Substituted Tetralins I: Synthesis and Analgesic Activities of Some 2-Aminotetralins

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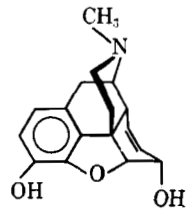
Abstract ☐ The synthesis of nine 4,4-dimethyl-2-aminotetralins is described and their analgesic potencies are reported. One of the series, *N,N*-dimethyl-4,4-dimethyl-2-naphthylamine, has an analgesic potency about two and one-half times that of codeine or meperidine.

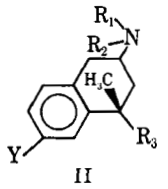
Keyphrases ☐ 2-Aminotetralins—synthesis ☐ Analgesic activity—2-aminotetralins ☐ IR spectrophotometry—identity ☐ UV spectrophotometry—identity ☐ NMR spectroscopy—identity

In 1954, Beckett and Casy (1) postulated that certain stereochemical and physiochemical properties were strategic for morphine-like analgesic compounds to fit a proposed receptor site. In 1955, Braenden *et al.* (2) concluded that potent analgesic compounds required four critical structural features: (*a*) a tertiary nitrogen atom; (*b*) a quaternary carbon atom; (*c*) a phenyl group, or a group isosteric with phenyl, connected to the quaternary carbon; and (*d*) a 2-carbon chain separating the tertiary nitrogen and the quaternary carbon. These minimum requirements had been deduced by noting the pharmacological actions of the remaining partial structures when portions of the morphine molecule were empirically removed. Although a number of potent analgesics not possessing all of these structural features have been reported and the validity of these hypotheses may now be questioned (3), they remain useful in designing new analgesic compounds.

Inspection of the morphine molecule (I) reveals that a 2-aminotetralin moiety is an integral part of its structure and that if it is properly substituted (II), it will possess all of the four requirements stated above. A number of investigators (4–9) have previously noted the potential value of substituted tetralins as analgesics. In none of the previously reported compounds, however, were all four of the requirements of Braenden *et al.* satisfied. Furthermore, in all of the compounds, the presence of hydrophilic groups (ketone, alcohol, carboxyl) in positions near the amino function may be suspected of interfering with potential analgesic activity. This paper reports the synthesis and analgesic activities of nine 2-aminotetralins that possess the structural requirements stated by Braenden *et al.*, except that Compounds VI, VII, and VIII are primary amines and Compounds XII and XV are secondary amines. Because analgesic activity is enhanced in morphine congeners by addition of a methoxyl group, and more intensely by a hydroxyl group, on a position comparable to the C-3 atom of morphine, 2-aminotetralins were prepared having a methoxyl or hydroxyl group on the C-6 atom. For further comparison, a 7-methoxy analog was also prepared.



