present in excess. The hydrogen bond of the sydnone to the solvent would then withdraw less electron density from the sydnone ring than does the linkage to another sydnone molecule. In confirmation of this picture, we note that the sydnone ring chemical shifts seem to be approaching common values in both solvents at high concentrations; these would be the values characteristic of the aggregates.

We next examine the effect of the substituent alkyl group on the chemical shifts of the ring hydrogens. Using the values extrapolated to zero concentration we find for the solutions in acetone one order, as shown in Table I, and for the solutions in chloroform almost exactly the reverse order. The order found in the acetone solutions is that expected from the electron-releasing properties of the alkyl groups concerned, and is similar to that found in monoalkylbenzenes: the more hydrogens attached to the carbon α to the aromatic ring, the more shielded is the hydrogen attached to the adjacent carbon in the aromatic. The reversal of the order in chloroform solutions would then be connected with the relative tendency of the chloroform to break up the aggregates of the molecules of differing size rather than with any property of the sydnone. In this respect, it must be emphasized that there is some latitude in the extrapolation of points in the case of the chloroform solutions, although the order of extrapolated shifts should be correct. It would appear that the aggregates of the molecules with larger side chains are more easily disrupted than those with smaller side chains, which is quite reasonable.

The final point in discussion of the spectra concerns the shifts of the hydrogens in the side chains. The most striking feature is the low field at which the hydrogens on the carbon α to the sydnone ring appear in the spectrum. For a methyl group in an aliphatic compound,[7] the usual value is $\tau = 9.1$; for a methyl group in toluene, 7.7; and for the methyl group attached to nitrogen in an amine, 7.8–7.9. But for methyl sydnone, the methyl peak appears below τ of 6, the exact position depending on the solvent. The methylene hydrogen chemical shift is about $\tau = 8.75$ in an aliphatic hydrocarbon, 7.38 in ethyl benzene, 7.4 to 7.6 for the α-hydrogens in alkyl amines, and approximately 5.5 in ethyl sydnone. For the methine hydrogens in isopropyl and *sec*-butyl sydnone, the shifts are in the range of $\tau = 5.3$ to 5.4, compared with a value in isopropylamine of 7.13. Finally, the phenyl protons in phenyl sydnone give a complex pattern with an average shift quite a bit below the normal position of unsubstituted benzene. The value of $\tau = 2.1$ may be compared with a value of 3.4 for the ring hydrogens in aniline.

All these data represent, then, a very strong unshielding of those protons of the substituent group which are located near the sydnone ring. This may best be interpreted as representing the combined unshielding effects of the electronegative nitrogen atom to which the group is attached, with the electronegativity accentuated by the positive charge on the ring, and of the ring current in the aromatic sydnone structure. This result represents the strongest proof, from the n.m.r. investigation, of the aromaticity of sydnones.

Acknowledgment.—This investigation was supported in part by PHS Research Grant Number GM-09343-02 from the Institute of General Medical Sciences, Public Health Service.

(7) Chemical shifts cited here are taken from other work in these laboratories and from G. V. D. Tiers, "Characteristic Nuclear Magnetic Resonance Shielding Values," Minnesota Mining and Manufacturing Company, 1958.

[JOINT CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF., AND OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

Optical Rotatory Dispersion Studies. XCII.[1] Some Observations on the Conformation of *cis*-10-Methyl-2-decalones[2]

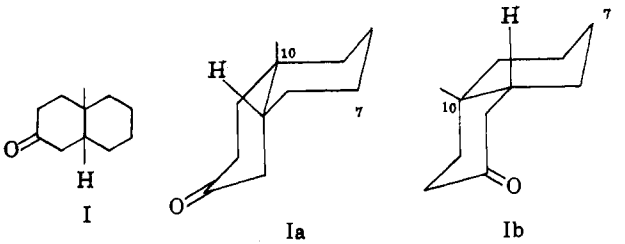
BY CARL DJERASSI, J. BURAKEVICH, J. W. CHAMBERLIN, D. ELAD, T. TODA, AND GILBERT STORK

RECEIVED AUGUST 29, 1963

cis-Decalones can exist in two all-chair conformations, commonly termed the "steroid" and "nonsteroid" forms. The latter conformation has been proposed for certain *cis*-10-methyl-2-decalones substituted at C-7 (*e.g.*, 7,7-dimethyl), since the generally accepted tenets of conformational analysis clearly favor such conformations. In the present work, optically active antipodes of known absolute configuration of such *cis*-decalones have been synthesized and it has been demonstrated by optical rotatory dispersion measurements that, contrary to the earlier held views, the "nonsteroid" conformation cannot play an important role.

The conformational problem among *cis*-2-decalones is a vexing one. Taking the bicyclic analog of the 3-keto 5β-steroids, *cis*-10-methyl-2-decalone (I) as an example, two all-chair forms (Ia and Ib) are possible, of which only the former can exist among steroids because of the additional B/C ring juncture.

Initially, it had been suggested[3] that *cis*-2-decalone would assume the "nonsteroid" conformation Ib, but on the basis of subsequent optical rotatory dispersion measurements[4] it was suggested that in *cis*-10-methyl-2-decalone, the "steroid" form predominates. This latter conclusion was based on the similarity in shape of the O.R.D. curves of the rigid model 3-keto 5β-steroid and that of *cis*-10-methyl-2-decalone (I) as well as on an analysis of the data by the octant rule.[5]



(1) Paper XCI: K. M. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 492 (1964).

(2) Financial support from the National Institutes of Health (grants No. GM-06840 and 5T4CA5061 to Stanford University) and from the National Science Foundation (to Columbia University) is hereby acknowledged.

(3) W. Klyne, *Experientia*, **12**, 119 (1956).

(4) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

(5) (a) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961); (b) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962); (c) C. Djerassi and W. Klyne, *ibid.*, 2390 (1963).

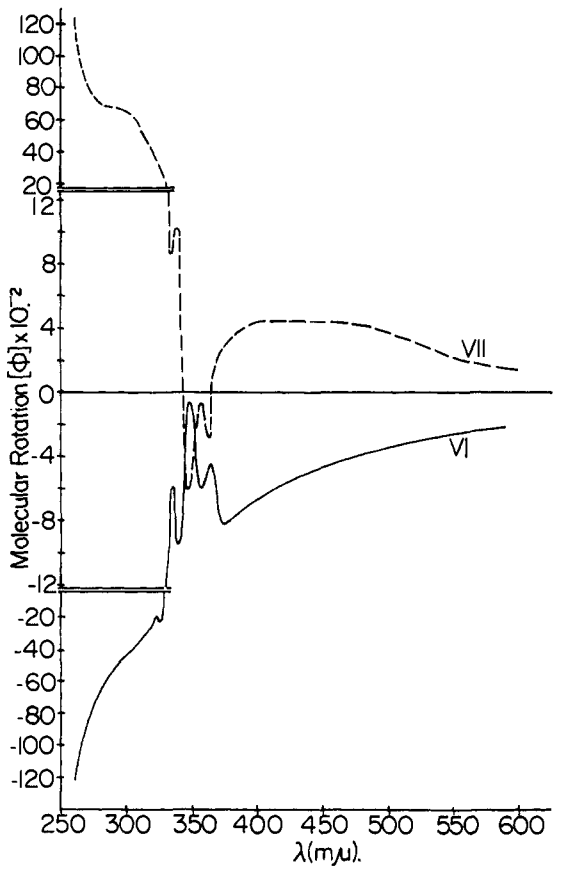
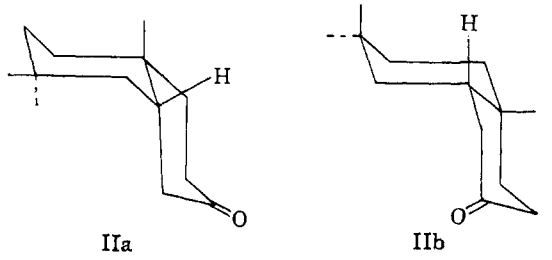


