2,3-Dimethyl-1,2,3,4-tetrahydronaphthalenes and 4,5-Dimethylcyclohexenes. Proton Magnetic Resonance and Stereochemistry

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Received August 31, 1966

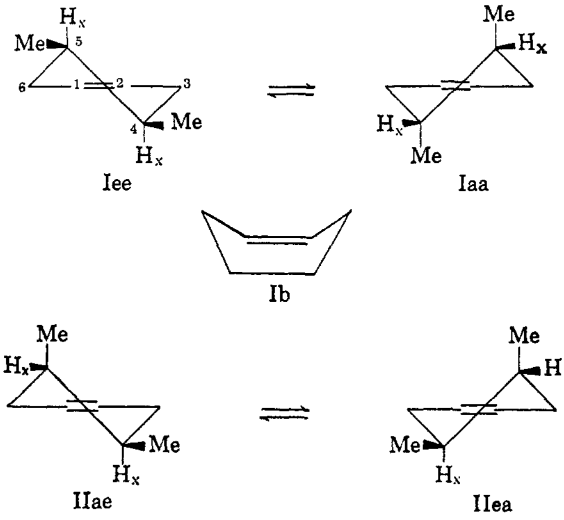
The proton magnetic resonance spectra of *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalenes and *cis*- and *trans*-4,5-dimethylcylcohexenes exhibit a chemical-shift difference in the signal corresponding to the protons adjacent to the methyl groups. This proton signal in the spectra of the *trans* isomers is about 0.5 ppm toward higher field from the corresponding signal in the spectra of the *cis* isomers. This chemical shift is attributed to the predominant axial orientation of these hydrogens in the half-chair conformation of the *trans* isomers in contrast to the average axial–equatorial orientation in the corresponding conformation of the *cis* isomers. This difference is interpreted in terms of the unequal shielding of axial and equatorial substituents resulting from the magnetic anisotropy effect of the carbon–carbon single bond. These compounds retained their conformational mobility to the practical temperature limit of −127 to −169°. The stereospecific synthesis of these compounds is described.

In cyclohexane derivatives the proton magnetic resonance (pmr) signal for axial hydrogen is found at higher frequencies than that for a corresponding equatorial proton, all other factors being equal;[2] in cyclohexane itself this chemical shift difference is about 0.5 ppm.[3] Studies on *cis*- and *trans*-2,3-disubstituted tetrahydroquinoxalines and analogous phenazines and triazanaphthalenes[4] demonstrated that assignment of configuration was possible based on the pmr spectra and founded upon the generalization that the signal for an axial proton adjacent to nitrogen consistently would be found at higher field than that of the corresponding equatorially oriented proton.

An unknown factor in attempting to deduce the reason for this chemical shift in the heterocyclic systems is the effect on the adjacent proton[5,6] exerted by the lone pair of electrons on nitrogen. We therefore sought to extend these studies to the analogous carbocyclic systems where the uncertainties introduced by the presence of the nonbonding electron pair do not exist. Although examples of the proton magnetic spectra of several dimethylcyclohexenes have been reported,[7] the desired spectra of *cis*- and *trans*-4,5-dimethylcyclohexenes and *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalenes were not published.

Unlike the saturated analogs, the conformational studies of cyclohexene and its derivatives are not extensive.[8] The introduction of an endocyclic double bond into a six-membered ring alters the favored conformation from that of a chair to a half-chair. Normal axial and equatorial substituents in cyclohexene exist only at the homoallylic positions 4 and 5 (formula Iee, Scheme I) while the allylic positions 3 and 6 exist only in quasi-axial and quasi-equatorial forms.[8,9] If the difference in average bond length between an endocyclic carbon–carbon double bond (1.33 A) and an aromatic "double bond" (1.39 A) is disregarded, the conformation requirements for cyclohexene and tetrahydronaphthalene derivatives should be much the same.[9]

SCHEME I



The energy barrier between the half-chair form and the boat form of cyclohexene has been calculated to be 2.7 kcal/mole in favor of the half-chair form.[10] Infrared and Raman spectral data[11] support this conclusion and X-ray electron diffraction studies on the solid derivatives, 3,4,5,6-tetrachlorocyclohexene[12] and penta-

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[1] (a) Parke, Davis Fellow, 1964–1965; (b) Parke, Davis Fellow, 1960–1963.

[2] (a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," The MacMillan Co., New York, N. Y., 1959, Chapter 7; (b) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 14; (c) N. C. Franklin and H. Feltkamp, *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965).

[3] (a) F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc.*, 145 (1964); (b) F. A. Bovey, F. P. Hood, III, E. W. Anderson, and R. L. Kornegay, *J. Chem. Phys.*, **41**, 2041 (1964).

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[7] "Nuclear Magnetic Resonance Spectra of Hydrocarbons and Their Derivatives," Humble Oil and Refining Co., Baytown, Texas, 1959, Spectra No. 60–65.

[8] (a) W. Klyne, "Progress in Stereochemistry," Vol. I, Butterworth and Co. (Publishers) Ltd., London, 1954, p 81 ff; (b) E. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 109 ff; (c) M. Hanack, "Conformational Theory," Academic Press Inc., New York, N. Y., 1965, p 146 ff; (d) F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.*, **87**, 3285 (1965).

