

Alkylation of 3,4-Methylenedioxyphenol with 1-Bromo-3-methylbut-2-ene and Catalytic Rearrangement of the Resulting Ethers

By Paolo Piccardi,* Silvana Marcaletti, Ennio Bianchini, and Luigi Abis, Montedison S.p.A., Istituto Ricerche Donegani, Via G. Fauser 4, 28100 Novara, Italy

Sodium and potassium 3,4-methylenedioxyphenolates have been alkylated with 1-bromo-3-methylbut-2-ene in a variety of solvents. Not only the products of *O*- and *C*-monoalkylation but also products of dialkylation have been obtained. In the *C*-alkylation products both 3-methylbut-2-enyl compounds and their 1,1-dimethylprop-2-enyl isomers were found. Factors which may influence the reaction course are discussed briefly. The rearrangement of 1-(3-methylbut-2-enyloxy)-3,4-methylenedioxybenzene (3) in decalin in the presence of zinc chloride gave largely 2-(3-methylbut-2-enyl)-4,5-methylenedioxyphenol (4) and 2,3-dihydro-2,2,3-trimethyl-5,6-methylenedioxybenzofuran (11). Similarly, 1-(3-methylbut-2-enyl)-2-(3-methylbut-2-enyloxy)-4,5-methylenedioxybenzene (7) yielded the phenol (4) and 2,6-bis-(3-methylbut-2-enyl)-3,4-methylenedioxyphenol (10).

A WIDE variety of phenolic natural products contain isoprenoid or polyisoprenoid chains.¹ Interest in the insertion of isoprene units into phenolic systems has increased in recent years; studies have been reported on the acid-catalysed reactions of prenyl alcohols² or prenyl halides³ with phenols. Although phenoxide ions have been widely studied⁴ in reactions with allylic halides, little is known of the orientation in condensations with prenyl halides.⁵ We now report our findings on the alkylation of 3,4-methylenedioxyphenol (1) with 1-bromo-3-methylbut-2-ene (2). This reaction is of interest in relation to ambident anion behaviour as well as for synthetic purposes. Some methylenedioxyphenyl terpenoid ethers possess significant juvenile hormone activity on several insect species.⁶

¹ W. D. Ollis and I. O. Sutherland, in 'Chemistry of Natural Phenolic Compounds,' ed. W. D. Ollis, Pergamon, Oxford, 1961, p. 74.

² R. J. Molineux and L. Jurd, *Tetrahedron*, 1970, **26**, 4743.

³ A. Pochini, R. Marchelli, and V. Bocchi, *Gazzetta*, 1975, **105**, 1245, and references cited therein.

The results of alkylation of the sodium and potassium salts of sesamol (1) with prenyl bromide (2) in solvents of differing polarity are shown in Table 1. From the products we isolated the monoprenylated derivatives (3)—(6) and the diprenylated derivatives (7)—(10). Mixtures were analysed by g.l.c. under conditions which did not permit rearrangement of isomers. The products reported were isolated pure and their structures established by elemental analysis and spectroscopic methods (see Experimental section). Compounds (3)—(10) were stable under the reaction conditions; no inter-conversion was detected. When an acidification step was used in the work-up, ring closure of the phenol (4) easily occurred to give the chroman (6).

Scheme 1 shows the reaction sequences which we believe account for the formation of all the products.

⁴ W. J. Le Noble, *Synthesis*, 1970, 1.

⁵ S. Yamada, F. Ono, T. Katagiri, and J. Tanaka, *Synth. Comm.*, 1975, **5**, 181, and references cited therein.

⁶ W. S. Bowers, *Mitt. schweiz. entomol. Ges.*, 1971, **44**, 115.

