57. *Extension of the Diels–Alder Reaction to Monocyclic Benzenes: Addition of Maleic Anhydride to Quinol.*

By R. C. Cookson and N. S. Wariyar.

At 190—200° quinol and maleic anhydride form the adduct (II), identified by Wolff–Kishner reduction to the known *trans*-diacid (III). Hydrochloric acid isomerises the *cis*-diketo-acid to a mixture of the two *trans*-diketo-acids (IV) and (V), the configurations of which are proved by the reduction of one isomer (IV) to the dilactone (VI).

This is the first instance of the 1 : 4-addition of a dienophil to a derivative of benzene.

As one of a series of analogues of santonide [1] we required ketones incorporating units of type (I). The most direct synthesis of *bicyclo*[2 : 2 : 2]octane substituted by oxygen at the required positions appeared to be by addition of a dienophil to quinol. Indeed at 190—200° quinol and maleic anhydride gave a 1 : 1 adduct, which gave a dicarboxylic acid and a dimethyl ester. In its ultraviolet spectrum the ester had no absorption greater than ε 500 beyond 200 mμ, demonstrating the absence of conjugation or of an aromatic ring, but showed a weak band (ε 60) at 289 mμ consistent with the presence of one or two carbonyl groups, the presence of which was confirmed by the infrared spectrum with maxima at 1726 (*cyclo*hexanone) and 1738 cm.$^{-1}$ (ester).

The correctness of the expected structure (II) of the adduct was proved by Wolff–Kishner reduction to the saturated *trans*-diacid (III), identical with a sample made by addition of maleic anhydride to *cyclo*hexadiene followed by hydrogenation and isomerisation of the adduct.[2]

Boiling hydrochloric acid converted the adduct (II) into an equilibrium mixture of the three possible stereoisomeric acids, which could be separated only with difficulty. As expected, the *cis*-acid was almost absent. One of the *trans*-acids formed a dimethyl ester melting at 120°, the other a dimethyl ester melting at 83°. Reduction of the latter ester,

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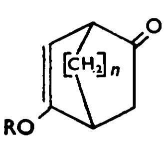
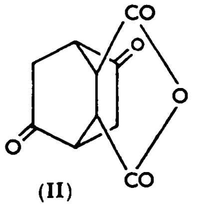
[1] Cookson and Wariyar, *J.*, 1956, 2302.
[2] Diels and Alder, *Annalen*, 1928, **460**, 98.

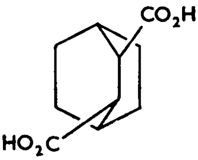
or of the corresponding acid, with sodium borohydride[3] produced the very high melting tetracyclic dilactone (VI) which has infrared absorption maxima at 1782 and 1765 cm.$^{-1}$ (in Nujol; γ-lactone). So the acid giving the ester melting at 83° must have structure (IV), and the acid giving the ester melting at 120° (which gave no neutral product with sodium borohydride) must have structure (V).



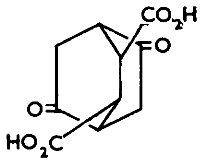
(I)



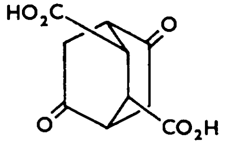
(II)



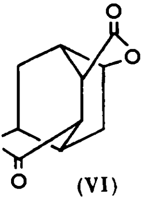
(III)



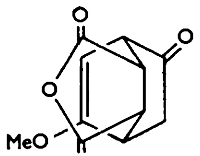
(IV)



(V)



(VI)



(VII)

No doubt, isomer (IV) predominates over (V) in the equilibrium mixture mainly because of the greater repulsion between a carboxyl group and a γ-situated tetrahedral CH_2 group than between a carboxyl and a spatially more distant γ-trigonal carbonyl group.

