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

Terpenoids. XXXVIII.[1] Interconversion of Eremophilone, Hydroxyeremophilone and Hydroxydihydroeremophilone. The Relative Stereochemistry of Eremophilone and its Reduction Products[2,3]

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Hydroxydihydroeremophilone (Ia) forms a monoacetate Ib, which can be deacetoxylated with calcium in liquid ammonia to provide *cis*-dihydroeremophilone (IX). Similar treatment of hydroxytetrahydroeremophilone acetate (Vb) leads to *cis*-tetrahydroeremophilone (VII). Both VII and IX have been obtained earlier from eremophilone (II) and these stereochemically unambiguous interconversions establish the relative configuration of eremophilone as well as of its reduction products (VI, VII, IX). *cis*-Decalones are more stable than the *trans* isomers in this series because of the β-oriented isopropenyl and isopropyl substituents. Bismuth oxide oxidation of hydroxydihydroeremophilone (Ia) provides a facile synthesis of hydroxyeremophilone (IVa).

Eremophilone (II), hydroxyeremophilone (IVa) and hydroxydihydroeremophilone (Ia) are three sesquiterpenes which have been isolated from the oil of the Australian tree *Eremophila mitchelli* and whose skeletal structures have been established by Simonsen, Penfold and their collaborators.[5] The most interesting feature of these substances is that they do not follow the isoprene rule, but can be considered[6] to arise by methyl migration of eudalene precursors possessing the usual isoprenoid skeleton. In order to gain insight into this biogenetic process, it is indispensable that precise information regarding the stereochemistry of these substances be accumulated. The present paper is concerned with the determination of the relative configuration of eremophilone (II) and several of its reduction products. This knowledge was needed in order to devise a stereochemically unambiguous synthesis—now under way in our laboratory—of eremophilone (or one of its transformation products) starting with an intermediate[7] of known, absolute configuration.

Any rigorous treatment of the stereochemistry of eremophilone (II) should start most conveniently with hydroxydihydroeremophilone (Ia) since its relative configuration[8] has been established by the elegant X-ray analysis[9] of Grant and Rogers. Two experimental interconversions have been reported by Simonsen, *et al.*, but neither is of any definite stereochemical validity insofar as ring B is concerned. The first[10] involves the conversion of eremophilone (II) into its epoxide III followed by successive treatment with acetic anhydride and sodium acetate and then alkali to furnish the naturally occurring hydroxyeremophilone (IVa).[11,12] Reduction of either hydroxydihydroeremophilone (Ia) or hydroxyeremophilone (IVa) with sodium in alcohol provided the same saturated glycol.[13] Since all asymmetric centers in ring B have been destroyed in converting eremophilone (II) into hydroxyeremophilone (IVa), this sequence of reactions relating II and IVa with the stereochemically defined[9] standard, hydroxydihydroeremophilone (Ia), proves only that all three naturally occurring sesquiterpenes have the same orientation with respect to the two methyl groups.

The second route[10] involved catalytic hydrogenation of hydroxydihydroeremophilone (Ia) to hydroxytetrahydroeremophilone (Va) followed by reduction with sodium amalgam in aqueous ethanol over a period of 12 hr., which furnished "tetrahydroeremophilone" (VII).[14,15] We have already shown earlier[15] that the ring juncture in tetrahydroeremophilone is readily inverted (VI → VII) and since the reduction of hydroxytetrahydroeremophilone (Va) was conducted over a prolonged period of time in a strongly alkaline medium, inversion of the ring juncture and/or the isopropyl group was quite conceivable[16] by proceeding *via* the ene-diol. This inherent uncertainty coupled

(1) Paper XXXVII, C. Djerassi, M. Cais and L. A. Mitscher, THIS JOURNAL, **81**, 2386 (1959).

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(3) Presented in part before the Division of Organic Chemistry at the Chicago Meeting of the American Chemical Society, September 9, 1958; see Abstracts of Meeting, p. 26-P.

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(5) For pertinent reviews see: (a) J. Simonsen and D. H. R. Barton "The Terpenes," Cambridge University Press, 1952, Vol. III, pp. 212–224; (b) D. H. R. Barton, *Proc. Chem. Soc.*, 81 (1958).

(6) This suggestion has been made over twenty years ago by R. Robinson (see R. Robinson "The Structural Relations of Natural Products," Oxford University Press, 1955, p. 12).

(7) A. J. Speziale, J. A. Stephens and Q. E. Thompson, THIS JOURNAL, **76**, 5011 (1954).

(8) We are employing an absolute representation which has recently been established in our Laboratory (ref. 31) by converting hydroxyeremophilone (IVa) into a synthetic intermediate of known absolute configuration. In an earlier paper (ref. 15), we suggested tentatively the opposite absolute configuration on the basis of rotatory dispersion comparisons with certain steroid models. This comparison was predicated on an α-oriented isopropenyl substituent and since the latter has now been shown to be β-oriented it is apparent that the conformational alteration in eremophilone (II)—produced by the interaction of the isopropenyl function and the angular methyl group—makes invalid our earlier comparisons with steroid reference ketones.

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

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

(11) For the sake of simplicity, we are using only the representation IV, a discussion of the various tautomeric forms being deferred for a future paper dealing with diosphenols in the eremophilone series.

(12) A mechanism for this unusual rearrangement (see also T. A. Geissman, THIS JOURNAL, **75**, 4008 (1953)) has been proposed by D. H. R. Barton and P. de Mayo, *Quart. Revs.*, **11**, 193 (1957).

