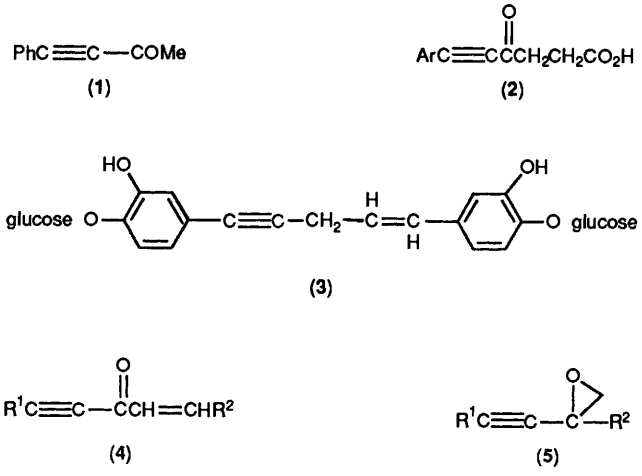
Reactivity and Reactions of Aromatic Acetylenic Acids and Ketones

Siegfried E. Drewes,* Deborah Douglass, Dean G. S. Malissar, Gregory H. P. Roos, and Perry T. Kaye†
Chemistry Department, University of Natal, PO Box 375, Pietermaritzburg 3200, South Africa

Some novel reactions of the acetylenic carboxylic acid, 4-oxo-6-phenylhexynoic acid with succinic anhydride are described. One of the products of the reaction is a butyrolactone derivative. Transformation of 4-phenylbut-3-yn-2-one results in the formation of α,β-acetylenic-α'-alkoxy epoxides which are of interest as anti-tumour compounds.

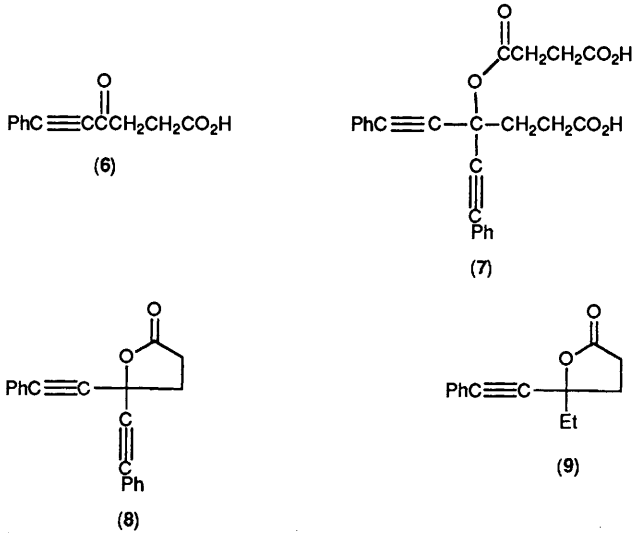
The pharmacological properties of acetylenes (anti-bacterial, anti-cancer) have long been of interest. This is exemplified by the numerous papers of Bohlmann,[1] and others,[2,3] on the subject. As far back as 1967 Schulte *et al.*[4] investigated the fungistatic and microbial effects of a wide range of acetylenic derivatives. These authors concluded that active, nonterminal acetylenes were characterised by the presence of an aromatic moiety coupled with an adjacent functionality such as a carbonyl group. Examples of acetylenes belonging to this category are the acetylenic ketone (**1**) and the acetylenic keto acid (**2**).

We,[5] and others,[6] have recently isolated the naturally occurring acetylene, named hypoxoside[6] (**3**), from natural sources and we have published a synthesis of the aglucone.[7] Our interest in this area includes the synthesis of analogues of the hypoxoside system. In particular two systems, exemplified by compounds (**4**) and (**5**), showed considerable promise in *in vitro* tests on various strains of cancer-cells.[8,9] Derivative (**5**) can be regarded as a masked prop-3-ynol derivative. We wish to describe here some interesting transformations which resulted from our attempts to prepare analogues related to compounds (**4**) and (**5**).



