GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF RESEARCH ADMINISTRATION

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RESEARCH PROJECT INITIATION

Project Title: Investigation of Non-Isoprenoid Sesquiterpenes

Project No.: B-1554

Project Director: Dr. Leon H. Zalkow

Sponsor: National Institute of Arthritis and Metabolic Diseases, Public Health Service

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National Institute of Arthritis and
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National Institutes of Health
Bethesda, Maryland 20014

Reports Required

Interim progress - when application is made for continuation or renewal support - (Form PHS-2590)
Final - upon completion of project.

Assigned to: School of Chemistry

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A. Summary Page

Title: Investigations of Non-Isoprenoid Sesquiterpenes

Grant No.: AM-05490 and AM-10097 B-1554*

Principal Investigator: Dr. L. H. Zalkow

Sponsoring Institution: Georgia Institute of Technology

Period Covered: Jan. 30, 1963 - Mar. 1, 1966

Date of Preparation: March 17, 1966

Summary:

All four of the thermodynamically stable C-8 and C-9 eremophilanones have been prepared and their physical and spectral properties reported. These ketones differ in configuration at the ring juncture, C-10, and/or at C-7, the isopropyl bearing carbon. Since all known eremophilane sesquiterpenes possess cis methyl groups at C-5 and C-4, the four ketones mentioned should, theoretically, be useful for correlation with any new eremophilane sesquiterpene. An example of this is the recent proof of structure and configuration of nootkatone, nootkatene and valencene (W. D. MacLeod, Jr., Tet. Let., 1965, 4779) which utilized one of the above mentioned ketones. The structures of two diosphenols derived from hydroxydihydroeremophilone have been determined.

2-α-methylcholestan-3-one has been used as a model for the development of synthetic approaches to hydroxeremophilone. This approach has not been successful.

Carvone has been transformed into a "biogenetic" precursor of dihydroeremophilone, γ-canarone. This substance is a double bond isomer of a recently reported sesquiterpene, canarone. On treatment with acid γ-canarone gave 1,6-dimethyl-3-isopropyl-6,7,8,9-tetrahydronaphthalene, which was readily dehydrogenated to 1,6-dimethyl-3-isopropyl naphthalene. The latter substance presumably has been prepared from canarone, but incorrectly identified.

B. Detailed Report

(1) Description of research accomplished

The following description of research accomplished includes two reprints, "Constitution and Absolute Configuration of Eremophilenolide", F. Sorm et al., L. H. Zalkow and S. Hu and C. Djerassi, Tetrahedron, 19, 1101 (1963) and "Studies in the Chemistry of the Eremophilane Sesquiterpenes", L. H. Zalkow, A. M. Shaligrim and Shih-En Hu and C. Djerassi, Tetrahedron, 22, 337 (1966) and a report of recent developments.

Tetrahedron 1963, Vol. 19, pp. 1101 to 1107. Pergamon Press Ltd. Printed in Northern Ireland

CONSTITUTION AND ABSOLUTE CONFIGURATION OF EREMOPHILENOLIDE

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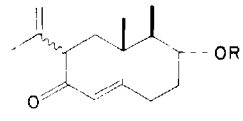
(*Received* 12 *December* 1962)

Abstract—Eremophilenolide, a naturally occurring sesquiterpenoid from *Petasites hybridus*, has been shown to be based on a *cis*-fused decalin system (IV) by multistep degradation to the *cis*-β-decalone (XIV), which could also be obtained from hydroxyeremophilone (XV). Since the absolute configuration of the latter is known, the present interconversion settles the absolute configuration of eremophilenolide as well as that of the other sesquiterpenes with which it has previously been inter-related.

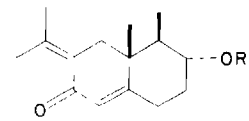
IN recent years there has been described the isolation,[4–6] structure proof[7,8] and establishment of absolute configuration[9,10] of petasin (I), isopetasin (II) and S-petasin (III). These three sesquiterpenoid constituents of *Petasites hybridus* (L.) Fl. Wett. (syn. *P. officinalis* Moench.) are based on the rare eremophilane skeleton (e.g. VIII) which does not follow the classical isoprene rule, although its biogenesis is readily accommodated[11] by methyl migration from an eudalenoid precursor. *Petasites officinalis* Moench. of Czechoslovak origin does not contain petasin (I) and its congeners, but rather a series of novel sesquiterpenes[12–15] of the eremophilane type with additional furan or α,β-unsaturated-γ-lactone groupings. One of these is the lactone eremophilenolide for which we now report the structure and absolute configuration IV.[16] Since this substance has already been related[12] to the other novel

[1] Paper CL in the series "On Terpenes" from the Czechoslovak Academy of Science. For preceding article see J. Vrkoč, V. Herout, F. Šorm, *Coll. Czech. Chem. Commun.*, **28**, 1084 (1963).
[2] Paper IV in the series "Terpenes" from Oklahoma State University. For preceding article see L. H. Zalkow, V. B. Zalkow and D. R. Brannon, *Chemistry & Industry*, **38** (1963).
[3] Paper LII in the series "Terpenoids" from Stanford University. For preceding article see C. Djerassi and R. McCrindle, *J. Chem. Soc.*, 4034 (1962).
[4] A. Stoll, R. Morf, A. Rheiner and J. Renz, *Experientia*, **12**, 360 (1956).
[5] A. Aebi, J. Büchi, T. Waaler, E. Eichenberger and J. Schmutz, *Pharm. Acta Helv.*, **30**, 277 (1955).
[6] A. Aebi, T. Waaler and J. Büchi, *Pharm. Weekblad*, **93**, 397 (1958).
[7] T. Waaler, Thesis, E.T.H., Zurich, Juris Verlag, 1957.
[8] A. Aebi and T. Waaler, "Über die Inhaltsstoffe von *Petasites hybridus* (L.) Fl. Wett., Verlag Helbing und Lichtenhahn, Basel, 1959.
[9] A. Aebi and C. Djerassi, *Helv. Chim. Acta*, **42**, 1785 (1959).
[10] D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, 82, 4337 (1960).
[11] R. Robinson, "The Structural Relations of Natural Products", Oxford University Press, 1955, p. 12. See also J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).
[12] L. Novotný, V. Herout and F. Šorm, *Tetrahedron Letters*, 697 (1961).
[13] L. Novotný, J. Jizba, V. Herout and F. Šorm, *Coll. Czech. Chem. Commun.*, **27**, 1393 (1962).
[14] L. Novotný, V. Herout and F. Šorm, *Coll. Czech. Chem. Commun.*, **27**, 1400 (1962).
[15] J. Hochmannová, L. Novotný and V. Herout, *Coll. Czech. Chem. Commun.*, **27**, 1870 (1962).

sesquiterpenoid constituents of this plant, the present absolute configurational assignments apply *ipso facto* to them.



I R = - COC (CH$_3$) = CHCH$_3$
III R = - COCH = CHSCH$_3$



II R = - COC(CH$_3$) = CHCH$_3$

Eremophilenolide ($C_{15}H_{22}O_2$) exhibits I.R. bands at 1760 and 1693 cm^{-1} typical of an α,β-unsaturated 5-membered lactone and the U.V. absorption spectrum ($\log \varepsilon_{max}^{220-224}$ 4·16) was compatible with such a chromophore. Confirmation was adduced by catalytic hydrogenation (acetic acid–platinum oxide) to dihydroeremophilenolide (V), the I.R. spectrum (1780 cm^{-1}) of which was now characteristic of a saturated γ-lactone. The carbon skeleton of eremophilenolide was established by the following reaction sequence:

Lithium aluminium hydride reduction of dihydroeremophilenolide (V) afforded the saturated diol VI, which was converted to the crystalline ditosylate. Treatment with lithium aluminium hydride gave a mixture consisting of a hydrocarbon ($C_{15}H_{26}$) and an ether ($C_{15}H_{26}O$). The hydrocarbon was unsaturated (VII) and upon catalytic hydrogenation provided the saturated liquid hydrocarbon VIII, the infrared spectrum of which was identical with eremophilane obtained earlier[15] from hydroxydihydroeremophilone (XVI). The other liquid constituent ($C_{15}H_{26}O$) of the lithium aluminium hydride reduction of the ditosylate of VI exhibited an I.R. spectrum identical with that of tetrahydrofuranoeremophilane (IX), the principal catalytic hydrogenation product[15] of the naturally occurring furanoeremophilane ($\bar{x}$). There remains only the question of the termination point of the lactone ring (C-6 or C-8)[17] and this was resolved in favor of C-8. Thus when the lithium aluminium hydride reduction of dihydroeremophilenolide (V) was performed under controlled conditions[18] and the intermediate hydroxyaldehyde XI immediately subjected to Huang-Minlon reduction,[19] there was isolated the crystalline hydroxyeremophilane (XII). Oxidation of the latter with chromium trioxide in acetone solution[20] provided the ketone XIII, characterized as the semicarbazone m.p. 161–164°, which could be isomerized with base to the ketone XIV, forming a higher melting semicarbazone (m.p. 196–198°). The I.R. spectrum of the unstable ketone exhibited a band at 1430 cm^{-1}, suggestive of a methylene group adjacent to a ketonic function (1711 cm^{-1}), an observation which pointed towards C-8 as the termination point of the lactone ring. Full confirmation for this structural supposition as well as evidence bearing on the stereochemistry of the ketones XIII and XIV was obtained in the following manner.

In the original proof of absolute configuration[21] of eremophilone, the methyl

[16] All structures in the present article imply absolute configuration assignments utilizing the conventional steroid notation.

[17] The numbering system (see IV) is based on that of the presumed eudalenoid biogenetic precursor.

[18] B. C. Bhattacharyya, A. S. Rao and M. Shaligram, *Chemistry & Industry*, 469 (1960).

[19] Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

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

[21] L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2914 (1959); *ibid.*, **82**, 6354 (1960).

ether (XVc) of hydroxyeremophilone was hydrogenated and after base equilibration at C-7, the methoxy function was removed with calcium in liquid ammonia and the intermediate C-8 hydroxyl group re-oxidized. The resulting ketone XVII exhibited a positive Cotton effect, typical[22] of A/B *trans*-fused 3-keto steroids, and proved to be identical with a synthetic specimen of known constitution and absolute configuration. During a recent repetition of this sequence, it was possible to isolate from the mother liquors of the 2,4-dinitrophenylhydrazone (m.p. 170–172°) of the *trans* ketone XVII a small amount of an isomeric dinitrophenylhydrazone (m.p. 169–170°), which did not give any melting point depression upon admixture with the 2,4-dinitrophenylhydrazone (m.p. 170–172°) derived from the base-equilibrated ketone XIV arising from the above described dihydroeremophilenolide (V) degradation. This latter ketone exhibited an optical rotatory dispersion curve characteristic[22] of A/B *cis*-fused 3-keto steroids indicating that in the catalytic hydrogenation[21] of hydroxyeremophilone methyl ether (XVc) there is produced a small quantity of the *cis* isomer in addition to the predominant *trans* ketone XVII.

In order to put this interconversion of eremophilenolide (IV) with hydroxyeremophilone (XVa) on a firm footing, attempts were made to increase the proportion of *cis*-fused hydrogenation product. Indeed, when the catalytic hydrogenation was performed with hydroxyeremophilone (XVa) itself, there was obtained an oily tetrahydro derivative (XVIIIa), the optical rotatory dispersion curve of which indicated the presence of substantial amounts of *cis*-fused isomer. Acetylation provided a mixture of tetrahydrohydroxyeremophilone acetate isomers (XVIIIb), the infrared spectrum and optical rotatory dispersion curve of which were virtually identical with those of the direct hydrogenation product of hydroxyeremophilone acetate (XVb). Deacetoxylation with calcium in liquid ammonia[23] and re-oxydation of over-reduced ketone furnished an approximate 1:1 mixture of the *cis* (XIV) and *trans* (XVII) ketones, which could be separated by fractional crystallization of their 2,4-dinitrophenylhydrazones and semicarbazones. The melting points of these two derivatives of the *cis*-ketone XIV proved to be identical with those of the specimens originating from eremophilenolide (IV) and the optical rotatory dispersion curves exhibited the typical negative Cotton effect, superimposed upon a positive background, as is so characteristic[22] of A/B *cis* fused 3-keto steroids.

