Substituted Tetralins IV: Synthesis and Stereochemistry of 4,4-Disubstituted 1,2,3,4-Tetrahydro-2-naphthoic Acids

EZZAT M. KANDEEL, LERAY J. ANDERSON, JOHN H. BLOCK*, ALLEN I. WHITE, and ARNOLD R. MARTIN▲

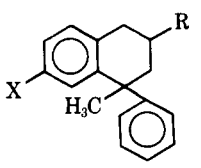
Abstract □ The syntheses of four 4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthoic acids are described. The stereospecific cyclization of the *cis*-isomers and proton NMR studies establishing *cis–trans* product ratios are also reported.

Keyphrases □ Tetralins, substituted—synthesis, stereochemistry of 4,4-disubstituted 1,2,3,4-tetrahydro-2-naphthoic acids □ 1,2,3,4-Tetrahydro-2-naphthoic acids, 4,4-disubstituted—synthesis, stereochemistry □ NMR spectroscopy—determination, stereochemistry of 4,4-disubstituted 1,2,3,4-tetrahydro-2-naphthoic acids □ Stereochemistry of 4,4-disubstituted 1,2,3,4-tetrahydro-2-naphthoic acids—determination, NMR spectroscopy

Because of continuing interest in the analgesic (1, 2) and cardiac antiarrhythmic (3, 4) properties of various substituted 2-aminotetralin derivatives, the synthesis and pharmacological evaluation of the isomers of *N,N*-dimethyl-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine (I) and its 6-methoxy analog (II), which were to be prepared sequentially from III and IV, respectively, were performed. Although a number of 1,2,3,4-tetrahydro-2-naphthoic acids have been reported in the literature (1, 2, 5, 6), to our knowledge no systematic studies assigning stereochemistry in such compounds have been reported. We report here an improved synthesis for 4,4-disubstituted 1,2,3,4-tetrahydro-2-naphthoic acids including III and IV, the stereospecific cyclization of the *cis*-isomers[1] III*a* and IV*a*, and proton NMR studies establishing *cis–trans* product ratios.

DISCUSSION

cis–trans Mixtures of III and IV were obtained *via* anhydrous hydrogen fluoride-catalyzed cyclization of the olefins V and VI followed by hydrolysis and decarboxylation of the resulting diesters VII and VIII (Scheme I). The olefins were prepared by alkylation of diethyl 2-benzylmalonate or diethyl 2-*p*-methoxybenzylmalonate with 3-bromo-2-phenyl-1-propene (IX). Compound IX was prepared by slight modifications of the method of Hatch and Patton (7), which gave a mixture of IX and 1-bromo-2-phenyl-1-propene (X). The separation of these isomers, as reported by Pines *et al.* (8), was not found to be practical. Therefore, the mixture was used without separation.



I: R = $N(CH_3)_2$, X = H
II: R = $N(CH_3)_2$, X = OCH_3
III: R = COOH, X = H
IV: R = COOH, X = OCH_3

To effect olefin cyclizations, anhydrous hydrogen fluoride was chosen instead of other acid catalysts as a result of the work of Darzens and Hienz (9), who obtained lactone XI using sulfuric acid as a catalyst for the cyclization of diethyl 2-allyl-2-(*p*-methylbenzyl)malonate. Similarly, lactone XII was obtained from the attempted cyclization of diethyl 2-(*p*-methoxybenzyl)-2-(2-methylallyl)malonate (XIV) with polyphosphoric acid (Scheme II). Treatment of the diethyl 2-benzyl-2-(2-methylallyl)malonates (XIII and XIV) with anhydrous hydrogen fluoride (Scheme II) gave the 2,2-dicarbethoxytetralins (XV and XVI, respectively), which were converted to the known acids XVII and XVIII by conventional procedures (1). Furthermore, hydrolysis and decarboxylation of XII, followed by treatment of the resulting lactone (XIX) with anhydrous hydrogen fluoride gave XVIII. That six-membered ring derivatives were obtained from these cyclizations was confirmed by methyl absorption in the NMR spectra.

