were pooled and chloroform extracted, and the crude steroidal metabolite was isolated as previously described. The extracts from the 12-, 24-, and 48-hr. incubations were analyzed by t.l.c. T.l.c. of the 12-hr. incubation product showed four compounds identified as progesterone ($R_f$ 0.72), androstenedione ($R_f$ 0.95), testosterone ($R_f$ 0.42), and testololactone ($R_f$ 0.24) by comparison with authentic samples. The relative intensity of the iodine-detected spots showed progesterone to be present in large amount. T.l.c. of the 24-hr. incubation product showed the same four spots but the relative amount of progesterone had decreased, androstenedione and testosterone appeared only in small amounts, and testololactone had increased significantly. T.l.c. of the 48-hr. incubation product showed the presence only of progesterone, testololactone, and 11β-hydroxytestosterone ($R_f$ 0.09). Androstenedione and testosterone had completely disappeared.

**Conversion of 11α-Hydroxyprogesterone[11] by** *A. tamarii*.—11α-Hydroxyprogesterone (1.20 g.) was incubated with *A. tamarii* for 48 hr. as previously described and 1.08 g. of crude amorphous product was obtained. T.l.c. showed two spots with $R_f$ 0.37 and 0.20. The crude chloroform extract was chromatographed on 70 g. of Merck acid-washed alumina (activity III). The ether–benzene (1:9) eluate gave 157 mg. of 11α-hydroxyprogesterone ($R_f$ 0.37): m.p. 169–172° (alone and on admixture with an authentic sample); $\nu^{KBr}$ 3450, 1710, 1670, 1620, and 870 cm.$^{-1}$. The ether eluate gave 655 mg. of 11α-hydroxytestosterone: m.p. 181–181.5° after recrystallization from ether (lit.[14] m.p. 181.5°); $R_f$ 0.20; $\nu^{KBr}$ 3450, 3320, 1660, 1620, and 865 cm.$^{-1}$; $[\alpha]^{26}D$ +94° (*c* 0.0284, $CHCl_3$), reported[14] [α] +93°; n.m.r. ($CDCl_3$) δ 1.83 (3H), 1.32 (3H), 2.20 (2H, which disappeared upon addition of $D_2O$ to the sample), 2.29 (1H), 2.35 (1H), and 5.74 (1H). None of the chromatography fractions showed six-membered lactone absorption, indicative of 11α-hydroxytestololactone, in the infrared.

**Conversion of 11β-Hydroxyprogesterone by** *A. tamarii*.—11β-Hydroxyprogesterone (167 mg.) was incubated with *A. tamarii* for 48 hr. as previously described. The usual work-up gave 145 mg. of crude product, whose t.l.c. showed only two spots, $R_f$ 0.35 and 0.09. The crude extract was chromatographed on 35 g. of Merck acid-washed alumina (activity III) and the ether–benzene (3:7) eluate gave 87 mg. of unchanged 11β-hydroxyprogesterone, m.p. 185–187°, $R_f$ 0.35, identical in all respects with authentic material. The ether–benzene (8:2) eluate afforded 46 mg. of 11β-hydroxytestosterone: $R_f$ 0.09; m.p. 237–240; $\nu^{KBr}$ 3500, 1670, and 1620 cm.$^{-1}$. This material was identical in all respects with 11β-hydroxytestosterone obtained as described above. None of the chromatography fractions showed the presence of six-membered lactones in their infrared spectra.

**Transformation of Δ⁴-Androstene-3,17-dione by** *A. tamarii*.—Δ⁴-Androstene-3,17-dione (332 mg.) was incubated with *A. tamarii* for 48 hr. as previously described and chloroform extraction gave 235 mg. of crude product. T.l.c. showed only two spots ($R_f$ 0.96 and 0.25). The crude extract was chromatographed on 65 g. of Merck acid-washed alumina (activity III). The ether–benzene (1:9) eluate gave 167 mg. of unchanged Δ⁴-androstene-3,17-dione: m.p. 169–172; $R_f$ 0.96; $\nu^{KBr}$ 1735, 1670, and 1620 cm.$^{-1}$. The ether–benzene (6:4) eluate gave 66 mg. of testololactone ($R_f$ 0.25).

**Conversion of Testosterone by** *A. tamarii*.—Testosterone (1.00 g.) was incubated with *A. tamarii* for 48 hr. as previously described and the usual work-up gave 877 mg. of crude product; the t.l.c. showed three spots ($R_f$ 0.43, 0.25, and 0.09). The crude extract was chromatographed on 20 g. of Merck acid-washed alumina (activity IV); the benzene eluate gave 624 mg. of noncrystalline material, the t.l.c. of which showed two spots of $R_f$ 0.43 and 0.25, corresponding, respectively, to testosterone and testololactone. Recrystallization of the combined chromatography fractions from benzene gave, after drying at 0.1 mm., 210 mg. of pure testosterone, m.p. 149–151°. Rechromatography of the residue from the recrystallization on 35 g. of Merck acid-washed alumina (activity IV) gave 363 mg. of pure testololactone, m.p. 205–207°, $R_f$ 0.25.

