Effect of a Cyclic Structure at P^{III} on the Reactivity of an Ester of Phosphorous Phosphoric Anhydride

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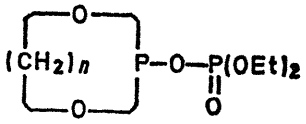
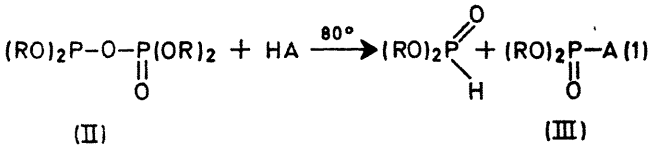
Summary The unusual inertness of P^{III} cyclic esters of phosphorous phosphoric anhydride towards protic acids is discussed in the light of Hudson's concept of steric retardation on quaternisation.

DURING our studies on the esters of phosphorous phosphoric anhydride[1-4] we have discovered that cyclic derivatives of type (I) are unusually inert toward reagents such as diethyl hydrogen phosphate and acetic acid, no reaction being observed on prolonged heating for 3 h at 110—120°,



(I) n = 2 or 3

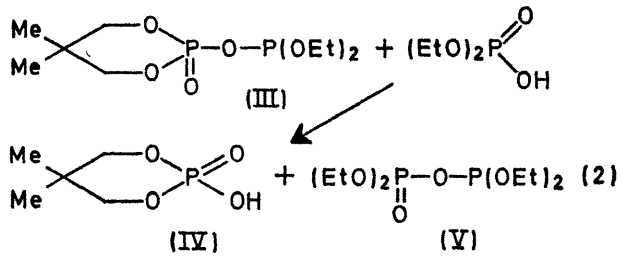
and distillation *in vacuo* giving almost quantitative recovery of (I). This behaviour contrasts with that of the acyclic analogues (II) which do react with protic acids[2] [equation (1)].



(II) (III)

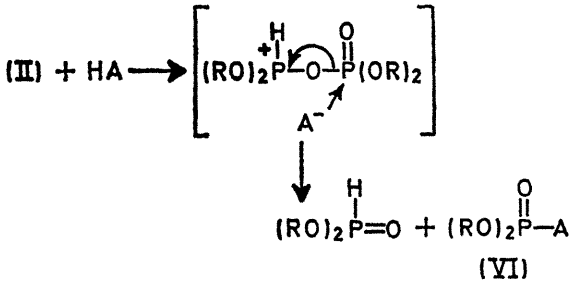
A = $(EtO)_2P(O)O$ or $MeCO_2$

The reactivity of esters of phosphorous phosphoric anhydride containing a cyclic phosphate system at P^V is comparable with that of (II). *E.g.* an equimolar mixture of the anhydride (III) and Et_2HPO_4 yields 2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (IV) and the tetraethyl ester of phosphorous phosphoric anhydride (V) in 65% yield when left overnight in benzene solution at room temperature [equation (2)].



(III) (IV) (V)

The mechanism in the Scheme can account for the formation of the mixed anhydride (VI). The natural angle of phosphite is *ca.* 100°, and when tervalent phosphorus



(VI)

acts as a nucleophile or base this should increase as a result of rehybridisation towards 109°. In the case of the cyclic compound the ring strain will increase and hence it should be less reactive than the acyclic analogue. It was recently shown by Greenhalgh and Hudson[5] and also by Aksnes and Eriksen[6] that cyclic phosphites are less readily attacked by electrophiles, *e.g.* alkylating agents, than the corresponding acyclic analogues. Our results strongly support Hudson's concept[5] of steric retardation on quaternisation of cyclic phosphites. The expected pronounced electrophilic reactivity of cyclic anhydrides (I), due to the release of ring strain in the transition state involving sp^3d hybridised phosphorus, has been also verified in our laboratory.[7]

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The Stereochemistry of a Tetraflavanoid Condensed Tannin from *Rhus lancea* L.f.