The NMR spectra of the mixtures of acids III*a*–III*b* (IV*a*–IV*b*) exhibited sharp singlets at 1.71 and 1.78 (1.71 and 1.76) δ. The acids were separated by fractional recrystallization (acetic acid and water), using the NMR methyl signals as a monitor; each was then treated with anhydrous hydrogen fluoride for 24 hr. at about 25°. A nearly quantitative yield of the bridged ketones XX and XXI was obtained from III*a* and IV*a*, whereas III*b* and IV*b* were recovered unchanged under the same conditions. It may be concluded that III*b* and IV*b* do not epimerize to III*a* and IV*a*, respectively, under the conditions employed. Julia *et al.* (10) obtained the similar ketone XXII from polyphosphoric acid-catalyzed cyclization of 4-phenyl-1,2,3,4-tetrahydro-2-naphthoic acid. Cyclization data thus established *cis*-stereochemistry for III*a* and IV*a* and *trans*-stereochemistry for III*b* and IV*b*.

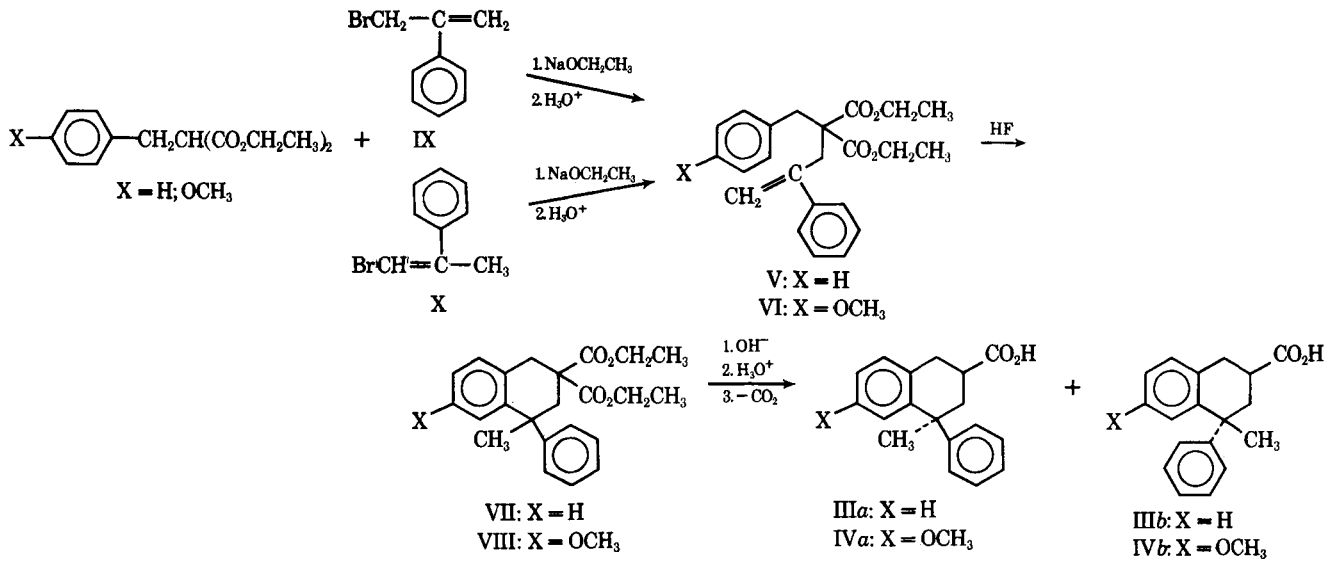
Because the half-chair conformation is considered the most energetically favored for the tetralin system (11), it is fair to assume that cyclization of III*a* and IV*a* proceeds through the half-chair conformation XXIII wherein the 2-carboxyl group is axial and the 4-phenyl group is quasiaxial.

