Tetrahedron Letters No.45, pp. 3991-3994, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE SYNTHESIS OF RACEMIC HYDROXYTREMETONE[‡]

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(Received 30 August 1965)

Hydroxytremetone is a constituent of Eupatorium urticaefolium, white snakeroot, whose chemical structure (I) was determined by Bonner and DeGraw in 1962 (1). We now wish to report the synthesis of racemic hydroxytremetone.

The synthesis started from the easily accessible compound, 2-acetyl-6-benzyloxybenzofuran (II) (2). The reaction of II with methylmagnesium iodide gave rise to the unstable, 2-(6'-benzyloxy-2'-benzofuryl)-2-propanol (III) which was not purified but directly hydrogenated using Raney nickel catalyst. The reduction product, IV, obtained in 80% yield, [m.p. 160-161°; IR, 3300 cm^{-1} and no carbonyl; U.V. λ max. 289 mμ (ε, 4350); C, 67.77% and H, 7.15%] could be monoacetylated with acetic anhydride and pyridine to give V in 82% yield (m.p. 88-89°; C, 65.95% and H, 6.91%) or diacetylated with isopropenyl acetate to give VI in 72% yield (m.p. 78-79°; C, 64.40% and H, 6.48%).

Acylation of V (and presumably VI) with trifluoroacetic anhydride and glacial acetic acid occurred at the 5-position along with acetylation of the tertiary hydroxyl to give VII in 91% yield [m.p. 109-110°; IR, carbonyls at 1760, 1720 and 1670 cm^{-1}; U.V., λ max. at 210, 229 and 277 mμ (ε, 11000,

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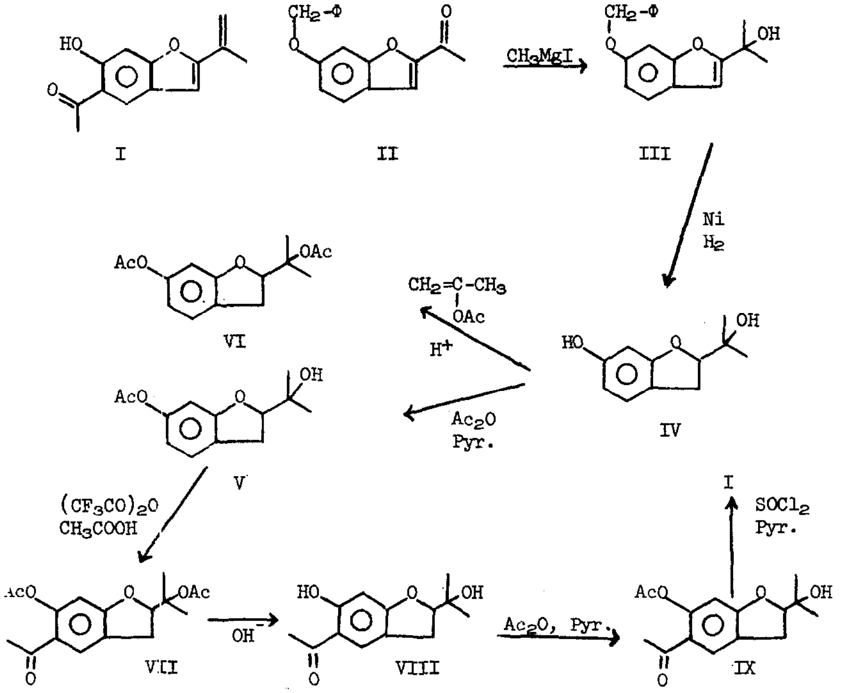
[‡] This research has been supported by Public Health Service Research Grant NB 04313 from the National Institute of Neurological Diseases and Blindness. Based on the Ph.D. thesis of Peter Gerike.



13000,11300); C, 63.46% and H, 6.26]. Although analogous acylations on similar substrates give rise to attack at the 5-position (3,4), the 7-position could not be excluded a priori. The substitution pattern as proposed was verified by infrared andnuclear magnetic resonance spectra. The infrared spectra of V and VI both show two hydrogen out-of-plane bending frequencies at 840 and 900 cm^{-1} for two adjacent and an isolated hydrogen respectively on an aromatic ring (5) while the acylated product, VII, retained only the 900 cm^{-1} band for isolated hydrogen. The nmr spectra is more definitive with V and VI both showing similar aromatic proton resonances, i.e., a doublet at 7.05 (6.98)δ (1 H with J = 9 cps ortho coupling) for the hydrogen at C-4 and a complex multiplet at 6.5 (6.45)δ (2 H) for the hydrogens at C-5 and C-7, typical of a 1,2,4-trisubstituted aromatic ring of this type (6). In contrast the nmr spectrum of the aromatic protons of VII was very simple with only two, sharp, one-hydrogen singlets at 7.48 and 6.33δ consistent only with the two isolated para-hydrogens of structure VII.

Since an attempt to eliminate the tertiary acetoxy function of VII with potassium t-butoxide to give hydroxytremetone directly was unsuccessful, VII was saponified to VIII in 87% yield (m.p. 91-92°; C, 66.16% and H, 6.84%) and monoacetylated with acetic anhydride and pyridine to IX in 79% yield (m.p. 161-162°; IR, 3500, 1760 and 1670 cm^{-1}; C, 64.96% and H, 6.77%). The tertiary hydroxyl of IX was finally eliminated thru the use of thionyl chloride and pyridine followed by saponification to give a mixture of products separable by column chromatography on Florisil. The benzene-ether (1:1) eluents gave racemic hydroxytremetone in 5% yield identified by spectral means. A comparison of the infra-red spectrum with the spectrum of known, optically active hydroxytremetone (7) showed them to be very similar and the ultraviolet spectrum in ethanol and 0.1 N. sodium hydroxide were the same as those reported (8).

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(7) We are indebted to Dr. Bonner for the infrared spectrum of authentic hydroxytremetone.

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