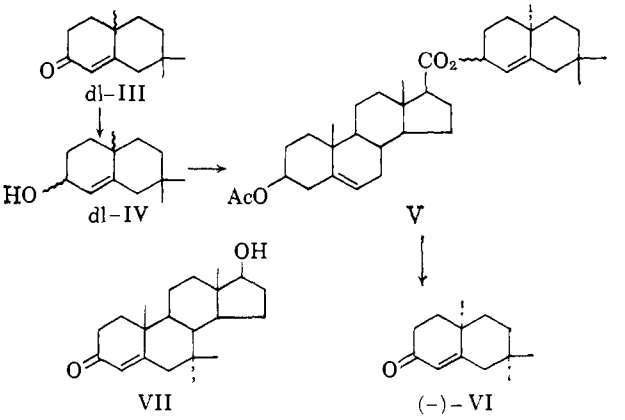
Fig. 1.—Optical rotatory dispersion curves (dioxane solution) of (−)-7,7,10-trimethyl-$\Delta^{1(9)}$-octalone-2 (VI) and 7,7-dimethyltestosterone (VII).

A much more clear-cut case seemed to be *cis*-7,7,10-trimethyl-2-decalone (II),[6] where the additional diaxial methyl–methylene interaction in the "steroid" form IIa led to the conclusion[6] that the "nonsteroid" conformation IIb would be preferred. It seemed desirable, therefore, to synthesize this substance in optically active form and to examine its rotatory dispersion curve in the light of the octant rule,[5] since such a study would also strengthen the basis of the earlier conclusions[4] about the preferred conformer of the simpler *cis*-10-methyl-2-decalone (I). In order to utilize such an approach, it was indispensable to have available an optically active antipode of II of established absolute configuration.



IIa IIb

The first approach to material of known absolute stereochemistry, employed in the Stanford laboratories, involved lithium aluminum hydride reduction of the known[6] 7,7,10-trimethyl-$\Delta^{1(9)}$-octalone-2 (III) to the octalol IV, followed by resolution through the 3β-acetoxy-Δ^5-etienate,[7] only one isomer (V) having been obtained in pure form. Cleavage of the etienate V with lithium aluminum hydride and reoxidation of the resolved allylic alcohol led to (−)-7,7,10-trimethyl-$\Delta^{1(9)}$-octalone-2 (VI). Its absolute configuration in terms of stereoformula VI (opposite absolute configuration to that of the steroids) follows[8] from the observation (Fig. 1) that its optical rotatory dispersion curve was essentially the mirror image of that of 7,7-dimethyltestosterone (VII),[9] which in turn was of the general Δ^4-3-keto steroid type.



The above-described procedure, though leading to material of satisfactory optical purity, is not suited for the preparation of substantial quantities of the octalone VI. Since this material also represents a useful precursor for terpene syntheses,[6,10] another approach was developed in the Columbia laboratories, which commenced with a naturally occurring optically active ketone and thus eliminated a resolution step.

The starting material was (+)-pulegone (VIII), which was transformed by a new route (see Experimental) into the known[11] (+)-*trans*-2,5-dimethylcyclohexanone (IX). The key step was cyanoethylation of IX, which, on the basis of the principle[12] of axial entry of acrylonitrile, should lead to a product X of fixed and known absolute configuration. Hydrolysis of the nitrile X to the carboxylic acid XI, followed by bromination (XII), diazomethane methylation, and dehydrobromination afforded the substituted cyclohexenone XIII. 1,4-Addition of methylmagnesium iodide was followed by conversion of the ester to the free carboxylic acid, and this was transformed into the enol lactone XIV by treatment with sodium acetate in refluxing acetic anhydride. The remaining steps followed well-trodden paths[13] in the steroid series and provided the (−)-octalone VI, the optical rotatory dispersion curve of which was very similar to that of the specimen obtained by the above-described resolution route. The rotation values of the octalone derived from the alkylation sequence, however, were lower, thus indicating lesser optical purity, and this conclusion was also confirmed (see Experimental) by the

(6) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956). See also F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959), and J. Meier, Thesis, E.T.H. (Zürich), 1958. We are indebted to Prof. A. Eschenmoser for details of this latter work.

(7) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959). For further examples see: C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960); C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961); C. Djerassi, P. A. Hart, and E. J. Warawa, *ibid.*, **86**, 78 (1964); C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, **86**, 85 (1964); R. B. Turner and P. E. Shaw, *Tetrahedron Letters*, **No. 18**, 24 (1960), have employed 3α-acetoxy-11-ketoetianic acid for resolution purposes.

(8) For details to this approach for absolute configuration assignments see Chapter 10 in C. Djerassi "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(9) S. Julia, C. Neuville, and M. Davis, *Bull. soc. chim. France*, 297 (1960), to whom we are indebted for a specimen.

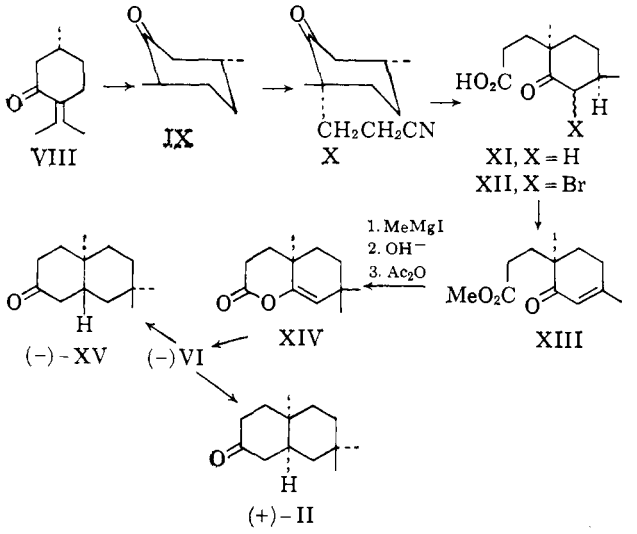
(10) J. A. Barltrop, J. D. Littlehailes, J. D. Rushton, and N. A. J. Rogers, *Tetrahedron Letters*, 429 (1962).

(11) A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **39**, 441 (1956).

(12) See, for instance, W. S. Johnson, *Chem. Ind.* (London) 167 (1956).

(13) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950); G. I. Fujimoto, *ibid.*, **73**, 1856 (1951).

melting point behavior of the *cis*-decalones obtained by catalytic hydrogenation of the two differently prepared octalone specimens. We conclude, therefore, that the cyanoethylation step (IX → X) had not proceeded in a completely stereospecific (axial) manner and that a small amount of the equatorial cyanoethyl epimer had also been formed.[14] Reduction[15] of (−)-7,7,10-tri-



methyl-$\Delta^{1(9)}$-octalone-2 (VI) with lithium in liquid ammonia provided the *trans* fused decalone XV, which is devoid of conformational ambiguity. The octant rule[5] predicts a negative Cotton effect for this antipode—all relevant substituents being located in a negative octant—and this prediction is in accord with the experimentally observed (Fig. 2) negative Cotton effect, thus affording independent substantiation of the absolute configuration of the precursor octalone VI.

