[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY, DETROIT, MICH.]

Terpenoids. XLVIII.[1] The Absolute Configuration of Eremophilone and Related Sesquiterpenes[2]

BY LEON H. ZALKOW,[3] F. X. MARKLEY AND CARL DJERASSI[4]

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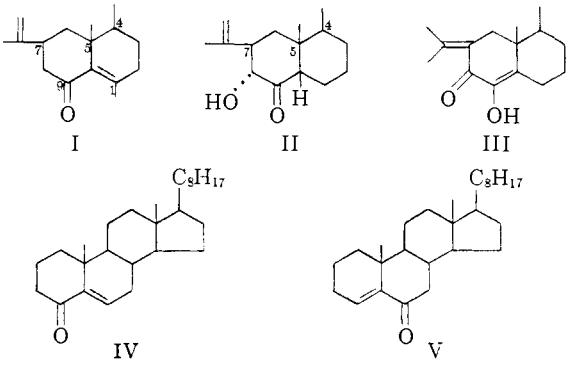
The absolute configurations of eremophilone (I), hydroxydihydroeremophilone (II) and hydroxyeremophilone (III) have been established by the synthesis of a common degradation product, *trans*-5,10-dimethyl-3α-isopropyl-decalone-2 (XXIX), from an intermediate of known absolute configuration. Judging from rotatory dispersion evidence, the carbonyl-containing ring of eremophilone (I) does not exist in a chair conformation. Attention is also directed to the demethoxylation of α-methoxy ketones with calcium in liquid ammonia.

Eremophilone (I) and its close relatives hydroxydihydroeremophilone (II) and hydroxyeremophilone (III) are, biogenetically, among the most interesting sesquiterpenes since they do not follow the isoprene rule. Their skeletal structures were established in a series of investigations by Simonsen, Penfold and their collaborators,[5] while the *relative* configuration of one member of this class, hydroxydihydroeremophilone (II), was settled by X-ray analysis.[6] The most notable feature of the relative stereochemistry of hydroxydihydroeremophilone (II) is the *cis* orientation of the substituents at C-5 and C-7,[7] which stabilizes the *cis* fusion of the two rings. If the ring juncture were *trans*, then there would be present a very unfavorable 1,3-diaxial interaction between the angular methyl group and the isopropenyl substituent. In eremophilone (I) itself, the 1–10 double bond requires a geometrical arrangement, which resembles a *trans*- rather than a *cis*-decalone and the question immediately arises whether the *cis* relationship of the C-5 and C-7 substituents in hydroxydihydroeremophilone (II) applies also to eremophilone (I).



We have already pointed out in an earlier paper[8] that the recorded[9] experimental interrelation of eremophilone (I) and hydroxydihydroeremophilone (II) is stereochemically ambiguous and cannot be used for purposes of stereochemical assignment at C-7 in eremophilone (I). For a proper evaluation (*vide infra*) of the plant biosynthetic precursor of eremophilone (I) it is first of all necessary to settle the absolute configuration of this sesquiterpene. In the absence of relevant chemical interconversions, the simplest approach appeared to be optical rotatory dispersion measurements.

In introducing this approach—comparison of the rotatory dispersion curve of a given optically active chromophore (in this instance a ketone) with that of a reference ketone of known absolute configuration—we have emphasized[8,10,11] that the bicyclic environment of the reference ketone must possess the same relative stereochemistry *as well as identical conformation* as the ketone, whose absolute configuration is to be determined. Δ^5-Cholesten-4-one (IV) and Δ^4-cholesten-6-one (V) represent suitable models for such rotatory dispersion measurements and it was noted[8] that, in agreement with expectation, their rotatory dispersion curves were of mirror image type.[12] Furthermore, it was found[8] that the rotatory dispersion curve of eremophilone (I) was similar to that of Δ^4-cholesten-6-one (V), whereupon it was concluded that the absolute configuration of eremophilone was the antipode of that represented by stereoformula I. This assignment was made[8] with the specific reservation that the isopropenyl group of eremophilone is equatorially oriented (hence involving a *trans* relationship between the

(1) Paper XLVII. C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun and J. N. Shoolery, *J. Org. Chem.*, **25**, in press (1960).

(2) Supported by grant No. RG-3863 from the Division of Research Grants, National Institutes of Health, U. S. Public Health Service.

(3a) Postdoctorate research fellow, 1957–1959. (3b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.

(4) To whom inquiries should be addressed: Department of Chemistry, Stanford University, Stanford, Calif.

(5) For summarizing reviews and leading references see: (a) J. Simonsen and D. H. R. Barton "The Terpenes," Cambridge University Press, New York, N.Y., 1952, Vol. III, pp. 212–224; (b) D. H. R. Barton "The Inaugural Simonsen Lecture," *Proc. Chem. Soc.*, 61 (1958).

(6) D. F. Grant and D. Rogers, *Chemistry & Industry*, 278 (1956); D. F. Grant, *Acta Cryst.*, **10**, 498 (1957).

(7) We are employing a numbering system based on that of the presumed eudalenoid biogenetic precursor.

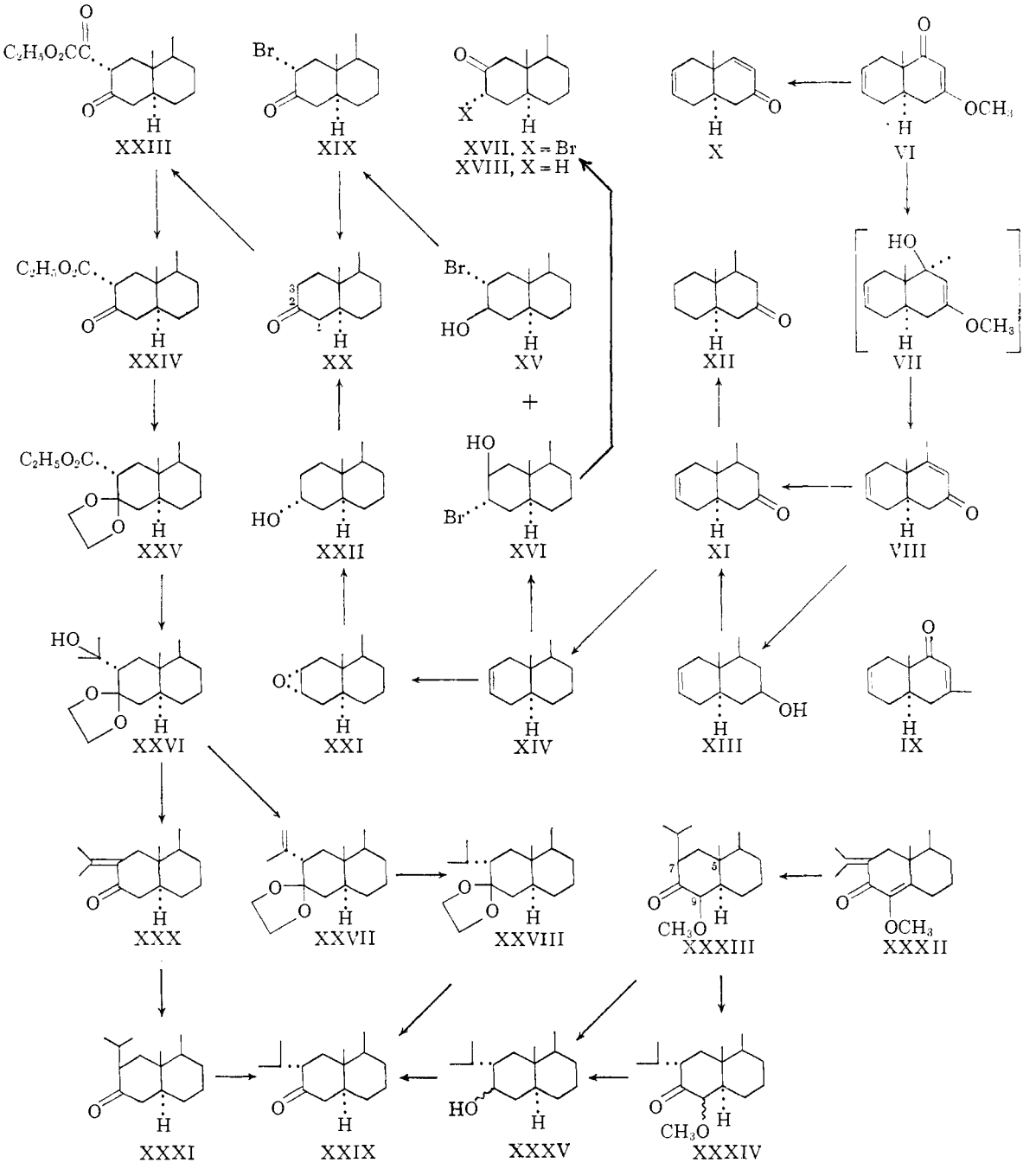
(8) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956), footnote 56.