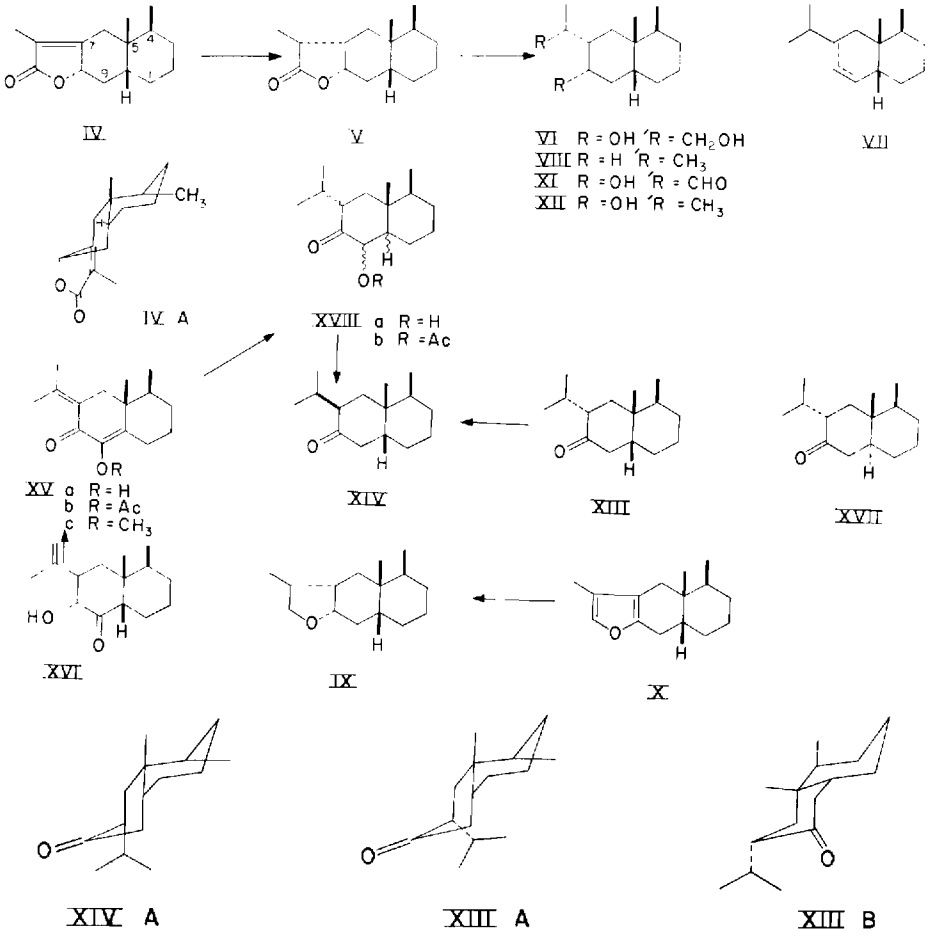
This interconversion of eremophilenolide (IV) and hydroxyeremophilone (XVa) completely settles the structure and absolute configuration of the former. Furthermore, the isolation of a base-labile (XIII) and a base-stable (XIV) *cis*-fused ketone permits unequivocal stereochemical assignment to C-7. Catalytic hydrogenation of a *cis*-octalin system (e.g. VII with 7-8 double bond or exocyclic double bond in IV) would be expected to occur predominantly from the less hindered β-side,[16] thus giving rise to the unstable ketone XIII, which could exist in either the "steroid" conformation XIIIA or the "non-steroid" conformation XIIIB (or in some intermediate distorted conformation). Either one would obviously be less favored than "steroid" conformation XIVA of the base-stable *cis* ketone and it should be noted that the negative

[22] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry", McGraw-Hill Book Co., New York, 1960.

[23] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956). See also J. S. Mills, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.*, **80**, 6118 (1958).

Cotton effect (see Experimental) of XIV is consistent, according to the octant rule,[24] with this conformational assignment. As indicated below, the *cis* ring fusion in eremophilenolide (IV) points towards the α-orientation of the C-8 oxygen atom.

The presence of the C-4 equatorial methyl group makes the "steroid-like" conformation (e.g. XIIIA or XIVA) of the decalin system clearly preferred over the "non-steroid" conformation (e.g. XIIIB). In the "steroid-like" conformation, the lactone ring in IV can only be formed with a hydroxyl group at C-8, which is α-oriented in a chair cyclohexane ring. A β-connection at C-8 would require that ring to exist in a very unfavorable boat form. While this is *a priori* not impossible in a natural product, application of the modified Klyne-Hudson[25] rule using the molecular rotation values of −12° (V) and +42° (IX) leads to an 8α (R)[26] stereochemical assignment and hence to the stable all-chair "steroid-like" conformation IVA. Catalytic hydrogenation of such a double bond should occur principally from the



[24] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

[25] V. Sýkora and M. Romaňuk, *Coll. Czech. Chem. Commun.*, 22, 1909 (1957).

[26] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, 12, 82 (1956).

unhindered β-face, thus leading to the α-orientation at C-7 (e.g. V, VI, IX, etc.) and hence to a base-labile ketone XIII.

EXPERIMENTAL

All m.p.'s were determined on the Kofler block. The rotatory dispersion curves were measured by Mrs. Ruth Records on a Nippon Bunko (Japan Spectroscopic Manufacturing Co.) automatically recording spectropolarimeter model ORD-2.

Dihydroeremophilenolide (V)[13]

Eremophilenolide (IV; 5·0 g) was hydrogenated at room temp and atm. press. over a period of 50 hr in acetic acid solution in the presence of 0·5 g platinum oxide catalyst. The product was purified by chromatography on neutral alumina (activity IV) and elution with pet ether. Recrystallization from pentane afforded 3·63 g of colorless crystals, m.p. 73–73·5°, $[\alpha]_D^{20}$ −5° (*c*, 5·86 in $CHCl_3$) (Found: C, 76·08; H, 10·13. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

Eremophilan-8,12-*diol* (VI)

Dihydroeremophilenolide (V; 3·77 g) was reduced with excess (5·0 g) lithium aluminium hydride in ether solution by heating under reflux for 5 hr. After decomposition with saturated sodium sulfate solution, the ether solution was washed, dried and evaporated to afford, after distillation 3·92 g diol VI as a colorless oil, b.p. 135°/0·02 mm (Found: C, 74·78; H, 11·44; active hydrogen 0·78. Calc. for $C_{15}H_{28}O_2$: C, 74·95; H, 11·74%; active hydrogen, 0·84).

Treatment of the diol VI (3·8 g) with *p*-toluenesulfonyl chloride in pyridine solution at 0° for 48 hr gave after recrystallization from ether–light petroleum 1·88 g *ditosylate* in two polymorphic forms, m.p. 75–76° and 85–86° (Found: C, 63·19; H, 7·02; S, 11·79. Calc. for $C_{29}H_{40}O_6S_2$: C, 63·47; H, 7·35; S, 11·68%).

Reduction of eremophilan-8,12-*diol* (VI) *ditosylate with lithium aluminum hydride*

The preceding ditosylate (1·88 g) was reduced with 1·2 g lithium aluminum hydride in boiling ether for 2 hr. The reaction mixture was decomposed with saturated sodium sulfate solution and the crude product separated by chromatography on alumina (activity III). The first light pet. ether eluates contained the unsaturated hydrocarbon *eremophil*-7(or 8)-*ene* (VII; 300 mg), which was redistilled *in vacuo* before analysis and which exhibited an I.R. band (neat) of weak intensity at 1669 cm^{-1}. (Found: C, 87·09; H, 12·76. Calc. for $C_{15}H_{26}$: C, 87·30; H, 12·70%).

Further elution with light pet ether afforded 410 mg *tetrahydrofuranoeremophilane* (IX), b.p. 97·5°/0·1 mm, $[\alpha]_D^{20}$ +19° (neat), the I.R. spectrum of which was identical with that of the hydrogenation product[15] of furanoeremophilane (X) (Found: C, 81·17; H, 11·70. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%).

Eremophilane (VIII)

Catalytic hydrogenation of 300 mg eremophilene (VII) in acetic acid solution in the presence of platinum oxide catalyst provided after distillation *in vacuo* a colorless oil, d_4^{20} 0·8944, n_D^{20} 1·4848, $[\alpha]_D^{20}$ −18·5° (neat) (Found: C, 86·70; H, 13·54. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·54%).

Eremophilan-8-*ol* (XII)

To a stirred solution of 2·25 g dihydroeremophilenolide (V) in 20 cc dry dioxane was added at −15° over a period of 20 min 4·5 cc ethereal solution of lithium aluminum hydride (1 cc = 19·63 mg of reagent). After 1 hr, the temp of the reaction mixture had reached 20° at which time 5N sulfuric acid was added and the product isolated in the usual manner. The total crude hydroxy aldehyde XI was heated for 4 hr at 195–200° with 2·5 g 75% hydrazine hydrate, 2·5 g sodium hydroxide and 10 cc ethylene glycol. The cooled mixture was acidified with tartaric acid and the crude product (2·8 g, isolated by extraction with ether) was chromatographed on 200 g activity IV alumina. The desired eremophilanol XII (0·5 g) was eluted with 1:1 benzene–light petroleum and exhibited m.p. 59–59·5° after recrystallization from aqueous ethanol. Its I.R. spectrum (chloroform solution) exhibited a band at 3624 cm^{-1} but no carbonyl absorption (Found: C, 79·92; H, 12·73. Calc. for $C_{15}H_{28}O$: C, 80·29; H, 12·58%).

(7α)-Eremophilan-8-one (XIII)

Oxidation of 0·71 g eremophilanol (XII) was effected at 20° in acetone solution over a period of 10 min by titration with a standard chromium trioxide solution.[20] The solvent was removed *in vacuo*, the product was extracted with chloroform and the liquid ketone XIII distilled at 97°/0·4 mm; yield, 0·70 g, I.R. carbonyl band (neat) at 1711 cm^{-1}. (Found: C, 80·90; H, 11·45. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%).

The *semicarbazone* was prepared in methanol solution at 20° (20 hr) by the semicarbazide acetate procedure and the solid recrystallized from ether, whereupon it showed m.p. 161–164° (Found: C, 68·42; H, 10·14; N, 14·96. Calc. for $C_{16}H_{29}N_3O$: C, 68·77; H, 10·46; N, 15·04%).

Preparation of the 2,4-dinitrophenylhydrazone on keeping the ketone XIII at room temperature for several hours in ethanolic solution with 2,4-dinitrophenylhydrazine effected also inversion at C-7 and after recrystallization from methanol there was isolated the 2,4-dinitrophenylhydrazone of the 7β-isomer XIV, m.p. 170·5–172·5° (Found: N, 13·72. Calc. for $C_{21}H_{30}N_4O_4$: N, 13·92%).

(7β)-Eremophilan-8-one (XIV)

(a) *From (7α)-eremophilan-8-one* (XIII). The ketone XIII (300 mg) was heated under reflux in a nitrogen atmosphere in methanol solution with a catalytic amount of sodium and the epimerized ketone XIV was extracted with ether and converted directly by the semicarbazide acetate procedure into the *semicarbazone*, which exhibited m.p. 196–198° after recrystallization from ethanol (Found: C, 68·72; H, 10·50; N, 15·23. Calc. for $C_{16}H_{29}N_3O$: C, 68·77; H, 10·46; N, 15·04%).

The free ketone XIV was obtained from the semicarbazone by steam distillation with a saturated oxalic acid solution and after redistillation exhibited the following optical constants: $[\alpha]_D^{20}$ +33° (*c*, 4·27 in $CHCl_3$); R.D. in methanol(*c*, 0·103): $[\alpha]_{589}$ +8°, $[\alpha]_{350-375}$ ~+50°, $[\alpha]_{314}$ −19°, $[\alpha]_{270}$ +404°. The 2,4-*dinitrophenylhydrazone* possessed m.p. 169–172° after recrystallization from ethanol and did not show any m.p. depression upon admixture with the specimen prepared directly from the 7α-epimer XIII.

(b) *From hydroxyeremophilone* (XVa). Hydrogen consumption equivalent to two molar equivalents ceased within 2 hr when 1·0 g hydroxyeremophilone (XVa) was hydrogenated in 20 cc 95% ethanol and 10% palladium–charcoal catalyst (0·2 g) at room temp and atm. press. Filtration of the catalyst, dilution with water, isolation of the product with ether and vacuum distillation provided 0·9 g *tetrahydrohydroxyeremophilone* (XVIIIa) as a colorless oil, b.p. 70°/0·01 mm, which oxidized to the α-diketone on standing in the air; R.D. in methanol (*c*, 0·21 to 310 mμ, then 0·042): $[\alpha]_{589}$ +73°, $[\alpha]_{345-375}$ ~+200° (broad), $[\alpha]_{332\cdot5}$ +107°, $[\alpha]_{285}$ +1870°, $[\alpha]_{250}$ −330°. The I.R. spectrum ($CHCl_3$) exhibited bands at 3450 and 1708 cm^{-1}. (Found: C, 75·56; H, 10·77; O, 13·84. Calc. for $C_{15}H_{26}O_2$: C, 75·58; H, 11·00; O, 13·42%).

