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A SYNTHETICALLY VERSATILE NOVEL DIENOPHILE, 2-HYDROXY-5-OXO-5,6-DIHYDRO-2H-PYRAN

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The Diels Alder reaction[1] has been widely used for the stereospecific construction of a wide range of varied carbon skeletons. Amongst the wide range of dienophiles investigated there exists a considerable paucity of asymmetric dienophiles substituted at either end of the double bond by two carbon atoms and one carbon atom respectively. Two such dienophiles trans dimethyl glutaconate[2] and coumalic acid[3] have recently been investigated. The trans stereochemistry of dimethyl glutaconate gives rise to stereoisomer problems in reactions with cyclic dienes in addition to the orientational isomer problem inherent in this class of asymmetric dienophile. The potential use of coumalic acid as a dienophile is compromised by the fact that it is also a diene, and indeed in its reactions with butadiene and its congeners, coumalic acid participates in an inverse electron demand reaction as a diene.

On account of the paucity of such substituted dienophiles an investigation of the properties of the readily accessible 2-hydroxy-5-oxo-5,6-dihydro-2H-pyran (1)[4] in the Diels-Alder reaction was of interest. This highly functionalised dienophile has a cis olefinic bond, and since the stereochemistry of the reactants is retained during Diels-Alder reactions, leads to a series of cis adducts. The two carbon and one carbon appendant groups can be readily distinguished as they occupy different oxidation levels. Epimerisation of the aldehydic centre leads to a trans series of adducts. The ketonic carbonyl function at C-5, which activates the olefinic double bond for the 4+2 addition reaction also, offers further potential for attaching carbon units and in this way this dienophile can be considered as the synthetic equivalent of coumalic acid[5]. Reductive removal of the ketonic carbonyl function in the addition products leaves two readily distinguishable simple side-chains suitable for further elaboration.

This versatile dienophile (1) readily reacts with a number of symmetrical and cyclic dienes under the conditions shown in the table. Its reactivity as a dienophile is immediately evident in that it reacts at room temperature with cyclopentadiene and at 100°C with butadiene.

TABLE I

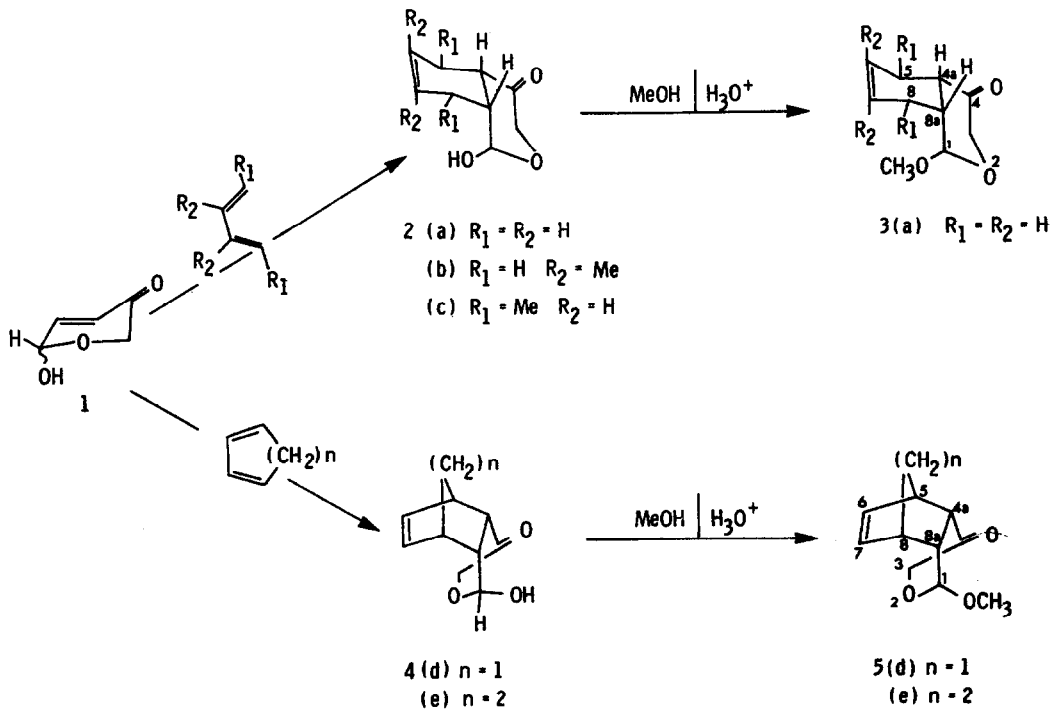
Diene	Ratio of Diene: Dienophile	Temp. 0°C	Time hr.	Yield of Isolated Product %	Isomer Ratio	VPC * Retention Time (min)	Boiling ** Point °C
Butadiene	2:1	100	16	62	57:43	2.85, 3.4	72-6/0.05mm
2,3-Dimethyl butadiene	2:1	120	24	82	68:32	5.1, 4.65	96-7/0.2mm
trans, trans 1,4-Dimethyl	2:1	130†	24	39	68:32	6.4, 7.9§	80-82/0.3mm
Cyclopentadiene	1.3:1	25	72	75	100	3.6	84-88/0.3mm
Cyclohexadiene	2:1	120	24	50	100	6.1	90-93/0.2mm

* Retention times were determined using 5% OV 17, 5' x ¼" column at 190°C.