EXPERIMENTAL[2]

3-Bromo-2-phenyl-1-propene (IX)—The procedure used was adapted from the one used by Hatch and Patton (7). A solution of 178 g. (1.0 mole) of *N*-bromosuccinimide, 118 g. (1.0 mole) of α-methylstyrene, and 300 ml. of dry carbon tetrachloride was heated at reflux for 48 hr. in an oven-dried, 1-l., three-necked, round-bottom flask equipped with a ground-glass stirrer and an efficient reflux condenser. The solid succinimide and unreacted *N*-bromosuccinimide were removed by filtration, and the flask was rinsed with carbon tetrachloride; the washing then was run through the filter cake. Excess α-methylstyrene and carbon tetrachloride were removed by distillation (water aspirator). Then 50 ml. of low boiling petroleum ether (30–60°) was added, causing the separation of a viscous oily liquid which was thick enough to be filtered off. The filtrate, on distillation, gave 148 g. of product, b.p. 90–

[1] For the purpose of this discussion, the *cis*-isomer is arbitrarily chosen to be the one wherein the 2-carboxyl and 4-phenyl groups bear a *cis*-relationship to each other.

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



Scheme I

100°/5 mm. The NMR spectrum of the mixture exhibited a sharp singlet due to the allylic CH_2 of IX at 4.02δ and a doublet due to the vinyl CH of X at 6.21δ. The ratio of these two peaks was taken as a measure of the percent of IX in the mixture (70%).

Diethyl 2-Benzyl-2-(2-phenylallyl)malonate (V)—In a dry 1-l., three-necked, round-bottom flask equipped with a stirrer, an addition funnel, and a Friedricks condenser with a drying tube was placed 350 ml. of dry absolute ethanol. With stirring and slight warming, 20.7 g. (0.9 g.-atom) of clean sodium was dissolved in alcohol. The flask was then cooled to room temperature, and 225 g. (0.9 mole) of diethyl 2-benzylmalonate was added from the addition funnel, with stirring, over a 5-min. period. With continuous stirring of the yellow solution, a 254.2-g. mixture of IX and X, calculated to contain 177.3 g. (0.9 mole) of IX, was added during 1 hr. at a rate to cause gentle refluxing. Stirring while heating at reflux was continued for 24 hr. Most of the alcohol was then removed (water aspirator), and 175 ml. of distilled water was added to dissolve the inorganic salt formed. The mixture was then transferred to a separator and extracted with benzene (4 × 100 ml.), after which the benzene fractions were combined and dried over anhydrous sodium sulfate. After the benzene had been removed (water aspirator), distillation gave 77 g. of the unreacted X, b.p. 90°/5 mm., and 275 g. (80.2%) of V as a viscous oil, b.p. 190°/0.2 mm. The NMR spectrum showed a doublet due to the CH_2= group at 5.40δ.

Anal.—Calc. for $C_{23}H_{26}O_4$: C, 75.39; H, 7.12. Found: C, 75.35; H, 7.22.

Diethyl 2-(*p*-Methoxybenzyl)-2-(2-phenylallyl)malonate (VI)—Diethyl 2-(*p*-methoxybenzyl)malonate (XII, 252 g., 0.9 mole) was treated with the mixture of IX and X under conditions described for V. The desired product (VI) distilled at 200°/0.25 mm., yielding 300 g. (84%). The NMR spectrum showed a doublet for the CH_2= group at 5.25δ.

Anal.—Calc. for $C_{24}H_{28}O_5$: C, 72.71; H, 7.11. Found: C, 72.60; H, 7.14.

