Substituted Tetralins III: Synthesis and Analgesic Activities of Some Substituted 2-Methyl- and 2-Benzyl-4,4-dimethyl-2-aminotetralins

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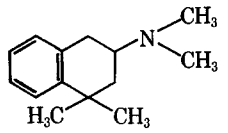
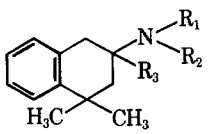
Abstract □ The synthesis of five 2-methyl- and 2-benzyl-4,4-dimethyl-2-aminotetralins is described and their analgesic potencies are reported. The introduction of methyl or benzyl substituents in the 2-position does not appear to significantly affect analgesic potency in the 2-aminotetralin series.

Keyphrases □ 2-Methyl- and 2-benzyl-4,4-dimethyl-2-aminotetralins, substituted—synthesis □ Analgesic activity—substituted tetralins □ IR spectrophotometry—identification □ NMR spectroscopy—identification

In a recent publication the synthesis and analgesic potency of some derivatives of 2-aminotetralin were reported (1). The observation that one of the series, *N,N*-dimethyl-1,2,3,4-tetrahydro-4,4-dimethyl-2-naphthylamine (I), has an analgesic potency about two and one-half times that of meperidine encouraged the authors to prepare 2-substituted-2-aminotetralins (II) as potential analgesics.

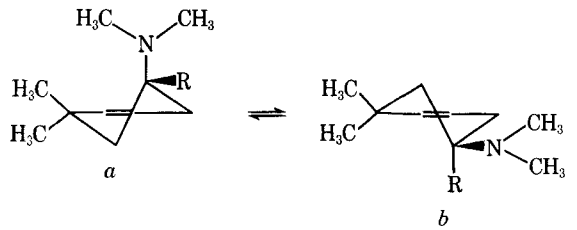


I



II

The decision to prepare 2-substituted derivatives was based on conformational considerations. Because the half-chair conformation is considered the most energetically favored in the tetralin system (2), it is fair to assume that the 2-aminotetralins reported exist predominantly as an equilibrium mixture of the half-chair conformers shown in Scheme I.



a *b*

Scheme I

If the 2-amino group was oriented axially in the half-chair conformation *a*, the molecules would be capable of fitting the analgesic receptor site proposed by Beckett and Casy (3) without using the cavity postulated to exist between an anionic site and a flat surface for an aromatic ring. However, it is likely that the active analgesic I exists predominantly as conformer *b* (R = H), wherein the 2-amino function is equatorial. A nonbonding interaction between the bulky 2-amino group and a quasiaxial methyl group in the 4-position is thereby avoided. The introduction of a second bulky group in the 2-position should increase the preference for conformer *a*, wherein the amino group is oriented axially.[1]

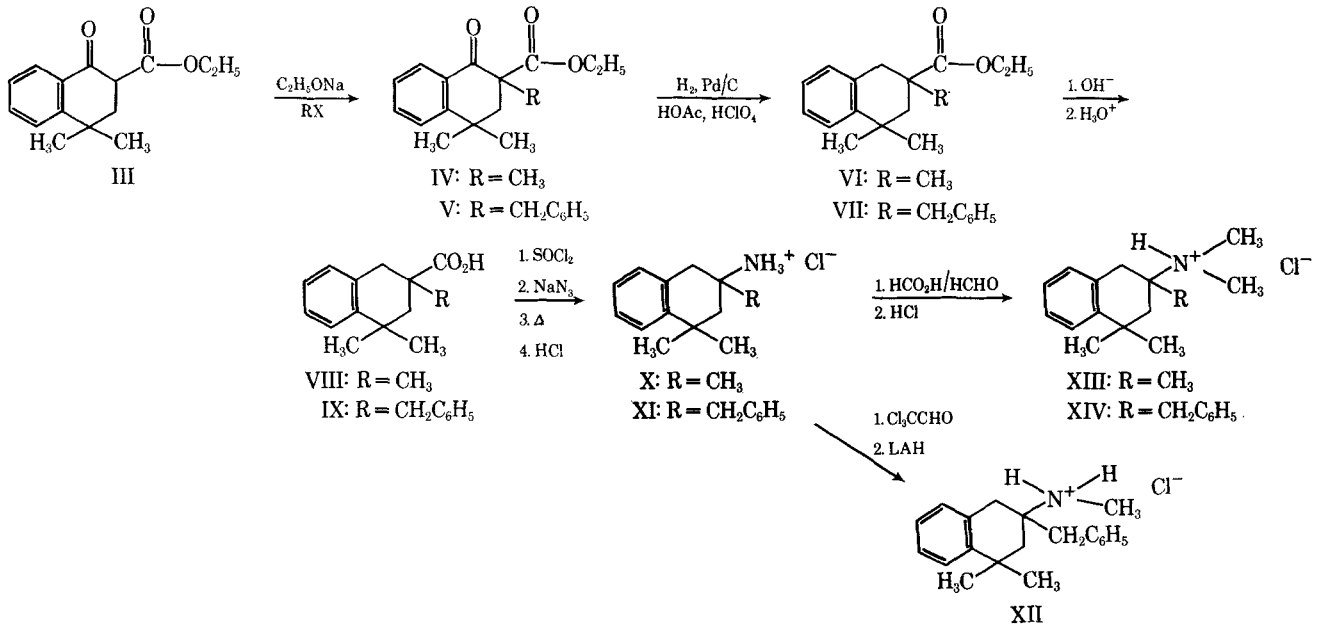
The synthesis of the desired amines was accomplished by the procedures outlined in Scheme II. Methylation and benzylation of ethyl 1,2,3,4-tetrahydro-4,4-dimethyl-1-oxo-2-naphthoate (III) were accomplished by the classical procedure of Kotz and Michaels (5), giving IV and V, respectively. Confirmation that *C*-alkylation had occurred in both instances was demonstrated by the NMR spectra of the alkylated products. Compound IV exhibited three methyl group singlets in the (relatively) shielded region of 1.2–1.4 p.p.m. and lacked the absorption at 3.5–4.0 p.p.m. anticipated for a methyl ether. The methylene protons associated with the 2-benzyl group of V appeared as an *AB* quartet centered at 3.21 p.p.m. The nonequivalence of the methylene protons can be ascribed to the presence of an asymmetric center in V.[2]

