Regio- and Stereo-selectivity in [$_{\pi}2 + _{\pi}2$] Photocycloaddition Reactions Between Cyclopent-2-enone and Electron-rich Alkenes

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The [$_{\pi}2 + _{\pi}2$] photocycloaddition reactions between cyclopent-2-enone and various electron-rich alkenes proceed in both good quantum yields and useful chemical yields. The stereochemistry of the cycloadducts (1)—(5) has been determined by chemical ionization mass spectrometry and chemical transformations. The regioselectivity increases with increasing nucleophilicity of the alkene, and the stereoselectivity depends on the steric properties of the alkene substituents. The reaction between cyclopent-2-enone and 1-ethoxy-1-ethylthioethylene occurs in a fully regio- and stereo-specific way.

NUMEROUS examples of synthetically applicable [$_{\pi}2 + _{\pi}2$] photocycloaddition reactions have been described.[1] Photoannelation reactions between cyclopent-2-enone and substituted alkenes yield *cis*-fused bicyclo[3.2.0]-heptan-2-one derivatives. Further transformations may lead to cyclobutane, cyclopentane, or cycloheptane derivatives upon cleavage of the appropriate carbon–carbon bonds.

Our interest in the use of cyclopentenones as substrates in the synthesis of natural products prompted us to investigate thoroughly the regio- and stereo-selectivity of photocycloadditions between cyclopent-2-enone and some electron-rich alkenes. We expected that the availability of a high-resolution separation and identification technique [combined g.l.c.–chemical ionization mass spectrometry (c.i.m.s.)], would make possible a more detailed product analysis than before. The reaction mixtures were found to be more complex than sometimes claimed in the literature.[2,3]

RESULTS AND DISCUSSION

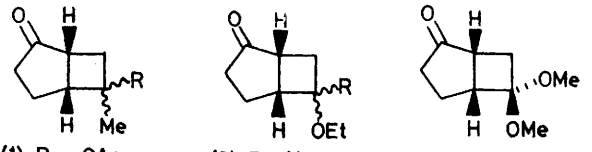
All photoreactions were achieved by selective irradiation in the region of the $n \longrightarrow \pi^*$ band of cyclopent-2-enone

[1] For reviews see *e.g.* P. E. Eaton, *Accounts Chem. Res.*, 1968, **1**, 50; P. G. Bauslaugh; *Synthesis*, 1970, **2**, 287; P. de Mayo, *Accounts Chem. Res.*, 1971, **4**, 41; W. C. Herndon, *Chem. Rev.*, 1972, **72**, 157; W. C. Herndon, *Fortschr. Chem. Forsch.*, 1974, **46**, 141; K. N. Houk, *Accounts Chem. Res.*, 1975, **8**, 361; S. M. Ali, T. V. Lee, and S. M. Roberts, *Synthesis*, 1977, **3**, 155.

[2] E. A. Hill, R. J. Theissen, C. E. Cannon, R. Miller, R. B. Guthrie, and A. T. Chen, *J. Org. Chem.*, 1975, **41**, 1191.

[3] E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, 1964, **87**, 5570.

(0.1—0.5 M). The alkenes were employed in a 20-fold excess and contained at least one substituent attached to the double bond by means of a singly bonded oxygen atom. They were of the vinyl ester type (1-acetoxy-1-methylethylene) or the vinyl ether type (1-ethoxyethylene,[3] and 1-ethoxy-1-ethylthioethylene). The cycloadducts formed are referred to as compounds (1)—(5) (Scheme 1; only the head-to-tail isomers are shown).



SCHEME 1

Very clean reactions were observed; as the ring fusion is always *cis*,[3] four stereoisomers may be produced: head-to-head (*HH*) or head-to-tail (*HT*) and *syn* or *anti*.*

The regioisomers were readily distinguished by analysis of the c.i.m.s. data.[4,5] The nearly exclusive fragmentation pathway of the *HH* isomers is a formal $[_{\pi}2 + _{\pi}2]$ cycloreversion process; the protonated cyclopent-2-enone (*m/e* 83) [ion (*c*)] is formed as well as the protonated alkene species [ion (*d*)]. The fragmentation is rationalized in Scheme 2. Compound *HH*-(4) gives upon protonation a quasi-molecular ion [QM^+; ion (*a*)], which exists in several forms, ion (*b*) being the most stable structure with carbenium ion character. Heterolytic cleavage of the 5,6-bond produces ion (*c*), and homolytic scission of the same bond with hydrogen migration, probably from C-4, yields ion (*d*). In Table 1 the relative intensities of the fragment ions (*c*) + (*d*), the ions (*f*), and the ions (*a*) for compounds (1)—(5) are given; the value of the ratio of intensities %[(*c*) + (*d*)]/%(*a*) is larger than unity for *HH* and smaller than unity for *HT* compounds. Case (1) is exceptional because acetic acid is very easily lost from ion (*a*).