Results and Discussion

The first analogue, 4-oxo-6-phenylhex-5-ynoic acid (**6**) has been prepared previously by Nightingale and Wadsworth[10] in very low yield (21%). It has also been tested by Schulte[4] but our added interest lies in the fact that the presence of a carboxyl group should overcome the deficiency of most of our analogues—low solubility in aqueous buffers. Reaction of phenylethynylmagnesium bromide with succinic anhydride afforded a crystalline dicarboxylic acid accompanied by a similar quantity of the anticipated monocarboxylic acid (**6**).[10]

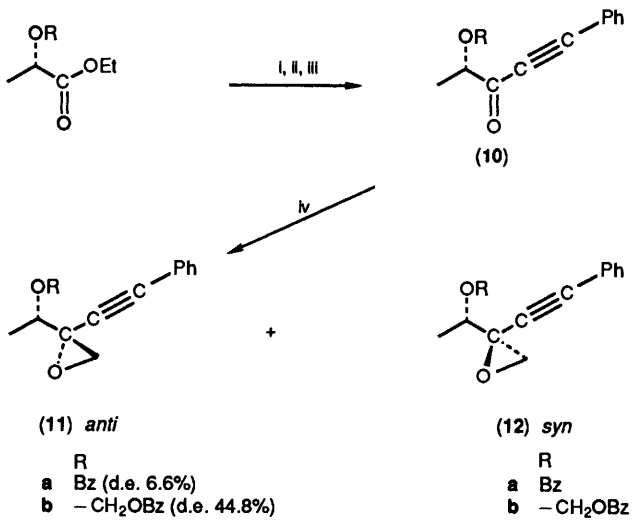


Based on the results of the X-ray analysis of a single crystal of the dicarboxylic acid (**7**) we confirm that aqueous Na_2CO_3 transformed acid (**7**) into lactone (**8**).

From the structure of acid (**7**) it is clear that the neutral transformation product is the butyrolactone (**8**) and this structure was confirmed by NMR spectroscopy. It is clearly formed by lactonisation of the tertiary alcohol which results from base hydrolysis of the ester side chain. Both compounds (**7**) and (**8**) are new compounds and represent interesting synthetic intermediates.

Since the butyrolactone ring found in compound (**8**) frequently occurs in natural products, and since we could obtain it in a respectable yield, we attempted the synthesis of related compounds. Our first aim was to increase the yield of acid (**6**) and, in a subsequent step, to treat it with a suitable nucleophile by attack at the 4-keto-position. However, for reasons not clear to us (but possibly connected with insolubility of intermediates) preparation of the substituted lactone by this procedure was unsuccessful. The only way in which a different (from phenylethynyl) substituent could be introduced at C-5 was to employ the 'one pot' procedure. This involved the addition of a second nucleophile, *e.g.* ethylmagnesium bromide to the reaction mixture after a period of time to give compound (**9**) as the minor product.

† *Present address:* Department of Chemistry, Rhodes University, Grahamstown, South Africa.



Scheme. *Reagents:* i, di-isobutylaluminium hydride; ii, $PhC{\equiv}C^{-}Mg^{+}Br$; iii, pyridinium dichromate; iv, $Me_2\overset{+}{S}-\bar{C}H_2$. Bz = benzyl, $PhCH_2$.

Our starting material for the second analogue, *i.e.* the masked prop-3-ynol (**5**), was the readily-available acetylenic ketone, 4-phenylbut-3-yn-2-one (**1**). By making use of Corey's[11] method, dimethylsulphanium methanide readily transformed the ketone into the corresponding epoxide in 70% yield. Encouraged by this result, we turned our attention to the synthesis of a similar system but possessing a chiral centre (Scheme).

The required ketones were synthesised by the oxidation of the prop-3-ynols synthesised *via* Burke's[12] recently-published procedure for the sequential addition of hydride ion and carbon nucleophiles to α-alkoxy esters. Since no metal chelating agent is present in the transformation of the chiral ketones into the corresponding epoxides, it can be assumed from the Felkin model[13] for asymmetric induction that the *anti*-isomer predominates. We believe that compounds (**11**) and (**12**) represent useful synthons and that higher chiral induction can be achieved by the use of bulkier alkoxy groups α to the chiral centre.

Experimental

M.p.s were measured on a Kofler hot stage apparatus and are uncorrected. NMR spectra were recorded on a Varian FT80A spectrometer and, unless specified otherwise, deuteriochloroform was used as solvent. Mass spectra were run on a Hewlett Packard HP 5988 gas chromatograph/mass spectrometer. Specific rotations were determined using an Atago Polax-D polarimeter.

