

From this amine and phenyl isothiocyanate there was obtained phenyl-2-ethylhexahydrobenzylthiourea as a heavy oil which hardened after standing for three days. When recrystallized twice from 50% ethanol and once from high-boiling petroleum ether it melted at 88°.

Anal. Calcd. for $C_{13}H_{24}N_2S$: C, 69.52; H, 8.75. Found: C, 69.52; H, 8.93.

Phenylthiourea of the Reduced Adduct.—From phenyl isothiocyanate and the amine obtained by the reduction of I⁴ there was obtained an oil which was induced to crystallize by cooling its alcoholic solution to -80°. After being recrystallized twice from 50% ethanol and once from high-boiling petroleum ether the product melted at 146-148°.

Anal. Calcd. for $C_{13}H_{24}N_2S$: C, 69.52; H, 8.75. Found: C, 69.57; H, 8.98.

Aromatization of I. A. Bromination with One Equivalent of Brominating Agent and Dehydrobromination.—To a solution of 5.0 g. (0.038 mole) of I⁴ in 50 ml. of ethylene dichloride was added 6.8 g. (0.038 mole) of purified N-bromosuccinimide, and the mixture was heated to boiling with stirring. After refluxing for one and one-half hours, the solution gave a negative test for active bromine with acidified potassium iodide solution. The mixture was cooled, the precipitated succinimide was removed by filtration and the ethylene dichloride was distilled. The bromide was separated from a small amount of succinimide by extraction of the residue with cold absolute ethanol. The alcohol was then removed by distillation. To the dark residual oil was added 12 g. of quinoline and the mixture was distilled (oil-bath temp. 170-180°) slowly under reduced pressure through a small column. The distillate boiling from 110-114° (16 mm.) was shaken with dilute hydrochloric acid to remove any quinoline and the nitrile was extracted with ether and redistilled.

Attempted hydrolysis of this mixture with 75% sulfuric acid yielded only tar. However, when 0.40 g. of the material was refluxed for forty-seven hours with 0.5 g. of potassium hydroxide in 6.5 ml. of 60% ethanol, in addition to unhydrolyzed nitrile, there was isolated a small quantity of a white crystalline material. After recrystallization from water and chloroform it melted at 151-152° and showed no depression in melting point when mixed with a sample of 2-ethylbenzamide.³ There was not enough of this material for analysis.

B. Bromination with Two Equivalents of Brominating Agent and Dehydrobromination.—To a solution of 5.0 g.

(4) Sample furnished by Dr. R. L. Myers.

(0.038 mole) of I⁴ in 85 ml. of benzene was added 13.7 g. (0.076 mole) of purified N-bromosuccinimide and the solution was heated to boiling with stirring. After refluxing for two hours a positive test for active bromine was still obtained. The reaction mixture was cooled to 0° and the precipitated succinimide was removed by filtration. Distillation of the benzene was accompanied by the evolution of hydrogen bromide. To the residual oil was added 16.8 g. of lepidine and the mixture was distilled slowly under reduced pressure through a small column. The distillate boiling at 80-88° (3 mm.) was collected, shaken with dilute hydrochloric acid, recollected in ether, and redistilled to yield a colorless oil that darkened rapidly.

A portion of this nitrile was hydrolyzed in alcoholic sodium hydroxide solution in the presence of 30% hydrogen peroxide.⁵ The alcohol was removed by distillation and the cold aqueous residue was extracted with chloroform. Concentration of the extract yielded 2-vinylbenzamide, which after recrystallization from chloroform melted at 151.5-152°.

Anal. Calcd. for C_9H_9ON : C, 73.45; H, 6.16; N, 9.52. Found: C, 73.15; H, 6.16; N, 9.71.

This amide showed no depression in melting point when mixed with 2-vinylbenzamide prepared by hydrolysis of 2-cyanostyrene.