Hydrogenolysis of the 2-methyl- and 2-benzyl-2-carbethoxytetralones, IV and V, using palladium-on-charcoal catalysts in glacial acetic acid to which a small amount of perchloric acid had been added, gave the reduced esters, VI and VII. Esters VI and VII were hydrolyzed to the corresponding 1,2,3,4-tetrahydro-2-naphthoic acids, VIII and IX. The Curtius procedure effected the conversion of VIII and IX to the primary amines X and XI, respectively. Eschweiler–Clarke methylation of X and XI gave the corresponding dimethyl amino derivatives, XIII and XIV. The secondary amine, XII, was obtained by treatment of XI with chloral, followed by lithium aluminum hydride reduction of the intermediate formyl derivative.

The analgesic potencies of the amines (Table I) were determined by the mouse hot plate assay of Eddy and Leimbach (6). For purposes of comparison, the ED_{50}'s are expressed as millimoles per kilogram since a variety of salts were employed. The 2-alkyl substituted compounds, XII, XIII, and XIV, although less active than the parent compound, I, retain significant analgesic activity comparable to that of meperidine and codeine. At the outset, it was anticipated that substitution of a bulky group at the 2-position of I would

[1] A similar objective was sought by Shelver and Burger (4) who reported the synthesis of certain 2-substituted-2-aminotetralins. Their compounds, which were inactive as analgesics, lacked a highly substituted central atom, and the 2-substituents possessed highly polar groups.

[2] Numerous examples of magnetic nonequivalence of methylene and isopropyl groups in asymmetric compounds have been reported. For examples, see E. I. Snyder, *J. Amer. Chem. Soc.*, **85**, 2624(1963); G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964); and references cited therein.



Scheme II

increase the conformational preference for the otherwise disfavored axial orientation of the dimethyl amino group. Since the amino functions of morphine and other established conformationally restricted analgesics are held in an axial orientation, substitutions increasing the preference for that orientation in the 2-aminotetralins were anticipated to increase analgesic activity in the series. However, the essentiality of an axial orientation of the amino function has recently been 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 (7, 8). In light of these reports and of the concept of Portoghese *et al.* (9) that differing modes of binding of various narcotic analgesics to analgesic receptors may occur, activity may reside in either half-chair (or some other) conformation of the 2-aminotetralins. The reduction in activity caused by the introduction of a 2-alkyl group may be the result of an unfavorable steric interaction of the group with the receptor. The role that stereochemistry may play in the relative activity of the 2-aminotetralins is under investigation.