Catalytic hydrogenation of the (−)-octalone VI led in the anticipated[15] fashion to the crystalline *cis*-7,7,10-trimethyl-2-decalone (II), which on the basis of the usual principles of conformational analysis should exist in the "nonsteroid" conformation IIb, as has in fact been stated[6] in the literature. Analysis of the "nonsteroid" form of the (+)-antipode of II by the octant rule[5] leads unambiguously to the prediction that this conformer should exhibit a strong negative Cotton effect since all contributing substituents are situated in negative octants. Experimentally, the surprising observation was made (see Fig. 2) that this decalone II actually shows a weak positive Cotton effect, which leads to the inescapable conclusion that the anticipated[6] "nonsteroid" conformation IIb does not play an important role in the conformer equilibrium of *cis*-7,7,10-trimethyl-2-decalone (II).[16]

This unexpected result prompted the synthesis of a second *cis*-10-methyl-2-decalone with a C-7 substituent placed in such an orientation that it should favor the "nonsteroid" conformation Ib. The choice of a 7-isopropyl substituent was based on earlier synthetic[17]

(14) Presumably because of equilibration through reversal of the alkylation step (*cf.* ref. 17).

(15) This reduction has already been performed on the racemate (ref. 6) where it was concluded that the metal–ammonia reduction afforded a *trans*-, and the catalytic hydrogenation, a *cis*-decalone.

(16) The only other and rather remote possibility is that the "nonsteroid" conformer IIb with the predicted large negative Cotton effect is indeed predominant, but that there is present a smaller amount of a conformer, other than IIa or IIb, with an extremely powerful positive Cotton effect. That one is dealing with a conformer mixture could be demonstrated by the low-temperature circular dichroism technique (K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963)). As illustrated in Fig. 3, the weakly positive circular dichroism curve of the decalone II becomes *more positive* upon lowering the temperature to −192°, thus demonstrating that whatever the positive contributor to the conformer equilibrium may be, it is of a lower energy content.

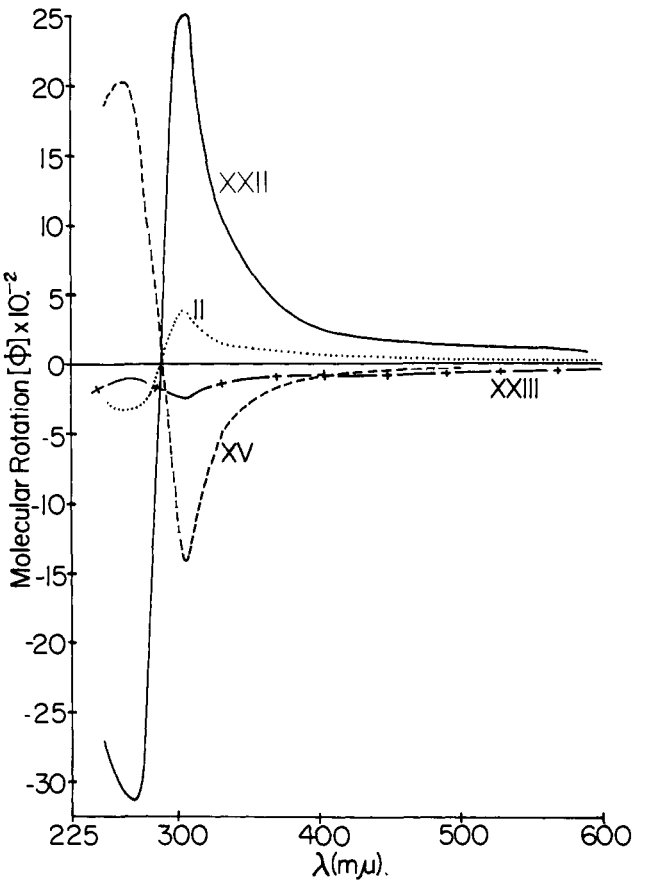


Fig. 2.—Optical rotatory dispersion curves (methanol solution) of (+)-*cis*-7,7,10-trimethyl-2-decalone (II), (−)-*trans*-7,7,10-trimethyl-2-decalone (XV), (+)-*trans*-7α-isopropyl-10β-methyl-2-decalone (XXII), and (−)-*cis*-7α-isopropyl-10β-methyl-2-decalone (XXIII).

and rotatory dispersion[5b] studies in the epi-α-cyperone series, where the interpretation of the conformational situation was complicated by an additional methyl group adjacent to the keto function. The synthesis of the desired decalone XXIII followed in principle, though not in detail, the sequence utilized by McQuillin[18] in the cyperone series.

(−)-Tetrahydrocarvone (XVI), derived from (+)-carvone of known[19] absolute configuration, was condensed[20] with 1,3-dichloro-2-butene and the resulting crude chloro ketone XVII was exposed to concentrated sulfuric acid to afford in 25% over-all yield an octalone mixture (5:1), which could be separated by gradient elution chromatography into the predominant component XVIII and the minor one XIX. The absolute stereochemistry at C-7 is already fixed in the starting material (XVI) and that at C-10 could be settled unambiguously in terms of stereoformulas XVIII and XIX by comparing[8] their optical rotatory dispersion curves (Fig. 4) with those of (+)-dihydroepi-α-cyperone (XX)[18,21] and (−)-10-methyl-$\Delta^{1(9)}$-octalone-2 (XXI),[4] both of which represent standards of known absolute configuration.

A more convenient route to the desired octalone XVIII involved condensation of (−)-tetrahydrocarvone (XVI) with 1-diethylamino-3-butanone followed by

(17) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 1194 (1958); 2670 (1956).

(18) F. J. McQuillin, *ibid.*, 528 (1955).

(19) See A. J. Birch, *Ann. Rept. Progr. Chem.*, **47**, 192 (1951).

(20) See O. Wichterle, J. Prochazka, and J. Hofman, *Collection Czech. Chem. Commun.*, **13**, 300 (1948); S. A. Julia, *Bull. soc. chim. France*, 780 (1954).