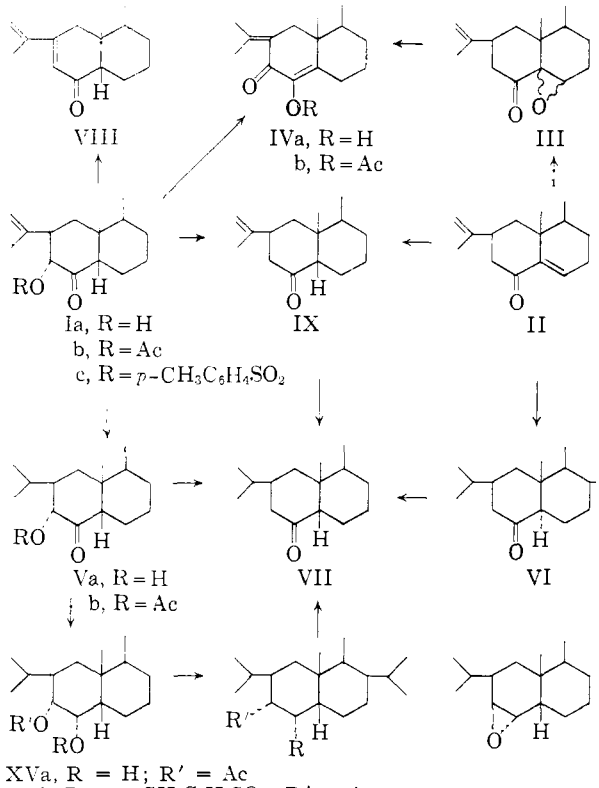
(13) See p. 221 in ref. 5a, as well as A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 87 (1939).

(14) No stereochemical assignments were made by Bradfield, Penfold and Simonsen (ref. 10) and we are anticipating our subsequent arguments by employing the correct relative configurations.

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

(16) See footnote 56 in ref. 15.

with the unspecified yield made it imperative to select another means of interconversion.



Our starting material was hydroxydihydroeremophilone (Ia), whose relative configuration is known.[9] Acetylation with acetic anhydride and pyridine either at 0° or at 100° afforded the crystalline *mono*-acetate Ib. Its melting point coincided exactly with that recorded by Simonsen and collaborators,[10] who, however, reported[10,17] that it was an enol-*di*acetate. Since the mono-acetate Ib represented the key intermediate in our subsequent transformations, its constitution was established as follows, Simonsen's assumption of an enol-diacetate[10,17] apparently being due to faulty analytical results. The presence of an isolated carbonyl group in the monoacetate Ib was demonstrated by the presence of a low intensity ultraviolet absorption band at 281 mμ and by an anomalous[18] rotatory dispersion curve typical[19] of a saturated ketone function. This rotatory dispersion was characterized by a negative Cotton effect curve superimposed on a positive background rotation[18] and was identical in shape with that of hydroxydihydroeremophilone (Ia), thus affording strong indication that no stereochemical alteration was involved. The presence of a single acetyl group was further established by the analytical results including acetyl determination. Furthermore, hydrogenation of hydroxydihydroeremophilone (Ia) led to hydroxytetrahydroeremophilone (Va)[10] and this upon acetylation also gave a monoacetate (Vb), identical with a specimen obtained by catalytic hydrogenation of hydroxydihydroeremophilone monoacetate (Ib). This sequence of reactions indicates that acetylation did not affect the olefinic system and it is also pertinent to note that the rotatory dispersion curves of hydroxydihydroeremophilone (Ia) and hydroxytetrahydroeremophilone (Va) were very similar in shape and amplitude.[18]

Our initial attempts to remove the hydroxyl function of hydroxydihydroeremophilone (Ia) in order to accomplish a tie-up with a derivative of eremophilone (II) involved treatment of its acetate Ib or tosylate Ic with zinc dust in acetic anhydride,[20] but in each case only unreacted starting material could be recovered. Heating of hydroxydihydroeremophilone tosylate (Ic) with sodium iodide resulted in partial elimination of the tosylate function, but difficulties in the purification of the dienone VIII led us to abandon this approach in favor of the calcium-ammonia deacetoxylation procedure[21] which has proved to be so successful in the steroid series.[22,23]

When hydroxydihydroeremophilone acetate (Ib) was submitted to these conditions[21-23] there was isolated without difficulty dihydroeremophilone (IX), which had been obtained earlier[10,15] by sodium–alcohol reduction of eremophilone (II) followed by oxidation with chromium trioxide. Mechanistically,[22,24] no inversion of the isopropenyl substituent is to be expected in the calcium–ammonia deacetoxylation, from which it follows that the orientation of the isopropenyl group of eremophilone (II) must be β[8] as has been established by X-ray analysis[9] for hydroxydihydroeremophilone (Ia). As pointed out below, this in turn requires a *cis* ring juncture, which in this case is the thermodynamically more stable one resulting from sodium–alcohol reduction (followed by reoxidation) of eremophilone (II). In agreement with this conclusion is the smooth catalytic hydrogenation in a neutral medium of (*cis*)-dihydroeremophilone (IX) to *cis*-tetrahydroeremophilone (VII).

When the calcium–ammonia procedure was applied to hydroxytetrahydroeremophilone acetate (Vb), there was obtained in good yield *cis*-tetrahydroeremophilone (VII),[25] which in turn is derived

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

(18) For nomenclature of rotatory dispersion results and recording of experimental data see C. Djerassi and W. Klyne, *Proc. Soc. Chem.*, 55 (1957).

(19) See C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

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

(21) J. H. Chapman, J. Elks and L. J. Wyman, *Chemistry & Industry*, 603 (1955).