The ether–benzene (8:2) eluate gave 217 mg. of 11β-hydroxytestosterone, m.p. 238–240°, $R_f$ 0.09, identical in all respects with that obtained as previously described.

**Acknowledgment.**—This work was supported in part by Oklahoma Agricultural Experiment Station, project 1182.

(14) S. H. Eppstein, *et al.*, *J. Am. Chem. Soc.*, **76**, 3174 (1954).

# Synthesis of 4-Demethyltetrahydroalantolactone

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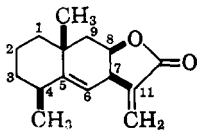
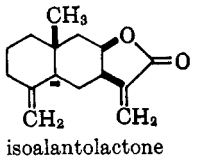
*Received October 16, 1964*

A synthesis of 4-demethyltetrahydroalantolactone (**17**) from 10-methyl-1(9)octal-2-one (**1**) is described. The most efficient route was found to be **1** → **2** → **3** → **4** → **10** → **12** → **13** → **15** → **16** → **17**. Isoalantolactone was degraded, *via* the ketone **18** and the thioketal **19**, to the natural isomer **17a** which was identical with the racemic lactone **17**.

We recently reported a new method for the synthesis of the α-methylene-γ-butyrolactone moiety found in numerous sesquiterpenes.[3] We now describe an application of this method to the synthesis of 4-demethyl-5,6-dihydroalantolactone (**16**) and 4-demethyltetrahydroalantolactone (**17**) a degradation product of isoalantolactone.



alantolactone



isoalantolactone

The required starting material, *trans*-10-methyl-2-decalone (**2**), was prepared from 2-methylcyclohexanone and methyl vinyl ketone, *via* octalone (**1**), in 35–40% over-all yield by an improved procedure.[4] Bromination of decalone **2** afforded the crystalline bromodecalone **3**[5] which was reduced using a slight excess of lithium aluminum hydride in ether. The resulting bromohydrin was treated with potassium hydroxide in refluxing isopropyl alcohol, according to steroid analogy,[6] giving a 9:1 mixture of β-oxide **4** and decalone **2** which was separated by fractional distillation. Reduction of bromo ketone **3** using a two- or threefold excess of lithium aluminum hydride for extended times (over-

(1) Fellow of the National Institute of General Medical Sciences, Public Health Service, 1963–1964.

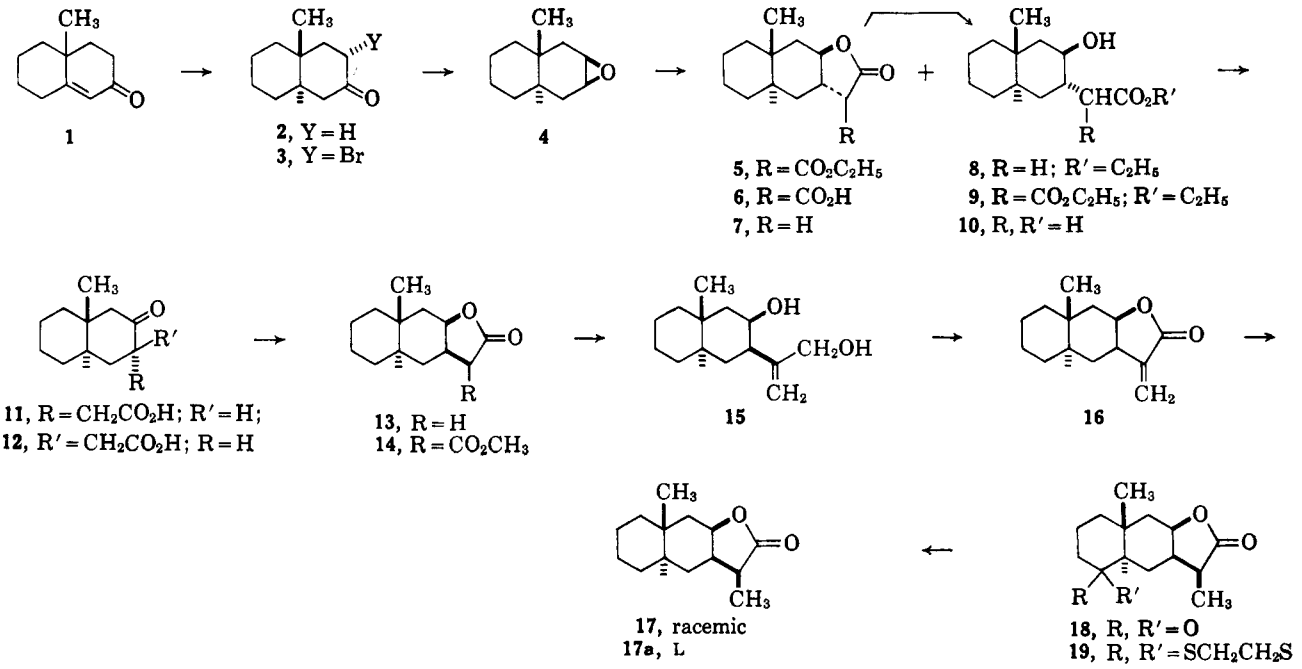
(2) Participant in the National Science Foundation Summer Undergraduate Research Program, 1964.