Acetylation of XVIIIa was effected in nearly quantitative yield with acetic anhydride and pyridine (42 hr at 5°) to furnish *tetrahydrohydroxyeremophilone acetate* (XVIIIb) as a viscous oil, b.p. 80°/0·05 mm, R.D. in methanol (*c*, 0·08): $[\alpha]_{589}$ +51°, $[\alpha]_{365-375}$ ~+165° $[\alpha]_{335}$ +42°, $[\alpha]_{300}$ +1294°, $[\alpha]_{270}$ +164° (Found: C, 73·29; H, 9·87; O, 17·43. Calc. for $C_{17}H_{28}O_3$: C, 72·82; H, 10·06, O, 17·12%).

Tetrahydrohydroxyeremophilone acetate (XVIIIb; 1·0 g) in 15 cc dioxane was added slowly to a solution of 0·5 g calcium in 70 cc liquid ammonia. The solution was maintained under reflux for 2 hr and the ammonia was then permitted to evaporate at room temp, followed by the addition of 5 cc 95% ethanol and 10 cc saturated aqueous solution of ammonium chloride. Neutralization with dil. hydrochloric acid and ether extraction gave an oil, the I.R. spectrum of which exhibited strong hydroxyl absorption. Consequently, the total product was oxidized in acetone solution[20] at 10° with chromium trioxide and the resulting ketone (700 mg colorless oil, b.p. 100°/0·1 mm) was transformed directly into the 2,4-dinitrophenylhydrazone with a methanolic hydrochloric acid solution of 2,4-dinitrophenylhydrazine. Fractional recrystallization of the crude derivative afforded approximately equal amounts of two dinitrophenylhydrazones.

The less soluble derivative, m.p. 170–172°, proved to be identical by mixed m.p. determination and I.R. comparison with the previously described[21] dinitrophenylhydrazone of the synthetic ketone XVII. For further characterization, the derivative was heated under reflux for 30 min in acetone solution with stannous chloride and hydrochloric acid,[27] followed by addition of 2N sodium hydroxide

[27] N. M. Cullinane and B. F. R. Edwards, *J. Chem. Soc.*, 1311 (1958).

solution and removal of the acetone. Acidification with hydrochloric acid, extraction with ether and distillation provided the pure *trans* ketone XVII, which was shown to be identical by optical rotatory dispersion and infrared spectral comparison with a totally synthetic specimen.[21]

The more soluble 2,4-dinitrophenylhydrazone, though sharp melting (m.p. 158–159°), represented a mixture of the derivatives of the ketones XIV and XVII. Purification was best effected by cleavage[27] of the 2,4-dinitrophenylhydrazone and conversion of the free ketone mixture to the semicarbazone by the semicarbazide acetate method followed by recrystallization from 95% ethanol. In this manner there was obtained the pure *semicarbazone* of (7β)-*eremophilan-8-one* (XIV), m.p. 192–194°, undepressed upon admixture with a specimen derived from eremophilenolide (IV) (Found: C, 68·63; H, 10·38. Calc. for $C_{16}H_{29}N_3O$: C, 68·77; H, 10·46%). The semicarbazone of the contaminating *trans* ketone XVII could be recovered from the mother liquors.

A portion (220 mg) of the semicarbazone of XIV was cleaved by heating under reflux for 2 hr with 10 cc 10% hydrochloric acid and the ketone XIV extracted with ether and distilled at 100°/0·1 mm; yield, 140 mg, rotatory dispersion curve of A/B *cis*-fused 3-keto steroid type as detailed above for the sample originating from eremophilenolide (IV) (Found: C, 80·99; H, 11·83. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%).

Transformation of the ketone to the 2,4-*dinitrophenylhydrazone* and recrystallization from ethanol gave yellow crystals of m.p. 169–170°, which did not depress the m.p. of the 2,4-dinitrophenylhydrazone of the ketone XIV obtained from eremophilenolide (IV), but which exhibited a marked depression (m.p. 150–160°) when mixed with the 2,4-dinitrophenylhydrazone of the *trans* ketone XVII[21] (Found: C, 62·54; H, 7·44. Calc. for $C_{21}H_{30}N_4O_4$: C, 62·66; H, 7·51%).

(c) *From hydroxyeremophilone acetate* (XVb). Hydroxyeremophilone acetate (XVb) was prepared as previously described,[28] and was hydrogenated with 10% palladium–charcoal catalyst in 95% ethanolic solution at room temp and atm. press. The resulting *tetrahydrohydroxyeremophilone acetate* (XVIIIb) exhibited an I.R. spectrum virtually identical with that of the above described sample obtained by acetylation of the hydrogenation product XVIIIa of hydroxyeremophilone (XVa). On treatment with calcium and liquid ammonia followed by reoxidation with chromium trioxide in acetone solution and separation *via* the 2,4-dinitrophenylhydrazones and semicarbazones, approximately equal amounts of the ketones XIV and XVII were isolated.

(d) *From hydroxyeremophilone methyl ether* (XVc). Hydroxyeremophilone methyl ether (XVc) had been converted previously[21] into the *trans* ketone XVII by the following sequence of reactions: (1) hydrogenation; (2) epimerization with base; (3) calcium–ammonia demethoxylation and (4) reoxidation. A careful reinvestigation of this sequence has shown that the crude ketone XVII initially isolated is contaminated with a small amount of the *cis* isomer XIV. When this crude ketone was converted to the semicarbazone, the derivative (m.p. 178–181°) of the predominant product (XVII) precipitated, uncontaminated with the semicarbazone (m.p. 192–194°) of the minor *cis* isomer. However, when the separation was effected through the 2,4-dinitrophenylhydrazones, recrystallization from ethanol provided the earlier described[21] dinitrophenylhydrazone (m.p. 170–172°) of the *trans* ketone XVII, as well as from the mother liquors a small amount of the 2,4-dinitrophenylhydrazone (m.p. 169–170°) of the *cis* isomer XIV. Identity was established in each instance by appropriate mixture melting point comparisons.

Acknowledgments—The work at Oklahoma State University and at Stanford University was supported by the National Institute of Health through grants AM-05490-02 and AM-06840-04. We are deeply indebted to Dr. Maurice D. Sutherland of the University of Queensland for supplies of hydroxyeremophilone and hydroxydihydroeremophilone.

[28] C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.*, **81**, 3424 (1959).

Tetrahedron, 1966, Vol. 22, pp. 337 to 350. Pergamon Press Ltd. Printed in Northern Ireland

STUDIES IN THE CHEMISTRY OF THE EREMOPHILANE SESQUITERPENES

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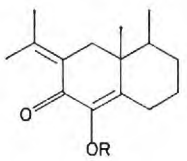
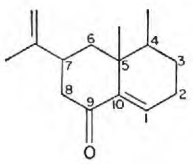
Abstract—The structures of hydroxyeremophilone and its various derivatives have been verified using NMR spectroscopy. All four of the thermodynamically stable C-8 and C-9 eremophilanones have now been prepared and their optical rotatory dispersion curves and NMR spectra compared. Three of these ketones have been prepared from the naturally occurring hydroxyeremophilone by variation of the experimental conditions. The fourth stable ketone has been prepared from the closely related sesquiterpenes eremophilone and hydroxydihydroeremophilone. Hydroxydihydroeremophilone has been converted into two diosphenols—A and B, by treatment with base and by hydrogenation followed by reaction with bismuth trioxide, respectively. The less stable diosphenol-B was converted into the more stable diosphenol-A with alkali. The two diosphenols were converted into eremophilanones of known configuration and the NMR spectra and optical rotatory dispersion curves of the diosphenols and their derivatives are discussed.

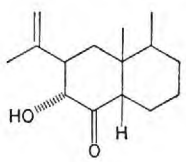
HYDROXYEREMOPHILONE (HE; I, R = H), eremophilone (II) and hydroxy-dihydroereomphilone (HDE; III) have been of considerable interest to natural products chemists since Penfold and Simonsen[3] first pointed out that these substances did not follow the "isoprene rule". Only recently has the absolute configuration of these



I



II



III

substances been determined by conversion of HE into the *trans* C-8 eremophilanone (IV) which itself was totally synthesized.[4] HE has also been interrelated with eremophilenolide (V) by the conversion of both substances into the *cis* C-8 eremophilanone (VI).[5] Compound V is one member of a family of furanoeremophilane compounds recently isolated by Sorm *et al.* from *Petasites officinalis* Moench.

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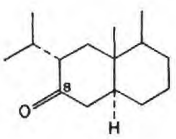
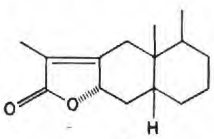
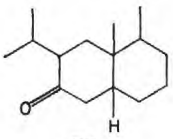
[3] A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 87 (1939).

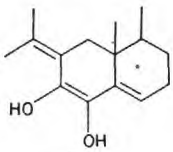
[4] L. H. Zalkow, F. X. Markley and Carl Djerassi, *J. Amer. Chem. Soc.* **82,** 6354 (1960).

[5] L. Novotnij, J. Jizba, V. Herout, F. Sorm, L. H. Zalkow, Shih-En Hu and Carl Djerassi, *Tetrahedron* **19,** 1101 (1963).


IV


V

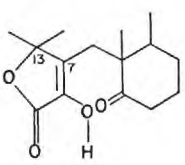

VI

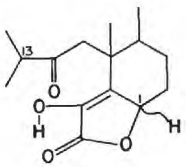

VII

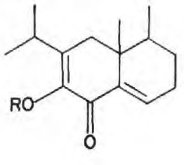
The original assignment of structure I (R = H) to HE was based on the assumption that the various derivatives of HE (I, R = $COCH_3$, CH_3 and COC_6H_5) possessed the same structure as HE itself.[6] That is, it was assumed that no rearrangement to other tautomeric forms occurred during preparation of the various derivatives. Yet, Simonsen *et al.*[7] showed by UV spectroscopy that HE and its benzoate existed in different tautomeric forms in ethanol solution and suggested that HE existed, under these conditions, predominantly in the trienic form VII. The earlier workers[6,8–10] provided ample evidence for the skeletal structure of HE and for the location of the potential 1,2-diketone system at C-8 and C-9, and later work has confirmed these findings.[11,12]

Modern instrumental methods, in particular, NMR spectroscopy are ideal for solving questions of tautomeric differences. Therefore, the NMR spectra of HE, its methyl ether, acetate and benzoate were run in deuteriochloroform and the spectra, which were similar, clearly indicated that all of these substances were correctly represented by structure I. The most important feature of these spectra was the position of the isopropyl methyl groups; in HE these methyls gave non-equivalent singlets integrating for three protons each at δ 1·97 and 2·18, whereas in the acetate, benzoate and methyl ether these signals were located at δ 1·83 and 2·10. No vinylic protons were evident in any of the spectra. Of the various tautomeric forms only I is consistent with these observations. However, reexamination of the UV spectrum of HE in the non-polar solvent cyclohexane still revealed the long wavelength band (λ_{max} 308 mμ, log ε 3·97) assigned by Simonsen *et al.*[7] to tautomeric structure VII).