I

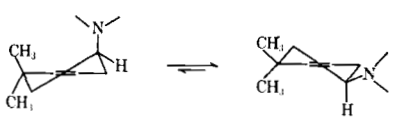


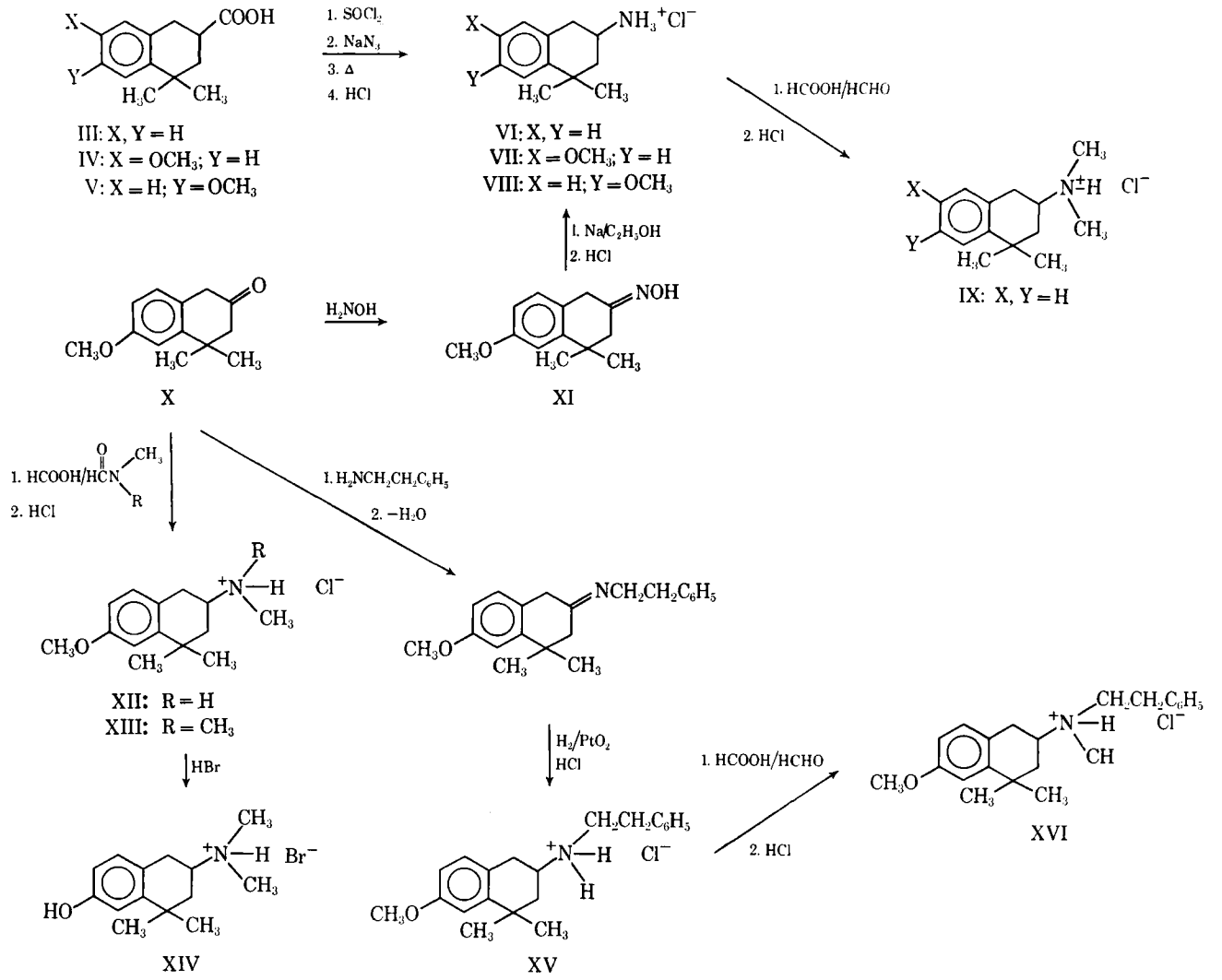
II

The stereochemical features of the 2-aminotetralins are of interest in connection with their potential analgesic activity. It may be noted that if the 2-amino group were oriented axially in the half-chair conformation of the tetralin system, the molecules would be capable of fitting Beckett's proposed receptor site without using the cavity postulated to exist between an anionic site and a flat surface for an aromatic ring. Because the half-chair conformation is considered to be the most energetically favored in the tetralin system, it is fair to assume that the compounds reported exist in that conformation. However, it is likely that the 2-amino group would reside predominantly in the equatorial position to avoid a nonbonded interaction between the *quasi* axial substituents in the 4-position and an axial 2-amino group. Although the amino group of morphine is held in an axial position, the essentiality of that position is disputed by the identification of a number of analgesic compounds in which the amino group is oriented in a position comparable to the equatorial position of the half-chair tetralin system (10, 11). In the light of those reports, and of the concept of Portoghese (12) that differing modes of binding of different narcotic analgesic receptors may occur, activity might reside in either conformation of the 2-aminotetralins. Furthermore, it is conceivable that the energy barrier to interconversion of the two half-chair conformations in the system[1] is not sufficiently large to prohibit a drug-receptor interaction from providing the force to reorient the amino group into the less stable axial conformation should it be required.

The synthesis of the desired amines was accomplished by two different routes (Scheme I). Substituted 1,2,3,4-

[1] The energy barrier to the interconversion of the following system is not known:



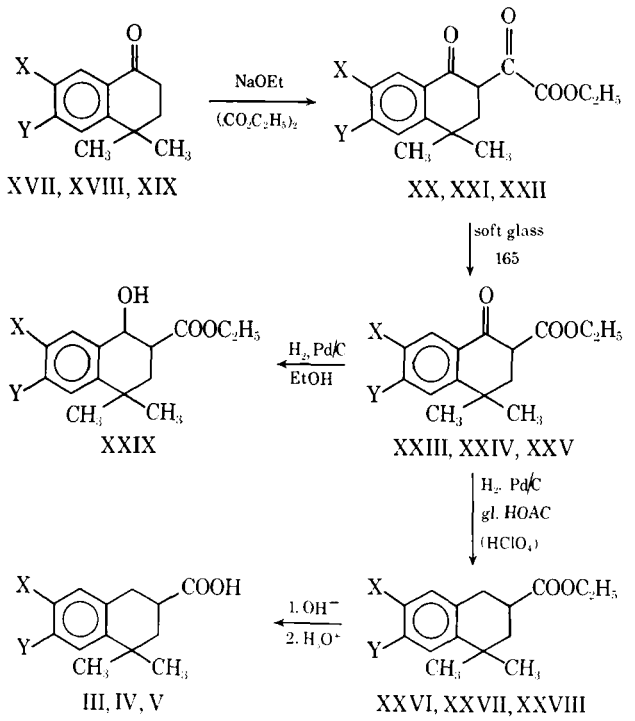


Scheme I

tetrahydro-2-naphthoic acids (III, IV, and V) were converted to analogous primary 2-amino compounds (VI, VII, and VIII) by the Curtius reaction. The dimethyl tertiary amine IX was prepared from VI by the Eschweiler-Clarke procedure. A more direct route proceeded through the synthesis of 6-methoxy-4, 4-dimethyl-2-tetralone (X). Conversion of X to the primary amine VIII was accomplished *via* the oxime XI. The catalytic reduction of the unisolated Schiff base of β-phenethylamine and the β-tetralone X yielded the secondary amine (XV) which was converted to the tertiary amine (XVI) by the Eschweiler-Clarke method of formylation. The Leuckart reaction was used to convert the β-tetralone X to the secondary methylamine XII with *N*-methylformamide and to the tertiary dimethylamine XIII with *N,N*-dimethylformamide. Cleavage of the ether by HBr yielded the 6-hydroxy analog XIV.

Crucial to the preparation of the desired 1,2,3,4-tetrahydro-2-naphthoic acids (III, IV, V), were the synthesis and reduction of the corresponding 2-carbethoxy-1-tetralones (Scheme II). Tetralone XVII was prepared by the method of Arnold *et al.* (13). Tetralone XVIII, first reported by Mukherjee (14), was prepared in 53% yield by a one-step process involving treatment of a mixture of γ,γ-dimethylbutyrolactone and anisole with polyphosphoric acid. The structure of XVIII was confirmed by comparison of its physical data with the cyclization product of 4-(*p*-methoxyphenyl)-4-methylvaleric acid (XXX). The latter compound was synthesized by the procedure previously reported (14) and also by the less ambiguous route beginning with nitration of 4-methyl-4-phenylvaleric acid and followed by reduction of the nitro group to the amine, diazotization and hydrolysis to the phenol, and finally, methylation to the methoxy compound. The previously unreported tetralone XIX was prepared in high yield by chromic acid oxidation of 1,2,3,4-tetrahydro-7-methoxy-1,1-dimethylnaphthalene. A better synthesis of the latter compound than that previously reported (15) was achieved by polyphosphoric acid catalyzed cyclization of 5-(*p*-methoxyphenyl)-2-methylpentanol (16). The conversion of the substituted 1-tetralones to corresponding 2-glyoxylates and the decarbonylation to desired 2-carbethoxy-1-tetralones was achieved by conventional procedures.

