Substituted Tetralins II: Preparation of 2-Amino-4-carbamyl-6-methoxy-4-methyltetralin

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Abstract □ The synthesis of 2-amino-4-carbamyl-6-methoxy-4-methyltetralin was accomplished by isonitrosation of the correspondingly substituted precursor 1-tetralone and subsequent catalytic reduction. This structural analog of meperidine exhibited only very slight analgesic activity.

Keyphrases □ 2-Amino-4-carbamyl-6-methoxy-4-methyltetralin—synthesis □ Analgesic activity—2-amino-4-carbamyl-6-methoxy-4-methyltetralin □ IR spectrophotometry—structure

Recently the preparation and analgesic potency of some 2-aminotetralin derivatives of general structure, I*a*, were reported (1). As part of a continuing study of structure activity relationships in the series, it was decided to prepare compounds having a carbonyl function (R_2 = C—R) in the 4-position. These derivatives are of
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interest because of their relationship to the meperidine and ketobemidone series of analgesics (III*a* and III*b*, respectively). The title compound (II) represents the first 4-carbonyl-containing derivative prepared in the authors' laboratory. It is anticipated that II can be converted to either I*b* or I*c* (X = H; Y = OCH_3) by conventional procedures and that separation of stereoisomers can be effected (see structures).

Attention had been focused since the early stages of the work in the authors' laboratory on the utility of 1-tetralones as useful intermediates for the introduction of 2-amino substituents into the tetralin moiety. A five-step sequence, beginning with a glyoxylation and ending with a Curtius reaction (26% overall yield), has been described previously (1). A more direct route, the isonitrosation of 1-tetralones followed by a catalytic reduction using the methods of Kindler and Peschke (2) and Rosenmund and Karg (3), appeared to be more suitable for the preparation of 4-carbonyl-2-aminotetralins.

PROCEDURE

A number of routes may be employed for the synthesis of 1-tetralones. The most common procedures are the cyclodehydration of γ-arylcarboxylic acids and the oxidation of the corresponding tetralins. Since a 6-methoxy substituent on the tetralin nucleus was also desired for the authors' purposes,[1] any direct cyclization to a 1-tetralone must, of necessity, proceed from less readily available *meta*-substituted phenyl intermediates. Moreover, the additional structural requirement imposed by the desire for a quaternary carbon atom to become C_4 in the tetralin system required the inclusion of an alkyl group on this carbon as well as the carbonyl moiety. A common general method for the preparation of a γ-quaternary carboxyl compound is a Michael condensation using acrylonitrile or methylacrylate on a tertiary carbon bearing a labile hydrogen atom. Thus, the starting material chosen for the sequence was *m*-methoxyhydratroponitrile (IV), which was prepared by the procedure of Kugita and Oine (4).

The synthesis of II is outlined in Scheme I. Compound V was prepared directly by carbomethoxyethylation of IV. The best results were obtained when IV was treated with methylacrylate and *N*-benzyltrimethylammonium hydroxide (5) without a solvent and by heating the mixture to reflux briefly after allowing it to stand overnight. In this manner, yields of up to 63% of V were obtained. The saponification of the ester (V), employing the procedure of Fuson and Miller (6), gave nearly quantitative yields of the cyano acid (VI) without affecting the nitrile group.

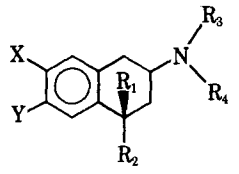
Cyclization of VI to a 1-tetralone was accomplished using several conventional cyclizing agents (stannic chloride, anhydrous hydrogen fluoride, and polyphosphoric acid). Aluminum chloride was not investigated because of its propensity to cause cleavage of ethers. The initial reagent employed was polyphosphoric acid, which has found extensive use in similar cyclizations (7–9). Although nearly a quantitative yield of crude ketonic material was obtained, the removal of a low-melting contaminant afforded only about a 75% yield of a pure tetralone, which was subsequently shown to be the amidotetralone (VIII) rather than the cyanotetralone (VII). Cyclodehydration by hydrogen fluoride (9–11) likewise gave about 75% yields of the same amidotetralone. This unexpected result had been obtained also by Price and Kaplan (11) in the cyclization of β-cyano-γ-(*p*-methoxyphenyl)-butyric acid. No doubt, entry of moisture into both the polyphosphoric acid and hydrogen fluoride-catalyzed reactions caused hydrolysis of the nitrile group. By far the most commonly employed reagent for cyclizations to tetralones is stannic chloride, either on the free acid (10, 11) or on the derived acid chloride (7, 8, 11–13). Moreover, from γ-cyano-γ-arylbutyric acids, Horning and Schock (8, 13) obtained good yields of 1-cyano-4-oxotetralins (hereafter designated 4-cyano-1-tetralones for simplicity and uniformity of nomenclature). By utilizing their procedure, yields well in excess of 90% of a quite pure product were obtained routinely.[2]

