Synthesis of the Antibiotics Uliginosin A and Dihydrouliginosin B

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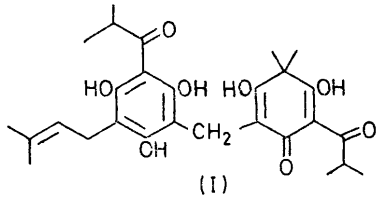
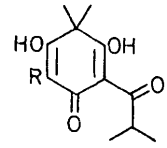
Summary The antibiotics uliginosin A, dihydrouliginosin B, and isodihydrouliginosin B have been synthesized.

EXTRACTION of the Mexican herb *Hypericum uliginosum* HBK, yielded two antibiotics,[1] uliginosin A (I) and uligino-

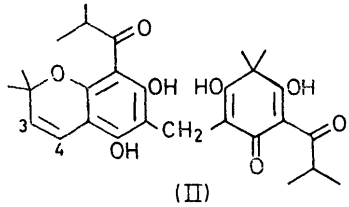
sin B (II). The structures were assigned on the basis of spectroscopic evidence[2] and a crystal structure analysis of bromouliginosin B.[3] In particular, the structure of uliginosin A (I) is a hybrid between those of the hop resins[4] and the male fern constituents.[5] We now report the synthesis of uliginosin A (I), dihydrouliginosin B (III), and isodihydrouliginosin B (IV).



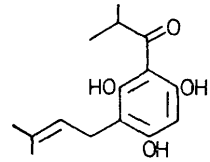
(I)



(V) R = $COPr^i$
(VI) R = H

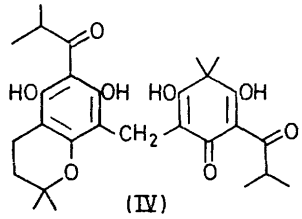


(II)

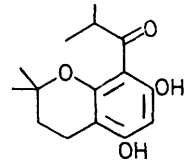


(VIII)

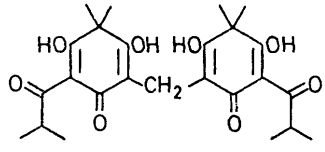
[(III) is 3,4-dihydro-(II)]



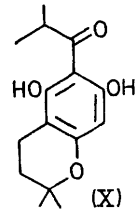
(IV)



(IX)



(VII)



(X)

Treatment of a mixture of anhydrous phloroglucinol and isobutyric acid with boron trifluoride yielded di-isobutyryl phloroglucinol which was methylated with an excess of methyl iodide-sodium ethoxide to give di-isobutyrylfilicinic acid (V). Selective deacylation with 80% sulphuric acid gave monoisobutyrylfilicinic acid (VI). Condensation of (VI) with formaldehyde afforded albaspidin (iBiB) (VII).[6]

Alkylation of phloroisobutyrophenone with 1-bromo-3-methylbut-2-ene (1 mol. equiv.) gave the previously unreported monoisoprenylphlorisobutyrophenone (VIII) (the di-, tri-, and tetra-isoprenylated derivatives are known[4]) Treatment of (VIII) with toluene-*p*-sulphonic acid gave a mixture of two chromans (IX), m.p. 145°, and (X), m.p. 142°, separated by fractional crystallisation. The structures were assigned on the basis of their u.v. and n.m.r. spectra. In addition, only (X) gave a positive reaction with Gibbs' reagent. Condensation of (VIII), (IX), and (X) individually with formaldehyde gave the corresponding methylene-bis-compounds [*cf.* (VII)].

Attempts to effect the mixed condensation of (VIII), (IX), or (X) with (VI) and formaldehyde gave mixtures from which only symmetrical products could be isolated. However, treatment of albaspidin, (iBiB), (VII) with an excess of the disodium salt of (IX), in methanol under reflux, afforded dihydrouliginosin B (III) (*ca.* 80%). The synthetic compound had m.p. 149° whereas that reported for the natural product, known to be contaminated with a higher homologue, is 138—141°; on admixture they melted at 143°. Similarly, the trisodium salt of (VIII) gave uliginosin A (I), m.p. and mixed m.p. 164° (50%), and the disodium salt of (X) gave isodihydrouliginosin B (IV), m.p. and mixed m.p. 159° (23%). The synthetic compounds had spectral properties identical with those reported[2] for the natural products.

Initial attempts to dehydrogenate (IX) and so effect the synthesis of uliginosin B have been unsuccessful but this study and the synthesis of analogues for biological evaluation is continuing.

We thank Dr. Francis Johnson of the Dow Chemical Company for carrying out the mixed m.p. determinations with (I) and (III) and for supplying authentic samples of (II) and (IV).

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