The ratio of *O*- to *C*-alkylation increases along the solvent series benzene < methanol \approx tetrahydrofuran < ethyl methyl ketone < dimethyl sulphoxide \approx dimethylformamide < hexamethylphosphoramide. Our results parallel earlier studies⁴ of medium effect on ambident anion

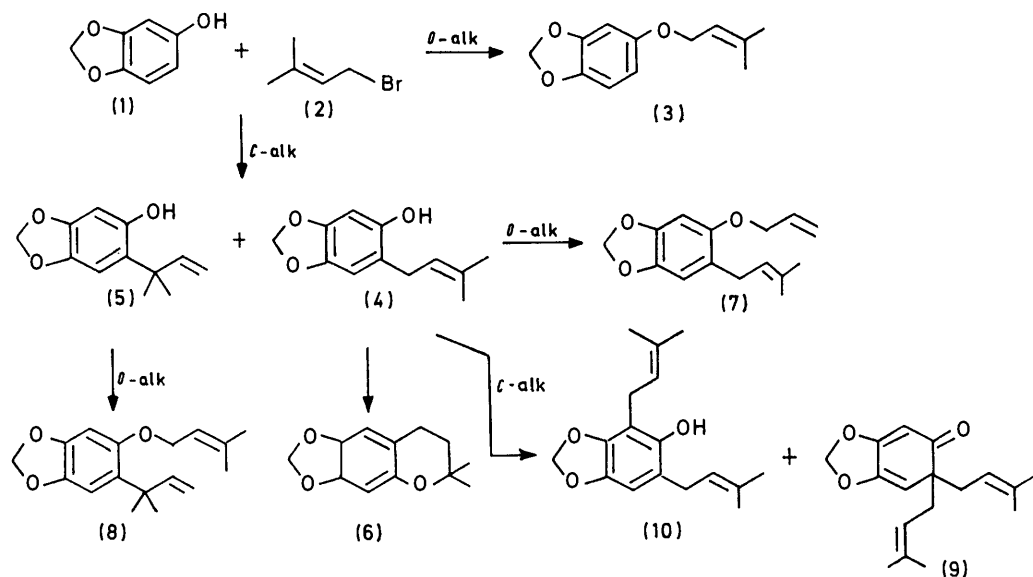
dienone (9). The coumaran (11) presumably arises by protonation of the intermediate phenol (5) and subsequent cyclisation in which phenonium ions participate (Scheme 2).

We have examined the possibility of obtaining the

TABLE I
Reactions of the phenol(1) with 1-bromo-3-methylbut-2-ene (2)

Reactants (mmol)		Solvent † (v/ml)	NaH (mmol)	K ₂ CO ₃ (mmol)	Time (h)	Temp. (°C)	Composition (mol%) of recovered products											O-Alkylation (%)
(1)	(2)						(1)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)		
14.5	20				3	55	11											5.5
14.5	20	HMPA (30)	15		4	18		98										98
14.5	20	DMSO (30)	15		4	18		88										89
14.5	20	DMSO (30)		14.5	48	35	43	49	3	1			10	0.4				86
14.5	20	DMF (30)	15		4	18		87	Trace	1			11.5	0.3	Trace			89
14.5	20	DMF (30)		14.5	48	35		91		2			7					92
14.5	20	EMK (30)	15		52	50		69		2			27					74
14.5	20	EMK (30)		14.5	52	50		82		2	0.5		15	Trace			0.5	84
14.5	22	THF (30)	15		52	50		46	2.5	0.5			36.5		14			55
14.5	20	THF (30)		14.5	52	50		50	26	2	0.5		15	1.5				55
14.5	20	MeOH (30)	15		52	50		34	32	21	1		10	Trace				54
14.5	20	MeOH (30)		14.5	52	50		14.5	36	22.5	5.5		8.5	Trace			13	42
29	40	C ₆ H ₆ (30)	30		52	80			0.5	49	4		1	6.5			11	6
14.5	20	C ₆ H ₆ (30)		14.5	52	80			Trace				96	1.5	2.5			1

† Hexamethylphosphoramide (HMPA), dimethylformamide (DMF), dimethyl sulphoxide (DMSO), ethyl methyl ketone (EMK), tetrahydrofuran (THF), methanol (MeOH), or benzene (C₆H₆).