(21) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

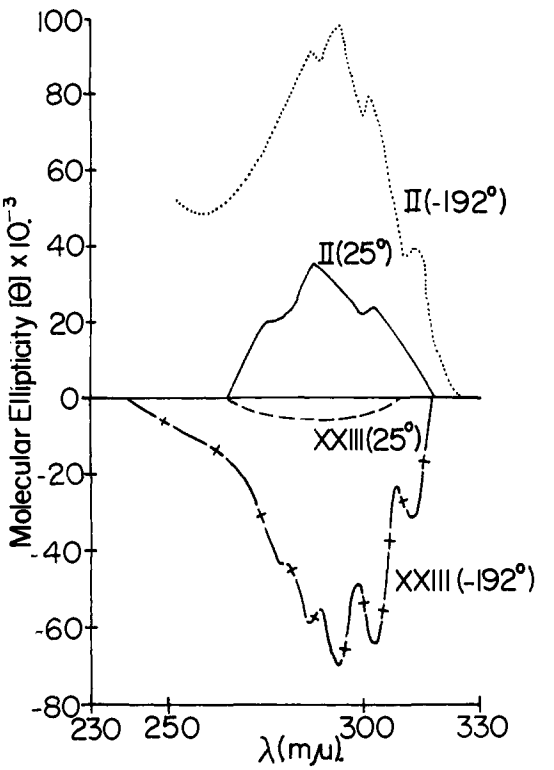
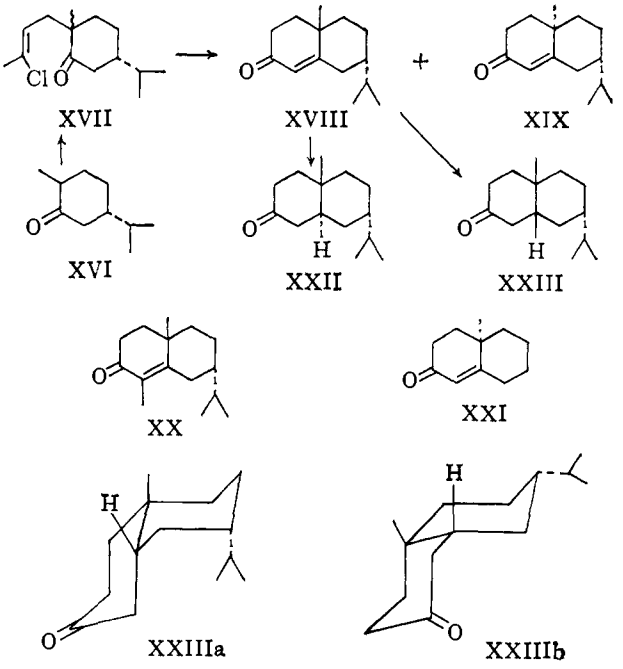


Fig. 3.—Circular dichroism curves (ether–isopentane–alcohol, 5:5:2) at 25° and −192° of (+)-*cis*-7,7,10-trimethyl-2-decalone (II) and (−)-*cis*-7α-isopropyl-10β-methyl-2-decalone (XXIII).

base-promoted cyclization of the unpurified intermediate diketone. Reduction of the octalone XVIII with lithium in liquid ammonia afforded the anticipated[17,22] *trans*-7α-isopropyl-10β-methyl-2-decalone (XXII), which exhibited a positive Cotton effect (Fig. 2) in accord with the octant rule.[5] Catalytic hydrogenation yielded the desired *cis*-7α-isopropyl-10β-methyl-2-decalone (XXIII) with a weakly negative Cotton effect. Since the octant rule[5] predicts a very strong positive Cotton effect for the "nonsteroid" conformation XXIIIb, it is again clear that this chair form—just as in the analogous (antipodal) 7,7-dimethyl case



(22) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960)

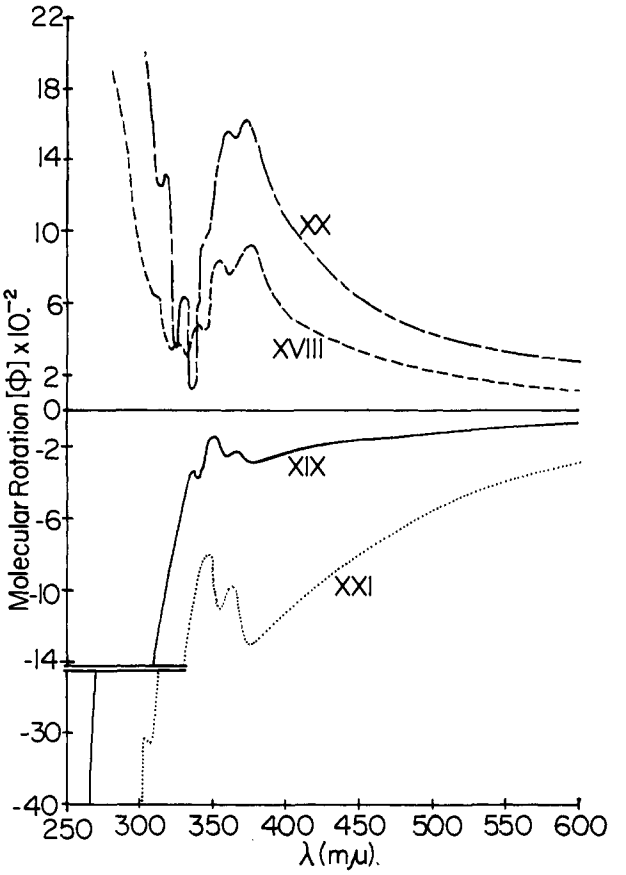


Fig. 4.—Optical rotatory dispersion curves (dioxane solution) of (+)-7α-isopropyl-10β-methyl-Δ[1(9)]-octalone-2 (XVIII), (−)-7α-isopropyl-10α-methyl-Δ[1(9)]-octalone-2 (XIX), (−)-10α-methyl-Δ[1(9)]-octalone-2 (XXI), and (+)-dihydroepi-α-cyperone (XX).

(VI)—does not constitute the exclusive or even predominant conformer[16] in solution. Low temperature circular dichroism measurements (see ref. 16) show (Fig. 3) that one is dealing here with a mixture of at least two conformers, the more negatively rotating one being of lower energy.

In summary, it can be stated that the present rotatory dispersion measurements with the substituted *cis*-10-methyl-2-decalones II and XXIII make it very unlikely that the "nonsteroid" chair conformation plays an important role.[16] This is especially startling if one considers that the "steroid-like" all-chair conformation should be the less favored one by *ca.* 1.8 kcal./mole[23] for the *gem*-dimethyl ketone IIa and presumably by an even larger factor in the case of the isopropyl analog XXIIIa.

If we subject the more favorable "nonsteroid" all-chair conformations IIb and XXIIIb to closer scrutiny, we note in particular three interactions: the C-10 methyl substituent with the axial hydrogens at C-1 and C-3, as well as the interaction of the C-8 methylene group with the carbonyl function ("3-alkyl ketone effect"). All three of these interactions, amounting to *ca.* 2.7 kcal./mole, can be greatly diminished or eliminated upon converting ring A into a boat with the C-2 ketone and the C-10 carbon atom representing the prow and stern. The well-known unfavorable interactions associated with such a classical boat are in turn largely relieved by rotating the axis of the carbonyl

(23) After cancelling common 1,3-axial interactions there are left a methyl–methylene interaction (3.6 kcal./mole) for the "steroid-like" form *vs.* a methyl–hydrogen (0.9 kcal./mole) and a "3-alkyl ketone" interaction (≦0.9 kcal./mole); see B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962), and N. L. Allinger and L. A. Freiberg, *ibid.*, **84**, 2201 (1962).

group toward C-4 by about 20°: *i.e.*, by making a twist with the points[24] at C-1 and C-4. Using the usual octant projection[5] one reaches the conclusion that such a form for the absolute configuration expressed by stereoformula II results in a positive and that of XXIII in a negative Cotton effect, in agreement with our experimental findings.

