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

Condensation of Hydroxyaromatic Compounds with Formaldehyde and Primary Aromatic Amines

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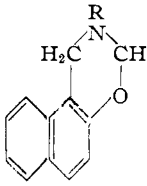
Reaction of primary aryl amines with formaldehyde and 2-naphthol resulted in high yields of 2,3-dihydro-2-aryl-1H-naphth[1,2-e]-*m*-oxazines. An alternate synthesis of the naphthoxazines from 1-arylaminomethyl-2-naphthols was described. Analogous products were obtained when *p*-substituted phenols were used in place of 2-naphthol.

Condensation of primary aliphatic and alicyclic amines with formaldehyde and substituted phenols has been found to yield several types of well defined monomeric products depending upon the particular amine, temperature and the nature and position of the substituents on the phenol.[1] The present investigation is concerned with the reaction of representative primary aromatic amines with formaldehyde and selected phenolic compounds. The primary aromatic amines are of particular interest in such studies since their chemical behavior can be modified considerably by ring substitution and they are capable of undergoing nuclear condensation with formaldehyde.

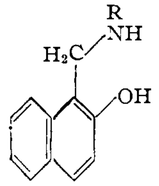
Work on such systems appears to have been limited. Bruson[2] reported the reaction of phenols with formaldehyde and sodium sulfanilate but the products were not characterized. Hardman,[3] in a more recent patent, described the preparation of several 1-arylaminomethyl-2-naphthols by the direct condensation of 2-naphthol with formaldehyde and primary aromatic amines. Related arylaminomethyl derivatives were synthesized earlier, however, by the reaction of phenolic compounds with preformed formaldehyde–amine condensates. 2-Phenylaminomethylphenol was obtained in this way by condensation of phenol with either methylene-bis-aniline[4] or 1,3,5-triphenylhexahydrotriazine,[5] and 1-arylaminomethyl-2-naphthols were prepared from 2-naphthol and methylene-bis-arylamines.[6,7]

In the present study, condensation of 2-naphthol with formaldehyde and *p*-toluidine in a 1:2:1 molar ratio at 5° in methanol solution resulted in a 91% yield of 2,3-dihydro-2-*p*-tolyl-1H-naphth[1,2-e]-*m*-oxazine (I). Replacement of *p*-toluidine with aniline, *p*-aminobenzoic acid, *p*-bromoaniline or *o*-toluidine resulted in analogous products. *p*-Phenylenediamine reacted almost immediately in the cold with four moles of formaldehyde and two of 2-naphthol to form 2,2′-*p*-phenylene-bis-(2,3-dihydro-1H-naphth[1,2-e]-*m*-oxazine). With *o*-nitroaniline, however, the only product isolated from a reaction in naphthoxazine proportions at room temperature was 1-(*o*-nitroanilinomethyl)-2-naphthol. When the condensation occurred in hot dioxane, the corresponding naphthoxazine was obtained in low yield (27%) along with the Mannich base (17% yield). Much higher yields of naphthoxazine were obtained when *m*- and *p*-nitroaniline (81 and 61%) were employed in place of the ortho isomer in hot dioxane and in neither instance were other products isolated. The tendency of *o*-nitroaniline to behave as a secondary amine in the condensation may be due to the favorable situation for chelation in this compound in contrast with the *m*- and *p*-derivatives. The only product isolated from an attempted condensation of equimolar quantities of *m*-nitrophenol, formaldehyde and 2-naphthol in dioxane at room temperature was bis-(*m*-nitroanilino)-methane (76% yield). Refluxing in dioxane was also required to effect naphthoxazine formation with the feebly basic *s*-tribromoaniline. The properties of the naphthoxazines are summarized in Table I. Attempts to prepare the hydrochloride of I resulted in a crystalline product, which, however, decomposed upon standing to a colored gum. This is in contrast with the behavior of the related naphthoxazines from aliphatic amines, which formed highly stable hydrochlorides.[1b]

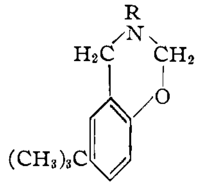
Condensation of 1-(*p*-toluidinomethyl)-2-naphthol (II) with formaldehyde in refluxing ethyl acetate provided an alternate synthesis of I (83% yield). Corresponding naphthoxazines from aniline and *p*-bromoaniline were also prepared in this way. In a study of the ring closure reaction, only starting material was recovered when II was treated with formaldehyde at room temperature. Since the condensation did not proceed satisfactorily under conditions more vigorous than those which were so effective in the direct synthesis of I, it would appear that II is not the normal intermediate in the direct synthesis.



