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AN UNUSUAL INTRAMOLECULAR DIELS–ALDER REACTION

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Abstract—The diene-ester (2) on heating undergoes an intramolecular Diels–Alder reaction *via* the intermediate (3). The β-alkyl furan moiety in 3 reacts as the dienophile adding to the cyclohexadiene unit to give 4.

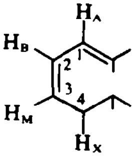
INTRODUCTION

A recent report described the structure and stereochemistry of the new furanoid diterpene (1) isolated from *Dodonea attenuata* var *linearis*[1]. As part of the investigation of its structure an attempt was made to react the corresponding methyl ester (2) with maleic anhydride. The product obtained was found not to have incorporated maleic anhydride and an investigation of its structure revealed it to be the dihydrofuran lactone (4) resulting from an intramolecular Diels–Alder type reaction in which the furan unexpectedly reacts as a dienophile.

RESULTS AND DISCUSSION

The reaction of maleic anhydride with 1,3-cyclohexadiene carboxylic acid esters is known[2] to occur to give [2,2,2] bicyclo - oct - 2 - ene - 1 - carboxylate - 5,6 - dicarboxylic acid anhydride derivatives.

Attempts to achieve the same reaction with the diene ester (2) and maleic anhydride in refluxing diglyme for 48 hr yielded a compound which could also be generated simply by heating 2 in refluxing diglyme. Monitoring the course of the reaction by TLC indicated that the ester (2) was first converted to a less polar compound (3) which in turn was converted to the Diels–Alder adduct (4). The intermediate compound (3) showed IR absorption at 1780 cm^{-1} attributed to a γ-lactone. UV absorption at 270 (ϵ 5,100) indicated the presence of a conjugated homo-annular diene. Comparison of the NMR spectra of 2 and 3 (Table 1) showed that the β-alkyl furan moiety was still present in 3 but the signal at δ 2·58 for the allylic 10-H in 2 was lacking in the spectrum of 3 as was the signal for the carbomethoxyl group. The appearance of an AB quartet at δ 3·94 and 4·42 (J_{AB} 8 Hz) further supported[3] the presence of a γ-lactone group in 3. Both the A and B proton showed long range coupling, J 1·5 and 0·5 Hz respectively, the smaller of which was due to a proton which gave rise to a doublet of triplets at δ 3·04 (J 3, 0·5 Hz). This signal was attributed to the 4β-H which showed the additional coupling to two vinylic protons. INDOR[4] and decoupling measurements allowed the resonance signals for the three vinylic protons to be identified as part of an ABMX system and gave the following relationships and coupling constants (Fig 1).



J_{MX}	3 Hz
J_{MB}	9
J_{MA}	1
J_{AB}	5·5
J_{BX}	3

Fig 1.

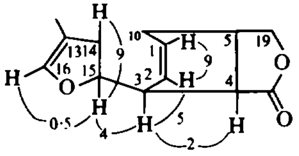
The above results can only be accommodated by assuming isomerisation of the doubly conjugated ester in the A-ring of 2 and lactone formation between the C-4 and C-5 substituents. It seems probable that the isomerisation occurs via a [1,5] sigmatropic shift of a hydrogen in which the 10β-H migrates suprafacially to the C-4 position.[5] The stereochemistry thus attained at C-4 (β-H) allows formation of the γ-lactone. The diene lactone (3) in refluxing diglyme was shown to be converted to an isomeric compound identical to that obtained by prolonged heating of 2 in diglyme. On the basis of the following results the compound is assigned structure 4. The IR spectrum of 4 showed absorption at 1770 cm^{-1} for the γ-lactone whereas in the UV spectrum no maximum above 216 nm was observed indicating loss of the conjugated diene system. The MS of 4 showed an M^+ at m/e 312 and fragmentations almost identical to those observed for 3. The NMR spectrum of 4 (Table 1) exhibited signals for a tertiary and a secondary Me at δ 0·82 and 0·88 (J 7 Hz) respectively and an AB quartet at δ 4·02 (J_{AB} 9 Hz) for the lactone α-methylene