(9) A. E. Bradfield, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 2744 (1932).

(10) C. Djerassi "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 10.

(11) C. Djerassi, *Rec. Chem. Progress*, **20**, 101 (1959), especially pp. 118–119.

(12) The ketone IV was characterized by a positive and V by a negative Cotton effect. However, their rotatory dispersion curves "crossed over" near 400 mμ, thus resulting in a negative rotation at the sodium D line for IV (in spite of its positive Cotton effect) and a positive rotation for V (in spite of its negative Cotton effect). Eremophilone (I) itself had a negative Cotton effect, which remained negative throughout the spectral range. Consequently, using molecular rotation differences at the D line, one arrives at the opposite conclusion (see W. Klyne, *J. Chem. Soc.*, 3072 (1953)) as compared to rotatory dispersion measurements. Obviously, this is only fortuitous, since there can be no rationale to employing monochromatic molecular rotation calculations at the D line if the use of rotatory dispersion curves is not permissible (see p. 135 in ref. 10).



C-5 and C-7 substituents in contrast to the *cis* situation prevailing in hydroxydihydroeremophilone (II)) in order not to give rise to possible conformational distortions which would make comparisons of rotatory dispersion curves with the all-chair steroid models IV and V invalid.

Recently,[13] it was possible to interrelate dihydroeremophilone (II) with eremophilone (I) by a stereochemically unambiguous sequence, thus demonstrating that eremophilone (I) actually possessed an axial isopropenyl substituent (as implied in stereoformula I).[14] Consequently, the condition[10,11] of identical relative configuration *and* conformation between eremophilone (I) and the two steroid models IV and V was not necessarily met and optical rotatory dispersion studies were not applicable to this case. In order to settle the absolute configuration of eremophilone (I) it was necessary to turn to a chemical approach and the present paper is concerned with a solution of this problem.[15]

The starting material in our synthetic work was the (+)-antipode of the hexalone VI, whose ab-

(13) C. Djerassi, R. Mauli and L. H. Zalkow, THIS JOURNAL, **81**, 3424 (1959).

(14) Throughout this paper correct absolute configurations are given using the steroid notation (solid bond (β) above the plane of the paper; dotted bond (α) below the plane).

(15) See L. H. Zalkow, F. X. Markley and C. Djerassi, THIS JOURNAL, **81**, 2914 (1959), for preliminary communication.

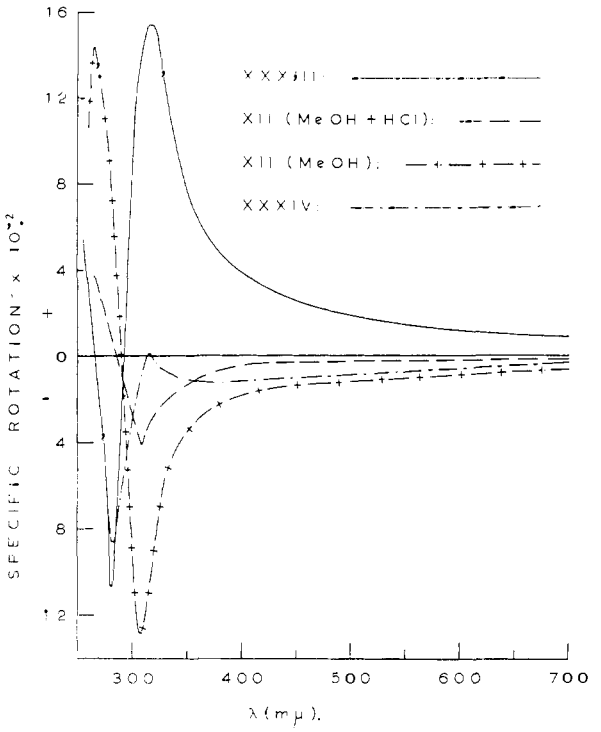


Fig. 1.—Optical rotatory dispersion curves in methanol solution.

solute configuration has been established securely.[16] Reaction with methyllithium in ether solution and acid hydrolysis of the presumed intermediate VII afforded in excellent yield the crystalline (+)-*trans*-4,10-dimethyl-$\Delta^{3,6}$-hexalone-2 (VIII). At this stage, the structure of the hexalone was confirmed by the close similarity of its rotatory dispersion curve with that[17] of (+)-*trans*-10-methyl-$\Delta^{3,6}$-hexalone-2 (X).[16] If 1,4-addition of methyllithium had occurred, then the isomer IX would have been produced (after acid-promoted β-elimination of the methoxy group) and its rotatory dispersion curve would have been expected to differ considerably from that of X. With the introduction of the C-4 methyl group of eremophilone completed, it was now necessary to generate the proper orientation, which is known to be equatorial from the X-ray studies[6] on hydroxydihydroeremophilone (II).

In order to examine the stereochemical course of the catalytic hydrogenation of the α,β-unsaturated ketone system of VIII, the substance was hydrogenated with palladium–charcoal catalyst to (−)-*trans*-4,10-dimethyldecalone-2 (XII). Its rotatory dispersion curve (Fig. 1) was characterized by the anticipated negative Cotton effect (mirror image of cholestan-3-one)[18] with an amplitude which was nearly identical with that of (−)-*trans*-10-methyldecalone-2.[8] The orientation of the C-4 methyl group could now be established by the rotatory dispersion ketal technique,[19] since a diminution of the amplitude upon addition of hydrochloric acid would only be anticipated in the equatorial 4β-isomer XII. The axial 4α-isomer would not be expected to react with methanol, since a new 1,3-diaxial interaction would be set up in the resulting ketal. As shown in Fig. 1, addition of one drop of hydrochloric acid to a methanol solution of the decalone XII resulted in a 69% reduction in amplitude of the original Cotton effect, a figure which is in excellent agreement with the 64–75% amplitude reduction observed with a variety of 3-keto steroids and their bicyclic analogs. The rotatory dispersion information summarized in Fig. 1 was not only of stereochemical utility, but also eliminated structure IX from further consideration since the rotatory dispersion curve of its reduction product would not have been changed[19] after addition of hydrochloric acid.

Having established that catalytic hydrogenation of the α,β-unsaturated carbonyl moiety led to the desired equatorial 4β-methyl group, we now sought to develop conditions which would effect such reduction of the conjugated ketone without affecting the isolated double bond in the adjacent ring since this was required for further introduction of an oxygen function. After some experimentation, it was found that catalytic hydrogenation of the hexalone VIII in ethanol solution in the presence of potassium hydroxide and with palladized calcium carbonate as catalyst ceased after the consumption of one molar equivalent of hydrogen and that the isolated double bond remained untouched. Alternatively, the hexalone VIII was transformed to *trans*-4,10-dimethyl-Δ^{6}-octalol-2 (XIII) by reduction with sodium in ethanol and then oxidized with chromium trioxide. The resulting (+)-*trans*-4,10-dimethyl-Δ^{6}-octalone-2 (XI) was then subjected to Wolff–Kishner reduction[20] to afford the key intermediate (+)-*trans*-1,9-dimethyl-Δ^{6}-octalin (XIV), which was shown to be homogeneous by vapor phase chromatography. Two approaches were examined in connection with the stereospecific introduction of an oxygen function into the unsaturated ring of the octalin XIV.

