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THE SYNTHESIS OF STRUCTURAL ANALOGUES OF THE PODOPHYLLUM LIGNANS: SELECTIVE WITTIG REACTIONS ON 1-ARYL-2-METHYL-TETRAHYDRONAPHTHOIC ACID ANHYDRIDE

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Summary: The title anhydride reacts with stabilised phosphorus ylids exclusively at the carbonyl remote from the 1-aryl substituent. These products have been converted into a variety of compounds related in structure to deoxyisopicrophyllotoxin.

Podophyllotoxin (1, X=OH) is one of the aryl tetralin lignans from Podophyllum peltatum, and is a potent inhibitor of microtuble assembly during mitosis.[1] The semi-synthetic derivatives etoposide (2) and teniposide (3) are in clinical use as anti-cancer agents.[2] Interestingly, their mode of action appears to be different from that of podophyllotoxin, and they cause breakage of DNA strands without effect on microtubules.[3] N.m.r. studies suggest that all of these compounds have a favoured conformation in solution in which the pendant aryl ring (E ring) is perpendicular (quasi-axial) to the rest of the system (ABCD rings).[4] The related lignan picrophyllotoxin (4) is essentially devoid of biological activity, and this has been ascribed to a favoured conformation (in solution) in which the 1-aryl substituent is roughly coplanar (quasi-equatorial) with respect to the ABCD ring system.

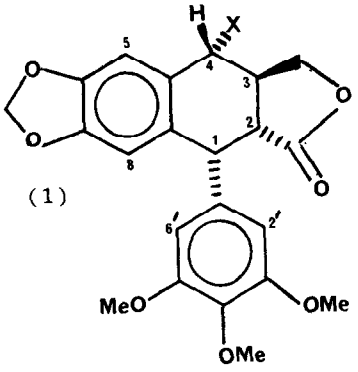
We have an interest in deoxyanalogues of these compounds, and seek to identify the conformational changes that accompany subtle variations in the structures. Our route to 1-aryl tetralins proceeds via a cycloaddition between o-quino-dimethane (5) and 2-substituted maleic anhydrides[5] to yield compounds of general structure (6). Reduction with K-Selectride® produces lactones (7) exclusively, and an X-ray structure of lactone (7, R=CH_3)[6]

showed that this had quasi-axial methyl- and aryl- groups. In addition, the ^{1}H-n.m.r. exhibited a two proton singlet at 6.41 p.p.m. for 2'-H and 6'-H, comparable with the corresponding signal in deoxypodophyllotoxin (1, X=H) (δ 6.34), and this encouraged us to produce a range of compounds for biological evaluation. In particular, an appendage remote from the 1-aryl group is desirable, since this would allow attachment of carbohydrates or short peptide sequences, thus mimicking the structures of (2) and (3).

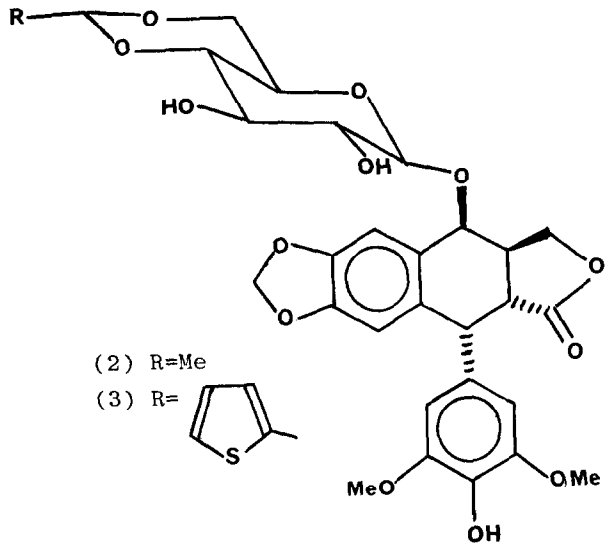
To this end, (6, R=CH_3) was treated with stabilised ylids (Ph_3P=CHX) (8a, X = $-CO_2CH_3$, and 8b, X = -CN) in benzene, with obtention of Wittig products (9a,b, X as for 8) in yields of 52 and 30% respectively after chromatography and recrystallisation. For these two compounds, the allylic coupling observed for the olefinic proton, and the deshielding of the protons at C-4 are best explained by structures (9a) and (9b). Interestingly, an X-ray structure of (9a) showed quasi-equatorial aryl- and methyl-groups, and it seems likely that this conformation is also adopted in solution since the C-2' and C-6' protons are strongly deshielded (relative to those of 7, R=CH_3), which would be consistent with a closer approach to the carbonyl group.

