Structure of the 1,4-Pentadiene–Maleic Anhydride Adduct

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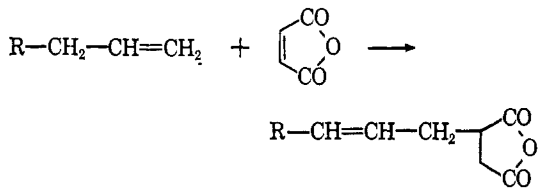
Received March 9, 1965

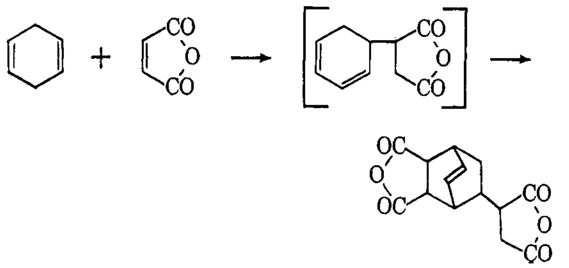
The structure of the adduct, $C_{12}H_{12}O_4$, formed from 1,4-pentadiene and 2 moles of maleic anhydride, and regarded by Alder and Münz as a keto anhydride, has been reinvestigated. Infrared spectra of the adduct and its derivatives support the spiro dilactone formula IIe. The bisanhydride I, the expected product of an initial "substitutive addition" followed by a normal Diels–Alder reaction, was the sole product isolated in most runs. Its role as an intermediate in the formation of IIe was confirmed by direct conversion to IIe by heating with sodium hydride.

In contrast to their well-known addition to 1,3-dienes, dienophiles such as maleic anhydride or acrylonitrile react with monoolefins by a process of "substitutive addition" (the "ene reaction," eq. 1).[2] This reaction has been shown to proceed by a cyclic transition state characteristic of thermal reorganization reactions.[3]



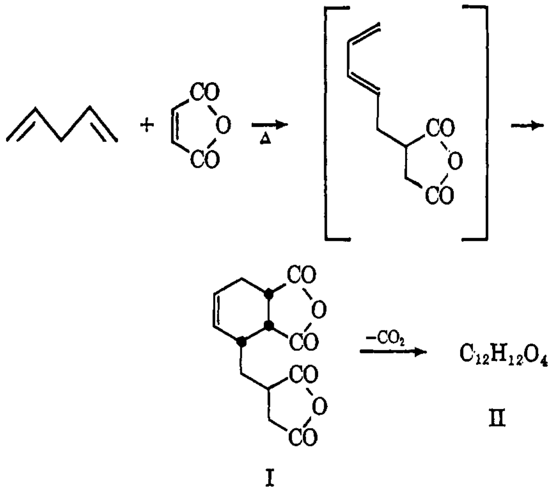
(1)

As part of their extensive investigation on the scope of this reaction, Alder and Münz[4] studied the reaction of maleic anhydride with several nonconjugated dienes. On heating with excess maleic anhydride at 200°, 1,4-cyclohexadiene was found to form an adduct resulting from "substitutive addition" followed by a normal diene addition (eq. 2).



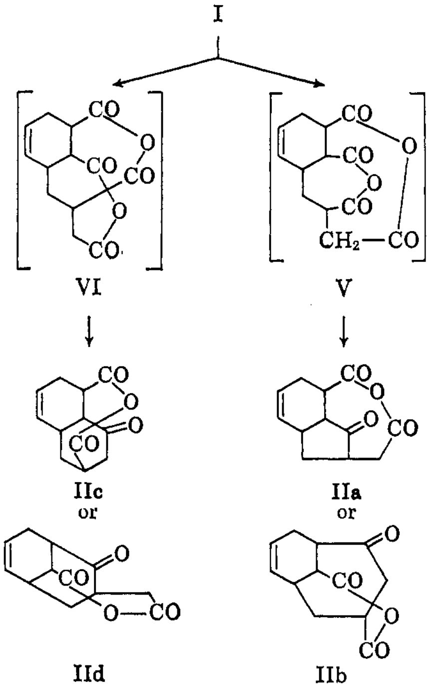
(2)

On the other hand, 1,4-pentadiene, which was expected to behave in a similar manner, gave a decarboxylated product (II) instead of the expected bisanhydride I (eq. 3). Adduct II, $C_{12}H_{12}O_4$, m.p. 151°, had the properties of an unsaturated keto anhydride. It was hydrolyzed to a keto diacid III, $C_{12}H_{14}O_5$, and esterified to a keto dimethyl ester IV, $C_{14}H_{18}O_5$, both of which formed semicarbazones. II could be reduced to a saturated dihydro compound, which gave a corresponding saturated keto diacid and keto diester. These properties established that II was an anhydride of an unsaturated bicyclic keto diacid.