The first route was concerned with the synthesis of (+)-*trans*-8,9-dimethyldecalone-2 (XVIII), which was required for comparison purposes with the earlier described[13] *cis* isomer derived from eremophilone (I). It has already been reported in the steroid field[21] that addition of hypobromous acid to 5α-Δ^{2}-olefins leads to the diaxial 2β-hydroxy-3α-bromo steroid arising from diaxial opening of the intermediate α-bromonium ion. Since the octalin XIV constitutes a bicyclic analog of such steroids, it was anticipated that the same stereochemical course would also be observed and qualitatively this proved to be the case. The intermediate bromohydrin (XVI contaminated by some XV) was oxidized with chromium trioxide in acetic acid solution to furnish as the predominant product the liquid (+)-*trans*-8,9-dimethyl-3α-bro-

(16) A. J. Speziale, J. A. Stephens and Q. E. Thompson, THIS JOURNAL, **76**, 5011 (1954); the racemate of this ketone had been synthesized earlier by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(17) C. Djerassi, R. Riniker and B. Rinker, *ibid.*, **78**, 6377 (1956).

(18) C. Djerassi, W. Closson and A. E. Lippman, *ibid.*, **78**, 3163 (1956).

(19) C. Djerassi, L. A. Mitscher and B. J. Mitscher, *ibid.*, **81**, 947 (1959).

(20) Huang-Minlon, *ibid.*, **71**, 3301 (1949).

(21) H. L. Slates and N. L. Wendler, *ibid.*, **78**, 3749 (1956).

modecalone-2 (XVII). The axial character of the halogen atom was established by the strongly positive Cotton effect with the anticipated[22] bathochromic displacement of its peak by 22.5 mμ as compared to the peak of its halogen-free ketone XVIII. Debromination with chromous chloride or with zinc produced (+)-*trans*-8,9-dimethyldecalone-2 (XVIII); the position of the carbonyl group at C-2 was proved by the observation that the amplitude of its positive Cotton effect in methanol solution was practically unaffected by the addition of hydrochloric acid, a behavior typical[19] of 2-keto steroids such as cholestan-2-one.

In addition to the liquid 3α-bromo-2-ketone XVII, there was isolated a small amount of a solid isomer. Its rotatory dispersion curve was only consistent[22] with an equatorial α-bromo ketone and debromination with zinc afforded (+)-*trans*-5,10-dimethyldecalone-2 (XX), identical with a specimen prepared as shown below. The solid bromo ketone must, therefore, be represented by (+) - *trans* - 5,10 - dimethyl - 3α - bromodecalone - 2 (XIX) and hence must have arisen from some diequatorial bromohydrin XV produced in small amounts in the hypobromous acid addition to the olefin XIV.

For our further work, substantial quantities of (+)-*trans*-5,10-dimethyldecalone-2 (XX) were required and these were prepared by the following alternate procedure.

There is ample precedent in the steroid literature[23] that epoxidation of Δ^2-olefins of the 5α-series gives almost exclusively the 2α,3α-epoxide, which is reduced with lithium aluminum hydride to the axial 3α-alcohol. Since the stereochemical situation in the octalin XIV is essentially the same, as has already been demonstrated by the above-described hypobromous acid addition, it was not surprising that perbenzoic acid oxidation of (+)-*trans*-1,9-dimethyl-Δ^6-octalin (XIV) afforded in high yield a homogeneous epoxide (XXI). Exposure of the epoxide XXI to lithium aluminum hydride led to the decalol XXII, which was oxidized to (+)-*trans*-5,10-dimethyl-decalone-2 (XX), identical with the specimen obtained by debromination of the bromo ketone XIX.

Again by analogy to 3-keto steroids of the 5α-series,[24] it could be assumed safely that condensation reactions with the decalone XX would occur at C-3 rather than at C-1, thus affording a means of introducing the three-carbon side chain of eremophilone in the required location. Condensation of (+)-*trans*-5,10-dimethyldecalone-2 (XX) with diethyl oxalate in the presence of sodium hydride gave in nearly 90% yield the glyoxalate XXIII, which was decarbonylated in the presence of powdered glass[25] to (+)-*trans*-3-ethoxycarbonyl-5,10-dimethyldecalone-2 (XXIV). Treatment with ethylene glycol in benzene solution in the presence of *p*-toluenesulfonic acid provided the ethylene ketal XXV as a low melting solid, convertible by means of methylmagnesium iodide into the crystalline ethylene ketal XXVI of *trans*-5,10-dimethyl-3-(1-methyl-1-hydroxy)-ethyldecalone-2 (XXVI). Initially, it was attempted to effect cleavage of the ketal grouping and β-elimination of the hydroxyl function in one step by acid treatment in order to afford *trans*-5,10-dimethyl-3-isopropylidenedecalone-2 (XXX). Since it was noted that dehydration was not complete under these conditions, the total product was dehydrated further with phosphorus oxychloride in pyridine to afford a separable mixture of the desired unsaturated ketone XXX and *trans*-5,10-dimethyldecalone-2 (XX), which was apparently formed by retroaldolization. Catalytic hydrogenation of the isopropylidene ketone XXX proceeded rapidly with consumption of one molar equivalent of hydrogen to afford *trans*-5,10-dimethyl-3β-isopropyldecalone-2 (XXXI). Its infrared spectrum was distinctly different from that of the 3α-isopropyl isomer XXIX, described in the following paragraph, but inversion of the axial isopropyl substituent was effected readily by treatment with an acidic solution of 2,4-dinitrophenylhydrazine to give the dinitrophenylhydrazone of XXIX.

An alternate and more desirable route for the introduction of the isopropyl function involved dehydration of the tertiary hydroxyl group of XXVI while retaining the ketal grouping. This led exclusively to the 3α-isopropenyl[26] ketal XXVII, which was hydrogenated to the 3α-isopropyl 2-ketal XXVIII and then cleaved with acid to *trans*-5,10-dimethyl-3α-isopropyldecalone-2 (XXIX), whose 2,4-dinitrophenylhydrazone proved to be identical with the reaction product of *trans*-5,10-dimethyl-3β-isopropyldecalone-2 (XXXI) with 2,4-dinitrophenylhydrazine. As recorded in the Experimental section, both ketones XXIX and XXXI show a positive Cotton effect, except that the amplitude of the latter is considerably greater. In the light of the octant rule,[27] this is consistent only with a chair conformation of XXXI, since the boat conformation would presumably exhibit a negative Cotton effect.

In our earlier paper[13] on the relative stereochemistry of eremophilone (I), there was reported a facile one-step conversion of hydroxydihydroeremophilone (II) to hydroxyeremophilone (III). Since hydroxydihydroeremophilone (II) has also been interrelated[9,13] with eremophilone (I), it was only necessary to establish a connection with one of these three sesquiterpenes and the synthetic ketone XXIX in order to settle the absolute configuration of the entire group. After extensive experimentation which will not be reported here, it was found that hydroxyeremophilone (III) would be the most suitable candidate for this purpose Its methyl ether XXXII[28] was hydrogenated to

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

(23) *E. g.*, A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(24) *Inter al.*, Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958); H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959).

(25) W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940).

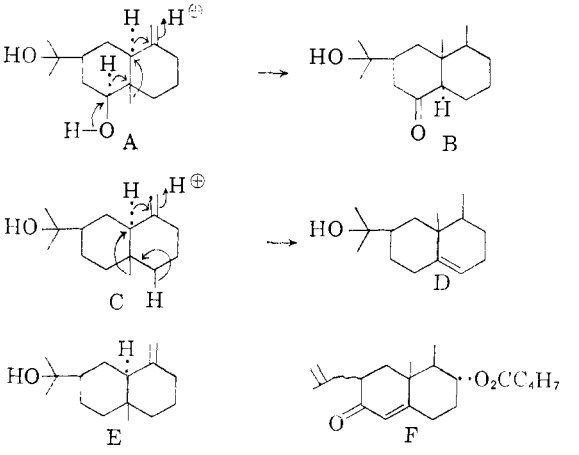
(26) We assume that the more stable α-orientation of the C-3 substituent is already generated during the formation of the ketal XXV.

