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SOME CHEMICAL TRANSFORMATIONS OF NORDITERPENE DILACTONES FROM PODOCARPUS SELLOWII

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Although twenty-six nor- and bisnor-diterpene dilactones have been reported since 1968 as hydrophilic constituents of nine species of Podocarpus,[1] the organic chemistry of these compounds has been relatively little investigated.[2] We have confirmed that many standard reactions on these polyfunctional substances give unexpected and frequently uninterpretable results. Starting material is frequently recovered, even under vigorous reaction conditions.[3] The lactone and epoxide groups show an unusual stability to many acids and bases, hydroxyls are often sterically protected from attack by normal reagents, and even a vinyl group (present in some members of the series) resists well-known double bond attacking reagents such as diborane and mercuric acetate. The insolubility of many of the compounds in any solvents other than pyridine, dimethylsulfoxide, or acetone (and often very sparing solubility even in these), has undoubtedly also contributed to the paucity of chemical transformations reported.

In the course of several years' work on the three new compounds (I-III) isolated from the Brazilian Podocarpus sellowii Klotzsch,[4] we have observed some new reactions which, together with observations on the mass spectral fragmentations of the products, merit discussion here.

Certain acid conditions give selective attack on the epoxy group in ring A of Sellowins A and B, without affacting the other epoxide in the molecule. For example, solution of Sellowin B (II) in trifluoroacetic acid gave slow modification of the portion of the NMR spectrum corresponding to the ring A protons, with formation of an easily hydrolyzed diol monotrifluoroacetate (M^+ 444 = $C_{20}H_{19}O_8F_3$). The corresponding diol showed coupling of the 2α-proton (δ 4.36 in pyridine-d_5) to the 1β-proton (δ 3.84) with J = 11 Hz, and to the 3β and 3α protons with J = 12.5 and 5 Hz, respectively, showing that the first three of these protons possess approximately *trans*-antiparallel relative dispositions. This requires a twist-boat conformation for ring A (IVa). Indeed, a Dreiding model of IV with ring A in the chair conformation either opens or flips to a

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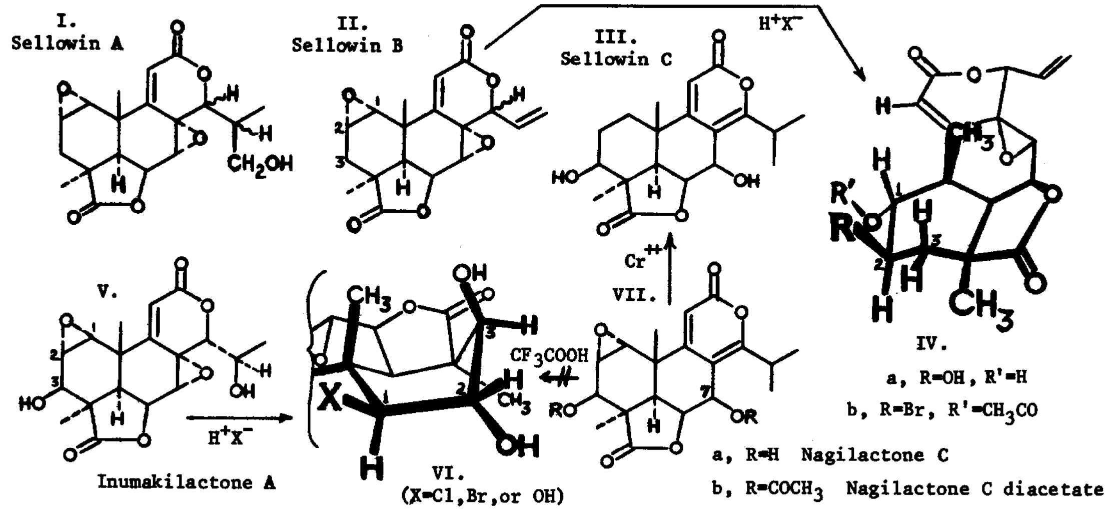
(§) Taken in part from the M.S. thesis of W.E.S.L., C.P.P.N./U.F.R.J., October 1973.