The reduction of the carbonyl group of substituted



XVII, XVIII, XIX

XX, XXI, XXII

XXIX

XXIII, XXIV, XXV

III, IV, V

XXVI, XXVII, XXVIII

III, XVII, XX, XXIII, XXVI: X, Y = H
IV, XVIII, XXI, XXIV, XXVII, XXIX: X = OCH_3; Y = H
V, XIX, XXIX, XXV, XXVIII,: X = H; Y = OCH_3

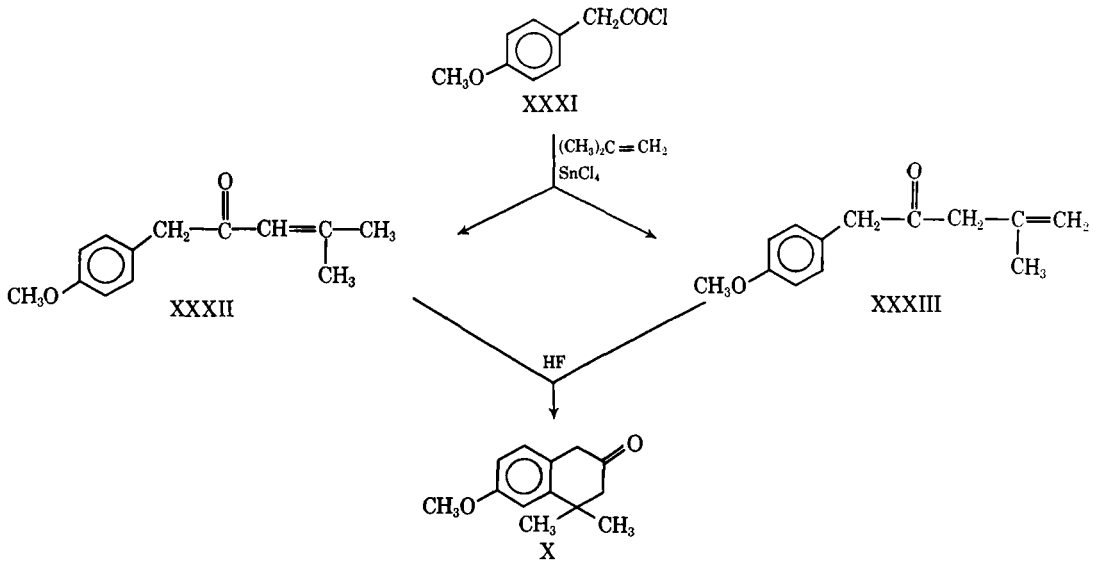
Scheme II

1-tetralones had presented difficulties to earlier investigators (17, 18). The Clemmenson reduction method is not suitable since the strongly acid conditions required would result in the cleavage or hydrolysis of other functional groups. Neither the Wolff-Kishner method nor the Huang-Minlon modification of it are of value for the reduction of β-ketoesters because under the reaction conditions pyrazolone derivatives would be formed (19). The authors' attempts to reduce 2-carbethoxy-1-tetralones in a system using absolute alcohol as the solvent and palladium-on-carbon as the catalyst yielded only carbethoxy-1-tetralols (*e.g.*, XXIX). Successful reductions were achieved by an adaptation of the method of Rosenmund and Karg (20) for the hydrogenolysis of ethyl benzoylbenzoate. The addition of small amounts of a 10% solution of perchloric acid in glacial acetic acid was required to complete reduction of some substituted 1-tetralones. When perchloric acid was omitted during the hydrogenation of XXIV, two fractions were obtained. One was the desired substituted tetralin XXVII and the other was the corresponding 1-tetralol XXIX. The fact that Compound XXIX was isolated suggests that 1-tetralols are intermediates in the reduction process and that further reduction to the corresponding hydrocarbons involves a hydrogenolysis step.

Although a number of variously substituted β-tetralones have been reported in the literature, the desired 6-methoxy-4,4-dimethyl-2-tetralone (X) has not been previously known. Colonge and Chambion (21) have prepared 4,4-dimethyl-2-tetralone by cyclization of a mixture of 4-methyl-1-phenyl-3-penten-2-one and 4-methyl-1-phenyl-4-penten-2-one. The precursor compounds had been obtained by a condensation of phenylacetyl chloride and isobutylene in a pressure bomb. A modification of their procedure beginning with *p*-methoxyphenylacetyl chloride (XXXI) led to the desired β-tetralone X (Scheme III).

The procedure produced a mixture of the olefinic ketones XXXII and XXXIII in 40–45% yields, an improvement over the 34% yield reported by Colonge and Chambion for the nonmethoxy analog. Attempts to improve the yield by use of Friedel-Crafts solvents such as nitrobenzene and tetrachlorethane were unfruitful. The IR spectrum of the mixture showed two C=O stretching modes corresponding to the findings of Colonge and Chambion on the mixture they obtained. Separation of the ketones XXXII and XXXIII was not attempted since in the cyclization procedure, both olefins form the same tertiary carbonium ion, producing the same product.

Cyclization of the mixture of olefinic ketones was accomplished in yields of 70% by the use of anhydrous HF as the catalyst. Attempts to effect cyclization by use of anhydrous $AlCl_3$ using a variety of conditions and



XXXI

XXXII

XXXIII

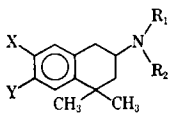
X

Scheme III

solvents were unsuccessful. A yield of 44% was obtained by use of polyphosphoric acid as a catalyst at 45° for 11 hr. The identity of the β-tetralone X was inferred from its IR spectrum which showed a single C=O stretching maximum at 1,718 cm.$^{-1}$, consistent with a 6-membered ring aliphatic ketone, and was confirmed by its conversion through the oxime XI to the 2-aminotetralin VIII. Compound VIII was shown to be identical when prepared by both routes herein described, by mixed melting points, and by identical IR spectra.

The analgesic potencies of the amines (Table I) were determined by the method of Eddy and Leimbach (22). For purposes of comparison, the ED_{50}'s are expressed as millimoles per kilogram since the 2-aminotetralins and the controls were administered in a variety of salt forms. Compound IX, *N,N*-dimethyl-1,2,3,4-tetrahydro-4,4-dimethyl-2-naphthylamine, was the only one of the series that showed important potency as an analgesic, being two and one-half times as potent as codeine or meperidine. The low activity of Compounds XIII and XIV that have an OCH_3 group or an OH group in positions analogous to similar groups in codeine or morphine is surprising. However, the data so far obtained do support the hypothesis that properly substituted 2-aminotetralins are capable of producing analgesic action. So far, only the racemic mixtures of the compounds have been evaluated. The role stereochemistry may play in the relative activity of the 2-aminotetralins is being investigated. It is worthy of note that 2-aminotetralins have been demonstrated to possess sympathomimetic activity (23) and it may be that the low order of activity found in most of these compounds is related to such a pharmacological effect. A number of reports (24) have indicated that sympathomimetic amines have analgesic properties. The autonomic properties of these amines are also being studied.