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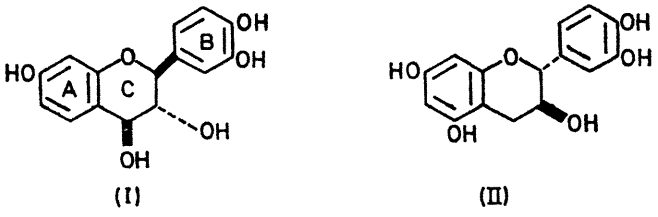
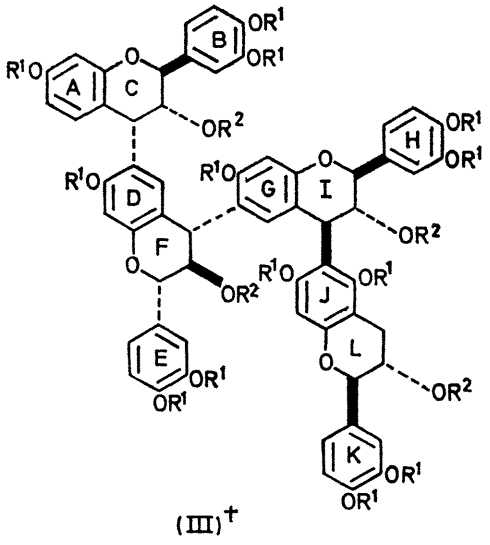
Summary The pure tridecamethyl ether tetra-acetate of an all-4,6-linked 2,3-*trans*-3,4-*cis*: 2′,3′-*trans*-3′,4′-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2‴,3‴-*trans*-trileucofisetinidin-(+)-catechin and its presumed precursors have been isolated from the karree (*Rhus lancea*).

MONO- and BI-FLAVANOIDS show almost no tanning properties towards collagen substrates, the adsorptive effects becoming significant at the triflavanoid level and increasing progressively with molecular weight [1] Those polyflavanoids which fall strictly within the category of tannins also exhibit a high incidence of rotational isomerism about their interflavanoid bonds,[2] an example being an all-*trans*-bileucofisetinidin-(+)-catechin from *Colophospermum mopane* [2] Against this, the present isolation of a pure derivative of a related tetraflavanoid condensed tannin represents a rare exception





The heartwood of the indigenous karree (*Rhus lancea*) contains in common with other Anacardiaceae (*Schinopsis* spp [3] and *Cotinus coggygria*[4]), one member of the exceptionally rare group of (2*S*) 5-deoxyflavonoids Thus (2*S* 3*R*: 4*S*)-flavan-3,3′,4 4′,7-pentaol (I) [(−)-leucofisetinidin] and (2*R* 3*S*)-flavan-3,3′,4′,5,7-pentaol (II) [(+)-catechin] were isolated, and apparently represent the fundamental precursors of most of the associated condensed tannins From amongst the latter a discrete fraction (R_F 0 78, 0 20 in water-satd butan-2-ol and 2% acetic acid) gave fisetinidin chloride in good yield, and fisetin (trace) from acid hydrolysis in alcoholic solution, and after further purification of appropriate derivatives by t l c gave an amorphous powder of the tridecamethyl ether tetra-acetate (III, R^1=Me, R^2=Ac), $C_{81}H_{84}O_{25}$, M^+ 1456, shown to be pure by n m r spectrometry at 220 MHz

Suitable solvent shifts induced by the progressive (10% *v/v*) change in the proportion of C_6D_6 to $CDCl_3$, showed the presence of thirteen methoxy and four acetyl groups Spin-decoupling of heterocyclic protons enabled demonstration of three ABX and one ABXY spin systems, shown to advantage in a 8·2 *v/v* C_6D_6:$CDCl_3$ mixture (Figure) The coupling constants of the F and I hetero-

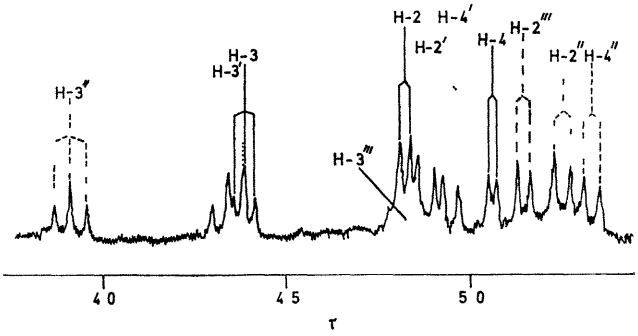


FIGURE *Assignments for the heterocyclic proton region from the 220 MHz n m r spectrum of the tridecamethyl ether tetra acetate derivative of the tetraflavanoid tannin in* C_6D_6 $CDCl_3$ (8 2 v/v)

cyclic rings ($J_{2,3}$ 10 0, $J_{3,4}$ 9 5 Hz) are typical of 2,3-*trans*-3,4-*trans* 2,4-biaryl half-chair heterocyclic ring systems in biflavanoids[5,6] while that of the C-ring ($J_{2\,3}$ 7·1, $J_{3,4}$ 5 0 Hz) is in agreement with the corresponding 2,3-*trans*-3,4-*cis* boat conformation [5] Residual heterocyclic protons with couplings and chemical shifts typical of those of (+)-2,3-*trans*-catechin ($J_{2,3}$ 7 8, $J_{3,4a}$ 8 5, $J_{3,4e}$ 5 0, $|J_{4a,4e}|$ 16 0 Hz) were evident at different stages of admixture of C_6D_6 to $CDCl_3$

