).—Repetition of the reaction above for the preparation of No. 3, excepting that tertiary-butyl-hydroquinone was used in lieu of tertiary-butyl-catechol, gave a 59% yield of No. 7, m.p. 183-184° C. (Analysis: $C_{18}H_{27}NO_2$: Calculated: C 74.70, H 9.41, N 4.84. Found: C 74.95, H 9.45, N 4.60).

Reaction of No. 7 with Formaldehyde and Cyclohexylamine.—To 1.29 mls. 40% formaldehyde (0.0169 moles) in 1-propanol dissolved in 10 ml. methanol was added dropwise from a pipette 0.97 ml. cyclohexylamine (0.0084 mole) at 15° C. Then 2.45 gms. of No. 7 (0.0084 mole) were added and the mixture was stirred with a mag-mix stirrer for 4 hours. The resulting solution was placed in a stoppered flask and set-aside for 24 hours. Upon evaporation of the solvents and washing the crude solid residue with ethyl acetate, 2.02 gms. of No. 7 (83% recovery) was obtained, m.p. 182-184° C. A mixed melting point with No. 7 gave no depression.

Summary

It has been shown that tertiary-butyl group ortho to a phenolic hydroxyl prevents the phenolic hydrogen from entering into Mannich condensations. When the tertiary-butyl group is meta to a phenolic hydrogen, the nuclear hydrogen ortho to both the tertiary-butyl group and to the phenolic hydroxyl is inactivated. Although both hydroquinone and catechol give bis-meta-benzoxazines upon reaction with primary amines and formaldehyde, neither para-tertiary-butyl catechol or tertiary-butyl hydroquinone yield bis-meta-benzoxazines; only mono meta-benzoxazines can be isolated.

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