Table I—Analgesic Activity of Substituted 2-Aminotetralins



Compd.	R_1	R_2	X	Y	ED_{50}[a]
VI[b]	H	H	H	H	0.1
VII[b]	H	H	OCH_3	H	0.1
VIII[b]	H	H	H	OCH_3	0.1
XII[b]	CH_3	H	H	OCH_3	0.1
XV[b]	$C_6H_5CH_2CH_2$	H	H	OCH_3	[c]
IX[b]	CH_3	CH_3	H	H	0.02
XIII[b]	CH_3	CH_3	H	OCH_3	0.1
XIV[d]	CH_3	CH_3	H	OH	0.1
XVI[b]	$C_6H_5CH_2CH_2$	CH_3	H	OCH_3	0.1
Codeine[e]					0.05
Meperidine[b]					0.05
Morphine[f]					0.005

[a] Expressed in mmoles/kg. [b] HCl salt. [c] Produced seizures and death. [d] HBr salt. [e] Phosphate salt. [f] Sulfate salt.

EXPERIMENTAL[2]

4-Methyl-4-(p-nitrophenyl)valeric Acid—The procedure used was adapted from the one used by Corse and Rohrman (25) for the synthesis of 5-methyl-3-(*p*-nitrophenyl)butanoic acid. Seventy-seven grams (0.4 mole) of 4-methyl-4-phenylvaleric acid (26) was added, with stirring, to 125 ml. of fuming nitric acid in a 1-l. round-bottom flask cooled to −30° in an acetone-dry ice bath. After the addition (which required about 1 hr.) the temperature was allowed to rise to 0° and stirring of the mixture was continued for an additional 2 hr. at 0°. The solution was then poured onto cracked ice. The solid material which separated was collected, washed with water (2 × 500 ml.), dried, and recrystallized four times from benzene to give white prisms, m.p. 114–114.5°.

Anal.—Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.91; neut. equiv. 237.3. Found: C, 60.94; H, 6.04; N, 5.80; neut. equiv. 238.3.

4-(p-Aminophenyl)-4-methylvaleric Acid—A solution of 24 g. (0.1 mole) of 4-methyl-4-(*p*-nitrophenyl)valeric acid dissolved in 100 ml. of methanol was placed in the reaction bottle of a Parr hydrogenator and 0.25 g. of Adams' catalyst was added. Hydrogen, under 3 Atm. of pressure, was introduced and the reaction bottle was shaken at room temperature until the pressure ceased to decrease. Slightly more than the theoretical quantity of hydrogen was taken up. The time required was about 2 hr. The catalyst was filtered from the mixture and the filtrate was evaporated to dryness. The residue was dissolved in 200 ml. of 10% hydrochloric acid solution. The resulting solution was washed with ether (3 × 150 ml.) and then 5% sodium hydroxide solution was added until the pH of the solution was 5. Precipitation of the amino acid occurred to yield 16 g. (77%) of brown flakes. The compound was dissolved in methanol, treated with charcoal three times, and recrystallized three times from methanol to give colorless prisms, m.p. 136.5–137.5°.

Anal.—Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.23; N, 6.76. Found: C, 69.43; H, 8.29; N, 6.82.

4-(p-Hydroxyphenyl)-4-methylvaleric Acid—To a solution composed of 20 ml. of concentrated sulfuric acid and 75 ml. of water in a 600-ml. beaker was added 21 g. (0.1 mole) of 4-(*p*-aminophenyl)-4-methylvaleric acid. After the amino acid had dissolved (heat was required), 75 ml. of water was added and the mixture was cooled to 0.5° in an ice bath. The solution was stirred continuously while a solution of 7.3 g. of sodium nitrite dissolved in water was added dropwise from an addition funnel which extended below the surface of the amino acid hydrochloride solution. The addition was continued until the end point was reached. (The end point was considered the point at which one drop of the diazotized solution produced an immediate and lasting blue color with starch-iodide paper.) The diazotized solution was then added slowly, with stirring, to 1 l. of a 5% solution of sulfuric acid in a beaker, previously heated to 50–60°. The heat was maintained at 50–60° until the evolution of nitrogen ceased. The hot aqueous solution was filtered and then allowed to cool. As the filtrate cooled, a white solid precipitated, yielding 14 g. (67%) of the crude phenolic acid. Three recrystallizations of a portion of the crude product from hot water gave colorless needles, m.p. 138–139°.

Anal.—Calcd. for $C_{12}H_{16}O_2$: C, 69.21; H, 7.75. Found: C, 68.70; H, 7.85.

4-(p-Methoxyphenyl)-4-methylvaleric Acid (XXX)—4-(*p*-Hydroxyphenyl)-4-methylvaleric acid, 8.3 g. (0.04 mole), was dissolved in a solution of 9.6 g. of sodium hydroxide in 35 ml. of water and the resulting solution was poured into a 100-ml. three-necked, round-bottomed flask equipped with an addition funnel, a reflux condenser, and a mechanical stirrer. The mixture was refluxed and 10.1 g. (0.08 mole) of methyl sulfate was added dropwise with continued stirring. After the addition of methyl sulfate was completed, the mixture was stirred and refluxed for 15 hr. The mixture was allowed to cool and rendered distinctly acidic by the cautious addition of 20% hydrochloric acid solution. A white solid precipitated from the solution. Recrystallization of the solid from an alcohol–water solution gave 8.8 g. (93%) of the crude XXX. Two additional recrystallizations of the prod-

[2] Melting points were determined on a calibrated Fisher-Johns apparatus and are corrected. IR spectra were recorded by a Beckman IR-5 spectrophotometer, UV spectra by a Beckman Model DB spectrophotometer, and NMR spectra by a Varian A-60 spectrometer. Analyses were performed by Drs. Weiler and Straus, Oxford, England, and by the Galbraith Laboratories, Knoxville, Tenn.

uct from an alcohol–water solution gave colorless needles, m.p. 66.5–67° [lit. (27) 66.5–66.7°].

Anal.—Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.87; H, 8.06.

3,4-Dihydro-7-methoxy-4,4-dimethyl-1(2H)-naphthalenone (XVIII)—*Route A*—In a 1-l., 3-necked, round-bottom flask, fitted with a thermometer, a stirrer, and an addition funnel, 400 g. of polyphosphoric acid (PPA) was placed and warmed to 70° with stirring. A mixture of 25.48 g. (0.236 mole) of anisole and 27 g. (0.236 mole) of 4,4-dimethylbutyrolactone was added in one portion. The temperature rose slowly and was maintained at 93–95° for 1 hr. by gentle heating. The reaction mixture was decomposed by pouring, with vigorous stirring, into a mixture of 400 ml. of ice-cold water and 200 ml. of chloroform. The chloroform phase was separated and the aqueous phase extracted with further portions of chloroform (3 × 200 ml.). The combined chloroform extracts were washed with 10% sodium bicarbonate solution, followed by water until the aqueous washings were neutral to pH paper. After the extract was dried overnight over anhydrous sodium sulfate, the solvent was removed and the product distilled *in vacuo* (aspirator). From the forerun 7.8 g. of lactone was recovered. The residual oil was distilled to yield 22 g. (53% based on unrecovered lactone) of a pale yellow liquid, b.p. 101–102° (0.2 mm.). The product was further purified by treatment with Girard's reagent to yield a colorless liquid, b.p. 105–106° (0.3 mm.), 89.5–90° (0.1 mm.), n_D^{20} 1.5523 [lit. (15) b.p. 130–135° (4 mm.)], $\lambda_{max.}^{EtOH}$: 225 mμ (ε8,280), 316 mμ (ε 2,840), $\nu_{max.}^{CCl_4}$: 1,686 cm.$^{-1}$ (C=O).