4-Oxo-6-phenylhex-5-ynoic Acid (**6**) *and* 4,4-*Bis(phenylethynyl)-4-butanolide* (**8**).—Phenylethynylmagnesium bromide was generated from phenylacetylene (4.70 g, 0.05 mol), ethyl bromide (5.0 g, 0.05 mol) and magnesium metal (1.18 g, 0.05 mol) in tetrahydrofuran (THF) at −5 °C. The reaction mixture was warmed to 35 °C, kept at this temperature for 2 h, then cooled to −60 °C before the addition of succinic anhydride (4.6 g, 0.05 mol) in dry THF (10 ml) over 2 h. After 24 h at 25 °C the mixture was basified with sodium hydrogen carbonate, extracted with ethyl acetate, acidified with dil. HCl and extracted once again with ethyl acetate. Concentration under reduced pressure afforded a semi-crystalline solid (7.7 g). TLC (pentane–ethyl acetate, 6:4) showed the presence of two polar compounds, both of which had acidic properties.* (These could be separated by flash chromatography.) The combined extracts were suspended in aq.$Na_2CO_3{\cdot}10H_2O$ (12 g) and the mixture was stirred for 12 h. After 30 min a white crystalline solid began to form. After the reaction was complete the crystalline material (2.6 g) was filtered off and the filtrate was acidified with dil. HCl and then extracted with ethyl acetate. Concentration under reduced pressure afforded a crystalline residue (3.7 g) of acid (**6**) which was recrystallised from chloroform, m.p. 83 °C (lit.,[10] 81 °C); λ_{max} 2 200 (C≡C) and 1 708 cm^{-1} (CO); δ_H(80 MHz) 2.86 (2 H, m, CH_2), 3.01 (2 H, m, CH_2), 7.27–7.63 (5 H, m, Ar), and 10.18 (1 H, s, CO_2H); δ_C(20 MHz) 27.88 (t, $-CH_2CO_2H$), 39.69 (t, $-COCH_2$), 87.30 (s, Ar*C*≡), 91.82 (s, ≡*C*–CO), 119.64 (s, C-1′), 128.67 (d, C-4′), 130.92 (d, C-2′,6′), 133.09 (d, C-3′,5′), 178.17 (s, CO), and 185.34 (s, CO_2H); *m/z* 202 (M^+, 2%), 149 (3), 129 (100), and 101 (7).

The white crystalline solid above was recrystallised from ethyl acetate–hexane to give needles of 4,4-bis(phenylethynyl)-4-butanolide (**8**), m.p. 53 °C (Found: C, 83.6; H, 5.0. $C_{20}H_{14}O_2$ requires C, 83.90; H, 4.93%); λ_{max} 2 246 (C≡C) and 1 760 cm^{-1} (CO); δ_H(80 MHz) 2.82 (4 H, s, $-CH_2CH_2-$) and 7.25–7.57 (10 H, m, Ar); δ_C(20 MHz) 28.46 (t, CH_2CH_2CO), 38.87 (t, $-CH_2CO$), 72.10 (s, quat C), 85.08 (s, ≡CAr), 86.12 (s, *C*≡CAr), 121.13 (s, C-1 and C-1′), 128.46 (d, C-3′,5′ or C-2′,6′ and C-3″,5″ or C-2″,6″), 129.43 (d, C-4′ or C-4″), 132.10 (d, C-3′,5′ or C-2′,6′ and C-3″,5″ or C-2″,6″), and 174.80 (CO) (Found: M^+, 286.0991. $C_{20}H_{14}O_2$ requires M^+, 286.0994); *m/z* 286 (M^+, 43%), 241 (61), 202 (95), and 129 (100).

