X (80 mg.) was heated under reflux with 1 cc. each of methanol and 2 *N* hydrochloric acid for 1 hr. or for 20 min. with 4 cc. of 5% methanolic potassium hydroxide solution. The isomerization product was purified by distillation at 105–110° at 15 mm., whereupon it exhibited $\lambda_{\max}^{\text{liquid film}}$ 5.81 μ; R.D. (Fig. 5) in methanol (*c* 0.097): $[\alpha]_{700}$ −38°, $[\alpha]_{589}$ −33°, $[\alpha]_{400-375}$ −51° (broad trough), $[\alpha]_{305}$ +335°, $[\alpha]_{265}$ −565°.

*Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92; O, 9.62. Found: C, 79.72; H, 10.82; O, 9.22.

**(+)-Δ$^6$-*trans*-4,4,9-Trimethyl-3-octalone (XXI).**—To an ice-cold solution of 300 mg. of (+)-Δ$^6$-*trans*-4,4,9-trimethyl-3-octalol (XIX)[52] in 5 cc. of acetone was added dropwise 0.4 cc. of 8 *N* chromic acid solution.[53] After standing for 3 minutes, the solution was poured into 60 cc. of water and extracted well with ether to yield, after washing, drying and evaporating, 290 mg. of oil. Chromatography on 15 g. of Merck acid-washed alumina and elution with hexane–benzene (4:6) furnished 280 mg., which was distilled at a bath temperature of 120–130° and 6 mm. to give 260 mg. of colorless oil, $\lambda_{\max}^{\text{liquid film}}$ 5.85 and 6.01 μ; R.D. (Fig. 3) in methanol (*c* 0.104): $[\alpha]_{700}$ +71°, $[\alpha]_{589}$ +133°, $[\alpha]_{310}$ +1190°, $[\alpha]_{265}$ +43°. The analytical sample was broken in transit and no new analysis was secured. The 2,4-dinitrophenylhydrazone was recrystallized several times from methanol–chloroform and was obtained as a yellow-orange micro-crystalline powder, m.p. 147.5–149°.

*Anal.* Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.48. Found: C, 61.48; H, 6.23.

**(+)-*trans*-4,4,9-Trimethyl-3-decalone (XXII).**—The trimethyloctalol XIX[52] (400 mg.) was hydrogenated with platinum oxide in 5 cc. of ethanol in a microhydrogenation apparatus. After consumption of 50 cc. of hydrogen (calcd. 54 cc.), the catalyst was filtered, the solvent removed and the solid residue was recrystallized from aqueous methanol and sublimed at 70° and 0.1 mm. to give 367 mg. of colorless needles of (+)-*trans*-4,4,9-trimethyl-3-decalol (XX), m.p. 87–89°, $[\alpha]_D$ +78° (*c* 0.3 in dioxane). This alcohol, just like the octalol XIX, showed a positive plain dispersion curve rising to about 250° at 275 mμ.

*Anal.* Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.58; H, 12.28.

The above decalol XX (310 mg.) was oxidized exactly as described above for the oxidation of the octalol XIX and afforded after chromatographic purification and distillation at 100° and 2 mm., 268 mg. of (+)-*trans*-4,4,9-trimethyl-3-decalone (XXII), $\lambda_{\max}^{\text{liquid film}}$ 5.82 μ; R.D. (Fig. 3) in methanol (*c* 0.154): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +49°, $[\alpha]_{320}$ +438°, $[\alpha]_{275}$ −133°.

*Anal.* Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.03; H, 10.93.

The 2,4-dinitrophenylhydrazone crystallized as orange leaflets, m.p. 158–159° from methanol–chloroform.

*Anal.* Calcd. for $C_{19}H_{26}N_4O_4$: C, 60.94; H, 7.00; N, 14.96; O, 17.09. Found: C, 60.50; H, 6.69; N, 15.11; 0.17.22.

**(−)-*cis*-9-Methyl-8-methoxycarbonyl-3-decalone (XVII)**,[43] R.D. (Fig. 2) in methanol (*c* 0.091): $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ −11°, $[\alpha]_{400}$ −31°, $[\alpha]_{312.5}$ +104°, $[\alpha]_{270}$ −374°, $[\alpha]_{260}$ −352°, $[\alpha]_{255}$ −569°.

**(+)-*cis*-9-Methyl-1-decalone (XVIII)**,[49] R.D. (Fig. 2) in methanol (*c* 0.0566): $[\alpha]_{700}$ +5°, $[\alpha]_{589}$ +16°, $[\alpha]_{312.5}$ +1350°, $[\alpha]_{275}$ −1695°, $[\alpha]_{255}$ −1345°.

***trans*-5,9-Dimethyl-3-decalone (XXIV)**,[55] R.D. (Fig. 3) in dioxane (*c* 0.159): $[\alpha]_{700}$ +24°, $[\alpha]_{589}$ +20°, $[\alpha]_{317.5}$ −915°, $[\alpha]_{285}$ +897°, $[\alpha]_{280}$ +860°.

**(+)-*trans*-3-Keto-9-methyl-Δ$^{1,6}$-hexahydronaphthalene (II)**,[12,54] R.D. (Fig. 4) in dioxane (*c* 0.059): $[\alpha]_{700}$ +149°, $[\alpha]_{589}$ +220°, $[\alpha]_{380}$ +1340°, $[\alpha]_{370}$ +1105°, $[\alpha]_{362.5}$ +1270°, $[\alpha]_{351.25}$ +575°, $[\alpha]_{337.5}$ +228°, $[\alpha]_{331.25}$ +497°, $[\alpha]_{325}$ +363°, $[\alpha]_{275}$ +2130°.

**(+)-*trans*-3-Keto-4,4,9-trimethyl-Δ$^{1,6}$-hexahydronaphthalene (XXIII)**,[52] R.D. (Fig. 4) in dioxane (*c* 0.151 (700–345 mμ), 0.033 (350–300 mμ)): $[\alpha]_{700}$ +150°, $[\alpha]_{589}$ +228°, $[\alpha]_{380}$ +1265°, $[\alpha]_{365}$ +966°, $[\alpha]_{360}$ +1030°, $[\alpha]_{350}$ +454°, $[\alpha]_{345}$ +700°, $[\alpha]_{337.5}$ +391°, $[\alpha]_{300}$ +1615°; R.D. in octane (*c* 0.137 (700–350 mμ), 0.029 (375–320 mμ)): $[\alpha]_{700}$ +152°, $[\alpha]_{589}$ +224°, $[\alpha]_{385}$ +1215°, $[\alpha]_{375}$ +785°, $[\alpha]_{365}$ +1520°, $[\alpha]_{355}$ +445°, $[\alpha]_{350}$ +817°, $[\alpha]_{342.5}$ +328°, $[\alpha]_{332.5}$ +915°, $[\alpha]_{327.5}$ +770°, $[\alpha]_{320}$ +1140°.