Anal.—Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.41; H, 8.09.

Route B—Using the procedure of Koo (28) 5.5 g. (0.025 mole) of XXX was treated with 55 g. of PPA at 70° for 25 min. (until a dark reddish color was reached). The PPA solution was hydrolyzed in ice water and the resulting solution extracted with three 75-ml. portions of ether. The ethereal solution was washed with 50 ml. of 5% sodium hydroxide solution and 50 ml. of 3% acetic acid solution. The ether was removed by distillation and the remaining oil distilled under vacuum. A 4-g. (78.4%) fraction distilling at 130° (1.5 mm.) was collected and determined by its IR spectrum to be identical to XVIII obtained by *Route A*.

1,2,3,4-Tetrahydro-7-methoxy-1,1-dimethylnaphthalene—Polyphosphoric acid (500 g.) contained in a 2-l. resin reaction flask fitted with a ground-glass cover equipped with an efficient mechanical stirrer, air condenser, addition funnel, and a thermometer extending into the liquid, was heated on a hot plate to 90°. From the funnel was then added dropwise 166 g. (0.8 mole) of 5-(*p*-methoxyphenyl)-2-methylpentanol-2 (16) with stirring over a period of 90 min. With the hot plate removed the rate of addition was adjusted so as to maintain the temperature between 90–97°. The heat source was returned and the temperature was maintained at about 90° with stirring for an additional 30 min. When the first material from the funnel was added, the mixture in the flask started to turn pink and by the end of the reaction the color had changed to a deep orange-red. (If the mixture was heated over 100° the color changed to a deep reddish-purple with a concomitant lowering of yield.) The top of the reaction flask was removed and the contents cooled to room temperature. To the flask was added about 250 ml. of ice and water which caused a decomposition of the thick reddish material with the formation of two layers which were not colored. This mixture was transferred to a separator, extracted with ether (4 × 125 ml.), and dried over anhydrous sodium sulfate. After the ether had been removed by distillation the desired product was vacuum-distilled through a Todd fractionating assembly with a 90-cm. glass helice-packed column (i.d. 12 mm.) to yield 138 g. (91%) of a colorless, nearly odorless liquid, b.p. 114° (4 mm.), n_D^{25} 1.5350 [lit. (15) b.p. and n_D^{25} not reported]. The product develops a pronounced characteristic odor on standing.

Anal.—Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.55. Found: C, 81.80; H, 9.67.

3,4-Dihydro-6-methoxy-4,4-dimethyl-1(2H)-naphthalenone (XIX)—In a 2-l. resin reaction flask partially immersed in an ice-salt bath was placed 133 g. (0.7 mole) of 1,2,3,4-tetrahydro-7-methoxy-1,1-dimethylnaphthalene dissolved in a mixture of 535 ml. of glacial acetic acid and 90 ml. of propionic acid. (Difficulty was encountered with the solution freezing if acetic acid alone was used as the solvent.) A ground-glass cover was fitted onto the flask and the apparatus equipped with an addition funnel, thermometer, and efficient mechanical stirrer. When the contents of the flask had been cooled to about 3° there was added from the funnel, dropwise and with stirring, a solution of 133 g. (1.48 moles) of chromic acid dissolved in 90 ml. of water and 300 ml. of glacial acetic acid. This required about 2 hr. during which time the temperature was maintained between 3–7°. During the addition of the chromic acid solution the mixture became greenish-black and by the time all of the acid had been added the mixture was very viscous. The ice bath was removed, the contents of the flask allowed to come to room temperature, and to stand overnight. With the flask heated to about 40° in a water bath, most of the water and the acetic-propionic acid mixture was removed *in vacuo* (aspirator) until only a purple semisolid residue remained. Ice and water (about 800 ml.) were added to slowly decompose the residue. The mixture was transferred to a large separator, extracted with ether (5 × 100 ml.), and dried over anhydrous sodium sulfate. After removal of the solvent by distillation the residual material was distilled to yield 130 g. (91%) of a very pale yellow, viscous liquid, b.p. 116–117° (0.4 mm.). The product solidified by careful cooling or by seeding with a crystal of the compound previously prepared. A white crystalline sample was obtained by several recrystallizations from petroleum ether (b.p. 30–60°), m.p. 52.8–53°; $\lambda_{max.}^{EtOH}$: 278 mμ (ε 17,600); $\nu_{max.}^{CCl_4}$: 1,678 cm.$^{-1}$.

Anal.—Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.46; H, 7.91.

Semicarbazone—It occurs as white crystals, m.p. 198–199°, when recrystallized from a water–ethanol mixture.

Anal.—Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33. Found: C, 63.91; H, 7.47.

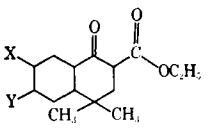
Preparation of Glyoxylates XX, XXI, XXII—The following was adopted from that of Bachmann and Wendler (29) for the preparation of ethyl 1,2,3,4-tetrahydro-1-oxo-2-naphthalene glyoxylate. A solution of 0.2 mole of a tetralone (XVII, XVIII, XIX) and 0.4 mole of diethyl oxalate in 125 ml. of dry benzene was added with stirring to a suspension of sodium ethoxide, prepared from 0.4 g. atoms of sodium and 150 ml. of anhydrous ethanol in 125 ml. of dry xylene. After allowing the reaction mixture to stand for 10 hr., it was poured with stirring into 750 ml. of water containing 250 g. of crushed ice. About 200 ml. of 3% sodium hydroxide solution was added (to at least pH 8), and after a further 0.25-hr. stirring period, the reaction mixture was extracted with ether. The combined ether extracts were washed once with 125 ml. of 3% sodium hydroxide solution and the alkaline washings added to the main aqueous phase. The combined aqueous phase was acidified to about pH 2 with HCl. The acidic mixture was kept in the refrigerator for 6 hr. and then the brown oil which had separated was extracted with ether. The combined ether extracts were washed with 100 ml. of 3% $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Removal of ether produced the glyoxylate in yields of 91–96%. The products were not purified further before transformation to the β-ketoesters.