In general, the loss of a small, stable molecule HY (see footnote *b*, Table 1) *via* ion (*e*) is the preferred fragmentation pathway in the c.i. mass spectra of the *HT* series (Scheme 2). The cycloreversion process has a lower probability, because the contribution of form (*b'*) is decreased. This is also reflected by the higher abundances of ions (*a*) for compounds (2) and (3) (Table 1).

The validity of this reasoning is proved by acidic hydrolysis of the main cycloadduct (5) (*HT*, 99.9%), affording *cis*-bicyclo[3.2.0]heptane-2,6-dione, which was fully characterized by spectroscopic data (see Experimental section).

The *syn* or *anti* sterochemistry could also be deduced from comparison of the c.i.m.s. data of the *HH* and the *HT* isomers. Some distinct differences are related to the *syn*- or *anti*-position of the main substituent. The *syn*-isomers must have more intense QM^+ peaks and correspondingly have a lower probability of expelling HY (see footnote *b*, Table 1). Indeed, for the *syn*-isomers, the proton transferred in c.i. can be co-ordinated between the carbonyl function and the oxygen atom in the ester or ether group. This is impossible for the *anti*-isomers, which consequently show an increased tendency to lose neutral HY molecules. The abundances of QM^+ happen to be the same in the HT series of compound (2); however the large difference in abundance of the ion at *m/e* 123 [($QM^+ - CH_3OH$); 89 *vs.* 4] allows the assignment to be made.

TABLE 1

Properties of cycloadducts

Compound	G.l.c. *k'* values (%) [a]	Ions (*c*) (*m/e* 83) + (*d*)(total %)	Ions (*f*) [= ion (*a*) − HY [b]] (%)	Ions(*a*)(%)	Assignment
(1)	9.3 (12.7)	83 + 101 (11)	123 (100)	183 (47)	*anti HH*
	10.7 (57.5)	(5)	(100)	(80)	*syn HT*
	11.2 (5.2)	(46)	(100)	(91)	*syn HH*
	11.5 (24.6)	(1)	(100)	(56)	*anti HT*
(2)	1.2 (1.0)	83 + 73 (131)	123 (46)	155 (53)	*syn HH*
	1.3 (0.5)	(146)	(13)	(14)	*anti HH*
	1.5 (87.0)	(41)	(89)	(100)	*anti HT*
	1.7 (11.5)	(11)	(4)	(100)	*syn HT*
(3)	7.7 (8.0)	83 + 73 (179)	109 (2)	155 (2)	*syn HH*
	8.1 (11.8)	(156)	(2)	(0.5)	*anti HH*
	8.5 (28.4)	(5)	(5)	(100)	*syn HT*
	8.9 (51.8)	(5)	(100)	(75)	*anti HT*
(4)	1.3 (100)	83 + 133 (22)	169 (80)	215 (4)	*syn HT*
			153 (100)		
(5)	2.0 (0.1)	83 + 89 (190)	139 (23)	171 (13)	*HH*
	2.2 (99.9)	(0)	(100)	(2)	*HT*

[a] Details in the Experimental section. [b] HY = AcOH for (1); EtOH for (3) and (4); MeOH for (2) and (5); and EtSH for (4).