Geissman[13] pointed out that a "phenol", $C_{12}H_{18}O_3$, isolated by Simonsen *et al.*[9] in the oxidative degradation of HE, its benzoate or its methyl ether could not be satisfactorily accounted for by structure I. After reexamination, the "phenol" was found to have the molecular formula $C_{15}H_{22}O_4$ and Geissman assigned it structure VIII on the basis of its UV spectrum, and it was stated that this structure constituted


VIII


XI

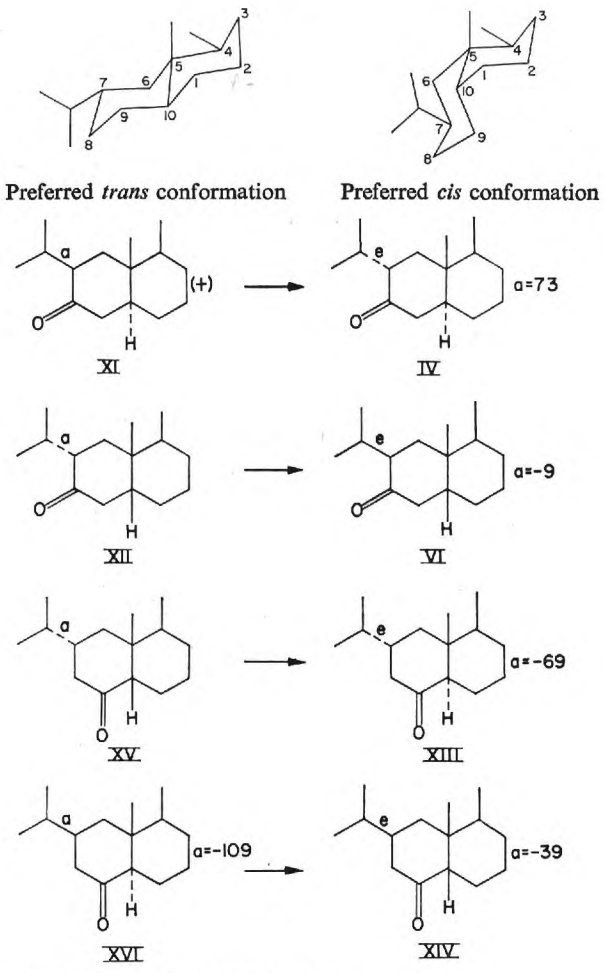

X

[6] For summarizing review see J. Simonsen and D. H. R. Barton, *The Terpenes*, Vol. III, pp. 212–224. Cambridge University Press, New York, N.Y. (1952).
[7] A. E. Gillam, J. I. Lynas-Gray, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 601 (1941).
[8] A. E. Bradfield, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 2744 (1932).
[9] A. E. Bradfield, N. Hellström, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 767 (1938).
[10] F. C. Copp and J. L. Simonsen, *J. Chem. Soc.* 415 (1940).
[11] C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.* **81,** 3424 ,1959).
[12] D. F. Grant and D. Rogers, *Chem. & Ind.* 278 (1956); D. F. Grant, *Acta Cryst.* **10,** 498 (1957).

additional evidence in support of structure I. However, the spectral data obtained could equally well be accommodated by structure IX. Compound IX could arise from HE or its derivatives if they were represented by tautomeric structure X by the same mechanism postulated for the formation of VIII.[13] The "phenol" was prepared as previously described and on the basis of the NMR spectra of it and its acetate, structure VIII can now be assigned with confidence. The *gem* dimethyl group at C-13 appeared as a singlet in VIII at δ 1·43 and as a pair of closely spaced singlets, δ 1·47 and 1·50, in the acetate of VIII. If structure IX had been correct these methyl groups would have been expected to appear as a doublet (J = 5–7 c/s) at higher field and the proton at C-1 would have been evident.

As previously mentioned, HE has been converted into the two thermodynamically stable C-8 eremophilanones IV and VI[4,5] (Diagram I). The corresponding less stable C-7 epimeric ketones (XI and XII) have been prepared by synthesis[4] and by degradation of eremophilenolide,[5] respectively, and were readily converted into the stable

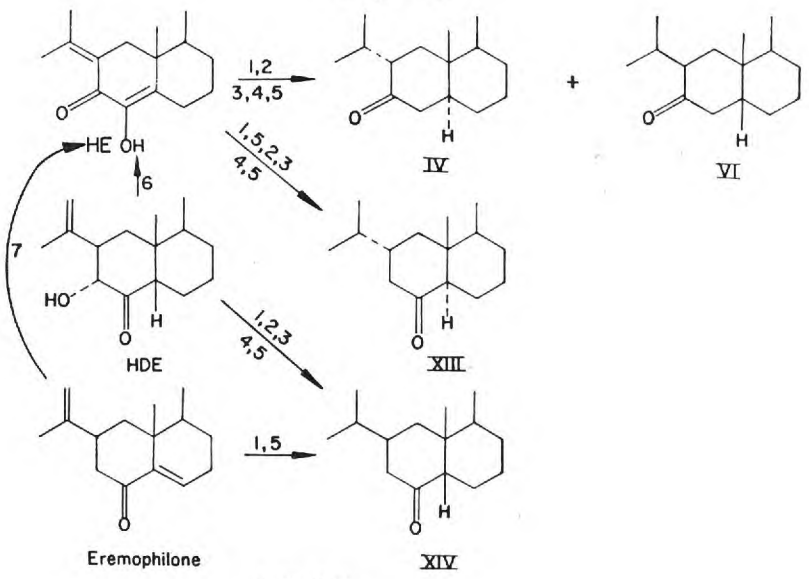
Diagram I



[13] T. A. Geissman, *J. Amer. Chem. Soc.* **75**, 4008 (1953).

isomers with base. A third stable ketone has now been prepared from HE which can be assigned structure XIII. Ketone XIII was obtained by hydrogenation of HE to give tetrahydrohydroxyeremophilone, followed by treatment with alkali, than acetylation and finally deacetoxylation with calcium in liquid ammonia; it was unchanged on treatment with acid or base. The spectral properties of XIII were unchanged after its conversion to its semicarbazone or 2,4-dinitrophenylhydrazone followed by exhaustive recrystallization of the derivative and finally regeneration of the ketone. Careful examination of the mother liquor remaining after precipitation of the derivatives failed to show the presence of other isomeric eremophilanones. The assignment of structure XIII is based on the following arguments. Since the ketone is thermodynamically stable, it must correspond in structure to IV, VI, XIII or XIV (Diagram 1). It was shown to differ from the stable C-8 eremophilanones (IV and VI) by comparison of IR, NMR and mass spectra and by optical rotatory dispersion; in addition, the semicarbazone and 2,4-dinitrophenylhydrazone of XIII depressed the m.ps of the corresponding derivatives of IV and VI. Thus, it was established that XIII was a stable C-9 eremophilanone. Of the two possible stable C-9 eremophilanones, XIII and XIV, the latter had been previously prepared[11] from eremophilone and from HDE and was found not to be identical with XIII in spectral properties and was not identical in its 2,4-dinitrophenylhydrazone and semicarbazone derivatives. Thus, structure XIII is firmly established and all of the thermodynamically stable C-8 and C-9 eremophilanones are now known and have been prepared as outlined in Diagram II. Also, all of the corresponding less stable epimeric ketones (XI, XII,

Diagram II

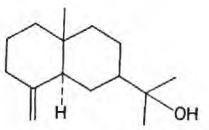


1. H_2, Pd/c
2. Ac_2O, Py
3. Ca, NH_3
4. CrO_3
5. OH^-
6. Bi_2O_3
7. See Ref. 6

XV and XVI of Diagram I) except for XV have been described in the literature.[4,5,11]

As illustrated in Diagram I, the more stable isomer, in each pair, possesses an equatorial isopropyl group at C-7 and the conversion of the bulky axial isopropyl group to the more sterically favorable equatorial conformation is the driving force for the epimerization of XI, XII and XV. The epimerization can take place to give an equatorial isopropyl group at C-7 in one of two ways, either by direct epimerization of the isopropyl group in the case of the C-8 eremophilanones as in the conversions of XI to IV and XII to VI or indirectly in the case of the C-9 eremophilanones by epimerization at C-10 as in the conversions of XV to XIII and XVI to XIV. In the preferred *trans* and *cis* conformations (Diagram I) the C-4 methyl group is also equatorial. In the alternative "non-steroid" *cis* conformation, the C-4 methyl group would exist in the axial conformation.

In Diagram I the amplitudes and signs of the Cotton effects, taken form the experimentally determined optical rotatory dispersion (ORD) curves are shown to the right of the formulas, and these are consistent with the conformations indicated as predicted by the octant rule.[14] The unusually large negative amplitude observed in the ORD curve of unstable ketone XVI has been ascribed to the existence of the A-ring in a "twist-boat" conformation resulting in relief of the isopropyl-methyl interaction.[15] The driving force for the epimerization of XVI, therefore, is found in the greater stability of the chair-chair conformation of XIV as compared to the boat-chair conformation of XVI. The NMR spectra of the stable ketones also support the assigned structures. For example, the C-5 methyl groups is *cis* ketones VI and XIV gave signals at δ 1·0 whereas in *trans* ketone IV this signal appeared at δ 0·93 and in *trans* ketone XIII it appeared at δ 0·63. It has been shown that in *trans*-10-methyl decalins and steroids the bridgehead methyl groups give signals at slightly higher field than in the corresponding *cis* isomers.[16] The large upfield shift observed for the C-5 methyl group in XIII results from shielding by the π-electron cloud of the C-9 carbonyl group and is analogous to that reported by Bates[17] for β-eudesmol, XVIII. However, keto groups at C-4 in steroids shield the C-10 bridgehead methyl groups to only a slight extent.[16b]



XVII

The conversion of HE to ketone XIII requires, at some stage, a rearrangement of the hydroxyl and carbonyl functions. The most likely place for this to occur is in the second step (Diagram II), when tetrahydrohydroxyeremophilone is treated with alkali.

During the course of an investigation of diosphenols derived from HDE, which

[14] C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry* McGraw-Hill, New York (1960).

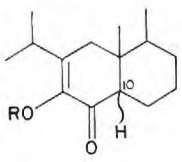
[15] C. Djerassi and W. Klyne, *Proc. Nat. Acad. Science* **48,** 1093 (1962); C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962).

[16] [a] J. I. Musher, *J. Amer. Chem. Soc.* **83,** 1146 (1961):
[b] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p. 19. Holden-Day, San Francisco (1964).

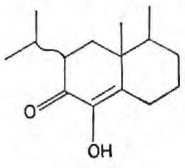
[17] R. B. Bates, *Chem. & Ind.* 1759 (1962).

is discussed below, a means of rapidly determining the composition of a mixture of ketones IV, VI, XIII and XIV was sought. Exhaustive studies with thin-layer chromatography (TLC) failed to reveal a means of separating the ketones while the 2,4-dinitrophenylhydrazones (2,4-DNP) of ketones IV, VI and XIV were indistinguishable by TLC but were readily separated from the more polar 2,4-DNP of XIII. Thus, the 2,4-DNP's of the C-8 eremophilanones can be separated by tedious recrystallizations as previously described,[5] while the 2,4-DNP's of the C-9 eremophilanones XIII and XIV can be distinguished by TLC.

It was noticed some time ago[18] that HDE was transformed into a different substance, diosphenol-A (m.p. 91–92°), on treatment with alkali. On standing at room temperature diosphenol-A changed to a viscous yellow gum. The IR and UV spectra indicated that diosphenol-A was an α,β-unsaturated ketone and a strong hydroxyl band also appeared in its IR spectrum. Diosphenol-A readily formed a monoacetate whose spectral properties again showed the presence of an α,β-unsaturated ketone; in addition, the carbonyl acetate band appeared at 1755 cm^{-1} suggesting an enol acetate. Diosphenol-A gave a deep blue color with ferric chloride and on addition of alkali its UV maximum shifted from 278 mμ to 322 mμ. Thus this substance was clearly an enolized α-diketone and could be represented either by XVIII or XIX.



XVIII a-10α
XVIII b-10β



XIX

When hydroxytetrahydroeremophilone, prepared by hydrogenation of HDE as previously described,[11] was treated with bismuth trioxide in acetic acid, diosphenol-B (m.p. 63–64°) was obtained.[18] The UV and IR spectra of diosphenol-B and its acetate were almost identical to those of diosphenol-A and its acetate respectively but on admixture a slight depression in m.p. was observed both for the two diosphenols and for their acetates. Both diosphenols gave similar ORD curves with positive Cotton effects, whereas the two corresponding acetates showed similar ORD curves with negative Cotton effects, and the acetate ORD curves were virtually unchanged on the addition of a trace of acid.[14] In every case diosphenol-A showed the more intense absorption bands (UV, ORD and $[\alpha]_D$). Thus, both diosphenols must be represented by either XVIII (R = H) and differ in stereochemistry at C-10 or by XIX and differ at C-7. The almost identical spectral properties observed for the two diosphenols and their acetates precluded the possibility that one was represented by XVIII (R = H) and the other by XIX; this was also evident from comparisons of the NMR spectra of the diosphenols and their acetates. On treatment with aqueous sodium hydroxide diosphenol-B was readily converted into the more stable diosphenol-A.

