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### Summary

The results of the electron diffraction investigation reported in this paper are collected in Table X. The re-investigation of benzene confirms the value 1.39 Å. for the C-C distance and provides a rough experimental value for the C-H distance. In pyridine and pyrazine the C-N distance is greater than expected for Kekulé resonance; the effect is attributed to extra reso-

nance with ionic structures. The electron diffraction results, electric dipole moment data, resonance energies, chemical information, and simple theoretical considerations indicate, almost uniformly, the order furan < pyrrole < thiophene for the degree of resonance stabilization of these molecules. The contributions of excited structures, other than those characteristic of the conjugated double bonds, are about 10, 24, and 34%, respectively. Part of the resonance of thiophene is with structures with ten electrons in the valence shell of the sulfur atom.

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## Naphthylaminoalkanes

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A number of phenyl and hydroxyphenyl substitution products of aminoethane and aminopropane such as epinephrine, neosynephrin, ephedrine and benzedrine have found extensive use as therapeutic agents.

Since there seems to be little information in the literature relative to the pharmacological activity of naphthyl analogs of compounds such as are mentioned above, we have prepared six naphthylaminoalkanes which, with the exception of  $\alpha$ -naphthylaminomethane, have been examined in the form of their hydrochlorides by Mr. L. W. Rowe of Parke, Davis and Company. It was found that the amines exhibited only a slight pressor activity upon initial intravenous injection in dogs with the development of tolerance to succeeding injections. An interesting property shown by the whole group is the production of a "cross tolerance," that is, little or no effect on blood pressure is produced by the administration of ephedrine if the injection of the latter is preceded by an injection of one of the naphthylaminoalkanes.

It seems that more effective compounds might be obtained by the introduction of hydroxyl groups into the naphthalene nucleus; however, Windaus and Bernthsen-Buchner<sup>2</sup> stated that  $\alpha$ -[1-(4-hydroxynaphthyl)]- $\beta$ -aminoethane exhibits only slight pharmacological activity.

(1) This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by C. E. Maxwell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Windaus and Bernthsen-Buchner, *Ber.*, **50**, 1120 (1917).

$\alpha$ -Naphthylaminomethane,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>CH<sub>2</sub>NH<sub>2</sub> (I), was obtained by interaction of  $\alpha$ -naphthylmethyl chloride and hexamethylenetetramine in chloroform.<sup>3</sup>

In order to obtain 1-( $\alpha$ -naphthyl)-1-aminoethane,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>CH(NH<sub>2</sub>)CH<sub>3</sub> (II), 1-( $\alpha$ -naphthyl)-1-aminopropane,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub> (IV) and 1-( $\alpha$ -naphthyl)-1-aminobutane,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (VI),  $\alpha$ -naphthylmagnesium bromide was allowed to react with aceto-, propio- and butyronitrile, respectively. The ketones, prepared in this manner, were converted into the oximes and the latter reduced to the amines with sodium and alcohol.

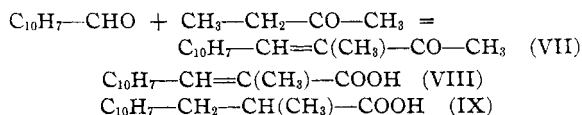
1-( $\beta$ -Naphthyl)-1-aminoethane,  $\beta$ -C<sub>10</sub>H<sub>7</sub>CH(NH<sub>2</sub>)CH<sub>3</sub> (III), was synthesized by reduction of  $\beta$ -acetone-naphthone oxime.