The present results with the substituted *cis*-10-methyl-2-decalones suggest that the simple *cis*-10-methyl-2-decalone (I) may also exist as a modified boat form of the "nonsteroid" conformation Ib. This representation as well as the "steroid-like" conformation Ia is in accord with the observed[4] rotatory dispersion results. Since the energy difference between these two forms is much smaller in this case than in the substituted decalones II and XXIII, a firm decision cannot be made with the presently available data, and a rigorous distinction will probably have to await the results of an X-ray analysis of I.

Experimental[25]

Resolution of 7,7,10-Trimethyl-$\Delta^{1(9)}$octalone-2 (III).—A suspension of 9.9 g. of 3β-acetoxy-Δ^5-etienic acid[26] in 100 cc. of benzene was dried by azeotropic distillation and then stirred at room temperature for 20 hr. with 17.5 cc. of oxalyl chloride. Removal of the solvent under reduced pressure and submission to a high vacuum for 3.5 hr. left a white solid of the acid chloride to which was added a solution of 6.43 g. of crude 7,7,10-trimethyl-$\Delta^{1(9)}$-octalol-2 (IV) (prepared by reduction of 6.5 g. of the ketone III[6] with an equal weight of lithium aluminum hydride in boiling ether (1 hr.) and decomposing by the sodium sulfate technique) in 75 cc. of dry pyridine. After stirring at room temperature for 43 hr., the mixture was poured into dilute hydrochloric acid and the product extracted with methylene chloride. Chromatography on 2 kg. of Merck alumina (activity II) and elution with benzene–hexane (6:4) provided 9 g. of crude etienate V. One crystallization from 200 cc. of methanol (containing just enough ethanol to dissolve the product) led to a mixture (6.2 g.) of needles and plates, m.p. 148–170°, $[\alpha]_D$ −23° (*c* 0.55). After four recrystallizations, constantly rotating material ($[\alpha]_D$ +8°) was secured, but even further recrystallization did not narrow the melting point range beyond 178–184°. The recovery of optically pure ($[\alpha]_D$ +8°) etienate was approximately 7%.

Anal. Calcd. for $C_{38}H_{52}O_4$: C, 78.31; H, 9.77. Found: C, 78.06; H, 9.50.

A sample (450 mg.) of etienate (m.p. 177–184°, $[\alpha]_D$ +8°) was stirred in ether solution (room temperature, 1 hr.) with 680 mg. of lithium aluminum hydride and, after decomposing by the sodium sulfate technique, the crude product was extracted with acetone, filtered from insoluble steroid diol, and 8 *N* chromium trioxide reagent[27] added dropwise until an orange color persisted. The product was purified by preparative thin layer chromatography on silica gel G using benzene (440 cc.)–ethyl acetate (60 cc.) for development and ultraviolet absorption for detection of the appropriate zone. Extraction with ether and distillation at 145° (5 mm.) yielded the **octalone VI** as a colorless oil, which solidified, m.p. 38.5–41.5°, $[\alpha]_D$ −132° (*c* 0.59), λ_{max}^{EtOH} 241 mμ (ε 18,000), $\lambda_{max}^{CHCl_3}$ 6.08 and 6.2 μ; R.D. (*c* 0.240 in dioxane) (Fig. 1): $[\phi]_{589}$ −221°, $[\phi]_{375}$ −825°, $[\phi]_{364}$ −452°, $[\phi]_{358}$ −605°, $[\phi]_{348}$ −67°, $[\phi]_{340}$ −940°, $[\phi]_{335}$ −595°, $[\phi]_{325}$ −2210°, $[\phi]_{260}$ −12,100°.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.43.

(+)-3-Methylcyclohexanone.—A mixture of pulegone (131.6 g.) and 125 cc. of concentrated hydrochloric acid in 375 cc. of water was brought to a slow reflux. Acetone was fractionated from the mixture for approximately 7 hr. The residue was steam distilled and the distillate was then saturated with sodium chloride. The separated oil was collected and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvent was removed and the residual oil was vacuum distilled; yield 60 g., b.p. 43–46° (3.5 mm.) (reported[28] 166.5–168° (735 mm.)), $n^{25}D$ 1.4480, $\alpha^{28}D$ +11.7 (reported[28] $[\alpha]^{26}D$ +12.01°). The 2,4-dinitrophenylhydrazone melted at 137.7–140°.

Ethyl 3-Methylcyclohexanone-6-glyoxylate.—A solution of 11.6 g. of sodium metal dissolved in 250 ml. of commercial absolute ethanol was cooled in an ice–salt bath. To this was added with vigorous stirring during 10 min. a mixture of 56.3 g. of (+)-3-methylcyclohexanone and 74.4 g. of freshly distilled ethyl oxalate. Stirring was continued for 1 hr. with ice cooling and then at room temperature for 18 hr. The reaction mixture was then cooled in ice and to it was added 14 cc. of concentrated sulfuric acid in 111 g. of ice. The oil was separated and the aqueous layer was extracted five times with benzene (approximately 150 cc. each time). The combined organic layers were washed with water and the benzene solution was then dried over magnesium sulfate. The benzene was removed on a rotary evaporator and the residue was vacuum distilled, giving 76.7 g., b.p. 102–171° (4.5 to 7.3 mm.).

Ethyl 3-Methylcyclohexanone-6-carboxylate.—Approximately 0.5 g. of powdered soft glass and a trace of powdered iron were mixed with the above 76.7 g. of crude glyoxylate. The mixture was stirred and heated in an oil bath at 155–165° for approximately 8 hr. (gas evolved). It was then distilled to give 69.3 g., b.p. 100–120° (5 mm.). The β-keto ester gave a purple color with methanolic ferric chloride.

(+)-*trans*-2,5-Dimethylcyclohexanone (IX).—A solution of 7.9 g. of sodium dissolved in 200 ml. of commercial absolute ethanol was cooled in an ice bath and to this was added, with vigorous stirring, 58 g. of the above β-keto ester. An immediate gelatinous precipitate appeared. More absolute ethanol was added to aid stirring (about 100 ml.). To this stirred and cooled solution was added 150 ml. of methyl iodide (freshly distilled after drying over calcium chloride). The ice bath was removed 15 min. after the addition was complete. The mixture was left stirring at room temperature for 8 hr. The precipitate disappeared, leaving a clear yellow solution. The mixture was then cooled in ice and to it was added 15 cc. of concentrated sulfuric acid in 123 g. of ice, and the mixture was then diluted to a volume of 1 l. with the addition of ice water. The separated oil was collected and the aqueous layer was extracted with ether. The combined organic layers were washed with aqueous sodium bicarbonate, and then with saturated salt solution containing some sodium thiosulfate. The ether solution was dried over magnesium sulfate. The magnesium sulfate was filtered off and washed, and the ether was removed by distillation through a fractionating column. The residual oil was dissolved in 339 ml. of concentrated hydrochloric acid, 483 ml. of acetic acid, and 97 ml. of water. The mixture was then refluxed for 6 hr. Solid sodium hydroxide was added to the mixture until no more could be seen to dissolve. After saturation with sodium chloride, the mixture was extracted with ether, and the ether layer was then washed with aqueous sodium bicarbonate and with saturated sodium chloride solution containing some sodium thiosulfate. The solution was dried over magnesium sulfate and the ether was removed by distillation through a fractionation column. The residue was then vacuum distilled with the receiver cooled in Dry Ice to give 31.1 g., b.p. 64–66° (7 mm.), $[\alpha]^{29}D$ +14.7° (*c* 3.59) (reported[11] $[\alpha]_D$ +13°), $n^{25}D$ 1.4456. The ketone gave a 2,4-dinitrophenylhydrazone, m.p. 166.5–168° after several crystallizations from ethanol (reported[11] m.p. 157–158°).