(27) See Chapter 13 in ref. 10 as well as W. Klyne in R. A. Raphael, E. C. Taylor and H. Wynberg (ed.), "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, pp. 333–341.

yield tetrahydrohydroxyeremophilone methyl ether which was contaminated by a small amount of demethoxylated material (presumably XXXI). Neither hydroxyeremophilone methyl ether (XXXII) nor its tetrahydro derivative XXXIII were crystalline, but the latter can be considered to be predominantly the 7β,9β-isomer, since its rotatory dispersion curve (Fig. 1) was characterized by a strong positive Cotton effect. When the tetrahydro methyl ether XXXIII was heated under reflux with methanolic sodium hydroxide, it was epimerized to an isomer, epitetrahydrohydroxyeremophilone methyl ether (XXXIV), whose rotatory dispersion amplitude (Fig. 1) was greatly reduced. Such diminution in amplitude would be consistent[27] with the conversion of the axial 7-isopropyl group to the equatorial 7α-isomer. There remained only the removal of the 9-methoxyl function and this was accomplished by treatment with calcium in liquid ammonia, a reagent which had been employed earlier for the deacetoxylation of α-acetoxy ketones in the steroid[29] and hydroxydihydroeremophilone[13] series. Mechanistically,[29,30] there existed no *a priori* reason why this reaction should not also be applicable to α-methoxy ketones and this was verified by exposing epitetrahydrohydroxyeremophilone methyl ether (XXXIV) to this reagent. The resulting product was principally the alcohol XXXV, most of the carbonyl group having been reduced to the alcohol during the demethoxylation, and upon oxidation it afforded *trans*-5,10-dimethyl-3α-isopropyldecalone-2 (XXIX), identical in all respects (including rotatory dispersion curve with positive Cotton effect) with the synthetic sample. This successful tie-up rigorously establishes the absolute configuration of eremophilone and its relatives at positions 4 and 5. Since the orientation of the C-7 substituent has already been related[13] to the angular methyl group, stereoformula I represents the complete expression for eremophilone.

At this point, it is profitable to return for a moment to the earlier rotatory dispersion data[8] accumulated with eremophilone and the two steroid reference ketones IV and V. The latter two ketones are conformationally unambiguous and if the steric interaction between the axial substituents at C-5 and C-7 in eremophilone (I) did not result in any conformational distortion of the oxygen-containing ring, then the rotatory dispersion curves of eremophilone (I) and Δ^5-cholesten-4-one (IV) should be very similar. In point of fact, they are of mirror image type,[8] thus demonstrating unequivocally the existence of conformational alteration in eremophilone.

Finally, we would like to consider the biogenetic implications of the absolute configurational assignments made in this paper. Robinson[31] has already noted that while eremophilone and its congeners do not follow the isoprene rule they could still be assumed to fall into the generally accepted scheme[32] of terpene synthesis from isoprenoid units if one assumed methyl migration at some stage of biosynthesis. There is every reason to believe that such rearrangements proceed stereospecifically[33] and, based on the presently established absolute configuration of eremophilone (I), appropriate precursors could be intermediates of type A[34] or C. Concerted rearrangement of A would lead to an intermediate B, which upon dehydrogenation and dehydration would yield eremophilone (I). The further conversion of B to hydroxydihydroeremophilone (II) and hydroxyeremophilone (III) is unexceptional and has already been discussed.[34] Alternatively, rearrangement could proceed from an intermediate such as C to D, which would again lead to eremophilone after allylic oxidation and dehydration. In any event, the significant point is that the presently demonstrated absolute configuration of eremophilone (I) requires an absolute configurational representation (A or C) for the eudalenoid precursor, which is completely consistent with the independently proved[35] absolute configuration E of β-eudesmol. The recently discovered[36] fourth member of the eremophilone group of sesquiterpenes, petasin (F), has also been shown[37] to possess the same absolute configuration so that it can be concluded that all hitherto discovered naturally occurring sesquiterpenes with the rearranged skeleton of eremophilone arise from eudalenoid precursors which possess the absolute configuration of eudesmol (E) rather than its mirror image.[38]



Acknowledgment.—We are greatly indebted to Dr. Maurice D. Sutherland of the University of Queensland, Brisbane, for a generous supply of

(28) A. E. Bradfield, N. Hellstrom, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 767 (1938).

(29) J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *ibid.*, 4344 (1956); see also J. S. Mills, H. J. Ringold and C. Djerassi, THIS JOURNAL, **80**, 6118 (1958).

(30) A. J. Birch and H. Smith, *Quart. Revs.*, **12**, 17 (1958).

(31) R. Robinson "The Structural Relations of Natural Products," Oxford University Press, New York, N. Y., 1955, p. 12.

(32) L. Ruzicka, *Experientia*, **9**, 357 (1953).

(33) For pertinent discussion in the triterpene series see A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(34) See J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(35) B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, THIS JOURNAL, **76**, 313 (1954).

(36) A. Aebi and T. Waaler "Über die Inhaltstoffe von *Petasites hybridus* (L.) Fl. Wett.," Verlag Helbing und Lichtenhahn, Basel, 1958.

(37) A. Aebi and C. Djerassi, *Helv. Chim. Acta*, **42**, 1785 (1959); D. Herbst and C. Djerassi, THIS JOURNAL, **82**, 4337 (1960).

(38) A number of eudalenoid sesquiterpenes with the antipodal configuration have been encountered recently. For pertinent references see S. C. Bhattacharyya, A. S. Rao and A. M. Shaligram, *Chemistry & Industry*, 469 (1960).

hydroxyeremophilone and to Monsanto Chemical Co., St. Louis, Mo., for a gift of the starting ketone VI.

Experimental[39]

(+)-*trans*-4,10-Dimethyl-$\Delta^{3,6}$-hexalone-2 (VIII).—A solution of 9.4 g. of (+)-*trans*-3-methoxy-9-methyl-$\Delta^{2,6}$-hexalone-1 (VI)[16] in 100 cc. of dry ether was added dropwise to methyllithium prepared from 1.6 g. of lithium and 6.5 cc. of methyl iodide in 100 cc. of ether, the entire operation being conducted in an atmosphere of nitrogen. The solution was stirred for 12 hr. at room temperature, then poured into ice-water and the ether layer separated. After washing with water and drying, the ether was removed through a fractionating column and the viscous oily residue (VII) was hydrolyzed by stirring for 3 hr. with 35 cc. of concd. sulfuric acid, 250 cc. of water and 300 cc. of dioxane. The dioxane–water solution was concentrated under reduced pressure, extracted with ether, the latter was dried and evaporated. Distillation of the residue at 99–103° (0.5 mm.) afforded 6.8 g. of the hexalone VIII, which solidified on cooling, m.p. 39–42°. The analytical sample crystallized from hexane as clear hexagonal prisms showing m.p. 42–44°, $\lambda_{max}^{CHCl_3}$ 6.04 and 6.21 μ, λ_{max}^{MeOH} 236 mμ, log ϵ 4.02, $[\alpha]_{589}$ +295° (*c* 0.155, in dioxane).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15; O, 9.08. Found: C, 81.68; H, 9.18; O, 9.45.

The semicarbazone was prepared in the presence of sodium acetate in dilute ethanol and recrystallized from the same solvent; m.p. 171–173°.

Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 6.86; O, 18.01. Found: C, 66.50; H, 8.45; N, 6.87; O, 17.94.

The red **2,4-dinitrophenylhydrazone** was recrystallized from dilute isopropyl alcohol; m.p. 173–175°, $\lambda_{max}^{CHCl_3}$ 389 mμ, log ϵ 4.45. Occasionally a second form melting at 154–156° was encountered.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; O, 17.96. Found: C, 60.81; H, 6.02; O, 17.75.

