Formation of a Benzobicyclo[4.1.0]heptane Lactone by Photochemical Rearrangement of a Steroid Ketol. Crystal Structure Determination of 5-Methoxy-des-A-14a-D-homo-14,17-cyclo-oestra-5,7,9-trien-15-one

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Photochemical rearrangement of 14β-hydroxy-5-methoxy-des-A-oestra-5,7,9,16-tetraen-15-one (1) gives the cyclopropane-lactone (4), the structure of which was established by *X*-ray crystallographic analysis. The lactone was isolated by reversed-phase high-performance liquid chromatography. A possible concerted mechanism for its formation is discussed.

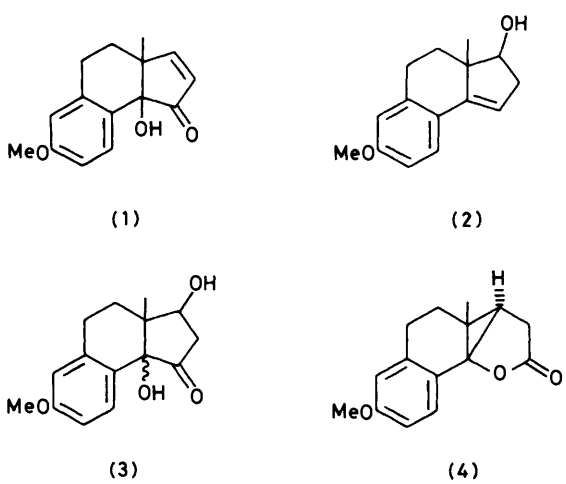
The tricyclic ketol (1) ($\nu_{max.}$ 1 710 cm^{-1}), one of a number of ketols obtained from the styrene (2) by oxidation with aromatic peracids,[1,2] is stable in the crystalline state but readily rearranges in solution to a less polar compound ($\nu_{max.}$ 1 780 cm^{-1}). The new compound was purified by preparative high-performance liquid chromatography (h.p.l.c.) on a reversed-phase[3] silica column using a variable wavelength u.v. detector. The marked increase in the carbonyl stretching frequency suggested a γ-lactone structure for the product,[4] and the lack of any hydroxy-absorption in its i.r. spectrum indicated that the hydroxy-oxygen of the ketol (1) had become bonded to its carbonyl carbon atom to form the lactone system.

The mass spectrum of the product showed it to be an isomer of the starting ketol (M^+, 244). The fragmentation pattern of the two isomers differed markedly (Figure 1), the ketol (1) having its base peak formed by loss of carbon monoxide (*m/z* 216), whereas that for the lactone involved loss of a methyl group (*m/z* 229). The lactone exhibited a much more prominent parent ion, while both compounds showed a prominent ion at *m/z* 148 corresponding to cleavage at the benzylic C–C bonds.

The ^1H n.m.r. spectrum of the lactone revealed that the two olefinic protons [at C(16) and C(17)] of the starting ketol, together with its hydroxy-proton, had been replaced by three new aliphatic protons. These appeared as a one-proton multiplet at δ 2.93 and a two-proton multiplet at δ 2.05, and were shown to be coupled. Otherwise there was little change in the chemical shifts of the remaining protons.

The u.v. spectrum of the lactone gave no further clues to its structure, beyond confirming the transformation of the Δ^{16}-15-ketone system, although it was very similar to that of the epimeric ketols (3).

