[Contribution from the School of Chemistry of the University of Minnesota]

PREPARATION AND REDUCTION OF 2-METHOXY-N-METHYL-1-NAPHTHALENEËTHYLAMINE[1]

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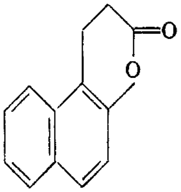
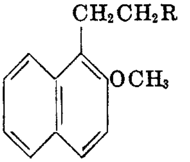
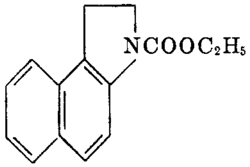
Comparatively simple substances related to morphine, the benzomorphans (1), might be obtained from 1-(β-methylaminoethyl)-2-tetralone. This tetralone is still unknown, however, and the present work shows that it cannot be obtained from 2-methoxy-N-methyl-1-naphthaleneëthylamine (IX) by sodium and alcohol reduction (2).

The compounds studied are formulated in the accompanying chart.

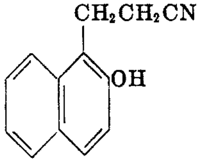


I



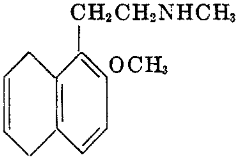


X



II

III R = COOH
IV $COOCH_3$
V $CONHNH_2$
VI NHCOOEt
VII NH_2
VIII N=CHAr
IX $NHCH_3$



XI

At first the important intermediate III was obtained by acid-catalyzed condensation of β-naphthol with acrylonitrile, through I, but the easier alkaline condensation, yielding II, was adopted as soon as it was published (3).

Attempts to convert III into VII directly by the Schmidt reaction, or through its amide by Hoffman degradation were unsuccessful. But the conversion was done easilyby Curtius degradation through IV and V.

A remarkable cyclization, to X, occurred when hydrolysis of the urethan VI was attempted using hot aqueous hydrochloric acid. In noteworthy contrast to the urethan, the amine itself (VII) was only demethylated when it was boiled with hydrobromic acid. Cyclization of the resulting hydroxyamine hydrobromide (to 4,5-benzoindoline) was slow in hot ethylene glycol.

Reduction of IX with sodium and alcohol (1, 4) did not yield the desired 1,4-dihydro compound, but instead it gave the 5,8-dihydro derivative (XI). Careful examination of the reduction product in light of the well known difficulty of

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[1] From the Ph.D. Thesis of H. E. Hood, September 1950.

purifying partially reduced naphthalenes (5), indicated that it contained some unchanged IX. Derivatives of the reduction product apparently were solid solutions containing the corresponding derivatives of IX. Neither crystallization nor chromatography effected complete purification. The benzoyl derivative, however, was obtained in a pure state by conversion into and then regeneration from its dibromide.

Location of the double bond in XI was based on the unreactivity of the dibromide of the benzoyl derivative towards alcoholic silver nitrate. If the double bond had been in any position other than 6,7-, the dibromide would have been reactive. Confirmation of the $\Delta^{6,7}$ structure of XI was found in the ultraviolet spectrum of the compound, which was similar to that of the tetrahydro compound (6) obtained from IX by longer treatment with sodium and alcohol.

EXPERIMENTAL

2-Hydroxy-1-naphthalenepropionic acid lactone (I). A mixture of 58 g. of β-naphthol, 24 g. of acrylonitrile, 18 g. of zinc chloride, and 300 ml. of dry ether was saturated at 0° with hydrogen chloride and allowed to stand at room temperature for 16 hours. Then 200 ml. of benzene and 150 ml. of water were added, and the mixture was boiled for one hour. From the organic layer there was obtained 32 g. of I, m.p. 73–74.5° [reported 69–70° (3)].

A solution of 9.9 g. of the lactone in 56 ml. of 10% potassium hydroxide was stirred while 6.3 g. of methyl sulfate was added dropwise at about 40°. After 15 minutes, 56 ml. more base and 6.3 g. more methyl sulfate were added. The mixture was stirred for a few minutes, then boiled and finally acidified. There was obtained 10 g. of 2-methoxynaphthalene-1-propionic acid, m.p. 130–131° [reported 128° (3), 131–132° (7)].