Although one of the ultimate goals of this investigation is to introduce an ester group at C_4 of a 2-aminotetralin system, no attempt was made in this synthetic scheme to convert either the amidotetralone (VIII) or the cyanotetralone (VII) to the corresponding ester because of the possibility of intramolecular aminolysis of the ester at C_4 by the primary amino group at C_2. Because the amide group does not react with primary amines and is resistant to catalytic reduction, it was decided to convert the cyanotetralone (VII) to the amidotetralone (VIII). The hindered nature of the nitrile group of VII became apparent when it was subjected to vigorous acid-catalyzed hydrolysis conditions without alteration. The nitrile (VII) was converted to the amide (VIII) in yields of 85–90% using alkaline hydrogen peroxide in a Radziszewski reaction (7, 15).

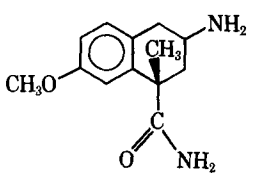
Nitrosations of aliphatic ketones have been reported using nitrous acid, nitrosyl chloride, nitrosyl sulfuric acid, nitrous fumes, and esters of nitrous acid (16). Acid or base is usually required as a catalyst with the last two reagents named. For the nitrosation of a carbon atom attached to a single activating group, such as a carbonyl, base catalysis is ordinarily not effective and acid must be used. However, cyclic ketones and phenones can be nitrosated in good yields using basic catalysts. 1-Tetralones and 1-indanones, being both cyclic and aromatic, are especially reactive toward nitrosation. Tetralones, however, seem to be quite susceptible to side reactions. Basic conditions promote oxidation of the products (dihydronaphthoquinone monoximes) to the quinoneimine tau-

[1] Substitution of an oxygen function in the 6-position of the tetralin system corresponds to a 3-oxygen function in the morphine series.

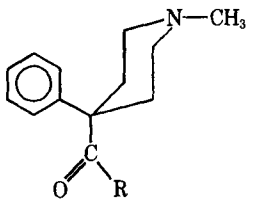
[2] The cyclization of γ-*m*-methoxyphenylbutyric acids or their chlorides can give rise to both 6- and 8-methoxy-1-tetralones. Although there have been occasional reports (12,14) of the formation of small amounts of the 8-methoxy analogs by cyclization into the *ortho*-position with reference to the methoxyl group, it has been shown (9,12) that excellent yields of the 6-methoxy analogs formed by cyclization into the *para*-position only are the usual result.



Ia, $R_1, R_2 = CH_3$;
R_3, R_4 = H or alkyl
b, $R_1, R_4 = CH_3$;
$R_2 = CO_2Et$
c, $R_1, R_3, R_4 = CH_3$; R_2 = COEt
X and Y = H, OH, OCH_3



II



IIIa, R = OEt
b, R = Et

tomers of 2-nitroso-1-naphthols. Acid reagents often cause rearrangements of substituents on the alicyclic ring.

The tetralones synthesized in this laboratory are resistant to aromatization because of the presence of a quaternary carbon at C_4. Therefore, the early attempts at the nitrosation of these compounds were conducted using concentrated hydrochloric acid and amyl nitrite in methanol according to the procedure of Perkin and Robinson (17). However, these initial experiments were uniformly unsuccessful as had been those of Horning and Schock (8) on a similar tetralone. Reports of successful nitrosations of variously substituted tetralones by the use of base (7, 18) prompted a trial of this catalyst. Using the procedure of Kornfeld *et al.* (7) a yield of about 30% of the desired isonitrosoamidotetralone (IX) was obtained in the initial trial run. Subsequent nitrosation experiments employing both acid- and base-catalyzed reactions on a number of tetralones revealed several beneficial modifications in both procedures[3] and led to good yields of IX by both methods.