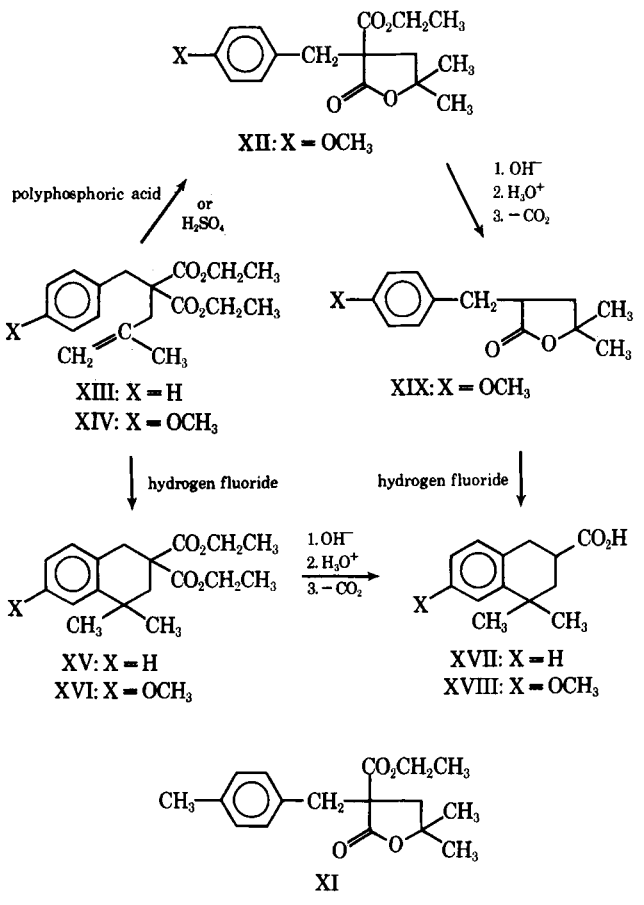
Diethyl 2-Benzyl-2-(2-methylallyl)malonate (XIII)—Diethyl (2-methylallyl)malonate, 192 g. (0.9 mole), was reacted with 113.4 g. (0.9 mole) of benzyl chloride under the same conditions used for V. The product (XIII) distilled at 125°/0.15 mm., yielding 175 g. (65%). The NMR spectrum showed a broad singlet for a CH_2= group at 4.60δ.

Anal.—Calc. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.97. Found: C, 70.95; H, 7.88.

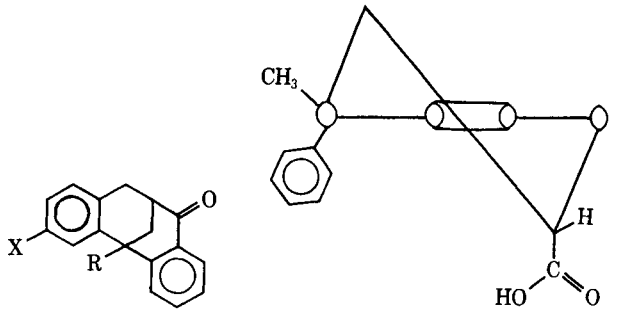
Diethyl 2-(*p*-Methoxybenzyl)-2-(2-methylallyl)malonate (XIV)—Diethyl 2-(*p*-methoxybenzyl)malonate, 252 g. (0.9 mole), was treated with 72 g. (0.9 mole) of 3-chloro-2-methylpropene under the same conditions described for V. The product XIV distilled at 170°/1.3 mm., yielding 258 g. (86%).

Anal.—Calc. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.58; H, 8.02.