In order to distinguish between structures XVIII (R = H) and XIX it was planned to convert the diosphenols into either a stable C-8 eremophilanone (IV and/or VI)

[18] This observation was first made by Dr. R. F. Mauli, Postdoctoral Fellow, Wayne State University, 1957–1958, whom we thank for preliminary experiments.

or a stable C-9 eremophilanone (XIII and/or XIV), under conditions which did not allow the hydroxyl enol groups and the keto groups to interchange. The initial plan was to hydrogenate the acetates and then remove the acetoxyl groups with calcium in liquid ammonia,[4] but surprisingly, all attempts to hydrogenate the diosphenol acetates under neutral conditions failed and gave back unchanged starting material. In addition several attempts to convert the carbonyl group of diosphenol-A acetate into a thioketal using ethanedithiol in acetic acid in the presence of boron trifluoride or *p*-toluene-sulfonic acid gave back unchanged diosphenol-A acteate. However, the free diosphenols were readily hydrogenated in the presence of Pd–C catalyst, and the resulting dihydro derivatives were acetylated and then treated with calcium in liquid ammonia in order to remove the acetoxyl groups. As usual in such cases,[4,5] the keto groups were also partially reduced and therefore the crude product from the calcium-ammonia reaction was oxidized with Jones' reagent[19] and then converted into their crystalline 2,4-DNP derivatives. The latter derivatives both from diosphenol-A and diosphenol-B were identified, after separation by numerous recrystallizations, as those of ketone IV with a small amount of ketone VI and the ketones themselves were obtained by acid cleavage of the derivatives.[5] If rearrangement did not occur in the conversion of diosphenols-A and B into ketones IV and VI, then structure XIX could be assigned to the diosphenols. However, with the evidence available rearrangement could not be precluded.

The methyl ether of diosphenol-A was prepared with alkaline methyl sulfate. Both diosphenol-A and B were unreactive toward diazomethane and since diosphenol-B is base labile its methyl ether could not be prepared. The similarity of the NMR spectra of diosphenol-A and its acetate and methyl ether indicated that all were to be represented by the same structure, XVIII (R = H) or XIX. Hydrogenation in the presence of Pd–C and chromatography of the crude product gave, in addition to the expected dihydrodiosphenol-A methyl ether, a small amount of ketone IV. In view of further evidence, to be described below, the most likely explanation for the formation of IV, in this case, is that it arises from the presence of a small amount of the methyl ether of XIX as a contaminant in diosphenol-A methyl ether. The methyl ether of XIX thus undergoes hydrogenation of the double bond, then loss of the methoxyl group by hydrogenolysis to give IV. Gas chromatography and NMR analysis failed to show the presence of the XIX—methyl ether contaminant but this is not surprising in view of its close similarity to diosphenol-A methyl ether (XVIIIa, R = CH_3). A small amount of ketone VI might very well have been present also and not detected because of the low yield of saturated ketones produced in the hydrogenolysis of diosphenol-A methyl ether. A careful chromatographic separation of the product obtained on hydrogenation of diosphenol-B also revealed the presence of about 10% of IV. In a similar manner HE was converted, in low yield, into IV.

The conversion of the diosphenols into IV may proceed by preferential catalytic reduction of the C-9 double bond in tautomeric form XX from the less hindered bottom side to give the 9-hydroxy-8-keto-10 α derivative. The C-7 double bond would be expected to be less readily reduced because of the bulky C-7 isopropyl group. The dihydro intermediate would then be further transformed into IV either by hydrogenolysis of the α-hydroxy group, or more efficiently by further conversion to the α-acetoxy derivative followed by deacetoxylation with calcium-ammonia. The

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

small amount of VI produced would arise in a similar manner by initial reduction, to a small extent, of the C-7 double bond from the more hindered top side. Diosphenol-A was recovered unchanged after exposure to the hydrogenation conditions in the absence of hydrogen.

When dihydrodiosphenol-A methyl ether, the major product of the reduction of diosphenol-A methyl ether, was treated with calcium in ammonia and then the crude product reoxidized with Jones' reagent[19] and then equilibrated with base, a saturated ketonic product was obtained, whose IR spectrum was essentially identical to that of XIV, but distinctly different from the spectra of IV, VI and XIII. However, a sharp melting crystalline derivative could not be obtained. The ORD curve of the ketonic product showed a weak negative Cotton effect, which could be explained as arising from XIV contaminated with about 20% of IV. The ORD curve was distinctly different from that of VI, which also showed a weak negative Cotton effect. Gas chromatography showed that the dihydrodiosphenol-A methyl ether used above did indeed contain about 15% of a saturated ketone with the same retention time as IV. These results strongly suggested that diosphenol-A was XVIIIa. The conversion of the 10α configuration in XVIIIa to the 10β configuration in XIV is readily explained by hydrogenation of XVIIIa (R = CH_3) from the bottom side to give a β axial isopropyl group at C-7 and this intermediate would then epimerize at C-10 to give the stable β-C-7, C-10 *cis* configuration. Several unsuccessful attempts were made to convert hydroxyeremophilone methyl ether (I, R = CH_3) into XIX for comparison with diosphenol-A methyl ether. Reduction of I (R = CH_3) with sodium borohydride in isopropyl alcohol led to reduction of the C-8 carbonyl group, as expected,[20] but the double bond of the isopropylidine group could not be isomerized under non-acidic conditions to give XIX. The use of pyridine as solvent in this reaction was also unsuccessful.[20]

Since the chemical interconversions mentioned above left something to be desired, instrumental methods were sought in order to arrive at the structure of the diosphenols. Three spectroscopic methods were utilized for this purpose; UV optical rotatory dispersion and NMR but only the latter appeared unambiguous. Diosphenol-A and B exhibited maxima in the UV at almost the same wavelength (278 mμ) reported[21] for the steroid diosphenol XXI; the wavelength calculated[22] for XVIII is 269 mμ while that calculated for XIX is 274 mμ. Diosphenol-A methyl ether showed a maximum at 254 mμ analogous to that reported[21] for XXII. Unfortunately, a steroid model similar in structure to XVIII was not available for comparison purposes.

Diosphenol-A methyl ether gave a negative multiple Cotton effect ORD curve similar to that given by Δ^4-3-keto steroids[14] and by the α,β-unsaturated ketone XXIII. The latter substance was prepared by reduction of HE-acetate (I, R = $COCH_3$), followed by pyrolysis. Reduction of XXIII with lithium in liquid ammonia, followed by chromic acid oxidation gave IV. Several attempts to convert ketone XXIII into the methyl ether of XIX via the intermediate epoxide using methyl sulfate as described in the steroid series[21] were unsuccessful. The two steroidal diosphenol methyl ethers

[20] D. Kupfer, *Tetrahedron* **15**, 193 (1961).

[21] W. Reusch and R. Le Mahieu, *J. Amer. Chem. Soc.* **85**, 1669 (1963).

[22] A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*" p. 232 Edward Arnold, London (1958).

XXII and XXIV, kindly supplied by Dr. Reusch,[21] were found to give identical negative multiple Cotton effect curves differing only in amplitude. Thus the use of ORD for distinguishing between XVIII and XIX did not appear promising.

The NMR spectra of diosphenols-A and B and their acetates and the spectrum of diosphenol-A methyl ether were all similar and support structure XVIII rather than

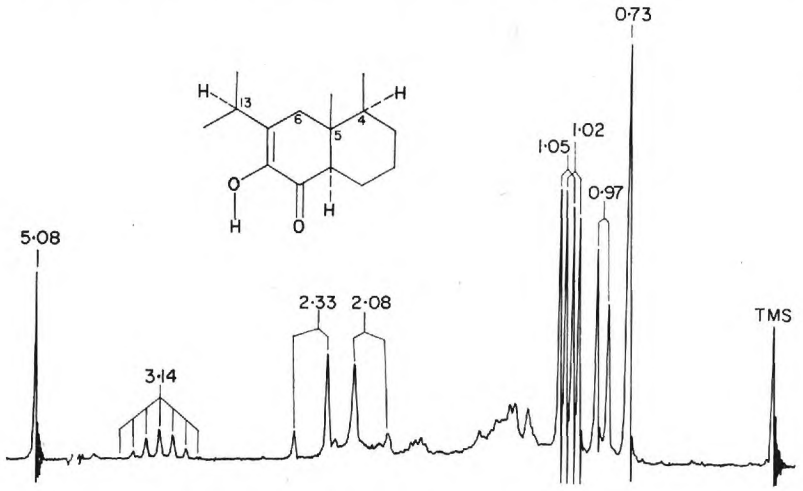
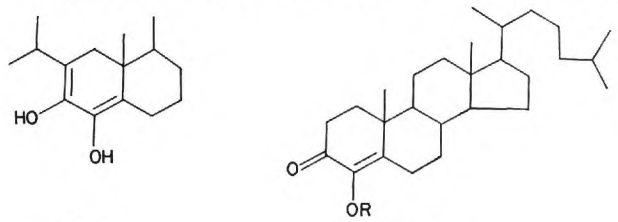
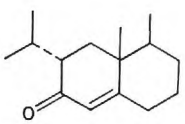


FIG. 1. 100 Mc Spectrum of Diosphenol-A. Chemical Shifts (δ) Relative to TMS

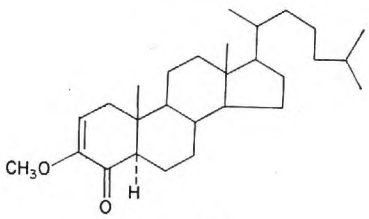


XX

XXI R=H
XXII R=CH_3



XXIII



XXIV

XIX. Of particular significance was the appearance of a septet which could be assigned to the proton between the isopropyl methyl groups in XVIII. If XIX had been correct, this proton would not be expected to appear so far downfield and it would be expected to show more than seven lines. Each of the above spectra also showed an AB quartet which could be assigned to the C-6 protons of XVIII; again this observation is not consistent with structure XIX. In Fig. 1 the 100 Mc spectrum of diosphenol-A is reproduced. It is clear that structure XVIII is consistent with this

spectrum. Thus the singlet at δ 0·73 arises from the C-5 methyl group, the doublet (J = 6 c/s) centered at δ 0·97 is due to the C-4 methyl group and the isopropyl methyl groups appear as a pair of overlapping doublets (J = 6·5 c/s) centered at δ 1·02 and δ 1·05 respectively. As mentioned above, the C-6 protons give a quartet which can be seen as a pair of doublets (J = 16·5 c/s) centered at δ 2·08 and δ 2·33, and the C-13 proton appears as a septet centered at δ 3·14. The region of the spectrum containing the C-6 and C-13 protons is shown expanded in Fig. 2 where the C-13 AB quartet

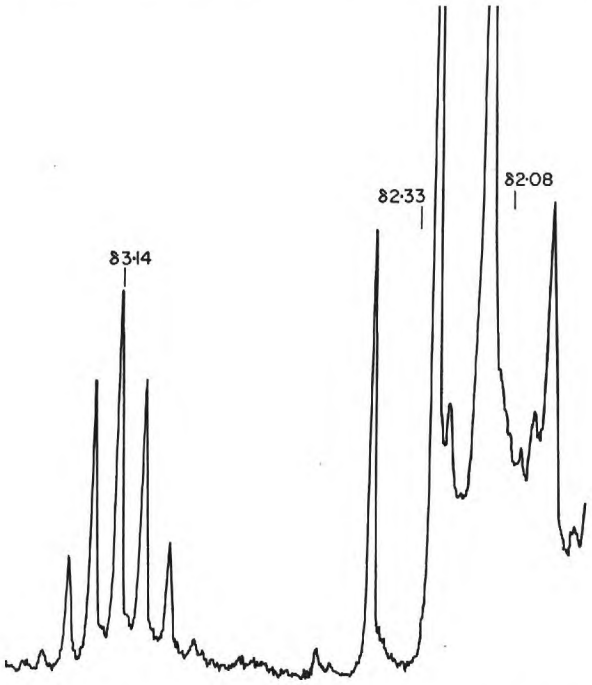


FIG. 2. Expanded 100 Mc Spectrum of C-6 and C-13 Protons of Diosphenol-A.

and C-6 septet are more clearly defined. The singlet at δ 5·08 in Fig. 1 is due to the hydroxyl proton of XVIII.

The thermodynamically more stable isomer, diosphenol-A is assigned the 10α configuration, XVIIIa. The increased number of lines in the NMR spectrum of diosphenol-B in the δ 1·7–3·5 (60 Mc) region of the spectrum suggest that it exists as a mixture of *cis* fused conformers.

EXPERIMENTAL

M.ps were taken on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. IR spectra were recorded with a Beckman IR-5 spectrophotometer and UV spectra were obtained with a Cary Model 14 spectrometer. NMR spectra were measured with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard (δ = 0) and $CDCl_3$ as a solvent. Rotatory dispersion curves were measured with a Japan Spectroscopic Co. Ltd. automatically recording spectropolarimeter model ORD-5.