2-Vinylbenzamide.—Hydrolysis of 0.50 g. of 2-cyanostyrene⁶ in the presence of 30% hydrogen peroxide by the same procedure as described above yielded 0.22 g. of crude 2-vinylbenzamide which melted at 143-147°. Recrystallization from chloroform raised the melting point to 151.5-152°.

Anal. Calcd. for C_9H_9ON : C, 73.45; H, 6.16. Found: C, 73.54; H, 6.36.

Summary

The Diels-Alder adduct of 1-cyano-1,3-butadiene with 1,3-butadiene is shown to be a 2-cyano-1-vinylcyclohexene. Proof of the carbon structure is accomplished by bromination of the adduct, dehydrobromination and hydrolysis to 2-ethylbenzamide and 2-vinylbenzamide.

(5) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 586.

(6) Sample furnished by Dr. C. S. Marvel; see Marvel and Hein, *THIS JOURNAL*, **70**, 1895 (1948).

URBANA, ILLINOIS

RECEIVED JULY 29, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Amine Replacement Reactions of α -Dimethylaminomethyl- β -methoxynaphthalene

BY H. R. SNYDER AND JAMES H. BREWSTER¹

α -Dimethylaminomethyl- β -naphthol, a typical phenolic Mannich base, possesses a labile amino group which can easily be replaced by an activated aromatic nucleus,² by a cyano³ group or by another amine residue.⁴ A methylene quinone has been suggested as an intermediate in the amine exchange reaction⁴; such an intermediate could also participate in the other amine replacement

reactions of phenolic Mannich bases. It has been suggested previously that a vinyl ketone is formed in the first step of amine replacement reactions of ketonic Mannich bases⁵ and their quaternary salts.⁶

In a test of the hypothesis that amine elimination is the first step in amine replacement reactions of Mannich bases, it was desired to prepare α -dimethylaminomethyl- β -methoxynaphthalene (V) and its methiodide (VI) and to subject these compounds to the conditions of amine exchange and amine replacement reactions.

β -methoxynaphthalene failed to undergo the

(5) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

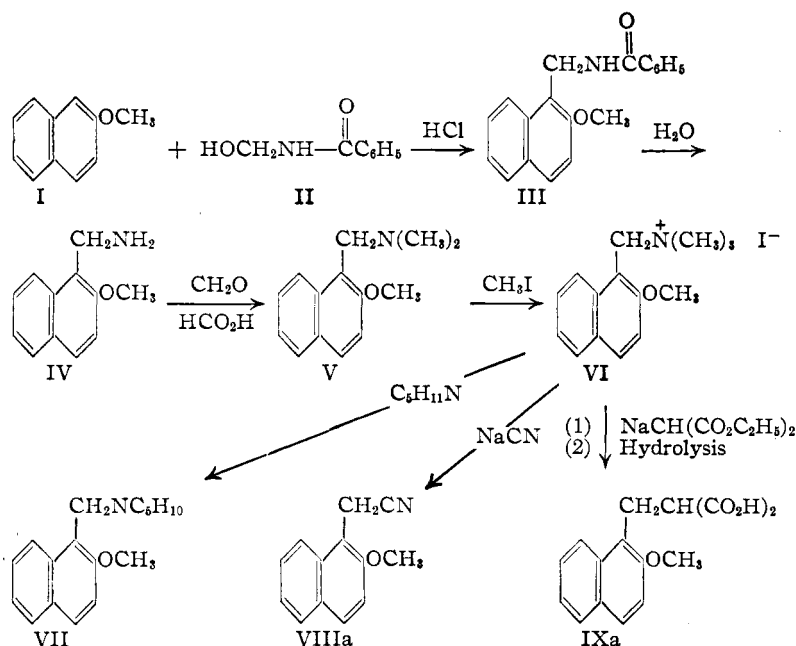
(6) du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

(1) Present address: Department of Chemistry, University of Chicago, Chicago, Illinois.

(2) Auwers and Dombrowsky, *Ann.*, **344**, 280 (1906).