I



II



III

R = *p*-$C_6H_4CH_3$

1,3-Oxazines from hydroxyaromatic compounds and primary aliphatic amines readily liberate formaldehyde along with an alkylaminomethyl derivative upon acid hydrolysis.[1] While treatment of I under such conditions yielded formaldehyde, the other product was a red resinous substance. Since it appeared that the resinification might have resulted from the condensation of the *p*-tolyl nucleus

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[1] (a) W. J. Burke, R. P. Smith and C. Weatherbee, THIS JOURNAL, **74**, 602 (1952); (b) W. J. Burke, M. J. Kolbezen and C. W. Stephens, *ibid.*, **74**, 3601 (1952).

[2] H. A. Bruson, U. S. Patent 2,112,434 (1938).

[3] A. F. Hardman, U. S. Patent 2,411,427 (1946).

[4] Lucius and Bruning Co., German Patent 109,498; *Chem. Zentr.*, **71** [II], 457 (1900).

[5] C. A. Bischoff and E. Frohlich, *Ber.*, **39**, 3964 (1906).

[6] D. Philpott and W. J. Jones, *J. Chem. Soc.*, **337** (1938).

[7] J. R. Feldman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942).

TABLE I

2,3-DIHYDRO-2-ARYL-1H-NAPHTH[1,2-e]-*m*-OXAZINES FROM 2-NAPHTHOL, FORMALDEHYDE AND PRIMARY ARYL AMINES

Amine[a]	M.p., °C.[b]	Yield, %	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Aniline	46–48[c]	78	$C_{18}H_{15}NO$	...	...	..	..	5.36	5.28
o-Toluidine	57–60[d]	83	$C_{19}H_{17}NO$	...	...	..	..	5.09	5.03
p-Toluidine	86–88[d]	91	$C_{19}H_{17}NO$	82.88	82.77	6.22	6.05	5.09	4.97
p-Phenylenediamine	217–219[e]	88	$C_{30}H_{24}N_2O_2$	...	...	..	..	6.30	6.60
p-Aminobenzoic acid	215[e]	59	$C_{19}H_{15}NO_3$	...	...	..	..	4.59	4.49
p-Bromoaniline	118–119[d]	91	$C_{18}H_{14}BrNO$	...	...	..	..	Br, 23.49	Br, 23.49
s-Tribromoaniline	99–100[d]	39	$C_{18}H_{12}Br_3NO$	...	...	..	..	Br, 48.14	Br, 47.61
o-Nitroaniline	108–109[f]	27	$C_{18}H_{14}N_2O_3$	70.58	70.41	4.61	4.83	....	....
m-Nitroaniline	133–134[g]	81	$C_{18}H_{14}N_2O_3$	70.58	70.51	4.61	4.82	....	....
p-Nitroaniline	168–170[h]	61	$C_{18}H_{14}N_2O_3$	70.58	70.65	4.61	4.62	....	....

[a] Prepared from 2-naphthol, formaldehyde and the primary aryl amine listed. [b] Uncorrected. [c] Recrystallized from methanol. [d] Recrystallized from ethyl acetate–methanol. [e] Recrystallized from pyridine. [f] Recrystallized from acetone. [g] Recrystallized from dioxane–methanol. [h] Recrystallized from N,N-dimethylformamide.

with liberated formaldehyde, means for avoiding such possible side reactions were sought. It was found that treatment of I in an acidic solution in the presence of an equimolar quantity 2,4-dinitrophenylhydrazine produced an almost quantitative separation of 2,4-dinitrophenylhydrazone of formaldehyde, while II was readily obtained in 34% yield upon neutralization of the mother liquor. An appreciable quantity (20% yield) of 1,1′-bis-(2-hydroxynaphthyl)-methane also was isolated from the hydrolysis mixture.

When *p*-*t*-butylphenol replaced 2-naphthol in the condensation with formaldehyde and *p*-toluidine in a molar ratio of 1:2:1, a high yield of 3,4-dihydro-6-*t*-butyl-3-*p*-tolyl-1,3-2H-benzoxazine (III) was obtained. This condensation as well as a similar one involving *p*-bromophenol, however, proceeded at a slower rate than when 2-naphthol was used. The *p*-toluidine–formaldehyde trimer, hexahydro-1,3,5-tri-*p*-tolyl-*s*-triazine, was isolated in low yield from the synthesis of the benzoxazine from *p*-*t*-butylphenol.

Benzene solutions of I and III gave a negative response to ferric chloride in absolute ether in contrast to the deep purple color developed immediately with II. Addition of II to benzene containing sodium resulted in the evolution of a gas but no reaction was observed with I or III. These results are consistent with the 1,3-oxazine structures assigned I and III.