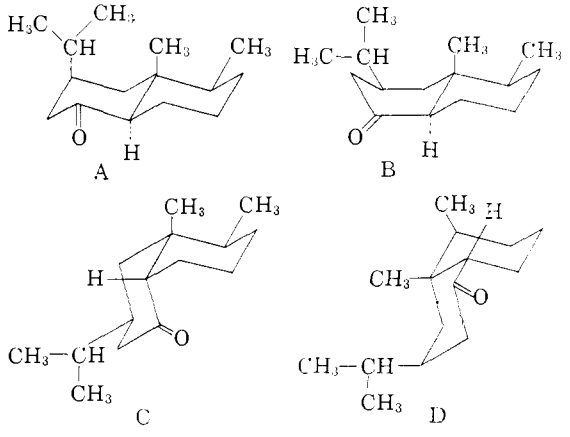
(22) J. H. Chapman, J. Elks, G. H. Phillipps and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(23) J. S. Mills, H. J. Ringold and C. Djerassi, THIS JOURNAL, **80**, 6118 (1958).

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

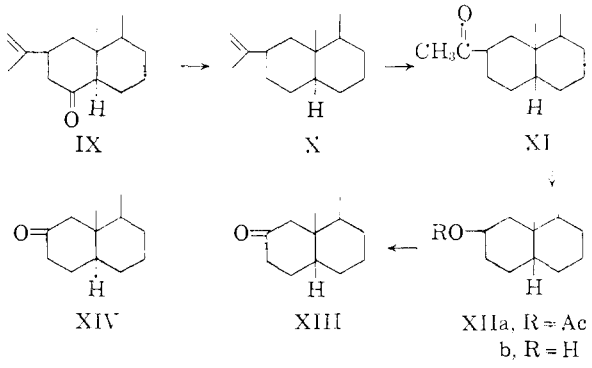
(25) In our earlier paper (ref. 15), we had assumed that the isopropenyl group was α-oriented, which required that the stable tetrahydroeremophilone should be assigned the *trans* and the unstable isomer the *cis* ring juncture. In view of the present demonstration of the β-configuration of the isopropenyl group, these assignments have to be reversed. This had already been assumed (private communication) by Dr. D. Rogers (University College, Cardiff), prior to our rigorous establishment of the β-orientation of the isopropenyl group.

from the acid isomerization[15] of the initially produced[15] hydrogenation product of eremophilone (II). This unstable product must, therefore, be the *trans* isomer VI and this complete reversal of the usual stability relationship of *trans*- (more stable) and *cis*-10-methyl-1-decalones[26,27] is due to the β-orientation of the bulky isopropyl (or isopropenyl in IX) substituent in the tetrahydroeremophilones VI and VII. The *trans* isomer VI exists either in the all-chair conformation A, possessing a very unfavorable diaxial interaction between the angular methyl group and the isopropyl substituent, or in the boat-chair conformation B. Either one appears to be distinctly less favorable than the all-chair conformation C[28] of the *cis* isomer VII, where no such interaction exists. If the isopropyl group had possessed the alternate α-orientation,[25] then this stability relationship would have been reversed.



With this information at hand, it was of interest to repeat Simonsen's sodium amalgam reduction[10] of hydroxytetrahydroeremophilone (Va). The resulting product was contaminated by unreacted starting material, but chromatographic separation afforded some *cis*-tetrahydroeremophilone (VII).

An alternate and more circumstantial demonstration of the *cis*-ring juncture—and *ipso facto* of the β-orientation of the isopropenyl group—in (*cis*)-dihydroeremophilone (IX) can be presented by the following experiments: Wolff–Kishner reduction of *cis*-dihydroeremophilone (IX) furnished[15] *cis*-desoxydihydroeremophilone (X)[29] which was ozonized to the methyl ketone XI. Oxidation with trifluoroperacetic acid[30] and saponification of the resulting acetate XIIa led to the alcohol XIIb, which was oxidized with chromium trioxide to the ketone XIII. The latter proved to be different from an authentic specimen of the *trans* isomer XIV, which has been obtained[31] in optically active form by an unambiguous synthesis.



The above interconversions between hydroxydihydroeremophilone (Ia) and eremophilone (II) settle the complete relative stereochemistry of eremophilone and of its reduction products (VI, VII, IX). As far as the remaining naturally occurring member of this group is concerned, hydroxyeremophilone (IVa) has so far only been obtained[10] from eremophilone (II) *via* the epoxide III. It was of interest to attempt a direct interconversion of hydroxyeremophilone (IVa) with the stereochemical standard[9] hydroxydihydroeremophilone (Ia), especially since hydroxyeremophilone was required by us for chemical transformations and at the time these investigations were started, only hydroxydihydroeremophilone (Ia) was available to us. After several unsuccessful attempts, an extremely simple and efficient process was discovered by oxidizing hydroxydihydroeremophilone (Ia) with bismuth oxide,[32] hydroxyeremophilone (IVa) being obtained directly. Identity with the natural material was confirmed by preparation of the crystalline enol acetate IVb[11] and direct comparison with an authentic specimen.

In connection with our synthetic studies[31] in the eremophilone series, attempts were made to prepare certain "relays" derived from one of the naturally occurring members of this group. These experiments failed but since they are of intrinsic interest they will be recorded briefly at this point. Emphasis was placed at removing the carbonyl group adjacent to the ring juncture in hydroxydihydro-(Ia) or hydroxytetrahydro-(Va) eremophilone, but we were unable to prepare in acceptable yield any carbonyl derivatives (semicarbazone, 2,4-dinitrophenylhydrazone, ethylenethioketal) of these substances or of hydroxytetrahydroeremophilone acetate (Vb). Apparently hindrance[33] of the carbonyl group by the shielding of ring A in conformation C coupled with the adjacent hydroxy or acetoxy substituent was sufficient to prevent formation of derivatives suitable for removal of the

(26) C. Djerassi and D. Marshall, THIS JOURNAL, **80**, 3986 (1958).