**β-5-(*trans*-2,5-Dimethyl-6-carboxy-1-decalone)-propionic acid (XXVII)**,[58] R.D. (Fig. 5) in dioxane (*c* 0.10): $[\alpha]_{700}$ +12°, $[\alpha]_{589}$ +26°, $[\alpha]_{500}$ +34°, $[\alpha]_{315}$ −670°, $[\alpha]_{280}$ +670°.

DETROIT, MICH.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

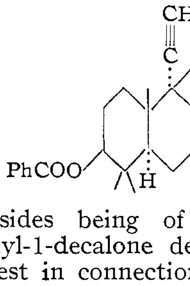
# Syntheses in the Terpene Series. VI.[1] Synthesis of 10-Methyl-1-decalone. The Stereochemical Stability Relationship in the 9-Methyldecalin Series

BY FRANZ SONDHEIMER AND DAVID ROSENTHAL[2]

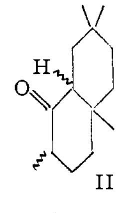
RECEIVED JANUARY 25, 1958

2,7,7,10-Tetramethyl-1-decalone (II) is required as an intermediate for the synthesis of pentacyclic triterpenes. As a model, 10-methyl-1-decalone has been synthesized from 10-methyl-Δ$^{1(9)}$-octal-2-one (VII) by a four-step sequence. This ketone was obtained as an equilibrium mixture which has been shown to contain 40% of the *cis* isomer XII and 60% of the *trans* isomer XIII, through conversion to a mixture of the *cis* and *trans* isomers of 9-methyldecalin. On the other hand, the reduction of 10-methyl-Δ$^{1(9)}$-octal-2-one (VII) with lithium in liquid ammonia was found to give a saturated ketone containing at least 95% of *trans*-10-methyl-2-decalone (XXIV). The significance of these results in connection with the stereochemical stability relationship in the 9-methyl-decalin series is discussed.

In the previous paper of this series,[1] the stereospecific synthesis of 1,1,6α,10β-tetramethyl-5α-ethynyl-*trans*-decalin-2β,5β-diol 2-monobenzoate (I) was described. This compound appears to be a potentially useful building block for the construction of the pentacyclic triterpenes. For instance condensation with 2,7,7,10-tetramethyl-1-decalone (II), preferably the *cis*-decalin isomer, will give an acetylenic 1,4-glycol which should be convertible to substances belonging to the β-amyrin group of triterpenes. It was for this reason that we were interested in developing a synthesis of derivatives of 10-methyl-1-decalone of type II.



I



II

Besides being of synthetic importance, 10-methyl-1-decalone derivatives of type II are of interest in connection with the question whether the *cis* or the *trans* isomer will be the more stable.

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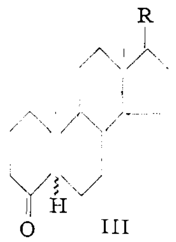
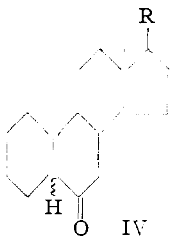
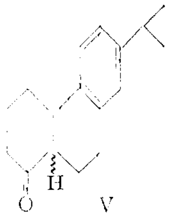
[1] For Part V, see F. Sondheimer and D. Elad, THIS JOURNAL, **80**, 1967 (1958).

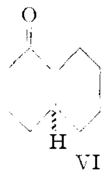
[2] U. S. Public Health Service Postdoctorate Research Fellow, 1956–1957.

In the case of α-decalone it is well known that the *cis* isomer on equilibration is converted almost quantitatively to the *trans* isomer.[3] This is in accord with the fact that *trans*-decalin has a lower heat content than *cis*-decalin by about 2.1 kcal. as judged by direct measurement[4] and by calculations based on conformational analysis.[5] For 9-methyldecalin, conformational analysis predicts the *trans* isomer to have a lower heat content than the *cis* by only 0.8 kcal.,[5] and it was uncertain whether the *cis*-(XII) or the *trans*-(XIII) isomer of 10-methyl-1-decalone would be the more stable since the heat content does not alone determine the stability relationship.[6] Experimentally it was known that in the case of the tetracyclic ketones of type III[7] and IV,[8] the *cis* isomer can be isomerized in high yield to the *trans* isomer, whereas the tricyclic ketone V after equilibration appeared to consist a mixture of the *cis* and the *trans* isomers.[9] The additional rings in these substances could well make the situation different from that in the bicyclic series. In the latter the only carbocyclic example which has been studied quantitatively is 9-methyl-1-decalone (VI), which after equilibration over palladium at 250° has been shown by Ross, *et al.*,[10] to give a mixture consisting of *ca.* 60% of the *cis* and 40% of the *trans* isomer.[11] Rather similar results were obtained on equilibration of related heterocyclic derivatives.[12]


III


IV


V


VI

Since the 9-methyl-1-decalone (VI) studied by Ross, *et al.*,[10] contains no hydrogen at the bridgehead adjacent to the carbonyl group, rather drastic conditions had to be employed for the equilibration and the results at best only show what the situation is at 250°. A much better substance to study is 10-methyl-1-decalone in which the equilibration can be brought about simply at room temperature. However, this compound was unknown when we started our work, despite the fact that the corresponding 2-keto, 3-keto and 4-keto compounds were well known. In this paper we describe the synthesis of 10-methyl-1-decalone as an equilibrium mixture of the *cis*-(XII) and *trans*-(XIII) isomers by a method which should allow also the obtainment of 2,7,7,10-tetramethyl-1-decalone (II), and the determination of the content of each of the two isomers.

The starting material for our work was 10-methyl-$\Delta^{1(9)}$-octal-2-one (VII) which is obtainable by the reaction between 2-methylcyclohexanone and 4-diethylamino-2-butanone methiodide, the preferable condensing agent being potassium *t*-butoxide in *t*-butyl alcohol.[13] After some experimentation, the following four-step route to 10-methyl-1-decalone was developed. Reaction of the unsaturated ketone VII with ethanedithiol in the presence of boron trifluoride etherate[14] produced in nearly quantitative yield the crystalline ethylenethioketal VIII, m.p. 59°, which on treatment with Raney nickel was smoothly converted to 10-methyl-$\Delta^{1(9)}$-octalin (IX).[15] That no double bond shift to the $\Delta^{1(2)}$-position had taken place in the desulfurization step was shown by the fact that the infrared spectrum of the olefin showed a band at 806 cm.$^{-1}$ (trisubstituted double bond), but no band in the 700 cm.$^{-1}$ region characteristic of a disubstituted *cis* double bond.