EXPERIMENTAL[3]

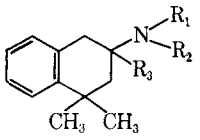
Ethyl 1,2,3,4-Tetrahydro-2,4,4-trimethyl-1-oxo-2-naphthoate (IV)—In a dry, 1-l., two-necked, round-bottom flask, equipped with a reflux condenser and an addition funnel, was placed 340 ml. of absolute ethanol, in which was dissolved 16.1 g. (0.7 g. atom) of sodium in small portions. To this solution of sodium ethoxide were added 34.65 g. (0.141 mole) of ethyl 1,2,3,4-tetrahydro-4,4-dimethyl-1-oxo-2-naphthoate (III) and 175 ml. of anhydrous benzene. After refluxing the reaction mixture for 2.5 hr., it was cooled to 25° and treated with 49 ml. (0.77 mole) of methyl iodide. The reaction mixture was maintained at 25° for 2 hr. with continuous stirring and then treated with a second 49-ml. portion of methyl iodide. After stirring continuously for 2 hr., the reaction mixture was warmed slowly, refluxed gently for 90 min., cooled, and neutralized with acetic acid. After being evaporated nearly to dryness, the mixture was treated with 200 ml. of benzene and 20 ml. of water. The benzene layer was separated, washed once with 5% sodium hydroxide solution, washed twice with distilled water, and dried over anhydrous sodium sulfate. The benzene was removed, and two distillations yielded 26.0 g. (71%) of a product, b.p. 113°/0.28 mm. The viscous oily product turned into a waxy solid within a short period. Recrystallizations from a mixture of warm ethanol and water yielded large rhomboid crystals, m.p. 50–50.4°. The IR spectrum (KBr) exhibited maxima of μ: 3.26, aromatic CH; 3.40–3.49, aliphatic CH; 5.75, ester carbonyl; and 5.85, ketone. The NMR spectrum exhibited values of δ: 1.12, triplet, 3H, ethyl CH_3; 1.25, 1.32, 2 singlets, 2 × 3H, gem-CH_3s; 1.39, singlet, 3H, αCH_3; 2.19, *AB* quartet, 2H, ring CH_2; 4.02, quartet, 2H, ethyl CH_2; 7.3, multiplet, 3H, aromatic; and 7.9, multiplet, 1H, aromatic.

Anal.—Calcd. for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.96; H, 7.41.

Ethyl 1,2,3,4-Tetrahydro-2-benzyl-4,4-dimethyl-1-oxo-2-naphthoate (V)—In a dry, 500-ml., two-necked, round-bottom flask, equipped with a reflux condenser and an addition funnel, was placed 100 ml. of absolute ethanol; in it was dissolved 2.6 g. (0.11 g. atom) of sodium in small portions. To this solution of sodium ethoxide was added 24.6 g. (0.1 mole) of ethyl 1,2,3,4-tetrahydro-4,4-dimethyl-1-oxo-2-naphthoate (III) dissolved in 100 ml. of anhydrous benzene. The reaction mixture was refluxed for 2 hr. and cooled. To this reaction mixture, 14 g. (0.115 mole) of benzyl chloride was added through the addition funnel over a period of 15 min. After the addition of benzyl chloride was completed, the reaction mixture was refluxed for another 3 hr., cooled, and neutralized with glacial acetic acid. After most of the solvent was removed from the reaction mixture, a solid was separated. To this, 100 ml. of water was added and the reaction mixture was extracted with ether (3 × 75 ml.). The combined ether extract was washed once with 5% sodium hydroxide solution and then with distilled water until it was neutral. After drying the extract over anhydrous sodium sulfate, the ether was removed by distillation, causing separation of a soild. Recrystallization of this solid from a mixture of ethanol and water yielded 24.0 g. (71.8%) of white hexagonal crystals, m.p. 100–100.5°. The IR spectrum (KBr) exhibited maxima of μ: 3.25, 3.30, aromatic CH; 3.37–3.54, aliphatic CH; 5.80, ester carbonyl; and 5.93, ketone. The NMR spectrum gave values of δ: 1.06, triplet, 3H, ethyl CH_3; 1.21, 1.28, 2 singlets, 2 × 3H, gem-CH_3s; 2.12, *AB* quartet, 2H, ring CH_2; 3.21, quartet, 2H, benzyl CH_2; 3.94, quartet, 2H, OCH_2; and 9 aromatic protons.

[3] Melting points were determined on a calibrated Fisher-Johns melting-point block. Microanalyses were performed by the Weiler and Strauss Microanalytic Laboratories, Oxford, England, and by the Galbraith Laboratories, Knoxville, Tenn. IR spectra were obtained with Beckman IR-5 and Beckman IR-8 spectrophotometers. NMR spectra were obtained with a Varian A-60 spectrometer, using approximately 15% concentrations of compound in CCl_4 with tetramethylsilane as an internal standard.