Diethyl 1,2,3,4-Tetrahydro-4-methyl-4-phenylnaphthalene-2,2-dicarboxylate (VII)—Compound V, 109.8 g. (0.3 mole), and 400 g. of anhydrous hydrogen fluoride in a 1-l. polyethylene bottle were kept in an ice bath for 12 hr. The hydrogen fluoride was then allowed to evaporate spontaneously during 24 hr. of stirring at room temperature. Water was then added, and the organic material was extracted several times with ether. The ether extracts were combined and washed with a 10% sodium bicarbonate solution until the solution remained slightly basic; then they were washed with a saturated solution of sodium chloride and dried over anhydrous sodium sul-



Scheme II



XX: X = H, R = CH_3
XXI: X = OCH_3, R = CH_3
XXII: X = H, R = H

XXIII

fate. The ether was then evaporated, and vacuum distillation gave 98.8 g. (90%) of a very viscous white oil at 200°/0.3 mm. The dicarboxylate crystallized out on standing. Crystallization from alcohol gave white crystals (100%), m.p. 52°, of VII. The NMR spectrum showed a sharp methyl singlet at 1.61δ.

Anal.—Calc. for $C_{23}H_{26}O_4$: C, 75.39; H, 7.12. Found: C, 75.28; H, 7.26.

Diethyl 1,2,3,4-Tetrahydro-6-methoxy-4-methyl-4-phenylnaphthalene-2,2-dicarboxylate (VIII)—Using the same cyclization procedure as was employed for VII, 118.8 g. (0.3 mole) of VI was treated with hydrogen fluoride. The desired product distilled at 195°/0.05 mm., yielding 100 g. (89%) of VIII. The NMR spectrum exhibited a singlet for the methyl group at 1.64δ.

Anal.—Calc. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 73.00; H, 6.95.

Diethyl 1,2,3,4-Tetrahydro-4,4-dimethylnaphthalene-2,2-dicarboxylate (XV)—Cyclization of 75 g. of XIII with hydrogen fluoride, using the same procedure as for VII, gave 68 g. (90%) of viscous oil, b.p. 150°/0.1 mm. The NMR spectrum exhibited a sharp singlet, corresponding to two CH_3 groups at 1.22δ, and no olefinic CH_2= group at 4.60δ.

Anal.—Calc. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.97. Found: C, 70.97; H, 7.84.

Diethyl 1,2,3,4-Tetrahydro-6-methoxy-4,4-dimethylnaphthalene-2,2-dicarboxylate (XVI)—By employing hydrogen fluoride as a cyclizing agent, 60 g. of XIV gave 51 g. (85%) of a very viscous clear liquid, b.p. 167–168°/0.9 mm. Crystallizations from benzene–petroleum ether (30–60°) yielded a crystalline waxy solid, m.p. 58°.

Anal.—Calc. for $C_{19}H_{26}O_5$: C, 68.23; H, 7.84. Found: C, 68.34; H, 7.68.

1,2,3,4-Tetrahydro-4-methyl-4-phenylnaphthalene-2,2-dicarboxylic Acid—An alcoholic solution of 51 g. (0.28 mole) of VII and 32 g. (0.56 mole) of potassium hydroxide was heated at reflux for 12 hr. The alcohol was allowed to evaporate, and the resulting solid was redissolved in water. The aqueous solution was extracted with ether and then acidified with 6 *N* hydrochloric acid. The resulting oil and/or solid were extracted with several portions of ether. The ether extracts were washed with water until neutral and then with a saturated solution of sodium chloride; they then were dried over anhydrous sodium sulfate. Reagent grade benzene was added to the dry ether, and the mixture was distilled (water aspirator) until it became turbid. Upon refrigeration, white crystals formed and were collected by filtration. The mother liquor was evaporated and the additional solid material collected was combined with the first batch. Recrystallization from methanol–benzene produced 43 g. (100%) of white crystals, m.p. 180° with effervescence. The partially purified diacid was subjected directly to decarboxylation without further purification.

1,2,3,4-Tetrahydro-6-methoxy-4-methyl-4-phenylnaphthalene-2,2-dicarboxylic Acid—Hydrolysis of 56 g. of VIII was carried out using the same procedure as for VII. The dicarboxylic acid was obtained as white crystals which, on recrystallization from methanol–benzene, gave 45 g. (100%) of white crystals, m.p. 172° with effervesence. The partially purified diacid was subjected directly to decarboxylation without further purification.