When 27.7 g. of the lactone was powdered and shaken for five minutes with 140 ml. of conc'd ammonium hydroxide and 45 ml. of alcohol, it was converted into 2-hydroxynaphthalene-1-propionamide, from dil. alcohol, 18.8 g., m.p. 173° dec. [reported 171–172° (3)].

Anal. Calc'd for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1.

Found: C, 72.7; H, 6.2.

With methyl sulfate and aqueous potassium hydroxide, the amide gave 68–70% yields of 2-methoxy-1-naphthalenepropionamide, crystals from alcohol, m.p. 171.5–172.5°.

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6.

Found: C, 73.4; H, 6.3.

The methoxy amide yielded the methoxy acid when it was boiled with dil. aqueous sodium hydroxide, but no definite product was obtained when it was treated with sodium hypobromite or hypochloride in water or methanol.

2-Hydroxy-1-napthalenepropionitrile (II) was obtained in 66% yield by action of sodium hydroxide on a benzene solution of acrylonitrile and β-naphthol (3).

2-Methoxy-1-naphthalenepropionitrile was obtained in 86% yield by stirring a suspension of 130 g. of the hydroxy nitrile in 1300 ml. of water while 185 g. of methyl sulfate and 350 g. of 30% aqueous sodium hydroxide were added alternately in small portions during two hours. The product formed crystals from alcohol, m.p. 71–72.5°.

Anal. Calc'd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2.

Found: C, 79.8; H, 6.2.

2-Methoxy-1-naphthalenepropionic acid (III) was obtained from the nitrile by long boiling with aqueous sodium hydroxide or better as follows. To a solution of 38 g. of potassium hydroxide in 110 ml. of warm glycol was added 110 g. of 2-methoxy-1-naphthalenepropionitrile. The mixture was warmed cautiously with a free flame until the nitrile melted and started to dissolve. The resulting exothermic reaction was allowed to run to completion, and the mixture then was boiled for one hour. There was obtained 110 g. of crude acid, m.p. 121–127°; a portion crystallized from water had m.p. 132–133°.

Methyl 2-methoxy-1-naphthalene propionate (IV), a colorless oil, b.p. 182–185° at 6 mm. was obtained in 74% yield from 110 g. of the acid, 1600 ml. of methanol, and 40 ml. of sulfuric acid.

Anal. Calc'd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6.
Found: C, 73.9; H, 6.6.

2-Methoxy-1-naphthalene propionhydrazide (V) was obtained in crude yield of 90% (m.p. 144–145°) by boiling a mixture of 30 g. of IV, 36 g. of 85% hydrazine hydrate, and 12 ml. of methanol for about 20 minutes. The mixture was allowed to cool for several hours, and the product was removed and washed with dilute alcohol. A portion recrystallized from 60% alcohol had m.p. 146–147°.

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6.
Found: C, 68.5; H, 6.8.

The hydrazide reacted with acetone to form *2-methoxy-1-naphthalenepropionisopropylidenehydrazide*, colorless crystals, m.p. 143–144° (mixture with V, m.p. 125–133°).

Anal. Calc'd for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.1.
Found: C, 72.1; H, 7.1.

2-Methoxy-1-naphthalenepropionbenzylidenehydrazide, crystals from alcohol, had m.p. 221°.

Anal. Calc'd for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.1.
Found: C, 75.7; H, 6.1.

When equal weights of 2-methoxy-1-naphthalenepropionic acid and its hydrazide were mixed and heated to 175°, or when an alcoholic solution of the hydrazide was warmed with iodine (8) there was obtained *bis-(2-methoxy-1-naphthalenepropionyl)hydrazine*, crystals from acetic acid, m.p. 245–246°.

Anal. Calc'd for $C_{28}H_{28}N_2O_4$: C, 73.7; H, 6.2.
Found: C, 73.5; H, 6.5.