Table 1. Proton chemical shifts (δ) in compounds **2–6**

Compound/ Solvent	1-H	2-H	3-H	4-H	10-H	13-H	14-H	15-H	16-H	9-Me	8-Me	Substituent on C-4	19-H$_2$
CDCl$_3$ **2**	6·27	6·11	6·87	—	2·58	—	6·18	7·18	7·33	0·84	0·86	3·77	3·79
C$_6$H$_6$	5·91	6·17	6·73	—	2·50	—	5·91 6·17	7·07	7·20	0·72	0·72	3·53	3·78
CDCl$_3$ **3**	5·93	6·12	5·49	3·04	—	—	6·28	7·24	7·37	0·87	0·93	—	4·42 3·94
C$_6$H$_6$	5·61	6·03	5·43	2·88	—	—	6·17	7·10 –	7·29	0·58	0·71	—	4·13 3·68
4 CDCl$_3$	6·29	6·16	3·39	1·98	—	—	3·44	4·74	5·82	0·82	0·88	—	4·02
CDCl$_3$ **5**	6·37	6·21	3·33	2·00	—	2·38 – 2·80	2·82	4·38	3·39– 3·69	0·81	0·84	—	4·00
C$_6$H$_6$	6·1	5·85	3·40	1·70	—	2·17	2·17	4·13		0·40	0·55	—	3·64
CDCl$_3$ **6**	6·21	6·06	2·60	1·35	—	2·00 – 2·40	2·85	4·32	3·32, 3·60	1·07	0·81	3·58	3·58 – 3·91
C$_5$D$_5$N	6·12		2·80	obscured	—	—	2·80	4·40	3·3 – 3·60	1·00	0·70	3·7 – 4·2	Multiplet obscured

protons. Signals corresponding to three vinylic protons were also observed. An eight line signal, each line broadened by further coupling, at δ 4·74 was assigned to a hydrogen geminal to oxygen.

A doublet at δ 1·98 (J 2 Hz) assigned to the 4β-H was found to be coupled to a proton which appeared as a multiplet at δ 3·39 and which showed further coupling (J 4 Hz) to the proton at δ 4·47 (15-H). INDOR measurements and decoupling results indicated the following relationships (Fig 2).



Other coupling constants

$J_{2,15}$	1·0
$J_{1,14}$	2·0
$J_{1,3}$	1·0
$J_{14,16}$	0·5

Fig 2. Coupling constants (Hz) obtained from INDOR and decoupling measurements on **4**.

A multiplet at δ 5·82 was assigned to a hydrogen geminal to an enol ether oxygen. The coupling observed (2 Hz) between the 14-H and the 1-H implies that these are four bonds apart and if this link is established consideration of the coupling constant between the olefinic protons indicates the presence of a cyclohexene unit as part of a[2.2.2] bicyclooctene system.

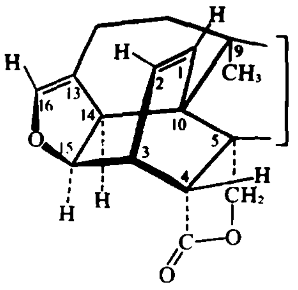
The structure which best accommodates these results is that shown in **4**. This compound can be considered to arise from a Diels–Alder reaction between the disubstituted double bond of the furan and the cyclohexadiene system. Alternative structures in which the furan reacts as the diene can be excluded from spectroscopic data as can the structure in which the alkyl substituted double bond of the furan adds to the diene system.

Stereochemistry

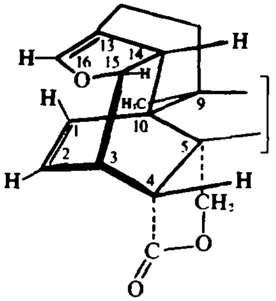
A priori the stereochemical possibilities allowed are those arising from *exo*- or *endo* addition of the furan from the α- or β- face of the cyclohexadiene group of **3**. Hydrogenation of **4** over Pt yielded a dihydro compound (**5**) in which the cyclohexene double bond was retained, implying that approach to this double bond is sterically hindered. This effectively discriminates against the adducts where the dihydrofuran is *anti*- to the bicyclooctene double bond since for these situations molecular models indicate that both olefinic double bonds are similarly available for hydrogenation. Of the two possibilities (part structures **A** and **B**) where the dihydrofuran is *syn*- to the bicyclooctene double bond, one (**A**) has the 14 and 15-H *syn* to the lactone. In the other (**B**) the two protons are *syn* to the 4β-H.

Reduction of **5** with LAH gave the diol (**6**) the NMR spectrum of which showed the signals for the 14-H and 15-H at δ 2·85 and 4·32 respectively, not significantly shifted from the positions (δ 2·82 and 4·38) observed for these protons in the spectrum of **5**. On the other hand the vinylic protons were shielded by 0·16 ppm in the spectrum of **6**.