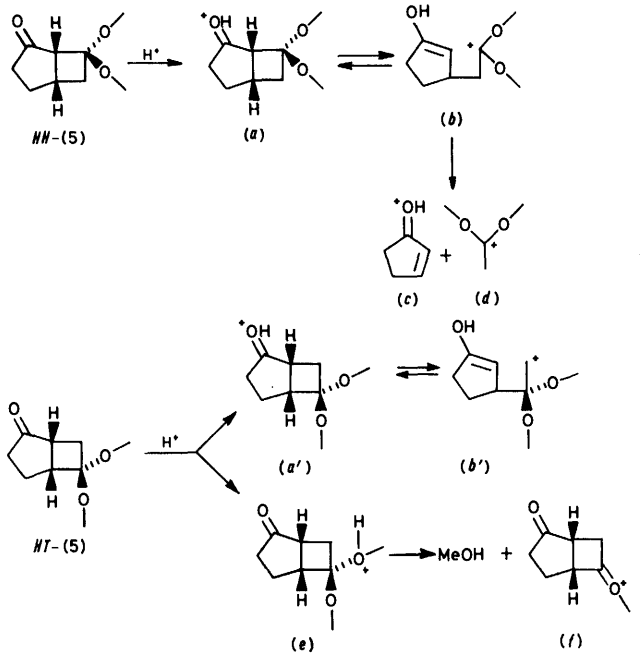
The structures were confirmed by the chemical reaction sequence depicted in Scheme 3. Reduction of (5) by borohydride, subsequent hydrolysis, and Grignard reaction produced only one diol, which, because of the preferred *exo*-attack, is most likely *syn,cis,syn*-bicyclo-[3.2.0]heptane-2,6-diol (6). The same compound is also obtained on reduction and hydrolysis of the main cyclo-

* *HH* refers to compounds in which the carbonyl function and the substituents are oriented in the same direction; *syn* means that the substituent with highest Sequence Rule priority is turned inwards with respect to the bicyclic system.

[4] H. Ziffer, H. M. Fales, G. W. A. Milne, and F. H. Field, *J. Amer. Chem. Soc.*, 1970, **92**, 1597.

[5] D. Termont, F. Van Gaever, D. De Keukeleire, M. Claeys, and M. Vandewalle, *Tetrahedron*, in the press.

adduct (1) (57.5% of the total reaction mixture). This chemical inter-relationship establishes the *syn*-configuration of the acetoxy-function, which is in complete accordance with c.i.m.s. analysis.



SCHEME 2

On the basis of the above-mentioned considerations, the *HT*/*HH* and the *anti*/*syn* compositions (Table 2) for

TABLE 2

Regio- and stereo-selectivity, and quantum yields

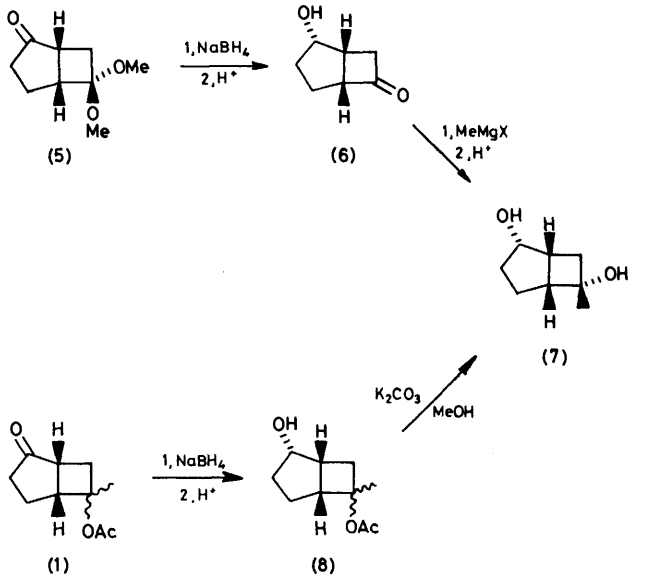
Compound	$\frac{HT}{HH}$ (%)	*anti*/*syn* (%)	[ϕ]
(1)	82.1/17.9	37.3/62.7	0.19
(2)	98.5/1.5	87.5/12.5	0.23
(3)	80.2/19.8	63.6/36.4	0.24
(4)	100/0	0/100	0.54
(5)	99.9/0.1		0.29

the cycloadditions studied can be determined from integration of g.l.c. peaks (for details see Experimental section). The quantum yields (see Experimental section) and chemical yields are high enough for efficient preparative-scale reactions to be carried out.

