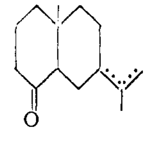
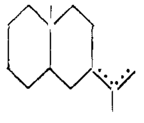
59.99; H, 8.04; neut. equiv., 100. Found: C, 59.91; H, 8.02; neut. equiv., 100, 104].

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



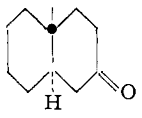
IX



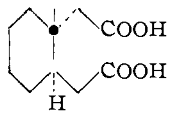
(IX) [b.p. 114–119° (13 mm.), n^{20}_D 1.4930, $[\alpha]_D$ −5° (*c* 1.8, $CHCl_3$), calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 86.86; H, 12.69]. Chromic acid oxidation of (IX) gave *trans*-9-methyl-3-decalone, isolated as the *dinitrophenylhydrazone* [m.p. 144–144.5° (from EtOH), $[\alpha]_D$ −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^8-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

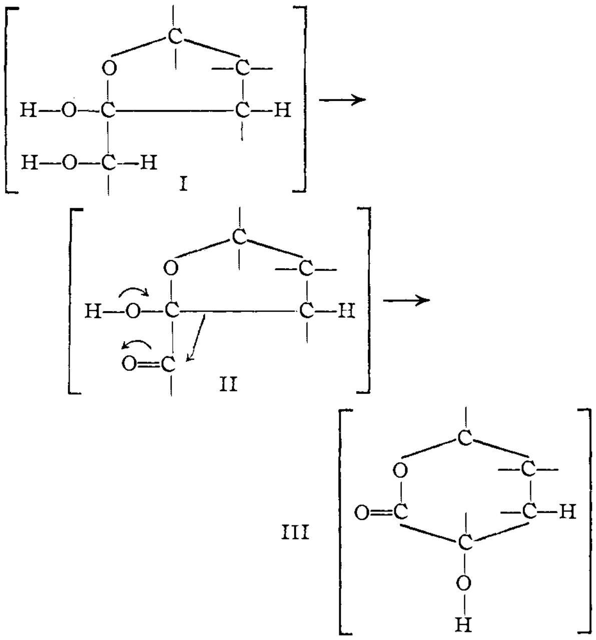
Sir:

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.; $[\alpha]^{22}_D$ −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



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[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.

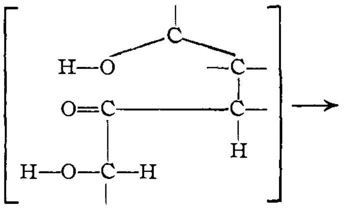
[2] D. H. R. Barton and J. F. Eastham, *J. Chem. Soc.*, 424 (1953).

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

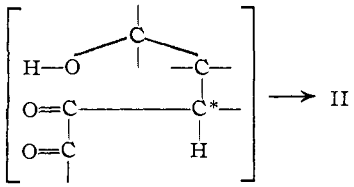
[4] D. H. R. Barton and C. J. W. Brooks, *Chem. and Ind.*, in press. We wish to thank Professor D. H. R. Barton for kindly communicating these results to us prior to publication.

oxidation of cevine and veracevine we regard as resulting from the series I → II → III.

The formation of the 6-membered lactone from cevagenine is explicable on the basis that the α-diketone (V) resulting from oxidation of the α-ketol (IV) epimerizes easily at C* and is converted to the hemiketal (II).



IV



V

Acknowledgment.—We should like to express our appreciation to Mrs. Mary Fieser and Professor R. B. Woodward for stimulating discussions and suggestions. The work was supported by grants from the National Institutes of Health and Research Corporation.

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RECEIVED DECEMBER 9, 1953

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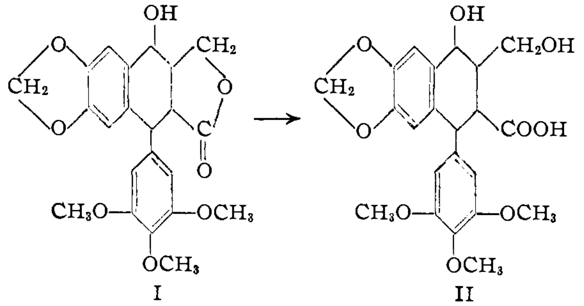
[5] On leave of absence from the Weizmann Institute of Science, Rehovot, Israel.