The naphthyl analog of benzedrine, 1-( $\alpha$ -naphthyl)-2-aminopropane,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>CH<sub>2</sub>CH(NH<sub>2</sub>)CH<sub>3</sub> (V), was obtained by the following series of reactions: diethyl malonate  $\rightarrow$  diethyl  $\alpha$ -naphthylmethylmalonate  $\rightarrow$  diethyl methyl- $\alpha$ -naphthylmethylmalonate  $\rightarrow$  methyl- $\alpha$ -naphthylmethylmalonic acid  $\rightarrow$   $\beta$ -( $\alpha$ -naphthyl)-isobutyric acid  $\rightarrow$   $\beta$ -( $\alpha$ -naphthyl)-isobutyramide  $\rightarrow$  1-( $\alpha$ -naphthyl)-2-aminopropane.

$\beta$ -( $\alpha$ -Naphthyl)-isobutyric acid (IX) was prepared by a second method according to which  $\alpha$ -naphthaldehyde was condensed with methyl ethyl

(3) For a discussion of this interesting reaction see Heidelberger, "An Advanced Laboratory Manual of Organic Chemistry," The Chemical Catalog Company, New York, N. Y., 1923, p. 24.

ketone to yield methyl  $\alpha$ -methyl- $\beta$ -( $\alpha$ -naphthyl)-vinyl ketone (VII). The latter was oxidized with sodium hypobromite to  $\alpha$ -methyl- $\beta$ -( $\alpha$ -naphthyl)-acrylic acid (VIII). Upon reduction of the acrylic acid with sodium amalgam there was obtained  $\beta$ -( $\alpha$ -naphthyl)-isobutyric acid.



Incidentally, diethyl methyl- $\alpha$ -naphthylmethylmalonate was condensed with urea to form methyl- $\alpha$ -naphthylmethylbarbituric acid.

### Experimental Part

**$\alpha$ -Naphthylmethylamine (I).**—A mixture of 19.4 g. (0.11 mole) of  $\alpha$ -naphthylmethyl chloride,<sup>4</sup> 14 g. (0.10 mole) of finely powdered hexamethylenetetramine and 50 cc. of chloroform was heated until the compounds began to react, the heat removed for a short time and the mixture then refluxed for one-half hour. The slightly turbid solution was cooled, 150 cc. of petroleum ether (30–60°) added and the gummy precipitate, which soon became solid, filtered and dried; yield 35 g. The material was placed in a distillation flask, 82 cc. of alcohol and 30 cc. of concd. hydrochloric acid added and the mixture distilled until about one-third of the liquid had been removed. The residue was cooled, the solid product filtered, dissolved in water, the solution made alkaline with concd. alkali and the amine extracted with ether; yield 11.5 g.; b. p. 200–205° (30 mm.).<sup>5</sup>

An ether solution of the amine, treated with hydrogen chloride, yielded the hydrochloride; m. p. 260–262°.<sup>6</sup>

**1-( $\alpha$ -Naphthyl)-1-aminoethane (II).**—To  $\alpha$ -naphthylmagnesium bromide, prepared from 103 g. of  $\alpha$ -bromonaphthalene, 12 g. of magnesium and 300 cc. of ether, there was added, during the course of one-half hour, 21 g. of acetonitrile, dissolved in 100 cc. of ether. The mixture was refluxed for one-half hour, cooled, stirred and 150 cc. of 10% hydrochloric acid added slowly, followed by the addition of 25 cc. of concd. hydrochloric acid. The ether layer was separated, dried, the solvent removed and the  $\alpha$ -acetophenone distilled; yield 62 g.; b. p. 145–147° (6 mm.).<sup>7</sup>

The oxime was formed in practically quantitative yield when 5 moles of sodium hydroxide was added, slowly, to one mole of the ketone, 1.5 moles of hydroxylamine hydrochloride, 360 cc. of alcohol and 75 cc. of water and the mixture refluxed for five minutes. The latter was poured into 550 cc. of concd. hydrochloric acid, diluted with 3600 cc. of water, the oxime filtered and recrystallized from dilute alcohol; m. p. 134–135°.<sup>8</sup>

(4) Coles and Dodds, *THIS JOURNAL*, **60**, 853 (1938).