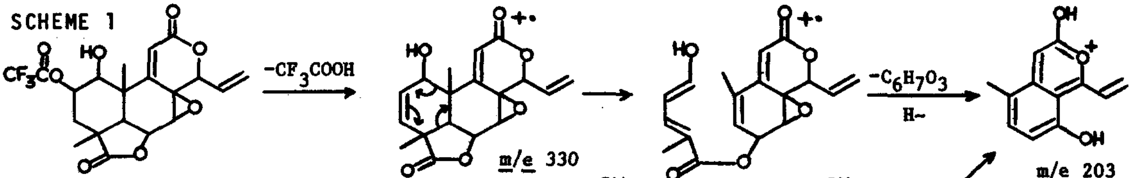
twist-boat with great ease, independent of substitution at C-2.

Attempted bromohydrin formation by electrophilic attack on the vinyl group of Sellowin B with N-bromoacetamide in 90% aqueous acetone gave very slow reaction, producing a substance which still possessed the vinyl group (by NMR) but was nevertheless a bromohydrin (by IR). The more tractable derived acetate showed coupling patterns for the 1β (δ 5.66 in pyridine-d_5), 2α (δ 4.74), and 3β and 3α protons identical to those observed in the diol IVa, indicating structure IVb.

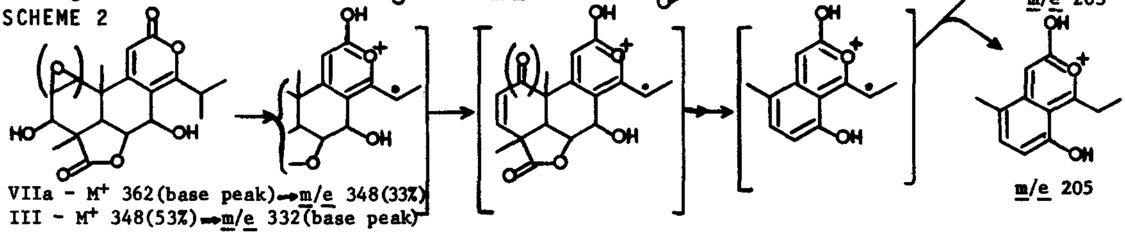
In both cases, attack of the nucleophile at the exposed 2-position of the protonated epoxide is evident in the structure (IV) of the product (the bromohydrin is apparently formed by slow release of HBr from the N-bromoacetamide reagent, to whose attack the vinyl group is resistant). This contrasts with the results recently published[5] for acid opening of the ring A epoxide in Inumakilactone A (V) and related compounds, giving VI by selective attack at the 1-position. In this case, the different regiospecific control of the reaction must be provided by interaction of the nucleophile with the 3β-hydroxyl group in V. Interestingly, attempted opening of the analogous epoxide in Nagilactone C (VIIa) with trifluoroacetic acid (as used for Sellowin B) led quantitatively to the 7-O-monotrifluoroacetate, leaving the epoxide intact.

The base peak (m/e 203) in the mass spectrum of the 2-O-monotrifluoroacetate precursor of the diol IVa, may be attributed to retro-Diels-Alder fragmentation of ring A with subsequent formation of a stable benzo-pyrylium ion (Scheme I). A related pair of significant peaks (m/e 203 and 205) in the spectra of 3-hydroxy compounds such as Nagilactone C (VIIa) and Sellowin C (III) may have a similar origin (Scheme 2).