(3) Salzer, U. S. Department of Commerce, U. S. Publication Board, P. B. Report, No. 706 (1946).

(4) Snyder and Brewster, *THIS JOURNAL*, **70**, 4230 (1948).



Mannich reaction,⁷ differing in this respect from 1-methylindole.⁸ Mannich bases of β -naphthol could not be etherified with either methyl iodide or dimethyl sulfate, apparently because quaternary salt formation occurred more readily. The method shown in the diagram was finally adopted for the preparation of V. In this synthesis α -aminomethyl- β -methoxynaphthalene (IV) was prepared by hydrolysis of the amide (III) with hot 20% sodium hydroxide solution; the stability of the primary amine (IV) to the alkaline solution is in marked contrast to the lability of naphthol Mannich bases in the presence of alkali.² The tertiary amine (V) also was stable to alkali; it could be distilled, and it yielded an isolable methiodide. In all these respects it differs from α -dimethylaminomethyl- β -naphthol. It failed to react with piperidine, piperidine acetate, sodium cyanide in aqueous ethanol or malonic ester in the presence of powdered sodium hydroxide. The low reactivity of the substance (V) indicates that the lability of the amino group in a phenolic Mannich base is great only when amine elimination is possible.

The quaternary salt (VI) reacted with piperidine by amine exchange, and with sodium cyanide and sodiomalonic ester by amine replacement. The activity of the salt (VI) in these reactions is similar to that of quaternary salts of benzylamine,^{9,10,11,12} and less than that of 1-methylgramine methiodide.⁸

(7) Blicke, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 303.

(8) Snyder and Eliel, *THIS JOURNAL*, **70**, 1703 (1948).

(9) Snyder and Speck, *ibid.*, **61**, 668, 2895 (1939).

(10) von Braun, Kühn and Coll, *Ber.*, **59**, 2330 (1926).

(11) von Meyer, *Abhandlung d. mathem.-phys. Klasse d. sächs. Gesellschaft d. Wissenschaften*, **31**, 179 (1908); [*Chem. Zentr.*, **80**, II, 1800 (1909)].

(12) Snyder, Smith and Stewart, *THIS JOURNAL*, **66**, 200 (1944).

Experimental^{13,14}

α -Benzamidomethyl- β -methoxynaphthalene (III) was prepared by modifications of the method described¹⁵ for the analogous α -chloroacetyl derivative. A mixture of 100 ml. of methanol, 31.6 g. of β -methoxynaphthalene¹⁶ and 30.2 g. of *N*-methylolbenzamide¹⁷ was stirred at 35–40° while a rapid stream of hydrogen chloride gas was introduced until a clear solution formed. Introduction of the gas was discontinued, and after six hours at room temperature the mixture was poured into ice and water. The thoroughly washed solid was dried, boiled for three hours with 300 ml. of methanol, recovered by filtration of the cooled suspension, washed repeatedly with water, and dried over calcium chloride to give 56 g. (97%) of III of m.p. 152–153°; recrystallization from eight parts of ethanol raised the m.p. to 153.5–154° (lit.¹⁸ 155°). Since the substance apparently has not been prepared previously by this method, a sample was analyzed.

Anal. Calcd. for $C_{19}H_{17}O_2N$: C, 78.35; H, 5.84; N, 4.82. Found: C, 78.26; H, 5.80; N, 4.75.

α -Aminomethyl- β -methoxynaphthalene (IV).—A mixture of 50 g. of III with a solution of 45 g. of sodium hydroxide in 50 ml. of water and 250 ml. of ethanol was refluxed twenty-four hours. The clear hot solution was poured into 1 l. of water; the solid was collected, washed, suspended in 1 l. of water and dissolved by the addition of about 25 ml. of 37% hydrochloric acid. The amine (IV) was recovered by the addition of alkali to the filtered, cooled solution. After washing and drying, the nearly pure IV (31.1 g., 96%) melted at 68–69° (lit. 41–42°¹³; ca. 100°¹⁵); it could be recrystallized from 75% ethanol or distilled at 141–142° (1 mm.).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 77.01; H, 6.94. Found: C, 76.90; H, 7.10.