The addition of maleic anhydride to quinol, contrasted with the failure of dienophils to add at positions 1 : 4 to other derivatives of benzene, shows that the lack of reactivity of the benzene nucleus in the Diels–Alder reaction is due less to the slowness of the forward reaction than to the unfavourable equilibrium constant. Benzene and its homologues as electron-donors form 1 : 1 associations of low stability with electron-acceptors such as maleic anhydride and benzoquinone.[4] Such charge-transfer associations may be intermediates in some Diels–Alder reactions,[5] but for benzene the large loss in resonance energy that it would entail effectively prevents consummation of the reaction. Indeed derivatives of *bicyclo*octadiene are well known to dissociate to olefin and benzene.[6] For the adduct (II) the rate of dissociation is probably proportional to the concentration of dienol tautomer, the initial adduct,* the equilibrium constant of which with the diketone (II) must be minute, thus allowing the diketone to accumulate.

We have not yet been able to convert the *cis*-adduct or its derivatives, such as the *N*-methylimide, into an enol ether, ester, or lactone incorporating a unit of type (I). The adduct of maleic anhydride and *p*-methoxyphenol was not the methoxy-compound (VII) or its stereoisomer, but was identical with the quinol adduct (II). Since the *p*-methoxyphenol was quite free from quinol, apparently the adduct (VII) first formed was demethylated by the *p*-methoxyphenol or other reaction products.

Almost at the same time as the preliminary announcement[7] of our preparation of the adduct (II) and proof of its structure, Takeda[8] mentioned the isolation of the same

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* The coupled equilibrium of the monoenol with maleic anhydride and the monoketo-tautomer of quinol is also, of course, involved—at least in principle.

[3] Cf. ref. 1.

[4] Barb, *Trans. Faraday Soc.*, 1953, **49**, 143; Andrews and Keefer, *J. Amer. Chem. Soc.*, 1953, **75**, 3776.

[5] Woodward, *ibid.*, 1942, **64**, 3058.

[6] Alder and Rickert, *Annalen*, 1936, **524**, 180; *Ber.*, 1937, **70**, 1354.

[7] Cookson and Wariyar, *Chem. and Ind.*, 1955, 915.

[8] Takeda, Abs. Int. Congr. Pure Appl. Chem., Zürich, 1955, p. 270.

substance and he and his colleagues have recently [9] described their experiments, including a somewhat different proof of structure.

EXPERIMENTAL

Reaction of Quinol with Maleic Anhydride.—Quinol (15 g.) and maleic anhydride (28 g.) were simmered gently under reflux (190—200°) in an atmosphere of carbon dioxide for 2 hr. The viscous product, while still warm, was dissolved in boiling ether (*ca.* 80 ml.). On cooling, crystals (1·1 g.) of 5 : 7-dioxo*bicyclo*[2 : 2 : 2]octane-2 : 3-dicarboxylic anhydride (II) separated; they had m. p. 270—272° (decomp.) after sintering from about 255° (sublimation occurs well below the m. p.) (Found: C, 57·5; H, 3·7. Calc. for $C_{10}H_8O_5$: C, 57·7; H, 3·9%). It is important to avoid over-heating, which gives a dark, viscous product from which the adduct cannot easily be separated. The tar produced by moderate over-heating can be kept in solution by addition of ethyl acetate.

Crystallisation of the adduct from water gave the *cis*-diacid, which began to sublime at about 220° and to sinter at about 255°, and melted at 272—273° (decomp.). When put in the m. p. block at 265° it melted at 273—275° (decomp.). In Nujol it had $\nu_{max.}$ 1744 and 1704 cm.$^{-1}$ (Found: C, 52·9; H, 4·55%; equiv., 106. Calc. for $C_{10}H_{10}O_6$: C, 53·1; H, 4·5%; equiv., 113).

The dimethyl ester, made with diazomethane in methanol–ether, crystallised from methanol in fine needles, m. p. 181—182°, $\nu_{max.}$ 1742 cm.$^{-1}$ (in $CHCl_3$), 1738 and 1726 cm.$^{-1}$ (in Nujol) (Found: C, 56·4; H, 5·3. Calc. for $C_{12}H_{14}O_6$: C, 56·7; H, 5·55%).