The last step in the reaction sequence, leading to the substituted 2-aminotetralin (II), consists of the reduction of the enol-nitroso (or keto-isonitroso) moiety. Nitrosation of aryl ketones followed by reduction of the resulting product has long been used as a standard method for the preparation of various derivatives of β-phenethylamine (19). However, catalytic reductions often lead to aryl α-aminoketones, aryl α-aminoalkylcarbinols, or diarylpiperazines (20). Lithium aluminum hydride reductions give aryl α-aminoalkylcarbinols (21).

The synthesis of nonoxygenated amines by hydrogenations using palladium catalysts was studied extensively by Rosenmund and Karg (3). It was found that strong Lewis acids such as sulfuric acid, boron trifluoride, zinc chloride, hydrochloric acid, and (most especially) perchloric acid promoted the hydrogenolysis to the benzyl group. The use of nonaqueous fatty acid solutions and elevated temperatures also was found to be beneficial. However, the fact that these conditions were not always necessary is demonstrated by the reduction of 3-carboxamido-7-methoxy-1-tetralone to 2-carboxamido-6-methoxytetralin by the use of palladium on carbon in absolute alcohol without the use of either an acid catalyst or solvent (11).

The reduction of IX to the corresponding 2-aminotetralin (II) was accomplished using essentially the original procedure of Rosenmund and Karg (3). The use of 10% palladium on carbon and anhydrous perchloric acid (22) caused the reduction to proceed with much greater ease. The first 2 moles of hydrogen (reduction of the oxime) were taken up in 2–3 min. and the uptake of the third mole (reduction of the carbonyl) required only another 15 min. at room temperature. Gentle heating was required to cause the hydrogenolysis to occur, the stoichiometric quantity being taken up in about 2 hr. at 45° but requiring less time if the temperature is raised slightly more. Rosenmund and Karg required a temperature of 80–90°; but a report (19) of reduction of the aromatic ring at about 100°, using essentially the same other reaction conditions, prompted a search for means to accomplish the desired reduction at a lower temperature. The aminotetralin (II) was isolated by the same procedure as used by Rosenmund and Karg. However, it was discovered that a large quantity of organic material (as the perchlorate salt?) remained adsorbed to the catalyst. A methanol extraction of the catalyst, using a continuous extraction apparatus, recovered 0.48 g. of material from reduction in which 1.05 g. of nitrosated tetralone had been used. The IR spectrum of the hydrochloride salt of reduction product was consistent with that of a primary amine salt. No evidence of OH absorption was observed.

When examined by the method of Eddy and Leimbach (23), Compound II (as the hydrochloride) exhibited only very slight analgesic activity at a dose of 0.34 mmole/kg. This order of activity is roughly equivalent to that previously reported (1) for primary amines of the tetralin series.

EXPERIMENTAL[4]

Methyl-γ-cyano-γ-(*m*-methoxyphenyl)valerate (V)—When the dropwise addition, with vigorous stirring, of 35.8 g. (0.417 mole) of freshly distilled methyl acrylate into 56.4 g. (0.350 mole) of *m*-methoxyhydratroponitrile (IV) and 1 ml. of a 35% *N*-benzyltrimethylammonium hydroxide in methanol solution was started, the temperature immediately rose to about 60°. After cooling the mixture to 45°, further additions of methyl acrylate did not produce a rise in temperature, but the addition of another 0.5 ml. of *N*-benzyltrimethylammonium hydroxide solution again caused the temperature to rise sharply. Subsequently, 1 drop of *N*-benzyltrimethylammonium hydroxide solution was added occasionally while the remaining methyl acrylate was being added, the temperature being held at 45–50° by external cooling. After the addition was completed, the mixture was stirred at 55° for 1 hr. and then allowed to stand overnight at room temperature. The solution was then refluxed (110°) for 15 min., cooled, diluted with ether, washed with water, and dried with sodium sulfate. Flash distillation of the ether followed by vacuum distillation of the residual oil gave 15.8 g. of a colorless oil, b.p. 95–97° (1.0 mm.); 54.4 g. (62.8%) of cyanoester (V), b.p. 133–136° (0.3 mm.) and 122° (0.15 mm.); and a high-boiling residue which solidified upon cooling.