The olefin IX on being allowed to react with perbenzoic acid took up one molar equivalent of the reagent and produced the epoxide X, probably as a mixture of isomers. Treatment of this epoxide with boron trifluoride etherate under a variety of conditions gave a mixture of products which in every case contained some ketonic material. Under the most favorable conditions, 10-methyl-1-decalone could be isolated in *ca.* 25% yield after chromatography. In addition two by-products were isolated, although not in the pure state. The first, less polar than the methyldecalone, showed an ultraviolet maximum at 234 mμ and contained no hydroxyl or carbonyl groups (infrared). We assign to it the 10-methyl-$\Delta^{1,8}$-hexalin structure XI. The second substance contained a hydroxyl but no carbonyl group (infrared), had no appreciable absorption in the ultraviolet and was an allylic alcohol, since manganese dioxide at room temperature gave an α,β-unsaturated ketone. The alcohol is most probably 10-methyl-$\Delta^{8}$-octal-1-ol (XIV).

That the 10-methyl-1-decalone thus obtained was inhomogeneous was shown by the fact that the crude semicarbazone, isolated in over 90% yield,

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[3] W. Hückel and E. Brinkmann, *Ann.*, **441**, 21 (1925).

[4] G. F. Davies and E. C. Gilbert, THIS JOURNAL, **63**, 1585 (1941).

[5] R. B. Turner, *ibid.*, **74**, 2118 (1952).

[6] *Cf.* N. L. Allinger (*J. Org. Chem.*, **21**, 915 (1956)) for a discussion regarding the dependence of "stability" on both heat content and entropy.

[7] (a) R. Stevenson and L. F. Fieser, THIS JOURNAL, **78**, 1409 (1956); (b) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956).

[8] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

[9] D. Arigoni, J. Kalvoda, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **38**, 1857 (1955); *cf.* G. Stork and A. Burgstahler, THIS JOURNAL, **73**, 3544 (1951).

[10] A. Ross, P. A. S. Smith and A. S. Dreiding, *J. Org. Chem.*, **20**, 905 (1955).

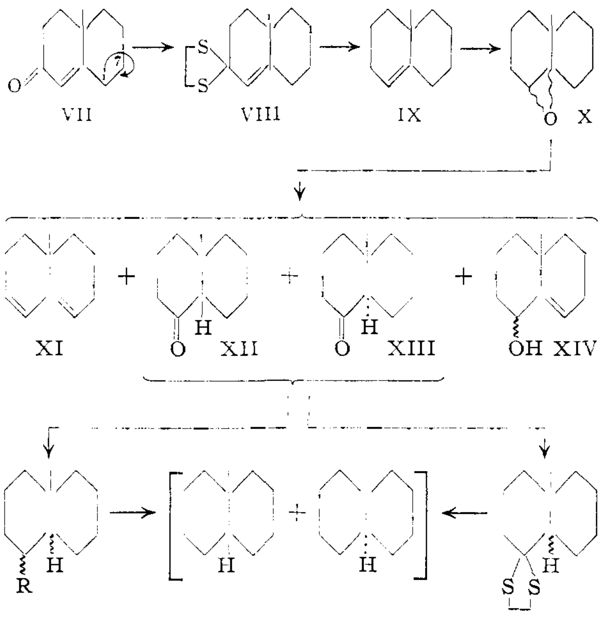
[11] See also C. Djerassi, *et al.* (footnote 7b), for pertinent experiments in the tetrahydroeremophilone series.

[12] W. E. Bachmann, A. Ross, A. S. Dreiding and P. A. S. Smith, *J. Org. Chem.*, **19**, 222 (1954).

[13] (a) E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937); (b) A. S. Hussey, H. P. Liao and R. H. Baker, THIS JOURNAL, **75**, 4727 (1953); (c) W. G. Dauben, J. B. Rogan and E. J. Blanz, *ibid.*, **76**, 6384 (1954).

[14] *Cf.* L. F. Fieser, *ibid.*, **76**, 1945 (1954).

[15] Since we prepared this substance, J. W. Rowe, A. Melera, D. Arigoni, O. Jeger and L. Ruzicka (*Helv. Chim. Acta*, **40**, 1 (1957)) have reported its synthesis by a different route.



XVa, R = OH
b, R = Br
c, R = OTs

showed m.p. 198-203° and gave a pure derivative (m.p. 209-211°) only after many crystallizations.[16a,16b] Cleavage of this pure derivative with pyruvic acid[17] regenerated the ketone which had an infrared spectrum completely identical with that of the original material and on reconversion to the semicarbazone again yielded a crude derivative with m.p. 198-203°. These results indicate that the original ketone is a mixture of the *cis*-(XII) and *trans*-(XIII) isomers.[18] The semicarbazone of one of the two isomers is obtained by the crystallization process and this on treatment with pyruvic acid undergoes equilibration and regenerates the original mixture. That this is indeed the equilibrium is shown by the fact that the infrared spectrum of the ketone is not changed when the latter is boiled with sodium ethoxide in ethanol and repurified.

Attempts to determine the proportion of XII and XIII in the mixture by direct methods, including the use of vapor phase chromatography, were unsuccessful. An indirect method was therefore employed. Reduction of the ketone with lithium aluminum hydride gave the corresponding 10-methyl-1-decalol mixture XVa[19] which was converted directly with phosphorus tribromide to the bromides XVb. Reduction by means of palladium-on-zinc and hydriodic acid in acetic acid, excellent conditions for replacing bromine by hydrogen,[20] then gave a mixture of the *cis*-(XVI) and *trans*-(XVII) isomers of 9-methyldecalin.[21] Both these isomers have been thoroughly studied by Dauben, *et al.*,[22] who have recorded their infrared spectra. Professor Dauben kindly provided us with samples of each of the pure isomers XVI and XVII. We found that of the several differences in their infrared spectra (liquid film), the most diagnostic was a sharp band which appeared at 11.87 $\mu$ in the *cis* and at 12.03 $\mu$ in the *trans* isomer with the same intensity. In synthetic mixtures of the two isomers both bands appeared as well resolved maxima. A mixture of unknown composition could therefore be analyzed; the approximate composition could be estimated from the relative intensities of these bands and synthetic mixtures were then prepared until the spectrum was identical with that of the sample under investigation. In this way it was found that the 9-methyldecalin mixture obtained by the reduction of the bromide XVb contained 40% of the *cis* and 60%[23] of the *trans* isomer. This identity not only indicated the relative proportions of the *cis* and *trans* isomers in the equilibrium mixture of 10-methyl-1-decalone but also proved that no rearrangement in the carbon skeleton had occurred during the treatment of the epoxide X with boron trifluoride.