Saturated alcoholic picric acid solution was added to a warm alcoholic solution of the amine. The bright yellow picrate precipitated as micro-needles. After it had been recrystallized from 95% ethanol it melted at 197–198°. Dey and Rajagopalan¹⁵ reported this picrate as melting at 215° and having a nitrogen content of 14.12 per cent., which they compared to the value of 14.00% based on the formula $C_{13}H_{16}N_4O_7$; however, the formula of the monopicate is $C_{13}H_{16}N_4O_8$ and the theoretical nitrogen content thus becomes 13.46%. The analysis of our sample was satisfactory.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 51.95; H, 3.85; N, 13.46. Found: C, 52.08; H, 4.02; N, 13.27.

α -Dimethylaminomethyl- β -methoxynaphthalene (V) was prepared from IV, 40% formalin and formic acid by modification of a standard procedure¹⁹ for the Clarke-Eschweiler reaction; the tertiary amine V, b.p. 146–150° (2 mm.), n_D^{20} 1.6002, was obtained in 60% yield.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.01; H, 7.86; N, 6.57.

(13) All melting points corrected.

(14) Microanalyses by Misses Theta Spoor and Emily Davis and Mr. Howard Clark.

(15) Einhorn and Spröngerts, *Ann.*, **361**, 163 (1908).

(16) Davis, *J. Chem. Soc.*, **77**, 37 (1900).

(17) Einhorn, Bischkopf and Szelinski, *Ann.*, **343**, 223 (1905).

(18) Dey and Rajagopalan, *Arch. Pharm.*, **277**, 359 (1939).

(19) Icke and Wisegarver, in "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

The picrate was prepared as above. It crystallized from alcohol in large bright yellow plates, m.p. 164–165°.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.02; H, 4.62; N, 12.55.

The methiodide VI, prepared (95% yield) in ether from a 40% excess of methyl iodide, melted at 158–159°.

Anal. Calcd. for $C_{15}H_{20}NOI$: C, 50.43; H, 5.64; N, 3.92; I, 35.53. Found: C, 50.14; H, 5.79; N, 3.73; I, 35.70.

α -Piperidinylmethyl- β -methoxynaphthalene (VII).—When a mixture of 1.78 g. of the methiodide (VI) and 8.5 g. of piperidine was heated under reflux a gaseous amine was evolved rapidly. After about three hours the mixture was added to aqueous alkali, and the ether-soluble portion was collected and freed of piperidine by evaporation, finally under diminished pressure. The acid-soluble portion of the residue was recovered and recrystallized from aqueous ethanol to give 0.60 g. (47%) of VII, m.p. 65–66°.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.41, 80.34; H, 8.58, 8.61; N, 5.45.

2-Methoxy-1-naphthaleneacetonitrile (VIIIa).—When aqueous solutions of the methiodide (VI) and excess sodium cyanide were refluxed for as long as a week, no amine replacement reaction occurred. The method of von Meyer¹¹ was finally employed. To a solution of 3.57 g. of α -dimethylaminomethyl- β -methoxynaphthalene methiodide (VI) in 10 ml. of water in a 50-ml. distilling flask was added 2.5 g. of sodium cyanide. The mixture was warmed until the cyanide had dissolved; a heavy oil separated. Water was slowly distilled from the solution at water-pump pressure until the solid residue was nearly dry. The bulb of the distilling flask was placed in a Wood's metal-bath which was heated (about 140°) until the material began to froth vigorously. The bath temperature was slowly raised to 250°. When evolution of trimethylamine had ceased, the mixture was distilled. The waxy product, b.p. 154° (0.5 mm.), was recovered from the side-arm of the flask by extraction with a small amount of hot acetone and crystallized from 50% aqueous acetone to yield 0.86 g. (43.5%) of light yellow crystals of 2-methoxy-1-naphthaleneacetonitrile (VIIIa) which melted at 111.5–112.5° (lit.²⁰ 111°). Alkaline hydrolysis of a portion of the nitrile gave 2-methoxy-1-naphthaleneacetic acid (VIIIb), m.p. 208–209° (lit. 208°, 210–211°).²²

