Diels-Alder Reactions involving 1,2-Isopropylidenedioxy-3-trifluoromethylcyclohexa-3,5-diene

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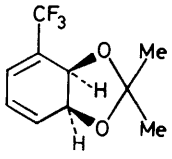
The title compound was treated with several dienophiles to give cycloadducts resulting from addition to the less hindered face of the molecule. An exceptional case was provided by *N*-ethylmaleimide which added in *endo*-fashion to both faces of the diene. 1,2-Isopropylidenedioxy-3-trifluoromethylcyclohexa-3,5-diene acted as a dienophile on addition to cyclopentadiene and underwent dimerization to give a stable [4 + 2] adduct.

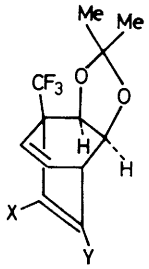
The microbial oxidation of benzene (and derivatives) using *Pseudomonas* sp. gives (3-substituted) *cis*-cyclohexadiene-1,2-diol.[1] While the chemistry of *cis*-cyclohexadiene-1,2-diol[2] and *cis*-3-methylcyclohexadiene-1,2-diol[3] has received some attention, the properties of other 3-substituted cyclohexadienediols produced by this fascinating series of biotransformations have not been reported heretofore. We report that the acetal (**1**) is readily prepared from the corresponding diol[4] and undergoes some interesting Diels–Alder reactions.

Discussion

Reaction of the diene (**1**) with dimethyl acetylenedicarboxylate furnished the adduct (**2**) (m.p. 95 °C) in 83% yield while with methyl propiolate it gave two isomers in the ratio 3:1 (54%).

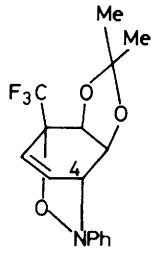


(**1**)

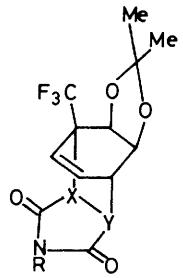


(**2**) X = Y = CO_2Me
(**3**) X = H, Y = CO_2Me
(**4**) X = CO_2Me, Y = H

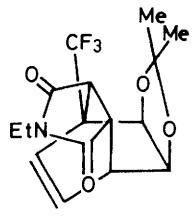
The major product was the ester (**3**) (m.p. 64.5 °C) (with the trifluoromethyl group and the ester moiety distant) and this compound was distinguished from compound (**4**) (m.p. 104—106 °C) by the coupling pattern of the lowfield alkene proton. Cycloaddition of the diene (**1**) and nitrosobenzene proceeded at room temperature to produce the adduct (**5**) (m.p. 80—81 °C) as needle-like crystals in 90% yield. Similarly, cycloaddition of the diene (**1**) with 4-phenyl-1,2,4-triazoline-3,5-dione gave the adduct (**6**) (60.5%), while *N*-ethylmaleimide gave two products, one formed by *endo*-addition to the open face of the diene [(**7**), 50% yield] and the other produced by *endo*-addition to the hindered face of the diene [(**8**), 38% yield].



(**5**)



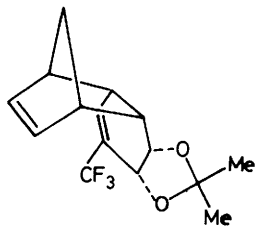
(**6**) X = Y = N, R = Ph
(**7**) X = Y = CH, R = Et



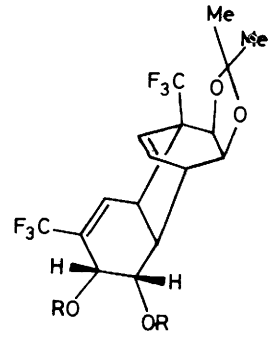
(**8**)

Not only can the alkene (**1**) enter into Diels–Alder reactions as the diene component but it can also act as a dienophile. Reaction of compound (**1**) with cyclopentadiene gave the adduct (**9**) albeit in low yield. The reactive nature of the acetal (**1**) as diene *and* dienophile is reflected in the ready dimerization of the compound when kept at 0—5 °C. The dimer (**10**), m.p. 157—158 °C was identified by conversion into the partially deprotected material (**11**) and the dibenzoate (**12**), followed by detailed n.m.r. studies.

