

A New Isoxazole Annellation; Application to the Synthesis of Dehydrofukinone

By MAMORU OHASHI

(*Department of Hydrocarbon Chemistry, Kyoto University, Kyoto, Japan*)

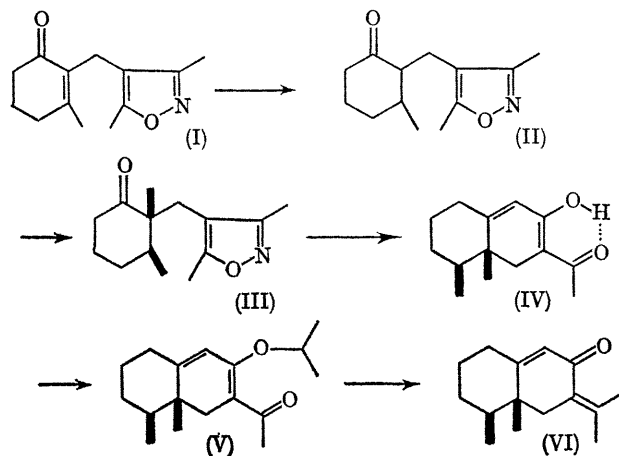
Summary The eremophilonoid sesquiterpene dehydrofukinone has been synthesised *via* isoxazole annellation.

IN connection with the synthesis of sesquiterpenes related to eremophilone, the preparation of the *cis*-1,8a-dimethyl-decalin system *via* Robinson annellation has been studied

extensively.¹ Continuing our isoxazole annellation studies^{2,3} we have devised a new annellation for the synthesis of this system. In general, isoxazole annellation consists of two steps, alkylation and ring formation. Since the alkylation step is affected by steric factors,⁴ the formation of a *cis*-dimethyl system could be achieved more easily than

Michael addition. Thus we attempted to devise a new general synthetic method for eremophilonoids *via* isoxazole annelation.

The starting isoxazole (I) was easily prepared by the alkylation of Hagemann's ester with 4-chloromethyl-3,5-dimethylisoxazole⁵ followed by the removal of the ethoxycarbonyl group with potassium hydroxide. Hydrogenation of (I) on Pd-C gave (II) in 66% yield.³ After the protection of the methylene group (at C-6) by the isopropoxymethylene method,⁶ methylation of (II) with sodium



hydride and methyl iodide in benzene-dimethylformamide followed by the removal of the protecting group gave (III), ν_{\max} 1705 and 1603 cm^{-1} , m/e 235(M^+) 110, 68, 43,⁷ δ (CDCl_3) 0.98(3H, s) 0.96(3H, d, J 5.5 Hz.) 2.18(3H, s) 2.31(3H, s) p.p.m.; semicarbazone, m.p. 208–210°, in about 40% yield after chromatography on silica gel. The solvent shift Δ ; +0.32 p.p.m. [$\delta(\text{CHCl}_3) - \delta(\text{benzene})$] of the secondary methyl signals in its n.m.r. spectra suggested that the methyl group is in the equatorial orientation,⁸ *i.e.*, the two methyl groups must be present in a *cis*-relationship.

Treatment of (III) with triethyloxonium fluoborate followed by heating under reflux with 1N-sodium hydroxide in 20% ethanol for 1 hr. furnished (IV), m.p. 50–53°, ν_{\max} 1630 and 1570 cm^{-1} , λ_{\max} 252(8900) 337(6830) nm. (in EtOH), m/e 220(M^+), δ (CDCl_3) 0.97(6H, s) 2.09(3H, s) 5.72(1H, t, J 1 Hz.) 15.80 (1H, s) p.p.m., FeCl_3 test, positive; in 38% yield, whose spectral properties were all in accord with an unsaturated diketone chromophore.⁹ The annelated product (IV) was converted into its enol ether (V) by heating under reflux with isopropyl iodide and potassium carbonate in ethyl methyl ketone for 48 hr. and then successive treatment of (V) with methyl-lithium, dilute hydrochloric acid, and phosphorous oxychloride in pyridine gave (\pm)-dehydrofukinone (VI) whose structure was confirmed by direct comparison of its spectral properties with those of the specimen derived from natural fukinone.¹⁰

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¹ J. A. Marshall, H. Faubl, and T. M. Warne, jun., *Chem. Comm.*, 1967, 753; R. M. Coates and J. E. Shaw, *ibid.*, 1968, 47; R. L. Hale and L. H. Zalkow, *ibid.*, p. 1249; H. C. Odom and A. R. Pinder, *ibid.*, 1969, 26; C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Letters*, 1968, 3451.

² G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, 1967, **89**, 5459; G. Stork and J. E. McMurry, *ibid.*, p. 5463.

³ M. Ohashi, T. Maruishi, and H. Kakisawa, *Tetrahedron Letters*, 1968, 719.

⁴ F. Giarrusso and F. E. Ireland, *J. Org. Chem.*, 1968, **33**, 3560.

⁵ N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. (U.S.S.R.)*, 1958, **28**, 2376.

⁶ W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1361.

⁷ M. Ohashi, H. Kamachi, H. Kakisawa, A. Tatematsu, H. Yoshizumi, H. Kano, and H. Nakata, *Tetrahedron Letters*, 1968, 379; *Org. Mass Spectrometry*, 1969, **2**, 195.

⁸ D. H. Williams and N. S. Bhacca, *Tetrahedron*, 1965, **21**, 2021.

⁹ R. N. Lacey, *J. Chem. Soc.*, 1960, 1625.

¹⁰ K. Naya, I. Takagi, Y. Yawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, 1968, **24**, 5871. We thank Professor Naya for a generous supply of dehydrofukinone.