Dehydroepiandrosterone (IV). To a warm solution of 374 mg. of III in 100 ml. of methanol and 70 ml. of pyridine was added 100 mg. of sodium borohydride in methanol. After standing for 20 hr. at room temperature the excess sodium borohydride was decomposed with acetic acid. The solvents were evaporated and the dry residue triturated with dilute hydrochloric acid, filtered and then dried.

The crude mixture of isomeric alcohols was suspended in 1 ml. of acetic acid, a mixture of 150 mg. of sodium acetate and 0.3 ml. of pyruvic acid in 1 ml. of acetic acid and a drop of water added, and heated for 1 hr. at 110°. During the heating period, 4 ml. of water was added to the solution. After cooling the mixture was extracted with ether, washed with a solution of sodium bicarbonate, water and dried over anhydrous sodium sulfate. The solvent was then evaporated. The 3β-alcohol was isolated through its digitonide which, after decomposition with pyridine, gave 117 mg. of crystalline IV, m.p. 139–141°, not depressed on admixture with authentic material.

This corresponds to an over-all yield, based on androstenedione, of 31%. The mother liquors of the digitonide were evaporated, extracted with ether and chromatographed over aluminum oxide. The benzene eluates gave 23 mg. (6% over-all yield) of crystalline androsta-3,5-dien-17-one [m.p. 87–89°; $[\alpha]_D^{24}$ −32° (*c*, 0.81 in ethanol); ultraviolet maxima at 228 mμ, 235 mμ, 247 mμ and infrared absorption spectrum identical with authentic material]. Mixtures of benzene-ethyl acetate (9:1) eluted first 68 mg. (17%) of crystalline androstenedione. Taking in account the recovery of the starting material, the over-all yield in 3β-hydroxyandrost-5-en-17-one was raised to 37%. Finally, 37 mg. (9%) of 3α-hydroxyandrost-5-en-17-one, m.p. 219–221°; $[\alpha]_D^{24}$ +1° (*c*, 1.1 in ethanol), infrared absorption spectrum identical with authentic material, was eluted with a mixture of benzene-ethyl acetate (9:1).

Progesterone-3-enol acetate-20-semicarbazone (IIIa). The 3-enol acetate of progesterone has been prepared as described by Westphal.[9] The 20-semicarbazone was obtained by the method used for preparation of III. The yield in crude semicarbazone was 63% (based on progesterone). Recrystallization from methanol to which a trace of pyridine was added gave light yellow crystals melting at 250–280° dec.; λ_{max} 233 mμ (ε 37000).

Anal. Calcd. for $C_{24}H_{35}O_3N_3$: C, 69.70; H, 8.53; N, 10.16. Found:, C 69.66; H, 8.61; N, 10.22.

3β-Hydroxypregn-5-en-20-one (IVa) *from* IIIa. The semicarbazone IIIa was reduced with sodium borohydride, the reduced product hydrolyzed with pyruvic acid and the hydrolyzed product isolated by precipitation with digitonin, as indicated for the conversion of III to IV. Thus, 628 mg. of IIIa yielded 198 mg. of IVa, m.p. 185–187° (26% based on progesterone).

The mother liquors, upon chromatography on aluminum oxide, furnished 4% of 3β-acetoxypregn-5-en-20-one, 6% of progesterone and 5% of 3α-hydroxypregn-5-en-20-one.

Taking in account the recovery of 6% of progesterone and the isolation of 4% of pregnenolone acetate, the over-all yield of IVa was raised to 32%.

3β-Hydroxypregn-5-en-20-one (IVa) *from pregn-5-en-3β,20β-diol.* To 190 mg. of pregn-5-ene-3β,20β-diol (obtained by sodium borohydride reduction of progesterone 3-enol acetate) were added 50 ml. of hot 90% ethanol and a hot solution of 800 mg. of digitonin in 80 ml. of 90% ethanol. After standing for 18 hr. at room temperature, 697 mg. of digitonide complex was filtered off, dried, dissolved in 40 ml. of glacial acetic acid, and oxidized with 60 ml. of a 1.2% solution of chromic acid in 60% acetic acid. After 30 min. a few drops of methanol were added. The solvent was evaporated *in vacuo*, and the dry residue heated for 1 hr. with pyridine. The digitonin was then precipitated by addition of ether and filtered off. The filtrate was concentrated *in vacuo* to a small volume, washed with water, dilute hydrochloric acid, water and then dried and chromatographed over neutral aluminum oxide. Mixtures of benzene–ethyl acetate (4:1) eluted 90 mg. (47% based on pregnenediol) of IVa, m.p. 185–187°, not depressed on admixture with authentic material.