SYNTHESIS OF A DL-STEREOISOMER OF PODOPHYLLIC ACID[1]

Sir:

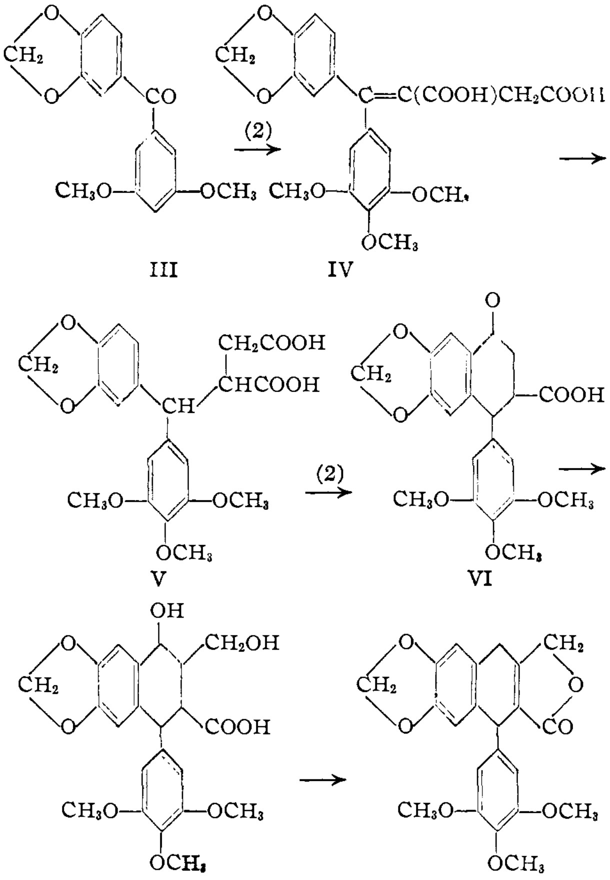
Podophyllic acid (II) is the hydrolysis product of the anti-cancer agent, podophyllotoxin (I),



I II

or of its epimer,[2] picropodophyllin.[2,3,4] We wish to report the synthesis of a racemic stereoisomer of this acid.

Stobbe condensation of ketone III[5] with ethyl succinate followed by saponification furnished the unsaturated dibasic acid IV, m.p. 191.4–192.2°. *Anal.* Calcd. for $C_{21}H_{20}O_9$: C, 60.6; H, 4.8. Found: C, 60.5; H, 4.8. This compound on hydrogenation gave a single product V, m.p. 192.7–193.2°. *Anal.* Calcd. for $C_{21}H_{22}O_9$: C, 60.3; H, 5.3. Found: C, 60.2; H, 5.3. The dibasic acid V was treated first with acetyl chloride to form the anhydride (a glass; *Anal.* Calcd. for $C_{21}H_{20}O_8$: C, 63.0; H, 5.0. Found: C, 62.9; H, 5.1), and then with aluminum chloride in nitrobenzene to form the cyclic keto acid VI, m.p. 221.7–222.5°. *Anal.* Calcd. for $C_{21}H_{20}O_8$: C, 63.0; H, 5.0. Found: C, 63.0; H, 5.2.[6] Keto acid VI with ethanol and sulfuric acid gave the corresponding keto ester (m.p. 153–154°. *Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.5; H, 5.6. Found: C, 64.3; H, 5.7), which on condensation with ethyl formate in the presence of sodium hydride followed by sodium borohydride reduction afforded a dihydroxy ester. Saponification yielded the desired product, dihydroxy acid VII, m.p. 228.6–229.6°. *Anal.* Calcd. for $C_{22}H_{24}O_9$: C, 61.1; H, 5.6. Found: C, 61.1; H, 5.7. The reported melting point of "natural" podophyl-



III IV V VI VII VIII

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[1] This work has been supported by grants-in-aid from the American Cancer Society upon recommendation of the Committee on Grants of the National Research Council.

[2] J. L. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951).

[3] W. Borsche and J. Niemann, *Ann.*, **494**, 126 (1932).

[4] W. R. Dustan and T. A. Henry, *J. Chem. Soc.*, **73**, 209 (1898); R. Kürsten, *Arch. Pharm.*, **229**, 220 (1891).

[5] E. Späth, F. Wessely and E. Nadler, *Ber.*, **66**, 125 (1933); W. J. Gensler and C. M. Samour, THIS JOURNAL, **73**, 5555 (1951).

[6] G. N. Walker, *ibid.*, **75**, 3390 (1953), reported m.p. 220–223° for keto acid VI prepared by a different route. We find that the melting point of the methyl ester is 180.7–181.2°. *Anal.* Calcd. for $C_{22}H_{22}O_8$: C, 63.8; H, 5.4. Found: C, 63.5; H, 5.3. The reported melting point is 173–175°.