7α, 10α *Eremophilan*-8-*one*. XIII

HE (1·4 g) was hydrogenated as previously described[5] to give the tetrahydro derivative (1·3 g) which was added to 10 cc ethanol, and to this solution 8 cc 5N NaOH was added. After refluxing in a N_2

atm. for 3 hr, the solution was neutralized with dil. HClaq and extracted with ether. After drying over $MgSO_4$, the ether extract was concentrated and the residue distilled (b.p. 70° at 0·01 mm) to give 1 g of the ketol 7α, 10α-eremophilan-8-ol-9-one; $\lambda_{max}^{CHCl_3}$ 2·9, 5·87μ; ORD (*c*, 0·189 in CH_3OH): $[\alpha]_{700}$ −310°, $[\alpha]_{589}$ −18°, $[\alpha]_{300}$ −302°, $[\alpha]_{270}$ +874°, $[\alpha]_{225}$ +132°. (Found: C, 75·71; H, 10·88; O, 13·38. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00; O, 13·42%.) This ketol differed in its IR spectrum from the isomeric ketols prepared by hydrogenation of HE and hydrogenation of HDE.

The above ketol (1 g) was transformed into its acetate (1 g) with acetic anhydride in pyridine by the usual procedure and the α-acetoxy ketone was deacetoxylated, as previously described,[5] with calcium in ammonia to give 0·4 g of XIII which was immediately transformed into its semicarbazone (420 mg) by the semicarbazide acetate method. Several further recrystallizations failed to raise the m.p. (208–210°) of the semicarbazone of XIII. (Found: C, 68.60; H, 10·43. $C_{16}H_{29}N_3O$ requires: C, 68·75; H, 10·46.)

Pure XIII was obtained in quantitative yield by refluxing the semicarbazone in 10% HClaq for 2 hr followed by the usual workup, and the analytical sample was obtained after distillation (b.p 100°/0·1 mm) and showed λ_{max}^{film} 5·85 μ; the fingerprint region of the IR spectrum of XIII differed from the spectra of isomeric ketones IV, VI and XIV. ORD (*c*, 0·246 in CH_3OH): $[\alpha_{589}]$ −81°, $[\alpha]_{306}$ −1609° (trough), $[\alpha]_{260}$ +2084 (peak). (Found: C, 80·96; H, 11·88. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79.)

The 2,4-dinitrophenylhydrazone derivative of XIII was prepared with a methanolic HCl solution of 2,4-dinitrophenylhydrazine and showed, after many recrystallizations, unchanged m.p. 125–126°. (Found: C, 62·37; H, 7·62. $C_{21}H_{30}N_4O_4$ requires: C, 62·66; H, 7·51.) Both the 2,4-dinitrophenylhydrazone and the semicarbazone of XIII showed m.p. depressions on admixture with the corresponding derivatives of IV, VI and XIV. The 2,4-DNP of ketone XIII (m.p. 125–126°) was hydrolyzed by refluxing in dil. HClaq containing $SnCl_2$ to give XIII which was immediately transformed into its semicarbazone of identical m.p. (208–210°) to that observed as mentioned above. A careful examination of the mother liquors remaining after removal of the 2,4-DNP and semicarbazone of XIII failed to reveal the presence of other isomeric ketones in both cases.

Diosphenol—A

The acetate and methyl ether of diosphenol—A. A solution containing 1 g HDE, 10 cc EtOH and 8 cc 5N NaOH was refluxed in a N_2 atm. for 2 hr. After cooling to room temp, the solution was neutralized with dil. HClaq, then extracted with ether. Evaporation on the dried ($MgSO_4$) ether extract gave a yellow oil which crystallized on standing and after three recrystallizations gave 0·83 g diosphenol-A, m.p. 92–93°. λ_{max}^{KBr} 2·91, 5·97, 6·08μ; λ_{max}^{EtOH} 277 mμ (log ε 4·03); $[\alpha]_D$ +41° (*c*, 1·89 in C_2H_5OH). ORD (*c*, 0·05 in dioxane): $[\alpha]_{589}$ +80°, $[\alpha]_{340}$ +1200° (peak), $[\alpha]_{330}$ +1050° (shoulder), $[\alpha]_{292}$ −4500° (trough). (Found: C, 76·34; H, 10·11; O, 13·72. $C_{15}H_{24}O_2$ requires; C, 76·22; H, 10·24; O, 13·54.) The crystalline diosphenol-A gradually turned to a yellow oil on standing.

Diosphenol-A (0·5 g) was dissolved in 6·6 cc pyridine and 3·3 cc acetic anhydride was added. After standing at room temp overnight the reaction was worked up in the usual manner to give the crude acetate as a viscous gum which was crystallized from EtOH–water to give m.p. 95–96° (0·5 g). $\lambda_{max}^{CHCl_3}$ 5·67, 5·92, 8·10μ. λ_{max}^{EtOH} 243 mμ (log ε 4·04). ORD (*c*, 0·19 in CH_3OH): $[\alpha]_{589}$ +10°, $[\alpha]_{335}$ −300° (trough), $[\alpha]_{280}$ +720° (peak). The negative Cotton effect curve was unchanged on addition of a trace of HClaq. (Found: C, 73·26; H, 9·27; O, 17·05. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41; O, 17·24.)

Diosphenol-A (210 mg) was dissolved in 10 cc acetone and 1·5 cc dimethyl sulfate was added to the solution which was then made alkaline (pH 10) by the addition of 20% NaOHaq. The solution was stirred overnight then refluxed for 1 hr. After dilution with water, the solution was extracted with ether and the ether extract was successively washed with H_2SO_4aq and water and finally dried over Na_2SO_4. Removal of the ether solvent left 200 mg crude methyl ether which was crystallized from EtOH to give m.p. 51–52°. λ_{max}^{film} 5·97, 6·10μ. λ_{max}^{EtOH} 254 mμ (log ε 3·93). ORD (*c*, 0·212 in dioxan): $[\alpha]_{589}$ −100°, $[\alpha]_{363}$ −6008° (trough), $[\alpha]_{355}$ −5508°, $[\alpha]_{347}$ −7260° (trough), $[\alpha]_{338-336}$ −2253° (shoulder), $[\alpha]_{310}$ 12,700° (peak). (Found: C, 76·77; H, 10·04. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47.)

Diosphenol-B *and diosphenol*-B *acetate*

Hydroxytetrahydroeremophilone (600 mg, m.p. 85–86°) prepared as previously described[11] by hydrogenation of HDE was dissolved in 10 cc glacial acetic acid; 1·1 g Bi_2O_3 was added and the

solution refluxed in a N_2 atm. for 1 hr, then an additional 600 mg Bi_2O_3 was added and reflux continued for another hr. The solution, after cooling, was filtered, the precipitate was washed with acetic acid and the combined filtrate and washings were poured on crushed ice, whereupon a white solid separated. After filtration and washing with water, diosphenol-B was recrystallized from water–EtOH (1:1) to give 210 mg pure material, m.p. 63–64°, while the mother liquor yielded after 2 days an additional 36 mg of diosphenol-B. λ_{max}^{KBr} 2·91, 5.97, 6.08μ; λ_{max}^{EtOH} 277 mμ (log ϵ 3·78); $[\alpha]_D$ +17° (*c*, 3·08 in C_2H_5OH). ORD (*c*, 0·19 in MeOH): $[\alpha]_{589}$ +15°, $[\alpha]_{330}$ +310° (peak), $[\alpha]_{300}$ −2000°. After standing for several days diosphenol-B turned to a yellow oil which showed a *negative* Cotton effect! (Found: C, 76·45; H, 10·36. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24.)

Diosphenol-B acetate was prepared as described above for diosphenol-A acetate in essentially quantitative yields, m.p. 62–64°. $\lambda_{max}^{CHCl_3}$ 5·67, 5·92, 8·10μ. λ_{max}^{EtOH} 243 mμ (log ϵ 4·01). ORD (*c*, 0·09 in CH_3OH): $[\alpha]_{340}$ −140° (trough), the negative Cotton effect curve was unchanged on addition of a trace of HClaq. (Found: C, 73·20; H, 9·25; O, 17·61. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41: O, 17·24.)

*Conversion of diosphenol-*B *to diosphenol-*A

A solution of diosphenol-B (100 mg) in 2 cc EtOH and 1 cc 5N NaOH was refluxed in a N_2 atm. for 3 hr and the solution was worked up as described above for the preparation of diosphenol-A to give in quantitative yield diosphenol-A, identical in all respects with that obtained directly by treatment of HDE with base.

Hydroxyeremophilone

The ORD curve of HE is recorded here since improved instrumentation now permits penetration into lower wavelengths than previously possible. ORD (*c*, 0·125 in dioxan): $[\alpha]_{589}$ +361°, $[\alpha]_{360}$ −1870° (trough), $[\alpha]_{279}$ +27,950 (peak), $[\alpha]_{248}$ −5280° (trough), $[\alpha]_{225}$ +9060 (peak).

*Conversion of diosphenol-*A *to ketones* IV *and* VI *by sequential hydrogenation*

Acetylation and calcium–ammonia deacetoxylation. Diosphenol-A (1 g) in 50 cc 95% EtOH was readily hydrogenated in the presence of 10% Pd–C catalyst at room temp. and atm. press. to give the dihydro derivative (850 mg, b.p. 110°/0·1 mm). λ_{max}^{film} 2·87, 5·82μ. (Found: C, 75·19; H, 10·91. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00.)

The dihydro derivative was converted into its acetate in quantitative yield by treatment with acetic anhydride in pyridine as previously described. B.p. 110°/0·1 mm, λ_{max}^{film} 5·72, 5·80, 8·05μ. (Found: C, 73·14; H, 10·11. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06.)

Dihydro-diosphenol-A acetate (0·5 g) was dissolved in 15 cc dioxan and this solution was slowly added to 70 cc liquid ammonia containing 0·5 g Ca. The ammonia solution was allowed to evaporate overnight at room temp. and the unreacted Ca was destroyed by the successive addition of 5 cc 95% EtOH, 10 cc sat. NH_4Claq and finally the solution was neutralized with dil. HClaq. The solution was then ether extracted and the dried ether extract evaporated to give a crude product which was directly oxidized with Jones' reagent.[19] After the usual workup, 350 mg of a colorless liquid product (b.p. 100°/0·1 mm) was obtained, which was transformed into its 2,4-DNP derivative (m.p. 165–166°). This 2,4-DNP derivative, although sharp melting, was found to be a mixture of the 2,4-DNP's of IV and VI as was previously observed[5] when HE was sequentially reduced to the tetrahydro derivative, acetylated to the α-acetoxy ketone and finally deacetoxylated with Ca–ammonia to yield IV and VI. The isolation of IV (positive Cotton effect ORD curve) and VI (negative Cotton effect ORD curve) was accomplished as previously described[5] by acid cleavage of the 2,4-DNP and conversion of the free ketone mixture to the semicarbazone followed by separation of the individual semicarbazones by numerous recrystallizations and finally acid cleavage of the semicarbazone derivatives to give the pure ketones. Ketones IV and VI obtained in this manner were identical in all respects with these ketones isolated as previously described.[5]

*Conversion of diosphenol-*B *to ketones* IV *and* VI *by sequential hydrogenation*

Acetylation and calcium–ammonia deacetoxylation. Diosphenol-B (1 g) was hydrogenated as described above for diosphenol-A to give 920 mg dihydro derivative, b.p. 110°/0·1 mm, λ_{max}^{film} 2·87, 5·82μ. (Found: C, 76·09; H, 11·16. $C_{15}H_{26}O_2$ requires: C, 75·52; H, 11·00.) As shown below, the product contained some hydrogenolysis product, which accounts for the high carbon content found for the dihydro product and its acetate.

Dihydro diosphenol-B was converted into its acetate (b.p. 120°/0·1 mm) as described above for dihydro diosphenol-A, λ_{max}^{film} 5·72, 5·81, 8·05μ. (Found: C, 73·51; H, 10·19. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06.) The high carbon content observed results, as mentioned above, from the presence of some hydrogenolysis product.

Dihydro diosphenol-B acetate was treated with Ca in liquid ammonia, to effect deacetoxylation, exactly as described previously for dihydro diosphenol-A acetate and an identical 2,4-DNP mixture (m.p. 165–166°) was obtained as in the diosphenol-A series.