Notable amongst the methoxy signals is the far upfield position of one (τ 6 93 in $CDCl_3$) which alone is not subject to a significant upfield shift on progressive addition of C_6D_6 (τ 6 94 in C_6D_6), and is accordingly[7] attributed to the 5-position in the J-ring Alternatively, this establishes a 4 6-link to the terminal unit (*i e* between I and J rings, respectively) ‡ As far as may be judged three high-field and two low-field singlets in the aromatic region tentatively attributed to the 8-positions of the D, G, and J rings and the 5-positions of the D and G rings, respectively, are evident from the series of ten spectra examined in the C_6D_6–$CDCl_3$ solvent systems The doublet and quartet assigned to the 8- and 6-positions of the A ring are readily visible, the latter to high field Accordingly 4,6-linkages between the C and D, and F and G rings were tentatively assigned, and confirmation sought by synthesis[8] of 2 4- and 4,6-dihydroxyisophthalic acids (IV and V) Degradation of the tannin by alkali microfusion under anhydrous

† The stereochemistry about the 4 6 interflavanoid bonds is unknown Note the inverted representation of flavanoid units containing the F and L heterocyclic rings, *i e* units which are stereochemically identical to (I) and (II), respectively

‡ Note added in proof The validity of solvent shift method where applied, as in this instance to abnormally shielded methoxy signals has very recently been discussed by A Pelter R Warren K K Chexal B K Handa and W Rahman *Tetrahedron* 1971 **27** 1625 for 3 8-biflavones

conditions[9] affords, in addition to resorcinol, phloroglucinol, and β-resorcylic and protocatechuic acids, a carboxylic acid which has the same R_F and colour reactions as the latter (V) on a kieselgel substrate in a system (butan-1-ol: methanol: conc. NH_3 7:2:1 by vol.) which also easily differentiates between these (IV and V).

The sequence of leucofisetinidin units follows from initial allocation of a 2,3-*trans*-3,4-*trans*-configuration to the position adjacent to the (+)-catechin moiety. Such assignment devolves from observation that the 4-proton highest upfield [*cf.* Figure, τ 5·33 in C_6D_6:$CDCl_3$ (8:2 *v/v*), $J_{3,4}$ 9·5 Hz] shows no pronounced benzylic coupling when examined at 300 MHz with a Varian C-8000 time-averaging computer (5 scans), whereas amongst the heterocyclic protons only the remaining 4-protons (τ 5·06. $J_{3,4}$ 5·0 Hz and τ 4·95, $J_{3,4}$ 9·5 Hz) show secondary splitting with marked line-broadening under the same conditions. This phenomenon is presumably due to the higher degree of benzylic coupling possible in the latter instance (two *ortho*-benzenoid protons available on different nuclei) as compared with the former [*cf.* ref. 5 and (III)]. Furthermore, the 4-proton of this 'adjacent" 2,3-*trans*-3,4-*trans*-unit has the same chemical shift (τ 5·39 in $CDCl_3$) as the corresponding proton observed in the spectrum of all-*trans*-bileucofisetinidin-(+)-catechin.[2]

Of the remaining alternatives, the 2,3-*trans*-3,4-*cis*-assignment is chosen for the "upper" position of the tannin molecule, considering agreement of the coupling constants ($J_{2,3}$ 7·1, $J_{3,4}$ 5·0 Hz) and chemical shifts (τ 4·51 in $CDCl_3$) of its 3-H triplet (quartet at 300 MHz) with those of identically-placed units amongst the bileucofisetinidins ($J_{2,3}$ 7·1; $J_{3,4}$ 5·0—5·1 Hz and τ 4·48, 4·50). In addition, a 2,3-*trans*-3,4-*trans* "upper" unit is apparently excluded due to the expected low-field position of its 3-H triplet as illustrated in the corresponding derivatives of all-*trans*-bileucofisetinidin-(+)-catechin[2] (τ 3·70—3·95) and all-*trans*-leucofisetinidin-(+)-catechin and its analogues (τ 3·90—3·99).[6]

From conformational analysis based on coupling constants, the 2- and 4-phenyl linkages to the heterocyclic ring systems of each flavanoid unit of the tetraflavanoid derivative (III; R^1 = Me, R^2 = Ac) are *equatorial*. The 3-acetoxy-groups attached to the heterocyclic rings are similarly *equatorial* except in ring C where the orientation is *axial*. With the knowledge that all 4,6-interflavanoid bonds are *equatorial*, and that strong intramolecular bonds between functional groups are likely in the free phenolic form (III; R^1 = R^2 = H), the tannin molecule should assume an approximately planar arrangement.

The suggested structure (III) of the tetraflavanoid tannin from *R. lancea* exhibits no less than fourteen points of chirality, with the absolute configurations of its constituent units reflecting those of their presumed precursors (I) and (II).

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