(3)

In order to account for this result, Alder and Münz suggested that the first-formed bisanhydride I might be equilibrated, during the reaction, with either of two isomeric bisanhydrides, V and VI. Either of these large-ring anhydrides could then undergo the well-known thermal conversion of cyclic anhydrides to ketones. Four different keto anhydrides (IIa–d) could conceivably result in this way, though no information was available to Alder and Münz to enable



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[1] Alfred P. Sloan Foundation Research Fellow.

[2] K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76**, 27 (1943); K. Alder and H. von Brachel, *Ann.*, **651**, 141 (1962), and intervening papers.

[3] (a) R. T. Arnold and J. F. Dowdall, *J. Am. Chem. Soc.*, **70**, 2590 (1948); (b) H. P. Koch, *J. Chem. Soc.*, 1111 (1948); (c) C. S. Rondestvedt, Jr., and B. H. Wark, *J. Org. Chem.*, **20**, 368 (1955); (d) R. T. Arnold and J. S. Showell, *J. Am. Chem. Soc.*, **79**, 419 (1957); (e) B. J. Sublett and N. S. Bowman, *J. Org. Chem.*, **26**, 2594 (1961); (f) R. K. Hill and M. Rabinovitz, *J. Am. Chem. Soc.*, **86**, 965 (1964).

[4] K. Alder and F. Münz, *Ann.*, **565**, 126 (1949).

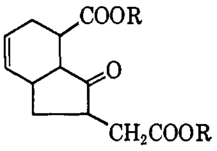
them to make a choice, and the problem was left unresolved at this stage.[5]

Though the general course of the reaction suggested by Alder and Münz seems reasonable, a stable eight-membered anhydride ring required by formulae IIa–d appears less so,[6] and we were led consequently to reinvestigate the structure of adduct II. Spectroscopic methods not available at the time of the original investigation have now shown that the carbon skeleton of the adduct is that of IIa, but that the adduct is not a cyclic anhydride.

Following the procedure of Alder and Münz, 1,4-pentadiene was heated with somewhat more than 2 equiv. of maleic anhydride in a sealed tube at 200°, using benzene or *o*-dichlorobenzene as solvent. In only *one* of 12 runs was the reported adduct obtained; it had the reported melting point and empirical formula, and could be converted to the diacid III and diester IV. In all the other runs, the only product isolated was a solid, m.p. 172°, which analyzed for $C_{13}H_{12}O_6$. It gave tests for unsaturation and had infrared absorption at 1850 and 1775 cm.$^{-1}$ typical of succinic anhydrides. The n.m.r. spectrum showed vinyl protons and protons attached to saturated carbons in the ratio 1:5. This compound thus appears to be the bisanhydride I, the "expected" product of the reaction. Attempts to aromatize the cyclohexene ring with selenium, chloranil, or palladium on charcoal were unsuccessful. Heating with sulfur, however, gave a small amount of crude product whose n.m.r. spectrum showed the disappearance of vinyl protons and the presence of aromatic and saturated protons in the ratio 3:5, but this material could not be obtained analytically pure.

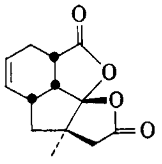
The obtention of the anhydride I strongly implies that it is indeed an intermediate in the formation of II. On the supposition that the cyclization of I to II might be a base-catalyzed reaction of the Claisen or Perkin type, and that the difference between our results and those of Alder and Münz might be due to traces of alkali in their glass tubes or reaction mixtures, I was heated with sodium hydride in toluene, whereupon II was formed.

With the sequence of steps confirmed, attention was turned to the structure of II. It was possible to make a definitive choice from among the four skeletons represented in IIa–d from an examination of the carbonyl region of the infrared spectrum of the dimethyl ester IV. In chloroform or carbon disulfide solution, IV showed a single carbonyl band at 1745 cm.$^{-1}$. This is consistent only with the cyclopentanone formula IV, since, while cyclopentanones and esters normally both absorb[7] in the region 1750–1735 cm.$^{-1}$, carbonyl groups in six- and seven-membered cyclic ketones absorb[7] at 1725–1705 cm.$^{-1}$.