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92. Found: C, 55.00; H, 6.26.

An oxime, m.p. 102–103°, was also prepared.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 68.02; H, 10.82.

2-Cyanoethyl-2,5-dimethylcyclohexanone (X).—To 27 g. of 2,5-dimethylcyclohexanone (IX), stirred with 0.7 cc. of Triton B (40% in methanol, K and K Laboratories, Inc.) was added dropwise with stirring over 1 hr. 45.3 g. of freshly distilled acrylonitrile. The addition lasted 50 min. and evolved considerable heat. The mixture was then stirred at room temperature for 7 hr. It was then diluted with ether (final volume 250 ml.) and washed with 2 *N* hydrochloric acid and then with water. After drying over magnesium sulfate the ether was removed and the residue was fractionated: fraction 1, b.p. 67–68° (8 mm.), yield 13.7 g. of starting material; fraction 2, b.p. 158–162° (5 mm.), yield 11.1 g., $n^{24}D$ 1.4745.

The 2,4-dinitrophenylhydrazone formed orange needles from ethanol; m.p. 163–164°.

Anal. Calcd. for $C_{17}H_{21}N_5O_4$: C, 56.81; H, 5.89; N, 19.49. Found: C, 56.63; H, 6.16; N, 19.50.

(24) For definition see C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962).

(25) Melting points are uncorrected. All rotatory dispersion measurements were performed by Mrs. Ruth Records using a Nippon Bunko (Japan Spectroscopic Co., Ltd.) automatically recording spectropolarimeter. Unless noted otherwise, specific rotations were measured in chloroform solution. The mass spectra are due to Drs. M. Ohashi, J. M. Wilson, and H. Budzikiewicz, while the microanalyses were performed by Messrs. E. Meier and J. Consul of the Stanford Microanalytical Laboratory.

(26) Prepared by the procedure of J. Staunton and E. J. Eisenbraun, *Org. Syn.*, **42**, 4 (1962), from Δ^5-pregnen-3β-ol-20-one generously donated by Syntex, S. A., Mexico City.

(27) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(28) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

Hydrolysis of X to the Keto Acid XI.—A mixture of 10.6 g. of the keto nitrile X with 50 ml. of 10% sodium hydroxide solution was refluxed for 7 hr. It was then diluted with water and extracted with ether. The aqueous layer was then acidified and saturated with sodium chloride. It was then extracted with ether and the ether layer was washed with saturated salt solution. The ether was then dried over magnesium sulfate and the ether was removed, leaving a yellow oil (11.3 g.). A small portion was microdistilled giving a colorless oil, showing a positive cotton effect and $n^{28}D$ 1.4789.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 66.64; H, 9.15. Found: C, 66.54; H, 9.16.

Bromoketo Acid XII.—The crude keto acid XI (10.4 g.) was dissolved in 100 cc. of glacial acetic acid containing 2 drops of 30% hydrogen bromide in acetic acid. To this solution was added 9.87 g. of bromine in 150 cc. of glacial acetic acid. The addition lasted about 2 hr. The mixture was then diluted with saturated sodium chloride solution and extracted with ether. The ether layers were washed with saturated sodium chloride solution and the ether was removed on a rotary evaporator. The residue was taken up in ether again and washed with saturated sodium chloride solution. The ether was dried over magnesium sulfate and was then removed, leaving a residue that was half oil and half solid (22 g.). The solid was removed from the mixture by filtration and was then recrystallized from acetone–*n*-hexane giving white crystals (0.713 g., m.p. 138.8–139.2°). After several recrystallizations from acetone–*n*-hexane it had m.p. 141–143°, $[\alpha]D^{26}$ −15.3° (*c* 1.96, chloroform), $\lambda_{max}^{CHCl_3}$ 5.81 μ.

Anal. Calcd. for $C_{11}H_{17}O_3Br$: C, 47.65; H, 6.35. Found: C, 47.69; H, 6.19.

The oily fraction obtained from the bromination had the same behavior on chromatoplates as did the solid. An attempted distillation on a small portion failed. The oily fraction resisted crystallization and was put on a rotary evaporator with a vacuum pump to remove the acetic acid. The residue was an orange, very viscous liquid of crude XII.

Dehydrobromination of XII to XIII.—The orange liquid (14.8 g.) resulting from the oily portion of the bromination product XII was esterified with diazomethane. The resulting bromoketo ester was then dissolved in 500 ml. of anhydrous dimethylformamide. To this solution was added approximately 15 g. of lithium bromide and about 15 g. of lithium carbonate. The mixture was stirred and heated at 95° for about 15 hr. After cooling, the solution was poured into cold water and acidified with hydrochloric acid. It was then extracted with ether (150 cc. × 6). The ether layers were combined and washed with water and then dried over magnesium sulfate. The ether was removed on a rotary evaporator and the residue was vacuum distilled to give a yellow oil (5.39 g.), b.p. 105–110° (0.15 mm.), $[\alpha]^{29}D$ +7.28° (*c* 1.51), λ_{max}^{EtOH} 235 mμ, ε 12,900; λ_{max}^{film} 5.74, 5.97 μ; negative Cotton effect. The 2,4-dinitrophenylhydrazone formed orange needles, m.p. 164–165°, from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{21}N_4O_6$: C, 55.38; H, 5.68. Found: C, 55.31; H, 5.82.

1,4-Grignard Addition on XIII.—A Grignard solution, made from 3.9 g. of magnesium turnings and 10 cc. of methyl iodide in 240 ml. of anhydrous ether, was cooled in an ice bath. To the cold solution was added 405 mg. of anhydrous cuprous chloride. Cooling and stirring were continued while 6.0 g. of unsaturated keto ester XIII was added in 80 cc. of anhydrous ether. The addition lasted about 8 min. The solution turned from black to clear. Cooling and stirring were continued for 30 min. and the Grignard solution was decomposed with cold saturated ammonium chloride solution containing some hydrochloric acid. The reaction mixture was extracted with ether and washed with saturated sodium chloride solution containing some sodium thiosulfate. The ether solution was dried over magnesium sulfate and the solvent was then removed leaving a yellow oil.

The yellow oil was filtered through about 150 g. of activity II alumina using petroleum ether. The first nine 100-ml. fractions contained a total of 2.2 g. of crude keto ester which was mixed with 30 cc. of 7% alcoholic potassium hydroxide and refluxed under nitrogen for 90 min. Most of the alcohol was then removed on a rotary evaporator. Water was then added to the residue and the mixture was extracted with ether. The aqueous layer was then acidified and saturated with solid sodium chloride. It was then extracted with ether and the ether extract was dried over magnesium sulfate. The ether was removed and the residue crystallized (1.07 g.). Recrystallization from hexane gave 711 mg., m.p. 79–82°, $[\alpha]^{26}D$ +18.4° (*c* 1.47 chloroform), positive Cotton effect. Further recrystallizations from hexane raised the m.p. to 85–87°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.87; H, 9.50. Found: C, 68.16; H, 9.41.

