[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NATIONAL UNIVERSITY OF CHEKIANG CHINA]

CONDENSATION OF AMINO ETHERS WITH NAPHTHOLS, CRESOLS, AND NAPHTHYLAMINES*

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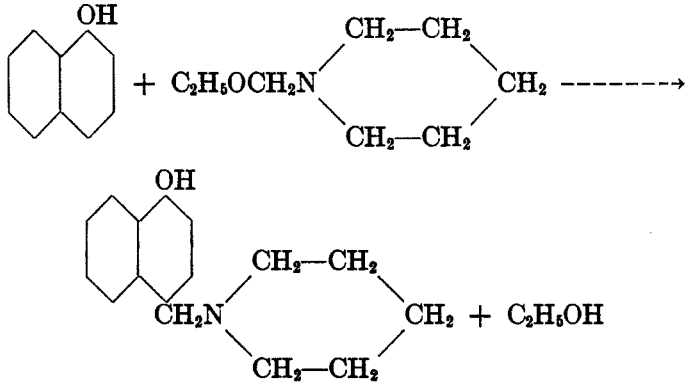
It is remarkable that, while the α-amino ethers have been known since 1921, little study has been made, up to the present, of their chemical behavior. Only Macleod and Robinson[1] made a brief study of the reactions of this class of compound with acetophenone and 2,4-dinitrotoluene. Although the reactions were not thoroughly investigated, the results indicated undoubtedly a condensation with the elimination of alcohol.

$$C_5H_{10}NCH_2OC_2H_5 + CH_3COC_6H_5 \rightarrow C_5H_{10}NCH_2CH_2COC_6H_5 + C_2H_5OH$$

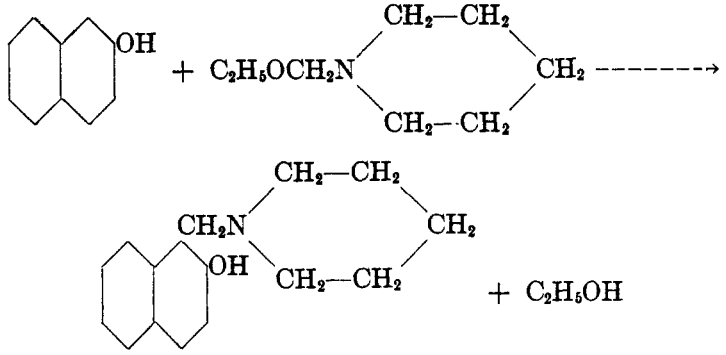
$$C_5H_{10}NCH_2OC_2H_5 + (NO_2)_2C_6H_3CH_3 \rightarrow C_5H_{10}NCH_2CH_2C_6H_3(NO_2)_2 + C_2H_5OH$$

The present authors think that this class of ethers awaits further investigation and that they may be susceptible of entering into reaction with various compounds containing active hydrogen atoms as revealed in other condensation reactions.

The research is begun with naphthols, cresols, and naphthylamines. With α- and β-naphthols the reactions with piperidinomethyl ethyl ether take place with such facility that no heating is necessary, and the reactions take uniquely the following course:

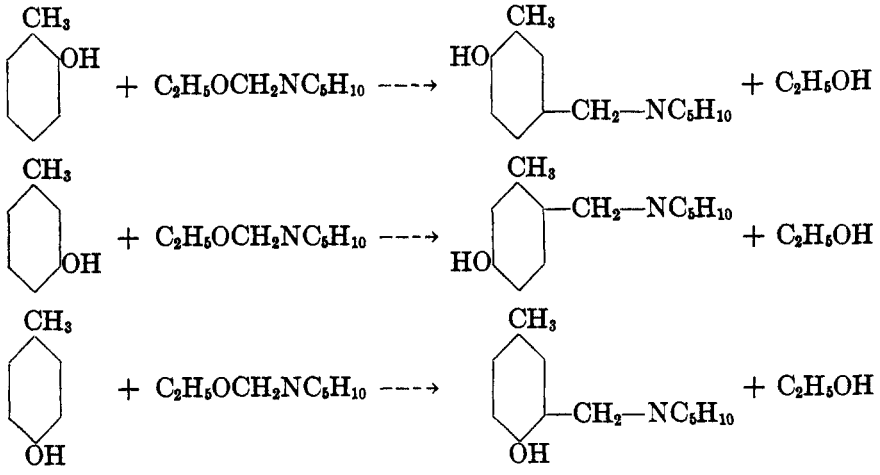


* *Editor's Note.*—This communication calls attention to an interesting synthesis of aminomethyl derivatives of compounds containing an active hydrogen atom. Although the authors offer no proof that the condensation takes the indicated course,



In both cases the yield is high when care is taken to carry out the condensation under moderate conditions. If heat is applied, a viscous mass is obtained, and the yield is considerably lowered.