1,2,3,4-Tetrahydro-4,4-dimethylnaphthalene-2,2-dicarboxylic Acid—The alkaline hydrolysis of 55 g. of XV gave 25 g. (54%) of 1,2,3,4-tetrahydro-4,4-dimethylnaphthalene-2,2-dicarboxylic acid as white crystals from benzene–carbon tetrachloride, m.p. 175° with effervescence. The partially purified diacid was subjected directly to decarboxylation without further purification.

1,2,3,4-Tetrahydro-6-methoxy-4,4-dimethylnaphthalene-2,2-dicarboxylic Acid—Alkaline hydrolysis of 55 g. (0.165 mole) of XVI gave 45 g. (100%) of 1,2,3,4-tetrahydro-6-methoxy-4,4-dimethylnaphthalene-2,2-dicarboxylic acid as a white crystalline solid, m.p. 171° with effervescence. The partially purified diacid was subjected directly to decarboxylation without further purification.

1,2,3,4-Tetrahydro-4-methyl-4-phenyl-2-naphthoic Acid (III)—Decarboxylation of 37.6 g. (0.12 mole) of 1,2,3,4-tetrahydro-4-methyl-4-phenylnaphthalene-2,2-dicarboxylic acid was accomplished by heating in a flask in an oil bath at 180° until the evolution of carbon dioxide ceased. It was noted that the weight had decreased by 12 g. more than the theoretical loss. One crystallization from glacial acetic acid resulted in 25 g. (78%) of a mixture of III*a* and III*b*, m.p. 120–145°. The NMR spectrum showed a doublet of equal intensity at 1.74δ for a methyl group.

A careful fractional recrystallization in glacial acetic acid resulted in 10 g. of III*b*, m.p. 187°. The NMR spectrum showed a methyl absorption at 1.78δ.

Anal.—Calc. for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.49; H, 6.94.

A second fraction of 10 g. of III*a*, m.p. 162°, was obtained from the mother liquors. The NMR spectrum showed a sharp singlet for the methyl group at 1.71δ.

Anal.—Calc. for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.11; H, 6.84.

1,2,3,4-Tetrahydro-6-methoxy-4-methyl-4-phenyl-2-naphthoic Acid (IV)—Decarboxylation of 40 g. (0.13 mole) of 1,2,3,4-tetrahydro-6-methoxy-4-methyl-4-phenylnaphthalene-2,2-dicarboxylic acid was accomplished at 175° (see III*a* and III*b*) to give 25.8 g. (72%) of a mixture of IV*a* and IV*b*, m.p. 125–142°. The NMR spectrum showed a methyl doublet at 1.74δ. A careful fractional recrystallization in acetic acid–water gave 11 g. of IV*a*, m.p. 156°. The NMR spectrum showed a sharp singlet for the methyl group at 1.71δ.

Anal.—Calc. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.84; H, 7.00.

A second fraction of 9 g. of IV*b*, m.p. 147°, was obtained from the mother liquors. The NMR spectrum showed a sharp singlet for the methyl group at 1.76δ.

Anal.—Calc. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.05; H, 6.76.

1,2,3,4-Tetrahydro-4,4-dimethylnaphthoic Acid (XVII)—Decarboxylation of 34 g. (0.14 mole) of 1,2,3,4-tetrahydro-4,4-dimethylnaphthalene-2,2-dicarboxylic acid gave 28 g. (93%) of XVII, m.p. 106° [lit. (1) m.p. 106°]. The NMR spectrum showed two singlets of equal intensity at 1.26 and 1.32δ corresponding to two methyl groups.

1,2,3,4-Tetrahydro-6-methoxy-4,4-dimethyl-2-naphthoic Acid (XVIII)—Decarboxylation of 45 g. (0.16 mole) of 1,2,3,4-tetrahydro-6-methoxy-4,4-dimethylnaphthalene-2,2-dicarboxylic acid yielded 30 g. (70%) of XVIII as white crystals. Recrystallization from benzene–petroleum ether (65–110°) gave a white crystalline solid, m.p. 154° [lit. (1) m.p. 154°].