(5) Von Braun, Blessing and Zobel [*Ber.*, **56**, 1996 (1923)], who reduced  $\alpha$ -naphthonitrile, found 155° (12 mm.).

(6) The melting point<sup>5</sup> is reported as 262–264°.

(7) Stobbe and Lenzer [*Ann.*, **380**, 95 (1911)] found 296–298°.

(8) (a) Rousset [*Bull. soc. chim.*, [3] **15**, 60 (1896)] found 135–136°; (b) St. Pfau and Ofner [*Helv. Chim. Acta*, **9**, 671 (1926)] reported 137–138°.

Twenty-five grams of the oxime was reduced with sodium and alcohol,<sup>9</sup> the alcohol removed under reduced pressure and the amine extracted with ether. The solution was dried with stick sodium hydroxide. The amine boiled at 141–142° (5 mm.).<sup>10</sup>; yield 15 g.

Hydrogen chloride was passed into an ether solution of the amine and the precipitated hydrochloride recrystallized from alcohol; m. p. 236–237°.<sup>11</sup>

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{NCl}$ : N, 6.75; Cl, 17.08. Found: N, 6.68; Cl, 17.02.

**1-( $\beta$ -Naphthyl)-1-aminoethane (III).**— $\beta$ -Acetophenone<sup>12</sup> was converted into its oxime as described above; m. p. 142–143°.<sup>12</sup> Eight and one-half grams of the oxime, reduced with sodium and alcohol, yielded 4.4 g. of the amine; b. p. 172–174° (29 mm.).<sup>13</sup> The amine hydrochloride melted at 279–280°<sup>14</sup> after it had been precipitated from an alcoholic solution by absolute ether.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{NCl}$ : N, 6.75; Cl, 17.08. Found: N, 6.61; Cl, 17.02.

**1-( $\alpha$ -Naphthyl)-1-aminopropane (IV).**— $\alpha$ -Propionaphthone was produced in 52% yield from propionitrile and  $\alpha$ -naphthylmagnesium bromide; b. p. 171–174° (12 mm.).<sup>15</sup>

The oxime was obtained in 88% yield; m. p. 55–57°.<sup>16</sup> Reduction of the oxime with sodium and alcohol yielded the amine in 50% yield; b. p. 148–149° (10 mm.).

The amine hydrochloride melted at 281–282° after precipitation by ether from an alcoholic solution.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{16}\text{NCl}$ : N, 6.32; Cl, 16.00. Found: N, 6.22; Cl, 15.81.

**Diethyl  $\alpha$ -Naphthylmethylmalonate.**—Two hundred and five grams of this compound was obtained from 288 g. of diethyl malonate, 360 cc. of dry, thiophene-free benzene, 20.7 g. of sodium and 158 g. of  $\alpha$ -chloromethylnaphthalene; b. p. 199–201° (3 mm.).<sup>17</sup>; yield 205 g.

**Diethyl Methyl- $\alpha$ -naphthylmethylmalonate.**—This compound was obtained in 89% yield in the usual manner from 17.5 g. of sodium, 380 cc. of absolute alcohol, 227 g. of diethyl  $\alpha$ -naphthylmethylmalonate and 170 g. of methyl iodide; b. p. 207–209° (2 mm.); m. p. 51–52° after recrystallization from alcohol. The compound is soluble in ether, benzene and alcohol.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_4$ : C, 72.59; H, 7.06. Found: C, 72.42; H, 7.12.

**Methyl- $\alpha$ -naphthylmethylmalonic Acid.**—A mixture of 130 g. of the ester, 1000 cc. of 60% alcohol and 79 g. of potassium hydroxide was refluxed for four hours, the alcohol removed and the residue made acid to congo red; yield 97 g.; m. p. 172–173° (dec.) after recrystallization from dilute alcohol. The acid is soluble in ether and alcohol, slightly soluble in benzene.

(9) See "Organic Syntheses," **11**, 58 (1931), for the general procedure.