SCHEME 1

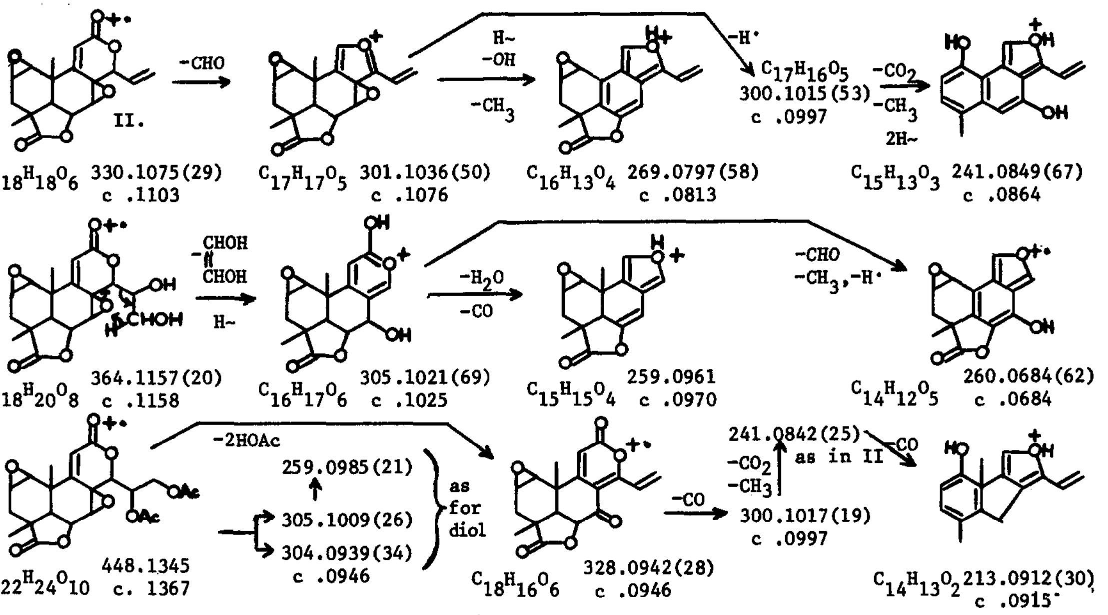


SCHEME 2



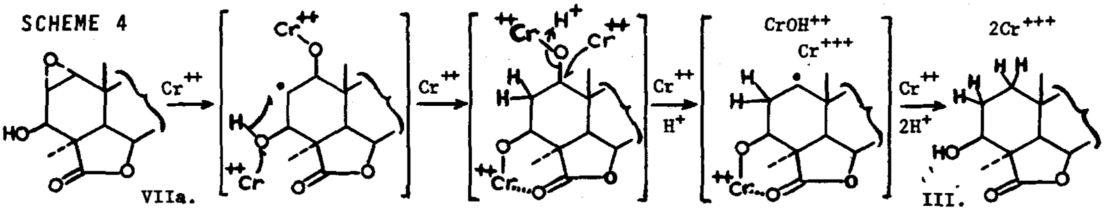
Successful oxidation of the vinyl group of Sellowin B was achieved only with OsO_4 in pyridine. The starting material, the product, and its diacetate were subjected to computer-assisted element mapping in high-resolution mass spectrometry.[6] A speculative outline of the principal fragmentations of these compounds (Scheme 3) suggests that furan formation in ring C[4] may be important even in compounds where principal peaks come from cleavage of the sidechain.

SCHEME 3 Formulae and measured mass; c = calculated mass fraction; ( ) = relative intensity



Further investigation of the reported[4] interconversion of Nagilactone C (VIIa) and Sellowin C (III) has led to the unexpected discovery that the reduction by Cr^{II} or the Zn-Cu couple is direct, producing III from VIIa in high yield under a variety of experimental conditions.[7] While removal of an epoxide to form a double bond,[8] and saturation of a conjugated double bond,[9] are known in Cr^{II} reductions, the direct reduction of a non-conjugated epoxide to a saturated derivative has not been previously observed with this reagent; with the Zn-Cu couple, it is rarely seen. Significantly, $CrCl_2$ treatment of Nagilactone C diacetate (VIIb) did not give any epoxide removal or reduction, even under forcing conditions. Apparently, the free hydroxyl at C-3 is participating in the four-electron reduction observed, possibly *via* a mechanism such as that represented in a simplified fashion in Scheme 4 (actually, it is unlikely that a "free" radical exists, and hydrogen atoms are probably transferred directly from water molecules in complex chromium ligands associated with the 3β-hydroxyl group).

SCHEME 4



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