(+)-*trans*-4,10-Dimethyl-Δ^6-octalone-2 (XI). (a) **By Catalytic Hydrogenation of VIII.**—The α,β-unsaturated ketone VIII (8.15 g.) was hydrogenated in 2% ethanolic potassium hydroxide solution (150 cc.) with 1.0 g. of 2% prereduced palladized calcium carbonate catalyst at room temperature and atmospheric pressure. Hydrogen uptake ceased after about 10 hr. when one molar equivalent had been consumed. The catalyst was removed by filtration, the filtrate neutralized with hydrochloric acid, sodium bicarbonate was added, the solution concentrated under reduced pressure, diluted with water and extracted with ether. After drying over sodium sulfate, the ether was removed and the residue fractionated to afford 6.64 g. of the octalone XI, b.p. 110–111° (1.5 mm.), λ_{max}^{capill} 5.78 μ, λ_{max}^{EtOH} 282 mμ, log ϵ 2.06; R.D. in dioxane (*c* 0.411): $[\alpha]_{589}$ +33°, $[\alpha]_{450-400}$ +49° (broad peak), $[\alpha]_{312.5}$ −409°, $[\alpha]_{290}$ +445°; in methanol solution (*c* 0.083) the trough occurred at $[\alpha]_{307.5}$ −368°.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.16; H, 10.18.

The semicarbazone was prepared in 80% ethanol in the presence of sodium acetate (10 min. heating) and recrystallized from aqueous ethanol; m.p. 210–212° dec.

Anal. Calcd. for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 65.87; H, 8.86; N, 18.10.

(b) **By Chemical Reduction of VIII.**—Small pieces of sodium (5 g.) were added to 973 mg. of the hexalone VIII in 50 cc. of absolute ethanol. When the reaction had subsided, the solution was heated under reflux for 1 hr., diluted with water and extracted with ether. Distillation of the ether residue afforded 712 mg. of *trans*-4,10-dimethyl-Δ^6-octalol-2 (XIII), which came over at a bath temperature of 80° (0.05 mm.). A small amount of the oil, which exhibited no carbonyl absorption in the infrared, was redistilled for analysis.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.38; H, 10.75.

(39) Melting points were determined on the Kofler block. Thanks are due to Mrs. A. James and Mrs. T. Nakano for the rotatory dispersion measurements, to Miss B. Bach for infrared determinations and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses.

The above alcohol XIII (515 mg.) in 25 cc. of acetic acid was oxidized (1 hr. at room temperature) with 250 mg. of chromium trioxide dissolved in 30 cc. of 80% acetic acid. Distillation at 70° (0.4 mm.) afforded 400 mg. of the ketone XI, whose infrared spectrum was identical with that of the sample prepared by procedure a.

(−)-*trans*-4,10-Dimethyldecalone-2 (XII).—Catalytic hydrogenation of either the hexalone VIII or the octalone XI in methanol solution with 5% palladized charcoal proceeded rapidly with the consumption of two or one molar equivalent of hydrogen, respectively. The reaction mixture was worked up in the usual manner, but infrared as well as rotatory dispersion examination of the total distilled product indicated that it consisted of a mixture of the decalone XII and its methyl ketal (or hemiketal). Consequently, the material was shaken for 1 hr. with a 1:1 mixture of 3 *N* hydrochloric acid and 25 cc. of dioxane, diluted with water and extracted with ether. Distillation at 70–73° (0.5 mm.) afforded the desired ketone as a colorless oil, $\lambda_{max}^{cyclohexane}$ 282 mμ, log ϵ 1.30, $\lambda_{max}^{CHCl_3}$ 5.83 μ (strong), $n^{25}D$ 1.4907; R.D. (Fig. 1) in methanol (*c* 0.092): $[\alpha]_{700}$ −60°, $[\alpha]_{589}$ −83°, $[\alpha]_{307.5}$ −1288°, $[\alpha]_{267.5}$ +1444°, $[\alpha]_{260}$ +1044°. After the addition of one drop of concd. hydrochloric acid the following results were encountered: $[\alpha]_{700}$ −22°, $[\alpha]_{589}$ −22°, $[\alpha]_{410}$ −400°, $[\alpha]_{265}$ +356°.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.71; H, 11.02.

An 80-mg. sample of the decalone XII was treated at room temperature with 150 mg. of 2,4-dinitrophenylhydrazine in methanolic hydrochloric acid solution. **The 2,4-dinitrophenylhydrazone** crystallized as long, orange-yellow needles (m.p. 136–138° after recrystallization from methanol), $\lambda_{max}^{CHCl_3}$ 368 mμ, log ϵ 4.39.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.95; H, 6.90; N, 15.46.

(+)-*trans*-1,9-Dimethyl-Δ^6-octalin (XIV).—The octalone-XI (5.67 g.) was added to 50 cc. of diethylene glycol containing 6 cc. of 85% hydrazine hydrate and 5.1 g. of potassium hydroxide and the mixture was heated under reflux for 1.5 hr. It was then distilled until the temperature reached 200°, whereupon refluxing was continued for 7 hr. The distillate, which contained some of the product, was combined with the reaction mixture, diluted with water and extracted with ether. After drying, the ether was removed through a fractionating column and the residue was distilled to afford 4.27 g. of the olefin XIV, b.p. 110–111° (28 mm.), plain positive rotatory dispersion curve (*c* 0.064 in methanol) starting at $[\alpha]_{589}$ +50° and rising to $[\alpha]_{267.5}$ +475°. The material proved to be homogeneous by vapor phase chromatography at 212–216° on a Celite–silicone packing.

Anal. Calcd. for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.54; H, 12.11.

(+)-*trans*-8,9-Dimethyl-3α-bromodecalone-2 (XVII) and (+)-*trans*-5,10-Dimethyl-3α-bromodecalone-2 (XIX).—N-Bromosuccinimide (5.2 g.) was added slowly over a period of 30 min. to a solution of 3.55 g. of the olefin XIV in 150 cc. of *t*-butyl alcohol and 45 cc. of 1 *N* sulfuric acid. After stirring at room temperature for 5 hr., water was added and the product extracted with ether. The organic layer was washed with sodium bicarbonate solution, then water, dried, evaporated and the residue distilled at a bath temperature of 90–100°/(0.005 mm.) to give 3.26 g. of viscous oil consisting largely of the bromohydrin XVI accompanied by a small amount of the isomer XV. This material was not purified further but used directly for the oxidation.

Anal. Calcd. for $C_{12}H_{21}BrO$: C, 55.14; H, 8.12; Br, 30.61; O, 6.13. Found: C, 53.99; H, 7.90; Br, 31.62; O, 6.24.

The bromohydrin (2.54 g.), dissolved in 125 cc. of glacial acetic acid, was oxidized with a solution of 0.67 g. of chromium trioxide in aqueous acetic acid. After 1 hr. at room temperature, the solution was diluted with water and the product isolated with ether. Distillation at a bath temperature of 85–90° (0.007 mm.) provided 1.884 g. of bromo ketone consisting largely of XVII as demonstrated[22] by the positive Cotton effect with a peak at $[\alpha]_{327.5}$ +4000° (*c* 0.014 in dioxane). Upon standing for several days, crystals appeared; pentane was, thereupon, added and the solid (81 mg., m.p. 155–160°) was filtered. Sublimation at 110° (0.3-mm.) afforded the analytical specimen of (+)-*trans*-5,10-dimethyl-3α-bromodecalone-2 (XIX), m.p. 155–157°, posi-

tive Cotton effect (c 0.082 in dioxane) with peak at $[\alpha]_{312.5}$ +1206°.

Anal. Calcd. for $C_{12}H_{19}BrO$: C, 55.57; H, 7.41; Br, 30.84; O, 6.17. Found: C, 55.98; H, 7.71; Br, 29.95; O, 6.53.

The pentane was removed from the filtrate and the liquid (+)-*trans*-**8,9-dimethyl-3α-bromodecalone-2 (XVII)** was redistilled for analysis.