6-Phenyl-4-phenylethynyl-4-(3′-carboxypropanoyloxy)hex-5-ynoic Acid (**7**).—The initial semi-crystalline solid (above) was flash chromatographed to yield compounds (**6**) and (**7**). Using pentane–ethyl acetate (6:4) as eluant, the dicarboxylic acid (**7**) had an R_F value of 0.1 and the monocarboxylic acid (**6**) had an R_F value of 0.24. The former was obtained as white needles, m.p. 113 °C (pentane–ethyl acetate, 3:2) (Found: C, 72.1; H, 5.1. $C_{24}H_{20}O_6$ requires C, 71.28; H, 4.95%); λ_{max} 2 237 (C≡C), 1 748 cm^{-1} (C=O); δ_H(80 MHz) 2.68 (8 H, br s, 2 × CH_2CH_2), 7.22–7.47 (10 H, m, Ar), and 7.55 (2 H, br s, 2 × CO_2H); δ_C(20 MHz) 29.53 (t, CH_2), 29.69 (t, CH_2), 30.23 (t, CH_2), 38.89 (t, CH_2), 68.21 (s, quat C), 85.83 (s, alkyne), 86.32 (s, alkyne), 122.49 (s, C-1 and C-1′), 129.25 (d, C-3′,5′ or C-2′,6′), 129.87 (d, C-4 and C-4′), 132.51 (d, C-3′,5′ or C-2′,6′ and C-3″,5″ or C-2″,6″), 170.15 (s, ester), 174.00 (s, CO_2H), and 174.21 (s, CO_2H); *m/z* 286 [(M^+ − succinic acid), 90], 258 (73), 241 (81), 202 (100), and 129 (60). The X-ray structure of acid (**7**) is shown in Figure 1.

Methylation of acid (**7**) (600 mg) with diazomethane afforded the pure methyl ester (200 mg), after column separation, as a pale yellow oil; δ_H(80 MHz) 2.62–2.79 (4 H, m, 2 × CH_2), 2.94–3.12 (4 H, m, 2 × CH_2), 3.70 (6 H, s, 2 × OMe), and 7.34–7.64 (10 H, m, Ar).

4-Ethyl-4-phenylethynyl-4-butanolide (**9**).—Phenylethynylmagnesium bromide (0.05 mol) was prepared as above and kept at −60 °C under nitrogen. Succinic anhydride (5.00 g, 0.05 mol) in dry THF (40 ml) was then added dropwise over 30 min. After 4 h at −60 °C ethylmagnesium bromide (0.05 mol) in dry THF (5 ml) was added to the reaction mixture. After a further 2 h at −60 °C the temperature was raised to 25 °C, then the reaction mixture was quenched with 6M HCl and extracted with ethyl acetate. The combined extracts were

* By performing the reaction under nitrogen and allowing the reaction at room temperature (25 °C) to proceed for only 2 h before work-up, the monocarboxylic acid (**6**) was effectively the sole reaction product with an overall yield of 55%.

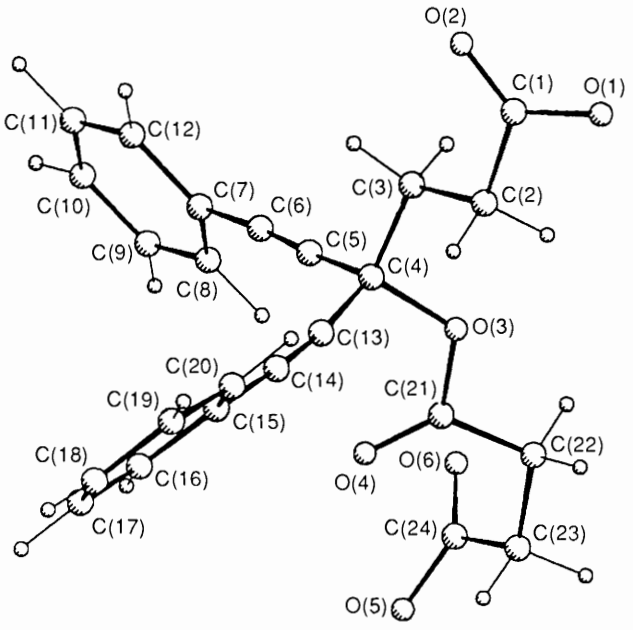


Figure 1. X-Ray structure of compound (**7**).