(10) (a) Samuelsson [Thesis, Univ. Lund, 1923; *C. A.*, **18**, 1833 (1924)] reported 153° (11 mm.); (b) Hayashi, *Sci. Pap. Inst. Phys. Chem. Res.*, **20**, 398; *Chem. Zentr.*, **104**, I, 1728 (1933)] found 183.5° (41 mm.).

(11) The melting point reported<sup>11</sup> is 220–221° (dec.).

(12) The melting points reported are 142–143°<sup>12a</sup> and 145–146°.<sup>12b</sup>

(13) Samuelsson<sup>10b</sup> found 142–143° (6–7 mm.).

(14) The reported melting point is 199–200°.<sup>10a</sup>

(15) Rousset<sup>8a</sup> found 166–168° (8 mm.).

(16) The melting point reported is 57–58°<sup>8a</sup> (p. 63).

(17) Mayer and Sieglitz [*Ber.*, **55**, 1843 (1922)] found 221° (11 mm.); they used  $\alpha$ -bromomethylnaphthalene.

*Anal.* Calcd. for  $C_{15}H_{14}O_4$ : C, 69.75; H, 5.47. Found: C, 69.63; H, 5.55.

**$\beta$ -( $\alpha$ -Naphthyl)-isobutyric Acid (IX).**—The malonic acid was heated, in 15-g. portions, at 175–180° in an oil-bath for three to four hours. The viscous residue crystallized when rubbed and melted at 91–92° after recrystallization from petroleum ether (90–100°). The acid is soluble in ether, benzene and alcohol.

*Anal.* Calcd. for  $C_{14}H_{14}O_2$ : C, 78.48; H, 6.59. Found: C, 78.60; H, 6.71.

According to a second procedure 11.5 g. of  $\alpha$ -naphthaldehyde bisulfite<sup>18</sup> compound was treated with 10% sodium carbonate solution, the aldehyde extracted with ether, the solution dried with fused sodium sulfate and the solvent removed. The aldehyde, mixed with 7.2 g. of methyl ethyl ketone, was kept cool, 0.9 g. of hydrogen chloride passed into it, the mixture shaken for sixteen hours, washed with water and then with sodium carbonate solution. The crude, oily methyl  $\alpha$ -methyl- $\beta$ -( $\alpha$ -naphthyl)-vinyl ketone (VII), which possessed a camphoraceous odor, was dissolved in 100 cc. of alcohol, stirred and cooled and sodium hypobromite, prepared from 24 g. of bromine, 20 g. of sodium hydroxide and 50 cc. of water, was added. During this process the temperature was kept below 20°. The mixture was stirred for one hour at ordinary temperature, filtered and about 7 g. of sodium bisulfite added to destroy any hypobromite. The mixture was evaporated to about one-half of its original volume on a steam-bath, treated with charcoal, filtered and acidified. The precipitated  $\alpha$ -methyl- $\beta$ -( $\alpha$ -naphthyl)-acrylic acid (VIII) weighed 6.4 g.; m. p. 149–150°<sup>19</sup> after recrystallization from benzene.

To 4.2 g. of the acrylic acid, dissolved in 10% sodium carbonate solution, there was added 58 g. of 4% sodium amalgam. After forty-eight hours the alkaline solution was separated, filtered and acidified. The gummy precipitate, which solidified when cooled, weighed 3.6 g. The crude isobutyric acid melted at 91–92°.

**$\beta$ -( $\alpha$ -Naphthyl)-isobutyramide.**—A mixture of 77 g. of the isobutyric acid and 50 g. of thionyl chloride was heated in an all-glass apparatus for three hours on a steam-bath, poured into 120 cc. of cold, 28% ammonia water, which was stirred vigorously, and the precipitated amide recrystallized from benzene; yield 73 g.; m. p. 134–135° after recrystallization from benzene.

The amide is soluble in alcohol and benzene and insoluble in ether.