(3) J. A. Marshall and N. Cohen, *Tetrahedron Letters*, 1997 (1964). For a comprehensive review, see W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

(4) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

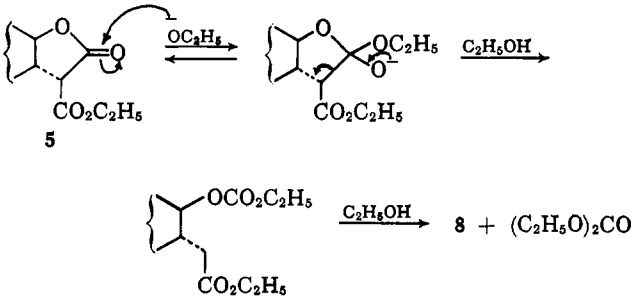
(5) M. Yanagita and K. Yamakawa, *ibid.*, **21**, 500 (1956).

(6) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953).

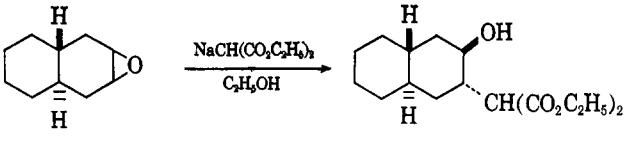



night) gave mainly *trans*-10β-methyl-2β-decalol[7] through hydrogenolysis of the intermediate bromohydrin.[8]

Condensation of diethyl sodiomalonate with β-oxide **4** in refluxing ethanol yielded, after 12 hr., 45% of lactone ester **5** and 25% of hydroxy ester **8**. None of the expected[9] hydroxy diester **9** was found. Lactone ester **5**, upon saponification and careful acidification of the alkaline solution, was converted to lactone acid **6** which underwent thermal decarboxylation to lactone **7**. Ethanolysis converted lactone **7** to hydroxy ester **8** in nearly quantitative yield thereby establishing the relationship between **5** and **8**. Hydroxy ester **8** was the major product of the reaction between oxide **4** and diethyl sodiomalonate when prolonged reaction time and excess sodium ethoxide were employed. Evidently, retrocarbethoxylation of lactone ester **5** is relatively facile.[10] This cleavage of lactone ester **5** may be rendered particularly favorable by relief of internal strain attending opening of the lactone ring as follows.




Saponification of lactone **7** or hydroxy ester **8** afforded hydroxy acid **10**. The same hydroxy acid was obtained from lactone ester **5**, or crude mixtures of **5** and **8**, by saponification and decarboxylation using refluxing ethylene glycolic potassium hydroxide. This proved to be the method of choice for preparation of hydroxy acid **10** which was thereby obtained from oxide **4** in 63% yield. Mild oxidation[11] of hydroxy acid **10** afforded keto acid **11**, m.p. 96.5–97.5°, which was epimerized in aqueous alkali to keto acid **12**, m.p. 89–90, 94–95, or 102–103°, depending upon the crystalline form. The nonidentity of keto acids **11** and **12** was established by mixture melting point and comparison of infrared spectra. Thus, the stereochemistry of keto acids **11** and **12** is secured[12] and the conclusion that oxide **4** undergoes diaxial opening[13] affording lactone ester **5**, in which the lactone-fused cyclohexane ring must adopt a boat conformation, is inescapable. A striking contrast to this result is provided by the condensation of oxide I with diethyl sodiomalonate, under identical reaction conditions, leading to hydroxy diester II in 94% yield.[9] The apparent instability of hydroxy diester **9** relative to II must arise from the additional nonbonded 1,3-diaxial $CH_3$–OH interaction present in **9** which contributes to the driving force for lactonization. This




I II

interaction also appears responsible for the formation of lactone acid **6** as the major hydrolysis product of lactone ester **5**. The hydroxy acid **10** shows less tendency toward lactonization indicating that the greater bulk of a malonic *vs.* an acetic acid side chain is likewise important. However, a detectable amount of lactone **7** resulted from distillation of hydroxy acid **10** or hydroxy ester **8** at temperatures above 120°.

(7) The prefixes "α" and "β" designate relative stereochemistry of racemic materials.

(8) Contrast with steroidal α-bromo ketones: H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

(9) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frish, L. Dreger, and V. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(10) For analogous findings, see W. Herz and L. Glick, *J. Org. Chem.*, **28**, 2970 (1963), and references cited therein.

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946). For the application of this reagent to the synthesis of readily epimerized ketones, see W. F. Erman and T. J. Flautt, *J. Org. Chem.*, **27**, 1526 (1962).

(12) See ref. 9 for an analogous proof of stereochemistry.