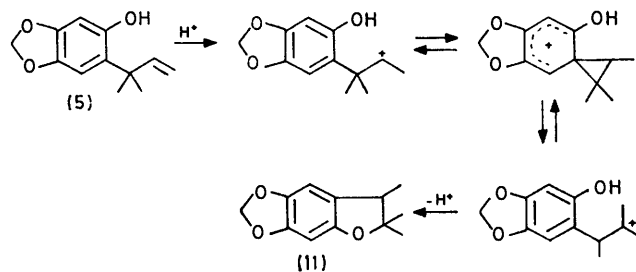
SCHEME 1

behaviour: the use of more highly basic aprotic solvents tends to promote *O*-alkylation.

The presence of the phenol (5) provides good evidence that in this case the *C*-alkenylation is not a simple S_N2 reaction and that the transition state possesses a high degree of S_N1 character. The formation of the phenol (5) could be expected also in the case of an S_N2' reaction; however the probability of such a mechanism is extremely small in view of the absence of steric hindrance at the α -position of the allylic bromide (2).

When compound (1) and prenyl bromide were heated at 55 °C under nitrogen in the absence of solvent and alkali, some starting phenol (1) was recovered and four products were separated. The major compound, formed in 80% yield, was the chroman (6); there was also isolated 11% of 2,3-dihydro-2,2,3-trimethyl-5,6-methylenedioxybenzofuran (11), 6% of compound (8) and 3% of the

phenol (5) by heating the ether (3) in decalin. However, compound (3) was thermally stable, being unchanged after 12 h at 200 °C.

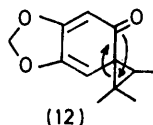


SCHEME 2

The ether (3) was smoothly isomerised by use of a catalytic amount of zinc chloride in decalin at 195 °C,

giving a mixture of the phenol (4), sesamol (1), the chroman (6), and the coumaran (11) in 74% yield after 3 h. The yield was not substantially increased by further heating. The structure of the allylic side chain of the phenol (4) formed suggests the occurrence of an intermolecular process, involving prenyl cations as alkylating agents.

The product (11) could be formed in various ways, possibly by sigmatropic rearrangements *via* the spirodienone (12) as reported by Schmid,⁷ or *via* the phenol (5) according to the pathway (Scheme 2) suggested above. Further information on the catalysed rearrangement of the ether (3) was provided by a similar reaction



with compound (7). When the ether (7) was heated in decalin in the presence of zinc chloride, a mixture of (4) and (10) in the ratio 1.14 : 1 was obtained, together with smaller quantities of two compounds having the same retention times as (8) and (11).

EXPERIMENTAL

Products were identified by elemental analysis, i.r. spectroscopy (Perkin-Elmer 257 spectrophotometer), ¹H n.m.r. spectroscopy (Bruker WH-90 instrument), and mass spectrometry (Varian MAT CH 5 spectrometer). Analytical g.l.c. was carried out with a glass column (2.4 m × 6.3 mm) packed (3%) with OV 17 on GasChrom Q (80–100 mesh) (100–200 °C; 4 °C min⁻¹). T.l.c. was performed on Merck silica gel 60 F₂₅₄ in hexane-ether (19 : 1).

General Procedure for Alkylations.—The results of a set of experiments all carried out by the same procedure are collected in Table 1. The phenol (1) (14.5 mmol) and powdered calcined potassium carbonate or sodium hydride (14.5 mmol) in the anhydrous solvent (20 ml) were stirred under nitrogen. The prenyl bromide (2) (*ca.* 20 mmol) in the solvent (10 ml) was added dropwise and the mixture was heated to the temperature and for the period of time indicated in Table 1. The mixture was then poured into cold water (200 ml), neutralised if necessary, and extracted with diethyl ether. The extract was washed (water), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was analysed by g.l.c. (Hewlett-Packard 5711 dual column instrument) with, for quantitative determination, n-tetradecane as internal reference. Integration of peak areas was carried out with a Hewlett-Packard 3380-A instrument. The alkylation in the absence of solvent and alkali was carried out by heating compounds (1) and (2) in a stream of dry nitrogen.