The 10-methyl-1-decalone equilibrium mixture on being converted to the corresponding ethylenethioketal XVIII and then treated with Raney nickel likewise gave a mixture of 9-methyldecalins containing 40% of the *cis*-(XVI) and 60%[23] of the *trans*-(XVII) isomer. This confirms the results obtained above, but in this case the amounts of the two isomers in the hydrocarbon mixture are not necessarily an indication of the composition of the ketones XII and XIII from which it was derived. It has been shown by Fieser and Stevenson[7a] that coprostan-4-one (XIX) gives the ethylenethioketal of cholestan-4-one (XXII) despite the fact that XIX is not inverted by the boron trifluoride used in the reaction. This was explained by postulating that XX and XXI are intermediates, *viz.*, that the asymmetric center at C-5 is destroyed and regenerated. In fact, in contrast to the ketones XII and XIII, both coprostan-4-one and cholestan-

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[16] (a) After completion of our work, U. Ghatak, N. N. Saha and P. C. Dutta (THIS JOURNAL, **79**, 4487 (1957)) reported the details of another synthesis of 10-methyl-1-decalone, the stereochemistry of which was not discussed. Rather surprisingly, this ketone was reported to give a quantitative yield of nearly pure semicarbazone. An analytical sample of this semicarbazone (m.p. 209–211°, determined by ourselves), very kindly sent to us by Dr. Dutta, was shown to be identical with ours through non-depression in melting point on admixture. We have repeated the Indian work and have found that the resulting ketone in fact gives the same semicarbazone mixture as does the ketone prepared by our method. The synthesis of the Indian workers suffers from the disadvantage that one of the steps, the conversion of 2-methyl-1-acetylcyclohexene to 4-carbethoxy-10-methyldecalin-1,3-dione proceeds in only *ca.* 5–10% yield (W. E. Bachmann, *et al.*, footnote 12; confirmed in these laboratories). (b) C. Djerassi and D. Marshall (THIS JOURNAL, **80**, 3986 (1958)) have carried out a synthesis of optically active 10-methyl-1-decalone by a route different from ours and obtained the apparently pure *cis* isomer, as well as the equilibrium mixture. We are indebted to Professor Djerassi for informing us of his results prior to publication.

[17] *Cf.* E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

[18] The equilibrium mixture is probably not formed directly in the boron trifluoride reaction, but is attained during the alumina chromatography which is employed for the purification of the ketone (*cf.* H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957)).

[19] D. S. Noyce and D. B. Denney (THIS JOURNAL, **72**, 5743 (1950)) have shown that an asymmetric center next to a carbonyl group is unaffected on lithium aluminum hydride reduction. In accord with this, D. N. Jones, *et al.* (footnote 8), have found that coprostan-6-one, which with acids or bases is inverted to cholestan-6-one, gives coprostan-$6\beta$-ol on lithium aluminum hydride reduction.

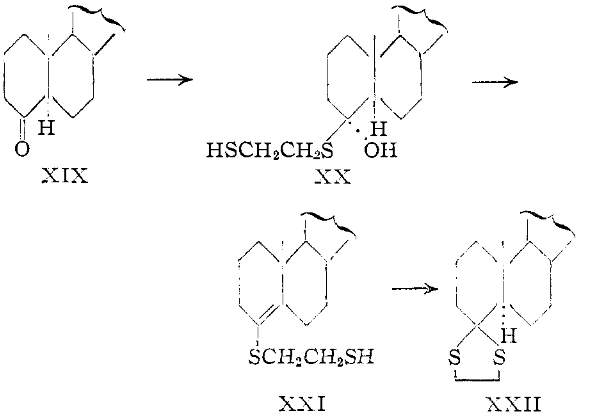
[20] *Cf.* N. Zelinsky, *Ber.*, **31**, 3203 (1898).

[21] An alternative procedure, the conversion of the alcohols XVa to the *p*-toluenesulfonates XVc, followed by lithium aluminum hydride reduction, was unsuccessful since the alcohols XVa were thereby regenerated.

[22] W. G. Dauben, J. B. Rogan and E. J. Blanz, THIS JOURNAL, **76**, 6384 (1954).

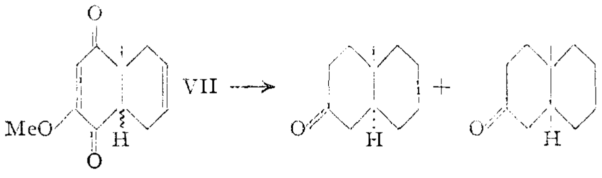
[23] The proportions are rounded off to the nearest 5%, the limit of accuracy of the method.

4-one on thioketal formation and desulfurization yield the *trans*-hydrocarbon cholestane, and this is another demonstration of the difference in relative stability of ketones vicinal to a bridge-head in the 9-methyldecalin and in the steroid series.


XIX XX XXI XXII

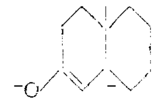
Although the pure semicarbazone of one isomer of 10-methyl-1-decalone was isolated, we cannot say at present whether it is the *cis* or the *trans* isomer. On being subjected to the Huang-Minlon modification of the Wolff-Kishner reduction, a mixture of 9-methyldecalins was obtained containing 55% of the *cis* and 45%[23] of the *trans* isomer. The strongly alkaline conditions of the reduction can of course cause isomerization and the composition of the 9-methyldecalin mixture obtained is dependent on the relative rates of reaction of the hydrazones of *cis*- and *trans*-10-methyl-1-decalone and on their relative rates of reverse enolization.[24]

The present finding that the equilibrium mixture of 10-methyl-1-decalone contains *ca.* 40% of the *cis* and 60% of the *trans* isomer is in marked contrast to the case of α-decalone where the *cis* isomer is almost quantitatively converted to the *trans*.[3] It is in keeping with the results of Ross, *et al.*,[10] obtained with 9-methyl-1-decalone (VI) (referred to above)[25] and with the findings of Woodward, *et al.*,[26] that equilibration of the more complex ketone XXIII gives comparable quantities of the *cis* and the *trans* isomer. On the other hand, the reduction of 10-methyl-$\Delta^{1(9)}$-octal-2-one (VII) with lithium in ammonia has been shown to yield mainly the *trans* isomer XXIV of 10-methyl-2-decalone.[27] Since this type of reduction has been reported to give the thermodynamically more stable products,[28] at least at the position beta to the carbonyl group,[29] it has been assumed by some workers


XXIII XXIV XXV

that in the 9-methyldecalin series in general the *trans* isomer is the more stable. We have repeated the reduction of the unsaturated ketone VII with lithium in ammonia and the total saturated ketone, obtained after reoxidation of the reduction mixture with chromium trioxide, was subjected to the Huang-Minlon modification of the Wolff-Kishner reduction. The infrared spectrum of the 9-methyldecalin thus obtained was nearly identical with that of the pure *trans* isomer and, by comparison with synthetic mixtures of the *cis* and *trans* isomers, must have contained at least 95% of the latter. The same result was obtained when the carbonyl group was removed by Raney nickel treatment of the ethylenethioketal.