Hydrogenolysis of diosphenol-B to yield ketone IV

Diosphenol-B (m.p. 64°, 280 mg) was dissolved in 90% EtOH (25 cc) and hydrogenated at room temp and atm. press. in the presence of 10% Pd–C (45 mg) for 40 hr. After removal of the catalyst by filtration and evaporation of the solvent 260 mg colorless oil was obtained, which was carefully chromatographed on Merck acid washed alumina (15 g, Activity I). Elution with pet. ether–benzene (1:1) and benzene gave 30 mg of a ketonic fraction (no O—H absorption in IR spectrum). This ketonic material was dissolved in 5 cc MeOH and 5 cc of 2N NaOH was added and the solution stirred under N_2 for 6 hr. After dilution with water, extraction with ether and evaporation of the dried ether extract, 20 mg of ketonic material was obtained. The latter was transformed into its semicarbazone derivative (m.p. 189–190°) and after two recrystallizations it showed m.p. 191–192°. This semicarbazone was shown to be identical with the semicarbazone of ketone IV (see next section) by m.p. and mixed m.p. and it showed a m.p. depression with the semicarbazones of ketones VI, XIII and XIV. Ketone VI may have been present in the hydrogenolysis product but its semicarbazone derivative was not isolated.

*Hydrogenation of diosphenol-*A *methyl ether*

Diosphenol-A methyl ether (m.p. 51–52°, 200 mg) was hydrogenated in 95% EtOH (25 cc) using 10% Pd–C catalyst (50 mg) for 60 hr. The reduction product, after isolation by the usual procedure, was dissolved in 10 cc MeOH and 3 cc 2N NaOH and this solution was stirred under N_2 overnight. After the usual workup, the product was chromatographed on 25 g Merck. acid-washed alumina (Activity I). Elution with pet. ether gave 10 mg substance, the IR (no C=O band) and NMR of which suggested it to be a methoxyeremophilane. Further elution with pet. ether–benzene (9:1) gave 125 mg dihydro-diosphenol-A methyl ether; b.p. 126–129°/0·5 mm; λ_{max}^{film} 5·86μ; NMR δ 3·20 (O—CH_3). (Found: C, 76·54; H, 11·20. $C_{16}H_{28}O_2$ requires: C, 76·14; H, 11·18%.) Elution with benzene gave 25 mg of saturated ketone fraction (no O—CH_3 present by NMR) which was transformed into its semicarbazone, m.p. 184–185°. After two recrystallization it gave m.p. 194–196° and was identical to the semicarbazone of IV, previously obtained from HE acetate[5] and showed m.p. depressions with the semicarbazones of ketones VI, XIII and XIV. The mother liquor remaining after the removal of the above semicarbazone yielded additional semicarbazone of IV which after three recrystallizations gave m.p. 194–196°. The previously reported[4] m.p. 176–180° for the semicarbazone of IV should be revised. The semicarbazone of IV (m.p. 194–196°) was cleaved by 10% HClaq to give pure IV which gave a positive Cotton effect ORD curve as previously described[4] but of increased magnitude. ORD (*c*, 0·10 in CH_3OH): $[\alpha]_{589}$ 0°, $[\alpha]_{313}$ +1176° (peak) $[\alpha]_{275}$ −2109° (trough), IR (Beckman IR-7): λ_{max}^{film} 5·83, 6·82, 6·90, 7·12, 7·29, 7·92, 8·25, 8·44, 8·82, 9·07, 9·40, 9·95, 10·29, 11·03, 11·87μ.

*Reaction of dihydrodiosphenol-*A *methyl ether with calcium ammonia*

Dihydrodiosphenol-A methyl ether (220 mg) in 2 ml dioxan was added to 70 ml liquid ammonia containing 1 g Ca. The solution was allowed to reflux for 2 hr then the ammonia was allowed to slowly evaporate overnight at room temp. EtOH (5 ml) and sat NH_4Claq were added to the residue which was then neutralized with dil HClaq at 0°. The aqueous solution was extracted with ether and the ether extract washed with water then dried over Na_2SO_4 and evaporated. The oily residue was immediately oxidized with Jones reagent[19] to give 148 mg saturated ketonic fraction, b.p. 115°/0·4 mm, the IR spectrum of which was essentially the same as that of ketone XIV. This substance was unchanged after equilibration with base and chromatography of alumina. ORD (*c*, 0·09 in MeOH): $[\alpha]_{589}$ +11·7°, $[\alpha]_{318}$ −40·9, $[\alpha]_{315}$ −35·1, $[\alpha]_{310}$ −40·9° (trough), $[\alpha]_{270}$ +445°, $[\alpha]_{260}$ +455°.

Preparation of eremophil-9-ene-8-one (XXIII)

HE acetate (580 mg) in EtOH was reduced in the presence of 10% Pd–C catalyst (50 mg) to give the dihydro derivative (508 mg) as previously described.[5] Pyrolysis of the tetrahydrohydroxyeremophilone acetate gave mostly unreacted starting material at <500°; the material (3·2 g) was, however, successfully pyrolyzed in a dynamic system at 500° where upon 2·25 g crude product was obtained, which after distillation (2·18 g) was chromatographed on alumina (50 g) to give 1·7 g pure XXIII in the pet ether–benzene eluant. B.p. 110–113°/0·1 mm; λ_{max}^{film} 5·94, 6·14 μ. ORD (*c*, 0·162 in dioxane): $[\alpha]_{589}$ +44°, $[\alpha]_{365}$ −285° (trough), $[\alpha]_{355}$ −252°, $[\alpha]_{352}$ −257° (trough), $[\alpha]_{300}$ +1200°. (Found: C, 81·81; H, 11·17. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.)

Conversion of ketone XXIII *to ketone* IV

Lithium ribbon (100 mg) was added to 30 cc dry liquid ammonia and after 30 min, XXIII (126 mg) in 5 cc dioxan was added to the solution. The ammonia was allowed to evaporate over a period of 2 hr and then 5 cc sat. NH_4Claq was added and the entire mixture heated on the steam bath for 10 min. The solution was extracted with ether and the ether extract successively washed with water, dil. HCl, water again and finally dried. Evaporation of the ether extract gave a crude product, whose IR spectrum showed strong O—H absorption. The crude product was oxidized with Jones reagent[19] and after the usual workup, 92 mg saturated ketone IV, b.p. 121°/0·5 mm was obtained. Ketone IV thus obtained was transformed into its semicarbazone, m.p. 192–194°, which showed no depression in m.p. with IV prepared from HE or from diosphenols-A and B but did show m.p. depressions with semicarbazones of ketones VI, XIII and XIV.

Hydrogenation and hydrogenolysis of HE to yield ketone IV

HE (1 g) was hydrogenated at room temp and atm pres. in EtOH (40 cc) in the presence of 300 mg Pd–C for 12 hr. The crude product, obtained after the usual workup, was transformed into its acetate with acetic anhydride and pyridine and the crude acetate chromatographed on 20 g Merck acid-washed alumina. Ketone IV (95 mg) was obtained from the pet ether eluant and transformed into its semicarbazone, m.p. 192–194°, which was found identical with the semicarbazone derivative of IV prepared as described above.

Acknowledgements—We are indebted to Dr. Maurice D. Sutherland of the University of Queensland for supplies of hydroxyeremophilone and hydroxydihydroeremophilone. We wish to thank Dr. Lois J. Durham for determining the 100 Mc NMR spectra. The work at Oklahoma State University was generously supported by USPHS–NIH grant AM-05490, while that at Stanford University was supported through USPHS–NIH grant GM-06840.

Studies In The Conversion of Carvone to Eremophilone

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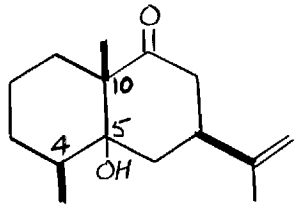
In 1939 Robinson offered an explanation[1] for the formation of the non-isoprenoid sesquiterpene eremophilone (II) in nature which involved a molecular rearrangement of a precursor I which obeyed the "isoprene rule". This has been a very satisfying explanation since a



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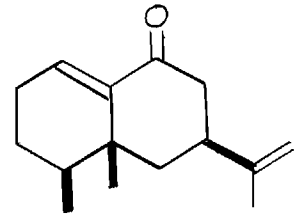
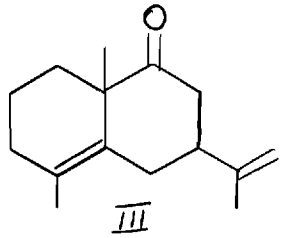


II

rather large number of sesquiterpenes have since been isolated which possess the eudesmane (selinane) skelton such as I. Most eudesmane sesquiterpenes have an absolute configuration at C-10 and C-4 as depicted in I and the finding that the absolute configuration of eremophilone is as shown in II[2] is consistent with our present knowledge of the stereochemical requirements of methyl migrations.[3]

We were therefore interested in attempting a laboratory synthesis which would utilize the "biogenetic" approach. In particular, we planned to synthesize III and subsequently convert it into eremophilone.



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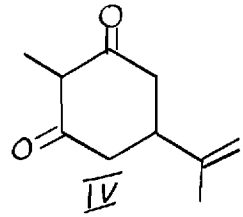

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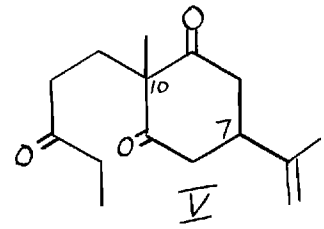
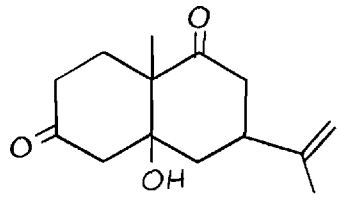
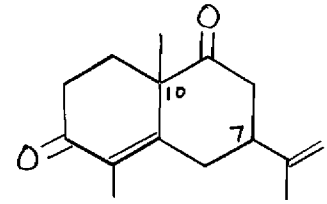


V

Carvone (d or l) was readily oxidized as previously described[4] to give diketone IV, which on condensation with ethylvinyl ketone gave V in good yield [ν_{max}^{film} 1720-1710, 1690, 1645cm^{-1}; δ 0.95 (3H, triplet, J=7cps) 1.12 (3H), 1.78 (3H), 4.80 (2H)]. Triketone V was converted into VI [m.p. 131-132°, ν_{max}^{nujol} 3420, 3080, 1715-1705; δ 1.07 (3H,



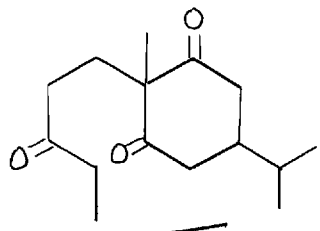
VI



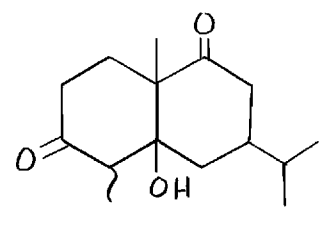
VII

doublet, J=6.5cps), 1.26 (3H), 1.78 (3H), 4.82 (2H)] with pyrrolidine in ether. The assignment of a cis ring fusion in VI is by analogy with recent work of Spencer et al.[5] Further treatment of VI with pyrrolidine in benzene at reflux using a water separator gave VII. [b.p. 148-152°/0.25mm; ν_{max}^{film} 3085, 1711, 1670, 1645cm^{-1}; δ 1.44 (3H), 1.76 (3H), 1.83 (3H), 4.86 (2H)]. Using the more drastic conditions V was converted directly into VII.