Preparation of β-Ketoesters XXIII, XXIV, XXV—A mixture of 50 g. of glyoxylate and 30 g. of powdered glass was heated to a temperature of 140–150° at which point copious evolution of gas occurred. The temperature was raised slowly to 165–170° and maintained there until no more gas was given off (about 40 min.). After cooling, 200 ml. of ether was added to the mixture, the glass filtered off, and washed with ether. The combined ether solutions were dried over anhydrous Na_2SO_4. Removal of the ether and distillation of the residual oil yielded the colorless liquid ketoesters reported in Table II.

Reduction of β-Ketoesters to Esters XXVI, XXVII, XXVIII—A solution of 0.1 mole of β-ketoester (XXIII, XXIV, or XXV) was dissolved in 200 ml. of glacial acetic acid and 6 g. of 5% palladium-on-carbon catalyst[3] and 5 ml. of 10% perchloric acid in glacial acetic acid was added. Reduction was carried out in a 500-ml. bottle attached to a Parr low-pressure hydrogenator, equipped with a heater, at a temperature of 65–70° and with an initial hydrogen pressure of 45–50 p.s.i. After the hydrogen uptake ceased (2–3 hr.), the catalyst was removed from the solution by filtration and the acetic acid was distilled off under reduced pressure. The residue was dissolved in ether and the ethereal

[3] Use of 10% palladium-on-charcoal also has been successful.

Table II—Ethyl 1,2,3,4-Tetrahydro-1-oxo-2-naphthoates



Compd.	X	Y	Yield, %	B.p., °C	$\nu_{max.}^{CCl_4}$, cm.$^{-1}$ COOR	C=O	COOR[a]	C=C[b]	Formula	Anal., % Calcd.	Found
XXIII	H	H	66	119° (0.4 mm.)	1748	1698	1653	1623	$C_{15}H_{18}O_3$	C, 73.14 H, 7.36	C, 73.01 H, 7.31
XXIV	OCH_3	H	58	114° (0.3 mm.)	1751	1689	1653	1626	$C_{16}H_{20}O_4$	C, 69.54 H, 7.30	C, 70.03 H, 7.59
XXV	H	OCH_3	65	167° (1.2 mm.)	1748	1695	1647	1616	$C_{16}H_{20}O_4$	C, 69.54 H, 7.30	C, 69.85 H, 7.65

[a] Absorption assigned to C=O of conjugate chelated ester. [b] Absorption assigned to conjugate chelated C=C.

solution was washed with 7% $NaHCO_3$ solution and then with water. After drying over anhydrous Na_2SO_4, the ether was removed and the residual oil distilled under reduced pressure to yield the esters reported in Table III.

Ethyl 1,2,3,4-tetrahydro-1-hydroxy-7-methoxy-4,4-dimethyl-2-naphthoate (XXIX)—When XXIV was subjected to the hydrogenation procedure described above, but without the addition of perchloric acid solution, two fractions were obtained upon distillation. The first fraction (31% yield) was identified as the desired reduced ester XXVII. The second fraction (60% yield) distilled over at 145–148° (0.28 mm.) and quickly solidified to a waxy solid. After three recrystallizations from ethanol–petroleum ether, the product consisted of white crystals, m.p. 81.5–82°, $\nu_{max.}^{CCl_4}$: 3,572 cm.$^{-1}$ (aliphatic OH) and 1,730 cm.$^{-1}$ (ester C=O). The compound gave a positive Lucas test and was converted to XXVII (95% yield) by hydrogenation, using the same process but adding perchloric acid solution to the mixture.

Anal.—Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.96. Found: C, 68.99; H, 7.79.

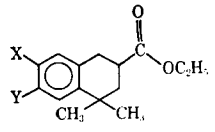
Hydrolysis of Esters to 1,2,3,4-tetrahydro-2-naphthoic Acids III, IV, V—A solution of 0.04 mole of ester (XXVI, XXVII, or XXVIII) was refluxed for 1.5 hr. in 100 ml. of ethanol and 100 ml. of 10% NaOH. After making the mixture slightly acidic with 6 *N* HCl, the ethanol was removed by distillation. After cooling the residue, the solid was filtered off and dried. Crystallization from ethanol–water gave the acids reported in Table IV.

1,2,3,4-Tetrahydro-4,4-dimethyl-2-naphthylamine Hydrochlorides VI, VII, VIII—The acid chloride from 5.1 g. (0.025 mole) of III, IV, or V was prepared with thionyl chloride and dissolved in reagent grade acetone. To this solution, cooled to 5°, was added, over a period of 5 min. with stirring, a solution of 1.75 g. (0.026 mole) of sodium azide in 5 ml. of ice water. The mixture was stirred for 75 min. at 5°, during which time a white precipitate formed. After the addition of 100 ml. of water, the mixture was extracted with toluene. The toluene solution was washed with 10% sodium bicarbonate solution, dried, and transferred to a dry flask immersed in a water bath at 5°. Rearrangement of the azide to the isocyanate was effected by applying vacuum (aspirator) to the flask while the contents were being vigorously stirred. The evolution of nitrogen was in evidence for a period of about 3 hr. The mixture was then heated at reflux temperature for 5 min. to complete the reaction. An IR spectrum of the cooled solution showed a maximum at 2,257 cm.$^{-1}$, consistent with an isocyanate.

The isocyanate solution was transferred to a dropping funnel and added over 20 min. to 25 ml. of 20% hydrochloric acid solution previously heated to 80°. A copious evolution of gas was noted during the addition. Stirring and heating were continued for an additional 2 hr. The mixture was cooled, transferred to a separator, and 120 ml. of ice water was added. The acidic aqueous phase was discarded. The toluene solution was extracted with 10% hydrochloric acid solution. The acidic solution was made alkaline to pH 12 by the addition, with cooling, of 20% sodium hydroxide solution and then extracted with ether. The ether extract was dried and mixed with ether saturated with anhydrous hydrogen chloride. The amine hydrochlorides formed were recrystallized from chloroform and ether to give the compounds reported in Table V.