An *X*-ray crystal structure determination revealed that the product contained a cyclopropane ring fused to a γ-lactone system [oxabicyclo[3.1.0]hexanone structure (4)]. The atomic arrangement in the molecule is shown in Figure 2. The cyclohexane ring approximates to a twist-boat conformation with the contiguous C(8), C(9), C(11), and C(14) coplanar and atoms C(12) and C(13) displaced by 0.87 and 0.63 Å, respectively, to the same side of the planes. The remaining rings adopt planar conformations and, as expected, there is considerable distortion from tetrahedral geometry at C(13), C(14), and C(17). The slight increase (*ca.* 7 nm) in the wavelength of the highest u.v. absorption band can thus be attributed to conjugation of the cyclopropane ring with the aromatic π-system.[5] The aliphatic protons in ring D (at δ 2.05 and 2.93) thus comprised the lone cyclopropane proton at the 17α-position and the protons of the methylene group at the 16-position adjacent to the lactone carbonyl group. The coupling



constants (*J* 8 and 18 Hz) of the single-proton double doublet at δ 2.93 suggested that this was one of the geminal protons (probably 16α), so that the 16β- and 17α-hydrogens overlapped at δ 2.05. Hydrogens on cyclopropane rings normally appear above δ 2.0, *e.g.* in the work of Gowda and McMurry[6] the non-benzylic cyclopropane protons fall within the range δ 1.25—1.7, apart from those adjacent to oxygen or carbonyl groups. In the lactone (4) the chemical shift of the cyclopropane proton is presumably influenced by its proximity to the aromatic ring.

A photochemical mechanism appeared to be the most likely one, as the rearrangement took place in sunlight. Irradiation of an ethanolic solution of the ketol (1) with a sunlamp was found to speed up the reaction, the changes being monitored by h.p.l.c. and u.v. The photochemistry of cyclopentenones has been extensively investigated and several rearrangement pathways are well established. In particular, Agosta *et al.*[7,8] have shown that irradiation of simple 5,5-disubstituted cyclopentenones (5) leads to either the formation of cyclopropyl ketenes (6) or the ring-closure of biradical intermediates to give bicyclic ketones. McMurry and co-workers[9] have reported that complex 5-hydroxycyclopentenones, such as 4-hydroxyphotosantonene, undergo photochemical rearrangement *via* a singlet excited state to afford the corresponding cyclopropane lactones. The hydroxycyclopropyl keten is the likely intermediate. Further work by Gowda and McMurry[6] on the photolysis of 5-hydroxycyclopentenones showed this type of rearrangement to be a general one, but, contrary to earlier indications, not a stereospecific process. In the work of the Dublin group, the compound (7) most closely related to our own ketol gave the