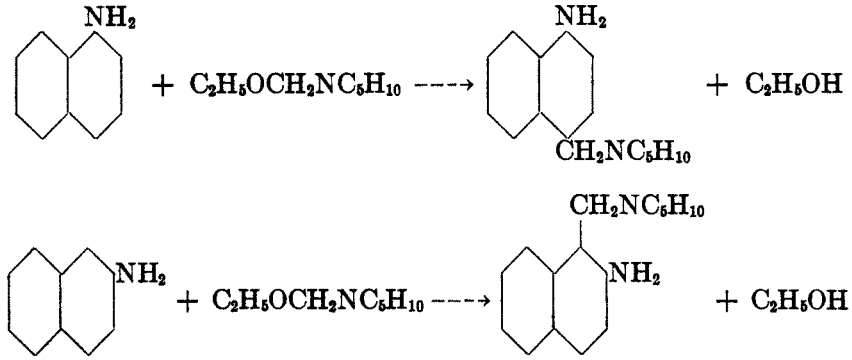
With cresols it is found that the working conditions are somewhat different from those with the naphthols, as heating is necessary to effect the reactions. With *ortho-*, *meta-*, and *para*-cresols the results of the condensation can be represented by the following equations:



or that the products obtained have the structure shown, we find that their conception of the reaction is correct. Five of the compounds described, namely the condensation products with α- and β-naphthol, and with *o*-, *m*-, and *p*-cresol, are already recorded in the literature [AUWERS AND DOMBROWSKI, *Ann.*, **244**, 289 (1906); HILDEBRANDT, *Arch. expt. Path. Pharmakol.*, **44**, 278 (1900); Farbenfabr. vorm. F. Bayer and Co., German Patent 89,979, March 1, 1895], and have the properties of the condensation products here reported. The paper is brought to publication because of its possible value to those interested in the preparation of such compounds. LYNDON F. SMALL.

[1] MACLEOD AND ROBINSON, *J. Chem. Soc.*, **119**, 1470 (1921).

When the reaction is extended to naphthylamines, the question which naturally arises is whether the hydrogen in the amino group or that in the nucleus is attacked. Experiments have shown that only the hydrogen attached to carbon atoms enters into reaction, because the end-products are shown by the benzenesulfonyl chloride test to contain the primary amino group. The reaction therefore takes the following course.



With aniline, benzamide, and phthalimide the amino ether reacts with the hydrogen atom attached to nitrogen. These are therefore not condensation reactions and cannot be discussed under the same topic.

EXPERIMENTAL

1-Hydroxy-4-piperidinomethylnaphthalene.—Twenty grams of α-naphthol was gradually added with stirring to twenty grams of piperidinomethyl ethyl ether in a beaker. The liquid became more and more viscous during the addition, until finally the whole was turned into a solid mass. The beaker was then put into a desiccator under vacuum to evaporate the alcohol formed in the condensation. After standing overnight, the solid was powdered and extracted repeatedly with a 10% sodium hydroxide solution to remove any unreacted naphthol, filtered under suction and washed with water until free from alkali. It was then recrystallized from acetone from which it separated as find needles. The yield of the crude product was thirty-two grams, and that of the pure compound twenty-four grams. The latter amounts to fifty-five per cent. of the theoretical quantity. It melts at 133°. It is soluble in most organic solvents, insoluble in water, and soluble in acid.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81.
Found: C, 79.7; H, 7.87; N, 5.90.

Picrate.—Yellow crystals from alcohol; m.p., 98°.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 11.91. Found: N, 12.05.

1-Piperidinomethyl-2-hydroxynaphthalene.—Twenty grams of β-naphthol was slowly added, with stirring, to twenty grams of piperidinomethyl ethyl ether. Much heat was developed. When all the naphthol was added a solid mass resulted. The alcohol was sucked off, and the residue was allowed to stand overnight under vacuum in a desiccator. The same treatment as in the preceding operation then followed and the product was finally recrystallized from alcohol. The pure compound consists of colorless needles melting at 96°. The yield is about sixty-five per cent. of the

theoretical quantity. It is soluble in common organic solvents and acids but insoluble in water.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.7; H, 7.87; N, 5.81.
Found: C, 79.9; H, 7.97; N, 5.89.

Picrate.—Yellow crystals melting at 101°.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 11.91. Found: N, 12.07.

1-Hydroxy-2-methyl-4-piperidinomethylbenzene.—To fifteen grams of *o*-cresol in a 200-cc. round-bottomed flask was slowly added twenty-two grams of piperidinomethyl ethyl ether. The mixture was then heated on the water bath under a reflux condenser protected from moisture by a calcium chloride tube. At the end of two hours the content, which became yellow in color, was transferred to a Wurtz flask and subject to vacuum distillation. The alcohol was first removed, together with some unreacted amino ether and methylene-bis-piperidine. The main portion distilled at 156–7° under 6 mm. pressure as a colorless liquid. The yield is 29 g.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 75.93; H, 9.51; N, 6.56.

Picrate.—Yellow crystals from alcohol; m.p. 177°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.65.