7,12-Dihydro-12-methyl-6,12-methanodibenzo[*a*,*d*]cyclooctene-5(6*H*)-one (XX)—Cyclization of 2.66 g. (0.01 mole) of III*a* with 40 g. of hydrogen fluoride was effected in a 250-ml. polyethylene bottle with stirring for 24 hr. at room temperature while allowing a spontaneous evaporation of the hydrogen fluoride. Water was then added, and the organic material was extracted several times with ether. The ether extracts were combined, washed with 10% sodium bicarbonate solution, washed with a saturated solution of sodium chloride, and dried over anhydrous sodium sulfate. The ether was then evaporated (water aspirator), leaving a white solid which, on recrystallization from ethanol, gave 2.6 g. (98%), m.p. 150°, of the cyclic ketone XX. The IR spectrum (KBr) exhibited a maximum of μ 5.97, cyclic C=O.

Anal.—Calc. for $C_{18}H_{16}O$: C, 87.09; H, 6.45. Found: C, 86.92; H, 6.52.

An attempt to cyclize III*b* under the same conditions resulted in 100% recovery of the starting material.

7,12-Dihydro-10-methoxy-12-methyl-6,12-methanodibenzo[*a*,*d*]-cycloocten-5-one (XXI)—Cyclization of 2.96 g. (0.01 mole) of IV*a*

was achieved using the same procedure employed for the cyclization of IIIa, yielding 2.86 g. (97%) of the cyclic ketone XXI, m.p. 120°. The IR spectrum (KBr) exhibited a maximum of μ 5.91, cyclic C=O.

Anal.—Calc. for $C_{19}H_{18}O_2$: C, 82.01; H, 6.47. Found: C, 82.10; H, 6.56.

An attempt to cyclize IVb under the same conditions resulted in 100% recovery of the starting material.

2-Carbethoxy-2-(*p*-methoxybenzyl)-4,4-dimethyl-γ-butyrolactone (XII)—To 155 g. (0.46 mole) of XIV in a 2-l. resin reaction flask, equipped with an efficient mechanical stirrer, an addition funnel, and a thermometer and cooled in an ice bath, was added 500 g. of polyphosphoric acid in a steady stream. Stirring, which was difficult due to the viscosity of the mixture, was carried on during the addition and then at the ice bath temperature for 30 min. thereafter. About 400 ml. of ice and water was added, and the reaction mixture was allowed to stand overnight to decompose the complex. When all of the mixture had been decomposed as evidenced by a change in color of the mixture from red to white, it was transferred to a separator and extracted with ether (4 × 100 ml.). The ether solutions were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue was distilled, b.p. 168–171°/0.5 mm., yielding 103 g. (73%) of XII as a viscous colorless liquid. The IR spectrum showed a maximum of μ 5.64, which is consistent with a γ-lactone C=O.

Anal.—Calc. for $C_{17}H_{22}O_5$: C, 66.64; H, 7.24. Found: C, 67.22; H, 7.45.