Table 2 shows that the regioselectivity parallels the π-electron-donating capability of the alkene. The *HT* regioselectivity observed with these electron-rich alkenes completes the picture of [$_{\pi}2 + {}_{\pi}2$] cycloadditions of the type studied. Indeed, *HH* regioselectivity has been found in cycloaddition reactions with electron-deficient double bonds such as in cyanoalkenes.[6,7]

The stereoselectivity on the other hand is related to subtle steric effects of the groups attached to the alkene. The difference in spatial interactions between an acetoxy- (1) or a methoxy-group (2) and a methyl group is well reflected by our data. Steric factors associated with an ethoxy- *vs.* an ethylthio-function are still more pronounced and, as a consequence, compound (5) is obtained in a fully stereospecific way. Since no trace of isomeric species was detected by g.l.c., the sole product formed in high quantum yield must be the *HT* cycloadduct carrying the ethoxy-group in the *syn*-position. Our results can be very well interpreted in terms of the Corey mechanism.[3] Since in the $n \longrightarrow \pi^*$ excited state of cyclopent-2-enone, which is the reactant state in this sort of reaction,[1,3,8] C-3 is quite negative relative to C-2,[3] the nucleophilic centre of the substituted alkene is preferentially oriented towards C-2 in initial complex formation. Hence, the more nucleophilic the alkene, the better is the regioselectivity. The possibility of free rotation [9] of the 1,4-diradical after collapse of the π-complex determines ultimately the stereoselectivity in formation of the *cis*-fused bicyclo[3.2.0]heptan-2-one derivative. This depends of course on steric differences between the substituents on the double bond.

Conclusion.—The orientational selectivity in the photocycloaddition of electron-rich alkenes to cyclopenten-2-one can be well controlled by appropriate choice of alkene substituents. When *gem*-disubstituted



SCHEME 3

alkenes are used, the highest degree of specificity is observed with substituents which are strong π-donors and which are sterically sufficiently differentiated.

EXPERIMENTAL

U.v. spectra were taken with a Cary 15 spectrophotometer and i.r. spectra with a Perkin-Elmer 337 instrument. ^{1}H n.m.r. spectra were obtained with Varian HA-60, EM-390, or HR-300 spectrometer (Me_3Si as internal reference), c.i. mass spectra with a Finnigan 3000 spectrometer (reactant

[6] R. Gompper, *Angew. Chem. Internat. Edn.*, 1969, **8**, 312.
[7] K. N. Houk and L. L. Munchausen, *J. Amer. Chem. Soc.*, 1976, **98**, 937.
[8] P. de Mayo, J. P. Pete, and M. F. Tchir, *Canad. J. Chem.*, 1968, **46**, 2535.
[9] W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *J. Amer. Chem. Soc.*, 1970, **92**, 1399.

gas isobutane; chamber pressure 1 atm; source temperature 120 °C), and e.i. (electron impact) mass spectra with a CEC 21–104 spectrometer.

G.l.c. analyses were performed with a Varian 1 200 gas chromatograph, equipped with either a 3 m 3% OV_1 column (A; i.d. 3 mm), a 3 m 15% Carbowax column (B; i.d. 3 mm), or a 100 m 5% SE-30 capillary column (C; i.d. 0.5 mm) (flame ionization detection in all cases). The flow rate of the carrier gas (N_2) was 3 ml s^{-1} (A,B) or 20 ml s^{-1} (C). Separations were performed isothermally at 150 °C (A), 200 °C (B), or 120 °C (C). Peak areas evaluated by the triangulation, and k' values were obtained on column A for compounds (1) and (2), on column B for compound (6), and on column C for compounds (3)—(5). All quantum yields were determined by ferrioxalate actinometry.[10]

General Irradiation Procedure.—Selective irradiation in the region of the $n \longrightarrow \pi^*$ band of cyclopent-2-enone was achieved at 366 nm in a Rayonet photoreactor or with light from a 450 W medium-pressure Hanovia lamp, filtered through Pyrex, in pentane solution. The concentrations employed were typically 0.1—0.5M of cyclopent-2-enone and a 20-fold excess of alkene. The reactions were monitored by t.l.c. (20—25 h). The reaction mixtures were fractionated by distillation. The fractions containing the photoadducts were analysed by g.l.c. and identified by spectroscopic techniques.

Preparation of the Reactants.—Cyclopent-2-enone was prepared by the method of Garbisch.[11] 1-Acetoxy-1-methylethylene (Fluka) and 1-ethoxyethylene (Aldrich) were distilled prior to use. 1-Methoxy-1-methylethylene was prepared by a modification of the procedure of Ansell and Gadsby.[12] The mixture from pyrolysis of 2,2-dimethoxypropane was collected over anhydrous K_2CO_3; distillation then gave the desired product; b.p. 33 °C (1 atm); yield 50%; δ (CCl_4; 60 MHz) 1.78 (3 H, s) 3.5 (3 H, s), and 3.8 (2 H, s). 1,1-Dimethoxyethylene was obtained by Corey's method,[3] and 1-ethoxy-1-ethylthioethylene as described in Houben-Weyl.[13]