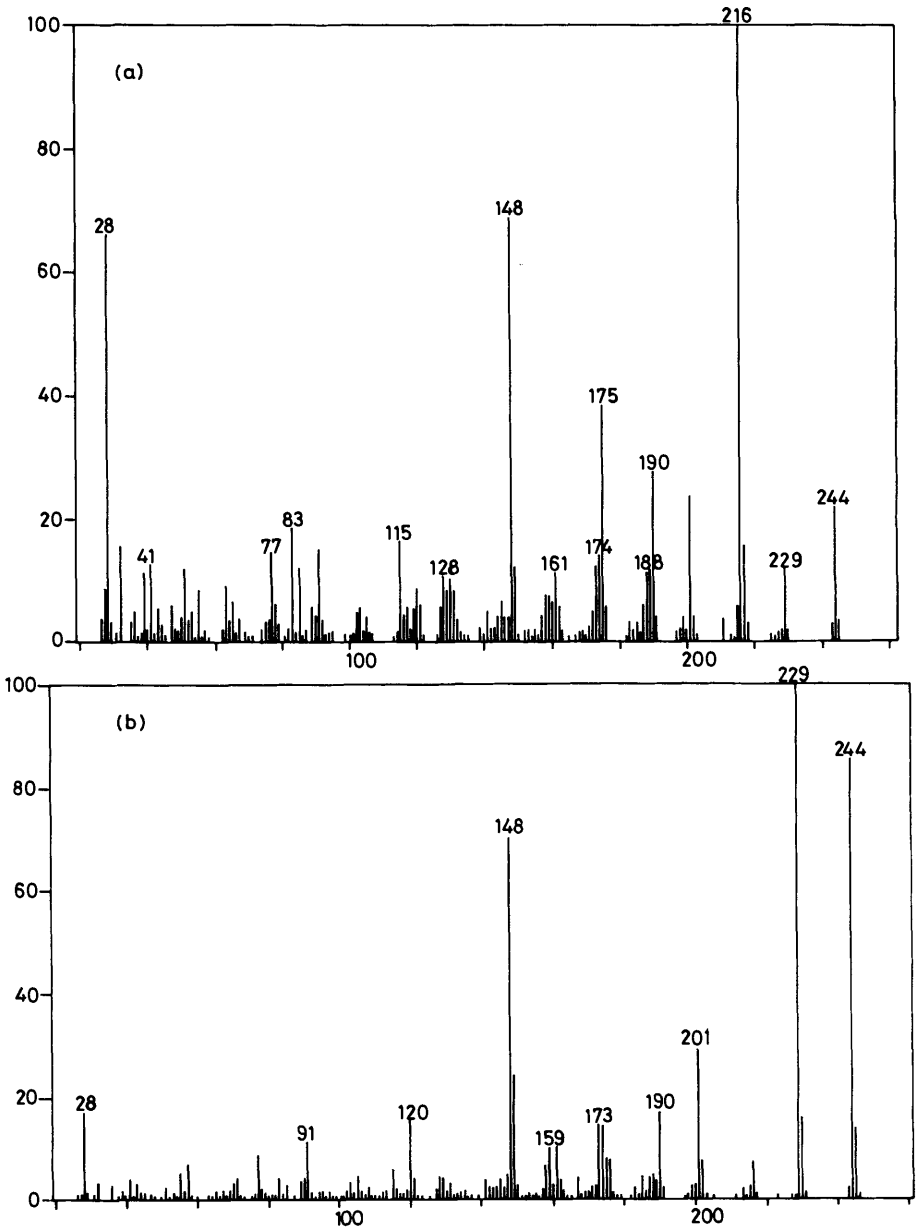


Figure 1. Mass spectra of (a) the ketol (1) and (b) the lactone (4)

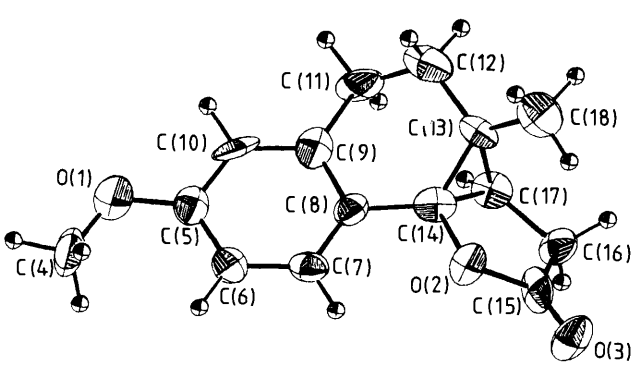
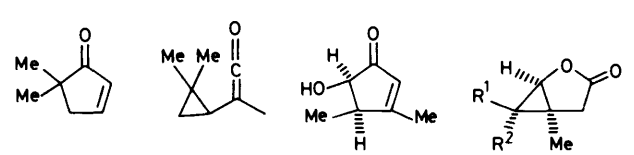