concentrated to a small volume and stirred with aq. Na_2CO_3 (12%; 50 ml) for 1 h. Extraction with ethyl acetate afforded a yellow oil which was chromatographed (silica gel) to afford 0.64 g of crystalline compound (**8**) (60%) and 0.43 g of compound (**9**) (30%) as an oil. (Found: C, 78.3; H, 6.70. $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.58%); δ_H(80 MHz) 1.16 (3 H, t, Me), 1.83–2.90 (6 H, m, 3 × CH_2), and 7.22–7.52 (5 H, m, Ar); δ_C(20 MHz) 8.73 (q, CH_3), 28.88 (t, $-CH_2$), 34.04 (t, CH_2), 34.89 (t, CH_2), 82.69 (s, quat C), 86.40 (s, ≡*C*Ar), 87.26 (s, *C*≡CAr), 121.71 (s, C-1′), 128.29 (d, C-2′,6′ or C-3′,5′), 128.83 (d, C-2′,6′ or 3′,5′), 131.67 (d, C-4′), and 175.91 (s, C=O); *m*/*z* 214 (M^+, 14), 185 (100), and 129 (14).

2-*Phenylethynyl*-2,3-*epoxypropane* (**5**; R^1 = Ph, R^2 = Me).[14]—A solution of NaH (0.833 g, 80% suspension in oil; 27.76 mmol) and DMSO (30 ml) was heated at 70–75 °C for 45 min under an atmosphere of nitrogen.[11] The solution was diluted with dry THF (30 ml) and cooled to −5 °C. The mixture was treated sequentially with trimethylsulphonium iodide (5.66 g, 27.76 mmol) in DMSO (60 ml) and dry THF (30 ml). After 5 min a solution of 1-phenylbut-1-yn-3-one (**1**)[15] (1.00 g, 6.94 mmol) in THF (5 ml) was added. Stirring was continued at −5 °C for 2 h. After 1 h at 25 °C the reaction mixture was poured into water (200 ml) and extracted with chloroform. Concentration of the extract under reduced pressure gave a residue which was purified by column chromatography to give a yellow oil (0.82 g, 75%) (Found: C, 83.8; H, 6.30. $C_{11}H_{10}O$ requires C, 83.51; H, 6.37%); δ_H(80 MHz) 1.59 (3 H, s, Me), 2.90 (2 H, dd, $-CH_2$), and 7.20–7.49 (5 H, m, Ar); δ_C(20 MHz) 22.88 (q, Me), 47.41 (s, quat C), 55.43 (t, CH_2), 81.89 (s, ≡*C*Ar), 88.49 (s, −*C*≡CAr), 122.03 (s, C-1′), 128.19 (d, C-3′,5′ or C-2′,6′), 128.52 (d, C-3′,5′ or C-2′,6′), and 131.81 (d, C-4′); *m*/*z* 158 (M^+, 51%), 127 (100), 102 (22), and 77 (49).

(S)-(−)-4-*Benzyloxy*-1-*phenylpent*-1-*yn*-3-*one*.—A solution of (*S*)-(−)-ethyl 2-benzyloxypropanoate[16] (2.00 g, 9.80 mmol) in dry THF (30 ml) was treated at −78 °C with a solution of 20% DIBAH in hexane (9.80 ml; 9.80 mmol) under an atmosphere of nitrogen. Phenylethynylmagnesium bromide (11.76 mmol) in THF was added after consumption of all the ester (monitored by TLC). After the temperature had risen to 25 °C over 30 min the reaction was quenched with saturated aqueous NH_4Cl. From the organic layer the crude alcohol could be separated. This was concentrated to a small volume, dissolved in CH_2Cl_2 (17 ml) and subsequently oxidised[12] with pyridinium dichromate (5.53 g, 14.7 mmol) and pyridine trifluoroacetate (0.76 g, 3.92 mmol) in an atmosphere of nitrogen. After being stirred for 3 h the reaction mixture was diluted with ether, filtered and concentrated. The residue was purified by column chromatography to yield 1.37 g (53%) of a yellow oil; $[\alpha]_D^{23}$ −72.1 (*c* 0.76 in $CHCl_3$) (Found: C, 82.0; H, 6.34. $C_{18}H_{16}O_2$ requires C, 81.79; H, 6.1%); δ_H(80 MHz) 1.49 (3 H, d, *J* 6.5 Hz, Me), 4.13 (1 H, q, *J* 6.5 Hz, –CH), 4.65 (2 H, dd, *J* 12.3 Hz, $-OCH_2Ar$), and 7.22–7.63 (10 H, m, 2 × Ar); δ_C(20 MHz) 17.62 (q, CH_3), 71.90 (t, $-OCH_2$), 80.74 (d, –CH), 86.5 (s, ≡*C*Ar), 93.74 (s, C≡*C*Ar), 119.56–137.49 (m, 2 × Ar), and 189.31 (s, C=O); *m*/*z* 234 (M^+ −30, 1.4%), 129 (100), 91 (67).