The above results can be rationalized in one of two ways. It is possible that the *cis* isomer in the 9-methyldecalin series is of comparable stability to the *trans* only when there is a carbonyl group next to the bridge-head, whereas the *trans* isomer is the stable one when the carbonyl group is further removed.[30,31] An explanation which seems more likely to us is that in all cases are the *cis* and *trans* isomers of 9-methyldecalin derivatives of comparable stability and that reduction of 10-methyl-$\Delta^{1(9)}$-octal-2-one (VII) has not in fact given the most stable configuration at C-9 in a quantitative sense. It is the protonation at the bridge-head of the dianion XXVI which determines the resulting ring junction in the lithium-ammonia reduction of VII.[23] The above-mentioned apparent anomaly


XXVI

may well be a reflection of the fact that the orbital

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[24] *Cf.* (a) C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166 (1956); (b) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); THIS JOURNAL, **78**, 1168 (1956).

[25] The higher proportion (60%) of *cis* isomer obtained by Ross, *et al.*, with VI may perhaps be due to the fact that their experiment had to be carried out at 250°. At increased temperatures the entropy term in the equation $\Delta F = \Delta H - T\Delta S$ becomes of greater importance and since the *cis* isomer has a larger $S$ value than the *trans*, the former should be comparatively more favored at elevated temperatures.

[26] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

[27] M. Yanagita, K. Yamakawa, A. Tahara and H. Ogura, *J. Org. Chem.*, **20**, 1767 (1955).

[28] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954). See also C. Djerassi and G. H. Thomas, THIS JOURNAL, **79**, 3835 (1957).

[29] The sterochemistry of the α-position is determined by the ketonization of the enolate originally formed in the lithium-ammonia reduction step and the less stable configuration at the α-carbon atom may result since ketonization proceeds by proton attack at the less hindered side of the enolic double bond (H. E. Zimmerman, footnote 24b; A. J. Birch, H. Smith and R. E. Thornton, *Chemistry & Industry*, 310 (1956)). From a practical point of view it is of course unimportant if the less stable configuration at the α-position results, since subsequent equilibration will give the more stable isomer.

[30] *Cf.* W. Klyne, *Experientia*, **12**, 119 (1956).

[31] A somewhat similar situation might seem to exist in the hydrindane series, where the *trans* isomer of hydridane and of 2-hydrindanone appear to be more stable than the *cis* as judged by the heats of combustion, whereas 1- and 4-hydrindanone (with the keto group next to the bridge-head) on equilibration give mainly the *cis* isomers [for leading references see R. P. Linstead, *Ann. Rep. Chem. Soc.* (*London*), 305 (1935)]. The explanation given for this by N. L. Allinger (footnote 6) is not that the position or absence of the carbonyl group is involved, but that the heat of combustion values are not alone indicative of the actual stability relationships since the entropy effect is neglected. Alternatively it is possible that the *cis* isomer is favored in the case of 1- and 4-hydrindanone since the conformation of the *cis* forms is favorable for the occurrence of hydrogen bonding (*cf.* R. A. Raphael in "Chemistry of Carbon Compounds," Editor E. H. Rodd, Elsevier Publishing Co., Amsterdam, 1953, Vol. IIA, p. 311). However neither of these explanations can be used to rationalize the results in both the case of 9-methyl-1-decalone and of 10-methyl-1-decalone.

occupied by the unshared electron pair at the bridge-head in the carbanion XXVI is not exactly equal in size to a C–H bond and a true equilibrium product is therefore not formed in this type of reduction when the two possible products are similar in energy content.

Since a method had been worked out for analyzing mixtures of *cis*- and *trans*-9-methyldecalin, we made use of it for quantitatively determining the course of the catalytic hydrogenation of 10-methyl-$\Delta^{1(9)}$-octal-2-one (VII), previously shown to give both the *cis*-(XXV) and *trans*-(XXIV) isomers of 10-methyl-2-decalone.[26] The total reaction product, obtained by the hydrogenation of VII in ethanol over a palladium–charcoal catalyst, was subjected to Wolff–Kishner–Huang-Minlon reduction, whereby a mixture containing 80% of *cis*- and 20%[23] of *trans*-9-methyldecalin was obtained. In order to see what effect the carbonyl group in VII has on the course of the hydrogenation, 10-methyl-$\Delta^{1(9)}$-octalin (IX) was hydrogenated under the same conditions. This experiment yielded 55% of *cis*- and 45%[23] of *trans*-9-methyldecalin and the presence of the keto group in VII therefore favors addition of hydrogen from the $\beta$-side.

Halsall and Thomas[32] already have described the synthesis of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (the 7,7-dimethyl derivative of VII) and this substance should be convertible to *cis*- and *trans*-7,7,10-trimethyl-1-decalone and thence by methylation to the required *cis* and *trans* isomer of 2,7,7,10-tetramethyl-1-decalone (II) by a method analogous to that described in this paper. This work is being continued.

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## Experimental[33]

**10-Methyl-$\Delta^{1(9)}$-octal-2-one (VII)** was prepared from 2-methylcyclohexanone and 4-diethylamino-2-butanone methiodide with potassium *t*-butoxide in *t*-butyl alcohol according to Hussey, *et al.*,[13b] except that the ratio of the ketone and methiodide was 2:1, essentially as recommended by Dauben, *et al.*[13c] Simple distillation gave a 46% yield of the crude ketone VII, b.p. 105–125° (6.5 mm.), the ultraviolet light absorption properties of which ($\lambda_{max}$ 239 m$\mu$, $\epsilon$ 7,300) showed it to be only *ca.* 50% pure. Further distillation through a 45-cm. helices-packed Fenske column gave a 32% over-all yield of the ketone VII, b.p. 106–116° (1 mm.), the ultraviolet spectrum of which showed it to be *ca.* 70% pure and which could be used in the next step. A completely pure sample ($\lambda_{max}$ 239 m$\mu$, $\epsilon$ 14,800) was obtained by conversion to the semicarbazone, one crystallization from ethanol to give material with m.p. 200–202° and regeneration by means of pyruvic acid in aqueous acetic acid.[17]

**10-Methyl-$\Delta^{1(9)}$-octal-2-one Ethylenethioketal (VIII).**—Boron trifluoride etherate (1.5 cc.) was added to a mixture of 3.3 g. of the pure unsaturated ketone VII and 3.0 cc. of ethanedithiol, with ice cooling and the mixture was then allowed to stand at room temperature for 10 minutes. Methanol (15 cc.) was added, the mixture was cooled in ice and scratched. The thioketal VIII (4.8 g., 99%) which thereby crystallized showed m.p. 52–55°. Crystallization from methanol–pentane gave the analytical sample, m.p. 58–59°, $\lambda_{max}$ 6.06 $\mu$ (weak) (double bond), no other bands in the carbonyl region.