(13) For an excellent review of the stereochemistry of nucleophilic oxide opening, see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

The *cis*-lactone **13** was obtained in high yield by hydrogenation of keto acid **12** over platinum in acetic acid. Carbomethoxylation of lactone **13** was smoothly effected with sodium hydride in dimethyl carbonate according to the procedure developed by Rhoads, *et al.*,[14] for cyclic ketones. The resulting enolate of lactone ester **14** was freed of dimethyl carbonate and reduced with lithium aluminum hydride in 1,2-dimethoxyethane.[3] The crystalline unsaturated diol **15** thus obtained[15] was oxidized with manganese dioxide[16] in benzene affording 4-demethyl-5,6-dihydroalantolactone (**16**). The relationship of lactone **16** to the alantolactones was established through hydrogenation of **16** to 4-demethyltetrahydroalantolactone (**17**) and comparison with the naturally derived lactone **17a** of the same structure.[17]

The required degradation product **17a** of isoalantolactone was prepared from the known keto lactone **18**[18] *via* the thioketal derivative. Desulfurization of the thioketal derivative **19** with Raney nickel produced lactone **17a** in excellent yield. The infrared spectrum of lactone **17a** was indistinguishable from its racemic counterpart **17**. The n.m.r. spectra of **17** and **17a** provided confirmatory evidence of their structural identity.

## Experimental[19]

***trans*-10-Methyl-2-decalone (2).**[20]—To a stirred solution of 76.0 g. of 10-methyl-1(9)-octal-2-one (**1**)[4] in 2.5 l. of ammonia and 450 ml. of anhydrous ether was cautiously added 21 g. of lithium wire in 2–5-cm. pieces. After 1.5 hr., 400 ml. of 1:1 ethanol–ether was added dropwise over 4 hr., followed by 140 g. of ammonium chloride in small portions. The ammonia was allowed to evaporate and the decalol was isolated with ether and benzene.[19c]

The crude decalol was dissolved in 250 ml. of reagent grade acetone and 96 ml. of 8 *N* chromic anhydride reagent[11] was added dropwise over 2.5 hr. with the temperature maintained between 0 and 5°. The orange color was discharged with isopropyl alcohol and the solution was decanted and concentrated under reduced pressure. The decalone was isolated with ether and benzene[19c] giving 51.1 g. (87% yield) of decalone **2**, b.p. 94–95° (1 mm.), lit. b.p. 130–133° (21 mm.)[5] and 86° (0.1 mm.).[20]

***trans*-10β-Methyl-3α-bromo-2-decalone (3).**[7]—Bromination of 51.1 g. of decalone **2** according to the procedure of Yanagita and Tahara[21] afforded 45.3 g. (60%) of bromo ketone **3**, m.p. 101.5–102.5° (reported m.p. 99–100°[21] and 101–102.5°[5]).

***trans*-10β-Methyl-2β,3β-oxidodecalin (4).**[7]—To a stirred solution of 8.0 g. of bromo ketone **3** in 120 ml. of anhydrous ether was cautiously added 0.34 g. of lithium aluminum hydride. After 10 min., 0.7 ml. of water and 0.6 ml. of 10% aqueous sodium hydroxide was carefully added. The mixture was stirred for 4 hr. and filtered, and the solvent was removed under reduced pressure affording 8.0 g. of oil.

A 7.6-g. portion of the residue was dissolved in 225 ml. of isopropyl alcohol containing 20.2 g. of potassium hydroxide and the mixture was maintained at 60° for 2.5 hr.[22] Most of the isopropyl alcohol was removed at 50° under reduced pressure and the residue was isolated with ether.[19c] Distillation gave 4.1 g. (80%) of colorless oxide **4**, b.p. 48° (0.4 mm.), containing about 10% of decalone **2** ($\lambda_{max}^{film}$ 5.84 μ) on the basis of the n.m.r. integration. The pure oxide **2** was obtained in 54% yield by careful fractionation of a subsequently prepared sample: b.p. 82–83° (1.8 mm.); $\lambda_{max}^{film}$ 9.47, 9.74, 11.88, and 12.40 μ; $\delta_{TMS}^{CCl_4}$ 2.96 (H-2, H-3) and 0.90 p.p.m. (angular $CH_3$).[23]

*Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.44; H, 10.93. Found: C, 79.3; H, 10.9.

A small amount of decalone **2** impurity was not detrimental to the subsequent condensation reaction and therefore samples of oxide **4** containing 5–10% of decalone **2** were usually used.

When bromo ketone **3** was reduced using a tenfold excess of lithium aluminum hydroxide for 18 hr. the major product was *trans*-10β-methyl-2β-decalol identified by comparison with an authentic sample.[24]

A 1.00-g. sample of crude bromohydrin (obtained in 99% yield from reduction of bromo ketone **3** as described above) was chromatographed on silicic acid. The fractions eluted with benzene to 2% ether in benzene afforded 0.76 g. (76%) of *trans*-10β-methyl-3α-bromo-2β-decalol, m.p. 65–66°. After two recrystallizations from pentane the material exhibited m.p. 67–68°; $\lambda_{max}^{CCl_4}$ 2.80 (OH), 8.32, 9.43, and 10.59 μ. A sample was sublimed at 50° (0.02 mm.) for analysis.