The combined product from several runs was fractionally distilled through a 0.91-m. (3-ft.) Podbielniak column to obtain the analytical sample, b.p. 158.1° (corrected) (1.5 mm.); n_D^{20}, 1.5129; d^{20}, 1.117; $\lambda_{max.}^{CCl_4}$, 2232 cm.$^{-1}$ (C≡N) and 1733 cm.$^{-1}$ (ester C=O).

Anal.—Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; saponification equiv., 247. Found : C, 67.65; H, 7.08; N, 5.66; saponification equiv., 250.

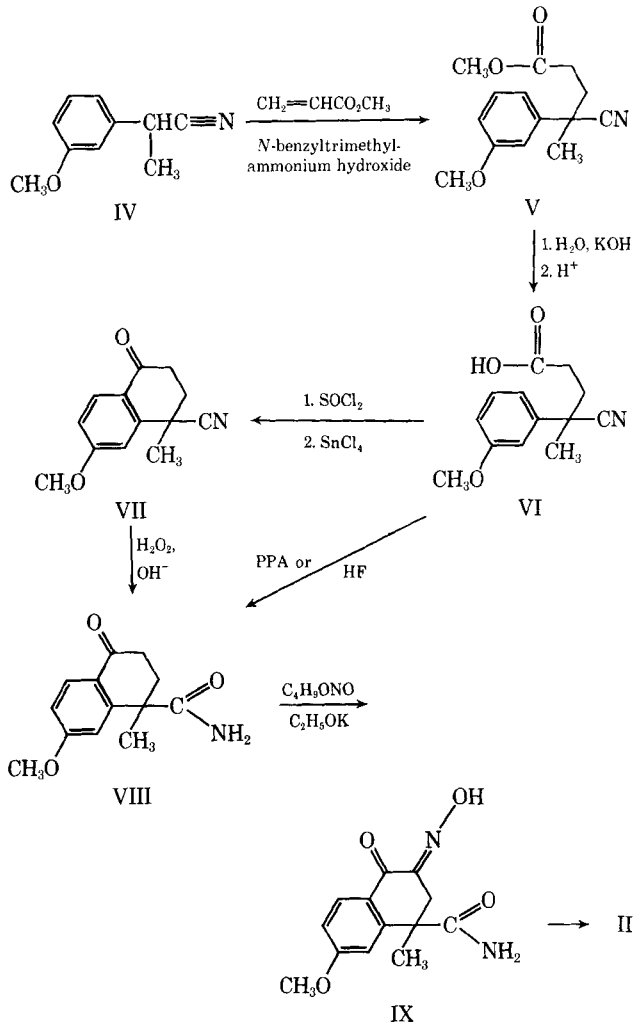
γ-Cyano-γ-(*m*-methoxyphenyl)valeric Acid (VI)—A mixture of 30.9 g. (0.125 mole) of V, 12 g. of potassium hydroxide, 12 ml. of water, and 60 ml. of methanol was warmed and then allowed to stand overnight at room temperature. After removing most of the methanol, the solution was diluted with water and washed with ether. The aqueous phase was acidified with 6 *N* hydrochloric acid, the oil which separated was removed, and the aqueous layer was extracted three times with ether. The organic phases were combined and washed with a saturated solution of sodium chloride. Concentration of the ethereal solution gave 28.9 g. (99.3%) of the cyanoacid as white prisms, m.p. 101.5–102.0° (ethanol–water), continuous submaxima between $\lambda_{max.}^{CHCl_3}$ 2440 and 3330 cm.$^{-1}$ (COOH), 2232 cm.$^{-1}$ (C≡N), and 1716 cm.$^{-1}$ (C=O).

Anal.—Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00; neut. equiv., 233. Found: C, 66.70; H, 6.43; N, 5.91; neut. equiv., 230.

