

The Total Synthesis of (\pm)- β -Vetivone

By JAMES A. MARSHALL* and PORTER C. JOHNSON

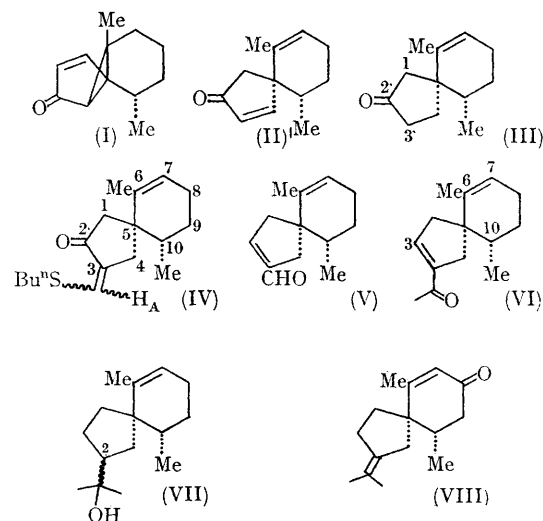
(Department of Chemistry, Northwestern University, Evanston, Illinois 60201)

WE recently presented evidence which called for revision of the long-accepted hydroazulenenic structure of β -vetivone to a structure based on spiro[4,5]decane.¹ This new structure has now been confirmed through a straightforward total synthesis.

The known spiro-cyclopropyl ketone (I),² upon treatment with acetic acid-acetic anhydride containing a trace of sulphuric acid, gave the spiro[4,5]decadienone (II)² in 50–55% yield. Selective hydrogenation (Pd-C in ethanolic NaOH) smoothly gave the corresponding unsaturated ketone (III) [λ_{\max} (film) 5.74, 7.10, 7.23, 8.56, 8.62, 11.81, 12.43 μ]. Condensation with ethyl formate (NaH-C₆H₆) and treatment of the resulting product with n-butanethiol and BF₃-etherate converted ketone (III) to its n-butylthiomethylene derivative³ (IV) [λ_{\max} (film) 5.87, 6.30, 8.30, 11.84, 12.31 μ ; δ (CDCl₃) 7.30 (H_A, t, *J* 3), 5.38 (H-7, *W*_{H/2} 9), 2.85 (-S-CH₂-CH₂-, t, *J* 7), 2.45–2.30 (C-1 CH₂, 4 lines), 1.57 (C-6 Me, d, *J* 2), 0.92 (CH₃-CH₂-, t, *J* 7), 0.87 p.p.m. (C-10, d, *J* 6 Hz)]. The observed long-range splitting of H_A and the 4 line pattern of the C-1 methylene protons

reinforce our *a priori* assumption that condensation at C-3 (*vs.* C-1) of ketone (III) would be preferred for steric reasons.

Reduction of ketone (IV) with methanolic



sodium borohydride followed by hydrolysis (H_2O , HCl , acetone) in the presence of mercuric chloride yielded the conjugated aldehyde⁴ (V) [λ_{max} (film) 3.67, 5.95, 6.14, 7.23, 7.38, 8.44, 10.22, 11.94, 12.48, 13.72] in 73% over-all yield. This aldehyde upon treatment with ethereal methyl-lithium afforded the expected allylic alcohol mixture (epimers) which was directly oxidized (DDQ)⁵ to the conjugated ketone (VI) [λ_{max} (film) 5.99, 6.14, 7.23, 8.53, 10.19, 11.95, 12.49 μ ; δ (CDCl_3) 6.70 (H-3, $W_{h/2}$ 6), 5.34 (H-7, $W_{h/2}$ 8 Hz), 2.30 (CH_3CO), 1.58 (C-6 CH_3 , d, J 2), 0.87 p.p.m. (C-10 CH_3 , d, J 6 Hz)] in 65% over-all yield. Selective reduction of the conjugated double bond with lithium in ammonia-ethanol followed first by oxidation (CrO_3) of the resulting alcohols and then addition of methyl-lithium yielded the tertiary alcohols (VII) [λ_{max} (film) 2.91, 7.25, 8.32, 10.68, 12.02, 12.53 μ ; δ (CDCl_3) 5.30 (H-7, $W_{h/2}$ 9 Hz), 1.67 (C-6 CH_3), 1.20 (*gem*-dimethyl), 0.92 p.p.m. (C-10 CH_3 , d, J 6 Hz)] as a 60:40 mixture of C-2 epimers. One epimer must correspond to racemic

hinesol⁶ and the other may be racemic agarospirol.⁷ The spectral properties of our synthetic alcohol mixture were entirely compatible with this assumption.

The alcohol mixture (VII) was converted to racemic β -vetivone (VIII) along the lines reported by Yoskioka and Kimura⁸ for the conversion of (–)-hinesol to (+)- β -vetivone. Thus, acetylation ($\text{NaOAc}-\text{Ac}_2\text{O}$) followed by oxidation ($\text{CrO}_3-\text{HOAc}-\text{Ac}_2\text{O}$) afforded racemic 8-oxohinesyl acetate and its C-2 epimer, both of which yielded (\pm)- β -vetivone, m.p. 44–46°, upon treatment with BF_3 etherate. The infrared and n.m.r. spectra of material thus secured were identical with the spectra of naturally derived (–)- β -vetivone. The gas chromatographic retention time was likewise identical (peak enhancement).

We gratefully acknowledge support from the Public Health Service and the Alfred P. Sloan Foundation.

(Received, February 12th, 1968; Com. 174.)

¹ J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, 1967, **89**, 2748; J. A. Marshall and P. C. Johnson, *ibid.*, p. 2750.

² P. J. Kropp, *J. Amer. Chem. Soc.*, 1965, **87**, 3914.

³ R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615.

⁴ R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1620.

⁵ D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, 1960, No. 9, 14.

⁶ W. Z. Chow, O. Motl, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1962, **27**, 1914.

⁷ K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, 1965, **21**, 115.

⁸ I. Yoskioka and T. Kimura, *Chem. and Pharm. Bull. Japan*, 1965, **13**, 1430.