*Anal.* Calcd. for $C_{13}H_{20}S_2$: C, 64.94; H, 8.39; S, 26.67. Found: C, 64.94; H, 8.35; S, 26.47.

When the reaction with ethanedithiol was carried out with the ketone VII of 70% purity, the yield of crystalline thioketal was 61% (87% based on pure ketone).

**10-Methyl-$\Delta^{1(9)}$-octalin (IX).**—A mixture containing *ca.* 20 g. of Raney nickel (W-2) and 2.9 g. of the thioketal VIII in 200 cc. of absolute ethanol was boiled under reflux for 15 hr. The nickel was removed, washed with ethanol and the combined filtrates were distilled off at 120 mm. through a Vigreux column. Distillation of the residue gave 1.1 g. (61%) of the olefin IX, b.p. 92–94° (35 mm.), $n^{22}_{D}$ 1.4929, $\lambda_{max}$ 6.03 and 12.41 $\mu$ (trisubstituted double bond); reported[15] b.p. 76–77° (10 mm.), $n^{21}_{D}$ 1.4926.

*Anal.* Calcd. for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.83; H, 11.93.

***cis*- and *trans*-10-Methyl-1-decalone (XII and XIII).**—10-Methyl-$\Delta^{1(9)}$-octalin (IX) (11.1 g.) was added slowly with ice cooling (temperature not above 8°) to 200 cc. of a standard solution of perbenzoic acid containing 55.6 mg. of the peracid per cc. The solution was then kept at *ca.* 8° by ice-water cooling. Aliquots (0.100 cc. each) were removed at intervals and titrated against standard sodium thiosulfate solution. The reaction was 80% complete after 15 minutes, 90% after 30 minutes, 95% after 60 minutes and 98% after 90 minutes. After 2 hr. the solution was washed with sodium hydroxide solution and saturated sodium chloride solution and then was dried over potassium carbonate and evaporated. The residual crude epoxide X (12.0 g.), which showed no hydroxyl or carbonyl bands in the infrared, was used directly in the next step. It was dissolved in 125 cc. of chloroform, cooled to 5° in an ice-bath and 10 cc. of boron trifluoride etherate was added dropwise during 10 minutes with magnetic stirring and continued cooling. The solution was kept at 5° for 10 minutes longer and a 10% sodium carbonate solution then was added. The aqueous phase was extracted twice with chloroform and the combined organic extracts, after being washed with saturated salt solution, were dried and evaporated. The residue then was chromatographed on 500 g. of alumina. The fraction (6.24 g.) eluted with ether on distillation through a small Vigreux column yielded 2.9 g. (24%) of 10-methyl-1-decalone as a mixture of the *cis*-(XII) and *trans*-(XIII) isomers, b.p. 126–130° (26 mm.), $n^{21}_{D}$ 1.4901; $\lambda_{max}$ (principal bands) 3.36, 5.84, 7.25, 7.33, 7.65, 7.85, 8.00, 8.30, 8.67, 9.16, 9.53, 9.60, 10.56, 10.80, 11.08, 12.05, and 12.22 $\mu$.

*Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.45; H, 10.87.

**The semicarbazone** was obtained in 93% yield as a solid with m.p. 198–203°. On crystallization from ethanol, the m.p. steadily rose until it reached the constant value 209–211°. There was no depression on admixture with a sample (m.p. 209–211°) provided by Dr. Dutta.

*Anal.* Calcd. for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.50; H, 9.60; N, 18.60.

The purified semicarbazone (218 mg.), anhydrous sodium acetate (237 mg.), freshly distilled pyruvic acid (200 mg.), glacial acetic acid (5 cc.) and water (1 cc.) were heated at 90° for 30 minutes. The mixture was cooled, poured into excess of sodium bicarbonate solution and the ketone was extracted with ether. After evaporation of the ether the regenerated ketone was distilled at 35 mm. and yielded 137 mg. (84%) of material, $n^{23}_{D}$ 1.4891, the infrared spectrum of which was completely identical with that of the original ketone. On being reconverted to the semicarbazone, the crude derivative again showed m.p. 198–203°. The infrared spectrum of the regenerated ketone was unchanged

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(32) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).

(33) Melting points and boiling points are uncorrected. The alumina used for all chromatograms was prepared from Alcoa activated alumina, grade F-20 (Aluminum Co. of America, Pittsburgh, Pa.) through neutralization by means of ethyl acetate and reactivation for 4 hr. at 200° (35 mm.). Ultraviolet spectra were measured in 95% ethanol solution on a Unicam model S.P. 500 spectrophotometer and infrared spectra in carbon disulfide solution (excepting for the mixtures of *cis*- and *trans*-9-methyldecalin which were taken as liquid films) on a Baird double beam recording spectrophotometer. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

after it (100 mg.) had been boiled with a solution of 84 mg. of sodium in 10 cc. of absolute ethanol for 2 hr., isolated with ether and then redistilled (recovery, 73 mg.).

**The 2,4-dinitrophenylhydrazone** first showed m.p. 148–155°, which on repeated crystallization from ethanol–ethyl acetate was raised to 159–161°.

*Anal.* Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 59.08; H, 6.33; N, 16.48.

The chromatography fractions eluted with petroleum ether gave a brown color with tetranitromethane and showed $\lambda_{max}$ 234 m$\mu$, $\epsilon$ 7,500, no hydroxyl or carbonyl bands in the infrared; they probably consist of crude 10-methyl-$\Delta^{1,8}$-hexalin (XI). The fractions eluted with ether–methanol (99:1) showed a hydroxyl band at 2.92 $\mu$, but no carbonyl band in the infrared and probably contain 10-methyl-$\Delta^8$-octal-1-ol (XIV); on oxidation with manganese dioxide in chloroform at room temperature overnight, an $\alpha,\beta$-unsaturated ketone was obtained (strong band at 6.02 $\mu$), which absorbed 86% of the theoretical amount of hydrogen on catalytic hydrogenation and gave a saturated ketone (strong band at 5.84 $\mu$).