[9] (a) D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee, *Chem. Ind.* (London), **31**, (1954); (b) M. A. Lasheen, *Acta Cryst.*, **5**, 593 (1952).

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[11] K. Sakashita, *J. Chem. Soc. Japan*, **77**, 1094 (1956); *Chem. Abstr.*, **51**, 859 (1957).

[12] O. Bastiansen and J. Markali, *Acta Chem. Scand.*, **6**, 442 (1952).

TABLE I

PMR SPECTRA OF *cis*- AND *trans*-DISUBSTITUTED CYCLOHEXENES

	Chemical shifts[a,b] (δ), ppm					Low-temp studies[c]		
Compd	$H_{CH=}$	H_{CH_2}	H_{CHMe}	H_{CH_3}	*J*, cps[d]	Solvent	Temp, °C[e]	$W_{h/2}$[f] in TMS, cps
cis-2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (**8**)	6.95 (s)	2.65 (q)	1.98 (p)	0.93 (d)	7	CF_3Br	−169[g]	10
trans-2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (**9**)	6.94 (s)	2.57 (m)	1.50 (b)	1.05 (d)	6	CCl_2F_2	−127[h,g]	6
cis-4,5-Dimethylcyclohexene (**24**)	5.48 (t)	1.84 (m)	1.95	0.85 (d)	6	CF_3Br	−161	11
trans-4,5-Dimethylcyclohexene (**28**)	5.47 (t)	1.87 (m)	1.45 (b)	0.94 (d)	5	CF_3Br	−153	16
Cyclohexene[i]	5.59 (t)	1.96 (m)	1.65 (m)[j]		5	CF_3Br[j]	−170	6[j]

[a] Chemical shifts (δ) in parts per million (ppm) relative to internal tetramethylsilane (TMS) as 0. Spectra taken in carbon tetrachloride solvent with Varian Associates A-60 (60-Mcps) spectrometer. Chemical shifts for the methine and methylene protons are only approximate because of the broadened nature of these signals. [b] The letters after the chemical shifts describe the shape of the signal: b, broad, unresolved multiplet; d, doublet; m, multiplet; q, quartet; p, pentuplet; s, singlet; t, triplet. [c] Taken on Varian Associates HR-60 (60-Mcps) nmr spectrometer with V4340 variable-temperature probe with dewar probe insert (V4331-THR). Spectra were calibrated by the audiofrequency spinning-side-band technique. [d] These numbers represent the line separations which are first order approximations of the coupling constants between the methyl and homobenzylic protons. Especially in the case of compounds 9 and 28 these may not be the true *J* values. [e] Temperatures were measured by copper–constantan thermocouple calibrated by various cold baths and accurate to ±2°. [f] $W_{h/2}$ refers to the width of the resonance signal at half-height in cycles per second (cps) at the temperature limit. In the low-temperature studies the $W_{h/2}$ for TMS was taken as a measure of the resolution of the instrument. [g] Spinner froze in probe at this temperature. [h] Sample crystallized from solution at this temperature. Sample also crystallized at higher temperatures from CS_2, CHF_2Cl, CF_3Br, and mixtures of these. [i] K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **83**, 1226 (1961). [j] F. A. L. Anet and M. Z. Haq [*J. Am. Chem. Soc.*, **87**, 3147 (1965)] report an inversion barrier of 5.3 kcal/mole for *cis*-3,3,4,5,6,6-hexadeuteriocyclohexene based upon the separation of the H_4–H_5 signal into a doublet at −164°. The chemical-shift difference between the resulting signals for axial and equatorial protons was estimated at 24 ± 2 cps (0.41 ppm). F. R. Jensen and C. H. Bushweller [*ibid.*, **87**, 3285 (1965)] reported a barrier of 5.9 ± 1 kcal/mole for the ring inversion in 4-bromocyclohexene with an observed chemical shift between axial and equatorial protons of 27.4 ± 0.4 cps (0.45 ppm).

chlorocyclohexene,[13] have also demonstrated that the half-chair form is the stable conformation.

Based upon the premise of the predominance of the half-chair conformation for cyclohexene derivatives, pmr has been used to make stereochemical assignments for three of the isomeric tetrachloro-1,2,3,4-tetrahydronaphthalenes.[14]

trans-4,5-Dimethylcyclohexene can exist in two different half-chair conformations (Iee $\rightleftharpoons$ Iaa). However, the two half-chair conformations of the isomeric *cis*-4,5-dimethylcyclohexene are equivalent (although enantiomorphic, IIae $\rightleftharpoons$ IIea). *A priori*, one might assume that Iee would be the predominant conformation based upon the known cyclohexane analogy. In 4,5-dimethylcyclohexene two of the 1:3-diaxial methyl–hydrogen interactions, which one would observe in the analogous cyclohexane case, are entirely absent and the remaining methyl–hydrogen interactions are 1:3 axial–pseudo-axial rather than 1:3 diaxial interactions. On the other hand, the boat form of cyclohexene has four eclipsed hydrogens, while the boat form of cyclohexane has eight eclipsed hydrogens. Both have a single 1:4 diaxial interaction. Rickborn and Lwo[15] have concluded, based on relative rates of epoxidation and isomer ratios, that the diequatorial form (Iee) is favored over the diaxial form (Iaa) by 1.1 kcal/mole. Sakashita[16] has reported that the dipole moment and infrared and Raman data on 4-halo- and 4,5-dichlorocyclohexene are best interpreted in terms of the diaxial form being more stable than the diequatorial form.