Curtius degradation through the urethan VI. A solution of 45 g. of 2-methoxy-1-naphthalenepropionhydrazide in 90 ml. of acetic acid, 9 ml. of conc'd hydrochloric acid, and 45 ml. of water was kept at 0–5° and stirred while 1.5 g. of sodium nitrite in 60 ml. of water was added dropwise. Stirring was continued for 15 minutes after the addition was done. The crystalline azide then was removed by filtration and dissolved in ether, where it was washed with aqueous soda and dried with calcium chloride. Absolute alcohol (50 ml.) was added, and the ether was removed by distillation. The alcohol solution was boiled for three hours, giving a little insoluble material and 2.5 g. of *N-carbethoxy-2-methoxy-1-naphthaleneëthylamine* (VI), needles from ligroin and then methanol, m.p. 71–72°.

Anal. Calc'd for $C_{16}H_{19}NO_3$: C, 70.3; H, 7.0.
Found: C, 70.2; H, 7.2.

When 5 g. of VI, 60 ml. of conc'd hydrochloric acid, and 40 ml. of water were mixed and boiled for 12 hours, *1-carbethoxy-4,5-benzoindoline* (X) was formed. It was isolated by cooling the acid solution and extraction with ether; colorless plates (1.4 g.) from alcohol, m.p. 118–119°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3.
Found: C, 74.7; H, 6.3.

Hydrolysis of the cyclized methane X was effected by boiling it for 30 minutes with 6% potassium hydroxide in glycol. The basic product was treated with sodium nitrite in aqueous hydrochloric acid, giving *1-nitroso-4,5-benzoindoline*, faintly yellow needles from alcohol, m.p. 177–179°.

Anal. Calc'd for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1.
Found: C, 73.0; H, 5.1.

Hydrolysis of the urethane VI in similar fashion with potassium hydroxide in glycol also gave a basic product. Treatment of this in dried ether solution with hydrogen chloride gave the *hydrochloride of 2-methoxy-1-naphthaleneëthylamine*, which darkened if it was kept in solution. Reprecipitated from alcohol with dry ether, the salt had m.p. 195–230° decomp.

Anal. Calc'd for $C_{13}H_{16}ClNO$: C, 65.7; H, 6.8.
Found: C, 65.5; H, 6.7.

Direct Curtius degradation. The azide from 36.6 g. of 2-methoxynaphthalenepropionhydrazide, washed with water on a filter but still moist, was added in small portions to 800 ml. of 1:1 hydrochloric acid, stirred and kept at 60–65°. At this temperature reaction proceeded smoothly; at 70° the azide reacted explosively. Addition of sodium hydroxide and extraction with ether gave 23.5 g. of crude amine. A portion with acetic anhydride in water gave *N-acetyl-2-methoxy-1-naphthaleneëthylamine,* colorless needles from dilute alcohol, m.p. 139–139.5°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0.

Found: C, 74.1; H, 7.3.

A portion of the crude amine was boiled for nine hours with 10 times its weight of 48% hydrobomic acid. The resulting *2-hydroxy-1-naphthaleneëthylamine hydrobromide* separated when the solution was cooled; crystals from alcohol and ether, m.p. 220° decomp.

Anal. Calc'd for $C_{12}H_{14}BrNO$: C, 53.7; H, 5.3.

Found: C, 53.4; H, 5.3.

A water solution of the salt gave a precipitate with sodium hydroxide, soluble in excess base. Only a little cyclization took place, and 50% of the hydrobromide was recovered after it had been heated to 200° in glycol. However when it was heated for five minutes in glycol containing excess potassium hydroxide, it gave a non-amphoteric basic product, which was converted into 1-nitroso-4,5-benzoindoline by nitrous acid.

2-Methoxy-N-methyl-1-naphthaleneëthylamine (IX). A mixture of 23.5 g. of 2-methoxy-1-naphthaleneëthylamine and 18.5 g. of piperonal was kept at 80° under reduced pressure for three hours. The resulting *2-methoxy-N-piperonylidene-1-naphthaleneëthylamine* (VIII) formed crystals from alcohol, m.p. 89–91°; yield 32 g.

Anal. Calc'd for $C_{21}H_{19}NO_3$: C, 75.6; H, 5.7.

Found: C, 75.6; H, 5.8.

A solution of 41 g. of the Schiff base (VIII) in 163 g. of methyl iodide was kept at 40–45° for five days. The solid methiodide then was removed, washed with ether, and boiled with 500 ml. of 0.1% hydrochloric acid. The regenerated piperonal was removed with ether, and the crude product (IX), a colorless oil (19 g.) was precipitated with sodium hydroxide. *2-Methoxy-N-methyl-1-naphthaleneëthylamine hydrochloride* formed colorless needles from alcohol-ether, m.p. 195–196°.