No significant chemical shift differences were observed for the 14 and 15-H when the spectrum was measured for a C$_5$D$_5$N solution of **6**. This evidence argues in favour of part structure **B**, and confirmation of this was obtained by NOE meas-



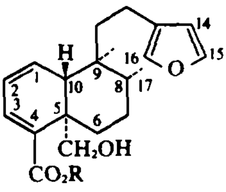
A



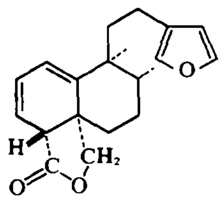
B

urements on 4 and 6. Saturation of the signal for the 4-H of 4 resulted in an increase of the integral for the 15-H of 10%. Irradiation of the signal for the C-9Me resulted in an 11% increase of the bicyclooctene olefinic protons placing these two groups *syn*. A similar but smaller increase (5%) was observed on saturation of the C-9Me signal in 6. Other NOE results (Table 2) provide further support for the stereochemical assignments. In view of these results the stereochemistry for the Diels–Alder adduct is as shown in 4 and consequently the dihydro derivative has the stereochemistry shown in 5. Furthermore a tentative assignment of the conformation is possible on the basis of the NOE results. Although both the B and C ring can achieve the chair conformation in 4 in this situation an NOE effect between the C-9Me and the olefinic protons would seem improbable. However these two groups can be brought nearer if ring C attains the halfboat conformation in which some 1,3-diaxial interactions can be relieved as well as steric crowding between the lactone methylene protons and the C-9Me.

The behaviour of furans as 1,3 dienes in Diels–Alder reactions is well documented and exceptions are known only in those cases where the furan is substituted by an electron withdrawing group.[6] The reaction of furans as dienophiles has



1: R = H
2: R = Me



3

Coupling constants (Hz) observed in the NMR spectrum of

2:	$J_{1,2}$	9·5	3:	$J_{1,2}$	5·5	$J_{19a,19b}$	8·0
	$J_{1,3}$	2·0		$J_{1,3}$	1·0	$J_{4,19a}$	0·5
	$J_{2,3}$	5·0		$J_{2,3}$	9·0	$J_{19b,6(?)}$	1·5
	$J_{1,10}$	< 1·0		$J_{2,4}$	3·0		
	$J_{3,10}$	2·0		$J_{3,4}$	3·0		
	$J_{8,17}$	7·0		$J_{8,17}$	6·0		

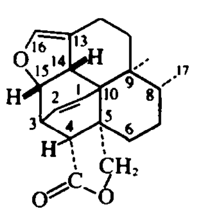
Table 2. NOE results[a] on 4 and 6

Irradiated	Resonance signals Observed (% increase in integral)					
Compound 4						
	1,2-H_2[b]	4-H	15-H	16-H	19-H_2	3,14-H_2[b]
C-9Me	11	—	0	−1	4	0
15-H	1	4	—	3	2	6
19-H_2	4	—	—	1	—	—
4-H[c]	< 1	—	10	3	2	4
3,14-H_2	4	1	10	2	—	—
Compound 6						
	1,2-H_2	3-H	14-H	15-H		
C-9Me	5	0	1	1		
15-H	1	2	4	—		

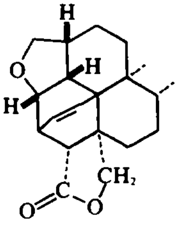
[a] Obtained at 90 MHz on degassed samples having a concentration of 10% (w/v).

[b] % increases on two proton integral. In some cases the actual value may be nearer to twice the value given.

[c] Signal irradiated obscuring parts of other proton signals.



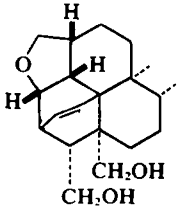
4



5

Coupling constants (Hz) observed in the NMR spectrum of

4.	$J_{1,2}$	9·0	$J_{3,15}$	4·0	5:	$J_{1,2}$	9·0	$J_{3,15}$	4·5
	$J_{2,3}$	5·0	$J_{8,17}$	7·0		$J_{2,3}$	6·0	$J_{8,17}$	6·6
	$J_{3,4}$	2·0	$J_{14,15}$	9·0		$J_{3,4}$	2·0	$J_{14,15}$	5·5
	$J_{1,3}$	1·0	$J_{19a,19b}$	9·0		$J_{1,3}$	2·0	$J_{16a,16b}$	7
	$J_{1,14}$	2·0	$J_{14,16}$	0·5		$J_{13,14}$	7·5	$J_{13,16a}$	8·5
	$J_{2,15}$	1·0	$J_{15,16}$	0·5		$J_{2,15}$	1·0	$J_{13,16b}$	12



