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SYNTHETIC ANALOGUES OF USNIC ACID[1]

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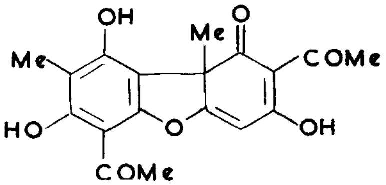
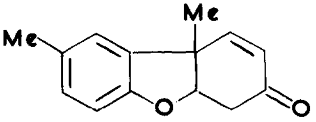
Usnic acid (I), one of the most common lichen metabolites, is of considerable interest because of its inhibitory effect on Gram-positive bacteria.[2,3] The only successful synthetic approach to usnic acid[4] and its simple analogues (e.g. Pummerer's ketone (II)[5]) has involved the oxidative coupling of two molecules of the appropriate phenol.



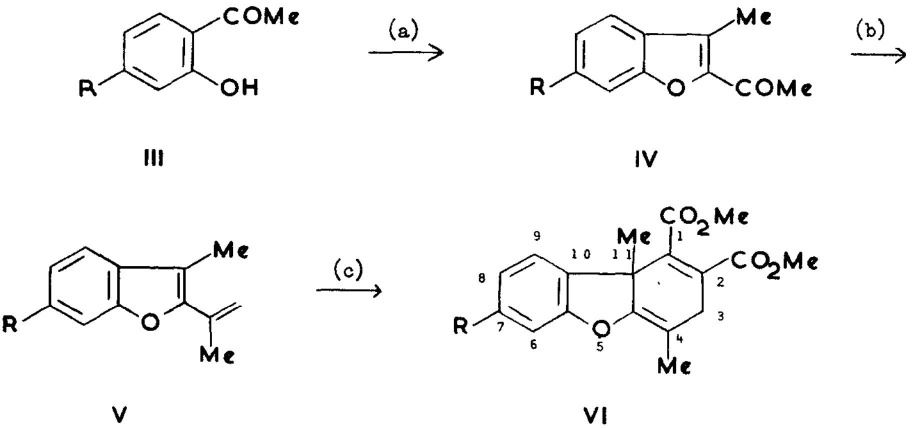
I



II

We now report a novel synthetic route to usnic acid analogues, where the key step involves the cyclo-addition of a dienophile to a 3-methyl-2-vinylbenzofuran (see Scheme I).

SCHEME I



(a) $ClCH_2COMe$, K_2CO_3, D.M.F., (b) $Ph_3P{=}CH_2$, (c) $MeO_2CC{\equiv}CCO_2Me$

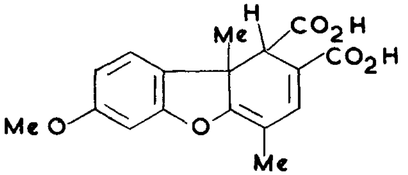
Alkylation of the *o*-hydroxyacetophenones (III) in dimethylformamide solution with chloroacetone in the presence of potassium carbonate, was accompanied by ring closure to give the corresponding 2-acetyl-3-methylbenzofurans (IV)^6 in high yield [R=H, 90% yield, pale yellow oil, ν (film) 1680 cm^{-1}, τ (CCl_4) 2.32-2.85 (4H,m), 7.42 (3H,s) and 7.45 (3H,s); R=OMe, 60% yield, yellow crystals m.p. 77-79°, ν (nujol) 1675 cm^{-1}, τ ($CDCl_3$) 2.58 (1H,d,J 9Hz), 3.10 (1H,s), 3.17 (1H,d,J 9Hz), 6.18 (3H,s) and 7.50 (6H,s)].

The Wittig reaction of the 2-acetyl-3-methylbenzofurans (IV) with methylenetriphenylphosphorane gave the expected 2-isopropenyl-3-methylbenzofurans (V) [R=H, 24% yield, colourless liquid, τ (CCl_4) 2.45-2.88 (4H,m), 4.52 (1H,s), 4.80 (1H,b.s), 7.66 (3H,s) and 7.79 (3H,b.s); R=OMe, 20% yield, colourless liquid, τ (CCl_4) 2.80 (1H,d,J 8.5Hz), 3.17 (1H,s), 3.27 (1H,d,J 8.5Hz), 4.60 (1H,b.s), 4.91 (1H,b.s), 6.24 (3H,s), 7.72 (3H,s) and 7.82 (3H,s)].

