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THE TOTAL SYNTHESIS OF A DEGRADATION PRODUCT OF PHYLLOCLADENE

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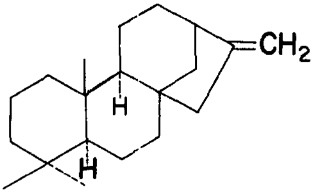
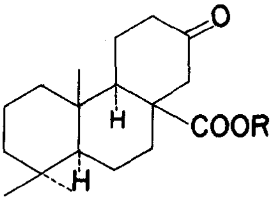
PERMANGANATE oxidation of phyllocladene (I) affords, among other products, the keto acid IIa, convertible into keto ester IIb, m. p. 161-162°, $[\alpha]_D$ -15° ($CHCl_3$),[1,2] for which optical rotatory dispersion evidence[2,3] suggests the stereochemistry indicated. We wish to report the total synthesis of IIb.



I



IIa, R=H
IIb, $R=CH_3$

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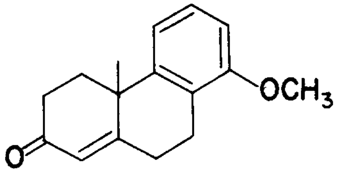
[1] C. W. Brandt, New Zealand J. Sci. Technol. 34B, 46 (1952); L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, Tetrahedron Letters No. 8, 8 (1959).

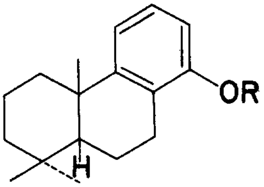
[2] P. K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

[3] C. Djerassi, M. Cais and L. A. Mitscher, J. Amer. Chem. Soc. 81, 2386 (1959).

The Cornforth-Robinson ketone (III) [4] was dimethylated with methyl iodide in the presence of potassium *t* -butoxide and gave 1, 2, 3, 4, 9, 12-hexahydro-8-methoxy-1, 1, 12-trimethyl-2-oxophenanthrene (IV), m.p. 109.5-110-5°, $\lambda_{max}^{CS_2}$ 5.84μ (Found: C, 79.66; H, 8.13. $C_{18}H_{22}O_2$ requires: C, 79.96; H, 8.20). Palladium-catalyzed hydrogenation of IV afforded the corresponding dihydro derivative (V), m.p. 90-93° (Found: C, 79.30; H, 8.63. $C_{18}H_{24}O_2$ requires: C, 79.37; H, 8.88), convertible by Clemmensen reduction into *trans* - 1, 2, 3, 4, 9,10, 11, 12-octahydro-8-methoxy-1, 1, 12-trimethylphenanthrene (VIa), m.p. 114-115° (Found: C, 83.48; H, 10.17. $C_{18}H_{26}O$ requires: C, 83.67; H, 10.14). The free phenol (VIb), m.p. 146-148° (Found: C, 83.62; H, 10.20. $C_{17}H_{24}O$ requires: C, 83.55; H, 9.90) was



III



VIa, R=CH_3
VIb, R=H

obtained by treatment of VIa with hydriodic acid in acetic acid. Hydrogenation of VIb over nickel gave a mixture of two epimeric, saturated alcohols, VIIa, m. p. 118-119° (Found: C, 81.76; H, 12.37.

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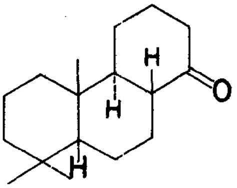
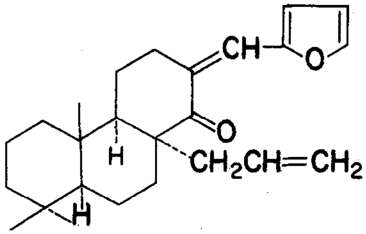
[4] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 1855 (1949).

$C_{17}H_{30}O$ requires: C, 81.53; H, 12.08), and VIIb, m.p. 99-100° (Found: C, 81.67; H, 11.99). On treatment with chromic acid in acetic acid VIIa and VIIb are both transformed into the base-stable ketone VIII, m.p. 67-68°, $\lambda_{max}^{CS_2}$ 5.83μ (Found: C, 82.09; H, 11.50. $C_{17}H_{28}O$ requires: C, 82.20; H, 11.36).


VIII


X

Condensation of VIII with furfuraldehyde yields the corresponding furfurylidene derivative (IX), m. p. 87.5-88°, $\lambda_{max}^{CS_2}$ 5.96μ (Found: C, 80.99; H, 9.42. $C_{22}H_{30}O_2$ requires: C, 80.93; H, 9.26), which is further transformed into X, m.p. 108-108.5°, $\lambda_{max}^{CS_2}$ 5.96, 10.08, 10.94μ (Found: C, 81.71; H, 9:30. $C_{25}H_{34}O_2$ requires: C, 81.92; H, 9.35) by treatment with allyl bromide and potassium t -butoxide. Ozonization of X, followed by treatment with chromic acid and esterification with diazomethane, yields an amorphous triester, which undergoes Dieckmann cyclization, hydrolysis, and decarboxylation to d, l-IIb, m. p. 130-131° (Found: C, 74.78; H, 9.94. $C_{19}H_{30}O_3$ requires: C, 74.47; H, 9.87). The infrared spectrum (CS_2) of the latter product was identical with that of the optically active degradation product of phyllocladene.

Resolution of the alcohol VIIa, obtained for this purpose by lithium aluminum hydride reduction of VIII, was accomplished by esterification with 3α-acetoxy-11-ketoetiocholanic acid.[5] The ester with lower rotation, m. p. 237-238°, $[\alpha]_D$ + 28° ($CHCl_3$) (Found: C, 76.69; H, 9.80. $C_{39}H_{60}O_5$ requires: C, 76.93; H, 9.93), was saponified and gave *l* -VIIa, m.p. 109-110°, $[\alpha]_D$ - 29° ($CHCl_3$). This substance and the succeeding optically active compounds were not analyzed; their constitutions were established by the identity of the infrared absorption spectra (CS_2 solution) with the spectra of the appropriate analyzed, optically inactive derivatives. Oxidation of *l* - VIIa afforded *l* - VIII, m.p. 87.5-88° $[\alpha]_D$ - 18° ($CHCl_3$) (negative Cotton effect)[6] which gave *d* - IX, m. p. 122.5-123°, $[\alpha]_D$ + 41° ($CHCl_3$), on condensation with furfuraldehyde. Alkylation to *l* - X, m. p. 88-88.5°, $[\alpha]_D$ - 115° ($CHCl_3$), oxidation, and cyclization completed the synthesis. The synthetic product *l* - IIb, m.p. 159-160°, $[\alpha]_D$ -12° ($CHCl_3$), did not depress the melting point of a specimen, m.p. 159-161°, $[\alpha]_D$ -11° ($CHCl_3$), obtained from phyllocladene, and the infrared spectra of the two samples were identical.

It is a pleasure to acknowledge financial support of this investigation by the Eli Lilly Co., and by the National Institutes of Health.

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[5] J. von Euw, A. Lardon and T. Teichstein, *Helv. Chim. Acta* **27**, 1287 (1944); R. B. Turner, V. R. Mattox, W. F. McGuckin and E. C. Kendall, *J. Am. Chem. Soc.* **74**, 5814 (1952).

[6] We are indebted to Dr. Max A. Marsh, Eli Lilly and Co., Indianapolis, for this result, from which the conclusion is drawn that *l* - VIII possesses the required absolute configuration, cf. C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill, New York (1960), p. 178, and C. Djerassi and W. Klyne, *Chemistry and Industry* 988 (1956).