Results

The 60-Mc pmr spectra, which were taken in carbon tetrachloride solvent are summarized in Table I and Figure 1. Because of the broad nature of the key signal for the proton adjacent to methyl, the chemical shift values reported are approximate. This signal in *cis*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalene (**8**) is centered at 1.98 ppm and is 0.48 ppm downfield from the corresponding signal of the *trans* isomer (**9**) centered at 1.50 ppm (Figure 1). With *cis*-3,4-dimethylcyclohexene (**24**) the signals for the corresponding protons overlap those for the methylene hydrogens. However, from the 100-Mc "decoupled" spectrum it is established that this H_x multiplet is centered at approximately 1.95 which is 0.5 ppm downfield from the corresponding signal of the *trans* isomer (**28**) centered at 1.45 ppm. This is the same situation which we observed previously with the analogous tetrahydroquinoxalines, phenazines, pteridines, and triazanaphthalenes; namely, there is a downfield chemical shift of approximately 0.5 ppm for the hydrogen (H_x) next to the ring substituents in going from the *cis* to *trans* from in this group of 2,3-disubstituted, six-membered carbocyclic or heterocyclic derivatives.

The results of the low-temperature studies are recorded in Table I. No significant alterations in the chemical shifts or coupling pattern were observed by cooling to the limiting temperature between −127° and −169° recorded in Table I.

Discussion

If we make the reasonable assumption that the cyclohexene ring in these derivatives exists primarily in the half-chain conformation and that there is no important contribution from boat forms, then we must conclude that both *cis* and *trans* compounds in this series exist in carbon tetrachloride solvent as a mixture of rapidly equilibrating half-chair conformers. In the *trans* compounds (**9** and **28**) the equatorial form (Iee) must be greatly favored and the signal for the homo-

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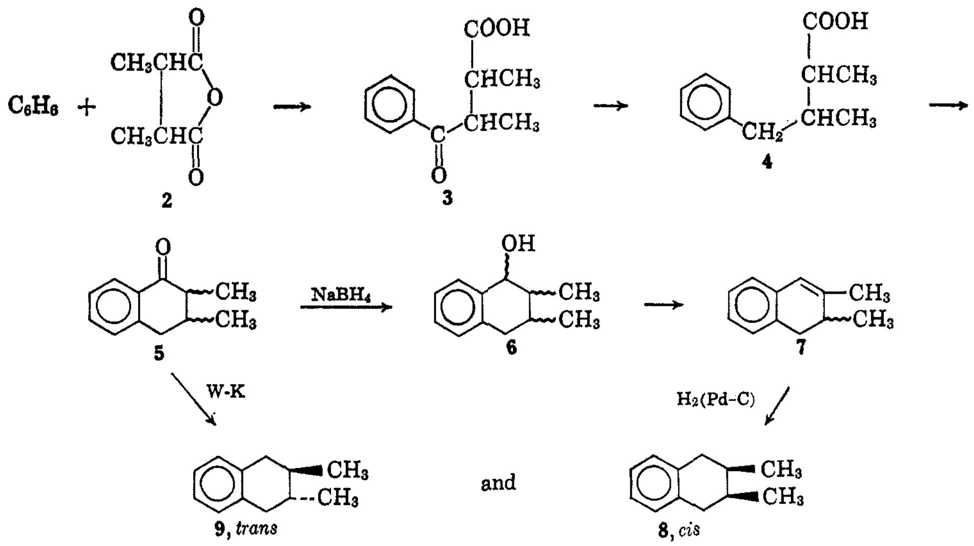
(13) R. A. Pasternak, *Acta Cryst.*, **4**, 316 (1951).

(14) P. B. D. de la Mare, M. D. Johnson, J. S. Lomas, and V. Sanchez del Olmo, *Chem. Commun.*, 483 (1965).

(15) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

(16) K. Sakashita, *J. Chem. Soc. Japan*, **74**, 315 (1953); *Chem. Abstr.*, **48**, 1087 (1954); *Nippon Kagaki Zasshi.*, **81**, 49 (1960); **80**, 972 (1959); *Chem. Abstr.*, **54**, 2008, 12015 (1960).

SCHEME II



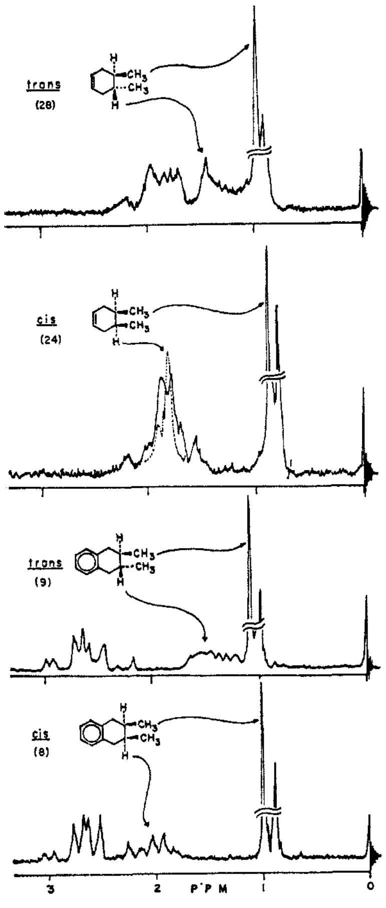


Figure 1.—Nmr spectra (60-Mc. Varian A-60 spectrometer) taken in carbon tetrachloride solvent (δ) in parts per million relative to TMS as 0. The dotted line in **8** (*cis*-3,4-dimethylcyclohexene) is the spectrum at 100 Mc in which the homoallylic hydrogens are decoupled with respect to the methyl groups.