*Anal.* Calcd. for  $C_{14}H_{15}ON$ : N, 6.57. Found: N, 6.60.

**1-( $\alpha$ -Naphthyl)-2-aminopropane (V).**—An alkaline hypobromite solution, prepared from 25.4 g. of bromine, 240 g. of sodium hydroxide and 2400 cc. of water, was cooled to 10–15° and 32 g. of the isobutyramide added. The mixture was heated at 70–80° for one and one-half hours, 24 g. of solid sodium hydroxide added and the mixture heated two hours longer; when cooled, the brown, oily precipitate became crystalline. The latter was extracted

with ether; 5 g. of ether-insoluble material proved to be unchanged amide. The ether solution was extracted with 25-cc. portions of 10% hydrochloric acid and the combined extracts made alkaline. The amine was extracted with ether, the solution dried with fused sodium sulfate and treated with hydrogen chloride; 4.8 g. of the amine hydrochloride precipitated. After it had been dissolved in the smallest possible amount of hot absolute alcohol and precipitated by addition of absolute ether the hydrochloride melted at 213–214°.

*Anal.* Calcd. for  $C_{13}H_{15}NCl$ : N, 6.32; Cl, 16.00. Found: N, 6.25; Cl, 15.93.

**1-( $\alpha$ -Naphthyl)-1-aminobutane (VI).**—The required  $\alpha$ -butyronaphthone was obtained by addition of 13.8 g. of butyronitrile, dissolved in 50 cc. of ether, to the Grignard reagent prepared from 51.8 g. of  $\alpha$ -bromonaphthalene, 6.0 g. of magnesium and 150 cc. of ether. The mixture was refluxed for one hour, the imine decomposed with hydrochloric acid and the ketone purified by distillation; yield 13 g.; b. p. 155–157° (3 mm.).<sup>20</sup>

The oxime, prepared in the manner described, was extracted from the acidified reaction mixture with ether; b. p. 185–187° (8 mm.).<sup>21</sup>

The amine was obtained by reduction of the oxime with sodium and alcohol. The ether extract of the crude amine was shaken with 10% hydrochloric acid whereupon about one-half of the amine separated as hydrochloride after the acidic solution had remained at ordinary temperature for some time. The salt was removed, the filtrate made alkaline and the rest of the amine extracted with ether; b. p. 142–143° (4 mm.).

The amine hydrochloride melted at 281–282° after it had been precipitated from a warm alcoholic solution by the addition of ether.

*Anal.* Calcd. for  $C_{14}H_{15}NCl$ : N, 5.92; Cl, 15.05. Found: N, 5.89; Cl, 14.91.

**Methyl- $\alpha$ -naphthylmethylbarbituric Acid.**—To sodium ethylate, prepared in 30 cc. of toluene, from 0.7 g. of sodium and 1.4 g. of alcohol, there was added 7.7 g. of diethyl methyl- $\alpha$ -naphthylmethylmalonate. The mixture was heated for four hours at 120–125°, shaken with about 100 cc. of water, the aqueous layer separated and acidified. The oily precipitate, which soon solidified, was recrystallized from a mixture of dioxane and petroleum ether (90–100°); m. p. 127–128°.

*Anal.* Calcd. for  $C_{16}H_{14}O_3N_2$ : N, 9.92. Found: N, 9.83.

## Summary

Several naphthylaminoalkanes—derivatives of methane, ethane, propane and butane—have been prepared and found to exhibit only slight pressor activity. A characteristic pharmacological feature of these compounds is the development of tolerance.

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(18) Ref. 16, p. 1846; also Ref. 4, p. 854.

(19) Rousset [*Bull. soc. chim.*, [3] 17, 813 (1897)], who used another preparative method, reported 151°.

(20) The boiling point recorded is 316–318°<sup>8a</sup> (p. 65).

(21) Rousset<sup>8a</sup> (p. 65) found 206–208° (13 mm.).