**Conversion of *cis*- and *trans*-10-Methyl-1-decalone (XII and XIII) to *cis*- and *trans*-9-Methyldecalin (XVI and XVII).** (a) *Via* **the Ethylenethioketals XVIII.**—The equilibrium mixture of the ketones XII and XIII (177 mg.) was mixed with 0.2 cc. of ethanedithiol and 3 drops of boron trifluoride-ether complex. After 10 minutes at room temperature, 5 cc. of methanol was added and the mixture was cooled. The methanol layer was separated and the crude thioketal layer was boiled under reflux for 10 hr. with 10 cc. of methanol and 2 g. of Raney nickel (W-2). The metal was removed, the filtrate was concentrated to *ca.* 5 cc. and water and pentane were added. The aqueous layer was washed twice more with pentane and the combined pentane extracts were dried, evaporated through a Vigreux column and the residue, redissolved in a little pentane, was filtered through 15 g. of alumina. The pentane eluates were evaporated and the residue was distilled in a sublimation tube at 90–100° (35 mm.). The infrared spectrum of the resulting hydrocarbon mixture (145 mg.) was completely identical with that of a synthetic mixture containing 40% of *cis*- and 60% of *trans*-9-methyldecalin.

(b) *Via* **the 10-Methyl-1-decalols (XVa) and the 1-Bromo-10-methyldecalins (XVb).**—The equilibrium mixture of the ketones XII and XIII (390 mg.) dissolved in 10 cc. of dry ether was added to 100 mg. of lithium aluminum hydride in 10 cc. of ether. The mixture was heated under reflux for 1 hr., the excess reagent was decomposed by the dropwise addition of just sufficient water and the salts were removed and washed with ether. The filtrates on being dried and evaporated yielded the alcohol mixture XVa, the infrared spectrum of which showed a hydroxyl band at 2.90 $\mu$, but no carbonyl bands. It was allowed to stand overnight with 325 mg. of freshly distilled phosphorus tribromide in 10 cc. of dry benzene. Addition of ice and isolation with ether in the usual way produced the bromide mixture XVb (372 mg.) which was reduced directly.

A palladium-on-zinc reagent was prepared as follows (*cf.* Zelinsky[20]): 10 g. of zinc powder was washed with 20 cc. of ethanol. It was then triturated with 20 cc. of 10% sulfuric acid until hydrogen was evolved vigorously, the acid was decanted and the metal was washed thoroughly with distilled water. A solution prepared by dissolving 200 mg. of palladium chloride in 20 cc. of distilled water and 10 drops of concd. hydrochloric acid was added dropwise with stirring to a suspension of the zinc in water during 5 minutes and the mixture was stirred for a further 5 minutes. The reagent was then collected and washed four times with methanol. The above bromide mixture dissolved in 10 cc. of glacial acetic acid and separately 10 cc. of concd. hydriodic acid (d. 1.70) was then added independently from two different dropping funnels to the freshly prepared palladium–zinc reagent in 20 cc. of acetic acid. The mixture was stirred vigorously throughout and the two liquids were added slowly during 30 minutes in such a way that vigorous evolution of hydrogen occurred all the time during the addition. After being allowed to stir for another 4 hr. at room temperature and then for 30 minutes at 50°, the mixture was cooled. The metal was removed and washed well with water and ether and the organic material was isolated with ether in the usual way. The hydrocarbon residue remaining after removal of the ether was dissolved in pentane and filtered through a column of 20 g. of alumina. The pentane was evaporated and the residue was distilled at 90–100° (35 mm.) in a sublimation tube. The infrared spectrum of the resulting 9-methyldecalin mixture (210 mg.) showed it to consist of 40% of the *cis* and 60% of the *trans* isomer in addition to a very small amount of unchanged bromide XVb.

**Wolff–Kishner Reduction of the 10-Methyl-1-decalone Semicarbazone of M.p. 209–211°.**—The purified semicarbazone (100 mg.), sodium hydroxide (190 mg.), 90% hydrazine hydrate (0.5 cc.) and diethylene glycol (3 cc.) were heated for 0.5 hr. under reflux at 190°, the condenser was then removed and the internal temperature was raised to 210° to remove the excess of water. The condenser was replaced and the solution was boiled under reflux for another 3 hr. It was then cooled, 5 cc. of water was added and the hydrocarbons were extracted with 3 × 5 cc. of pentane. The pentane extracts were washed with dilute hydrochloric acid and water and were then dried and evaporated. The residue after being passed through 10 g. of alumina in pentane and distilled at 90–100° (35 mm.) as usual gave a 9-methyldecalin mixture, the infrared spectrum of which showed it to contain 55% of the *cis* and 45% of the *trans* isomer.

**Reduction of 10-Methyl-$\Delta^{1(9)}$-octal-2-one (VII) with Lithium in Liquid Ammonia.**—The pure unsaturated ketone VII (1.0 g.; regenerated from the semicarbazone) dissolved in 5 cc. of dry ether was added dropwise during 5 minutes to a stirred solution of 0.3 g. of lithium in 100 cc. of liquid ammonia. The mixture was then stirred for another 1 hr. after which time ammonium chloride was added until the blue color was discharged. The ammonia was allowed to evaporate, water was added to the residue and the organic material was isolated with ether in the usual way. The residue, the infrared spectrum of which showed it to consist of about equal amounts of saturated ketone and of alcohol, was dissolved in 10 cc. of glacial acetic acid and 0.75 g. of chromic acid in 10 cc. of acetic acid and 0.5 cc. of water was added slowly with cooling and stirring. The mixture was allowed to stand overnight at room temperature, 5 cc. of methanol was added and the product was then isolated with ether. The total residue (0.85 g.) consisted almost entirely of saturated ketone, as judged from its ultraviolet and infrared spectra. A 0.2-g. portion of this saturated ketone was mixed with 0.4 g. of potassium hydroxide, 1 cc. of 90% hydrazine hydrate and 10 cc. of diethylene glycol and the mixture was heated under reflux in an oil-bath maintained at 160° for 1.5 hr. The condenser was set for distillation and the temperature was increased until the internal temperature of the mixture reached 195°, the distillate being collected. Refluxing was then continued for 4 hr. The mixture was cooled, water and the above distillate were added and the product was isolated with ether in the usual manner. The resulting hydrocarbon (0.13 g.), after being passed through alumina in pentane solution and then distilled, showed an infrared spectrum almost indistinguishable from that of pure *trans*-9-methyldecalin. By comparing the spectrum with that of synthetic mixtures of *cis*- and *trans*-9-methyldecalin (5% *cis* and 95% *trans*; 10% *cis* and 90% *trans*) it was shown that the product could not have been contaminated with more than 5% of *cis*-9-methyldecalin. Exactly the same result was obtained when the carbonyl group was removed from the saturated ketone by conversion to the ethylenethioketal and then desulfurization with Raney nickel.