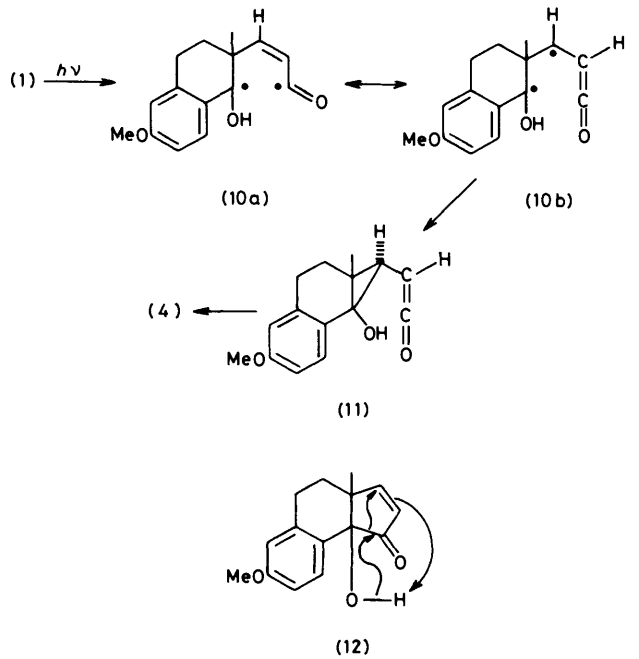
Figure 2. The atomic arrangement in the lactone (4)



(5) (6) (7) (8) R′ = H, R¹ = Me (9) R′ = Me, R² = H

lactones (8) and (9) in roughly equal amounts. The much lower yields are probably due to a competing photo-enolization process in the ketol (7), which lacks a quaternary carbon adjacent to its carbonyl group. The reaction involves a Norrish Type I fission to a biradical intermediate, which cyclises to a cyclopropanol keten; the possibility of free rotation in the intermediate prior to cyclisation leads to loss of stereospecificity. The reaction is completed by intramolecular trapping of the keten by the hydroxy-group to give the lactones. Photochemical rearrangement of saturated ketols to lactones has been reported by Cookson *et al.*[10]

Photolysis of the ketol (1) is thought to proceed *via* the diradical (10a, b) to the hydroxycyclopropyl keten (11),



Scheme.

although this process could be concerted. In either case the reaction should be stereospecific, since there is no free rotation in our intermediate. A further possibility is that the whole process is concerted, *i.e.* 1,5-sigmatropic shift of the hydroxy-hydrogen to C-16 [*cf.* (12) arrows].

The fact that the reaction proceeds readily by irradiation through Pyrex may be explained by the long-wavelength absorption of the starting ketol (1) at 339 nm, even though the absorption band is of low intensity. Orbital overlap between the carbonyl group and the aromatic π-system of the ketol (1), as reflected in the u.v. absorption, may also be a factor in facilitating the rearrangement relative to that of simple cyclopentenones. It has previously been reported that lactones are not obtained in the case of cyclopentenones having a 4-phenyl substituent.[6]

Experimental

Liquid chromatography was carried out using a Magnus P3000 solvent pumping system equipped with an Altex Model 155-11 preparative flow cell linked to an Hitachi Model 100-10 spectrophotometer set at 240 nm. Sensitivity routinely employed was 0.2 absorption units full scale. A 10μ Lichrosorb RP-8 column (Magnus Scientific) measuring 25 cm × 4.6 mm i.d. was employed, and the mobile phase of ethanol–water (1 : 1, v/v) was pumped at 1.2 ml/min (1 700 lb in^{-2}) at ambient temperature. Samples were injected by means of a Rheodyne 7 125 valve using a 20 μl loop.

N.m.r. spectra were determined on a Perkin-Elmer R34 (220 MHz) spectrometer for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference.

For other general directions see ref. 11.

5-Methoxy-des-A-14a-*oxa*-D-*homo*-14,17-*cyclo-oestra*-5,7,9-*trien*-15-*one* (4).—A solution of 14β-hydroxy-5-methoxy-des-A-oestra-5,7,9,16-tetraen-15-one [1] (1) (20 mg) in ethanol (3 ml) was left in a Pyrex flask for 48 h in intermittent sunlight. The solvent was evaporated to low volume under reduced pressure and the crude product was purified by preparative

