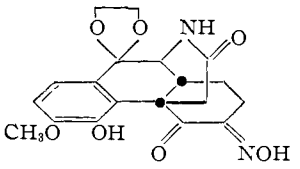
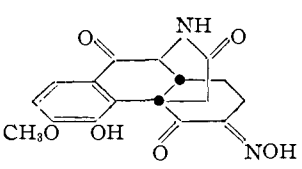
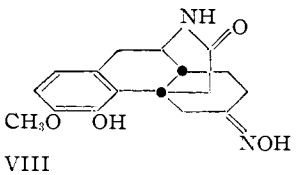


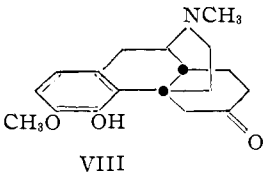
V



VI



VIII



VIII

Modified Huang-Minlon reduction of VI removed the two free carbonyl groups and yielded the oxime-lactam, VII, m.p. 210–213°, which depresses the m.p. of VI. Acid treatment hydrolyzed the oxime to the ketone which was obtained as a viscous oil. Lithium aluminum hydride reduction in tetrahydrofuran gave an oily mixture of epimeric *des*-N-methyl-dihydrothebainols which was methylated by means of formaldehyde–formic acid to a mixture of epimeric dihydrothebainols. Oxidation with potassium *t*-butoxide in the presence of benzophenone afforded racemic dihydrothebainone (VIII) whose infrared spectrum was indistinguishable from that of *l*-dihydrothebainone. Treatment of the racemate in acetone solution with one-half molar equivalent of D-tartaric acid gave *l*-dihydrothebainone D-tartrate, found C, 58.2; H, 6.2; $[\alpha]^{21}_{D}$ + 18.2° (*c* 1.1 water). Generation of the free base with ammonium hydroxide gave *l*-dihydrothebainone hydrate, m.p. 121–151°, $[\alpha]^{21}_{D}$ −75° (*c* 0.77 alc.).[4]

(4) C. Schöpf and L. Winterhalder, *Ann.*, **452**, 232 (1927), report $[\alpha]^{18}_{D}$ −72.5° (abs. alc.); A. Skita, *et al.*, *Ber.*, **54**, 1560 (1921), report $[\alpha]^{20}_{D}$ −80.12° (alc.).

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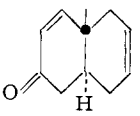
RECEIVED NOVEMBER 23, 1953

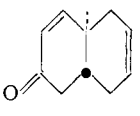
A DIRECT STEREOCHEMICAL CORRELATION OF A SESQUITERPENE ALCOHOL WITH THE STEROIDS

Sir:

The availability of the pure enantiomeric ketones (I) and (II), and the conversion of the *levorotatory*

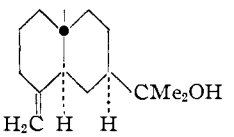


I

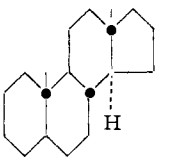


II

isomer into natural steroids,[1] provides an opportunity for effecting the direct stereochemical correlation of the steroids with other groups of natural products. We wish to record the results of such a study in the case of the sesquiterpene alcohol β-eudesmol (III).[2]

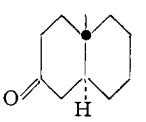


III

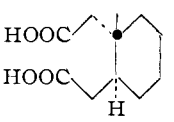


IV

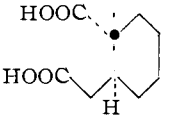
If it be accepted that the absolute configuration of the natural steroid nucleus is correctly represented by (IV),[3] the levorotatory bicyclic ketone [m.p. −3.7°, b.p. 74–78° (1 mm.), $[\alpha]^{25}_{D}$ −239° (*c* 2.0, $CHCl_3$); $\lambda_{max.}$ 226 mμ (ε = 9600) must be (I)]. This ketone has now been converted into three further reference compounds: the *trans*-9-methyl-3-decalone (V), and the diacids (VI) and (VII). Hydrogenation of (I) in methanol over Pd-$CaCO_3$