allylic proton must represent that of an axial hydrogen. The corresponding signal for the *cis* compounds must represent a time average of two equivalent conformers (IIae and Iea). Thus the chemical shift for a *homoallylic equitorial* proton next to a methyl group in these cyclohexene derivatives is about 1 ppm downfield from that of a *homoallylic axial* proton.

Long-range deshielding of the axial hydrogens in positions 2 and 3 of the tetrahydronaphthalene derivatives by the ring currents of the aromatic system[4,17] can make only minor contributions to this observed chemical shift as evidenced by the fact that the same shift of approximately 0.5 ppm is observed in both *cis*- and *trans*-4,5-dimethylcyclohexenes as well as 2,3-dimethyl-2,3,4-tetrahydronaphthalenes. It has been established that a hydrogen situated above a double bond is abnormally shielded.[3a] However, such an effect on the homoallylic axial protons in the present examples must be small since a similar chemical shift of about 0.4–0.5 ppm is observed between axial and equatorial protons in saturated cyclohexane derivatives.[2,18] We must conclude, therefore, that this downfield shift in the signal for the H_x protons (Scheme II) in going from the *trans* to the *cis* isomers for both the carbocyclic and heterocyclic[4] systems must be caused primarily by the magnetic anisotropy of carbon–carbon and carbon–nitrogen bonds.[2b,19]

Since the only change in the pmr spectra as the temperature was lowered was the expected temperature-dependent line broadening, we conclude that the ring inversions are still fast on a pmr time scale at these low temperatures[20] and that the free energy of activation for the ring-inversion process is less than 7 kcal/mole for the two isomeric 4,5-dimethylcyclohexenes and less than 5 kcal/mole for *cis*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalene. These results are in accord with the results reported for cyclohexene itself[20,21] and with the observation that the barrier to inversion of the dimethylcyclohexanes is about the same as that for cyclohexane itself.[18]

Synthesis

Coulson[22] in 1938 reported that *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalenes were isolated by fractional distillation from the high-temperature, high-pressure ammonium molybdate catalyzed hydrogenation product of 2,3-dimethylnaphthalene.

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(17) C. E. Johnson and F. H. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(18) N. Muller and W. C. Tosch, *ibid.*, **37**, 1167 (1962).

(19) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).

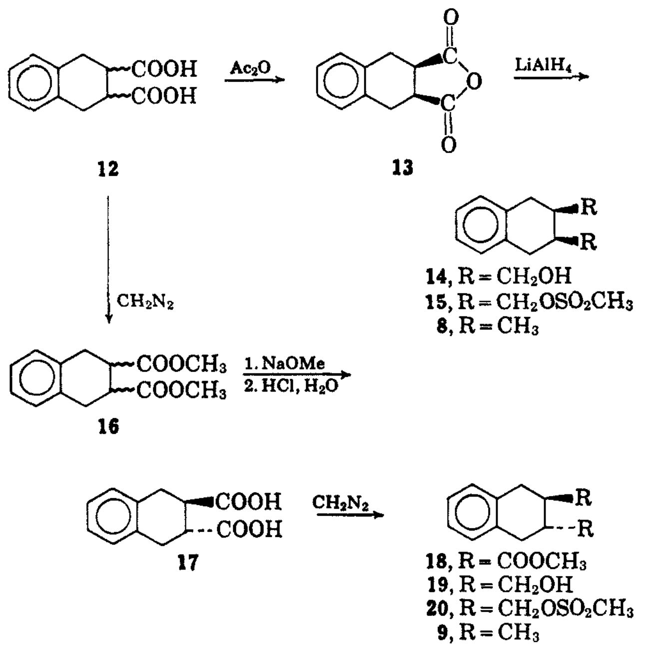
(20) J. E. Anderson, *Quart. Rev.* (London), **19**, 426 (1965).

(21) See Table I, footnote *j*.

(22) E. A. Coulson, *J. Chem. Soc.*, 1305 (1938).

Assignment of configuration was not possible, but one isomer was reported to have a melting point of −5 to −8° and the other +4 to 8°. We have prepared these compounds *via* a rational synthetic scheme (Scheme III) and after purifying by gas chromatography find that the *cis* isomer (**8**) does not freeze above −75° and that the *trans* has a melting point of 38.5–40.0°. Considering the complexity of Coulson's hydrogenation mixture, these results are not surprising.