(27) F. Sondheimer and D. Rosenthal, *ibid.*, **80**, 3995 (1958).

(28) The alternate "non-steroid all chair *cis*" conformation D of VII is clearly excluded since it contains three rather than just one (as in C) axial alkyl substituents.

(29) This substance was called in our earlier paper (ref. 15) "*trans*-desoxydihydroeremophilone" for reasons outlined in ref. 25. It is appreciated that the unstable ring juncture could have been generated during this Wolff–Kishner reduction by a "kinetic inversion" (see C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166 (1956)) and the absence of such inversion was only demonstrated by the non-identity of the final product XIII with the corresponding *trans* isomer XIV.

(30) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955).

(31) L. H. Zalkow, F. X. Markley and C. Djerassi, *ibid.*, **81**, 2914, (1959).

(32) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(33) Simonsen and collaborators (ref. 10) report the formation in unspecified yield of 2,4-dinitrophenylhydrazones of Ia and Va, but since the method of preparation of these derivatives was not disclosed, we were unable to duplicate their experiments. In our hands, all of the conditions outlined in the Experimental section furnished largely recovered starting material and intractable oils.

carbonyl function. If the ketone is not flanked by an additional substituent as in VII and IX, then derivatives can be obtained readily, the 2,4-dinitrophenylhydrazones being particularly suitable for characterization purposes.

As an alternate approach, there were examined the sodium borohydride reduction of hydroxytetrahydroeremophilone acetate (Vb), since it was hoped that the expected monoacetate XVa upon conversion to the tosylate XVb followed by treatment with lithium aluminum hydride would lead to the alcohol XVIa. In actual fact, the sodium borohydride reduction took an unexpected course: the reaction product consisted of a chromatographically separable mixture of glycol (XVc)[34] and hydroxy-monoacetate, but the latter apparently did not have the anticipated constitution XVa. Rather it should be represented by the isomeric representation XVd—arising from base-catalyzed ester interchange[35a]—since converison to the acetate-tosylate XVe followed by reduction with lithium aluminum hydride led to an alcohol which had to be XVIb because of its oxidation to the known *cis*-tetrahydroeremophilone (VII). An alternate explanation for the formation of the alcohol XVIb (rather than the expected XVIa) based on the tosylate-acetate structure XVb might be production of an oxide XVII in the lithium aluminum hydride reduction of XVb (the acetate function being cleaved first and the resulting anion displacing the tosylate)[35b] followed by further "diaxial opening" of the oxide XVII. Such a reaction course, however, appears less likely since the stereochemistry of XV[34] is not favorable for oxide XVII formation.

Further work in the eremophilone series, particularly with regard to the establishment of absolute configuration, is now in progress.

Acknowledgment.—We are indebted to Messrs. H.H.G. McKern and F. R. Morrison of the Museum of Applied Arts and Sciences, Sydney, Australia, for the initial specimen of eremophilone and hydroxydihydroeremophilone. Special thanks are due to Dr. Maurice Sutherland of the University of Queensland, Brisbane, Australia, who supplied us generously and continuously with hydroxydihydroeremophilone and hydroxyeremophilone. The presently reported investigation could not have been carried to completion without his help.

Experimental[36]

Hydroxydihydroeremophilone Acetate (Ib).—A solution of 236 mg. of hydroxydihydroeremophilone (Ia)[37] in 2 cc. of pyridine and 1 cc. of acetic anhydride was kept on the steam-bath for 2.5 hr., poured into water and extracted with chloroform. After washing with dilute acid, base and water, drying and evaporating, the residue was recrystallized twice from aqueous methanol to yield 147 mg. of colorless crystals, m.p. 68–70°. When the reaction was conducted for 2 days in the refrigerator, the yield of identical acetate Ib was raised to 192 mg. The analytical sample possessed the same m.p. and exhibited $\lambda_{max}^{CHCl_3}$ 5.75, 5.80, 6.07, 7.95–8.00 and 11.12 μ; λ_{max}^{EtOH} 286 mμ, log ϵ 1.77; R.D. in methanol (*c* 0.243 (700–305 mμ), 0.0486 (300–265 mμ)): $[\alpha]_{700}$ +82°, $[\alpha]_{589}$ +120°, $[\alpha]_{335-340}$ +369°, $[\alpha]_{310}$ +206°, $[\alpha]_{278}$ +1331°, $[\alpha]_{265}$ +1034°.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41; O, 17.24; acetyl, 15.46. Found: C, 73.38; H, 9.27; O, 17.87; acetyl, 13.52.

The crystalline acetate was recovered unchanged after heating under reflux with ten times its weight of zinc dust in xylene solution or with mossy zinc (pretreated with dilute hydrochloric acid, then washed with acetone and ether) in acetic anhydride.[20]

Hydroxydihydroeremophilone Tosylate (Ic).—A solution of 472 mg. of hydroxydihydroeremophilone (Ia) and 1.14 g. of *p*-toluenesulfonyl chloride in 5 cc. of pyridine was kept at room temperature for 2 days and then poured into ice-water. The resulting precipitate was collected and recrystallized from methanol and then aqueous methanol, whereupon it exhibited m.p. 138–140°. The analytical sample was obtained from hexane and showed the same m.p.; R.D. in methanol (*c* 0.258 (700 – 300 mμ), 0.0516 (295–275 mμ)): $[\alpha]_{700}$ +61°, $[\alpha]_{589}$ +93°, $[\alpha]_{345-350}$ +255°, $[\alpha]_{313}$ +15°, $[\alpha]_{280}$ +1240°, $[\alpha]_{275}$ −1255°.

Anal. Calcd. for $C_{22}H_{30}O_4S$: C, 67.63; H, 7.74. Found: C, 68.01; H, 7.68.