Identification of the Cycloadducts (1)—(5).—6(7)-Acetoxy-6(7)-methylbicyclo[3.2.0]heptan-2-one (1) had b.p. 70—80 °C at 0.15 mmHg; R_F 0.44 in EtOAc–iso-octane (70 : 30); yield 65% (Found: C, 64.9; H, 7.65. Calc. for $C_{10}H_{14}O_3$: C, 65.35; H, 7.7%); $\nu_{max.}$ 3 000m, 1 740s, 1 370m, 1 260s, 1 150m, and 1 020m cm^{-1}. The methoxy-analogue (2) had b.p. 70 °C at 12 mmHg; R_F 0.57 in EtOAc; yield 65% (Found: C, 69.45; H, 9.0. Calc. for $C_9H_{14}O_2$: C, 70.1; H, 9.1%); $\nu_{max.}$ 3 480w, 2 980s, 2 840m, 1 745s, 1 275s, 1 230s, 1 105s, and 1 060s cm^{-1}. The ethoxy-derivative (3) had b.p. 70 °C at 12 mmHg; R_F 0.6 inEtOAc; yield 60% (Found: C, 69.50; H, 9.25. Calc. for $C_9H_{14}O_2$: C, 70.05; H, 9.1%); $\nu_{max.}$ 2 980s, 2 880s, 1 735s, and 1 110s cm^{-1}. The ethoxyethylthio-derivative (4) had b.p. 80 °C at 0.01 mmHg (decomp.) after purification by column chromatography (silica gel; EtOAc–iso-octane, 60 : 40); yield 55%; R_F 0.67 in EtOAc (Found: C, 61.5; H, 8.35. Calc. for $C_{11}H_{18}O_2S$: C, 61.7; H, 8.4%); $\nu_{max.}$ 3 000s, 1 740s, 1 260m, and 1 100m cm^{-1}; δ(CCl_4; 90 MHz) 1.18 (1 H, m), 1.28 (6 H, t, J 7 Hz), 1.6—3 (9 H, m), and 4.23 (2 H, q, J 7 Hz). The dimethoxy-derivative (5) had b.p. 104 °C at 12 mmHg; m.p. 28—29 °C; R_F 0.55 in EtOAc; yield 65% (Found: C, 63.25; H, 8.05. Calc. for $C_9H_{14}O_3$: C, 63.55; H, 8.25%); $\nu_{max.}$ 2 970s, 2 835m, 1 740s, 1 145s, and 1 045s cm^{-1}; δ (C_6H_6; 300 MHz) 1.35—1.52 (1 H, m), 1.87—2.04 (3 H, m), 2.22—2.48 (3 H, m), 2.63 (1 H, m), 2.82 (3 H, s), and 2.86 (3 H, s).

Bicyclo[3.2.0]*heptane-2,6-dione.*—To a solution of the dimethoxy-ketone (5) (0.229 g, 0.134 mol) in ether (0.25 ml) was added sulphuric acid (0.01 ml; 1.5%). After stirring for 20 min, the mixture was extracted with ether. Evaporation left a residue, which was chromatographed on silica gel with EtOAc–iso-octane (60 : 40) (R_F 0.54) to give the *diketone* (0.015 g, 89%) (Found: C, 66.95; H, 6.45. $C_7H_8O_2$ requires C, 67.7; H, 6.45%); $\lambda_{max.}$ (pentane) 288 nm (ε 29); $\nu_{max.}$ 2 980w, 1 785s, and 1 740s cm^{-1}; δ(C_6H_6; 300 MHz) 1.18 (1 H, m, ^1J 13, ^2J 11, 9.2, and 9.2 Hz), 1.62 (1 H, m, ^1J −13, ^2J 11, 9, and 9 Hz), 1.70 (1 H, m, ^1J −18, ^2J 11, and 9, ^3J 2.8 Hz), 1.85 (1 H, m, ^1J −18, ^2J 11, and 9.2, ^3J 0.4 Hz), 2.22 (1 H, 8 lines, ^2J 10.5, 7.4, and 4.3, ^3J 0.4 Hz), 2.38 (1 H, 8 lines, ^1J −18, ^2J 4.3, ^3J 3.4 Hz), 2.79 (1 H, 8 lines, ^1J −18, ^2J 10.5, ^3J 3.6 Hz), 2.97 (1 H, m, ^2J 9.2, 9, and 7.4, ^3J 3.6 and 3.4 Hz) (the J value of 7.4 Hz between the bridgehead H atoms is indicative of *cis* geometry [9]); *m/e* (e.i.) 39 (100%) and 124 (1%, $M^{+\cdot}$).