** The molecular composition of the products was analysed by VPC-MS.

† I.r. analysis reveals incomplete reaction with respect to dienophile.

§ Retention time recorded for a 2% OV 17, 5' x ¼" column at 140°C.



2 (a) $R_1 = R_2 = H$
(b) $R_1 = H$ $R_2 = Me$
(c) $R_1 = Me$ $R_2 = H$

3(a) $R_1 = R_2 = H$

4(d) n = 1
(e) n = 2

5(d) n = 1
(e) n = 2

The reactants were mixed in 1,2-dimethoxyethane solution in the molar ratios indicated and heated in sealed tubes at the temperatures and for the times reported. The primary Diels-Alder adducts (2 a-c) and (4 d-e) were treated with methanol at reflux for 1-2 hours using acid Amberlite 120H resin[6] as catalyst. In this way the aldehydic function was completely protected thus facilitating the isolation and characterisation of the adducts. The methyl acetals (3 a-c) and (5 d-e) were purified by fractional distillation and analysed by gas liquid chromatography.

The stereochemical assignments for the cyclo-addition products were based largely on a complete analysis of the n.m.r. spectrum of 1-methoxy-4aβ,5,8,8aβ-tetrahydro-5,8-methano-1H,3H-2-benzopyran-4-one, the cyclopentadiene adduct (5 d). This adduct was homogeneous as evidenced by g.l.c. and n.m.r. spectroscopy. N.m.r. spin-decoupling experiments revealed the following structurally significant proton coupling constants $J_{4a,8a}$ = 10 c.p.s., $J_{4a,5}$ = 4 c.p.s., $J_{8,8a}$ = 3.5 c.p.s. and $J_{8a,1}$ = 4.5 c.p.s. In addition to the usual norbornene proton couplings[7] a small trans carbonyl coupling of the H_{4a} proton with both H_3 protons, $J_{3a,4a} = J_{3e,4a}$ = 1.5 c.p.s. was demonstrated by irradiating the H_3 protons individually and observing the collapse of the H_{4a} signal to a doublet. The magnitude of the $J_{8a,8}$ and $J_{4a,5}$ norbornene ring coupling constants conclusively define the stereochemistry of the ring junction between the pyran ring and the norbornene system as cis-endo, the usual stereochemistry observed for a room temperature Diels-Alder addition reaction with cyclopentadiene. This stereochemical assignment was further consolidated by the absence of any observed coupling between the anti-proton attached to the methano bridge and the exo protons at C_{4a} and C_{8a}, whereas if either of these protons had endo stereochemistry a planar "W coupling" would invariably be observed. Attachment of the methoxyl group at C_1 on the convex side of the molecule in a pseudo-axial conformation was compatible with the observed coupling constant $J_{8a,1}$ = 4.5 c.p.s. and a dihedral angle approaching 45°. The n.m.r. spectrum of the analogous single adduct from cyclohexadiene (5 e) was consistent with a cis-endo stereochemistry, with the 1-methoxyl group placed on the convex face.

The primary Diels-Alder adducts (2 a-c) from the symmetrically substituted butadienes gave after protection of the aldehydic function a mixture of two stereoisomers resolvable by gas liquid chromatography. The n.m.r. spectra of the resolved isomers whilst being largely similar can be distinguished by means of the distinct doublets observed for the protons attached to carbon atom one. The mass spectra of these individual isomers confirm their

molecular size and differ mainly in the relative intensity of the peaks at M-30 and M-32. The spectroscopic evidence was consistent with these isomers being epimeric about C_1 with the stereochemistry of the ring junction exclusively cis in all isomeric pairs. The well known propensity of the Diels-Alder reaction to proceed with retention of configuration consolidates these spectroscopic deductions. The adducts obtained from trans trans-1,4-dimethyl butadiene must be assigned the all-cis stereochemistry as this diene reacts in a similar fashion with a number of analogous dienophiles.

The further elaboration of these highly functionalised Diels-Alder adducts by removal of the ketonic carbonyl function and elaboration of the side chains to prostaglandin intermediates or the addition of single carbon units on to the ketonic group leading to iridoid synthons will be the subject of further investigations.

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