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Preparation of *cis*- and *trans*-4-*t*-Butyl-α,α-dimethylcyclohexanemethanol

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As part of a study of conformational equilibria and reactivity of cyclohexane derivatives, we have prepared two stereoisomeric tertiary alcohols: *cis*- and *trans*-4-*t*-butyl-α,α-dimethylcyclohexanemethanol (*cis*-II and *trans*-II). These alcohols differ from *cis*- and *trans*-1,4-di-*t*-butylcyclohexane only in the replacement of one methyl group by a hydroxyl group. The *cis*-1,4-disubstituted cyclohexane derivatives which have bulky substituents, such as *cis*-1,4-di-*t*-butylcyclohexane and *cis*-II, would be expected to exist in non-chair conformations in significant populations at ordinary temperatures.[1,2]

Each alcohol, *cis*-II and *trans*-II, was prepared stereospecifically from the corresponding stereoisomer of 4-*t*-butylcyclohexanecarboxylic acid. Several methods have been reported recently for preparation of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid.[2–7] The procedure for isolation of the *cis*-acid described by Lau and Hart[5] was repeated with excellent results. The *trans*-acid was prepared conveniently by use of the method of Tichý, Jonáš and Sicher.[6] Each pure acid was converted to its methyl ester (*cis*-I and *trans*-I) in excellent yield by use of diazomethane.[6,7] Addition to excess of the Grignard reagent, prepared from iodomethane and magnesium in ether, of each pure ester yielded the desired tertiary alcohols (*cis*-II and *trans*-II).

The *trans*-alcohol (*trans*-II) would be expected to exist in the chair conformation in which both bulky

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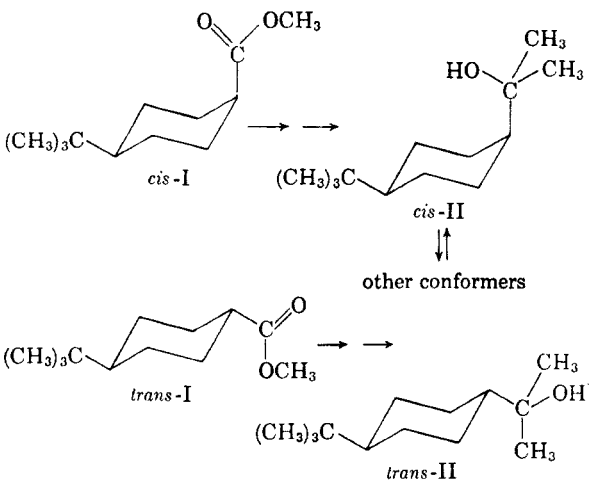

groups are equatorial; no significant populations of non-chair or diaxial-chair conformations would be expected to be present at ordinary temperatures. On the other hand, the *cis*-alcohol (*cis*-II) might be expected to exist with both possible chair conformations as well as certain non-chair conformations populated significantly.[1,2] The tertiary alcohols were examined to determine whether the expected conformational heterogeneity of the *cis*-alcohol would cause multiple absorption peaks in the O—H stretching region of the infrared spectrum. No such multiplicity was detected.

NMR spectra have been recorded for methyl cyclohexanecarboxylate and *cis*- and *trans*-I. The NMR results are consistent with the concepts of conformational analysis,[8] but the spread of chemical shift values for the *methoxyl protons* is too small to permit quantitative interpretation in terms of conformational equilibria of methyl cyclohexanecarboxylates. Clearly, in the compounds studied, the three hydrogen nuclei of the methoxyl group are located too far from the cyclohexane ring to be affected significantly by the conformation of the ring, or by the presence or absence of a 4-*t*-butyl group on the ring.

EXPERIMENTAL[9]

cis- and trans-4-t-Butylcyclohexanecarboxylic acid.[3-7] A 70:30 mixture of the *cis*- and *trans*-acids was prepared by catalytic hydrogenation of *p*-*t*-butylbenzoic acid, as described previously.[10] The *cis*-acid, m.p. 117.5–118° (cor.), was isolated in 55% yield (based on *p*-*t*-butylbenzoic acid) by way of the ammonium salt.[5] The acid mixture obtained upon acidification of the ammonium salt filtrates was equilibrated in order to increase the proportion of *trans*-isomer, as described elsewhere.[6] Recrystallization of the product from hexane gave the *trans*-acid, m.p. 174–175°.