(S)-(−)-4-*Benzyloxymethoxy*-1-*phenylpent*-1-*yn*-3-*one*.—This was prepared by the foregoing procedure from (*S*)-(−)-ethyl 2-(benzyloxymethoxy)propanoate.[17] The desired *acetylenic ketone* was isolated in 57% overall yield as an oil; $[\alpha]_D^{32}$ −62.4 (*c* 1.36 in $CHCl_3$); (Found: C, 77.6; H, 6.15. $C_{19}H_{18}O_3$ requires C, 77.53; H, 6.16%); δ_H(80 MHz) 1.49 (3 H, d, *J* 6.5 Hz, Me), 4.40 (1 H, q, *J* 6.5 Hz, –CH), 4.68 (2 H, s, OCH_2Ar), 4.88 (2 H, s, OCH_2Ar), 4.88 (2 H, s, $-CH_2O$), and 7.27–7.62 (10 H, m, 2 × Ar); δ_C(20 MHz) 17.63 (q, Me), 70.08 (t, $-OCH_2Ar$), 78.72 (d, –CH), 86.23 (s, ≡*C*Ar), 94.07 (t, $-OCH_2$–OAr and s, –C≡*C*Ar), 119.76–137.58 (m, 2 × Ar), and 188.23 (s, –C=O); *m*/*z* 220 (M^+, −74, 1.2%), 158 (11), 129 (100), and 91 (81).

(S)-2-*Benzyloxy*-3-*phenylethynyl*-3,4-*epoxybutane* (**11a**) *and* (**12a**).—The same procedure as described for compound (**10**) was used. (*S*)-(−)-4-Benzyloxy-1-phenylpent-1-yn-3-one (1.00 g, 3.79 mmol) was treated with dimethylsulphanium methanide (15.16 mmol) derived *in situ*. Column chromatography (SiO_2, ethyl acetate–hexane) afforded the epoxides (**11a**) and (**12a**) as a mixture of diastereoisomers (0.42 g, 40%). NMR studies using the chiral shift reagent [Eu(fod)$_3$] on the crude mixture were used to establish the diastereoisomeric excess (d.e.) (Scheme). (Found: C, 81.65; H, 6.7. $C_{19}H_{18}O_2$ requires C, 81.99; H, 6.52%); δ_H*(80 MHz) 1.39 (1.45) (3 H, d, *J* 6.6 Hz, Me), 2.86 (3.06) (2 H, dd, epoxy CH_2), 3.43 (3.51) (1 H, q, *J* 6.6 Hz, CH), 4.59 (4.71) (2 H, dd, *J* 12.3 Hz, $-OCH_2Ar$), and 7.19–7.52 (10 H, m, Ar); δ_C*(20 MHz) 17.84 (17.89), (q, Me), 50.99 (53.26) (t, epoxy CH_2), 54.29 (s, ≡C–*C*–O), 71.26 (71.89) (t, OCH_2Ar), 75.59 (77.34) (d, CH), 84.49 (84.59) (s, ≡*C*Ar), 84.93 (85.58) (s, *C*≡CAr), and 122.01–138.35 (m, 2 × Ar); *m*/*z* 170 (M^+ −180, 100%).