Anal. Found for $C_{12}H_{19}BrO$: C, 55.62; H, 7.49; Br, 31.13.

(+)-*trans*-**8,9-Dimethyldecalone-2 (XVIII).**—The above-described liquid (+)-*trans*-8,9-dimethyl-3α-bromodecalone-2 (XVII) (813 mg.) was dissolved in 8 cc. of acetic acid containing 2 drops of water and warmed with stirring at 60° with an equal weight of zinc dust. After 15 min., the zinc was filtered, the filtrate diluted with water and the product isolated by ether extraction. Distillation of the dried solution afforded 335 mg. of colorless oil, b.p. 100–105° (1 mm.) Alternatively, 140 mg. of the bromo ketone was dissolved in 10 cc. of acetone and debrominated with a chromous chloride solution prepared[40] from 2.5 g. of chromic chloride. After the usual work-up there was obtained after distillation at 80–90° (0.3 mm.) 80 mg. of the ketone XVIII, whose infrared spectrum was identical with that of the product obtained from the zinc dust debromination.

The analytical sample was redistilled at 100° (1 mm.) and the distillate solidified at 0°, but melted at room temperature; λ_{max}^{capill} 5.80 μ. The rotatory dispersion curve of this ketone in methanol and in methanol–hydrochloric acid (9% reduction in amplitude) has already been recorded.[19]

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18; O, 8.88. Found: C, 80.19; H, 11.05; O, 8.99.

The yellow **2,4-dinitrophenylhydrazone** was obtained in 75% yield after recrystallization from methanol; m.p. 140.5–141.5°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.46; H, 6.79; N, 15.77.

(+)-*trans*-**5,10-Dimethyldecalone-2 (XX).** (a) **By Debromination of (+)-*trans*-5,10-Dimethyl-3α-bromodecalone-2 (XIX).**—A mixture of 25 mg. of the crystalline bromo ketone XIX, 2 cc. of glacial acetic acid (containing 1 drop of water) and 25 mg. of zinc dust was warmed for 5 min. on the steam-bath and then diluted with water. The product was isolated with ether and converted directly into the **2,4-dinitrophenylhydrazone** (17 mg., m.p. 166–170°). One recrystallization from methanol raised the m.p. to 172.5–173.5°, undepressed upon admixture with the derivative of XX prepared by procedure b.

(b) **By Sequential Epoxidation, Lithium Aluminum Hydride Reduction and Oxidation of (+)-*trans*-1,9-Dimethyl-Δ⁶-octalin (XIV).**—To 345 mg. of the octalin XIV in 50 cc. of chloroform was added 10 cc. of a chloroform solution of perbenzoic acid (3.7 mmoles). After standing for 19 hr. at room temperature, the solution was washed with potassium iodide solution, sodium thiosulfate solution, sodium carbonate solution, water, dried and fractionated. The **epoxide XXI** was distilled at a bath temperature of 120–130° (15 mm.) (yield 320 mg.) and exhibited a plain positive dispersion curve rising to $[\alpha]_{300}$ +70° (c 0.092 in dioxane).

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18; O, 8.88. Found: C, 79.68; H, 11.17; O, 9.02.

To 0.4 g. of lithium aluminum hydride in 75 cc. of ether was added a solution of 300 mg. of the epoxide XXI in 25 cc. of ether. After standing at room temperature for 20 hr., the excess hydride was destroyed with methanol and after the usual treatment there was obtained 220 mg. of the **decalol XXII**, b.p. 115–120° (1.5 mm.) solidifying on standing.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.06; H, 12.16. Found: C, 78.86; H, 11.96.

The above alcohol XXII (200 mg.) was oxidized (30 min., room temperature) in acetic acid solution with 100 mg. of chromium trioxide. After the customary work-up, the product was distilled at a bath temperature of 105° (1 mm.) to afford 140 mg. of (+)-*trans*-5,10-dimethyldecalone-2 (XX), which solidified to a waxy solid (m.p. 29–30° (after pressing on a porous plate; λ_{max}^{capill} 5.80 μ. The optical rotatory dispersion data in methanol and in methanol–hydrochloric acid (68% reduction in amplitude) have already been reported.[19]

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.72; H, 10.95.

The yellow **2,4-dinitrophenylhydrazone** exhibited m.p. 172.5–173.5° after recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55; O, 17.76. Found: C, 60.04; H, 6.69; N, 15.50; O, 17.67.

trans-**5,10-Dimethyl-3α-isopropyldecalone-2 (XXIX).**—Sodium hydride (520 mg.) was added to 850 mg. of (+)-*trans*-5,10-dimethyldecalone-2 (XX) dissolved in 20 cc. of dry benzene and 1.8 cc. of redistilled diethyl oxalate, and the solution was stirred vigorously in an atmosphere of nitrogen. After 17 hr. the excess sodium hydride was destroyed with methanol and the mixture was partitioned between ether and 3% aqueous sodium hydroxide solution. The aqueous alkaline layer was acidified with cold 6 *N* hydrochloric acid and the product was extracted with ether. Distillation afforded 1.17 g. of the **glyoxalate XXIII** as a colorless oil, b.p. 90–100° (0.7 mm.); $\lambda_{max}^{CHCl_3}$ 5.70, 6.15 and 6.30 μ. The substance gave a deep purple color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; O, 22.83; OC_2H_5, 16.07. Found: C, 68.64; H, 8.72; O, 23.02; OC_2H_5, 15.97.

The glyoxalate was distilled at 30 mm. in the presence of powdered soft glass, a vigorous gas evolution occurring at 175°. **The β-keto ester XXIV** distilled over as a light yellow distillate and was redistilled at 65° (0.01 mm.) to afford a colorless oil (72% yield); $\lambda_{max}^{CHCl_3}$ 5.75, 5.85, 6.05 and 6.18 μ, giving a purple color with ferric chloride solution.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 70.89; H, 9.14; O, 19.60.

The above β-keto ester XXIV (3.39 g.), 1 cc. of ethylene glycol, 10 cc. of dry benzene and a few crystals of *p*-toluenesulfonic acid were heated under reflux under a water separator for 15 hr. when a negative test (ferric chloride and infrared spectrum) for β-keto ester was obtained. Ether was added, the organic solution was washed with water, dried and evaporated. Distillation at 80–90° (0.01 mm.) yielded 3.0 g. of the **ketal XXV** as a low melting solid, which liquefied at room temperature; $\lambda_{max}^{CHCl_3}$ 5.77 μ.

Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52; O, 21.60. Found: C, 68.52; H, 9.52; O, 22.09.

The ketal ester XXV (2.84 g.) in 10 cc. of dry ether was added dropwise to a solution prepared from 1.55 cc. of methyl iodide, 0.61 g. of magnesium and 10 cc. of ether and the mixture was heated under reflux for 3 hr., care being taken that all moisture was excluded. After hydrolysis with 20 cc. of 20% ammonium chloride solution, the ether layer was separated, dried and evaporated to give 2.46 g. of the crude **tertiary alcohol XXVI** (no carbonyl absorption in the infrared) which was used directly in the next step. An analytical sample was distilled at 80–100° (0.005 mm.), whereupon the distillate solidified (m.p. 55–60°).

Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.61; H, 10.41.

The crude alcohol XXVI (2.01 g.) was allowed to stand overnight with 8 cc. of phosphorus oxychloride and 17 cc. of pyridine and the mixture was then poured into 2 l. of ice-water. The product was extracted with ether, dried over magnesium sulfate and passed through a column of Merck acid-washed alumina. Evaporation of the ether and distillation at 90–105° (0.1 mm.) produced 1.63 g. of the isopropenyl ketal XXVII, $[\alpha]_{589}$ +4° (c 0.35 in methanol), $\lambda_{max}^{CHCl_3}$ 6.08 and 11.15 μ.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67; O, 12.10. Found: C, 76.61; H, 10.89; O, 12.50.