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Experimental

2,3-Dihydro-2-*p*-tolyl-1H-naphth[1,2-e]-*m*-oxazine (I).—Paraformaldehyde (6.0 g., 0.2 mole) was dissolved in 10 cc. of hot methanol in the presence of 0.01 g. of potassium hydroxide. The resulting solution was cooled and added slowly with cooling to a cold solution of 10.7 g. (0.1 mole) of *p*-toluidine in 10 cc. of methanol. After addition of 14.4 g. (0.1 mole) of 2-naphthol in 20 cc. of methanol, a white solid began to separate out almost immediately. After two days at 5° the white, crystalline cake (19.2 g.) was removed by filtration. An additional 5.8 g. of product was obtained from the mother liquor. The compound was recrystallized from ethyl acetate–methanol (2:5 by volume); needles, m.p. 86–88°, yield 91%. This and related condensations were also carried out at room temperature with similar results. A benzene solution of the product did not become colored upon the addition of ferric chloride in ether. No evolution of gas was observed when the compound was added to sodium in dry benzene.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.77; H, 6.05; N, 4.97.

1-(*o*-Nitroanilinomethyl)-2-naphthol.—Methanol (32 ml., total volume) solutions of *o*-nitroaniline (6.9 g., 0.05 mole), paraformaldehyde (3.0 g., 0.10 mole) and 2-naphthol (7.2 g., 0.05 mole) were combined at 0°. After five days at room temperature, the reaction mixture was concentrated and chilled. The bright orange crystalline product (2.3 g.) melted at 152–155°. An additional 6.0 g. of crude material was obtained from the mother liquor; m.p. 156–158° after recrystallization from acetone; yield 56%.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79. Found: C, 69.34; H, 4.72.

Reaction of *o*-Nitroaniline and Formaldehyde with 2-Naphthol in Hot Dioxane.—A mixture of 6.9 g. of *o*-nitroaniline (0.05 mole), 11.25 ml. of 37% aqueous formaldehyde (0.15 mole) and 7.2 g. of 2-naphthol (0.05 mole) in 90 ml. of dioxane was heated at 70–90° for five hours. Removal of most of the solvent under reduced pressure resulted in the deposition of a yellow crystalline product (1.1 g., m.p. 196–198°, after recrystallization from N,N-dimethylformamide), which was not identified. Removal of solvent from the mother liquor yielded a waxy residue, which was triturated in methanol. The insoluble yellowish-green crystalline material (4.2 g., 27% yield) was removed by filtration; m.p. 105–110°. The naphthoxazine melted at 109–110° after recrystallization from acetone.

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61. Found: C, 70.41; H, 4.83.

Evaporation of the methanol filtrate to dryness at room temperature yielded 2.5 g. (17%) of orange needles; m.p. 152–157°. The product melted at 156–157° after recrystallization from acetone. The m.p. was not depressed when the product was mixed with 1-(*o*-nitroanilinomethyl)-2-naphthol, prepared as described above.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79. Found: C, 69.09; H, 4.72.

When *m*- or *p*-nitroaniline was treated with 2-naphthol and formaldehyde under conditions similar to the above, the only products isolated were the corresponding naphthoxazines.

Bis-(*m*-nitroanilino)-methane.—A mixture of 14.4 g. of 2-naphthol (0.1 mole), 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) and 13.8 g. of *m*-nitroaniline (0.1 mole) in 120 ml. of dioxane was kept at room temperature for 24 hours. The crystalline product (11 g., 76% yield) which separated upon cooling melted at 211–212° after recrystallization from N,N-dimethylformamide; lit. m.p. 213°.[8]

Anal. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.16; H, 4.20. Found: C, 54.53; H, 4.36.

Conversion of 1-(*p*-Toluidinomethyl)-2-naphthol (II) to I with Formaldehyde.—To a solution of 0.183 g. of II

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[8] G. Pulvermacher, *Ber.*, **25**, 2762 (1892).

(0.00069 mole) in 7 cc. of ethyl acetate was added a methanol solution containing 0.208 g. (0.0069 mole) of paraformaldehyde. After the reaction mixture was gently refluxed for two hours, the solvent was removed under reduced pressure and the residue dissolved in methanol, seeded and set aside in the cold where it crystallized. The m.p. of resulting product and mixed m.p. with 2,3-dihydro-2-*p*-tolyl-1H-naphth[1,2-e]-*m*-oxazine (I) was 86–88°; yield 0.159 g. (83%).

In a similar manner 1-(anilinomethyl)-2-naphthol and 1-(*p*-bromoanilinomethyl)-2-naphthol were converted to the corresponding naphthoxazines in 69 and 81% yields, respectively. Only starting material was recovered when II was treated with a twofold excess of formaldehyde at room temperature for 20 hours.

1-(*p*-Bromoanilinomethyl)-2-naphthol.—A methanol solution containing 0.05 molar quantities of *p*-bromoaniline, paraformaldehyde and 2-naphthol was kept at room temperature for two days. The crystalline product (9.2 g.) which separated melted at 132–133°, after recrystallization from benzene; yield 56%.