Scheme III

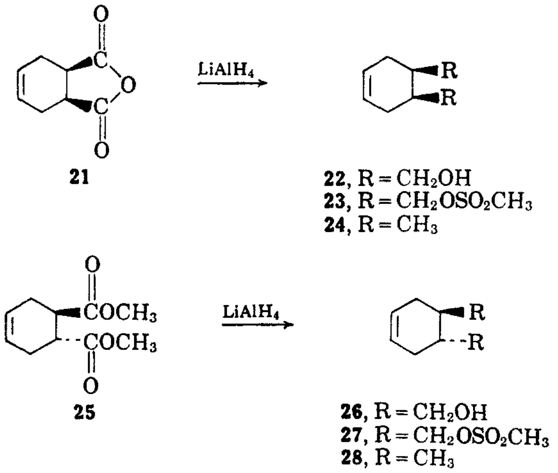


We first attempted the synthesis of the *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalenes *via* the Friedel–Crafts approach outlined in Scheme II with the anticipation that the Wolff–Kishner reduction performed under basic conditions would yield the *trans* isomer (**9**), presumably the thermodynamically more stable, and that low-temperature catalytic hydrogenation would produce the *cis* isomer (**8**), presumably *via* kinetic control. The properties of the two products obtained by these two approaches were almost identical, including a single peak with the same retention time on a series of different gas chromatography columns. From the pmr spectra, however, it appeared likely that each consisted of an approximate 70:30 mixture of *cis* and *trans* isomers. Ultimately, after the pure isomers had been synthesized by another route, it was found that they could be separated on a bentone–silicon oil column. It is perhaps not surprising in retrospect that the Wolff–Kishner product was a mixture[23] and that the palladium-catalyzed hydrogenation[24] gave some of the *trans* form.

Pure *cis*- and *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalenes were made by the method outlined in Scheme III from the previously described[25] *cis* anhydride and *trans*-dicarboxylic acid. Although we used the procedure in the first reference, that in the second, which did not come to our attention until this work was done, would probably have been preferable. The key transformation was that of the anhydride group or 2,3-dicarboxyl group to the 2,3-dimethyl group. This was accomplished by reduction with lithium aluminum hydride (to give **14** and **19**), conversion of the diol to the mesylates (**15** and **20**), and displacement of the mesylate group using a large excess of lithium aluminum hydride to give **8** and **9**, respectively. The over-all yield in the *trans* series (40%) was better than in the *cis* series (21%).

The pure *cis*- and *trans*-4,5-dimethylcyclohexenes (**24** and **28**) were also prepared in a stereospecific manner as indicated in Scheme IV, from the *cis* anhydride (**21**) and the *trans* diester (**25**), both of which were readily available *via* the Diels–Alder reaction of butadiene with maleic anhydride[26] and dimethyl fumarate,[27] respectively.

Scheme IV



The same sequence of conversions of the *cis* anhydride (**21**) and *trans* diester (**25**) to the diols (**22** and **26**), dimesylates (**23** and **27**), and final *cis*- (**24**) and *trans*-dimethyl (**28**) compounds were followed. Each of these dimethylcyclohexene isomers has been prepared previously by essentially this same scheme.[15,28,29] Again, the over-all yield in the *trans* series was better (46%) than that in the *cis* series (17%). Some of the complications involved in a comparable series of transformations in related structural situations have been described.[30,31]

Experimental Section

All compounds were optically inactive; the prefix *dl* has been omitted. Melting points were determined in a capillary and are uncorrected unless otherwise noted. Microanalyses were by Messrs. E. Meier and J. Consul of the Stanford Microanalytical Laboratory. Details for the pmr determinations are given in the footnotes to Table I.

2,3-Dimethyltetralone (5).—This was synthesized as a mixture of *cis* and *trans* forms starting from the mixed *dl*- and *meso*-2,3-dimethylsuccinic anhydrides[32] (2) in an over-all yield of 52%

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[23] F. Johnson and S. Malhotra, private communication; *Chem. Eng. News*, **44** (13), 39 (1966).

[24] S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6087 (1960).

[25] (a) R. D. Haworth and F. D. Slinger, *J. Chem. Soc.*, 1321 (1940); (b) K. Alder and M. Fremery, *Tetrahedron*, **14**, 190 (1961).

[26] A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, **72**, 983 (1950).

[27] A. A. Petrov and N. P. Sopov, *Sb. Statei Obshch. Khim.*, **2**, 853 (1953); *Chem. Abstr.*, **49**, 5329 (1955).

[28] H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **83**, 4552 (1961).

[29] D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).

[30] G. A. Haggis and L. N. Owen, *ibid.*, 389, 408 (1953).

[31] G. Stork, E. E. van Tamelen, L. J. Friedman, and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953).

[32] L. F. Fieser and W. D. Daudt, *ibid.*, **63**, 782 (1941).

according to the reaction sequence represented in Scheme II and well documented in the literature. The Friedel–Crafts acylation (2 → 3) was carried out by the method which Rothstein and Saboor[33] used for the pure *trans* isomer; the carbonyl group was replaced by methylene (3 → 4) by hydrogenation with 10% palladium-on-carbon catalyst.[34] The ring closure (4 → 5) was accomplished by the method of Tucker, Whalley, and Forrest:[35] bp 121–122° (2 mm); $\lambda_{\max}$ 247.5 mμ (ε 13,260), 292 mμ (ε 20,320).