Table I—Analgesic Activity of Substituted 2-Methyl- and 2-Benzyl-4,4-dimethyl-2-aminotetralins



Compound	R_1	R_2	R_3	ED_{50}[a]
I[b]	CH_3	CH_3	H	0.02
X[b]	H	H	CH_3	0.10
XI[b]	H	H	$CH_2C_6H_5$	0.13
XII[b]	H	CH_3	$CH_2C_6H_5$	0.06
XIII[b]	CH_3	CH_3	CH_3	0.05
XIV[b]	CH_3	CH_3	$CH_2C_6H_5$	0.06
Meperidine[b]				0.05
Codeine[c]				0.05
Morphine[d]				0.005

[a] Expressed in millimoles per kilogram. [b] HCl salt. [c] Phosphate salt. [d] Sulfate salt.

Anal.—Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.37; H, 7.21.

Ethyl 1,2,3,4-Tetrahydro-2,4,4-trimethyl-2-naphthoate (VI)—In a 500-ml. pressure bottle were placed 19.5 g. (0.075 mole) of ethyl 1,2,3,4-tetrahydro-2,4,4-trimethyl-1-oxo-2-naphthoate (IV), 175 ml. of glacial acetic acid, 30 ml. of a 1.25% solution of perchloric acid in glacial acetic acid prepared according to Rosenmund and Karg (10), and 5.0 g. of 10% palladium-on-carbon catalyst. The bottle was attached to a Parr hydrogenation apparatus equipped with a heater; after evacuation and heating the contents to 60°, hydrogenation was carried out with an initial pressure of 48 p.s.i. The temperature was maintained between 60–63°, with the theoretical amount of hydrogen being taken up during a 2-hr. period. The contents were cooled and the catalyst was removed by filtration and washed with hot alcohol (3 × 10 ml.). The washings and the filtrates were combined and transferred to a distillation assembly, and most of the acetic acid was removed *in vacuo* (aspirator). To the residue, 200 ml. of distilled water was added, and the mixture was extracted with ether (4 × 150 ml.). The combined ethereal extract was washed once with 10% sodium bicarbonate solution, followed by washing with water until the aqueous washings were neutral to short-range pH paper. The ether extract was dried overnight over anhydrous sodium sulfate; after removal of the solvent, the residue was distilled to yield 15.0 g. (82%) of a clear, colorless liquid, b.p. 91°/0.4 mm. The liquid immediately crystallized in the receiver while the distillation was still in progress, yielding transparent rhomboid crystals. Recrystallizations from an ethanol–water mixture yielded large rhomboid crystals, m.p. 59.5–60°. The IR spectrum (KBr) showed maxima of μ: 3.26, aromatic CH; 3.40–3.48 aliphatic CH; and 5.76, ester carbonyl. The NMR spectrum exhibited values of δ: 1.13, triplet, 3H, ethyl CH_3; 1.20, 1.32, 2 singlets, 2 × 3H, gem-CH_3s; 1.24, singlet, 3H, αCH_3; 1.92, *AB* quartet, 2H, "aliphatic" ring CH_2; 2.87, *AB* quartet, 2H, benzylic ring CH_2; 3.97, quartet, 2H, ethyl CH_2; and 7.02, multiplet, 3H, aromatic.

Anal.—Calcd. for $C_{16}H_{22}O_2$: C, 78.00, H, 9.00. Found: C, 77.85; H, 9.10.

Ethyl 1,2,3,4-Tetrahydro-2-benzyl-4,4-dimethyl-2-naphthoate (VII)—In a 500-ml. pressure bottle were placed 20.0 g. (0.065 mole) of ethyl 1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-1-oxo-2-naphthoate (V), 150 ml. of glacial acetic acid, 30 ml. of a 1.25% solution of perchloric acid in glacial acetic acid, and 3.0 g. of 5% palladium-on-carbon catalyst. The bottle was attached to a Parr hydrogenator equipped with a heater. After evacuation and heating the contents to about 50°, the hydrogenation was carried out with an initial pressure of 50 p.s.i. over a period of 5 hr., after which no more hydrogen was consumed. The contents were cooled, and the catalyst was removed by filtration and washed with hot alcohol (3 × 10 ml.). The washing and the filtrate were combined, and most of the acetic acid was removed by distillation under vacuum (aspirator). To the residue, 80 ml. of distilled water was added and the mixture was extracted with ether (3 × 75 ml.). The ether extract was washed with 10% sodium bicarbonate solution followed by washing with distilled water until the aqueous washings were neutral. After drying over anhydrous sodium sulfate, the solvent was removed from the ether extract and a solid separated. Recrystallization from an alcohol–water mixture gave 16.5 g. (86.4%) of white rhomboid crystals, m.p. 81.5°. The IR spectrum (KBr) exhibited maxima of μ; 3.25, 3.30, aromatic CH; 3.37–3.48, aliphatic CH; and 5.76, ester carbonyl. The NMR spectrum gave values of δ: 0.95, triplet, 3H, ethyl CH_3; 1.13, 1.27, 2 singlets, 2 × 3H, gem-CH_3s; 1.96, *AB* quartet, 2H, "aliphatic" ring CH_2; 2.80, 2 overlapping *AB* quartets, 4H, benzyl CH_2s; 3.84, quartet, 2H, ethyl CH_2; and 9 aromatic protons.