A total of 334 mg. of unchanged tosylate Ic was recovered when 410 mg. of it was heated under reflux for 15 min. with 575 mg. of zinc dust and 10 cc. of acetic anhydride. In another experiment, 390 mg. of the tosylate Ic was heated in a bomb at 100° for 10 hr. with 1.5 g. of sodium iodide and 20 cc. of acetone. The precipitate of sodium *p*-toluenesulfonate (182 mg.) was filtered, most of the acetone was removed by distillation *in vacuo* and the residue was taken up in chloroform. After washing with dilute sodium thiosulfate solution and water, the chloroform extract was dried and evaporated leaving 227 mg. of yellowish oil. Two distillations at 0.01 mm. and a bath temperature of 60–90° furnished a colorless oil, whose spectroscopic properties indicated that it represented the dienone VIII contaminated with a product possessing a saturated carbonyl group: $\lambda_{max}^{CHCl_3}$ 5.83 and 6.00 μ (strongest band of spectrum), λ_{max}^{EtOH} 268 mμ, log ϵ 3.66 mμ.

Hydroxytetrahydroeremophilone Acetate (Vb). (a) By Acetylation of Hydroxytetrahydroeremophilone (Va).—The hydrogenation of 472 mg. of hydroxydihydroeremophilone (Ia) was conducted at atmospheric pressure and 30° in ethyl acetate solution (5 cc.) with 10% palladized charcoal catalyst, hydrogen consumption stopping after 15 min. The solution was filtered, the solvent was evaporated and the residue was recrystallized twice from aqueous methanol to provide 325 mg. of pure **hydroxytetrahydroeremophilone (Va)**,[10] m.p. 84–85°, λ_{max}^{EtOH} 281 mμ, log ϵ 1.77; R.D. in methanol (*c* 0.246 (700–300 mμ), 0.0492 (295–270 mμ)): $[\alpha]_{700}$ +48°, $[\alpha]_{589}$ +70°, $[\alpha]_{355-360}$° +176°, $[\alpha]_{310}$ −114°, $[\alpha]_{278}$ +963°, $[\alpha]_{270}$ +590°.

Attempts to prepare a 2,4-dinitrophenylhydrazone with Brady solution at room temperature for 1–3 days led to recovered starting material and about 2% of a 2,4-dinitrophenylhydrazone, m.p. 226–234° (lit.[10] m.p. 210–220°), which was not investigated further. Treatment of hydroxytetrahydroeremophilone (Va) with semicarbazide hy-

(34) We are assigning the axial orientation to the newly formed hydroxyl group by analogy to the stereochemical course of the hydride reduction of coprostan-6-one (D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955)).

(35) (a) A similar observation has been made recently in the sodium borohydride reduction of a steroidal 21-acetoxy-20-ketone which furnished the 20-acetate of the 20,21-glycol (D. Taub, R. D. Hoffsommer and N. L. Wendler, American Chemical Society, New York, September, 1957, Abstracts, Division of Organic Chemistry, p. 23-P); (b) see H. L. Goering and C. Serres, THIS JOURNAL, **74**, 5908 (1952).

(36) Melting points were determined on the Kofler block. We are indebted to Miss B. Bach for the infrared spectra and to Mrs. T. Nakano for the rotatory dispersions. The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany.

(37) This material was recrystallized from aqueous ethanol and then from hexane. The colorless crystals exhibited m.p. 99–102°, λ_{max}^{EtOH} 281 mμ, log ϵ 2.54, λ_{max}^{MeOH} 281 mμ, log ϵ 2.50 and λ_{max}^{diox} 281 mμ, log ϵ 2.50 the large value for log ϵ may be due to the presence of small amounts of the corresponding diosphenol; R.D. in methanol (*c* 0.338 (700–337.5 mμ), 0.0676 (330–307.5 mμ), 0.0135 (305–285 mμ)): $[\alpha]_{700}$ +55°, $[\alpha]_{589}$ +76°, $[\alpha]_{340-345}$ +250°, $[\alpha]_{305}$ −103°, $[\alpha]_{285}$ +2103°. The product was recovered largely unchanged when treated with 2,4-dinitrophenylhydrazine in acetic acid solution for 40 hr. When kept with Brady solution for 3 days at room temperature, there was obtained a 3% yield of a derivative, m.p. 242–245° (reported m.p. 241° in ref. 10, 33), whose infrared spectrum did not show any more the infrared band at 11.2 μ typical of the isopropenyl double bond.

drochloride and sodium acetate in ethanol solution at room temperature for 2 days or heating a methanol–pyridine solution with semicarbazide hydrochloride under reflux for 20 hr. under nitrogen led to recovered starting material in 74–84% yield.

Acetylation of 2.0 g. of hydroxytetrahydroeremophilone (Va) was accomplished by leaving a solution of it in 15 cc. of pyridine and 10 cc. of acetic anhydride at 0° for 2 days. After processing in the usual manner, there was obtained 2.23 g. of colorless crystals, m.p. 51–53°, which were suitable for further transformations. The analytical sample, recrystallized from aqueous methanol, exhibited m.p. 51–53° and was distilled at 0.03 mm. before analyzing; λ_{max}^{EtOH} 287 mμ, log ε 1.29; R.D. in methanol (*c* 0.216 (700-292.5 mμ), 0.043 (290-257.5 mμ)): $[\alpha]_{700}$ +94°, $[\alpha]_{589}$ +140°, $[\alpha]_{330-325}$ +547°, $[\alpha]_{300}$ +417°, $[\alpha]_{292.5}$ +1797°, $[\alpha]_{257.5}$ +1676°.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06; O, 17.12. Found: C, 72.48; H, 9.92; O, 17.02.