6

Coupling constants (Hz) observed in the NMR spectrum of

6:	$J_{1,2}$	9·0	$J_{14,15}$	5·5
	$J_{1,3}$	3·0	$J_{3,15}$	4·0
	$J_{2,3}$	6·0	$J_{14,13}$	7·5
	$J_{2,15}$	1·5	$J_{16a,16b}$	7·0
	$J_{4,18}$	6·0	$J_{13,16a}$	8·0
	$J_{3,4}$	1·5	$J_{13,16b}$	11·5
	$J_{1,14}$	~1·0	$J_{8,17}$	6·0

been observed[7] with *ortho*-quinone and to our knowledge this is the only example in the literature. The conversion of 3 to 4 can best be rationalized as a case of a Diels–Alder reaction with inverse electron demand[8] and represents another case in which furan can act as a dienophile.

EXPERIMENTAL

General experimental details are as described previously.[9]

Diels-Alder reaction on 2

(a) The compound (100 mg) in diglyme (25 ml) was heated under reflux for 6 hr. Removal of the solvent gave a reaction product which consisted of three compounds. The major compound (80 mg) was isolated by chromatography on alumina (Act. III; elution with light petroleum: $CHCl_3$; 1 : 1) and recrystallized from ether-light petroleum as prisms of the *diene-lactone* (3), m.p. 99–100°, $[\alpha]_D$-173 (*c*, 0·7) (Found: C, 76·81; H, 7·90. $C_{20}H_{24}O_3$ requires: C, 76·89; H, 7·74%); $\nu_{max}^{CCl_4}$ 3050 (olefins), 1780 (γ-lactone); λ_{max}^{EtOH} 270 (ε 5100), 223 nm (ε 4100); MS *m/e* 312 (M^+; 72%), 231 (5), 217 (54), 173 (18), 159 (56), 131 (87), 117 (100). The two minor components were identified as starting material and the Diels–Alder adduct (4, see b).

(b) The diene (2, 750 mg) was heated in refluxing diglyme under N_2 for 48 hr. The product recovered was filtered through alumina (Act. III) and the compound eluted with 30% $CHCl_3$: light petroleum was recrystallized from MeOH as needles of *dihydrofuran lactone* (4, 675 mg), m.p. 218–220°, $[\alpha]_D$-59° (*c* 0·7). (Found: C, 76·82; H, 7·77. $C_{20}H_{24}O_3$ requires: C, 76·89; H, 7·74%) $\nu_{max}^{CS_2}$ 3050, 1770 cm^{-1} λ_{max}^{EtOH} 216 nm (ε 4100) MS: *m/e* 312 (M^+; 100%), 217 (50), 173 (14), 159 (36), 131 (57), 117 (64).

(c) Heating the diene-lactone (3) in refluxing diglyme for 32 hr under N_2 yielded a compound identified as the dihydrofuran-lactone.

Hydrogenation of the dihydrofuran lactone (4). The compound (270 mg) in EtOH was hydrogenated over PtO_2 at ambient temp and pressure. H_2 uptake (1 mole equiv) stopped after 1·5 hr. The compound recovered (245 mg) was recrystallized from ether-light petroleum as needles of the *tetrahydrofuran lactone* (5), m.p. 163–165°, $[\alpha]_D$+23° (*c*, 0·7). (Found: C, 76·44; H, 8·22. $C_{20}H_{26}O_3$ requires: C, 76·40; H, 8·33%). $\nu_{max}^{CS_2}$ 3020, 1770 cm^{-1}. MS *m/e* 314 (M^+; 100%), 286 (10), 285 (8), 284 (6), 258 (16), 220 (40), 175 (40), 173 (31).

Reduction of the tetrahydrofuran lactone (5). The compound 5 (49 mg) in dioxan (10 ml) and LAH (100 mg) was heated at 95° for 2 hr. The compound recovered (33 mg) was recrystallized from $CHCl_3$-light petroleum as needles of the diol (6), m.p. 115°–116°, $[\alpha]_D$+93° (*c*, 0·1). MS: M^+ observed: 318·21923 ($C_{20}H_{30}O_3$ requires: 318·21950); 300 (49%), 288 (19), 270 (20), 213 (18), 193 (40), 175 (100). $\nu_{max}^{CS_2}$ 3610, 3030 cm^{-1}.

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