Products.—1-(3-Methylbut-2-enyloxy)-3,4-methylenedioxybenzene (3) was obtained from a preparative scale run by fractional distillation (Found: C, 69.6; H, 6.8. C₁₂H₁₄O₃ requires C, 69.9; H, 6.85%); b.p. 106–108° at 0.3 mmHg; ν_{max.} 1 670 cm⁻¹ (C=C); *m/e* 206 (*M*⁺, 41%), 151(100), and 121(8). 2-(3-Methylbut-2-enyl)-4,5-methylenedioxyphenol (4) was obtained as a liquid from a preparative scale run by layer chromatography on silica gel (Found: C, 70.0; H, 6.9. C₁₂H₁₄O₃ requires C, 69.9; H, 6.85%); b.p. 128–130° at 0.2 mmHg; ν_{max.} 3 470 (OH) and 1 670 cm⁻¹ (C=C);

m/e 206 (*M*⁺, 40%), 189(48), and 151(100). 2-(1,1-Dimethylprop-2-enyl)-4,5-methylenedioxyphenol (5) was obtained as a liquid from a preparative scale run by layer chromatography; n_D²³ 1.539 8; ν_{max.} 3 470 (OH) and 1 630 cm⁻¹ (C=C); *m/e* 206 (*M*⁺, 100%), 191(98), 161(90), and 189(9). 2,2-Dimethyl-6,7-methylenedioxychroman (6) was obtained by preparative layer chromatography and crystallisation from hexane (Found: C, 69.9; H, 6.7. C₁₂H₁₄O₃ requires C, 69.9; H, 6.85%); 81–82 °C; ν_{max.} 1 370 and 1 380 cm⁻¹ (CMe₂); *m/e* 206 (*M*⁺, 81%), 151(100), 121(34); δ(CDCl₃) 1.27 (6 H, s, 2 × CH₃), 1.72 (2 H, t, *J* 6.5 Hz, 3-H₂), 2.64 (2 H, t, *J* 6.5 Hz, 4-H₂), 5.81 (2 H, s, O-CH₂-O), 6.31 (1 H, d, *J* 0.3 Hz, 8-H), and 6.48 (1 H, td, *J* 0.8 and 0.3 Hz, 5-H).

1-(3-Methylbut-2-enyl)-2-(3-methylbut-2-enyloxy)-4,5-methylenedioxybenzene (7) was prepared by the reaction of the phenol (4) (3.7 g, 17.9 mmol), sodium hydroxide (0.36 g, 15 mmol), and prenyl bromide (2) (2.98 g, 20 mmol) in HMPA for 4 h at 18 °C. The usual work-up gave a pale yellow oil which was purified by layer chromatography (4.4 g, 16 mmol, 89%) (Found: C, 74.6; H, 8.2. C₁₇H₂₂O₃ requires C, 74.45; H, 8.1%); n_D²³ 1.519 4; ν_{max.} 1 670 cm⁻¹ (C=C); *m/e* 274 (*M*⁺, 51%), 219(62), 203(27), and 163(100). 2-(3-Methylbut-2-enyloxy)-1-(1,1-dimethylprop-2-enyl)-4,5-methylenedioxybenzene (8) was obtained similarly from the phenol (5) and (2) in HMPA, giving an oil (90%) (Found: C, 74.5; H, 8.3. C₁₇H₂₂O₃ requires C, 74.45; H, 8.1%); n_D²³ 1.518 7; ν_{max.} 1 630 and 1 670 cm⁻¹ (C=C); *m/e* 274 (*M*⁺, 40%), 259(6), 205(23).

2,3-Dihydro-2,2,3-trimethyl-5,6-methylenedioxybenzofuran (11) was obtained as a liquid from a preparative scale run by layer chromatography on silica gel (Found: C, 70.1; H, 7.0. C₁₂H₁₄O₃ requires C, 69.9; H, 6.85%); b.p. 90–95° at 0.2 mmHg; ν_{max.} 1 370 and 1 385 cm⁻¹ (CMe₂); *m/e* 206 (*M*⁺, 99%), 191(100), and 161(83); δ(CDCl₃) 1.12 (3 H, d, *J ca.* 7 Hz, CHCH₃), 1.25 and 1.42 (6 H, s, CMe₂), 3.02 (1 H, q, *J ca.* 7 Hz, CHCH₃), 5.81 (2 H, s, O-CH₂-O), 6.32 (1 H, s, 7-H), and 6.57 (1 H, s, 4-H).