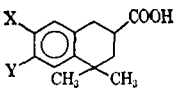
N,N-Dimethyl-1,2,3,4-tetrahydro-4,4-dimethyl-2-naphthylamine Hydrochloride (IX)—A toluene solution of the isocyanate prepared from 3.71 g. (0.018 mole) of III by the procedure described above was concentrated to about 20 ml. To it was added 10 ml. of 98% formic acid and the mixture was refluxed for 2 hr. The volatile constituents were removed, 18 ml. of 88% formic acid followed by 18 ml. of formaldehyde solution were added, and the mixture was refluxed for 15 hr. Concentrated hydrochloric acid, 20 ml., was added and the excess formic acid and formaldehyde were removed *in vacuo*. The solution was cooled, made alkaline to pH 12 with 20% sodium hydroxide solution, and extracted with ether. The ether extract was washed with water,

Table III—Ethyl 1,2,3,4-Tetrahydro-2-naphthoates



Compd.	X	Y	Yield, %	B.p., °C	n_D^{20}	$\nu_{max.}^{COOR}$, cm.$^{-1}$	Formula	Anal., % Calcd.	Found
XXVI	H	H	85	85 (0.2 mm.)	1.5145	1739	$C_{15}H_{20}O_2$	C, 77.54 H, 8.67	C, 77.33 H, 8.64
XXVII	OCH_3	H	85	130 (0.4 mm.)	1.5143	1730	$C_{16}H_{22}O_3$	C, 73.25 H, 8.45	C, 73.47 H, 8.54
XXVIII	H	OCH_3	76	140 (0.2 mm.)	1.5228	1727	$C_{16}H_{22}O_3$	C, 73.25 H, 8.45	C, 73.54 H, 8.56

Table IV—1,2,3,4-Tetrahydro-2-naphthoic Acids



Compd.	X	Y	Yield, %	M.p., °C.	$\nu_{max.}^{COOH}$, cm.$^{-1}$	Formula	Anal., % Calcd.	Found
III	H	H	91	106	1709	$C_{13}H_{16}O_2$	C, 76.43 H, 7.89	C, 76.13 H, 7.60
IV	OCH_3	H	88	132	1701	$C_{14}H_{18}O_3$	C, 71.77 H, 7.74	C, 71.56 H, 7.59
V	H	OCH_3	93	154	1706	$C_{14}H_{18}O_3$	C, 71.77 H, 7.74	C, 71.87 H, 7.86

dried, and saturated with anhydrous hydrogen chloride. The amine hydrochloride formed was recrystallized from absolute ethanol and ether to give 1.85 g. (43%) of small colorless crystals, m.p. 220°.

Anal.—Calcd. for $C_{14}H_{22}ClN$: C, 70.12; H, 9.25; Cl, N, 5.84; 14.78. Found: C, 70.39; H, 9.23; Cl, 14.66 N, 5.70;.

1-(p-Methoxyphenyl)-4-methyl-3-penten-2-one (XXXII) and 1-(p-Methoxyphenyl)-4-methyl-4-penten-2-one (XXXIII)—To 42.5 g. (0.2 mole) of freshly distilled *p*-methoxyphenylacetyl chloride (XXXI) cooled to −10° was added with stirring about 40 g. (0.75 mole) of liquefied isobutylene. After the addition of the isobutylene, 10 g. (0.13 mole) of anhydrous stannic chloride was added dropwise to the mixture, with constant stirring. As the stannic chloride was being added, the solid chunks of acid chloride began to dissolve and a single homogeneous phase was gradually formed. The mixture was stirred 1 hr. at 10° following the addition of stannic chloride and then allowed to stand an additional hour at 0°. The mixture was decomposed by stirring it into 500 ml. of ice water. The brown mass which separated was extracted with ether. The ether solution was filtered from the insoluble material, collected in a separator, washed successively with water, 10% hydrochloric acid solution, 10% sodium bicarbonate solution, and again with water, and dried. The ether was removed and the residue distilled *in vacuo*, giving 41 g. (40%) of a colorless liquid, b.p. 126–128° (2 mm.). Attempts to obtain a pure analytical sample by fractional distillation were not successful. $\nu_{max.}^{CHCl_3}$ 1,723 cm.$^{-1}$ (C=O), 1,686 cm.$^{-1}$ (C=C—C=O), and 1,248 cm.$^{-1}$ (C—O).

2,4-Dinitrophenylhydrazone—Reaction of the mixture of ketones with 2,4-dinitrophenylhydrazine reagent gave red-orange needles, m.p. 189–195°. After several recrystallizations from ethanol–ethyl acetate, brick-red needles were obtained, m.p. 199°.

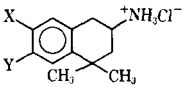
Anal.—Calcd. for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.20. Found: C, 59.21; H, 5.22.

3,4-Dihydro-6-methoxy-4,4-dimethyl-2(1H)-naphthalenone (X)—To 41 g. (0.2 mole) of the mixture of XXXII and XXXIII in a dry polyethylene bottle was added, with occasional mixing, about 250 ml. of anhydrous hydrogen fluoride. The mixture was allowed to stand at 25° for 48 hr. while the excess hydrogen fluoride evaporated. The residue was then poured, with stirring, into 250 ml. of ice water and extracted with ether. The ether solution was washed with water, then with 5% sodium bicarbonate solution, and again with water, and dried. Removal of the ether followed by distillation of the residue gave 30.5 g. (70%) of a pale yellow liquid, b.p. 104–106° (0.4 mm.), $\nu_{max.}^{CHCl_3}$ 1,718 cm.$^{-1}$ (C=O), 1,238 cm.$^{-1}$ (C—O). The β-tetralone (7 g., 0.035 mole) was converted by method of Nelson and Sinclair (30) to the oxime XI (5.9 g., 84.5%). Recrystallization from benzene and hexane gave colorless, sublimable needles, m.p. 136–138° in a sealed tube. $\nu_{max.}^{CHCl_3}$ 3,546 cm.$^{-1}$ (free OH), 3,205 cm.$^{-1}$ (broad) (bonded OH), and 1,661 cm.$^{-1}$ (C=N).

Anal.—Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.83; H, 7.60; N, 6.61.