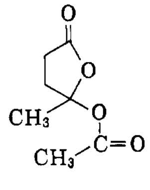


III, R = H
IV, R = CH_3

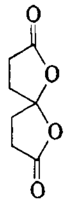
The final question concerned the nature of the "anhydride" linkage in II. Suspicion of the eight-membered anhydride ring of IIA was heightened by the ready reconversion of the keto diacid III to II on heating in acetic anhydride. A definitive answer was again provided by the infrared spectrum, which showed a *single* carbonyl band at 1795 cm.$^{-1}$. This is clearly incompatible with IIa or any carboxylic anhydride, and is consistent[8] only with an alternate dehydration product, the spirodilactone IIe. The thermal conversion of I to II finds an exact parallel in the formation of the spirodilactone (VIII) of γ-ketosebacic acid by the pyrolysis of succinic anhydride.[9]



IIe



VII



VIII

On the basis of generalizations of the steric course of the Diels–Alder reaction,[10] the bisanhydride I may be assigned the configuration shown, in which the protons on the three adjacent asymmetric centers are *cis;* the configuration at the remaining asymmetric center is unspecified. The spiro dilactone IIe can be constructed in only one strain-free configuration, which fixes the relative stereochemistry as shown. Since all but one of the asymmetric centers adjoin a carbonyl group in I, and are therefore capable of epimerization during the rigorous reaction conditions, there is no guarantee that the configuration of IIe corresponds to that of I.

Experimental[11]

Reaction of 1,4-Pentadiene with Maleic Anhydride.[4]—A mixture of 5.0 g. of 1,4-pentadiene and 16.0 g. of maleic anhydride in 25 ml. of benzene was heated in a sealed tube at 200° for 60 hr. The contents of the tube were poured into a little water and allowed to stand overnight. The oily crystals were filtered, washed with water, and dried, to afford 7.79 g. (40%) of **bisanhydride I,** m.p. 156–159°. Recrystallization from ethyl acetate gave colorless crystals, m.p. 170–172°, infrared absorption (Nujol mull) 1850 and 1775 cm.$^{-1}$. The n.m.r. spectrum showed a broad multiplet centered at τ 4.3 (2H) and overlapping multiplets between τ 6.5 and 8.5 (10H).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 58.92; H, 4.42.

In one run, carried out just as described, a small explosion occurred on opening the sealed tube, which caused some loss of material. The remainder was worked up as described and recrystallized from benzene to give the **spiro dilactone IIe,** m.p. 150–151° (lit.[4] m.p. 151°). The infrared spectrum (Nujol or

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[5] In a later lecture Alder listed the keto diacid corresponding to IIa as the structure: Proceedings of the 14th International Congress of Pure and Applied Chemistry, Zürich, 1955, Birkhäuser Verlag, Basel, 1955, p. 108.

[6] Adipic and higher dibasic acids usually give polymeric rather than cyclic anhydrides: W. H. Carothers, *J. Am. Chem. Soc.*, **51**, 2548 (1929).

[7] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 132, 147, 179.

[8] A close spectroscopic model is γ-acetoxy-γ-valerolactone (VII), in which the lactone carbonyl absorbs at 1797 cm.$^{-1}$: R. S. Rasmussen and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949).

[9] J. Volhard, *Ann.*, **253**, 206 (1890).

[10] J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

[11] Melting points were taken in open capillaries and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer and calibrated with polystyrene film. N.m.r. spectra were taken on a Varian A-60 spectrometer, in trifluoroacetic acid solution, with tetramethylsilane as an internal standard.

chloroform) showed a single carbonyl absorption band at 1795 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.50; H, 5.45.

Attempted Aromatization of I.—The bisanhydride I (1.0 g.) was heated with 0.2 g. of sulfur in a sublimation tube at 220° for 30 min. Hydrogen sulfide was copiously evolved. The residue was sublimed at 100° and 0.75 mm. for 24 hr., and the sublimate was leached with carbon disulfide for 12 hr. Extraction of the residue with ether and concentration of the extracts gave a yellow solid. Its infrared spectrum (Nujol) showed anhydride bands at 1850 and 1785 cm.$^{-1}$, and the n.m.r. spectrum showed aromatic protons (3H) at τ 2.3 and unresolved multiplets from τ 6.3 to 7.3 (5H). The substance could not be obtained analytically pure.

Conversion of I to IIe.—A mixture of 2.5 g. of the bisanhydride I and 1.0 g. of sodium hydride (50% dispersion in mineral oil) in 30 ml. of toluene was refluxed under nitrogen for 24 hr. The toluene solution was filtered, washed with water, and concentrated under reduced pressure to yield 0.41 g. (20%) of dilactone IIe. Recrystallized from ethyl acetate, it melted at 150–151°, alone or admixed with an authentic sample, and its infrared spectrum was identical with that of the dilactone obtained above.