The hydrogenation of 756 mg. of the isopropenyl derivative XXVII was conducted at atmospheric pressure in ethyl acetate solution (20 cc.) in the presence of 80 mg. of 10% palladized charcoal catalyst, one molar equivalent of hydrogen being taken up in 2 hr. The catalyst was filtered, the ethyl acetate was removed and the **isopropyl ketal XXVIII** was distilled at 80–90° (0.1 mm.), $[\alpha]_{589}$ −25° (c 2.32 in methanol). The infrared bands at 6.08 and 11.15 μ associated with the isopropenyl double bond were absent.

Anal. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35; O, 12.01. Found: C, 76.77; H, 11.06; O, 12.33.

(40) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

The cyclic ketal XXVIII (470 mg.) was cleaved by stirring overnight at room temperature with 12 cc. of methanol, 2 cc. of water and 2 drops of concd. hydrochloric acid. Dilution with water, extraction with ether, washing with bicarbonate solution and water, drying and evaporation left the desired **ketone XXIX** as a colorless oil, λ_{max}^{capill} 5.83 μ, after distillation at a bath temperature of 60–70° (0.01 mm.). The ketone was unchanged (infrared spectrum) after heating under reflux for 5 hr. (nitrogen atmosphere) with 13 cc. of 1.5 *N* methanolic sodium hydroxide solution. The ketone exhibited a positive Cotton effect (peak at $[\alpha]_{312}$ +529°) starting at $[\alpha]_{589}$ −15° in methanol solution (*c* 0.21).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.12; H, 11.71.

The 2,4-dinitrophenylhydrazone exhibited m.p. 169–172° after recrystallization from pentane.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.66; H, 7.51. Found: C, 62.75; H, 7.49.

The semicarbazone was prepared by the sodium acetate method and recrystallized from aqueous ethanol. Sublimation at 0.1 mm. yielded colorless crystals, m.p. 176–180°.

Anal. Calcd. for $C_{16}H_{29}N_3O$: C, 68.75; H, 10.46; N, 15.04. Found: C, 68.89; H, 10.29; N, 14.94.

trans-**5,10-Dimethyl-3β-isopropyldecalone-2 (XXXI).**—A solution of 2.2 g. of the crude ketal XXVI, 15 cc. of methanol, 10 cc. of water and 5 drops of concd. hydrochloric acid was heated under reflux for 1 hr. and then partitioned between water and ether. The product obtained by evaporation of the washed and dried ether extract showed a strong hydroxyl band in the infrared and an attempt was made, therefore, to dehydrate it further by stirring at room temperature for 3 hr. with 50 cc. of dioxane, 35 cc. of water and 5 cc. of concd. sulfuric acid. After the usual work-up, the oil was distilled (1.42 g., b.p. 60° (0.04 mm.), λ_{max}^{EtOH} 258 mμ, log ϵ 3.73) but its infrared spectrum still exhibited hydroxyl absorption.

Consequently, this partially dehydrated material (1.41 g.) was dissolved in 20 cc. of pyridine and heated on the steam-bath for 1 hr. with 5 cc. of freshly distilled phosphorus oxychloride. Dilution with water, extraction with ether, washing with dilute sulfuric acid, bicarbonate solution and water, drying and evaporation left 392 mg. of colorless oil, which lacked infrared hydroxyl absorption but contained two carbonyl bands at 5.80 and 5.93 μ. That the former was due to some (+)-*trans*-5,10-dimethyldecalone-2 (XX), produced by retro-aldolization, was demonstrated by chromatography and conversion to the 2,4-dinitrophenylhydrazone, m.p. 170–172°. Acidification of the original aqueous pyridine solution with 3% hydrochloric acid and extraction with ether gave a further amount of oil. After proper washing, drying and evaporation of the ether, there was obtained an additional quantity of oil which was distilled at 70–80° (0.01 mm.) to give 562 mg. of distillate, which appeared to be virtually pure 3-isopropylidene-2-ketone XXX ($\lambda_{max}^{CHCl_3}$ 5.93 μ).

In view of its instability, the unsaturated ketone XXX was not analyzed but 426 mg. was hydrogenated in 40 cc. of ethanol with 150 mg. of 10% palladized charcoal catalyst at 28° and atmospheric pressure, hydrogen uptake corresponding to one molar equivalent being complete within a few minutes. The catalyst was filtered, the filtrate was diluted with water and the product was isolated with ether. Distillation at a bath temperature of 70° (0.01 mm.) led to 300 mg. of the ketone XXXI, whose infrared spectrum (λ_{max}^{capill} 5.81 μ) differed substantially from that of the equatorial 3α-isomer XXIX. The substance exhibited a strongly positive Cotton effect in methanol solution (*c* 0.116): $[\alpha]_{589}$ +67°, $[\alpha]_{310}$ +1321°, $[\alpha]_{275}$ −954°.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.97; H, 11.52.

Warming with Brady solution produced a yellow **2,4-dinitrophenylhydrazone**, which melted at 170.5–172.5° after recrystallization from pentane and was shown by mixture melting point determination to be identical with the 2,4-dinitrophenylhydrazone of the 3α-isomer XXIX. Evidently, epimerization of the axial β-isopropyl group to the favored 3α-orientation had occurred during the preparation of the derivative.

Conversion of Hydroxyeremophilone Methyl Ether (XXXII) to *trans*-5,10-Dimethyl-3α-isopropyldecalone-2 (XXIX).—Hydroxyeremophilone (III) (2.02 g.) was methylated with dimethyl sulfate according to the literature directions[28] to yield 2.17 g. of the methyl ether which was distilled at a bath temperature of 80° (0.01 mm.). The pale yellow oil exhibited $\lambda_{max}^{CHCl_3}$ 6.05 and 6.20 μ, λ_{max}^{MeOH} 265 mμ, log ϵ 3.95, and a shoulder at 285 mμ, log ϵ 3.93; R.D. in dioxane (*c* 0.095): $[\alpha]_{589}$ +177°, $[\alpha]_{425}$ +386°, $[\alpha]_{390}$ +289°, $[\alpha]_{340}$ +1180°, $[\alpha]_{320}$ +831°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74; O, 12.88. Found: C, 76.96; H, 9.60; O, 13.24.

Hydroxyeremophilone methyl ether (XXXII) (551 mg.) was hydrogenated in 20 cc. of ethanol using 90 mg. of 10% palladized charcoal at room temperature and atmospheric pressure. Hydrogen uptake stopped after 90 min. when two molar equivalents had been consumed. After working up in the usual manner, there was obtained 485 mg. of **tetrahydrohydroxyeremophilone methyl ether (XXXIII)** which was distilled at a bath temperature of 65–70° (0.1 mm.). The pale yellow oil showed $\lambda_{max}^{CHCl_3}$ 5.79 μ (shoulder at 5.83 μ), while its rotatory dispersion curve (*c* 0.285 in methanol) is reproduced in Fig. 1: $[\alpha]_{589}$ +130°, $[\alpha]_{317.5}$ +1535°, $[\alpha]_{260}$ −1065°, $[\alpha]_{255}$ +542°.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18; O, 12.68; OCH_3, 12.29. Found[41]: C, 76.48; H, 10.97; O, 12.59; OCH_3, 10.90.

Epimerization of 170 mg. of tetrahydrohydroxyeremophilone methyl ether (XXXIII) was effected by heating under reflux for 5 hr. (nitrogen atmosphere) with 12 cc. of 1 *N* methanolic sodium hydroxide solution. The resulting oil (140 mg.) was distilled at 60–70° (0.01 mm.); its infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.81 μ without any shoulder) was completely different in the finger print region from that of its precursor XXXIII. The rotatory dispersion curve of **epitetrahydrohydroxyeremophilone methyl ether (XXXIV)** measured in methanol solution (*c* 0.092) is reproduced in Fig. 1.: $[\alpha]_{589}$ −67°, $[\alpha]_{317.5}$ +6°, $[\alpha]_{282.5}$ −855°, $[\alpha]_{275}$ −633°.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18; O, 12.68; OCH_3, 12.29. Found:[41] C, 76.70; H, 11.15; O, 12.41; OCH_3, 10.98.