Anal.—Calcd. for $C_{22}H_{16}O_2$: C, 81.94; H, 8.12. Found: C, 81.61; H, 8.16.

1,2,3,4-Tetrahydro-2,4,4-trimethyl-2-naphthoic Acid (VIII)—A solution of 10.8 g. (0.043 mole) of ethyl 1,2,3,4-tetrahydro-2,4,4-trimethyl-2-naphthoate (VI) in 190 ml. of ethanol was refluxed for 2 hr. with 170 ml. of 10% sodium hydroxide solution contained in a 500-ml., one-necked, round-bottom flask equipped with a reflux condenser. At the end of the reflux period, the clear and colorless solution was made slightly acidic to a pH of 6.6 with acetic acid. The condenser was replaced with a Claisen distilling head with the condenser turned downward, and the alcohol was removed by distillation *in vacuo* (aspirator). After a small amount of ethanol was removed, a white solid started to separate and continued to increase in amount as the alcohol was being removed, leading to some troublesome bumping. This solid was filtered off, dried, and weighed (7.2 g.). From the filtrate, the rest of the ethanol was distilled off and the flask was kept in a refrigerator overnight. The white solid, which separated out as small granular crystals, was filtered off, dried, and weighed (2.0 g.). When combined with the previously collected crop, the total yield was 9.2 g. (96%). Recrystallizations from a saturated solution of the compound in ethanol, to which a few drops of water were added, led to large, transparent, six-sided crystals, m.p. 151.5–152°. The IR spectrum exhibited maxima of μ: 3.75 (broad), bonded OH; 5.86, carbonyl.

Anal.—Calcd. for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.60; H, 8.39.

1,2,3,4-Tetrahydro-2-benzyl-4,4-dimethyl-2-naphthoic Acid (IX)—A solution of 15.0 g. (0.046 mole) of ethyl 1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-2-naphthoate (VII) in 100 ml. of 95% ethanol was refluxed with 200 ml. of 10% sodium hydroxide solution for 15 hr. At the end of this period, the alcohol was removed by distillation *in vacuo* and the mixture was acidified with dilute hydrochloric acid and cooled. The crystals formed were filtered and recrystallized from a mixture of ethanol and water, giving 13.5 g. (97.4%) of white needle-shaped crystals, m.p. 148–148.5°. The IR spectrum (KBr) exhibited maxima of μ: 3.6–4.0 (continuous series), bonded OH; 5.89, carbonyl.

Anal.—Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.47; H, 7.70.

1,2,3,4-Tetrahydro-2,4,4-trimethyl-2-naphthylamine Hydrochloride (X)—To 4.36 g. (0.02 mole) of 1,2,3,4-tetrahydro-2,4,4-trimethyl-2-naphthoic acid (VIII) contained in a 500-ml., two-necked, round-bottom flask, equipped with a drying tube and an inlet tube with a stopcock, was added 17 ml. of thionyl chloride. The mixture was warmed to 40° and maintained at that temperature for 5 min. with simultaneous stirring. The flask was flushed with dry nitrogen gas, and the mixture was allowed to stand at room temperature overnight. The drying tube was replaced with a glass stopper, and the unreacted thionyl chloride was removed *in vacuo* (aspirator), producing a buff-colored solid. The acid chloride thus formed was dissolved in 40 ml. of anhydrous reagent grade acetone, and the solution was cooled in an ice bath. To it was added, over a period of 5 min., 1.37 g. (0.021 mole) of sodium azide dissolved in 4 ml. of water *via* an addition funnel. The solution was stirred for 1 hr., maintaining the temperature between 6–10°, and then was allowed to warm slowly to room temperature (23°) over a period of 45 min. At the end of that period, a white granular solid settled out and the supernatant liquid became turbid. To this mixture, 90 ml. of water was added, and the mixture was extracted with xylene (4 × 60 ml.). The xylene extracts were combined, washed with 20 ml. of 10% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The acidified sodium bicarbonate solution yielded 0.66 g. of starting material. The xylene solution was filtered into a 500-ml. round-bottom flask, maintaining anhydrous conditions.

The rearrangement of the azide to the isocyanate was accomplished in the usual manner by applying vacuum (aspirator) until

no further evolution of nitrogen was in evidence. The IR spectrum showed a maximum at 4.44 μ, which is consistent with an isocyanate.

