THE STRUCTURE OF CASSAIC ACID

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IN 1955 Humber and Taylor [1] established the location of the α,β-unsaturated carboxyl function in cassaic acid and suggested structure I (without stereochemical designations) for this substance, which is obtained along with N-dimethyl-ethanolamine by hydrolysis of the Erythrophleum alkaloid cassaine.[2] The recent correlation of vouacapenic acid with cassaic acid [3] demonstrates the identity of the carbon skeletons in these two compounds, and evidence for the transfusion of rings A and B in both acids has also been provided.[3] We wish at this time to report observations that conclusively prove the correctness of the speculations of Humber and Taylor regarding the structure of cassaic acid.

Ozonization of cassaic acid as the acetate methyl ester affords II, m.p. 169-170°, $[\alpha]_D$ -16° (ethanol) (Found: C, 72.03; H, 8.74. $C_{20}H_{30}O_4$ requires C, 71.82; H, 9.04). The latter product undergoes epimerization on passage over alumina and furnishes III, m.p. 150.5-151.5°, $[\alpha]_D$ -26°

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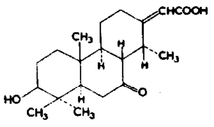
[1] L. G. Humber and W. I. Taylor, J. Chem. Soc. 1044 (1955); see also R. Tondeur, Dissertation, E. T. H., Zurich (1950).

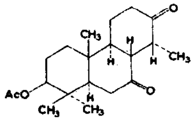
[2] L. Ruzicka and G. Dalma, Helv. Chim. Acta 22, 1516 (1939).

[3] F. E. King, T. J. King, and J. M. Uprichard, J. Chem. Soc. 3428 (1958).

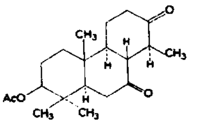
(ethanol) (Found: C, 71.86; H, 9.23). Bromination of III followed by dehydrobromination yields IV, m.p. 186.5-187.5°, $[\alpha]_D$ -7° (ethanol) (Found: C, 71.97; H, 8.54. $C_{20}H_{28}O_4$ requires C, 72.26; H, 8.49), ν_{max} 1718, 1678 cm^{-1} ($CHCl_3$), which exhibits ultraviolet absorption, λ_{max} 266.5 mμ, ϵ 10,800, characteristic of an enedione. III is regenerated from IV by mild treatment with zinc and acetic acid. The relationship of the keto group of cassaic acid to the previously located[2] acid side chain is thereby established.



I



II



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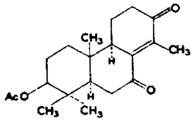

IV

The further details of structure are revealed by total synthesis of compounds III and IV in optically inactive form. Methylation of 6-methoxy-2-tetralone by the enamine procedure,[4] and condensation of the resulting monomethyl derivative with dimethylaminobutanone methiodide yields 2:3:4:9:10:12-hexahydro-7-methoxy-12-methyl-2-oxophenanthrene, m.p. 106-108°.[5] Dimethylation of this ketone by the conventional procedure[6]

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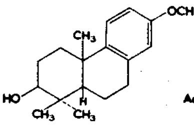
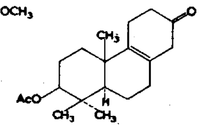
[4] G. Stork, R. Terrell and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).

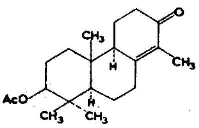
[5] F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.* 1248 (1958).

[6] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.* 1131 (1957).

followed by reduction with lithium aluminum hydride furnishes the expected unsaturated alcohol, m.p. 127-128° (Found: C, 79.35; H, 8.64. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88), Which is further converted into V, m.p. 140-141° (Found: C, 78.84; H, 9.60. $C_{18}H_{26}O_2$ requires C, 78.79; H, 9.55), by catalytic hydrogenation over palladium. Compound V undergoes Birch reduction to the corresponding dihydro derivative, m.p. 139-139.5° (Found: C, 77.98; H, 10.21. $C_{18}H_{28}O_2$ requires C, 77.21; H, 10.21), which on acetylation and treatment with oxalic acid in aqueous ethanol yields the β,γ-unsaturated ketone VI, m.p. 103.5-104.5° (Found: C, 75.06; H, 9.01. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27). Reaction of this substance with methyl iodide in the presence of potassium <u>tert</u>.-butoxide affords VII, m.p. 136-137°, λ_{max} 249 mμ, ε 17,500, ν_{max} 1730, 1664 cm $^{-1}$ (CS_2) (Found: C, 75.28; H, 9.46. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50), which gives the racemic modification of IV, m.p. 165-165.5°, λ_{max} 266 mμ, ε 11,300, ν_{max} 1718, 1678 cm $^{-1}$ ($CHCl_3$) (Found: C, 71.97; H, 8.38), on oxidation with chromium trioxide in acetic acid at 60°. The infrared spectra ($CHCl_3$ soln.) of the synthetic sample and of that derived from natural sources are identical. Reduction of <u>d</u>,<u>l</u>-IV with zinc and acetic acid gives <u>d</u>,<u>l</u>-III, m.p. 158-160° (Found: C, 71.90; H, 8.83), the infrared spectrum of which is likewise identical with that of the corresponding optically active product. The above facts strongly support the stereochemical assignments of formula I.


V


VI


VII

The details of this work and of additional experiments not here reported will be published shortly. The financial support of the National Heart Institute, National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.