

Formation of a Tetracyclic Furan Derivative from Usnic Acid and Diazomethane

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In the reaction of (+)-usnic acid in methylene chloride with ethereal diazomethane a tetracyclic furan derivative (II) has been isolated in low yield. Its formation and rate of racemisation are discussed.

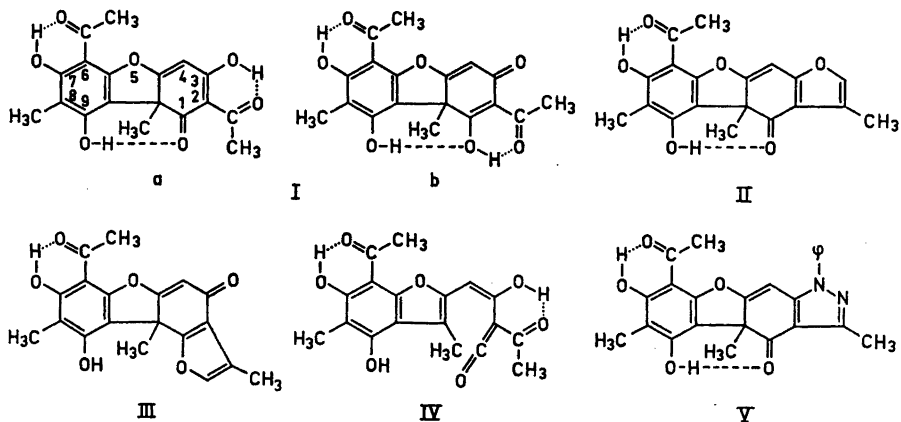
In a recent publication the synthesis of 7-*O*-methylusnic acid was described.¹ The attempted synthesis of 7,9-di-*O*-methylusnic acid failed and evidence was presented, mainly from a study of rates of racemisation of usnic acid and some of its derivatives, which indicated that the stability of the usnic acid ring system is decreased by substituents on the 9-hydroxyl group.

At an early stage in this work, methylation was attempted using diazomethane. No simple *O*-methyl derivative was detected in the complex reaction mixture but a deep yellow product was isolated (14 %). Since its structure points to a somewhat unexpected mode of reaction by the diazomethane, it will be described in some detail.

(+)-Usnic acid (Ia or less likely Ib) in methylene chloride was treated for three days with an excess of ethereal diazomethane. The alkali-insoluble part of the reaction mixture when chromatographed on a polyamide column afforded, besides non-crystallisable fractions containing several components, a compound A, C₁₉H₁₆O₆, m.p. 189–190.5°, $[\alpha]_D^{22} +816^\circ$ (*c* 0.54, chloroform). Its mass spectrum showed the molecular ion, M⁺=340 m.u., as the base peak. The composition of compound A corresponds to the addition of CH₂ to usnic acid with the loss of one molecule of water. The NMR spectrum contains all signals found in the spectrum of usnic acid except the signals from the protons of the *C*-acetyl and enolic hydroxyl groups in the β-tricarbonyl system of usnic acid at δ 2.67 and 19.20 ppm, respectively.² Instead the spectrum contains signals characteristic of an aromatically bound methyl group, δ 2.26 ppm (3H; doublet, *J*=1.3 cps) and an aromatic proton, δ 7.25 ppm (1H; quartet, *J*=1.3 cps). These results suggest a tetracyclic ring system for compound A, containing a furan ring fused linearly (II) or angularly (III) to the usnic acid ring system. The chemical shifts and the coupling constants of the

methyl group and the proton of the condensed furan ring agree with those reported for 3-methyl substituted furans.³

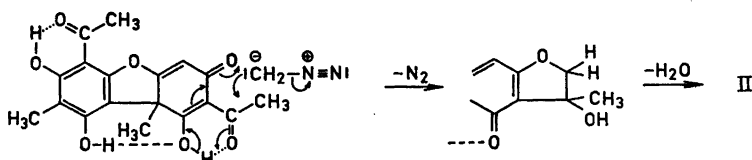
Evidence in favour of the linear formula (II) is furnished by the chemical shift, 11.07 ppm, of the 9-hydroxyl proton. This value indicates a hydrogen bond to the 1-oxygen atom of about the same strength as in usnic acid and



its derivatives with a free phenolic 9-hydroxyl group where the corresponding shifts fall within 10.90–11.07 ppm.^{1,2} The hydrogen bond in III between the 9-hydroxyl group and a furan oxygen would be less pronounced and cause shielding of the hydroxyl proton.

The racemisation of II in dioxan has been studied at 79.5° where a first order rate constant $k = 1.1 \times 10^{-3} \text{ h}^{-1}$ was found for the racemisation reaction. This value is markedly lower than the corresponding value for usnic acid,¹ $k = 5.5 \times 10^{-3} \text{ h}^{-1}$, and supports a mechanism for the racemisation of usnic acid involving a ketene intermediate (IV) as proposed by Stork.⁴ The formation of a ketene type intermediate from II would be more difficult than from usnic acid as it involves the disruption of the π -electron system of the fused furan ring. The reported failure of usnic acid anhydrophenylhydrazone⁵ (V) to racemise has been interpreted along similar lines by Stork.⁴

The formation of II from usnic acid might involve an oxirane type intermediate,⁶ which is subsequently opened, *e.g.* by attack of the 3-hydroxyl group. An analogous cyclodehydration occurs in the acid-catalysed formation of menthofuran from an oxirane derivative.⁷ Alternatively, diazomethane could attack tautomer Ib in a concerted reaction with subsequent aromatisation to II:



It is noteworthy that the formation of II has been observed in methylene chloride and (by TLC) in chloroform but not in tetrahydrofuran, acetone, or acetonitrile. NMR-measurements^{1,2} in CDCl_3 indicate the occurrence of a single tautomer of usnic acid, most probably Ia. However, the occurrence of small amounts of Ib and the dependence of the tautomeric equilibria on solvent composition cannot be excluded.