The isocyanate was converted to the amine hydrochloride by adding the xylene solution dropwise, during a period of about 30 min., to 20 ml. of concentrated hydrochloric acid saturated with hydrogen chloride while being heated to about 80° and stirred in a 1-l. round-bottom flask. A copious evolution of gas was noted during the addition. The stirring and heating were continued for an additional 2 hr., during which time a white solid separated out and remained dispersed in the xylene phase. The solid was filtered off, dried, and weighed, yielding 2.3 g. (53%) of X. The aqueous acidic phase was separated, and the xylene phase was washed with 10% hydrochloric acid solution (3 × 300 ml.). The combined acidic extracts were evaporated nearly to dryness to obtain additional amine hydrochloride.

The solid obtained was dissolved in hot water, and the solution was made alkaline to a pH 12 and extracted with ether (4 × 70 ml.). The ether extracts were washed with dilute acetic acid followed by water and thoroughly dried over anhydrous sodium sulfate. Dry hydrogen chloride gas was bubbled through the filtered ethereal solution to produce a white precipitate of the amine hydrochloride. Recrystallizations from a mixture of hot absolute alcohol and anhydrous ether yielded a white amorphous solid, m.p. 295–296° (*in a nitrogen-filled, sealed, capillary tube*). The IR spectrum (KBr) showed maxima of μ: 3.5–4.3 (continuous), amine salt; 4.83 (NH_3^+).

Anal.—Calcd. for $C_{13}H_{20}ClN$: C, 69.15; H, 8.92; Cl, 15.70; N, 6.20. Found: C, 69.17; H, 8.92; Cl, 15.45; N, 6.31.

1,2,3,4-Tetrahydro-2-benzyl-4,4-dimethyl-2-naphthylamine Hydrochloride (XI)—To 2 g. (0.0067 mole) of 1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-2-naphthoic acid (IX) contained in a 200-ml., two-necked, round-bottom flask, equipped with a drying tube and an inlet tube with a stopcock, was added 6 ml. of freshly purified thionyl chloride. The mixture was stirred and kept overnight. The drying tube was replaced with a glass stopper, and the unreacted thionyl chloride was removed *in vacuo*, giving a white waxy solid. The resulting acid chloride was dissolved in 80 ml. of anhydrous toluene; to this was added 3.0 g. of freshly activated sodium azide. The suspension was refluxed for 24 hr. while protected from moisture by a calcium chloride tube. The cooled suspension was filtered with suction directly into a 200-ml. round-bottom flask, maintaining anhydrous conditions. The flask was rinsed with a little toluene which was poured through the filter. The IR spectrum of the unisolated intermediate in toluene solution showed a maximum at 4.44 μ, which is consistent with an isocyanate.

To the filtrate in the round-bottom flask was added 60 ml. of concentrated hydrochloric acid, and the mixture was heated to about 80° when a vigorous reaction was observed. The reaction mixture was refluxed for another 2 hr. and cooled; 100 ml. of distilled water was added, and the acid layer separated from the toluene layer. The toluene layer was extracted with dilute hydrochloric acid (2 × 25 ml.). The combined acid solution was made alkaline by 10% sodium hydroxide solution and extracted with ether (4 × 50 ml.). The ether extract, after washing with distilled water until neutral, was dried over anhydrous sodium sulfate. To this dried ethereal solution was added ether saturated with dry hydrogen chloride gas to yield 1.46 g. (72.6%) of the amine hydrochloride (XI) as a heavy, white precipitate. Recrystallization from water and a few drops of ethanol gave a white solid, m.p. 256°. The IR spectrum (KBr) gave maxima of μ: 2.8–3.0 (broad) and 3.6–4.2 (continuous), amine salt; 4.9, NH_3^+.

Anal.—Calcd. for $C_{19}H_{24}ClN$: C, 75.6; H, 8.01; N, 4.64. Found: C, 75.6; H, 8.08; N, 4.65.

***N*-Methyl-1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-2-naphthylamine Hydrochloride (XII)**—A solution of 2 g. of XI in 50 ml. of water was made alkaline by the addition of 5% sodium hydroxide solution, and the free amine formed was extracted with ether (4 × 50 ml.). The ether extract was washed with distilled water until neutral; after drying over anhydrous sodium sulfate, the ether was removed by distillation. To the residue of the free amine dissolved in 50 ml. of chloroform in a 100-ml. round-bottom flask, equipped with an addition funnel and a thermometer, 1.0 g. of chloral was added dropwise while the reaction mixture was kept between 0–5° with the aid of an ice bath. After the addition of the chloral was completed, the reaction mixture was stirred for 6 hr. at room temperature and refluxed for another 2 hr. over a steam bath. The chloroform was removed by distillation, and the solid was recrystallized once from a mixture of ether and chloroform to give 1.2 g. of the formyl derivative, m.p. 170–173°. The IR spectrum showed a strong absorption at 6.02 μ assignable to the C=O group of the formyl derivative.