In a larger scale experiment, 3.02 g. of epitetrahydrohydroxyeremophilone methyl ether (XXXIV) was chromatographed on 150 g. of Merck acid-washed alumina. Elution with benzene (800 cc.) removed 1.48 g. of material and the infrared spectrum of the earlier eluted portion (500 mg.) indicated the presence of some 9-demethoxylated material. Analysis of a distilled portion of one of the early benzene eluates confirmed this assumption.

Anal. Found for $C_{16}H_{28}O_2$: C, 78.25; H, 11.17; OCH_3, 5.95.

The benzene–ether eluates (700 cc.) yielded various fractions (totaling 1.28 g.) whose infrared spectra were identical and these were also superimposable upon those of the later benzene eluates. Distillation of a portion afforded an analytical sample which was pure **epitetrahydrohydroxyeremophilone methyl ether (XXXIV)**. Its rotatory dispersion curve was identical with the above-described specimen.

Anal. Found for $C_{16}H_{28}O_2$: C, 76.04; H, 11.31; OCH_3, 12.08.

Since the calcium–ammonia demethoxylation proceeded in an identical fashion with either the pure methyl ether XXXIV or the partially demethoxylated material (methoxyl analysis, 5.95) only the experiment with the pure substance is reported.

The pure epitetrahydrohydroxyeremophilone methyl ether (XXXIV) (1.08 g.) in 10 cc. of dioxane was added dropwise to a solution of 1.5 g. of calcium dissolved in 150 cc. of liquid ammonia and the mixture was permitted to reflux for 1 hr. under a Dry Ice–acetone cold finger condenser. The condenser was then removed, the ammonia was allowed to evaporate overnight, methanol and then saturated ammonium chloride solution were added and the mixture extracted with ether. After washing, drying and evaporation, the residue (937 mg.) was distilled at 70–80° (0.05 mm.) to afford *ca.* 800 mg. of viscous oil solidifying to a gummy solid. The infrared spectrum indicated the presence of only a trace of ketone, the bulk of the substance being the

(41) The analytical results indicate some contamination with demethoxylated ketone and this was confirmed below by chromatographic separation.

alcohol XXXV. The entire material was oxidized in acetic acid solution with 0.4 g. of chromium trioxide and then processed in the standard manner. Distillation of the crude product gave a colorless oil, whose infrared spectrum (run as a film as well as in chloroform solution) was completely superimposable upon that of synthetic *trans*-5,10-dimethyl-3α-isopropyldecalone-2 (XXIX). The substance exhibited a positive Cotton effect, similar to that of the synthetic ketone XXIX, the only difference being that the amplitude was somewhat reduced (peak in methanol solution at $[\alpha]_{312}$ +436°). A portion of the ketone was transformed into its semicarbazone, m.p. 178–181°, which proved to be identical by mixture melting point determination with the semicarbazone of the synthetic specimen.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH.]

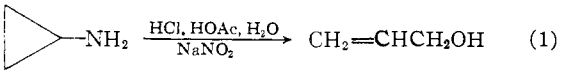
Cyclopropane Chemistry. IX. Nitrous Acid Deamination of 1-Amino- and 1-Aminomethylnortricyclene[1,2]

BY HAROLD HART AND ROBERT A. MARTIN

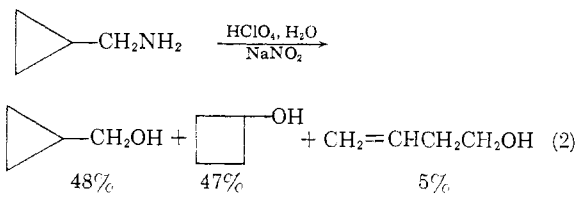
RECEIVED JUNE 16, 1960

The bridgehead cyclopropylamine 1-aminonortricyclene (XI), when treated with nitrous acid in glacial acetic acid, gave a single acetate, 1-acetoxynortricyclene (XII) in 55% yield, confirming earlier work of Lipp and Padberg[6] on apotricyclylamine. 1-Aminomethylnortricyclene (XV), a cyclopropylcarbinylamine, gave under similar conditions a comparable yield of esters, *91–92% of which was unrearranged acetate XVI.* The balance was 5% of 6-acetoxynorcamphor (XVII) and 3–4% of nitrate ester. Thermal rearrangement of the acetates (XVI → XVII) was observed on vapor chromatography (silicone, 132°). Possible reasons for the relatively small amount of rearrangement on deamination of XV are discussed.

As with most primary aliphatic amines, the nitrous acid deamination of both cyclopropylamine and cyclopropylcarbinylamine is known to give large percentages of rearranged products. Thus allyl alcohol is reportedly[3] the only neutral product from the action of aqueous nitrous acid on cyclopropylamine. In aqueous perchloric acid, the three alcohols shown in 2 were obtained from

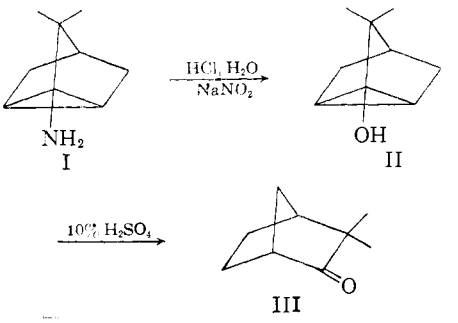


cyclopropylcarbinylamine in 60% yield[4]; the methylene carbons were extensively scrambled.[5]



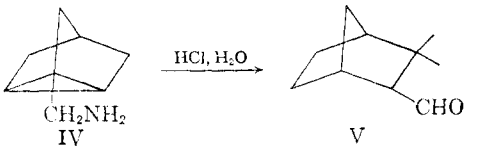
The number of cyclopropyl compounds of this type that has been studied, however, is relatively small and the only precise work by modern standards is that of Roberts.[4,5]

A few examples appear in the older terpene literature, of deaminations of primary amines in which the amino group is either directly attached to, or one carbon removed from, a three-membered ring. Lipp and Padberg[6] reported that apotricyclylamine (I) hydrochloride gave apotricyclol (II) in 50–55% yield. The structure was inferred from the ready conversion of II to camphenilone



(III) with acid.[7] The tricyclic structure of I precludes rearrangement of the cyclopropyl cation to an allylic structure[8]; hydride or methyl shifts are conceivable but were not observed.

Lipp also investigated the corresponding carbinylamine (ω-aminotricyclylamine, IV.[8] The amine itself was relatively unstable in acid. An aqueous solution of its hydrochloride, when saturated with hydrogen chloride and heated for 10 minutes, gave camphenilaldehyde (V) on steam distillation.[9] With aqueous nitrous acid, IV-hydrochloride



gave an aldehyde-smelling oil which reduced ammoniacal silver.[8,10]

Two cyclopropylcarbinyl amines are reportedly deaminated without rearrangement. The reduc-

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(2) For the previous paper in this series, see H. Hart and J. A. Wrede, *J. Org. Chem.*, **25**, 1811 (1960).

(3) P. Lipp, J. Buchkremer and H. Seeles, *Ann.*, **499**, 1 (1932).

(4) J. D. Roberts and R. H. Mazur, THIS JOURNAL, **73**, 2509 (1951).

(5) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(6) P. Lipp and C. Padberg, *Ber.*, **54B**, 1316 (1921).

(7) II was obtained analytically pure only as the phenylurethane; the alcohol itself was an unstable solid, m.p. 75–80°, which became an oil on standing for a few hours in air.

(8) P. Lipp, *Ber.*, **53B**, 769 (1920).

(9) An analogous rearrangement of 2-aminotricyclene to camphor (and polymer) was reported by H. L. Hoyer, *ibid.*, **87**, 1849 (1954).

(10) The product was obviously a mixture (it contained nitrogen) and was not further investigated by Lipp. The statement in J. L. Simonsen, "The Terpenes," 2nd Ed., Vol. 2, Cambridge University Press, 1949, pp. 335–336, is somewhat misleading, in that V is reported to be the product of the reaction of IV with nitrous acid. Lipp[8] did not make this claim in the original paper.