1,2,3,4-Tetrahydro-7-methoxy-1-methyl-4-oxonaphthonitrile (VII)—To a solution of 34.9 g. (0.150 mole) of cyanoacid (VI), in

[3] A more complete discussion of the acid- and base-catalyzed isonitrosation of 1-tetralones, plus an attempt to interpret the structure of the oxamino ketones formed on the basis of their spectral properties, will be the subject of a future publication from the authors' laboratory.

[4] Melting points were determined on a calibrated Fisher-Johns melting point block and are corrected unless otherwise specified. The IR spectra were obtained with a Beckman IR-5 spectrophotometer; all spectra of solutions were determined in a cell with a 0.1-mm. pathlength. The analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England, or by the Galbraith Laboratories, Inc., Oxford, Tenn.



Scheme I

150 ml. of anhydrous ether and 10 drops of pyridine, was added 19.5 g. (0.165 mole) of thionyl chloride. The mixture was allowed to stand overnight and then the ether and excess thionyl chloride were removed *in vacuo* (aspirator) from a 40° water bath. Forty milliliters of anhydrous benzene was added and removed *in vacuo* as above; then another 40 ml. of benzene was added and removed similarly, removing the last traces *in vacuo*. The residual yellow oil was dissolved in 20 ml. of anhydrous benzene and chilled, with stirring, in an ice–brine bath until about half the benzene had frozen to the wall of the flask. A solution of 35 ml. of stannic chloride in 35 ml. of anhydrous benzene was added rapidly, producing a sticky red complex which was not stirrable. After standing for 30 min., the complex was decomposed with 100 ml. of concentrated hydrochloric acid, 100 g. of ice, and 100 ml. of ether. The aqueous layer was separated and extracted with ether and then with benzene. The combined organic phases were washed with 5% hydrochloric acid, with 5% sodium hydroxide solution, and finally with a saturated solution of sodium chloride. Evaporation of the volatile solvents deposited 31.1 g. (96.2%) of VII as long white needles, tinged with yellow, m.p. 95°. (The yellow color could be washed off with cold ethanol without significant loss of cyanotetralone.) Two recrystallizations from methanol afforded the analytical sample, m.p. 101.5–102.0°, $\lambda_{max.}^{CHCl_3}$ 2235 cm.$^{-1}$ (C≡N) and 1689 cm.$^{-1}$ (C=O).

Anal.—Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.95; H, 6.52; N, 6.44.

1,2,3,4-Tetrahydro-7-methoxy-1-methyl-4-oxo-1-naphthamide (VIII)—*By Cyclization of VI with Polyphosphoric Acid*—A mixture of 3.0 g. (13 mmoles) of VI with 25 ml. of polyphosphoric acid was stirred at 90–100° for 1 hr. When the orange-brown reaction mixture was poured into 250 ml. of water and 250 ml. of chloroform, stirred by a magnetic stirrer, the viscous mass quickly dissolved. The phases were separated and the greenish-yellow fluorescent aqueous layer was extracted twice with chloroform; then the combined extracts were washed twice with 5% sodium hydroxide and twice with water. After drying with sodium sulfate, evaporation of the chloroform extracts afforded 2.9 g. (97%) of yellowish amidotetralone (VIII). Two recrystallizations from water with the use of decolorizing carbon afforded white crystals, m.p. 179.0–179.5°; $\lambda_{max.}^{CHCl_3}$ 3484 cm.$^{-1}$ (free NH), 3378 cm.$^{-1}$ (bonded NH), and 1675 cm.$^{-1}$ (amide C=O).

Anal.—Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.16; H, 6.39; N, 5.98.

By Cyclization of VI with Hydrogen Fluoride—About 75 ml. of anhydrous hydrogen fluoride was added to 5.0 g (21 mmoles) of cyanoacid (VI) in a polyethylene bottle. When all of the hydrogen fluoride had evaporated, the residue was poured onto ice, the solution was made alkaline, and the solid was removed by filtration and washed with ice water. The dried solid, 4 g. (75%), m.p. 178–180°, did not depress the melting point of the amidotetralone obtained from the polyphosphoric acid cyclization, and the IR spectra of the two samples were identical.