The formyl derivative, without further purification, was dissolved in 150 ml. of dry ether. The solution was added little by little, with constant stirring, to an ice-cold suspension of 0.3 g. of lithium aluminum hydride in 50 ml. of ether in a 500-ml., three-necked, round-bottom flask. After the addition was completed, the reaction mixture was stirred and refluxed for 6 hr. At the end of this period, the reaction mixture was cooled, and 10 ml. of distilled water was added dropwise to it to destroy the unreacted lithium aluminum hydride. The reaction mixture was filtered through a sintered-glass funnel, and the inorganic matter was washed with ether. After the combined ether solution was dried over anhydrous sodium sulfate, ether saturated with dry hydrogen chloride gas was added to it. The white precipitate formed was filtered and recrystallized from an ethanol–ethyl acetate–ether mixture, giving 0.7 g. (33.5%) of the amine hydrochloride XII, m.p. 208°.

Anal.—Calcd. for $C_{20}H_{26}ClN$; C, 76.04; H, 8.29; N, 4.43. Found: C, 75.96; H, 8.12; N, 4.36.

***N,N*-Dimethyl-1,2,3,4-tetrahydro-2,4,4-trimethyl-2-naphthylamine Hydrochloride (XIII)**—To 5.46 g. (0.025 mole) of 1,2,3,4-tetrahydro-2,4,4-trimethyl-2-naphthoic acid (VI) in a 250-ml. two-necked flask, equipped with a drying tube and an inlet tube with a stopcock, was added 15 ml. of thionyl chloride. The mixture was warmed to 40° with stirring for 5 min. The flask was then flushed with dry nitrogen and allowed to stand at room temperature overnight. The excess thionyl chloride was removed *in vacuo* (aspirator), leaving a white solid. To the solid was added 50 ml. of acetone (A.R.) previously dried over calcium chloride. The resulting solution was cooled to 0–5°; 1.63 g. (0.026 mole) of sodium azide, dissolved in 5 ml. of distilled water, was added *via* an addition funnel over a period of 5 min. The solution was stirred at 6–10° for 1 hr. and then allowed to warm to 25° over a period of 45 min. During this period, a white solid separated. Water (75 ml.) was added, and the mixture was extracted with toluene (3 × 75 ml.). The toluene extracts were combined, washed with sodium bicarbonate (2 × 25 ml.) and 50 ml. of water, and filtered through anhydrous sodium sulfate. The azide in the filtrate was rearranged to the isocyanate with the aid of vacuum (aspirator) over a 2-hr. period, and the filtrate then concentrated to about 20 ml. Twelve milliliters of 98% formic acid was added, the mixture was refluxed for 2 hr., and the volatile constituents were removed *in vacuo*. To the residue were added 25 ml. of 88% formic acid and 25 ml. of 37% formaldehyde solutions; then the mixture was refluxed for 12 hr. Twenty-five milliliters of concentrated hydrochloric acid was added, and the excess formaldehyde and formic acid were removed with the aid of the aspirator. The residue was made alkaline to pH 12 with cold 20% sodium hydroxide solution and then extracted with ether (3 × 100 ml.). The ether extracts were washed with water and filtered through anhydrous sodium sulfate. To the ether solution was added 200 ml. of anhydrous ether saturated with anhydrous hydrogen chloride, causing the amine hydrochloride (XIII) to precipitate as a white solid. The solid was collected on a filter and then recrystallized from absolute ethanol and ether to give 5 g. (78.9%) of white needles, m.p. 249–250° (*sealed tube*). The IR spectrum (KBr) exhibited maxima of μ: 3.7–4.8 (continuous), amine salt.

Anal.—Calcd. for $C_{15}H_{24}ClN$: C, 70.98; H, 9.51; Cl, 13.97; N, 5.52. Found: C, 70.70; H, 9.56; Cl, 13.77; N, 5.77.