(b) By Hydrogenation of Hydroxydihydroeremophilone Acetate (Ib).—The hydrogenation of 43.4 mg. of hydroxydihydroeremophilone acetate (Ib) was performed in a microhydrogenation apparatus in methanol solution with 10% palladized charcoal catalyst, the hydrogen uptake corresponding to 1.03 equivalents. Filtration of the catalyst, concentration of the solution to a volume of 0.5 cc. and addition of a few drops of water provided 37 mg. of Vb, m.p. 51–53°. Identity with a specimen of hydroxytetrahydroeremophilone acetate (Vb) prepared according to procedure a was established by mixture melting point determination as well as coincidence of the infrared spectra and rotatory dispersion curves; R.D. in methanol (*c* 0.103 (700–290 mμ), 0.0206 (285–265 mμ)): $[\alpha]_{700}$ +94°, $[\alpha]_{589}$ +150°, $[\alpha]_{330-325}$ +502, $[\alpha]_{312.5}$ +406°, $[\alpha]_{270}$ +1703°, $[\alpha]_{265}$ +1480°.

The acetate Vb did not form a 2,4-dinitrophenylhydrazone when heated under reflux for 3–5 min. with a solution of 2,4-dinitrophenylhydrazine in ethanol–hydrochloric acid; only unreacted acetate Vb and some hydroxytetrahydroeremophilone (Va)—produced by acid cleavage—were isolated. Similar failure was encountered in attempts to prepare the semicarbazone in ethanol–water (4 hr., room temperature) with semicarbazide hydrochloride and sodium acetate, 84% of pure acetate being recovered. When the acetate Vb was treated with ethanedithiol in the presence of boron trifluoride[38] or perchloric acid,[39] no mercaptal was isolated but 76–85% of unreacted acetate was encountered.

***cis*-Dihydroeremophilone (IX) from Hydroxydihydroeremophilone Acetate (Ib).**—A toluene solution of 278 mg. of hydroxydihydroeremophilone acetate (Ib) was added with vigorous stirring over a period of 5 min. to 2.0 g. of calcium metal dissolved in 50 cc. of liquid ammonia at −33°. The mixture was stirred for an additional 5 min. under anhydrous conditions, 2 cc. of bromobenzene[22] was then added cautiously followed by 10 cc. of water. The ammonia was allowed to evaporate over a 3-hr. period, the suspension was then concentrated *in vacuo* to near dryness and the residue was partitioned between chloroform and hydrochloric acid. Evaporation of the washed and dried organic phase followed by distillation at 0.01 mm. and a bath temperature of 110–140° yielded a pale yellow oil in *ca.* 80% yield. Redistillation provided the analytical sample of *cis*-dihydroeremophilone (IX), whose infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.83, 6.02 and 11.18 μ) was identical (run as microcapill.) with that of a specimen[10,15] derived from eremophilone (II); R.D. in methanol (*c* 0.247 (700–320 mμ), 0.0494 (315–290 mμ), 0.0247 (285–275 mμ)): $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +38°, $[\alpha]_{400-395}$ +63°, $[\alpha]_{313}$ −372°, $[\alpha]_{275}$ +1732°.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98; O, 7.26. Found: C, 82.21; H, 10.66; O, 7.03.

The 2,4-dinitrophenylhydrazone of IX was prepared in ethanolic hydrochloric acid (2 min. refluxing) and crystallized as yellow needles, m.p. 173–174°, from methylene dichloride–methanol. The identical derivative (mixture melting point and infrared comparison) was obtained from *cis*-dihydroeremophilone (IX) derived[15] from eremophilone (II).

Anal. Calcd. for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99; O, 15.98. Found: C, 62.77; H, 7.08; N, 14.10; O, 15.93.

***cis*-Tetrahydroeremophilone (VII). (a) By Calcium–Ammonia Deacetoxylation of Hydroxytetrahydroeremophilone Acetate (Vb).**—The deacetoxylation of 1.39 g. of the acetate Vb in 50 cc. of toluene was performed exactly as described above for the acetate Ib, using 10 g. of calcium and 200 cc. of liquid ammonia except that the addition required 15 min. and that stirring was continued for an additional 30 min. The resulting *cis*-tetrahydroeremophilone (VII) (0.95 g.) was distilled at 0.005 mm. and a bath temperature of 110° and submitted for analysis. The infrared spectrum was identical with that of *cis*-tetrahydroeremophilone (VII) obtained[15,25] by catalytic reduction of eremophilone (II) followed by acid isomerization of the initially produced *trans* isomer VI.[15,25]

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.64; H, 11.55.

A sample of the ketone was transformed into its yellow 2,4-dinitrophenylhydrazone (ethanol–hydrochloric acid, 2 min. reflux) and the crude product (m.p. 175–178°) after one recrystallization from methylene dichloride–methanol exhibited m.p. 179–181°, undepressed upon admixture with an authentic specimen (m.p. 179–180°).[10,15] The infrared spectra in chloroform solution were superimposable.

(b) From *cis*-Dihydroeremophilone (IX).—A 32-mg. sample of *cis*-dihydroeremophilone (IX) obtained by calcium–ammonia deacetoxylation of hydroxydihydroeremophilone acetate (Ib) in ethanol solution consumed 3.49 cc. of hydrogen (97.8%) within one hour in the presence of 10% palladized charcoal. Distillation of the reduction product provided a colorless oil, whose infrared spectrum was identical with that of authentic *cis*-tetrahydroeremophilone (VII).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.93; H, 11.67.