2,2-Bis-(3-methylbut-2-enyl)-4,5-methylenedioxy-cyclohexa-3,5-dienone (9) and 2,6-Bis-(3-methylbut-2-enyl)-3,4-methylenedioxyphenol (10).—The phenol (1) (4 g, 29 mmol) was added to a suspension of sodium hydride (2.78 g, 115.8 mmol) in anhydrous benzene (50 ml) under nitrogen. Prenyl bromide (2) (17.3 g, 116 mmol) was added dropwise, and the mixture was stirred at room temperature for 50 h. After dilution with water and extraction with ether, the organic layer was washed repeatedly with water, dried (Na₂SO₄), and evaporated to yield a liquid residue (6.8 g) shown by g.l.c. to contain compounds (3) (1.15 g, 5.6 mmol, 19%), (7) (1.07 g, 3.9 mmol, 13%), (9) (3.13 g, 11.4 mmol, 39%), and (10) (1.43 g, 5.2 mmol, 18%). The residue was chromatographed on silica. Elution with hexane-ether gave the *dienone* (9) (Found: C, 74.3; H, 8.0. C₁₇H₂₂O₃ requires C, 74.45; H, 8.1%), m.p. 86°; ν_{max.} 1 650 (C=O) and 1 615 cm⁻¹ (C=C); *m/e* 274 (*M*⁺, 2%), 206(53), and 151(100); δ(CDCl₃) 1.57 and 1.62 (12 H, m, CH₃), 2.21 and 2.53 (4 H, AB part of ABX, *J*_{AX} = *J*_{BX} = 7.2, *J*_{AB} 13.8 Hz, CH₂), 4.91 (2 H, X part of ABX, CH₂-CH=), 5.41 (1 H, d, *J* 0.5 Hz, 6-H), 5.59 (1 H, d, *J* 0.5 Hz, 3-H), and 5.80 (3 H, s, O-CH₂-O); and the *phenol* (10) (Found: C, 74.5; H, 8.2. C₁₇H₂₂O₃ requires C, 74.45; H, 8.1%), m.p. 49–50°; ν_{max.} 3 470 (OH), and 1 670 cm⁻¹ (C=C); *m/e* 274 (*M*⁺, 60%), 257(35), 219(38), and 163(100).

⁷ F. Scheinmann, R. Barner, and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1603.

Rearrangement of the Ether (3).—The rearrangement was carried out in decalin with a catalytic amount of zinc chloride at 195 °C. No reaction occurred on heating (3) alone at 195 °C for 12 h in decalin. Compound (3) (1 g,

retention times and weight/area factors. The results are listed in Table 2.

Rearrangement of the Ether (7).—The ether (7) (1 g, 3.64 mmol) was heated in the presence of zinc chloride (20 mg) under reflux in decalin (20 ml) in an atmosphere of nitrogen for 3.5 h. The mixture was shown by g.l.c. to contain (wt %) component (4) (39%), (8) (7%), (10) (47%), and (11) (7%). The mixture was separated by layer chromatography to give compounds (4) (0.208 g, 1.36 mmol, 37%) and (10) (0.327 g, 1.19 mmol, 33%).

N.m.r. Spectra.—N.m.r. chemical shifts and coupling constants of compounds (1), (3)—(5), and (7)—(9) are listed in Supplementary Publication No. SUP 21957 (3 pp.).*

[6/1569 Received, 10th August, 1976]

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

TABLE 2

Rearrangement of the ether (3) at 195 °C

Reaction time (h)	Products (wt %)				
	(1)	(3)	(4)	(6)	(11)
0.5	6.5	45	24	6.5	18
1.5	7	33	25	7.5	27.5
3.5	7	24.5	24.5	8	36

4.8 mmol) and zinc chloride (20 mg) in decalin (20 ml) were heated under reflux for 3.5 h in an atmosphere of nitrogen. The reaction was monitored by quantitative g.l.c. analysis, having previously obtained characteristic