***N,N*-Dimethyl-1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-2-naphthylamine Hydrochloride (XIV)**—A solution of 2.5 g. (0.008 mole) of 1,2,3,4-tetrahydro-2-benzyl-4,4-dimethyl-2-naphthylamine hydrochloride in 50 ml. of water was made alkaline by adding 5% sodium hydroxide solution to it. The free amine formed was extracted with ether (4 × 50 ml.). The ether extract was washed with distilled water until the washings were neutral and then dried over anhydrous sodium sulfate. The ether was removed by distillation; to the milky residue obtained was added 4 ml. of 98% formic acid. A vigorous reaction was noticed. After the reaction subsided, the excess formic acid was removed *in vacuo* to yield a white solid. To this solid were added 5 ml. of 35% formaldehyde solution and 5 ml. of 88% formic acid solution, and the mixtue was refluxed for 12 hr. on a water bath. After the evolution of carbon dioxide ceased, the formaldehyde and formic acid were removed *in vacuo*. To this residue, 20 ml. of concentrated hydrochloric acid was added, and the mixture was refluxed on a water bath for 2 hr. The acid solution was

cooled, made alkaline with sodium hydroxide, and extracted with ether (3 × 75 ml.). The combined ether extract, after washing with distilled water and drying over anhydrous sodium sulfate, was added to an ethereal solution of dry hydrogen chloride to yield a white precipitate. Recrystallization from a mixture of ethanol–ethyl acetate–ether yielded 2.1 g. (76%) of white needle-shaped crystals, m.p. 210°. The IR spectrum (KBr) exhibited maxima of μ: 3.9–4.9 (continuous), amine salt.

Anal.—Calcd. for $C_{21}H_{28}ClN$: C, 75.93; H, 9.17; N, 4.21. Found: 76.09; H, 8.97; N, 4.34.

REFERENCES

(1) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *J. Pharm. Sci.*, **58,** 340(1969).

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp. 109–111.

(3) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6,** 986(1954).

(4) W. H. Shelver and A. Burger, *J. Pharm. Sci.*, **52,** 250(1963).

(5) A. Kotz and A. Michaels, *Annalen*, **350,** 212(1906).

(6) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107,** 385(1953).

(7) P. S. Portoghese, H. Kupferberg, and A. Mikhail, *Pharmacologist*, **8,** 2(1966).

(8) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9,** 455 (1966).

(9) P. S. Portoghese, *ibid.*, **8,** 609(1965).

(10) K. W. Rosenmund and E. Karg, *Chem. Ber.*, **75,** 1850(1943).

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Use of an Analog Computer to Simulate and Interpret Data Obtained from Linear Nonisothermal Stability Studies

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Abstract □ An analog computer program was developed to simulate drug decomposition induced during linear nonisothermal stability studies. From the analog computer values used to generate the simulation curve best-fitting experimental data, the activation energy, the reaction rate constant at any temperature, and the predicted shelflife at that temperature can be determined. By using the decomposition data reported for the first-order, linear nonisothermal degradation of *N*-acetyl-*p*-aminophenol and the analog computer program presented here, kinetic parameters identical with published values were obtained. The analog computer program can be easily modified to accommodate nonlinear heating regimens as well as reactions of any order.

Keyphrases □ Linear nonisothermal stability studies—simulation □ Analog computer simulation—stability studies □ Shelflife prediction—kinetic parameters □ Diagram—analog computer program

The customary procedure for predicting the shelflife of a drug involves the determination of the degradation rate constant at a few elevated temperatures, the determination of the activation energy, and finally the extrapolation of this information to room temperature. This requires large numbers of samples and ultimately a great deal of personnel time. By means of a rapid and simple concentration–time–temperature study in which temperature is changed at a preselected rate, it is possible to obtain these parameters in 1 or 2 days.

The concept of using programmed elevated temperatures to arrive at the kinetic parameters required to predict shelflife is not new. Borchardt and Daniels (1) obtained the rate, order, and activation energy for the decomposition of benzenediazonium chloride by analysis of the slope, height, and area of a differential thermal analysis curve. Davies (2) followed a chemical reaction by observing the change in optical density of one reactant with time as its temperature was progressively raised. Reaction kinetics were also followed using differential scanning calorimetry (3) and thermogravimetric analysis (4).

Various heating regimens have been employed. Cole and Leadbeater (5) studied the reaction rate of several compounds. They employed the temperature program designed by Rogers (6) in which the inverse of the temperature was varied logarithmically with time. Eriksen and Stelmach (7) obtained the necessary kinetic parameters from a single experiment, using the following time–temperature relationship:

$$\frac{1}{T} = \frac{1}{T_0} - at \qquad \text{(Eq. 1)}$$

where a is a reciprocal heating constant, and T_0 and T are the absolute temperatures at the initial time and at time t, respectively. Zoglio *et al.* (8) followed the first-order decomposition of *N*-acetyl-*p*-aminophenol and procainamide hydrochloride as the temperature was raised linearly with time according to the expression

$$T = bt + C \qquad \text{(Eq. 2)}$$

where b is the heating rate and C is the initial temperature. These authors employed digital computation to obtain 384 slopes or rate constants, which were then used to generate a series of degradation curves corresponding to various activation energies. The analytical