The 2,4-dinitrophenylhydrazone exhibited m.p. 179–181°, undepressed upon admixture with an authentic sample.[15]

(c) From Hydroxytetrahydroeremophilone (Va).—The reduction of 238 mg. of hydroxytetrahydroeremophilone (Va) with 5 g. of 4% sodium amalgam was performed exactly as reported by Simonsen and collaborators.[10] The crude product (130 mg.) was distilled at 0.01 mm. and a bath temperature of 60–90°, but since the distilled sample still exhibited hydroxyl absorption in the infrared, it was chromatographed on Merck acid-washed alumina. The material (*ca.* 20 mg.) initially eluted with hexane, was distilled again and now exhibited an infrared spectrum (chloroform solution), which was very similar to that of authentic *cis*-tetrahydroeremophilone (VII), minor differences being noted at 10.0, 10.5 and 11.4 μ. The later eluates upon evaporation left a crystalline residue (m.p. 82–84°) which proved to be unreacted hydroxytetrahydroeremophilone (Va).

(d) From Hydroxytetrahydroeremophilone Acetate (Vb).—A mixture of 1.14 g. of hydroxytetrahydroeremophilone acetate (Vb), 0.60 g. of sodium borohydride and 25 cc. of methanol was left at room temperature for 2.5 hr., part of the methanol was distilled off on the steam-bath and aqueous hydrochloric acid was added until the solution was neutral. The product was isolated by ether extraction and was then chromatographed on Woelm alumina. The benzene–chloroform eluted material crystallized (m.p. range of different fractions 62–78°, 64–83° and 58–81°) and since it did not contain any carbonyl band in its infrared spectrum, it was assumed to be the glycol XVc and was not examined further.

The fraction eluted with pure benzene did not crystallize and since it exhibited infrared bands corresponding to hydroxyl and acetate functions, it was distilled for analysis at 0.03 mm. and a bath temperature of 140–160°. For reasons outlined in the Discussion section, this substance is believed to be the **hydroxy acetate XVd.**

Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.87; H, 11.37.

A portion of the hydroxy acetate XVd was heated in pyridine solution with an excess of *p*-toluenesulfonyl chloride for 1 hr. on the steam-bath and the crude **acetoxy-tosylate XVe** was purified by chromatography on Woelm alumina and eluted with benzene and benzene–chloroform (9:1).

(38) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

(39) D. L. Klass, M. Fieser and L. F. Fieser, *ibid.*, **77**, 3829 (1955); C. Djerassi, C. H. Robinson and D. B. Thomas, *ibid.*, **78**, 5085 (1956).

Recrystallization from hexane provided the analytical specimen, m.p. 129–131°.

Anal. Calcd. for $C_{24}H_{36}O_5S$: C, 66.03; H, 8.31. Found: C, 66.12; H, 8.42.

The above tosylate XVe (118 mg.) in 15 cc. of ether was added to a solution of 380 mg. of lithium aluminum hydride in 25 cc. of ether and after heating under reflux for 30 min., the excess reagent was decomposed with ethyl acetate. Addition of hydrochloric acid, extraction with ether, washing, drying and evaporation left 63 mg. of a colorless oil which was distilled at 0.01 mm. and which exhibited only hydroxyl absorption in the infrared. This alcohol (44 mg.), assumed to be *cis*-**tetrahydroeremophilol** (**XVIb**), was oxidized with chromium trioxide in acetic acid (15 min., room temperature) and the resulting ketone (40 mg.) was distilled at 0.005 mm. and a bath temperature of 50–80°. Its infrared spectrum was essentially identical as that of *cis*-**tetrahydroeremophilone** (VII) and identity was established conclusively by conversion to the 2,4-dinitrophenylhydrazone, m.p. and mixture m.p. 178–180°.

Conversion of *cis*-Desoxydihydroeremophilone (X) to 8,9-Dimethyl-2-acetyl-*cis*-decalin (XI).—The removal of the carbonyl group of *cis*-dihydroeremophilone (IX) has already been accomplished[15] by the Wolff–Kishner procedure, but the Huang-Minlon modification[40] proved to be more convenient. Nitrogen was bubbled through a solution of 475 mg. of *cis*-dihydroeremophilone (IX) and 0.3 g. of potassium hydroxide in 3 cc. of diethylene glycol, 0.4 cc. of 85% hydrazine hydrate and 0.4 cc. of absolute ethanol while heating in an oil-bath (160–165°) for 3 hr. The condenser was removed until the oil bath temperature reached 220° whereupon refluxing was continued for 6 hr. After cooling, the mixture was poured into water and extracted with ether. The washed and dried ether solution was concentrated by careful fractionation and the residue was then distilled at 10 mm., the distillate (286 mg., 64%) representing *cis*-desoxydihydroeremophilone (X) as demonstrated by infrared comparison with an authentic sample.[15]

An excess of ozone was passed through a solution of 265 mg. of *cis*-desoxydihydroeremophilone (X) in 12.5 cc. of acetic acid at room temperature and the mixture was then stirred for 2 hr. with 0.5 g. of ferrous sulfate and 35 cc. of water, poured into water and extracted with ether. The ether layer—after washing with bicarbonate solution, drying over sodium sulfate and distilling—gave 157 mg. of a pale yellow oil (b.p. 90–110° at 0.5–0.6 mm.) which represented the desired ketone XI, $\lambda_{max}^{CHCl_3}$ 5.80 μ; R.D. in dioxane (*c* 0.086 (700–310 mμ), 0.017 (300–285 mμ)): $[\alpha]_{700}$ +10.3°, $[\alpha]_{589}$ −5.8°, $[\alpha]_{312.5}$ −286°, $[\alpha]_{295}$ +211°.

For purposes of characterization, a portion of the ketone was treated in methanol–hydrochloric acid solution with 2,4-dinitrophenylhydrazine yielding an immediate yellow precipitate of the **2,4-dinitrophenylhydrazone of XI**, m.p. 132–135° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27. Found: C, 61.80; H, 7.50.