V



VI

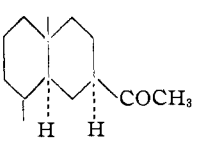


VII

leads to (V) [b.p. 123–125° (10 mm.), $[\alpha]_D$ +33° (*c* 1.14, $CHCl_3$), calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.27; H, 10.76], characterized further as the *dinitrophenylhydrazone* [m.p. 144–144.5° (from EtOH), $[\alpha]_D$ +24° (*c* 0.83, $CHCl_3$), calcd. for $C_{17}H_{22}O_4N_4$: C, 58.94; H, 6.40. Found: C, 58.97, H, 6.51]. Oxidation of (V) by boiling concentrated nitric acid gave (VI) [m.p. 194–195.5° (from Me_2CO/hexane), $[\alpha]_D$ −31° (*c* 1.14, Me_2CO), calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.44; H, 8.62]. Treatment of (V) with bromine in acetic acid gave the *2-bromoketone* [m.p. 136.5–138°, $[\alpha]_D$ +29° (*c* 4.5, $CHCl_3$), calcd. for $C_{11}H_{17}OBr$: C, 53.89; H, 6.99; Br, 32.59. Found: C, 53.69; H, 7.19; Br, 33.44], which was converted to 9-methyl-Δ^1-octalone-3 *dinitrophenylhydrazone* [m.p. 193–194.7°, calcd. for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.39; H, 5.87; N, 16.74, $\lambda\lambda_{max.}$ 256.5 mμ (ε = 17,000) and 383 mμ (ε = 29,000)], or less satisfactorily, to the corresponding *semicarbazone* [m.p. 174–176°, calcd. for $C_{12}H_{19}ON_3$: C, 65.13; H, 8.65; N, 18.99. Found: C, 64.95; H, 8.67; N, 19.15]. The free octalone, on oxidation with potassium permanganate, gave the diacid (VII)[4] [m.p. 146–147°, $[\alpha]_D$ −11° (*c* 1.0, Me_2CO), calcd. for $C_{10}H_{16}O_4$: C,

(1) The preparation of these ketones and conversion of the levorotatory isomer into natural steroids, through methods based on those developed earlier with racemic intermediates [Woodward, Sondheimer, Taub, Heusler and McLamore, THIS JOURNAL, **74**, 4223 (1952); *cf.*, also, Barkley, Farrar, Knowles and Raffelson, *ibid.*, **75**, 4110 (1953)], was carried out in the laboratories of the Monsanto Chemical Company in St. Louis. We are deeply indebted to Dr. Oliver Weinkauff and his associates for communicating their results to us privately, and for providing us with generous samples of the levorotatory ketone.

(2) As to relative configurational relationships: for *trans* locking of rings, *cf.* D. H. R. Barton, *Chem. and Ind.*, 664 (1953), and W. Klyne, *J. Chem. Soc.*, 3072 (1953); the placing of the α-hydroxy*iso*propyl group in the equatorial position is based upon the configurational stability of the ketone i [$[\alpha]_D$ +3° (*c* 1.95, $CHCl_3$), dinitrophenylhydrazone, m.p. 141–142°]; the ketone is reconverted to dihydroeudesmol with methylmagnesium iodide [*cf. Helv. Chim. Acta*, **14**, 1132 (1931)], and on treatment with 10% alcoholic potash at 210° gives an alcohol [m.p. 65°, $[\alpha]_D$ +24° (*c* 0.50, $CHCl_3$)] which is reoxidized to (i) by chromic acid.



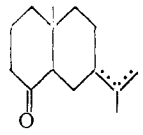
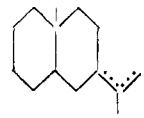
i

(3) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953).

(4) The use of this acid in establishing other stereochemical correlations will be reported in further communications.

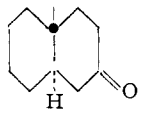
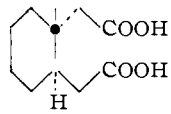
59.99; H, 8.04; neut. equiv., 100. Found: C, 59.91; H, 8.02; neut. equiv., 100, 104].

We have converted β-eudesmol, by ozonization followed by dehydration, to the ketone (VIII)[5] [b.p. 100–102° (0.15 mm.), $n^{22}D$ 1.5030, $[\alpha]D$ +21° (*c* 0.80, $CHCl_3$), calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.32; H, 10.72], and thence, by Wolff–Kishner reduction to the hydrocarbon

VIII  IX 

(IX) [b.p. 114–119° (13 mm.), $n^{20}D$ 1.4930, $[\alpha]D$ −5° (*c* 1.8, $CHCl_3$), calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 86.86; H, 12.69]. Chromic acid oxidation of (IX) gave *trans*-9-methyl-3-decalone, isolated as the *dinitrophenylhydrazone* [m.p. 144–144.5° (from EtOH), $[\alpha]D$ −22° (*c* 0.80, $CHCl_3$), found: C, 58.93; H, 6.48], and a *diacid* [m.p. 194–195.5° (from $Me_2CO/CHCl_3$), $[\alpha]D$ +33° (*c* 1.0, Me_2CO), found: C, 61.48; H, 8.60]. The infrared spectrum of this acid (Nujol) is rich in detail, and identical with that of the acid (VI), prepared from (I).