(β -Methoxy- α -naphthylmethyl)-malonic Acid (IXa).—Freshly cut sodium (0.25 g.) was converted to sodium sand under xylene. The xylene was decanted and replaced by absolute diethyl carbitol²³ (25 ml.). Diethyl malonate (4.0 g.) was added, and the solution was stirred

with cooling until all of the sodium had reacted. α -Dimethylaminomethyl- β -methoxynaphthalene methiodide (VI) (3.57 g.) was added and the mixture was heated with stirring at 120–130° for seventy-two hours and finally at 150–160° for one hour. Trimethylamine was evolved during the entire heating period. The cooled mixture was treated with 40 ml. of 10% hydrochloric acid and extracted with benzene. The benzene solution was extracted with 10% sodium hydroxide, then with 37% hydrochloric acid (to remove diethyl carbitol) and finally with water. The dried benzene solution was concentrated and the thick oily residue was treated with a hot solution of 5 g. of sodium hydroxide in 5 ml. of water and 2 ml. of ethanol. A thick white paste formed when the mixture was stirred. After one-half hour the saponification mixture was warmed for a few minutes on a steam cone. The substituted malonic acid, recovered by dilution with water and acidification, was recrystallized from 10% ethanol. The white micro-crystals of (β -methoxy- α -naphthylmethyl)-malonic acid (IXa) weighed 1.73 g. (61%) and melted at 158–159° (dec.).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.15; neutral equivalent, 137. Found: C, 65.90; H, 5.39; neutral equivalent, 138.4.

2-(β -Methoxy- α -naphthyl)-propionic Acid (IXb).—The malonic acid (IXa) (0.4 g.) was heated under reflux for one hour with pyridine (4. g.).²⁴ The solution was cooled and 10% hydrochloric acid (40 ml.) was added. The white precipitate was collected and crystallized from a 10% ethanol. The propionic acid (IXb) formed white needles melting at 131–132° (lit.²⁶ 128°).

Anal. Calcd. for $C_{14}H_{14}O_4$: neut. equiv., 230. Found: neut. equiv., 230.2.

Summary

α -Dimethylaminomethyl- β -methoxynaphthalene (V) was prepared by benzamidomethylation of β -naphthyl methyl ether, followed by hydrolysis of the amide so formed and methylation of the primary amine. The dimethylamino group of V could not be replaced by reaction with piperidine, sodium cyanide or ethyl malonate; the compound was stable to alkali. The phenolic hydrogen atom appears to participate in the amine exchange and replacement reactions of phenolic Mannich bases.

The methiodide of V reacted by amine replacement with piperidine, sodium cyanide and sodio malonic ester. The reactivity of this quaternary salt resembles that of quaternary salts of benzylamine.

URBANA, ILLINOIS

RECEIVED JULY 26, 1948

(24) Grigsby, Hind, Chanley and Westheimer, *THIS JOURNAL*, **64**, 2606 (1942).

(25) Barger and Starling, *J. Chem. Soc.*, **99**, 2033 (1911).

(20) Cook, Downer and Hornung, *J. Chem. Soc.*, 502 (1941).

(21) Mayer, Schafer and Rosenbach, *Arch. Pharm.*, **267**, 571 (1929).

(22) Mauthner, *J. prakt. Chem.*, [2] **95**, 55 (1917).

(23) Commercial diethyl carbitol was distilled, b. p. 92–93° (30 mm.), the distillate was heated for eight hours with 1% of its weight of sodium, and finally distilled from the sodium that remained. The distillate was almost inert to sodium and after it was redistilled over sodium it failed to react even with molten sodium. The yield of absolute diethyl carbitol was about 70–80%.