Anal. Calc'd for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2.

Found: C, 66.7; H, 7.3.

The *picrate,* yellow plates from alcohol, had m.p. 177–178°.

Anal. Calc'd for $C_{20}H_{20}N_4O_8$: C, 54.0; H, 4.5.

Found: C, 54.3; H, 4.7.

1-(2-Methoxy-1-naphthaleneëthyl)-1-methyl-3-phenyl-2-thiourea, from IX with phenyl isothiocyanate, formed faintly yellow crystals from alcohol, m.p. 179–180°.

Anal. Calc'd for $C_{21}H_{24}N_2OS$: C, 71.6; H, 6.9.

Found: C, 71.8; H, 6.9.

N-Benzoyl-2-methoxy-N-methyl-1-naphthaleneëthylamine, from IX with benzoyl chloride in aqueous sodium hydroxide, formed colorless plates from dilute alcohol, m.p. 125–127°.

Anal. Calc'd for $C_{21}H_{21}NO_2$: C, 79.0; H, 6.6.

Found: C, 79.0; H, 6.8.

N-Azoyl-2-methoxy-N-methyl-1-naphthaleneëthylamine, from IX with *p*-phenylazobenzoyl chloride in pyridine, formed orange crystals from dilute alcohol, m.p. 129–130°. The substance gave a single band when adsorbed from benzene on a column of alumina. The material eluted from the top half of the band had m.p. 130.5–131.0°, that from the bottom half, 130.5–131.5°.

Anal. Calc'd for $C_{27}H_{25}N_3O_2$: C, 76.6; H, 6.0.

Found: C, 76.9; H, 6.0.

Reduction of IX. A solution of 5.9 g. of the crude dry amine in 150 ml. of absolute alcohol was heated to boiling and treated with 6.7 g. of sodium. After the metal had dissolved, the mixture was acidified and distilled to dryness under reduced pressure. Water and sodium hydroxide were added, and the basic product was removed with ether and dried over potassium hydroxide. As noted above this reduction product was mainly 5,8-dihydro-2-methoxy-N-methyl-1-naphthaleneëthylamine (XI) containing an indefinite amount of the unhydrogenated compound. It was isolated as its *hydrochloride*, colorless crystals from alcohol-ether, m.p. 211° decomp., yield 2.9 g.

Anal. Calc'd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.95.

Found: C, 66.11; H, 8.03.

The *picrate* of the reduction product formed orange needles, m.p. 156° decomp.

Anal. Calc'd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97.

Found: C, 53.85; H, 4.99.

The substituted *phenylthiourea* from the reduction product formed needles, m.p. 174–175°.

Anal. Calc'd for $C_{21}H_{24}N_2OS$: C, 71.6; H, 6.9.

Found: C, 71.8; H, 6.9.

The *azoyl derivative* (0.9 g. from 1 g. of the hydrochloride) formed orange crystals from ligroin, m.p. 115–117°, not changed by repeated crystallization. A chromatogram on alumina, developed with chloroform in ligroin, was a broad continuous band. Five equal sections of the band were found to contain approximately equal amounts of material (0.17 g.); m.p.'s (top) 122–124°, 121–123°, 119–121.5°, 116.5–119°, 114–115° (bottom). Separate chromatography of these fractions led nowhere, and the compound was not analyzed.

The *benzoyl derivative,* from the reduction product, benzoyl chloride, and aqueous sodium hydroxide, formed crystals from dilute alcohol. Various preparations had different melting points, between 121 and 126°. The sample used for u.v. spectrum determination had m.p. 122.5–124.5°. The analytical sample had m.p. 125–126° (mixture with the benzoyl derivative of IX, 116–124°).

Anal. Calc'd for $C_{21}H_{23}NO_2$: C, 78.45; H, 7.21.

Found: C, 78.15; H, 7.28.