By the Radziszewski Reaction on VII—A suspension of 21.5 g. (0.100 mole) of cyanotetralone (VII) in 41 ml. of 30% hydrogen peroxide and 200 ml. of 95% ethanol was warmed to 60° with stirring. The addition of 2 ml. of 7.5 *N* sodium hydroxide caused the solution to reflux, accompanied by a rapid evolution of oxygen. The clear, colorless solution was refluxed a total of 45 min. with the addition of more sodium hydroxide solution, as was necessary, to maintain the pH at about 9.5. After neutralizing the mixture, the ethanol was removed *in vacuo*, water was added, and the mixture was heated to boiling and filtered before chilling to crystallize the product. The white crystals of crude amidotetralone amounted to 20.4 g. (88%). Its identity was established by comparison of its IR spectrum with an authentic sample prepared as previously described and by mixed melting point (no depression).

1,2,3,4-Tetrahydro-3-isonitroso-7-methoxy-1-methyl-4-oxo-1-naphthamide (IX)—*By Acid Catalysis*—A chilled mixture of 1.8 ml. (22 mmoles) of precooled concentrated hydrochloric acid and 2.8 ml. (2.6 g., 25 mmoles) of cold, dry *n*-butyl nitrite (24) was added rapidly, with vigorous stirring, to a suspension of 4.7 g. (20 mmoles) of amidotetralone (VIII) in 30 ml. of reagent methanol chilled in ice. The ice bath was removed and the white suspension was allowed to warm spontaneously. When the temperature reached 15° the mixture took on a green tint and a mild exothermic reaction set in. At 25°, evolution of a colorless gas began and the exothermic reaction became more vigorous; the temperature rose to 42° and then fell to 35° while most of the solid dissolved. Warming the yellowish-green suspension at 40° for 2 hr. produced a copious white precipitate which was removed by filtration and washed with ice-cold methanol. After drying, the white microcrystalline oxime (IX) weighed 3.1 g. (59%), m.p. 210–218° (dec.).

The filtrate from the reaction mixture and the methanol washings of the crystals were returned to the flask and warmed at 40–45° for another hour. Adding 0.5 ml. of *n*-butyl nitrite to the dark-green solution and raising the bath temperature slightly caused the color of the solution to change to yellow and caused more solid to separate. After another 45 min. at 50°, 0.1 g. (2%) of IX, m.p. 217–222° (dec.), was filtered off. The product was soluble in aqueous alkali and sodium carbonate, giving a deep-yellow solution, but was almost insoluble in water and all common organic solvents except methanol, acetic acid, pyridine, dimethylformamide, and methyl cellosolve. Recrystallization from methanol–methylene chloride (1:1) gave stubby, very pale needles which darkened at about 205°, sintered at about 215°, and melted (in an evacuated capillary) at 220.1–224.1° (corrected) with evolution of a gas. The oximinotetralone (IX) gave an immediate strong orange color with ferric chloride in ethanol which faded upon warming or acidification. It dissolved in concentrated sulfuric acid to give a deep-yellow color rather than the intense red color which is typical of oximes of α-diketones (17). A yellow solution of its sodium or potassium salt gave the characteristic intense blue color with ferrous sulfate (25).

Anal.—Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68 Found: C, 60.06; H, 5.68; N, 10.49.

The solubility and melting behavior of the crude product suggested the presence of a less-polar, lower-melting isomer. Attempts to separate the suspected mixture on anionotropic alumina (Woelm) were unsuccessful.

By Alkaline Catalysis—A solution prepared by dissolving 0.86 g.

(0.022 g. atoms) of potassium in 4 ml. of absolute ethanol and 8 ml. of anhydrous toluene was added to a suspension of 4.7 g. (20 mmoles) of VIII in 75 ml. of anhydrous toluene with vigorous stirring in a nitrogen atmosphere. The clear, dark solution was chilled to 5° in an ice bath, and 2.8 ml. (2.6 g., 25 mmoles) of cold *n*-butyl nitrite was added slowly. When the exothermic reaction ceased, the ice bath was removed and the suspension was allowed to warm spontaneously to room temperature. The brown mixture was stirred at 45° for 1.5 hr., cooled, diluted with an equal volume of anhydrous ether, allowed to stand overnight, and dried in a vacuum oven.