It is clear that the ketone and the diacid prepared from β-eudesmol are the enantiomers [(X) and (XI)] of the corresponding substances [V and VI]

X  XI 

from (I). These results thus provide an unambiguous correlation of β-eudesmol with the natural steroids, and permit the assignment of the absolute configuration represented in (III) to the sesquiterpene alcohol.[6]

(5) *Cf.* Ruzicka, Plattner and Fürst, *Helv. Chim. Acta*, **25**, 1364 (1942).

(6) W. Klyne (ref. 2) has independently pointed out that the molecular rotation differences for the pairs α-eudesmol/dihydroeudesmol and α-selinene/tetrahydroselinene, as compared with Δ^5-cholestene/cholestane, suggest the relationship which is proved in this communication.

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RECEIVED DECEMBER 18, 1953

SCHOENOCAULON ALKALOIDS. II. ON THE NATURE OF THE VERACEVINE-CEVAGENINE-CEVINE ISOMERIZATIONS

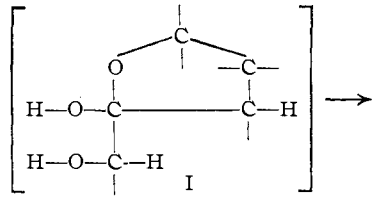
Sir:

In a recent communication[1] we suggested that veracevine be formulated as a labile α-ketol hemiketal which, under mild alkaline conditions, is opened and epimerized at a center alpha to the carbonyl group to give the α-ketol, cevagenine. The isomerization of cevagenine to cevine under strong alkaline conditions was formulated as proceeding through epimerization at both carbon atoms flanking the carbonyl group, followed by ring closure to form the stable α-ketol hemiketal system of cevine.[2] We wish to report now two series of experiments which lend support to our earlier proposal.

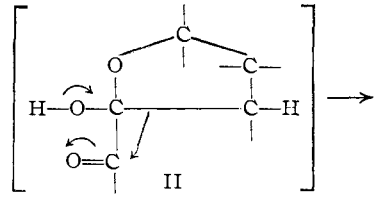
Oxidation of veracevine with bismuth oxide in acetic acid[3] and chromatography of the crude product on sulfuric acid-washed alumina yielded a crystalline lactone, m.p. 252–253° dec.; $[\alpha]_D^{22}$ −33° (*c* 1.07, chf.). *Anal.* Calcd. $C_{27}H_{41}O_8N$: C, 63.88; H, 8.14. Found: C, 63.56; H, 8.17. The infrared spectrum of the product showed a strong band at 5.72 μ, indicative of a six-membered lactone. Similar oxidation of cevagenine and cevine *afforded the same product.*

Veracevine has been found to consume two moles of oxidant upon treatment with periodic acid, paralleling the behavior of cevine.[2] Veracevine triacetate was found to be stable to chromic acid in acetic acid, and this compound consumed one mole of periodic acid. This behavior parallels that of the recently described analog, cevine triacetate.[4]

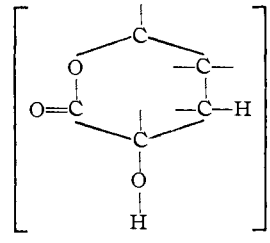
Evidence for the presence of a 5-membered hemiketal ring in cevine has been presented by Barton and Brooks.[4] Our results are consistent with the view that veracevine and cevine contain the same α-ketol-5-membered hemiketal system, and that the alkamines differ only in the configuration of the hydroxyl group of the α-ketol system. The 6-membered lactone obtained upon bismuth oxide



I



II



III

(1) S. M. Kupchan, D. Lavie, C. V. Deliwala and B. Y. A. Andoh, THIS JOURNAL, **75**, 5519 (1953). After submission of this paper on the native alkamine of the schoenocaulon ester alkaloids, "protocevine," S. W. Pelletier and W. A. Jacobs, *ibid.*, **75**, 3248 (1953), reported their independent isolation of the native alkamine and proposed the name "veracevine" for the compound. Drs. Jacobs and Pelletier have kindly compared a sample of "protocevine" with "veracevine" and have reported to us that the two samples are identical. Out of respect to Dr. Jacobs' position in the field and to avoid needless complication of the nomenclature in this series, we have adopted the name "veracevine" for the alkamine of cevadine, veratridine and cevacine.

(2) D. H. R. Barton and J. F. Eastham, *J. Chem. Soc.*, 424 (1953).

(3) W. Rigby, *ibid.*, 793 (1951).

(4) D. H. R. Barton and C. J. W. Brooks, *Chem. and Ind.*, in press. We wish to thank Professor D. H. R. Barton for kindly communicating these results to us prior to publication.