Alternate Procedure for the Synthesis of 1,2,3,4-Tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine Hydrochloride (VIII)—A solution of 2.2 g. (0.01 mole) of the oxime XI dissolved in 250 ml. of dry ethanol was heated until it began to reflux rapidly. The heat was then removed and rapid refluxing was maintained by the addition of 3 g. (0.13 mole) of sodium metal in pea-sized chunks. As soon as the last of the sodium had dissolved, the mixture was cooled, and 200 ml. of 10% hydrochloric acid was cautiously added. The alcohol, water, and hydrochloric acid were removed (aspirator) with careful heating. The bright red residue that remained was dissolved in 100 ml. of 10% hydrochloric acid solution, washed with benzene, and rendered alkaline by the addition of 125 ml. of 10% sodium hydroxide solution. The mixture was extracted with benzene and dried. Anhydrous hydrogen chloride was bubbled into the benzene solution to cause precipitation of the amine hydrochloride that was contaminated with a small amount of bright red material. The color was removed by precipitating the amine hydrochloride from a chloroform solution with anhydrous ether to give 1.5 g. (63%) of

Table V—1,2,3,4-Tetrahydro-4,4-dimethyl-2-naphthylamine Hydrochlorides



Compd.	X	Y	Yield, %	M.p., °C.	$\nu_{max.}^{+NH_3}$, cm.$^{-1}$	Formula	Anal., % Calcd.	Found
VI	H	H	46	259–260	1961	$C_{12}H_{18}ClN$	C, 68.06 H, 8.56 Cl, 16.74 N, 6.61	C, 67.89 H, 8.30 Cl, 16.46 N, 6.81
VII	OCH_3	H	67	239–240	2053	$C_{13}H_{20}ClN$	C, 64.58 H, 8.33 Cl, 14.67 N, 5.79	C, 64.35 H, 8.59 Cl, 14.40 N, 5.94
VIII	H	OCH_3	63	261–262	2049	$C_{13}H_{20}ClN$	C, 64.58 H, 8.33 Cl, 14.67 N, 5.79	C, 64.74 H, 8.19 Cl, 14.58 N, 5.76

[a] Absorption measured in mineral oil.

a white solid, which, after recrystallization from chloroform and ether, gave small white needles, m.p. 261–262°. A mixed melting point with the amine hydrochloride VIII prepared from the acid V *via* the Curtius reaction (see above) showed no depression.

N-Acetyl Derivative—Colorless needles, m.p. 158–160°. A mixed m.p. with a sample of the acetyl derivative of amine hydrochloride prepared from the acid V showed no depression.

N-Methylamino-1,2,3,4-tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine Hydrochloride (XII)—A solution of 12 g. (0.06 mole) of β-tetralone X dissolved in 7.1 g. (0.12 mole) of *N*-methylformamide was added over a period of 1 hr. to a solution of 11 g. (0.24 mole) of formic acid and 7.1 g. (0.12 mole) of *N*-methylformamide, previously heated to 120°. The solution was refluxed for 10 hr. and the excess formic acid and formaldehyde were removed *in vacuo*. The reaction mixture was cooled, 30 ml. of 20% hydrochloric acid solution was added, and the mixture was refluxed for 7 hr. The reaction mixture was then extracted with ether and the ether extracts were discarded. The acidic aqueous solution was then rendered alkaline to pH 12 with 20% sodium hydroxide solution and extracted with ether. The ether extracts were combined, dried, and saturated with anhydrous hydrogen chloride to give 9.2 g. (61%) of the amine hydrochloride, m.p. 250° after recrystallization from absolute ethanol.

Anal.—Calcd. for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67; N, 5.48. Found: C, 65.40; H, 8.48; N, 5.44.

N,N-Dimethyl-1,2,3,4-tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine Hydrochloride (XIII)—A yield of 7 g. (52%) of the desired amine was obtained, using the Leuckart reaction conditions described above, with 10.1 g. (0.05 mole) of the β-tetralone X and 14.8 g. (0.25 mole) of *N,N*-dimethylformamide. Recrystallization from absolute ethanol and ether gave colorless needles, m.p. 208°.

Anal.—Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.77; H, 8.66; N, 5.30.

N,N-Dimethyl-1,2,3,4-tetrahydro-6-hydroxy-4,4-dimethyl-2-naphthylamine Hydrobromide (XIV)—A solution of 2.5 g. (0.009 mole) of XIII in 25 ml. of 48% hydrobromic acid was refluxed for 70 min. The system was flushed with nitrogen throughout the course of the reaction. The water and excess hydrogen bromide were removed *in vacuo* and the residue was recrystallized from absolute ethanol and ethyl acetate to give a quantitative yield of the amine hydrobromide as colorless needles, m.p. 284°.

Anal.—Calcd. for $C_{14}H_{22}BrNO$: C, 56.00; H, 7.38; N, 4.67. Found: C, 55.81; H, 7.35; N, 4.68.

N-(β-Phenylethyl)-1,2,3,4-tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine Hydrochloride (XV)—A solution of 25 g. (0.12 mole) of the β-tetralone X and 14.8 g. (0.123 mole) of freshly distilled β-phenylethylamine in 250 ml. of benzene was refluxed for 10 hr. The water formed during the reaction was collected in a Dean-Stark trap. Distillation of the benzene gave a residue of a yellow oil (Schiff base) which was dissolved in glacial acetic acid and hydrogenated in the presence of reduced platinum oxide catalyst for 16 hr. beginning with a pressure of 3 Atm. The solution was filtered from the catalyst and the acetic acid was removed. The residue was dissolved in 6 *N* hydrochloric acid, extracted with ether, then made alkaline with 20% sodium hydroxide solution, and again extracted with ether. The latter ether extracts were combined, dried, and saturated with anhydrous hydrogen chloride to give 25 g. (61%) of colorless needles, m.p. 236°, after recrystallization from absolute ethanol and ethyl acetate.

Anal.—Calcd. for $C_{21}H_{28}ClNO$: C, 72.92; H, 8.16; N, 4.05. Found: C, 73.08; H, 8.11; N, 3.87.

N-Methyl-N-(β-phenylethyl)-1,2,3,4-tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine Hydrochloride (XVI)—The secondary amine XV (20.4 g., 0.062 mole) was methylated by the Eschweiler-Clarke procedure using 18.5 ml. of 88% formic acid and 5.6 g. 37% formaldehyde solution. Following cessation of CO_2 evolution, 15 ml. of hydrochloric acid was added to the cooled solution and the excess formic acid and formaldehyde removed by vacuum evaporation. The acidic solution was washed with ether and then rendered basic with 30% sodium hydroxide solution. The basic solution was extracted with ether and, after drying, the ethereal solution was treated with an ethereal solution of hydrogen chloride to precipitate the amine hydrochloride. A yield of 14.5 g. (56%) of XVI was obtained as colorless needles, mp.. 208°, after recrystallizations from absolute ethanol and ethyl acetate.

Anal—Calcd. for $C_{22}H_{30}ClNO$: C, 73.40; H, 8.40; N, 3.89. Found: C, 73.66; H, 8.59; N, 3.90.

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