Enol Lactone XIV.—The keto acid X (647 mg.) was mixed with 104 mg. of anhydrous sodium acetate and 10 cc. of acetic anhydride. It was refluxed overnight under nitrogen. The solution was allowed to cool and ice was added to the mixture which was then extracted with ether. The ether layer was washed with sodium bicarbonate and then with saturated salt solution and was dried over magnesium sulfate. The solvent and residual acetic anhydride were removed under high vacuum leaving a tan solid (582 mg.). After recrystallization by dissolving in *n*-pentane (very soluble) and cooling in ice, the m.p. was 51–58°. A pure sample had m.p. 62–63.5°, $[\alpha]^{27}D$ +40.7 (*c* 0.64, chloroform).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.48; H, 9.29.

(−)-7,7,10-Trimethyl-$\Delta^{1(9)}$-octalone-2 (VI) from Enol Lactone XIV.—To an ice-cold solution of 195 mg. of the enol lactone XIV in 3 cc. of dry ether was added 0.3 cc. of 3.6 *M* ethereal methylmagnesium bromide solution and the mixture stirred at 3° for 20 hr. After decomposing with ammonium chloride, the product was extracted with ether and after appropriate washing and evaporation of the solvent, the residue was stirred at 25° for 20 hr. with 35 cc. of methanol, 5 cc. of water, and 1 g. of sodium hydroxide. Evaporation of the methanol, extraction with ether, and preparative thin layer chromatography followed by vacuum distillation left 39 mg. of the oily octalone VI, $[\alpha]D$ −91° (*c* 0.53); R.D. (*c*, 0.07, dioxane): $[\phi]_{589}$ −148°, $[\phi]_{375}$ −368°, $[\phi]_{363}$ −219°, $[\phi]_{359}$ −273°, $[\phi]_{350}$ −27°, $[\phi]_{339}$ −463°, $[\phi]_{335}$ −273°, $[\phi]_{326}$ −858°, $[\phi]_{325}$ −832°, $[\phi]_{260}$ −3540°.

(+)-*cis*-7,7,10-Trimethyl-2-decalone (II).—The catalytic hydrogenation of 45 mg. of the octalone IV, derived from the etienate resolution, was effected in the usual manner[6] in ethanol solution with 28 mg. of 10% palladium-on-charcoal. After 45 min., the catalyst was filtered, the solvent evaporated, and the crystalline residue sublimed at 60° (20 mm.) and recrystallized from aqueous methanol to afford 13 mg. of colorless needles, m.p. 87–88°, $\lambda_{max}^{CHCl_3}$ 5.90 μ; R.D. (Fig. 2) in methanol (*c* 0.141): $[\phi]_{589}$ 0°, $[\phi]_{303}$ +378°, $[\phi]_{260-265}$ −320°, $[\phi]_{250}$ −262°. Repetition of the hydrogenation with octalone derived from the enol lactone XIV gave needles with a much wider melting point, m.p. 68–81°, suggesting some contamination by the other antipode, which in turn arises from lower optical purity of the octalone precursor: R.D. in methanol (*c* 0.11): $[\phi]_{589}$ +47.5°, $[\phi]_{306}$ +388° $[\phi]_{260}$ −34.8°, $[\phi]_{246}$ +51.7°.

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41; mol. wt., 194. Found: C, 80.39; H, 11.35; mol. wt., 194 (mass spec.).

(−)-*trans*-7,7,10-Trimethyl-2-decalone (XV).—A sample of the octalone VI (derived from the enol lactone XIV) was reduced with lithium in liquid ammonia as reported previously[6] for the racemate. The product, purified by thin layer chromatography and vacuum distillation exhibited λ_{max}^{capill} 5.89 μ, mass spectral molecular ion peak at *m/e* 194; R.D. (Fig. 2) in methanol (*c* 0.09): $[\phi]_{500}$ −48.5°, $[\phi]_{306}$ −1380°, $[\phi]_{260}$ +2060°, $[\phi]_{250}$ +1890°.

Condensation of (−)-Tetrahydrocarvone (XVI) with 1,3-Dichloro-2-butene.—The procedure was patterned after that of Julia[20] in the 2-methylcyclohexanone series. To an ice-cold solution of 5.0 g. of (−)-tetrahydrocarvone (XVI) and 4.07 g. of freshly distilled 1,3-dichloro-2-butene in 16 cc. of dry benzene was added dropwise in an atmosphere of nitrogen 18 cc. of a sodium *t*-amylate solution, prepared by heating under reflux for 20 hr. 1.77 g. of sodium, 4.41 g. of *t*-amyl alcohol, and 25 cc. of benzene. After keeping at room temperature for 1.5 hr. and heating under reflux for 3 hr., the mixture was cooled, diluted with ether, neutralized with acetic acid, washed with water, dried, and evaporated. The residual yellow oil was fractionally distilled through a Vigreux column and the lower-boiling (b.p. 38–41° (0.25 mm.)) material (1.1 g.) identified as recovered starting ketone XVI. The higher-boiling (b.p. 98–100° (0.22 mm.)) fraction (4.31 g.) exhibited an infrared spectrum (λ_{max}^{capill} 5.88 (ketone) and 6.0 μ (double bond)) consistent with the chloroketone structure XVII, but since thin layer chromatography (benzene) indicated the presence of three closely spaced spots, the material was employed directly in the next step.

Sulfuric Acid Cyclization of the Chloroketone XVII.—Following the procedure of Julia,[20] a 3.9-g. sample of the above-described chloroketone XVII was cooled in ice, and 7.4 cc. of concentrated sulfuric acid was added slowly with stirring. The red mixture was kept at room temperature for 27 hr., then poured into water and extracted with ether. After thorough washing, drying, and evaporation of the ether, the resulting oil (2.3 g., λ_{max}^{EtOH} 239 mμ, ε 12,200) was chromatographed on 170 g. of neutral alumina (activity II) using a gradient elution technique in which a 4:1 solution of petroleum ether–ether was added dropwise to petroleum ether. The initial fractions exhibited λ_{max}^{capill} 5.85 and 6.0 μ, indicating the presence of some saturated ketone, while the later eluates provided 1.48 g. of oily **7α-isopropyl-10-methyl-$\Delta^{1(9)}$-octalone-2**, λ_{max}^{capill} 6.00 and 6.20 μ. Gas-phase chromatography showed a partially resolved doublet owing to the presence of the two C-10 isomers XVIII and XIX

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.32; H, 10.92.

Separation of the isomers was effected by rechromatographing the 1.48 g. of isomer mixture on 250 g. of alumina by the identical gradient elution procedure and monitoring the various fractions by gas-phase chromatography. In this fashion, there was isolated from the earlier eluted portion 0.46 g. of oil, λ_{max}^{capill} 6.00, 6.20, 10.20, and 11.70 μ, the optical rotatory dispersion curve (Fig. 4) of which demonstrated that it was the desired **7α-isopropyl-10β-methyl-Δ$^{1(9)}$-octalone-2** (**XVIII**). After an intermediate fraction (0.741 g.), consisting of varying amounts of both isomers XVIII and XIX, there was finally eluted 68 mg. of the pure **7α-isopropyl-10α-methyl-Δ$^{1(9)}$-octalone-2** (**XIX**) (λ_{max}^{capill} 6.00, 6.20, 8.20, and 11.60 μ) the optical rotatory dispersion curve (Fig. 4) of which established the configuration at C-10.