8,9-Dimethyl-*cis*-decalone-2 (XIII).—To 126 mg. of the ketone XI in 3 cc. of methylene dichloride was added a solution prepared by adding 0.6 cc. of trifluoroacetic anhydride to 0.1 cc. of 90% hydrogen peroxide in 2 cc. of methylene dichloride at 0°. After stirring at room temperature for 30 min. followed by heating under reflux for 45 min., the methylene dichloride solution was washed with 5% sodium carbonate solution, dried over sodium sulfate and concentrated to a small volume. To the residue consisting of the **acetate XIIa** was added 2 cc. of 1 *N* aqueous sodium hydroxide and enough ethanol to yield a homogeneous solution. After heating under reflux for 3 hr., an additional 2 cc. of 1 *N* sodium hydroxide was added and heating was continued for 45 min., whereupon the solution was poured into water and extracted with ether. Washing, drying and evaporation afforded **8,9-dimethyl-*cis*-decalol-2 (XIIb)** which was oxidized without purification in 5 cc. of acetic acid with 0.1 g. of chromium trioxide dissolved in 1 cc. of water and 5 cc. of acetic acid. After standing for 1 hr. at room temperature, much water was added, the product was extracted with ether, washed with water, dried and evaporated. Distillation of the residue at 0.5 mm. and a bath temperature of 70–90° yielded 39 mg. of **8,9-dimethyl-*cis*-decalone-2 (XIII)** as a colorless oil, whose infrared spectrum ($\lambda_{max}^{microcapill}$ 5.80 μ) differed considerably in the fingerprint region from that of the corresponding *trans* isomer XIV,[31] and its rotatory dispersion curve was also different; R.D. in methanol (*c* 0.078): $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −29°, $[\alpha]_{315}$ −178°, $[\alpha]_{307.5}$ +229°.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94: H, 11.18. Found: C, 80.25; H, 10.99.

The ketone failed to yield a crystalline 2,4-dinitrophenylhydrazone (even after chromatographing twice) in contrast to the *trans* isomer XIV, whose 2,4-dinitrophenylhydrazone[31] crystallized readily (m.p. 142–144°).

Bismuth Oxide Oxidation of Hydroxydihydroeremophilone (Ia) to Hydroxyeremophilone (IVa).—A solution of hydroxydihydroeremophilone (Ia) (1.926 g.), bismuth trioxide (4.0 g.) and acetic acid (20 cc.) was stirred in an atmosphere of nitrogen and the temperature was raised slowly to 100–105°, where it was maintained for one hour. After cooling to room temperature, the black and white precipitates were removed by filtration and the filtrate was poured on ice with stirring. A 91% yield of crude yellow hydroxyeremophilone (IVa) was obtained after washing with water and drying, and this material gave a black ferric chloride test. Recrystallization from ethanol led to 800 mg. of crystals, m.p. 62–63° raised to m.p. 64.5–65° upon further recrystallization from methanol. From the mother liquor an additional 675 mg. of material was obtained, melting from 55 to 60°. The pure specimen exhibited $\lambda_{max}^{CHCl_3}$ 2.95, 6.10 and 6.23 μ; λ_{max}^{EtOH} 309 mμ, log ϵ 4.01 (shifted to λ_{max} 356 mμ, log ϵ 3.79 upon addition of one drop of potassium hydroxide solution); $[\alpha]_{5461}$ +152° (*c* 2.41 in methanol). Identity with the natural material[10] (m.p. 62–63°, $[\alpha]_{5461}$ +153° (*c* 2.50 in methanol); λ_{max}^{EtOH} 310 mμ, log ϵ 4.02; $\lambda_{max}^{EtOH-KOH}$ 357 mμ, log ϵ 3.82) was shown by mixture melting point determination and coincidence of the infrared spectra; R.D. in dioxane (*c* 0.055 (700–370 mμ), 0.011 (370–360 mμ)): $[\alpha]_{700}$ +102°, $[\alpha]_{589}$ +138°, $[\alpha]_{360}$ −491°.

The identical acetate IVb (mixture melting point, infrared spectrum) was obtained from the natural and synthetic hydroxyeremophilone (IVa): a solution of 113 mg. of hydroxyeremophilone (IVa), 1.5 cc. of pyridine and 0.75 cc. of acetic anhydride was allowed to stand at room temperature for 2.5 days. The solution was then concentrated under reduced pressure and the residue taken up in ether. The ether solution was washed with cold dilute hydrochloric acid, bicarbonate solution, water and finally dried over magnesium sulfate. After removal of the ether the residue was distilled to give 88 mg. of a colorless viscous oil, b.p. 90–100° (0.09 mm.), whose infrared spectrum was identical with the crystalline material. This oil was crystallized from ethanol–water to give needles, m.p. 65–66°. The melting point was raised to 67.5–68° after several recrystallizations (methanol then pentane); $\lambda_{max}^{CHCl_3}$ 5.66, 5.99, 6.10, 8.60 and 9.80 μ; λ_{max}^{EtOH} 255 mμ, log ϵ 4.02 and flat shoulder at 285 mμ, log ϵ 3.90; R.D. in methanol (*c* 0.100 (700–370 mμ), 0.020 (370–317.5 mμ)): $[\alpha]_{700}$ +92°, $[\alpha]_{589}$ +156°, $[\alpha]_{420-415}$ +336°, $[\alpha]_{387.5}$ +260°, $[\alpha]_{337.5}$ +540°, $[\alpha]_{317.5}$ −180°.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; O, 17.37. Found: C, 73.60; H, 8.89; O, 17.56.

DETROIT, MICH.

(40) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).