Isolated examples of enol ethers obtained in high yields from β -tricarbonyl compounds with diazomethane have been reported^{8,9} but the formation of a furan ring has apparently not been observed under these reactions or in analogous methylations of β -dicarbonyl compounds or *o*-acylphenols.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. IR spectra were recorded on a Perkin-Elmer No. 221 and UV spectra on a Beckman DK-2 spectrophotometer. NMR spectra were measured in CDCl_3 -solutions on a Varian A-60 spectrometer at 60 Mc/s. Tetramethylsilane was used as internal standard and the chemical shifts are reported as δ_{TMS} . Mass spectra were obtained on an LKB 9000 instrument with an all-glass heated inlet system at 20–30°.

Reactions and separation procedures were followed by TLC on polyamide (Merck) with methanol as solvent or by chromatography on paper impregnated with formamide as described previously.^{1,2}

Reaction of usnic acid with diazomethane. To (+)-usnic acid (Schuchardt, *cf.* Ref. 1) (8.0 g) in methylene chloride (1500 ml) was added a solution of diazomethane in ether (0.61 M; 94 ml). After 70 h at +4° in the dark, acetic acid (2 ml) was added and the solution was evaporated to dryness. The oily residue was dissolved in chloroform (150 ml) and the solution was extracted with aqueous sodium hydroxide (1 M; 4 × 30 ml).

The combined extracts were acidified and extracted with chloroform. Evaporation of the dried chloroform solution gave a syrup (4.6 g) which on treatment with chloroform-methanol (1:9) afforded (+)-usnic acid (1.8 g) (m.p., IR, spec. rotation). TLC of the mother liquor gave several spots all of which appeared yellow under UV-light ($\lambda=254$ nm). It was not further investigated.

The chloroform solution containing alkali-insoluble material was washed with hydrochloric acid (1 M), and water and then dried. Evaporation gave a syrup (3.6 g). TLC showed three spots, R_F 0.56, 0.67, and 0.75, all of which were dark under UV-light. After storing the syrup for 14 days at 20°, TLC of it showed no spot, R_F 0.67, but a new spot, R_F 0.08. The stored syrup was fractionated on a polyamide column (ϕ 50 mm; 190 g polyamide (Woelm), prewashed with methanol) using methanol as eluent. Fractions of 50 ml were collected. Fractions Nos. 23–27 were combined and evaporated. The syrup (1.6 g) showed one spot, R_F 0.75, on TLC but three spots on paper chromatography. It was not further investigated.

Fractions Nos. 28–33 were combined and evaporated to give a residue (R_F 0.56) which was dissolved in chloroform and filtered through a short polyamide column to remove polyamide impurities. Evaporation of the filtrate gave a syrup (1.20 g). Crystallisation from chloroform-methanol (1:9) afforded the furan derivative (II) (0.86 g, 14 %, calc. on reacted usnic acid), m.p. 189–190.5°, $[\alpha]_D^{25} +816^\circ$ (*c* 0.54, chloroform). (Found: C 67.1; H 4.81; O 27.8. $\text{C}_{15}\text{H}_{16}\text{O}_6$ (340.34) requires C 67.1; H 4.74; O 28.2). λ_{max} (EtOH) 220 nm (ϵ 41 700), 286 nm (16 000), 402 nm (3 800), ν_{max} (CHCl_3) 1675 (s), 1625 (vs), 1589 cm^{-1} (m), mass spectrum (the largest peaks above 60 m.u. as per cent of the base peak): 340 (M^+ , 100 %), 325 (77 %), 312 (23 %), 297 (45 %), 283 m.u. (25 %). NMR spectrum: δ 1.74 (3H), 2.08 (3H), 2.26 (3H; doublet, $J=1.3$ cps), 2.68 (3H), 6.26 (1H), 7.25 (1H; quartet, $J=1.3$ cps), 11.07 (1H), 13.43 ppm (1H).

(+)-Usnic acid (40 mg) in a solvent (8 ml; chloroform, methylene chloride, acetone, acetonitrile, and tetrahydrofuran, respectively) was treated with ethereal diazomethane (0.25 M; 1.2 ml) for 70 h at +4°. The solutions were investigated by TLC. Spots chromato-

graphically indistinguishable from the spot of the furan derivative (II) were detected only in the chloroform and methylene chloride solutions.

Racemisation experiments. The racemisation of II was measured in purified dioxan solution (5.0 mM) at 79.5° using a Perkin-Elmer Model 141 photoelectrical polarimeter as described elsewhere.¹ The experiment was run for 15 h. A final value of $\alpha/\alpha_0 = 98.3\%$ ($\alpha_0 = 1.245^\circ$) was observed. The first order rate constant $k = 1.1 \times 10^{-3} \text{ h}^{-1}$ was obtained graphically.

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