2,3-Dimethyl-1,2-dihydronaphthalene (7).—Sodium borohydride (0.4 g) reduction of the mixed tetralones (5, 3.48 g, 20 mmoles) in refluxing ethanol for 1 hr gave a 90% yield (3.14 g) of the crude mixed tetralols (5) which were immediatedly dehydrated according to the method of Traynelis, *et al.*[36] A solution of the crude tetralols (1.75 g, 10 mmoles) in dimethyl sulfoxide (10 ml) was heated at 160° for 14 hr. The mixture was poured into water, extracted with pentane, and dried over magnesium sulfate and the solvent was removed under vacuum. The residue was purified by preparative vapor phase chromatography (Apiezon column) to give 1.47 g (93%). This compound has been prepared previously[37] by thermal dehydration.

2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (8 and 9).—A solution of the foregoing dihydronaphthalene (0.248 g, in 10 ml of methanol) was subjected to atmospheric hydrogenation at room temperature with 10% palladium-on-carbon catalyst for 3 hr, after which time the theoretical amount of hydrogen had been absorbed. The oil which remained after filtration of the mixture and evaporation of solvent was purified by vpc (silicone oil column) to give 0.21 g (73% yield). This product was shown to consist of a mixture of 65% *cis*- and 35% *trans*-2,3-dimethyl-1,2,3,4-tetrahydronaphthalene by analytical vpc (15% Bentone 34–35% SE-52, 0.25 in. × 6.5 ft column, helium flow of 80 ml/min).

The Huang-Minlon modification of the Wolff–Kishner reduction of 2,3-dimethyl-1-tetralone (1.74 g, 10 mmoles) was carried out with 95% hydrazine (3 ml), diethylene glycol (20 ml), and potassium hydroxide (2.5 g) at reflux for 1 hr. After water was distilled, at 200° for 2 hr, the product was purified by vpc (5 ft × 0.25 in. silicone rubber column, 163°, He flow rate of 40 ml/min, R_f 31 min) and analyzed, using the Bentone column under the previous conditions: 75% *cis* (8) and 25% *trans* (9).

Mixture of *cis*- and *trans*-1,2,3,4-Tetrahydronaphthalene-2,3-dicarboxylic Acids (12).—Naphthalene-2,3-dicarboxylic acid (Aldrich Chemical Co.) was converted to the anhydride by treatment with acetic anhydride[38,39] in 88% yield. This anhydride (2.0 g) was reduced with 4% sodium amalgam (400 g) by the procedure of Haworth and Slinger[25] to give the mixed *cis*- and *trans*-tetralin-2,3-dicarboxylic acids (12, 1.55 g). The carbon dioxide atmosphere is necessary for maintaining the pH of the solution and cannot be replaced with nitrogen. We were unable to accomplish the separation of *cis* and *trans* diacids from acetyl chloride as described.[25]

***cis*-1,2,3,4-Tetrahydronaphthalene-2,3-dicarboxylic Anhydride (13).**—By refluxing the mixture of acids 12 (1.2 g) with freshly distilled acetic anhydride (3.2 g) for 2 hr under nitrogen according to the procedure of Haworth and Slinger,[25] there was obtained upon purification by sublimation the *cis* anhydride **13**: 0.878 g, mp 183–184° (lit.[25] mp 183° and 185°).

***cis*-2,3-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (14).**—A solution of the *cis* anhydride **13** (0.80 g, 3.96 mmoles) in anhydrous tetrahydrofuran (THF, 50 ml) was added to a slurry of lithium aluminum hydride (0.20 g, 5.3 mmoles) in THF (50 ml). After a short reflux period the excess lithium aluminum hydride was hydrolyzed with saturated sodium sulfate solution. Solvent was removed under vacuum from the combined, dried (Na_2SO_4) THF layer and extracts, and the residue was recrystallized from benzene to give white needles of **14**: 0.516 g (67%); mp 100–101°; $\nu_{\max}^{\text{KBr}}$ 3500–3100, 1035, 1020 cm^{-1} (hydroxyl, no carbonyl absorption). Thin layer chromatographic analysis (Merck silica gel G, 45:8:4 benzene–methanol–acetic acid) showed only one spot.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.36.

Dimethanesulfonate Ester of *cis*-2,3-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (15).—The *cis*-diol (14, 0.471 g, 2.44 mmoles in 1 ml of anhydrous pyridine) was added with stirring to a solution of freshly distilled methanesulfonyl chloride (2.55 g, 22.3 mmoles) in anhydrous pyridine (0.5 ml) at 0°. During a 7-hr period, additional pyridine (8 ml) was added to the mixture at 0° after which it was allowed to warm to room temperature over a 10-hr period. The reaction mixture was poured onto ice and extracted with chloroform, and the extracts were washed successively with water, 1 *N* hydrochloric acid, saturated sodium bicarbonate, water, and saturated sodium chloride. Solvent was removed under vacuum from the dried (Na_2SO_4) extracts and the crude residue was crystallized from 50:50 benzene–pentane to give white plates of **15**: 0.479 g (56%); mp 95–96°; $\nu_{\max}^{\text{KBr}}$ 1490, 1330 cm^{-1} (sulfonate, no hydroxyl absorption). Thin layer chromatographic analysis (Merck silica gel G, 80:20 benzene–ethyl acetate) showed only one spot.

Anal. Calcd for $C_{14}H_{20}O_6S_2$: C, 48.27; H, 5.79; S, 18.39. Found: C, 48.39; H, 5.84; S, 18.60.