**Catalytic Hydrogenation of 10-Methyl-$\Delta^{1(9)}$-octal-2-one (VII).**—The pure unsaturated ketone VII (0.25 g.; regenerated from the semicarbazone) in 20 cc. of ethanol was shaken in hydrogen over 0.12 g. of a 10% palladium-charcoal catalyst. After 6 minutes the theoretical amount of hydrogen had been taken up and absorption stopped. After 15 minutes, the catalyst was removed, the solvent was evaporated and the residue (0.25 g.) was subjected to the Huang-Minlon modification of the Wolff–Kishner reduction, exactly as described in the preceding experiment. Purification by chromatography and distillation, as usual, then yielded a 9-methyldecalin mixture, the infrared spectrum of which was identical with that of a synthetic mixture containing 80% of the *cis* and 20% of the *trans* isomer.

**Catalytic Hydrogenation of 10-Methyl-$\Delta^{1(9)}$-octalin (IX).**—10-Methyl-$\Delta^{1(9)}$octalin (IX) (0.16 g.) in 20 cc. of ethanol was shaken in hydrogen over 0.12 g. of a 10% palladium–charcoal catalyst. After 30 minutes, 98% of the theoretical amount of hydrogen had been absorbed and uptake stopped.

Removal of catalyst and solvent gave 0.15 g. of a 9-methyldecalin mixture, the infrared spectrum of which showed it to contain 55% of the *cis* and 45% of the *trans* isomer. Exactly the same result was obtained when the hydrogenation was carried out in glacial acetic acid solution.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

# Optical Rotatory Dispersion Studies. XVII.[1] Detection of Conformational Alterations. Effects of Alkyl Groups and Double Bonds in Polycyclic Systems[2]

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Since alterations in conformation in a cyclic system incorporating a carbonyl group change the asymmetric environment, it can be expected that this would be reflected in the rotatory dispersion curve of such ketones. This supposition has now been verified by measurements on a large group of related polycyclic ketones. In particular, it was found that introduction of alkyl groups and double bonds in certain locations have a pronounced effect upon the rotatory dispersion curve of the corresponding unsubstituted ketone and this must be due to conformational distortion of the system. The subtlety of the conformational effects uncovered by the rotatory dispersion approach is illustrated by the pronounced dispersion change accompanying 4,4-dimethylation in 3-keto-5$\alpha$-steroids which is not due to interactions with the angular methyl group at C-10 nor produced by a sole axial substituent located at C-4. The utility of these observations for stereochemical assignments is exemplified in the santonin and butyrospermol series and attention is called to the fact that determination of the rotatory dispersion curve or the rate of condensation with benzaldehyde seems to be a measurement of the same conformational factor operating in polycyclic ketones.

Most of the rotatory dispersion work carried out in this Laboratory[3] has dealt with carbonyl compounds since this chromophore exhibits rather low ultraviolet absorption in a suitable spectral range which permits rotatory dispersion measurements through the region of maximal absorption.[4] The resulting ketonic wave, represented either by a single (saturated ketone or aldehyde) or multiple (usually $\alpha,\beta$-unsaturated ketone) Cotton effect curve,[5] is a consequence of the asymmetric environment in which the carbonyl chromophore has been placed. It is not surprising, therefore, that in cyclic systems, changes in conformation should reflect themselves in the rotatory dispersion curve and isolated examples of this phenomenon have been recorded in some of our past publications.[1,4b,6,7] A sufficient number of measurements on diverse polycyclic compounds have now been carried out so that a detailed discussion is in order and the present paper is concerned with an examination of the effect of alkyl (chiefly methyl) substituents and of double bonds upon the conformation of cyclic ketones and its detection by rotatory dispersion. As will become apparent in the sequel, under certain circumstances the optical rotatory dispersion curve will yield information on conformational distortion which at the present time cannot be secured readily by any other physical tool.

The most notable rotatory dispersion changes attributable to conformational distortion have so far been observed in $\alpha,\beta$-unsaturated ketones. Particularly striking examples are the pair[6] $\alpha$-cyperone (I) and *epi*-$\alpha$-cyperone (II), where the axial isopropenyl grouping of the latter inverts the multiple Cotton effect of the $\Delta^4$-3-ketone, or 8-iso-$\Delta^4$-3-ketosteroids[4b] such as 8-isotestosterone (III) where this same dispersion change is due to the fact that rings B or C must assume a boat conformation in contrast to the all-chair situation obtaining in the usual steroids. Another interesting case is represented by the 6-halo-$\Delta^4$-3-ketosteroids[8] where the axial 6$\beta$-bromine or chlorine atom produces an inversion of the Cotton effect of the unsubstituted $\Delta^4$-3-ketone, while axial fluorine affects the amplitude and resolution of the curve but does not invert it. In order to determine whether steric or electronic factors were primarily responsible for this markedly different behavior between fluorine on the one hand and chlorine or bromine on the other, it was of very considerable interest to measure the rotatory dispersion curves of the recently synthesized[9] epimeric 6-methyltestosterones (IV, V). As shown in Fig. 1, the equatorial 6$\alpha$-methyl group had no effect since the dispersion curve of 6$\alpha$-methyltestosterone (IV) closely follows that of testosterone.[4b] On the other hand, a completely different curve is observed with the axial 6$\beta$-methyl isomer V, its most characteristic feature being the appearance of fine structure in the 370 m$\mu$ region with positive rather than negative rotation values. To that extent, the curve resembles[10] that of 8-isotestosterone (III) and 6$\beta$-chloro- and -bromotestosterone thus suggesting a common con-

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[1] Paper XVI, C. Djerassi and D. Marshall, THIS JOURNAL, **80**, 3986 (1958).

[2] Supported by a research grant (No. CY-2919) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

[3] For review see C. Djerassi, *Bull. soc. chim. France*, 741 (1957), and Abstracts, 15th National Org. Chem. Symposium, Rochester, N. Y., 1957, pp. 12–20.

[4] For details see (a) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955); (b) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

[5] For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

[6] C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

[7] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

[8] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958).

[9] H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

[10] There are changes below 330 m$\mu$ where the 6$\beta$-methyl derivative again moves toward positive rotation values while the two 6$\beta$-halo ketones continue in a negative direction without exhibiting important fine structure. These differences would suggest that the steric factor alone is not the only one entering into the picture.