*Anal.* Calcd. for $C_{11}H_{19}BrO$: C, 53.42; H, 7.77; Br, 32.34. Found: C, 53.7; H, 7.8; Br, 32.1.

The epoxide **4** was the sole product when the crystalline bromohydrin was treated with base as described above.

**Ethyl (*trans*-10β-Methyl-3β-hydroxy-2α-decalyl)malonate Lactone (5).**[7] **A. 12-Hr. Reaction Time.**—The procedure of Johnson, *et al.*,[6] was employed, but the work-up was modified. To a solution of 1.1 g. of diethyl malonate in 10 ml. of ethanolic sodium ethoxide (from 0.15 g. of sodium) was added 1.0 g. of oxide **4** over a 0.5-hr. period. The mixture was stirred under reflux for 12 hr.,[19d] allowed to cool, and filtered with the aid of a small quantity of anhydrous ether. The dry filter cake was treated with dilute hydrochloric acid and the product was isolated with ether[19c] giving 0.71 g. (42% yield) of pale yellow lactone ester **5**: $\lambda_{max}^{CHCl_3}$ 5.61 (lactone CO), 5.77 (ester CO), 8.65, and 9.85 μ. Recrystallization from hexane afforded 0.60 g., m.p. 90.5–91.5°.

*Anal.* Calcd. for $C_{16}H_{24}O_4$: C, 68.53; H, 8.64. Found: C, 68.6; H, 8.9.

The filtrate from the reaction mixture provided an additional 0.12 g. (7% yield) of crystalline lactone ester **5** after isolation of the crude organic product and chromatography on silicic acid.

**B. 24-Hr. Reaction Time.**—A mixture of 1.55 g. of diethyl malonate and 1.46 g. of oxide **4** in 20 ml. of ethanolic sodium ethoxide (from 0.22 g. of sodium) was allowed to stir under reflux for 24 hr.[19d] Filtration of the reaction mixture and isolation of the product as described in part A afforded 0.55 g. (22%) of lactone ester **5**, m.p. 90–92°.

The filtrate was shaken with saturated aqueous ammonium chloride and extracted with ether[19c] yielding 1.75 g. of orange oil. The volatile starting materials were removed under high vacuum and the residual 1.13 g. of oil was chromatographed on 60 g. of silicic acid. The 5% ether in benzene fractions gave 0.19 g. (8%) of crystalline lactone ester **5**.

**Ethyl (*trans*-10β-Methyl-3β-hydroxy-2α-decalyl)acetate (8).**[7] **A. From Oxide 4.**—The 20–50% ether in benzene fractions from part B of the above experiment were combined and distilled, b.p. 82° (bath temperature) (0.02 mm.), affording 0.81 g. (36% yield based on oxide **4**) of colorless oil: $\lambda_{max}^{film}$ 2.89 (OH), 5.76 (ester CO), 8.45, 8.85, 9.64, and 9.90 μ.

*Anal.* Calcd. for $C_{15}H_{26}O_3$: C, 70.81; H, 10.32. Found: C, 70.9; H, 10.4.

**B. From Lactone 7.**—A solution of 0.25 g. of lactone **7** in 5 ml. of 0.3 *N* ethanolic sodium ethoxide was allowed to stand for 18 hr.[19d] The product was isolated with ether[19c] affording 0.31 g. (100%) of pale yellow oil which displayed an infrared

(14) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

(15) The by-products from related reductive eliminations are under investigation and will be identified in a forthcoming report.

(16) R. F. Church, Doctoral Dissertation, University of Michigan, 1961, p. 87.

(17) The steric course of comparable hydrogenations has recently been established by W. Cocker and M. A. Nisbet [*J. Chem. Soc.*, 534 (1963)].

(18) L. Ruzicka and P. Pieth, *Helv. Chim. Acta*, **14**, 1090 (1931).

(19) (a) The prefix DL is omitted from the names of racemic substances. (b) Melting points were determined on a Fisher-Johns hot stage. (c) The isolation procedure consisted of thorough extraction and back-extraction with the specified solvent, washing the combined extracts with saturated brine, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a steam bath. (d) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere. (e) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(20) B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958).

(21) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953).

(22) This is essentially the procedure of Corey.[6]

(23) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).

(24) R. H. Baker, L. S. Minckler, and A. S. Hussey, *J. Am. Chem. Soc.*, **81**, 2397 (1959).

spectrum identical with that of hydroxy ester **8** obtained according to part A.

(*trans*-10β-Methyl-3β-hydroxy-2α-decalyl)acetic Acid Lactone (**7**).[7] **A. From Lactone Ester 5.**—A mixture of 706 mg. of lactone ester **5** and 15 ml. of 1 *N* aqueous sodium hydroxide was stirred under reflux for 4 hr.[19d] The cooled aqueous solution was washed with ether and acidified with cold 10% hydrochloric acid at 0° in an ice bath. The resulting solid was filtered, washed with water, and dried affording 581 mg. (91.6%) of lactone acid **6**: m.p. 159–161° dec.; $\lambda_{max}^{mull}$ 2.95–3.15 (acid OH), 5.71 (lactone CO), and 5.89 (acid CO) μ. This material was not further purified owing to thermal instability.