Table 1. Fractional atomic co-ordinates (× 10^4) with e.s.d.'s

O(1)	1 676(11)	2 079	−1 999(8)
O(2)	2 298(9)	4 815(25)	3 098(7)
O(3)	1 452(11)	5 966(28)	4 736(7)
C(4)	847(15)	3 770(41)	−2 567(11)
C(5)	1 872(13)	2 361(33)	−881(11)
C(6)	1 234(13)	4 093(34)	−261(10)
C(7)	1 514(12)	4 178(33)	870(10)
C(8)	2 427(12)	2 638(32)	1 390(10)
C(9)	3 093(12)	835(33)	773(10)
C(10)	2 778(12)	750(35)	−342(11)
C(11)	4 105(15)	−838(34)	1 331(11)
C(12)	5 088(13)	323(36)	2 187(12)
C(13)	4 286(12)	1 899(32)	3 018(10)
C(14)	2 846(12)	2 694(30)	2 571(11)
C(15)	1 919(15)	4 441(34)	4 177(11)
C(16)	2 206(14)	1 876(32)	4 483(11)
C(17)	2 851(13)	787(32)	3 438(10)
C(18)	5 242(15)	3 333(34)	3 770(12)
H(4A)	786(15)	3 364(41)	−3 373(11)
H(4B)	1 319(15)	5 331(41)	−2 474(11)
H(4C)	−155(15)	3 819(41)	−2 260(11)
H(6)	578(13)	5 270(34)	−624(10)
H(7)	1 030(12)	5 409(33)	1 320(10)
H(10)	3 218(12)	−527(35)	−789(11)
H(11A)	3 517(15)	−2 063(34)	1 707(11)
H(11B)	4 723(15)	−1 583(34)	757(11)
H(12A)	5 612(13)	−923(36)	2 616(12)
H(12B)	5 811(13)	1 303(36)	1 788(12)
H(16A)	1 278(14)	1 078(32)	4 678(11)
H(16B)	2 913(14)	1 764(32)	5 122(11)
H(17)	2 568(125)	−758(116)	3 096(90)
H(18A)	4 624(15)	4 284(34)	4 273(12)
H(18B)	5 856(15)	4 393(34)	3 316(12)
H(18C)	5 884(15)	2 280(34)	4 224(12)

Table 2. Bond lengths (Å) with e.s.d.'s

O(1)–C(4)	1.403(20)	C(8)–C(14)	1.468(17)
O(1)–C(5)	1.366(16)	C(9)–C(10)	1.371(18)
O(2)–C(14)	1.466(20)	C(9)–C(11)	1.488(22)
O(2)–C(15)	1.370(16)	C(11)–C(12)	1.513(21)
O(3)–C(15)	1.189(21)	C(12)–C(13)	1.547(22)
C(5)–C(6)	1.381(23)	C(13)–C(14)	1.490(17)
C(5)–C(10)	1.396(22)	C(13)–C(17)	1.558(18)
C(6)–C(7)	1.384(17)	C(13)–C(18)	1.496(21)
C(7)–C(8)	1.362(21)	C(14)–C(17)	1.513(22)
C(8)–C(9)	1.420(22)	C(15)–C(16)	1.538(26)
C(16)–C(17)	1.536(20)		

Table 3. Valency angles (°)