In most cases, complete assignment of all ^{1}H and ^{13}C



(**9**)



(**10**) R, R = Pr^i
(**11**) R = H
(**12**) R = Bz

resonances was possible including individual methyl peaks. This was achieved by combination of homonuclear ^{1}H{^{1}H} decoupling, selective heteronuclear ^{13}C{^{1}H} decoupling and observation of ^{19}F-^{13}C coupling constants. Any structural ambiguities were resolved by n.O.e.-difference spectroscopy. For example, the structure of compound (**5**) was proved by observation of a massive enhancement of the signal from 4-H when the aromatic region was irradiated. Saturation of the protons in the methine groups bonded to oxygen atoms in compound (**7**) led to a very large (*ca.* 20%) enhancement of the signals associated with protons in the methine groups labelled X and Y. For adduct (**8**) a through-space interaction was found between the lower field methyl group and the methine protons of the succinimide moiety. In addition both the regio- and stereochemistry of compound (**11**) were confirmed by finding through-space connections between the two methyl groups and neighbouring methine and alkene protons. Similarly, compound (**9**) was found to be in the *endo* rather than the *exo* form by observation of n.O.e. correlations between the pair of methylene protons and the pair of bridge methine protons.

Selected Experimental Data.—Column chromatography was carried out under pressure on MN-Kieselgel 60 230—400 mesh with the eluant specified in parentheses. The benzene used as solvent was dried with sodium wire. Chemical shifts are reported in δ values relative to Me_4Si as an internal standard. Accurate mass determinations were made on compounds estimated to be >95% pure by H^1 n.m.r. spectroscopy and thin layer chromatography.

Preparation of the Cycloadduct (**2**).—The acetal (**1**) (0.11 g, 0.5 mmol) and dimethyl acetylenedicarboxylate (0.5 ml) were dissolved in dry benzene (3.0 ml). The mixture was refluxed for 75 h under an atmosphere of nitrogen. The benzene was removed by distillation at reduced pressure to give a yellow oil. The oil was subjected to column chromatography over silica gel. Elution with ethyl acetate in light petroleum (b.p. 60—80) (1:4, v/v) afforded compound (**2**) (0.15 g, 83%, m.p. 95 °C). δ_H(250 MHz) ($CDCl_3$) 1.28 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 3.77 (3 H, s, CH_3), 3.82 (3 H, s, CH_3), 4.44 (1 H, m, CH), 4.47 (1 H, m, CH), 4.62 (1 H, dm, *J* 7 Hz, CH), 6.37 (1 H, dm, *J* 7.6 Hz, C=CH), and 6.56 (1 H, ddm, *J* 7.6 and 7.5 Hz, C=CH) [Found: $(M + NH_4)^+$ 380.1327. $C_{16}H_{17}F_3O_6$ requires $(M + NH_4)$ 380.1321].

Preparation of the Cycloadducts (**7**) *and* (**8**).—The acetal (**1**) (0.22 g, *ca.* 1.0 mmol) was dissolved in dry benzene (2.5 ml) and *N*-ethylmaleimide (0.12 g *ca.* 1.0 mmol) in dry benzene (2.5 ml) was added. The resultant mixture was refluxed under nitrogen for 72 h. Work-up as described above furnished the crude product (0.40 g) as a white crystalline solid. The crude product

was subjected to chromatography over silica gel [eluant ethyl acetate–light petroleum (b.p. 60—80 °C) (1:3, v/v)]. The first component eluted from the column was the adduct (**8**) (0.13 g, 38%, m.p. *119*—*123* °C); $\delta_H(CDCl_3)$ 1.06 (3 H, t, CH_3), 1.35 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 3.48 (5 H, m, NCH_2, CH × 3), 4.23 (1 H, dd, *J* 8.1 and 3.5 Hz, CH), 4.3 (1 H, d, *J* 8.1 Hz, CH), 6.08 (1 H, d, *J* 8.5 Hz, C=CH), and 6.28 (1 H, dd, *J* 8.5 and 6.6 Hz, C=CH) [Found: $(M + NH_4)^+$, 363.1528. $C_{16}H_{18}F_3NO_4$ requires $(M + NH_4)$ 363.1531]. The more polar compound was the adduct (**7**) (0.17 g, 50%, m.p. 169 °C); $\delta_H(CDCl_3)$ 1.08 (3 H, t, CH_3) 1.29 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 2.88 (2 H, m, CH × 2), 3.48 (2 H, q, NCH_2), 3.57 (1 H, m, CH), 4.39 (2 H, m, CH × 2), 6.08 (1 H, d, *J* 8.7 Hz, C=CH), 6.22 (1 H, dd, *J* 8.7, 6.4 Hz, C=CH) [Found: $(M + NH_4)^+$, 363.1528. $C_{16}H_{18}F_3NO_4$ requires $(M + NH_4)^+$ 363.1531].

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4 The reaction conditions are essentially the same as those used for the protection of cyclohexa-3,5-diene-1,2-diol: I. C. Cotterill, S. M. Roberts, and J. O. Williams, *J. Chem. Soc., Chem. Commun.*, 1988, 1628.

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