The crude lactone acid **6** was heated at 190–200° for 1.5 hr.[19d] The resulting oil was dissolved in benzene and washed with aqueous sodium bicarbonate. The benzene was removed and the residual 450 mg. (92.8%) of lactone **7** was distilled: b.p. 130–140° (bath temperature) (0.02 mm.); $\lambda_{max}^{film}$ 5.64 (lactone CO), 7.76, and 8.26 μ.

*Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70. Found: C, 75.0; H, 9.8.

**B. From Hydroxy Acid 10.**—A 485-mg. sample of hydroxy acid **10** was heated at 180–200° for 2 hr.[19d] The work-up procedure described in part A was employed affording 325 mg. (73.7%) of distilled lactone **7**.

(*trans*-10β-Methyl-3β-hydroxy-2α-decalyl)acetic Acid (**10**).[7] **A. From Hydroxy Ester 8.**—A mixture of 784 mg. of hydroxy ester **8** and 10 ml. of 1 *N* aqueous sodium hydroxide was stirred under reflux for 4 hr.[19d] The cooled solution was washed with ether and acidified with cold 10% hydrochloric acid. The resulting solid was filtered, washed well with water, and dried affording 515 mg. (73.7%), m.p. 165–168°. A sample was recrystallized from ethyl acetate giving white prisms: m.p. 167–168°; $\lambda_{max}^{mull}$ 2.9–4.1 (OH), 5.84 (acid CO), 8.30, 9.70, 9.96, and 10.40 μ.

*Anal.* Calcd. for $C_{13}H_{22}O_3$: C, 68.97; H, 9.82. Found: C, 69.1; H, 9.7.

The lactone **7** afforded hydroxy acid **10** in 96% yield by the above procedure.

**B. From Epoxide 4.**—The mixture of lactone ester **5** and hydroxy ester **8**, obtained from the condensation of 2.00 g. of epoxide **4** and diethyl sodiomalonate (from 2.4 g. of diethyl malonate and 0.50 g. of sodium in 35 ml. of ethanol) under reflux for 44 hr., was refluxed with 20 ml. of 5% ethylene glycolic potassium hydroxide for 8 hr.[19d] The cooled solution was dissolved in water, washed with ether, and acidified. The product was isolated with ether and benzene[19c] and recrystallized from ethyl acetate yielding 1.23 g., m.p. 164–166°, and 0.34 g., m.p 162–164° (63% based on oxide **4**).

(*trans*-10β-Methyl-3-oxo-2α-decalyl)acetic Acid (**11**).[7]—A solution of 300 mg. of hydroxy acid **10** in 10 ml. of reagent grade acetone maintained at 0° was efficiently stirred while 0.33 ml. of 8 *N* chromic acid[11] was added dropwise. After 5 min., the product was isolated with ether[19c] affording 293 mg. (98.4%) of keto acid **11**, m.p. 92–95°. After two recrystallizations from hexane–benzene, white plates, m.p. 96.5–97.5°, were obtained: $\lambda_{max}^{CHCl_3}$ 2.8–4.1 (acid OH), 5.85 (CO), 8.25, 8.55, and 9.05 μ.

*Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.60; H, 9.00. Found: C, 69.5; H, 8.9.

(*trans*-10β-Methyl-3-oxo-2β-decalyl)acetic Acid (**12**).[7]—A solution of 150 mg. of keto acid **11** in 5 ml. of 1 *N* aqueous sodium hydroxide was allowed to stand at room temperature for 82 hr. The solution was cooled to 0° and acidified with cold 10% aqueous hydrochloric acid, and the product was isolated with ether[19c] affording 150 mg. (100%) of pale yellow solid. After three recrystallizations from hexane–benzene, the material was obtained as white needles: m.p. 94–95°; $\lambda_{max}^{CHCl_3}$ 2.8–4.1 (acid OH), 5.85 (CO), 8.43, 8.54, 8.70, 8.99, and 9.97 μ.

*Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.60; H, 9.00. Found: C, 69.4; H, 8.8.

A mixture of the keto acids **11** and **12** exhibited m.p. 62–78°. The keto acid **12** was also obtained as prisms, m.p. 89–90°, and cubes, m.p. 102–103°.

The keto acid **12** was isolated in 87% yield (m.p. 92–93°) by oxidation of hydroxy acid **10**, as described above, followed by extraction of the crude keto acid **11** with aqueous sodium hydroxide. The combined alkaline extracts were heated on a steam bath for 0.5 hr. and, after an additional hour at room temperature, the keto acid **12** was obtained by acidification and extraction.