(S)-2-*Benzyloxymethoxy*-3-*phenylethynyl*-3,4-*epoxybutane* (**11b**) *and* (**12b**).—This was obtained from treatment of (*S*)-(−)-4-benzyloxymethoxy-1-phenylpent-1-yn-3-one (see above) (1.00 g, 3.40 mmol) with dimethylsulphanium methanide (13.60 mmol). After column chromatography a mixture of diastereoisomers (0.37 g, 34.5%) was obtained. (Found: C, 77.7; H, 6.7. $C_{20}H_{20}O_3$ requires C, 77.89; H, 6.54%); δ_H*(80 MHz) 1.41 (1.46) (3 H, d, *J* 6.3 Hz, Me), 2.94 (3.07) (2 H, dd, *J* 5.7 Hz, epoxy CH_2), 3.69 (3.73) (1 H, q, *J* 6.3 Hz, –CH), 4.65 (2 H, s, OCH_2Ar), 4.83 (4.89) (2 H, dd, $-OCH_2OAr$), and 7.16–7.58 (10 H, m, 2 × Ar); δ_C*(20 MHz) 17.46 (17.80) (q, Me); 51.78 (53.07) (t, epoxy CH_2); 53.55 (54.12) (s, ≡C–*C*–O), 54.59 (70.01) (t, $-OCH_2Ar$), 74.35 (74.89) (d, –CH), 84.34 (84.44) (s, ≡*C*Ar), 85.12 (85.51) (s, −*C*≡CArO), 93.23 (93.84) (t, $-OCH_2OAr$),

* *Note:* The values quoted in parentheses refer to the other diastereoisomer.

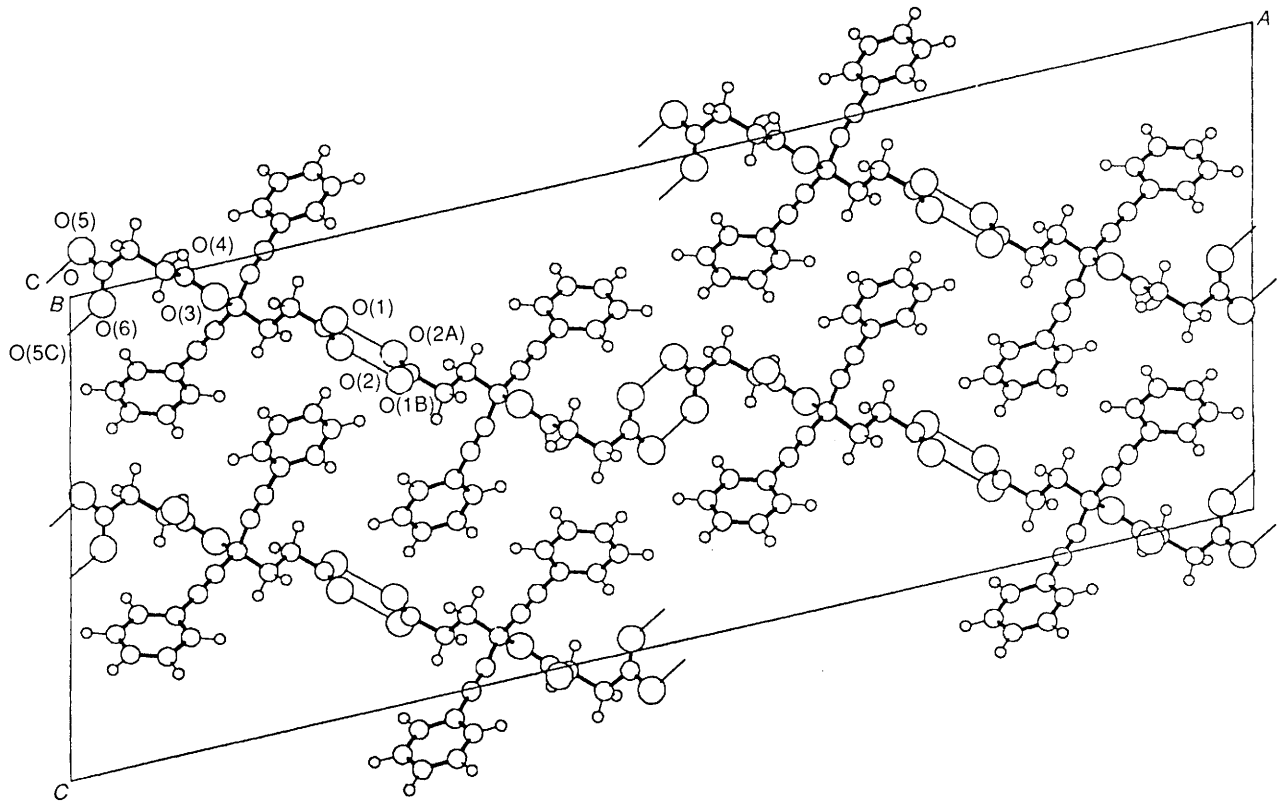


Figure 2. Packing diagram of compound (7) showing intermolecular H-bonding.