2-(*p*-Methoxybenzyl)-4,4-dimethyl-γ-butyrolactone (XIX)—The lactone XII dissolved in 40 ml. of ether was placed in a 250-ml. round-bottom flask equipped with a reflux condenser. To this was added 15 g. of potassium hydroxide in 50 ml. of water, and the mixture was heated under reflux for 2 hr. The ether was removed (aspirator), and the aqueous solution was transferred to a separator and extracted with ether (2 × 50 ml.). Only a slight amount of residue remained upon evaporation of the ether solution. The aqueous solution was acidified with concentrated hydrochloric acid, causing the separation of a white solid which was removed by filtration and dried. The dry solid was transferred to a 100-ml. round-bottom flask and heated to 175–180° for 2 hr. until no further evolution of gas was seen. The material in the flask was cooled and dissolved in 200 ml. of ether, and the ether solution was extracted with 10% sodium bicarbonate solution (2 × 75 ml.). Acidification of the combined aqueous bicarbonate solutions produced only a slight turbidity. The ether solution was evaporated to dryness, leaving an oily semisolid which solidified when left in the refrigerator overnight. The solid was dissolved in hot 5% sodium hydroxide solution. The resulting solution was cooled to room temperature and washed with 50 ml. of ether. The alkaline solution was acidified with concentrated hydrochloric acid, causing a white precipitate. The solid was recrystallized three times from petroleum ether (65–110°) to which had been added a small amount of benzene to yield shiny white crystals of the lactone (XIX), m.p. 45°. The IR spectrum showed a maximum of μ 5.67, which is consistent with a γ-lactone C=O.

Anal.—Calc. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.64; H, 7.73.

Formation of 1,2,3,4-Tetrahydro-7-methoxy-4,4-dimethyl-2-naphthoic Acid (XVIII) from XIX—To 10.5 g. (0.045 mole) of the decarbethoxylated lactone contained in a dry 250-ml. polyethylene bottle was added, with occasional mixing, about 100 ml. of liquid anhydrous hydrogen fluoride. The bottle was allowed to stand in the hood at room temperature for several days until all of the hydrogen fluoride had evaporated. There resulted a solid residue which was dissolved in ether. The ether solution was transferred to a separator, washed with 50 ml. of a saturated sodium chloride solution, and then extracted with a 10% sodium bicarbonate solution (4 × 75 ml.). Insoluble material that separated in the funnel was removed by filtration. The aqueous bicarbonate extracts were combined and acidified with concentrated hydrochloric acid. The solid material which separated was removed by filtration and dried to yield 4.7 g. (45%) of a white solid. The solid was dissolved in hot benzene, and petroleum ether (65–110°) was added to the point of incipient cloudiness. Upon cooling, a white crystalline compound formed. A second recrystallization produced crystals, m.p. 153.6–154.2°. There was no depression in melting point when mixed with a sample of the acid XVIII prepared by decarboxylation of 1,2,3,4-tetrahydro-6-methoxy-4,4-dimethylnaphthalene-2,2-dicarboxylate.

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) V. S. Pai, A. P. Parulkar, A. R. Martin, and A. I. White, *ibid.*, **60**, 201(1971).

(3) D. M. Graeff, W. E. Johnson, C. D. St. Dennis, and A. R. Martin, *J. Med. Chem.*, **14**, 60(1971).

(4) W. E. Johnson, D. M. Graeff, A. R. Martin, and A. I. White, *Life Sci.*, **9**, 471(1970).

(5) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 941(1959).

(6) M. S. Newman and J. R. Mangham, *J. Amer. Chem. Soc.*, **71**, 334(1949).

(7) L. F. Hatch and T. L. Patton, *ibid.*, **76**, 2705(1954).

(8) H. Pines, A. Husni, and M. Kolobielski, *J. Org. Chem.*, **22**, 1113(1957).

(9) G. Darzens and A. Hienz, *Compt. Rend.*, **184**, 33(1927); G. Darzens and A. Levy, *ibid.*, **200**, 469(1935).

(10) S. Julia, M. Julia, and C. Huynh, *Bull. Soc. Chim. Fr.*, **1960**, 84.

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

(12) A. L. Buckle, A. McGookin, and A. Robertson, *J. Chem. Soc.*, **1954**, 3981.

ACKNOWLEDGMENTS AND ADDRESSES

Received November 10, 1971, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication April 5, 1972.

Supported in part by Grant NB-02054, National Institutes of Health, U. S. Public Health Service, Bethesda, MD 20014

* Present address: College of Pharmacy, Oregon State University. Corvallis, Ore.

▲ To whom inquiries should be directed.