***cis*-2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (8).**—The *cis* dimesylate (15, 0.448 g, 1.3 mmoles in 9 ml of THF was added to a stirred slurry of lithium aluminum hydride (0.500 g, 13 mmoles in anhydrous THF, 10 ml) and the reaction mixture was refluxed for 1 hr. After hydrolysis with sodium sulfate solution, the solvent was removed under vacuum from the combined, dried (Na_2SO_4) THF layer and ether extracts, (and the residue was purified by evaporative distillation to yield the *cis*-dimethyl compound (0.113 g, 55%) which was further purified by vpc (15% Bentone 34–45% SE-52, 0.25 in. × 6.5 ft at 100°, He flow rate of 80 ml/min, R_f 33 min). The product gave a single peak upon reinjection in the same column and gave a double peak when admixed with the subsequently prepared *trans* isomer. Thin layer chromatographic analysis (Merck silica gel G, 80:20 benzene–ethyl acetate) showed a single spot; infrared spectrum showed $\nu_{\max}^{\text{film}}$ 3005, 2985, 2950, 1580, 1450, 1440, 1375, 740 cm^{-1}; pmr spectrum is given in Table I.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.63; H, 10.00.

***trans*-1,2,3,4-Tetrahydronaphthalene-2,3-dicarboxylic Acid (17).**—The mixed dicarboxylic acids (12) were converted to the mixed methyl esters (16) by treatment with diazomethane to give 2.64 g (94%) of distilled product, mp 40–58°. The pure *cis*-dimethyl ester is reported[25] to melt at 65° and the *trans* isomer melted at 45°. The *cis* isomer in this mixture was isomerized to the *trans* compound by a process analogous to that used by Ayres and Raphael[29] for the corresponding case in the cyclohexene series. These mixed dimethyl esters (18, 2.5 g, 10 mmoles) were refluxed for 16 hr under nitrogen with sodium methoxide (10 mmoles in 10 ml of methanol). The solvent was removed under vacuum and the residue was hydrolyzed by refluxing with 6 *N* hydrochloric acid for 4 hr to give a product which, after crystallization from 50% ethanol (20 ml), yielded the white *trans* diacid (17): 1.47 g (68%); mp 225–227° (lit.[25] mp 226–227°). We were unable to accomplish the separation of the mixed diacids (12) from acetyl chloride as reported.[25]

***trans*-2,3-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (19).**—The purified *trans* diacid (17) was reconverted with diazomethane in 97% yield to the *trans*-dimethyl ester (1.46 g, 5.9 mmoles), mp 43–44° (lit.[25] mp 45°), which was dissolved in 100 ml of ether and reduced with lithium aluminum hydride (1.0 g, 26 mmoles in 50 ml of ether). The reaction mixture was hydrolyzed with sodium sulfate solution and the solvent was removed under vacuum from the combined, dried (Na_2SO_4) ether layer and extracts. The residue was recrystallized from 50:50 benzene–cyclohexane to give white needles of **19** (0.885 g, 78%, mp 129–130°) which showed only one spot upon thin layer chromatographic analysis (Merck silica gel G, 45:8:4 benzene–methanol–acetic acid).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.54; H, 8.31.

***trans*-2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (9).**—The *trans* diol (19, 0.850 g, 4.4 mmoles) in pyridine (2 ml) was converted to the dimesylate (20) by adding to a solution of methanesulfonyl chloride (7.5 g, 66 mmoles) in anhydrous pyridine (1.5 ml) at 0°. Additional anhydrous pyridine (6 ml) was added over a 10-hr period and the reaction mixture was then allowed to warm to room temperature over 8 hr. The mixture was worked up as described under the *cis* isomer to give (from 50:50 benzene–

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hexane) 0.858 g (58%), mp 73–74°, of **20**. This gave a single spot on thin layer chromatographic analysis (Merck silica gel G; 45:8:4 benzene–methanol–acetic acid).

Anal. Calcd for $C_{14}H_{20}O_6S_2$: C, 48.27; H, 5.79; S, 18.39. Found: C, 48.01; H, 5.65; S, 18.24.

This dimesylate (**20**, 0.800 g, 2.3 mmoles, in 10 ml of THF) was added to a slurry of lithium aluminum hydride (1.5 g, 39 mmoles) in anhydrous THF (10 ml). After the mixture was refluxed for 1 hr, it was hydrolyzed with sodium sulfate solution and the solvent was removed under vacuum from the combined, dried (Na_2SO_4) THF layer and ether extracts. The crude product was purified by evaporative distillation to give 0.336 g (91%): mp 38.5–40.0°; $\nu_{\max}^{\mathrm{KBr}}$ 3101, 2910, 2875, 1495, 1465, 1435, 735 cm^{-1}. This product gave a single peak on vpc analysis (retention time, 39 min) and a single spot on thin layer chromatography under the same conditions indicated for the *cis* isomer; pmr spectrum is reported in Table I.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.63; H, 10.02.