(*trans*-10β-Methyl-3β-hydroxy-2β-decalyl)acetic Acid Lactone (**13**).[7]—A solution of 1.50 g. of keto acid **12** in 12 ml. of acetic acid was hydrogenated over 0.60 g. of platinum oxide at 40 p.s.i. for 7 hr. The mixture was filtered and the acetic acid was removed under reduced pressure. The residue was dissolved in ether and thoroughly washed with aqueous sodium bicarbonate, saturated brine, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the residue was recrystallized from hexane affording 1.05 g., m.p. 82–83°, and 0.04 g., m.p. 75–77° (72.5%): $\lambda_{max}^{CCl_4}$ 5.63 (lactone CO), 8.50, 8.69, 9.80, 10.24, 10.51, 10.69, and 11.10 μ.

*Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.94; H, 9.68. Found: C, 75.0; H, 9.6.

2-(*trans*-10β-Methyl-3β-hydroxy-2β-decalyl)-2-propen-1-ol (**15**).[7]—The mineral oil was removed from 0.30 g. of 51% sodium hydride dispersion by washing with two 5-ml. portions of dry benzene and dry dimethyl carbonate. The resulting sodium hydride was suspended in 15 ml. of dry dimethyl carbonate containing 416 mg. of lactone **13**. The mixture was stirred under reflux for 2.5 hr. after hydrogen evolution commenced and the dimethyl carbonate was carefully removed by distillation under reduced pressure. The dry residual solid enolate was suspended in 30 ml. of dry 1,2-dimethoxyethane and 0.25 g. of lithium aluminum hydride was added. After 3.5 hr. at reflux, the slurry was cooled, diluted with 50 ml. of ether, and carefully treated with 1 ml. of water. The mixture was stirred until the salts became granular and filtered. The salts were washed with hot ethyl acetate and the solvent was removed from the combined filtrates under reduced pressure. The residue was triturated with hexane and recrystallized from ethyl acetate to give 180 mg. (40.2%) of diol **15**: m.p. 115–117°; $\lambda_{max}^{CHCl_3}$ 2.97 (OH), 6.09 (C=$CH_2$), 9.64, 9.83, and 10.90 μ. The analytical sample, m.p. 119–120°, was obtained after two recrystallizations from ethyl acetate–heptane.

*Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.94; H, 10.79. Found: C, 75.0; H, 10.8.

DL-4-Demethyl-5,6-dihydroalantolactone (**16**).—A solution of 79 mg. of diol **15** in 4.5 ml. of anhydrous benzene was stirred with 1.2 g. of manganese dioxide[16] for 5.5 hr. The mixture was filtered and the solid cake was washed with chloroform. The solvent was removed from the filtrate under reduced pressure and the solid residue was recrystallized from hexane affording 50 mg. (63%) of lactone **16**: m.p. 83–84°; $\lambda_{max}^{CCl_4}$ 5.65 (lactone CO), 5.98 (C=$CH_2$), 7.91, 8.25, 9.05, 9.62, 9.92, 10.35, and 10.60 μ.

*Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.1; H, 9.3.

DL-4-Demethyltetrahydroalantolactone (**17**).—A solution of 42 mg. of unsaturated lactone **16** in 6 ml. of methanol was hydrogenated over 25 mg. of platinum oxide at atmospheric pressure and room temperature. The theoretical volume of hydrogen was absorbed within 0.5 hr. The mixture was filtered and the methanol was removed under reduced pressure whereupon the residue was recrystallized from hexane giving 33 mg., m.p. 81–83°, and 5 mg., m.p. 78–80° (90%). The material exhibited a double m.p. 83–84° and 103–108° after two recrystallizations from hexane: $\lambda_{max}^{CCl_4}$ 5.63 (lactone CO), 8.59, 8.90, 9.87, 10.02, 10.29, and 10.44 μ; $\delta_{TMS}^{CCl_4}$ 4.25–4.50 (H-8), 1.11 (C-11 $CH_3$, $J$ = 7 c.p.s.), and 0.91 p.p.m. (C-10 $CH_3$).

*Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C, 75.6; H, 9.8.

Ethylene Thioketal of L-4-Oxotetrahydroalantolactone (**19**).—To a solution of 40 mg. of keto lactone **18**[25] in 0.6 ml. of acetic acid and 0.1 ml. of 1,2-ethanedithiol was added 0.06 ml. of boron trifluoride etherate.[26] The solution was allowed to stand for 2 hr. and poured into 40 ml. of saturated aqueous sodium bicarbonate. The product was isolated with ethyl acetate[19c] and recrystallized from ethyl acetate–heptane yielding 45 mg. (85%), m.p. 182–183°. The analytical sample exhibited m.p. 183–183.5° from ethyl acetate–heptane; $\lambda_{max}^{CHCl_3}$ 5.67 (lactone CO), 8.56, 9.94, and 10.30 μ.

*Anal.* Calcd. for $C_{16}H_{24}O_2S_2$: C, 61.49; H, 7.74; S, 20.53. Found: C, 61.4; H, 7.7; S, 20.6.