Mannich Base Condensation of (−)-Tetrahydrocarvone (XVI).—(−)-Tetrahydrocarvone (XVI) (5.0 g.) was heated for 1 hr. at 85° in an atmosphere of nitrogen with a small piece (size of small pea) of sodium, and after all of it had dissolved, there was added 3.3 g. of 1-diethylamino-3-butanone[29] and heating (92°) continued with stirring for 2.3 hr. Isolation with ether in the conventional manner yielded 5.3 g. of orange colored oil, from which unreacted starting ketone XVI was removed by distillation at 33–39° (0.3 mm.). The distillation residue was dissolved in 20 cc. of methanol containing 0.2 g. of sodium and was heated under reflux for 4 hr. in an atmosphere of nitrogen. After neutralization with acetic acid, the product was isolated with ether and chromatographed on 125 g. of activity II neutral alumina. Elution with 10% ether in petroleum ether afforded 1.78 g. of **7α-isopropyl-10β-methyl-Δ$^{1(9)}$-octalone-2** (**XVIII**) (λ_{max}^{EtOH} 239 mμ, ε 16,100; λ_{max}^{capill} 6.00, 6.20, 10.20, and 11.70 μ; $[\alpha]_D$ +65° (*c* 1.44, methanol)) the identity of which was established by infrared spectrometric, optical rotatory dispersion, and gas-phase chromatographic comparison with isomer XVIII from the chloroketone route. **The 2,4-dinitrophenylhydrazone** was recrystallized from methanol–ethyl acetate, whereupon it exhibited m.p. 195–197°, $\lambda_{max}^{CHCl_3}$ 390 mμ (ε 34,000).

Anal. Calcd. for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.00; H, 6.70; N, 14.37.

***cis*-7α-Isopropyl-10β-methyl-2-decalone (XXIII).**—Catalytic hydrogenation of 150 mg. of the octalone XVIII in 5 cc. of ethyl acetate and 15 mg. of 5% palladium-on-charcoal catalyst provided 148 mg. of a partially crystalline reduction product, which by gas-phase chromatography (diethylene glycol succinate column operated at 146°) was shown to consist of seven parts *cis* (XXIII) and one part *trans* (XXII) ketones. A pure specimen of the *cis*-ketone XXIII was secured by chromatography on neutral alumina (activity II) and elution with petroleum ether, followed by sublimation at 42° (0.1 mm.) and low temperature crystallization from pentane; m.p. 55–57°, λ_{max}^{KBr} 5.88 μ; R.D. (Fig. 2) in methanol (*c* 0.2): $[\phi]_{589}$ −32°, $[\phi]_{396}$ −221°, $[\phi]_{275}$ −115°, $[\phi]_{250}$ −147°.

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.46; H, 11.31.

***trans*-7α-Isopropyl-10β-methyl-2-decalone (XXII).**—The chemical reduction of 330 mg. of the octalone XVIII was performed in the usual manner[30] by adding an ethereal solution of it to 70 mg. of lithium dissolved in 40 cc. of liquid ammonia (condensed directly from tank by the use of a Dry Ice-acetone bath). An additional 30 mg. of lithium was added and after 10 min., the blue color had disappeared, whereupon solid ammonium chloride was added and the ammonia allowed to evaporate. The product, isolated by ether extraction, exhibited both hydroxyl and carbonyl absorption (5.88 μ due to reduction product and 6.00 μ due to unreacted octalone) in the infrared and was, therefore, oxidized in 15 cc. of acetone with 0.4 cc. of 8 *N* chromium trioxide solution.[27] The resultant oil (325 mg.) was purified by chromatography on 40 g. of neutral alumina and elution with petroleum ether. Gas-phase chromatographic analysis of the various crystalline fractions (70 mg.) showed that none contained more than 6–9% of the *cis*-decalone XXIII as a contaminant. Recrystallization of the solid *trans*-decalone XXII from pentane at low temperatures afforded the pure isomer, m.p. 103–105°, λ_{max}^{KBr} 5.88 μ; R.D. (Fig. 2) in methanol (*c* 0.13): $[\phi]_{589}$ +84°, $[\phi]_{307}$ +2500°, $[\phi]_{290}$ 0°, $[\phi]_{267}$ −3160°, $[\phi]_{250}$ −2690°.

Anal. Calcd. for $C_{14}H_{24}O$: mol. wt., 208. Found: mol. wt., 208 (mass spec.). Further elution with ether–petroleum ether (1:4) yielded 170 mg. of recovered octalone XVIII.

(29) A. L. Wilds, R. M. Nowak, and K. E. McCaleb, *Org. Syn.*, **37**, 18 (1957).

(30) See J. E. Starr in C. Djerassi, Ed., "Steroid Reactions: An Outline for Organic Chemists," Holden-Day, San Francisco, Calif., Chapter 7.

[CONTRIBUTION FROM THE CHANDLER LABORATORIES OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

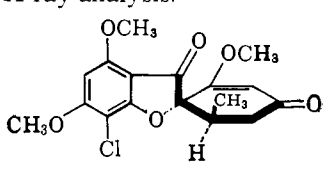
A New Synthesis of Cyclohexenones: The Double Michael Addition of Vinyl Ethynyl Ketones to Active Methylene Compounds. Application to the Total Synthesis of *dl*-Griseofulvin[1]

BY GILBERT STORK AND MARIA TOMASZ

RECEIVED AUGUST 19, 1963

It is shown that certain vinyl ethynyl ketones can undergo Michael addition with suitable molecules to form cyclohexenones. This new synthesis, applied to the specific case of the hitherto unknown ethoxyethynyl vinyl ketones, has been used to synthesize the antibiotic griseofulvin.

The important orally active antifungal antibiotic griseofulvin (I) has established itself in medicine over the last few years.[2] Originally isolated from *penicillium griseofulvum*,[3] the antibiotic was eventually shown to have the structure[4] and stereochemistry[5] indicated in I. This stereochemistry has now been confirmed by X-ray analysis.[6]



I

Two of the interesting features of griseofulvin which caught our attention when we began considering possible routes to its total synthesis were the presence of the spiro system formed by the two ketonic rings and the fact that one of the rings is the enol ether of an *unsymmetrical* β-diketone. Should it be possible to construct cyclohexenone derivatives by double Michael reactions involving the addition of a suitable active methylene compound to a cross-conjugated vinyl ethynyl ketone (*cf.* A), the specific use of the coumaranone II as the active methylene compound and of methoxyethynyl propenyl ketone IV, R = CH_3, as the acceptor could produce directly the griseofulvin structure (we will defer a discussion of the stereochemical problem at this point).

It was especially attractive that such a process would lead to the proper enol ether as well as allow the synthesis of the griseofulvin system in essentially one operation. The simplicity of the scheme served to emphasize that a number of serious problems had to be resolved before its success could be contemplated. The most serious of these problems were: (1) Alkoxyethynyl ketones were still unknown in spite of attempts

(1) Preliminary communication: G. Stork and M. Tomasz, *J. Am. Chem. Soc.*, **84**, 310 (1962).

(2) For a recent review, see J. F. Grove, *Quart. Rev.* (London), **17**, 1 (1963).

(3) A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, **33**, 240 (1939).

(4) J. F. Grove, J. McMillan, T. P. C. Mulholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3977 (1952).

(5) J. McMillan, *ibid.*, 1823 (1959).

(6) W. A. C. Brown and G. A. Sim, *ibid.*, 1050 (1963).