Anal. Calcd. for $C_{17}H_{14}BrNO$: Br, 24.35. Found: Br, 23.91.

Acid Hydrolysis of I.—To 0.72 g. of 2,4-dinitrophenylhydrazine (0.0036 mole), 4.8 ml. of concentrated sulfuric acid and 7 ml. of water in 22 ml. of ethanol was added 1.00 g. of the *p*-tolylnaphthoxazine (I, 0.0036 mole). I slowly went into solution with concurrent separation of a flocculent, yellow precipitate. The reaction flask was then agitated vigorously on a mechanical shaker for 45 minutes. After standing overnight the voluminous precipitate (0.758 g.) was removed by filtration and recrystallized from ethyl acetate; m.p. 162–163°. The m.p. of the product was not depressed when mixed with the 2,4-dinitrophenylhydrazone of formaldehyde (m.p. 162–163°; lit. m.p. 166°[9]), yield 99%.

The filtrate of the reaction mixture was carefully neutralized by dropwise addition of a solution of 10.0 g. of potassium hydroxide in 25 ml. of ethanol. The precipitate of potassium sulfate and free amine was added to 450 ml. of water. The water-insoluble free amine was removed by filtration (0.321 g., m.p. 128–130°) and recrystallized from benzene; fluffy, micro-needles, m.p. 134–135°. A mixed melting point determination with 1-(*p*-tolylaminomethyl)-2-naphthol (II) showed no depression; yield 34%.

The neutral filtrate obtained after removal of the potassium sulfate and the amine II was diluted with water and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of the ether was recrystallized from benzene; 0.112 g., m.p. 196–197°. The m.p. of the product was not depressed when mixed with 1,1′-methylene-bis-2-naphthol (m.p. 196–197°, lit. m.p. 200°[10]) yield 20%.

When I was heated with methanol containing hydrochloric acid, formaldehyde was liberated and identified as the 2,4-dinitrophenylhydrazone (m.p. and mixed m.p. with an authentic specimen, 162–163°). A dark red gum separated from solution. Addition of ferric chloride in ether to a benzene solution of II produced an immediate intense purple coloration. A gas was evolved when II was added to sodium in dry benzene.

3,4-Dihydro-3-*p*-tolyl-6-*t*-butyl-1,3,2H-benzoxazine.—A solution of 30 g. of paraformaldehyde (1.0 mole) in 30 ml. of methanol at 0° was added to a solution of 75.1 g. of *p*-*t*-butylphenol (0.5 mole) and 53.5 g. of *p*-toluidine (0.5 mole) in 75 ml. of methanol at 0°. After one day at room temperature, 1.4 g. of by-product was removed by filtration; m.p. 223–227°. The solvent was slowly removed from the filtrate by evaporation at room temperature. After twelve days the resulting product (97.7 g., 69% yield) was removed by filtration; m.p. 87–88°, after recrystallization from methanol. The product gave negative responses with both ferric chloride in absolute ether and sodium in benzene.

Anal. Calcd. for $C_{19}H_{23}NO$: N, 4.98. Found: N, 4.95.

A solution of the by-product (m.p. 223–227°) in boiling pyridine deposited white needles upon concentration and chilling; m.p. 125–126°, after recrystallization from acetone–water (40:1 by volume). Benzene, acetone or ethyl acetate solutions of the lower melting needles gradually deposited the original higher melting material upon standing at room temperature; m.p. 224–226°. The interconversions, melting points and solubility behavior of the lower and higher melting compounds correspond to the cyclic trimer and higher polymeride, respectively, of N-methylene-*p*-toluidine. The m.p. of the trimer, hexahydro-1,3,5-*p*-tolyl-*s*-triazine, is reported in the literature as 127° (127.9° cor.) while that of the higher polymeride is 225–227°.[11] The analyses below are for the product which melted at 223–227°.

Anal. Calcd. for $(C_8H_9N)_3$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.79; H, 7.41; N, 11.53.

3,4-Dihydro-3-*p*-tolyl-6-bromo-1,3,2H-benzoxazine.—Methanol solutions of *p*-toluidine (5.4 g., 0.05 mole), *p*-bromophenol (8.6 g., 0.05 mole) and paraformaldehyde (3.5 g., 0.12 mole) were combined at room temperature and cooled under the tap until the reaction mixture ceased to evolve heat. The reaction mixture was concentrated the next day to a mobile oil, which crystallized upon cooling. The product (10.5 g., 69% yield) melted at 79–80° after recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{14}BrNO$: Br, 26.27. Found: Br, 26.08.

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[9] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 229.

[10] K. Fries and H. Hubner, *Ber.*, **39**, 439 (1906).

[11] J. G. Miller and E. C. Wagner, THIS JOURNAL, **54**, 3698 (1932).