C(5)–O(1)–C(4)	117.4(11)	C(6)–C(5)–O(1)	124.8(13)
C(10)–C(5)–O(1)	116.6(13)	C(15)–O(2)–C(14)	112.2(13)
C(8)–C(14)–O(2)	110.7(12)	C(13)–C(14)–O(2)	114.0(11)
C(17)–C(14)–O(2)	107.3(10)	O(3)–C(15)–O(2)	121.6(17)
C(16)–C(15)–O(2)	109.4(13)	C(16)–C(15)–O(3)	129.0(13)
C(10)–C(5)–C(6)	118.7(12)	C(7)–C(6)–C(5)	119.1(14)
C(9)–C(10)–C(5)	123.1(15)	C(8)–C(7)–C(6)	122.1(15)
C(9)–C(8)–C(7)	119.9(11)	C(14)–C(8)–C(7)	125.4(14)
C(14)–C(8)–C(9)	114.6(13)	C(10)–C(9)–C(8)	117.1(14)
C(11)–C(9)–C(8)	120.3(11)	C(13)–C(14)–C(8)	123.9(11)
C(17)–C(14)–C(8)	130.7(15)	C(11)–C(9)–C(10)	122.6(14)
C(12)–C(11)–C(9)	112.6(15)	C(13)–C(12)–C(11)	114.4(10)
C(14)–C(13)–C(12)	112.0(11)	C(17)–C(13)–C(12)	112.9(14)
C(18)–C(13)–C(12)	115.6(10)	C(17)–C(13)–C(14)	59.5(9)
C(18)–C(13)–C(14)	123.9(15)	C(17)–C(14)–C(13)	62.5(9)
C(18)–C(13)–C(17)	121.2(11)	C(14)–C(17)–C(13)	58.0(9)
C(16)–C(17)–C(13)	116.3(13)	C(16)–C(17)–C(14)	106.1(14)
C(17)–C(16)–C(15)	105.0(12)		

Table 4. Torsion angles (°) with e.s.d.'s

C(4)–O(1)–C(5)–C(6)	4.6(20)
C(15)–O(2)–C(14)–C(8)	145.9(12)
C(15)–O(2)–C(14)–C(17)	−1.9(15)
C(14)–O(2)–C(15)–C(16)	0.2(16)
C(10)–C(5)–C(6)–C(7)	0.1(22)
C(6)–C(5)–C(10)–C(9)	−1.5(23)
C(6)–C(7)–C(8)–C(9)	−1.8(22)
C(7)–C(8)–C(9)–C(10)	0.4(21)
C(14)–C(8)–C(9)–C(10)	−177.9(13)
C(7)–C(8)–C(14)–O(2)	−7.3(20)
C(7)–C(8)–C(14)–C(17)	130.6(17)
C(9)–C(8)–C(14)–C(13)	29.8(20)
C(8)–C(9)–C(10)–C(5)	1.3(22)
C(8)–C(9)–C(11)–C(12)	−39.6(19)
C(9)–C(11)–C(12)–C(13)	49.7(18)
C(11)–C(12)–C(13)–C(17)	42.7(17)
C(12)–C(13)–C(14)–O(2)	−158.0(12)
C(12)–C(13)–C(14)–C(17)	104.3(13)
C(17)–C(13)–C(14)–C(8)	−122.4(16)
C(18)–C(13)–C(14)–C(8)	128.4(16)
C(12)–C(13)–C(17)–C(14)	−103.0(13)
C(14)–C(13)–C(17)–C(16)	−93.2(14)
C(18)–C(13)–C(17)–C(16)	20.3(19)
O(2)–C(14)–C(17)–C(16)	2.7(15)
C(8)–C(14)–C(17)–C(16)	−136.2(15)
O(2)–C(15)–C(16)–C(17)	1.5(16)
C(15)–C(16)–C(17)–C(13)	59.3(16)
C(4)–O(1)–C(5)–C(10)	−175.9(13)
C(15)–O(2)–C(14)–C(13)	−68.9(15)
C(14)–O(2)–C(15)–O(3)	180.0(14)
O(1)–C(5)–C(6)–C(7)	179.5(13)
O(1)–C(5)–C(10)–C(9)	179.0(13)
C(5)–C(6)–C(7)–C(8)	1.5(23)
C(6)–C(7)–C(8)–C(14)	176.2(14)
C(7)–C(8)–C(9)–C(11)	179.3(14)
C(14)–C(8)–C(9)–C(11)	1.1(20)
C(7)–C(8)–C(14)–C(13)	−148.3(15)
C(9)–C(8)–C(14)–O(2)	170.8(12)
C(9)–C(8)–C(14)–C(17)	−51.3(21)
C(11)–C(9)–C(10)–C(5)	−177.6(14)
C(10)–C(9)–C(11)–C(12)	139.3(15)
C(11)–C(12)–C(13)–C(14)	−22.2(18)
C(11)–C(12)–C(13)–C(18)	−171.6(13)
C(12)–C(13)–C(14)–C(8)	−18.0(19)
C(17)–C(13)–C(14)–O(2)	97.7(13)
C(18)–C(13)–C(14)–O(2)	−11.5(19)
C(18)–C(13)–C(14)–C(17)	−109.2(16)
C(12)–C(13)–C(17)–C(16)	163.8(12)
C(18)–C(13)–C(17)–C(14)	113.5(15)
O(2)–C(14)–C(17)–C(13)	−108.6(12)
C(8)–C(14)–C(17)–C(13)	112.5(17)
C(13)–C(14)–C(17)–C(16)	111.3(13)
O(3)–C(15)–C(16)–C(17)	−178.3(16)
C(15)–C(16)–C(17)–C(14)	−2.5(15)