cis-**3,4-Dimethylcyclohexene** (**24**).—This isomer was synthesized by methods delineated in the literature. *cis*-Cyclohexene-4,5-dicarboxylic anhydride[26,40] (**21**) was reduced with lithium aluminum hydride to give the *cis*-diol[41] (**22**, 87% yield, $n^{20}\mathrm{D}$ 1.5091) which was converted to the *cis* dimesylate[15,28] (**23**, 60% yield) which in turn was treated with lithium aluminum hydride to give *cis*-dimethylcyclohexene (42% yield). The product[15,28,29] ($n^{20}\mathrm{D}$ 1.4462; $\nu_{\max}^{\mathrm{film}}$ 3024, 2950, 2880, 1650, 1450, 1380, 1020, 750 cm^{-1}) gave a single peak on vpc analysis (Carbowax 20 M, 20 ft × 0.25 in. column at 70°, He flow at 25 ml/min, R_f 47 min) and the correct carbon hydrogen analysis. The pmr spectrum is reported in Table I.

trans-**3,4-Dimethylcyclohexene** (**28**).—*trans*-Cyclohexene-4,5-dicarboxylic acid methyl ester was made from methyl fumarate and butadiene in 88% yield by the method of Petrov and Sopov.[27] This was converted by the method of Walborsky, Barash, and Davis[42] by lithium aluminum hydride to the *trans*-diol (**26**, 99% yield), then to the *trans* dimesylate (**27**, 97% yield) and finally to the *trans*-4,5-dimethylcyclohexene by lithium aluminum hydride displacement (48% yield). The product[42,43] was purified by vpc under the same conditions as the *cis* isomer (R_f 44 min; $\nu_{\max}^{\mathrm{film}}$ 3040, 2970, 2890, 1660, 1450, 1430, 1370, 1010, 880, 650 cm^{-1}) and analyzed correctly for carbon and hydrogen. The pmr spectrum is reported in Table I.

Registry No.—*cis* **5**, 10074-95-0; *trans* **5**, 10294-74-3; **8**, 10074-96-1; **9**, 10074-97-2; **14**, 10074-98-3; **15**, 10074-99-4; **19**, 10075-00-0; **20**, 10075-01-1; **24**, 4300-00-9; **28**, 3685-01-6.

Acknowledgment.—We acknowledge with gratitude our appreciation to Dr. L. J. Durham for the nmr determinations and many helpful discussions concerning them, and to Parke, Davis and Co. for fellowship support.

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The Decarboxylation of 3-Carboxy-2-isoxazolines. 3β,17α-Dihydroxypregn-5-en-20-one-16α-carbonitrile

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Received July 1, 1966

The pyrolysis of [16,17-d]-3′-carboxyisoxazolinopregn-5-en-3β-ol-20-one (II) has been shown to yield 3β,17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III) as well as either 3β,17β-dihydroxy-17α-methyl-D-homopregn-5-en-17a-one-16β-carbonitrile (IV) or 3β,17α-dihydroxy-17β-methyl-D-homopregn-5-en-17a-one-16α-carbonitrile (VIII) according to pyrolysis conditions.

In an earlier publication,[1] we described the reaction sequence shown below for the hydrolysis and decarboxylation products of [16,17-*d*]-3′-carbethoxyisoxazolino steroids (see Scheme I).

The normal steroid structure of IIIa was assigned principally from the nmr data, and the structure of III was assigned on the basis of analogy with IIIa.

In this paper we present evidence showing that the compound thought to have the normal structure III has a D-homo structure, 3β,17β-dihydroxy-17α-methyl-D-homopregn-5-en-17a-one-16β-carbonitrile (IV). We also show that pyrolysis of II yields, in addition to IV, the product with the normal steroid structure 3β,17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III). An independent synthesis of III was devised using the 20-ethylenedioxy function to avoid rearrangement during the pyrolytic decarboxylation step. Compound IIIa retains the normal steroid structure as shown.

[16,17-*d*]-3′-Carbethoxyisoxazolinopregn-5-en-3β-ol-20-one 3β-acetate[1] (I, Scheme I) was converted to the 20-ethylenedioxy derivative (VIa) prior to alkaline hydrolysis to [16,17-*d*]-3′-carboxyisoxazolino-20-ethylenedioxypregn-5-en-3β-ol (VIb). Pyrolytic decarboxylation of the latter yielded 3β,17α-dihydroxy-20-ethylenedioxypregn-5-en-16α-carbonitrile (VII) in 43% yield, after crystallization (see Chart I). Acid hydrolysis now furnished 3β,17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III) in 75% yield. The nmr spectra of both III and III acetate showed normal steroid characteristics (Table I).

The ORD data for III and for IIIa show positive single Cotton effect curves.[2] Djerassi[3,4] indicates that the positive single Cotton effect curve for a normal steroidal C_{20} ketone is qualitatively unchanged by the introduction of a 17α-hydroxyl.

In contrast to III and IIIa, IV showed an abnormal, negative ORD curve.[2] Klyne[5] has reported that a 17a-oxo-D-homo steroid (3β-hydroxy-5α-D-homoandrostan-

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[2] We are indebted to Dr. W. Nagata and his colleagues for first determining the ORD and CD curves of our sample (IV) and for supplying ORD and 100-Mc nmr measurements on subsequent samples. Dr. Nagata's use of our sample in establishing the structure of the epimeric material [W. Nagata, M. Yoshioka, and T. Okumura, *Tetrahedron Letters*, 847 (1966)] and his correspondence during the work are deeply appreciated.

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