The adduct (II) (1 g.) was heated on a steam-bath with 40% aqueous methylamine (0·4 ml.) for 10 min. After evaporation of methylamine and water under reduced pressure the solid residue was boiled for 30 min. with acetyl chloride (20 ml.). Removal of the acetyl chloride and crystallisation from water gave the N-*methylimide*, which after several recrystallisations from water had m. p. 234—235° (Found: C, 59·5; H, 4·9; N, 6·35. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

Reaction of maleic anhydride with *p*-methoxyphenol under the same conditions as with quinol gave, on crystallisation from anhydrous ether, the anhydride (II), m. p. 250—255° (decomp.) (Found: C, 57·8; H, 4·1; OMe, 0%). The derived dimethyl ester had m. p. and mixed m. p. 181—182°.

Wolff–Kishner Reduction.—The *cis*-diketo-acid (550 mg.) was heated for 15 hr. at 180° with hydrazine (0·3 ml.) and ethanol (1·5 ml.) in which sodium (100 mg.) had been dissolved. The mixture was treated with an excess of dilute hydrochloric acid, and the resulting solution was heated. On cooling, crystals separated. After being extracted with boiling water they had m. p. 234°, not depressed by *bicyclo*[2 : 2 : 2]octane-2 : 3-*trans*-dicarboxylic acid (III) of the same m. p. made from *cyclo*hexadiene.[3]

Isomerisation of the cis-*Diketo-acid.*—The *cis*-acid (1 g.) was boiled for 24 hr. with concentrated hydrochloric acid, which was then removed under reduced pressure. As a solution of the residue in boiling water cooled, crystals of the trans-*acid* (V) (177 mg.) separated, having m. p. 265° (Found: C, 52·8; H, 4·6. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·5%).

Treatment of the *trans*-acid (V) with diazomethane in methanol–ether gave the *dimethyl ester*, crystallising from methanol in fine needles, m. p. 119—120° (Found: C, 56·7; H, 5·6. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%).

The acids in the aqueous filtrate from which the *trans*-acid (V) had been removed were treated with diazomethane. A solution in ether of the resulting syrupy mixture of esters deposited needles of the *dimethyl ester* of the isomeric *trans*-acid (IV), m. p. 76—77°, raised to 82—83° by two recrystallisations (Found: C, 56·9; H, 5·6%). Mixtures of pairs of the three isomeric esters had much depressed m. p.s.

No clear-cut separation of the equilibrated acids was effected by chromatography of the acids or their esters on alumina or of the esters on silica gel.

Preparation of the Dilactone.—The mixture (1·5 g.), obtained by boiling the *cis*-diacid with hydrochloric acid, in water (50 ml.) was gradually treated with potassium borohydride (6 g.). After a day the solution was acidified with dilute hydrochloric acid, gently warmed, and left overnight. The crystals that separated were washed with sodium hydrogen carbonate solution. The insoluble *dilactone* (VI) then had m. p. 318—321° (decomp.), raised to 330° (decomp.) by

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Takeda, Kitahonoki, and Igarashi, *Pharm. Bull.* (*Japan*), 1956, **4**, 12.

crystallisation from methanol (Found : C, 61·75; H, 5·1. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·15%). It showed no maximum in the ultraviolet region above 210 mμ; in the infrared $\nu_{max.}$ were 1782 and 1765 cm.$^{-1}$ (in Nujol).

Reduction of neither of the isolated acids (V or the acid from II) in the same way gave any trace of neutral product, so that the dilactone must have come from the acid (IV) that did not crystallise from solution but gave the ester, m. p. 83°.

We appreciate the interest and encouragement of Professor D. H. R. Barton, F.R.S. One of us (N. S. W.) is indebted to the University of Travancore for study leave.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, September 5th,* 1956.]