A solution of 1.17 g. of the benzoyl derivative in carbon tetrachloride was treated at 5° with 0.42 g. of bromine. The mixture was brought to room temperature, decanted from a sticky red by-product, and then evaporated under reduced pressure. The residue was crystallized twice from dilute alcohol (giving 0.5 g. m.p. 117–140°) and four times from dilute acetone, giving 0.1 g. of *N-benzyol-6,7-dibromo-2-methoxy-N-methyl-5,6,7,8-tetrahydro-1-naphthaleneëthylamine*, m.p. 152.0–152.5°. Qualitative tests showed that the sample contained bromine and nitrogen, did not react with alcoholic silver nitrate, and developed no acidity when it was boiled with methanol for five hours.

Anal. Calc'd for $C_{21}H_{23}Br_2NO_2$: C, 52.4; H, 4.8.

Found: C, 52.2; H, 5.0.

A solution of 0.21 g. of the dibromide in 25 ml. of absolute alcohol was treated with 3 g. of acid-washed (9) twenty-mesh zinc and boiled for two hours. The resulting pure *N-benzoyl-5,8-dihydro-N-methyl-2-methoxynaphthaleneëthylamine* formed colorless crystals from alcohol, m.p. 122–124°. A mixture with the benzoyl derivative of the reduction product (m.p. 125–126°) had m.p. 121–123°.

Anal. Calc'd for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2.

Found: C, 78.7; H, 7.5.

Tetrahydro derivative of IX. A solution of 17 g. of IX in 150 ml. of boiling absolute alcohol was treated with 11 g. of sodium. The mixture was boiled for two hours, then 100 ml. more alcohol and 12 g. more sodium were added. After one hour, the solution was cooled, acidified, and distilled to a small volume. Addition of water caused a red oily hydrochloride to separate, nearly insoluble in water or benzene. This was extracted well with water, the extracts containing the soluble hydrochloride being combined and basified. The resulting amine was taken up in ether, dried, and acidified with ethereal hydrogen chloride, giving 4.0 g. of brown crystals, m.p. 205–206°. This material was converted into a benzoyl derivative in presence of aqueous sodium hydroxide, colorless needles from alcohol, m.p. 121.5–123.5°. A solution of 0.4 g. of this benzoyl derivative in 20 ml. of carbon tetrachloride was treated at 0–5° with 0.1 g. of bromine. The small amount of insoluble sticky material formed was discarded, and the soluble part was recrystallized from dilute acetone, giving colorless halogen-free crystals of *N-benzoyl-2-methoxy-N-methyl-5,6,7,8-tetrahydro-1-naphthaleneëthylamine*, m.p. 119.5–120.5°.

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.
Found: C, 77.95; H, 7.94.

Ultraviolet spectra

Substance	λ_{max} in mμ	Log E
N-Benzoyl-N-methyl-2-methoxy-1-naphthaleneëthylamine (IX-Bz)	231–232 272 282–283 295 325 336	4.83 3.65 3.75 3.69 3.39 3.45
Benzoyl derivative of reduction product, m.p. 122.5–124.5°	280–281 323 335	3.36 2.24 2.52
N-Benzoyl-N-methyl-5,8-dihydro-2-methoxy-1-naphthalene-ethylamine (XI-Bz)	280	3.30
N-Benzoyl-N-methyl-5,6,7,8-tetrahydro-2-methoxy-1-naphthaleneëthylamine	279–280 334–337	3.35 1.04

The weak bands at 323 and 335 mμ in the spectrum of the benzoyl derivative of the reduction product indicate contamination of the material by the unreduced substance (IX-Bz) which in pure state has *i.a.* bands at 325 and 336 mμ. The pure dihydro derivative regenerated from the dibromide has no bands in this region. It is likely that the weak absorption of the tetrahydro derivative at 334–337 mμ is also a result of contamination by the unreduced substance.

SUMMARY

Simple reactions starting with acrylonitrile and β-naphthol were used to prepare 2-methoxy-1-naphthalenepropionic acid. Curtius degradation of this acid went well, and conditions were worked out for monomethylating the amine so produced. However, contrary to hopes based on analogy, sodium and alcohol reduction of the methylated amine did not yield an aminoethyltetralone, for hydrogen was added to the unsubstituted ring of the naphthalene nucleus.

MINNEAPOLIS 14, MINNESOTA

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