The brown salt (5.9 g., 97% yield) was dissolved in 20 ml. of water containing 1 ml. of 10% sodium hydroxide solution and filtered to remove a few milligrams of dark-green solid. (An ether extraction of the filtrate removed more of the green compound.) Chilling the aqueous phase and acidifying to pH 4 with glacial acetic acid caused 3.9 g. (74%) of light-brown, gummy solid, m.p. 161–179°, to separate. Triturating the solid with ice-cold methanol in a chilled mortar afforded 1.8 g. of buff-colored powder which softened at 200° and melted from 208–219°. Recrystallization from methyl cellosolve–water (1:1) gave yellow needles, m.p. 216–220°, which did not depress the melting point of IX prepared by acid catalysis and which had an identical IR spectrum. Its sodium salt gave the characteristic deep-blue color with Fe^{++} (24).

Evaporation of the methanol filtrate from the trituration of the gummy solid left a dark-brown gum which was dissolved in chloroform and from which a buff-colored solid was precipitated by petroleum ether. Recrystallization of the material from dilute ethanol gave a yellow solid, m.p. 156–165°; $\lambda_{max.}^{mineral\ oil}$ 3185 and 1692 cm.$^{-1}$; $\lambda_{max.}^{CHCl_3}$ 3663, 3344, 3205, and 1692 cm.$^{-1}$. This material has not yet been identified.

3-Amino-1,2,3,4-tetrahydro-7-methoxy-1-naphthamide Hydrochloride (II)—A mixture of 1.050 g. (4.00 mmoles) of IX, 1.05 g. of 10% palladium on carbon, 4.4 ml. of a 2 *N* solution of anhydrous perchloric acid in glacial acetic acid (8.8 mmoles), and 45 ml. of glacial acetic acid were placed in a Parr hydrogenator at an initial pressure of 3.5 atm. When shaking was started, the first 2 moles of hydrogen were taken up in 3–4 min., the next 0.5 mole in about 10 min., and the next 0.5 mole in about 30 min., by which time the uptake of hydrogen had practically ceased. Warming the mixture to 40–45° caused the uptake of hydrogen to recommence. After 2 more hours the slow, steady uptake ceased with a total consumption of 108% of the theoretical amount of hydrogen. (Increasing the temperature causes the reduction to become complete in a shorter time.) The catalyst was removed by centrifugation and the solution was concentrated to dryness at the water pump. The residue, which was dissolved in water, was rendered distinctly alkaline and extracted first with ether and then with chloroform. The organic extracts were dried separately with potassium carbonate followed by potassium hydroxide pellets and then treated with anhydrous hydrogen chloride. Only 7 mg. of amine hydrochloride was obtained from the ether extract, and only 27 mg. was obtained from the chloroform extract. Therefore, the alkaline aqueous phase was placed in a liquid–liquid continuous extractor and extracted overnight with ether. After drying the ether phase as above, 315 mg. of the amine hydrochloride was precipitated with hydrogen chloride. The total recovery was 349 mg. (32.2%). (From the methanol extraction of the catalyst in a continuous extraction apparatus, 0.48 g. of crystalline material was obtained. Assuming that the material was the perchlorate salt of II, that weight represents another 37% of product.)

The amine hydrochloride was dissolved in 12–15 ml. of absolute alcohol, a small amount of insoluble material was filtered off, and the solution was diluted with about two to three volumes of anhydrous ether. The product separated as shiny white microcrystalline plates. A second recrystallization afforded the analytical sample, which darkened at 255°, softened at 263°, and melted (in an evacuated capillary) at 267.5–270.0°; $\lambda_{max.}^{mineral\ oil}$ 3390 and 3279 cm.$^{-1}$ (NH), 2012 cm.$^{-1}$ (NH_3^+), and 1647 cm.$^{-1}$ (amide C=O).

Anal.—Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: C, 57.67; H, 7.07; N, 10.35; Cl, 13.10. Found: C, 57.23; H, 7.12; N, 10.21; Cl, 12.94.

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