6-*Methylbicyclo*[3.2.0]*heptane-2,6-diol* (7).—(i) (a) *Reduction of the adduct* (5). Sodium borohydride (0.2014 g, 0.016 mol) was added to the adduct (5) (0.9 g, 0.0106 mol) in dioxan (20 ml) and 2M-potassum dihydrogen phosphate (20 ml). The mixture was stirred for 30 min and acidified (2.4N-HCl), the dioxan was evaporated off, the water layer was extracted (3 ×) with ether, and the combined ether layers were dried ($MgSO_4$), filtered, and evaporated. The hydroxy-ketone (6) was purified by column chromatography (silica gel; EtOAc; R_F 0.34); yield 67% (0.045 g); $\nu_{max.}$ 3 460m, 2 970m, 1 780s, and 1 060m cm^{-1}; δ(CCl_4; 300 MHz) 1.60 (2 H, m), 1.90 (1 H, m), 1.97 (1 H, m), 2.47 (1 H, s), 2.80 (1 H, m), 2.86 (1 H, 8 lines), 303 (1 H, 8 lines), 3.43 (1 H, m), and 4.39 (1 H, m, ^2J 9.2 Hz indicating a *cis*-orientation with respect to the bridgehead hydrogen atom [11]); *m/e* (e.i.) 39 (100%) and 108 (8%, $M^{+\cdot}$). G.l.c. analysis of the trimethylsilyl ether on column A at 120 °C showed only one main peak (98%).[14]

(b) *Grignard reaction of the hydroxy-ketone* (6). Compound (6) (0.2 g, 0.0016 mol), dissolved in a minimal quantity of tetrahydrofuran, was added to methylmagnesium bromide [from magnesium (0.116 g, 0.048 g atom)] in tetrahydrofuran. After 30 min the mixture was poured into ice–water and acidified (2.4N-HCl), and the tetrahydrofuran was evaporated off prior to extraction with ether. The extract was evaporated after drying ($MgSO_4$) and the residue was eluted with EtOAc through a silica gel column yielding the *diol* (7) (R_F 0.2) (0.180 g, 79%) (Found: C, 67.65; H, 9.85. $C_8H_{12}O_2$ requires C, 67.6; H, 9.85%); $\nu_{max.}$ 3 400s, 2 970s, 2 880s, 1 070m, and 1 055m cm^{-1}; δ(CCl_4; 90 MHz) 1.3 (3 H, s), 1.5—2.2 (6 H, m), 1.5—2.7 (2 H, s), 2.3—2.6 (2 H, m), and 4.3 (1 H, m).

(ii) (a) *Reduction of the adduct* (1). This was carried out as for the preparation of (6) with compound (1) (0.96 g, 0.0053 mol) and $NaBH_4$ (0.02014 g, 0.0106 mol); the yield of hydroxy-ester (8) was quantitative; $\nu_{max.}$ 3 500s, 2 980s, 1 750s, 1 380m, 1 260s, 1 080m and 1 055m; *m/e* (e.i.) 43 (100%) (no $M^{+\cdot}$).

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[11] E. W. Garbisch, jun., *J. Org. Chem.*, 1965, **30**, 2109.
[12] M. F. Ansell and B. Gadsby, *J. Chem. Soc.*, 1958, 3388.
[13] Houben-Weyl, Sauerstoffverbindugen II, Teil, 4, p. 427, Thieme Verlag, Stuttgart, 1968.
[14] T. Svensson, *Chemica Scripta*, 1973, **3**, 171.

(b) *Hydrolysis of the hydroxy-ester* (8). Compound (8) (0.970 g, 0.00527 mol) was stirred with anhydrous potasium carbonate (1.822 g, 0.0132 mol) in dry methanol (3 ml) during 3 h; methanol was evaporated off and water was added to the residue. Extraction of the water layer with ether, drying of the extract ($MgSO_4$), filtration, and removal of the solvent, left an isomeric mixture (7). The main compound (78%) was shown by g.l.c. (column B) to be identical with the diol (7) obtained from (5) [k' 10.5 in both cases; only the g.l.c. peak with k' 10.5 in the mixture increases on addition of pure diol (7) obtained from (5)].

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