Platinichloride.—Yellow crystals, soluble in hot hydrochloric acid, insoluble in water and organic solvents; m.p. 194°.

Anal. Calc'd for $C_{26}H_{40}Cl_6N_2O_2Pt$: Pt, 23.78. Found: Pt, 23.52.

1-Hydroxy-3-methyl-4-piperidinomethylbenzene.—Ten grams of *m*-cresol was mixed with fifteen grams of piperidinomethyl ethyl ether in a 200-cc. round-bottomed flask and heated under reflux on the water bath for three hours. The content was then subjected to vacuum distillation. The main portion was collected at 158–61°. The colorless distillate crystallized in the form of needles on cooling. The yield was about 18 g. The recrystallized product (from ether) melts at 56°. It is colorless and soluble in most organic solvents, slightly soluble in water, and soluble in acids.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 76.31; H, 9.42; N, 7.03.

Picrate.—Yellow crystals from alcohol; m.p. 127°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.81.

1-Hydroxy-4-methyl-6-piperidinomethylbenzene.—Twenty-two grams of piperidinomethyl ethyl ether was mixed with fifteen grams of *p*-cresol in a 200-cc. round-bottomed flask and the content was heated on the water bath for four hours. After evaporating the low-boiling fraction the content of the flask solidified to a compact mass. It was then recrystallized from alcohol, yield 28 g. It consists of snow white crystals melting at 45°C. It is soluble in most organic solvents, slightly soluble in water, and soluble in acids.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.36; N, 6.81.
Found: C, 76.14; H, 9.52; N, 6.91.

Picrate.—Yellow crystals from alcohol; m.p., 149°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: N, 12.90. Found: N, 12.78.

Platinichloride.—Yellow crystals; m.p. 199°. It is soluble in hot hydrochloric acid, insoluble in water and organic solvents.

Anal. Calc'd for $C_{26}H_{40}CL_6N_2O_2Pt$: Pt, 23.78. Found: Pt, 23.70.

1-Amino-4-piperidinomethylnaphthalene.—Ten grams of piperidinomethyl ethyl ether was added to ten grams of α-naphthylamine in a 200-cc. round-bottomed flask. The mixture was then heated on the water bath for two hours. The content turned into a dark-red, viscous, fluorescent liquid which solidified on standing. To facili-

tate the formation of crystals 10 cc. of petroleum ether was added and strongly stirred while the flask was kept in a freezing mixture. The crystals which formed were recrystallized twice from benzene. The melting point is 124°. The yield is almost quantitative.

Anal. Calc'd for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41; N, 11.66.
Found: C, 80.09; H, 8.45; N, 11.31.

Benzenesulfonyl chloride test.—To 4 cc. of 5% sodium hydroxide solution 0.2 g. of *p*-piperidinomethyl-α-naphthylamine was added, followed by 0.2 g. of benzenesulfonyl chloride, and the mixture was heated gently. The liquid was then filtered and acidified. The precipitate which formed assumed leaf-like crystalline form on standing. On recrystallization from ether it gave the pure compound melting at 163°.

1-Piperidinomethyl-2-aminonaphthalene.—Twenty grams of piperidinomethyl ethyl ether was added to twenty grams of β-naphthylamine in a 200-cc. round-bottomed flask. The mixture was heated on the water bath for four hours. A red fluorescent viscous liquid was obtained. On cooling in freezing mixture and vigorous stirring, the content solidified. After recrystallization from benzene, white crystals melting at 114° were obtained. The yield is almost quantitative.

Anal. Calc'd for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41; N, 11.66.
Found: C, 79.80; H, 8.58; N, 11.41.

Benzenesulfonyl chloride test.—To 4 cc. of a 5% sodium hydroxide solution was added 0.2 g. of 1-piperidinomethyl-2-amino-naphthalene, followed by 0.2 g. of benzenesulfonyl chloride. The mixture, after being gently heated, was filtered and acidified. The precipitate was filtered by suction and recrystallized from ether; m.p. 83°.

SUMMARY

(1) Piperidinomethyl ethyl ether reacts with α- and β-naphthol to form 1-hydroxy-4-piperidinomethylnaphthalene and 1-piperidinomethyl-2-hydroxynaphthalene respectively.

(2) With *o*-, *m*-, and *p*-cresol a similar condensation, with the elimination of alcohol, was observed. The products were 1-hydroxy-2-methyl-4-piperidinomethylbenzene, 1-hydroxy-3-methyl-4-piperidinomethylbenzene and 1-hydroxy-4-methyl-6-piperidinomethylbenzene.

(3) When piperidinomethyl ethyl ether acts on α- and β-naphthylamine the amino group is not attacked. The products obtained were 1-amino-4-piperidinomethylnaphthalene and 1-piperidinomethyl-2-aminonaphthalene respectively.

(4) With aniline, benzamide and phthalimide the amino ether reacts only with the hydrogen attached to nitrogen.