Table. Fractional co-ordinates ($\times 10^4$) for compound (7).

	x/a	*y/b*	*z/c*
O(1)	2 223(1)	5 650(6)	1 714(2)
O(2)	2 271(1)	2 070(6)	2 301(2)
C(1)	2 135(1)	3 415(8)	1 812(2)
C(2)	1 848(1)	2 694(8)	1 248(2)
C(3)	1 662(1)	834(7)	1 574(2)
C(4)	1 393(1)	−198(6)	972(2)
C(5)	1 209(1)	−1 771(7)	1 353(2)
C(6)	1 065(1)	−3 033(7)	1 701(2)
C(8)	564(1)	−4 368(14)	1 852(3)
C(9)	376(2)	−5 900(17)	2 164(4)
C(10)	499(2)	−7 598(14)	2 668(5)
C(11)	809(2)	−7 855(12)	2 890(4)
C(12)	1 004(2)	−6 345(9)	2 590(3)
C(7)	878(1)	−4 582(8)	2 058(2)
C(13)	1 506(1)	−1 476(7)	369(2)
C(14)	1 626(1)	−2 607(7)	−53(2)
C(16)	1 609(1)	−6 050(10)	−930(3)
C(17)	1 748(2)	−7 534(12)	−1 383(4)
C(18)	2 041(2)	−7 182(13)	−1 443(4)
C(19)	2 203(2)	−5 262(15)	−1 040(4)
C(20)	2 064(1)	−3 736(13)	−595(4)
C(15)	1 765(1)	−4 127(7)	−536(2)
O(3)	1 213(1)	1 985(4)	665(1)
C(21)	959(1)	1 642(7)	114(2)
O(4)	878(1)	−304(5)	−159(2)
C(22)	798(1)	4 018(7)	−100(3)
C(23)	500(1)	3 643(9)	−685(3)
C(24)	278(1)	2 037(9)	−387(3)
O(5)	97(1)	737(7)	−895(2)
O(6)	269(1)	2 045(8)	286(2)

* For details of the deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans.* 2, in the January issue,

and 121.94–137.85 (10 H, m, 2 × Ar); *m/z* 170 ($M^+ - 138$, 100%).

Crystal Structure Determination of Compound (7).—Crystals of compound (7), $C_{24}H_{20}O_6$, $M = 404$, are monoclinic, space group $C2/c$, $a = 44.657(14)$, $b = 5.463(5)$, $c = 17.872(3)$ Å; $\beta = 102.30(2)$, $D_m = 1.24$ g cm^{-3}, $Z = 8$, $D_x = 1.26$ g cm^{-3}. Data were collected on a Nonius CAD-4 four circle diffractometer (NCRL, CSIR, Pretoria) with graphite monochromated Mo-K_α radiation in the range $3 < \theta < 25°$. The structure was solved by direct methods with the SHELX-86 programme[18] using 2 952 *Lp*-corrected, but not absorption-corrected reflections with $I > \sigma(I)$. All non-hydrogen atoms were assigned anisotropic temperature factors and their positions were refined using full-matrix least-squares techniques. The hydrogen atoms (with the exception of the carboxylic acid hydrogens) were placed in calculated positions and included in the final refinement with two, overall, refined isotropic temperature factors [U_{iso} (ArH) = 0.13(1) and U_{iso} (CH_2) = 0.074(6) Å^2]. Final R and R_w values of 0.0992 and 0.1171 were obtained [$w = 0.1162/\sigma^2F + 0.024494F^2$]. Fractional co-ordinates for non-hydrogen atoms are given in the Table. Temperature factors and bond lengths, and bond angles for the non-hydrogen atoms are available from the Cambridge Crystallographic Data Centre.* From the packing diagram (Figure 2) it is apparent that molecules of compound (7) are associated in linear arrays by inter-molecular hydrogen bonding involving both carboxylic acid groups.

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