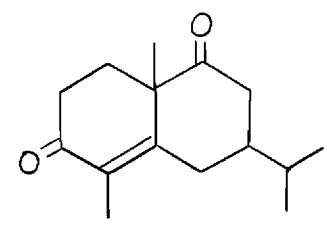
Before proceeding further it was necessary to establish the relative configuration at C-7 and C-10 in VII. For our purposes, it was required that the methyl group at C-10 and the isopropenyl group at C-7 be cis. Fortunately, this was indeed found to be the case as follows. Triketone V was catalytically reduced to give VIII



VIII

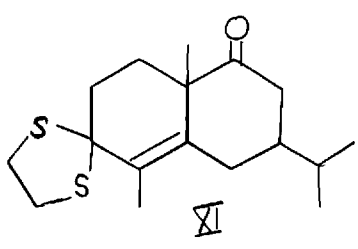


IX

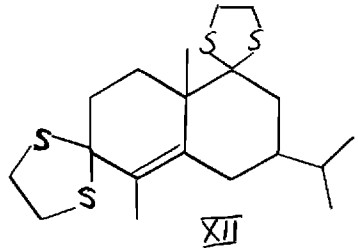


X

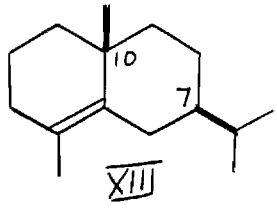
[ν_{max}^{film} 1720-1717, 1690cm^{-1}; δ 0.95 (3H, triplet, J=7cps), 0.96 (3H, doublet, J=5.5), 1.06 (3H)] which was converted into IX [m.p. 131-132°; ν_{max}^{nujol} 3450, 1715-1700cm^{-1}; δ 0.94 (6H, doublet, J=5.5cps) 1.02 (3H, doublet, J=6.5cps), 1.27 (3H)] as described above. Simarilarly ketone X [ν_{max}^{film} 1710, 1670cm^{-1}; δ 0.97 (6H, doublet, J=5.5cps.), 1.38 (3H), 1.75 (3H)] was prepared from VIII or IX as previously described. Diketone X was converted into a mixture of monthioketal XI dithioketal XII



XI



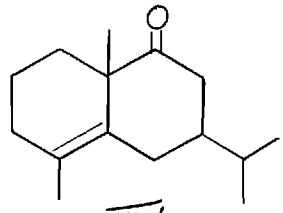
XII



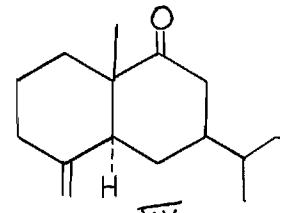
XIII

with ethanedithiol and XI could be further converted into XII with excess ethanedithiol. Thioketals XI and XII were readily separated by chromatography on alumina, XII being eluted first [m.p. 107.5°; ν_{max}^{nujol} 1620cm^{-1}; δ 0.94 (6H, doublet, J=5.5cps), 1.25 (3H), 1.86 (3H), 3.20 (8H)]. Desulfurization of XII with Raney nickel gave, after chromatography on silica gel-silver nitrate, hydrocarbon XIII in excellent yield. The latter product was identical (g.l.c., I.R., N.M.R.) with an authentic sample of XIII prepared from neointermedeol[6]. Since neointermedeol has been synthesized from eudesmol, of known absolute configuration, the stereochemistry of V-XIII is established as cis at C-7 and C-10. Thus the condensation of IV with ethylvinylketone is stereospecific.

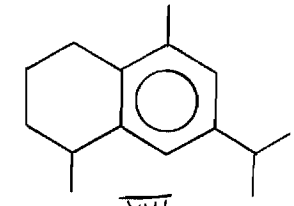
Monothioketal XI [m.p. 74.5-75°; ν_{max}^{film} 1703, 1620cm^{-1}; δ 0.94 (6H, doublet, J=5.5cps), 1.23 (3H), 1.88 (3H), 3.27 (4H)] on desulfurization gave the unsaturated ketone XIV [ν_{max}^{film} 1703, 1652cm^{-1}; δ 0.94 (6H, doublet, J=5.5cps), 1.64 (3H), 1.78 (3H)] after chroma-



XIV



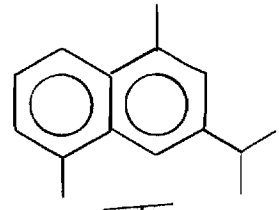
XV



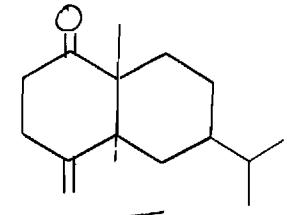
XVI

tography on silica gel-silver nitrate. Ketone XIV, which we refer to as γ-canarone[7], is a double bond isomer of the recently reported[8] sesquiterpene canarone, XV. Studies are now underway to convert XIV into XV and thus complete the synthesis of XV.

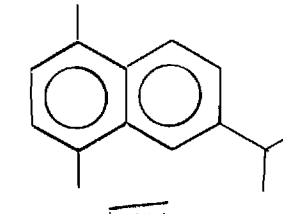
On treatment with acid, under many different conditions, XIV rapidly gave the aromatic compound XVI in excellent yield rather than the desired dihydroeremophilone. Structure XVI [ν_{max}^{film} 1615, 1576cm^{-1}; λmax 268 mμ (E 335), 276 (E=280); δ1.19 (9H, doublet, J=6.5cps), 2.06 (3H), 6.78 (1H), 6.86 (1H)] was assigned on the basis of its spectral properties and its further conversion to the naphthalenic derivative XVII [δ1.35 (6H, doublet, J=6.5cps), δ 2.67 (6H), δ2.97 (1H, multiplet), five



XVII



XVIII



XIX

aromatic protons]. Originally Bhattacharyya et al.[9] assigned structure XVIII to canarone; on reaction with methyl magnesium iodide followed by dehydrogenation of the resulting alcohol, XIX was reported to be obtained from canarone. This product should now be represented by structure XVII. A direct comparison of XVI prepared by us and the aromatic product obtained by Bhattacharyya[9] will be made.

Two recent reports[10,11] have described a similar methyl migration and aromatization when α,α-disubstituted-β,γ-unsaturated ketones of the 4,4-dimethyl steroid type were treated with acid. However, we have observed that under conditions where XIV readily gave XVI, X was unaffected. This lead is now being further investigated.

Correct elemental analyses were obtained for all compounds described in this communication. In addition mass spectra of XVI and XVII, were kindly provided by Dr. C. C. Sweeley, University of Pittsburgh. These showed the correct molecular weights and their further interpretations are being studied.

[1] Quoted in A. R. Penfold and J. L. Simonsen, J. Chem. Soc., 1939, 87.

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[3] J. F. King and P. de Mayo, "Terpenoid Rearrangements" Chp. 13 in P. de Mayo, "Molecular Rearrangements", Part 2, Interscience Publishers, New York, 1964.

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[6] V. B. Zalkow, A. M. Shaligram and L. H. Zalkow, Chem. and Ind., 194 (1964).

[7] By analogy with the nomenclature used for the eudesmol isomers.

[8] V. K. Hinge, A. D. Wagh, S. K. Paknikar and S. C. Bhattacharyya, Tetrahedron, 21, 3197 (1965).

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The Use of 2-α-Isopropylcholestan-3-one As A Model for the Synthesis Of Eremophilane Sesquiterpenes

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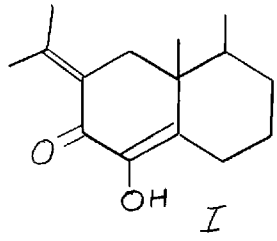
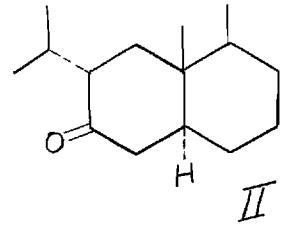
Schools of Chemistry,

Oklahoma State University and Georgia Institute of Technology

Hydroxyeremophilone, I, has been degraded to the trans C-8 eremophilanone II, which has been totally synthesized in optically



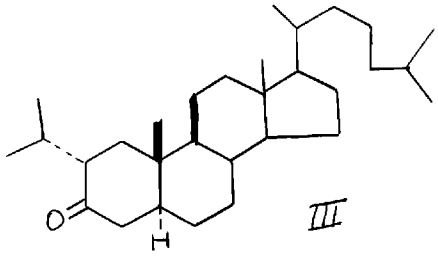
I



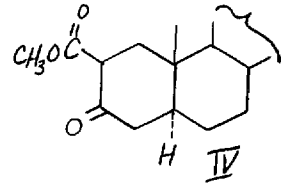
II

active form.[1] Thus the reconversion of II to hydroxyeremophilone would constitute a total synthesis. Unfortunately, in the transformation of I to II a second ketone, cis C-8 eremophilanone is also formed and its separation from II is extremely tedious[2]. Thus, it was decided that a model compound would be desirous for studying the conversion of II to I in view of the difficulty in obtaining II in quantity either by synthesis or by degradation.

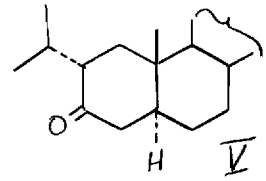
The model compound chosen was 2α-isopropyl-cholestan-3-one, III; the similarity to II is obvious. Our initial goal was to synthesize 2-isopropylcholesta-3,4-dione (diosphenol) in good yield. Although



III



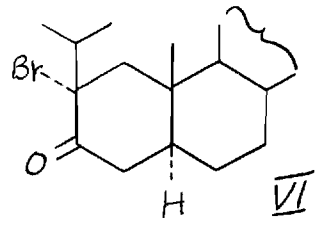
IV



V

the synthesis of III has been reported[3], we were not able to repeat the synthesis in the reported yields and modified it as follows. Cholestan-3-one was converted directly into IV with dimethyl carbonate[4]. Ketalization of IV gave a number of side products and only a yield of 30% could be realized by using diglyme as a cosolvent. The ketal was further converted into 2α-isopropylcholestan-3-one, V, as previously described[3]. Since this preparation of V was tedious and proceeded in modest overall yield much effort was expended in attempting to improve the process but without success. Some of the attempted procedures involved use of the pyrrolidine enamine[5] of cholestan-3-one with isopropyl bromide, ethyl chloroacetate and ethyl α-bromopropionate; all of these proceeded in extremely low yield if at all. Another approach used the 2β, 3β epoxide of cholestane and still another used the 4β, 5β epoxide of cholestan-3-one[6] but in neither case could the isopropyl group be introduced at C-2 efficiently. Likewise, we were unable to introduce an isopropyl group at C-2 in 3-hydroxy-cholest-3-en-2-one[7] or in 4-methoxycholest-4-en-3-one[8].

Dibromination of V (at C-2 and C-4) did not proceed in good yield but the dibromide obtained was shown to be the C-2, C-4 dibromide by N.M.R. (δ 3.86, J=11 cps). It could be dehydrobrominated to give 2-isopropyl-cholesta-1,4-diene. Monobromination of V under thermo-dynamic conditions gave VI [m.p. 136-136°; λ_{max}^{KBr} 5.87μ; λmax 315 mμ (E 115)] in which the bromine atom appears

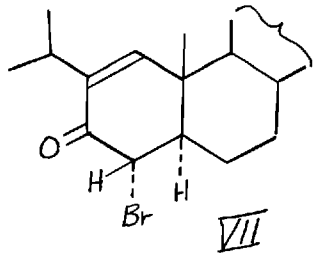


VI

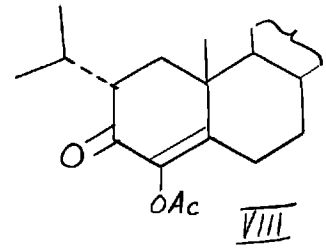
to be axial and the A ring is probably therefore in a boat conformation. The further attempted conversions of the bromo derivatives into useful compounds are discussed later in this report.

Selenium dioxide oxidation[9] of V gave little conversion to useful products under a number of conditions. Isoamylnitrite[10] failed to yield the 4-isonitrosoketone in decent yield and hydroperoxidation[9,11] of V gave no diosphenol.

2, 4-Dibromo-2-isopropylcholestan-3-one when heated with dimethyl sulfoxide[12] failed to yield a diosphenol, as did the reaction of the dibromide with sodium azide[13]. The most promising result to date in this area has been the reaction of 2-isopropyl-2, 4-dibromocholestan-3-one with sodium acetate in acetic acid to give VII [m.p. 84-85.5°; λ_{max}^{KBr} 5.96, 6.13, 6.32μ; δ 4.38 (1H, doublet, J=12 cps), 6.68 (1H); λmax 247.5mμ (E9,450] and VIII [m.p. 112-116°; λmax 5.68, 5.94, 6.08, 8.18μ; λmax 243mμ (E 11,690); δ 2.18 (3H)]. Correct elemental



VII



VIII

analyses were obtained for VII and VIII. Attempts are underway to improve the conversion of V to VIII.

[1] L.H. Zalkow, F. X. Markley and C. Djerassi, J. Am. Chem. Soc., 82, 6354, (1960).

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B. Detailed Report

(2) List of Publications

"Constitution and Absolute Configuration of Eremophilenolide", F. Sorm et al., L. H. Zalkow and S. Hu and C. Djerassi, Tetrahedron, 19, 1101 (1963).

"Studies in the Chemistry of the Eremophilane Sesquiterpenes," L. H. Zalkow, A. M. Shaligram and Shih-En Hu and C. Djerassi, Tetrahedron, 22, 337 (1966).

(3) Staffing

Dr. Shih-En Hu, research associate, Jan. 1, 1962-Dec. 31, 1962, full time.

Dr. A. M. Shaligram, research associate, Jan. 1963-Dec. 1964, full time.

Dr. K. R. Varma, research associate, Jan. 1965-Aug. 31, 1965, full time

Dr. B. Lacoume, research associate, Sept. 15, 1965-to present, full time

Dr. L. H. Zalkow, principal investigator, Sept. 1, 1961 to present, 15% time.