h.p.l.c., collecting the major component (R_t 9.1 min). Minor components were present in the range R_t 4.8—5.2 min. Evaporation of the aqueous ethanol, followed by crystallisation of the residue from hexane–diethyl ether (1 : 1) and recrystallisation from ethanol, gave *the lactone* (4) as colourless needles (14 mg, 70%), m.p. 107.5—108.5 °C (Found: M^+, 244.1097. $C_{15}H_{16}O_3$ requires M, 244.1099); $\lambda_{max.}$ (EtOH) 284 and 291 nm (ε 1 750 and 1 680); $\nu_{max.}$ 1 780, 1 270, 1 165, 1 145, 1 100, 1 070, 1 025, 985, 925, 860, 815, 810, and 775 cm^{-1}, δ($CDCl_3$) 1.21 (s, 18-Me), 1.73 (m, 12-CH_2), 2.05 (m, 17α and 16β-H), 2.55 (m, 11-CH_2), 2.93 (dd, J 8 and 18 Hz, 16α-H), 3.77 (s, 5.0 Me), 6.63br (s, 10-ArH), 6.78br (d, J 9 Hz, 6-ArH), 7.50 (d, J 9 Hz, 7-ArH); m/z 244 (M^+, 63%), 230 (9), 229 (100), 201 (24), 190 (11), 174 (10), 173 (11), 159 (8), 148 (79), 120 (14); m_1*, 215 (calc. for 244 ⟶ 229 : 214.9) and m_2* 176.5 (calc. for 229 ⟶ 201: 176.4). The lactone had R_F 0.54 on t.l.c. on silica gel using hexane–diethyl ether (1 : 2) as eluant [*cf.* R_F 0.39 for the ketol (1)].

Crystal Data.—$C_{15}H_{16}O_3$, M = 244.1, monoclinic, a = 9.188(21), b = 5.735(17), c = 12.058(60) Å, β = 91.13(31)°, U = 635.3 Å, D_c = 1.28 g cm^{-3}, Z = 2, F(000) = 260, Space group $P2_1$, μ(Mo-K_α) = 0.51 cm^{-1}.

Crystallographic Measurements and Structure Analysis.—Intensity measurements were obtained on a Nicolet P3 automated diffractometer using monochromatized Mo-K_α radiation. The final R = 7.7% over 694 reflexions. The crystal structure was elucidated by direct methods using the 'MULTAN' programme,[12] and refined using the SHELX programme.[13] In the final cycles of full-matrix least-squares refinement the positional parameters for all atoms, anisotropic thermal parameters for the C and O atoms, and a common isotropic thermal parameter for the H atoms, were varied. The C–H bond lengths were restricted to 1.0 Å during refinement.

Final positional parameters are listed in Table 1, bond lengths in Table 2, valency angles in Table 3, and torsion angles in Table 4. Structure amplitudes and thermal parameters are listed in Supplementary Publication No. SUP 23538 (6 pp.).*

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* For details of the Supplementary publications scheme, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

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