L-4-Demethyltetrahydroalantolactone (**17a**).—A solution of 38 mg. of thioketal **19** in 10 ml. of ethanol was stirred at room

(25) This material, m.p. 196–199°, was prepared from dihydroisoalantolactone according to Ruzicka and Pieth.[11]

(26) This is the method of L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

temperature for 1 hr. and under reflux for 2 hr. with 1 g. of freshly prepared W-2 Raney nickel.[27] The cooled mixture was filtered and the ethanol was removed affording 25 mg. (93.7%) of white solid with an infrared spectrum which was indistinguishable from that of racemic lactone **17**. After two recrystallizations from hexane, 11 mg. of material with m.p. 119–121° was obtained.

*Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C, 75.7; H, 9.9.

The close similarity of the n.m.r. spectrum of this material with that of the racemic lactone **17** further substantiated the structure assigned to **17**.[28]

**Acknowledgment.**—We thank the Public Health Service for support of this work through a Research Grant (AI-04965, National Institute of Allergy and Infectious Diseases) and a Fellowship (5-F1-GM-19,839 to N. Cohen).

(27) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(28) A Varian A-60 spectrometer was used.

# Bicyclic Ketones. II. The 2-Acetylbicyclo[2.2.1]hept-5-ene and 2-Acetylbicyclo[2.2.1]heptane Systems[1,2]

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*Received July 13, 1964*

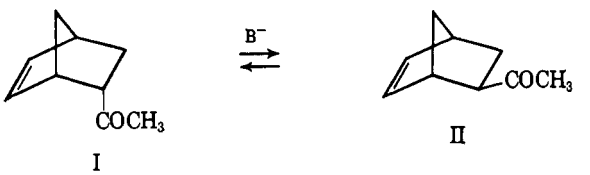
The base-catalyzed equilibration of mixtures of *endo*- and *exo*-2-acetylbicyclo[2.2.1]hept-5-ene and of mixtures of their saturated derivatives was studied as a means of preparing the pure ketone isomers. The equilibrium constants, $K_{exo-endo}$, were determined to be 2.25 and 3.25, respectively. Each isomer has been separated and characterized by derivatives.

Although the Diels–Alder adduct of cyclopentadiene and methyl vinyl ketone has been known for some time,[4–6] no reports were found concerning the stereochemistry of the product. Laszlo and Schleyer[7] have recently separated *endo*-2-acetylbicyclo[2.2.1]hept-5-ene (I) from the Diels–Alder adduct mixture by preparative vapor phase chromatography (v.p.c.). Isomer I was one of a number of *endo*-2-bicyclo[2.2.1]-hept-5-en-2-yl derivatives used in a study of their n.m.r. spectra. For our purposes, however, larger quantities of I and *exo*-2-acetylbicyclo[2.2.1]hept-5-ene (II) were needed in connection with another problem.[8] It was thought to be of interest to investigate the *endo–exo* equilibrium of the Diels–Alder mixture of I and II and to attempt to use this as means of getting both isomers from the *endo*-rich[9] mixture.

## Results and Discussion

The Diels–Alder reaction between methyl vinyl ketone and cyclopentadiene proceeded exothermally in diethyl ether to give a near quantitative yield of the adduct mixture of I and II. Analysis of the adduct by v.p.c. showed the mixture to be composed of 62% I and 38% II. It was determined during purification of the mixture by distillation, that some separation of the isomers was occurring although no change in boiling point was observed. The *exo* isomer II was predominant in the early fractions.

A procedure similar to that of Cope, Ciganek, and LeBel[10] was used for equilibration to enrich the mixture in isomer II, and possibly to make distillation a feasible method for obtaining pure II. Mixtures of I and II of varying compositions were equilibrated with sodium methoxide in refluxing absolute methanol. The resulting mixtures were analyzed by v.p.c. The results of the epimerizations and the calculated equilibrium constants, $K_{exo-endo}$, are shown in Table I. The standard free energy ($\Delta G°$), at 338.6°K. for the process I $\rightleftharpoons$ II, using the equilibrium constant obtained, is calculated to be −550 cal./mole.




I II

TABLE I

RESULTS OF THE EQUILIBRATION OF I AND II

| Starting compn. % *endo* | Starting compn. % *exo* | Hr. of reflux | Final compn. % *endo* | Final compn. % *exo* | $K_{exo-endo}$ |
|---|---|---|---|---|---|
| 92 | 8 | 240 | 33.1 | 66.9 | 2.02 |
| 90 | 10 | 44 | 30.2 | 69.8 | 2.31 |
| 50 | 50 | 44 | 31.3 | 68.7 | 2.18 |
| 20 | 80 | 44 | 28.7 | 71.3 | 2.54 |
| 5 | 95 | 36 | 31.7 | 68.3 | 2.15 |
| | | Av. | 31.0 | 69.0 | 2.25 |
| | | Std. dev. | 1.65 | 1.65 | 0.20 |

It would appear that, due to the structural similarities between the bicyclo[2.2.1]hept-5-en-2-yl ketones (I and II) and the methyl esters (III and IV) of the corresponding carboxylic acids, the relative position of equilibrium would be very similar. This is not the

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(2) Presented in part at the 37th Annual Meeting of the South Carolina Academy of Science, Aiken, S. C., April 25, 1964.

(3) Abstracted from the thesis presented by S. P. M. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May 1964.

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