Methyl cis-4-t-butylcyclohexanecarboxylate (*cis*-I). Into a solution of 24.5 g. (0.133 mole) of *cis*-4-*t*-butylcyclohexanecarboxylic acid in 50 ml. of ether, excess diazomethane (prepared from 47.5 g., 0.22 mole, of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) was codistilled with ether.[6,7] Evaporation of the ether under reduced pressure gave a solid which melted at room temperature. Recrystallization from methanol-water at about −15° yielded white crystals, 24.5 g. (93%), m.p. 24–25°; reported,[7] m.p. 26.1–26.7°.

Methyl trans-4-t-butylcyclohexanecarboxylate (*trans*- I). The *trans*-acid, treated as above with excess diazomethane, yielded 11.3 g. (86%) of *trans*-I, b.p. 78–83° (1–4 mm.), n_D^{25} 1.4540; reported[6] b.p. 106–107° (10 mm.), n_D^{20} 1.4547; also[7] b.p. 84° (0.9 mm.).

NMR spectra of the methyl esters. In the NMR spectra (60 megacycles; carbon tetrachloride solution; degassed, sealed tubes; chemical shifts relative to 3% internal tetramethylsilane; ±1 c.p.s.) a sharp single peak attributable to the three equivalent protons of the methoxyl group appeared at 217 c.p.s. for *cis*-I, at 214 c.p.s. for *trans*-I, and at 215 c.p.s. (τ = 6.42) for methyl cyclohexanecarboxylate.

cis-4-t-Butyl-α,α-dimethylcyclohexanemethanol (*cis*- II). A solution of 24.1 g. (0.122 mole) of *cis*-I in 25 ml. of anhydrous ether was added to the Grignard reagent prepared from 8.7 g. (0.36 g.-atom) of magnesium turnings and 51.3 g. (0.36 mole) of iodomethane in 250 ml. of anhydrous ether. The reaction mixture was heated under reflux for 6 hr. and then was poured into a stirred mixture of ice and aqueous ammonium chloride solution. The ether layer was separated, combined with two 100-ml. ether extracts of the aqueous layer, washed with 100 ml. of water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure. The orange-yellow residue was crystallized from petroleum ether (b.p. 60–70°) at about −75° and the product was recrystallized from methanol-water at about −15° to yield 13.2 g. (55%) of white crystals, m.p. 46–47°. Recrystallization from acetonitrile yielded *cis*-II, m.p. 49.5–50° (cor.).

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.22. Found: C, 78.78; H, 13.30.

trans-4-t-Butyl-α,α-dimethylcyclohexanemethanol (*trans*-II). A solution of 9.76 g. (0.049 mole) of *trans*-I in 10 ml. of anhydrous ether was added to the Grignard reagent prepared as above (except in quantities two-thirds as great). The crude product residue, obtained as above, was crystallized from acetone-water at about 0°. Recrystallization from 5:5:2 methanol-acetone-water at about 0° gave 6.8 g. (70%) of purified product, m.p. 101–101.5°. Further recrystallization yielded *trans*-II, m.p. 103–104° (cor.), in the form of fine white needles.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.22. Found: C, 78.85; H, 13.42.

The infrared spectra of 0.05*M* solutions of the alcohols (*cis*-II and *trans*-II) in carbon tetrachloride show differences in the region 1500–800 cm.$^{-1}$, but do not differ significantly in the region 4000–1500 cm.$^{-1}$ In the latter region of the infrared spectrum, observed absorption was assigned exclusively to O—H and C—H stretching vibrations. At 0.05-*M*, neither alcohol exhibits marked absorption attributable to intermolecular hydrogen bonding, but each gives a single symmetrical "free" hydroxyl absorption peak (*cis:* 3621 cm.$^{-1}$, *trans:* 3623 cm.$^{-1}$).

A Perkin Elmer Model 221G infrared spectrophotometer with prism-grating interchange was used with 1-mm. sodium chloride cells at room temperature, *ca.* 25°. The absolute values of frequency are accurate to ±4 cm.$^{-1}$; the relative values, ±1 cm.$^{-1}$

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(9) Melting points and boiling points are uncorrected, unless labeled otherwise. The microanalyses were performed by Dr. Stephen M. Nagy. We are indebted to Dr. Joseph Casanova, Jr. and Mr. Luther Herrick for the determination of the NMR spectra.

(10) See ref. (2), experimental procedure B.