Catalytic hydrogenation of (9a) produced a major product (10a) which again exhibited a low field signal for the C-2' and C-6' protons (a 2 proton singlet at 6.92 p.p.m.), suggesting that this also possessed quasi-equatorial aryl- and methyl-groups. A minor product (10b) (2'-H and 6'-H at 6.36 p.p.m.) was converted into (10a) upon treatment with $Bu_4N^+OH^-$ in CH_3OH/H_2O, reinforcing the impression that the essentially flat structure of (10a) represents the preferred conformation for this compound.

This deshielding effect observed when the 1- and 2-substituents are quasi-equatorial appears to be general (it has been seen with analogues 7 as well) and should be useful for the prediction of conformational preference and hence likely biological activity.

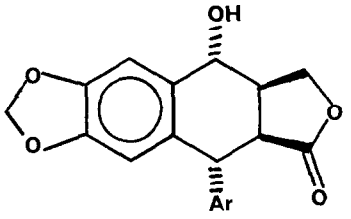


(1)

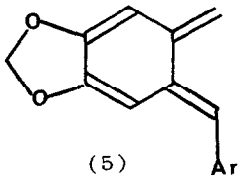


(2) R=Me

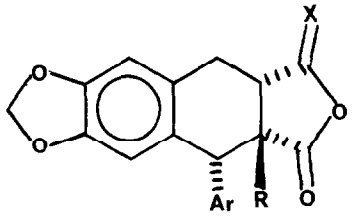
(3) R=



(4) Ar=3,4,5-trimethoxyphenyl

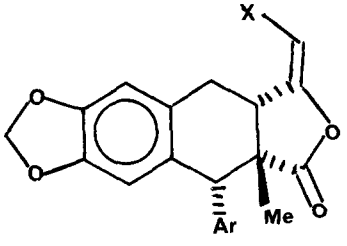


(5)

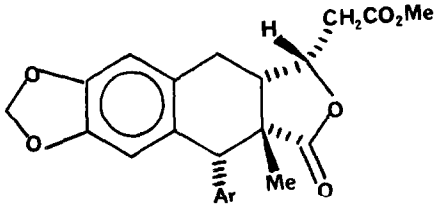


(6) X=O

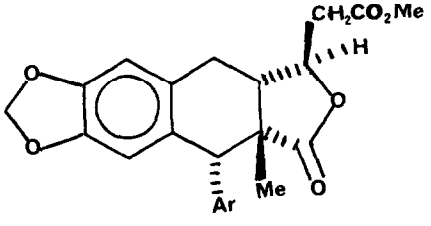
(7) X=H_2



(9a) and (9b)



(10a)



(10b)

TABLE: ^{1}H Chemical Shifts and Assignments

	1-H	3-H	4-H	5-H	8-H	2'-H and 6'-H	Other
1(X=H)	4.60	2.72	2.78 & 3.07	6.66	6.51	6.34	-
7(R=CH_3	3.93	2.91-3.05	2.65-2.71	6.71	6.59	6.41	-
9a	4.00	3.78	3.12-3.26	6.68	6.55	7.05	5.68 d 2Hz (olefinic H)
9b	3.86	3.60	3.30-3.40	6.80	6.62	6.66	5.02 d 2Hz (olefinic H)
10a	3.86	2.85	2.30-2.60	6.72	6.58	6.92	
10b	4.00	2.40	2.90	6.74	6.64	6.36	

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3. Long, B.H., Musial, S.T., and Brattain, M.G., 1984, Biochemistry, 23, 1183, and references therein.
4. Rithner, C.O., Bushweller, C.H., Gensler, W.J., and Hoogasian, S., 1983, J.Org.Chem., 48, 1491.
Brewer, C.F., Loike, J.O., Horwitz, S.B., Sternlicht, H., and Gensler, W.J., 1979, J.Med.Chem., 22, 215.
5. Mann, J., Piper, S.E., and Yeung, L.K.P., 1984, Perkin Trans.I, 2081. In this paper we also reported a cycloaddition between o-quinodimethane (5) and dimethylmaleate. Following comments in a recent paper by Durst and Charlton (Tet.Letters, 1984, 5287), we have repeated this experiment. Under very carefully controlled conditions the all-cis cycloadduct is obtained (as we reported). However, traces of acid in the solvent, or prolonged reaction at high temperature, result in the formation of the 1,2-trans, 2,3-trans cycloadduct.
6. Beard, A.R., Mann, J. and Wong, L.T.P. unpublished results - this X-ray structure and several others will be published together with corresponding biological data in due course.

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