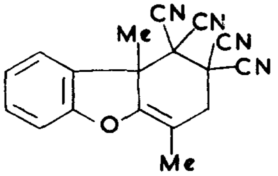
The olefins (V) underwent ready cyclo-addition with dimethyl acetylenedicarboxylate in boiling xylene (V, R=H) or toluene (V, R=OMe) to give the dimethyl 4,11-dimethyl-3,11-dihydrodibenzofuran-1,2-dicarboxylates (VI) [R=H, 52% yield, pale yellow prisms m.p. 79-82°, ν ($CHCl_3$) 1729, 1634, 1612, 1590 cm^{-1}, λ max (90% EtOH) 230 (sh) nm (ε11400), 280 (3150) and 285 sh

(3010), τ(CCl_4) 2.70-3.20 (4H,m), 6.22 (3H,s), 6.25 (3H,s), 6.92 (2H,s), 8.13 (3H,s) and 8.51 (3H,s); R=OMe, 40% yield, yellow crystals m.p. 115-116°, ν (nujol) 1720, 1635, 1625, 1590 cm^{-1}, λ max (90% EtoH) 222 nm (ε10400), 286 (3170) 291 sh (2780), τ ($CDCl_3$) 2.99 (1H,d,J 8.5Hz), 3.45 (1H,s), 3.52 (1H,d,J 8.5Hz), 6.10 (3H,s), 6.18 (6H,s), 6.83 (2H,b.s), 8.09 (3H,s) and 8.50 (3H,s).

Hydrolysis of the diester (VI, R=OMe) with alcoholic potassium hydroxide was accompanied by a rearrangement involving conjugation of the double bonds, to give 4,11-dimethyl-1,11-dihydro-7-methoxydibenzofuran-1,2-dicarboxylic acid (VII) [88% yield, yellow needles m.p. 219-221°, ν max (nujol) 1715, 1650, 1630 cm^{-1}, λ max (90% EtOH) 286 nm (2520) and 350 (2970), τ (d6-dMSO) 2.72 (1H,d,J 9Hz), 2.80 (1H,s), 3.40 (1H,s), 3.47 (1H,d,J 9Hz) 6.20 (4H,b.s), 8.10 (3H,s) and 8.62 (3H,s)]. It is interesting to note that the thermodynamically stable diacid (VII) has the same arrangement of double bonds as does usnic acid itself.



VII



VIII

Tetracyanoethylene reacted readily with 2-isopropenyl-3-methylbenzofuran (IV, R=H) at room temperature to give 4,11-dimethyl-1,1,2,2-tetracyano-1,2,3,11-tetrahydrodibenzofuran (VIII) as colourless prisms, m.p. 142-143° [ν ($CHCl_3$) 2230 cm^{-1}, λ max (90% EtOH) 233 nm (ε9770), 284 (2270), τ($CDCl_3$) 2.35-3.01 (4H,m), 6.65 (2H,d), 8.09 (3H,s) and 8.16 (3H,s)]. Thus the 2-vinyl-3-methylbenzofurans (IV) add to both reactive acetylenic and olefinic dienophiles. This is rather unexpected for not only does the addition rupture the aromaticity of the benzofuran ring, but it also involves the sterically unfavourable approach of the dienophile to a terminally disubstituted diene (at the 3-position).

These Diels-Alder additions provide a general route to simple, synthetic analogues of usnic acid. The scope of the reaction and the chemistry of the adducts are under investigation.

NOTES AND REFERENCES

1. Annelated Furans. II. For part I, see W.J. Davidson and J.A. Elix, Tetrahedron Letters, 4589 (1968).
2. A. Stoll, A. Brack and J. Renz, Experimentia, 3, 115 (1947).
3. J.B. Stark, E.D. Walter and H.S. Owens, J.Amer.Chem.Soc., 72, 1819 (1950).
4. D.H.R. Barton, A.M. Deflorin and O.E. Edwards, J.Chem.Soc., 530 (1956).
5. V. Arkley, F.M. Dean, A. Robertson and P. Sidisunthorn, J.Chem.Soc., 2322 (1956).
6. Satisfactory elemental analyses or high resolution mass spectra were obtained for all new compounds.