Preparation of Dimethyl Ester IV.—Following the procedure of Alder and Munz,[4] 0.6 g. of IIe was refluxed in 6 ml. of methanol containing 5 drops of concentrated sulfuric acid for 2 hr. Extraction of the cooled reaction mixture with ether and concentration of the extracts gave 0.47 g. (64%) of the ester. Recrystallized from aqueous methanol, it melted at 63–64° (lit.[4] m.p. 65°). The infrared spectrum (in chloroform, carbon tetrachloride, or carbon disulfide) showed a single, sharp band in the carbonyl region at 1745 cm.$^{-1}$.

Interconversion of Dilactone IIe and Diacid III. A.—A mixture of 0.20 g. of IIe, 0.1 g. of sodium carbonate, and 6 ml. of water was refluxed for 2 hr. The solution was filtered and acidified with concentrated hydrochloric acid. On cooling, 0.07 g. (32%) of crystalline diacid III precipitated; after recrystallization from acetonitrile, it melted at 177–179° (lit.[4] m.p. 177–179°). The infrared spectrum (Nujol) showed carbonyl bands at 1733 and 1700 cm.$^{-1}$.

B.—A solution of 70 mg. of diacid III in 2.5 ml. of acetic anhydride was refluxed for 2 hr., filtered, and concentrated at reduced pressure. The residue was recrystallized from ethyl acetate to afford 39 mg. (60%) of dilactone IIe, m.p. 150–151°. Identity was confirmed by comparison of infrared spectra and mixture melting point determination.

Acknowledgment.—We wish to express our gratitude to the Procter and Gamble Company for a fellowship to Hugh J. Barger, Jr.

The 2-Thia-1,2-dihydro- and -tetrahydrodicyclopentadienes[1]

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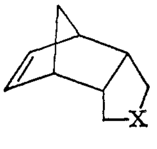
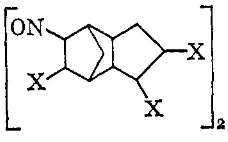
Received October 7, 1964

The preparation of methanesulfonate esters of six bicyclic 1,4-butanediols and the synthesis of *endo*- (IV), *exo*- (V), and *trans*-2-thia-1,2-dihydrodicyclopentadiene (VI) and the respective saturated sulfides (VII, VIII, and IX) are reported. The sulfonium salt (XVIII), which represents a new ring system, is also discussed.

It has been of particular interest in this laboratory to investigate the effect of hetero atoms at the 2-position of 1,2-dihydro-*endo*-dicyclopentadiene upon the steric course of reactions with acidic reagents. Compounds such as 2-oxa-1,2-dihydro-*endo*-dicyclopentadiene (I) and 2-aza-1,2-dihydro-*endo*-dicyclopentadiene (II) have been prepared and their chemical reactivity has been investigated.[2-7] Haloamines (alkyl halides) of one of these compounds[2,5] (II) and several *vic*-dihalo-1,2-dihydrodicyclopentadienenitroso halide dimers[8] (III) appear to contain an incipient mustard moiety which reacts like an alkylating agent with certain nucleophilic substances. In a search for additional compounds in which incipient mustard agents (evidenced by anchimeric and/or interannular effects) may be present, a variation of an established synthetic method has been successfully employed to prepare 2-thia-1,2-dihydro-*endo*-dicyclopentadiene (IV), the first of a new sulfide type. Also, 2-thia-1,2-dihydro-*exo*-dicyclopentadiene (V) and the *trans* isomer (VI) have been synthesized, as well as the three saturated sulfides, 2-thiatetrahydro-*endo*-dicyclopentadiene (VII), the *exo* isomer (VIII), and the *trans* isomer (IX).



I, X=O
II, X=NH



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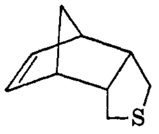

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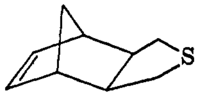

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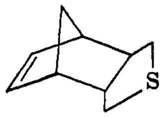

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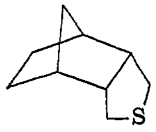

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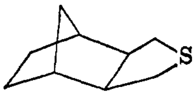

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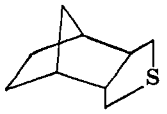

IX

It is of considerable interest that the progenitors of these sulfides, the methanesulfonate esters of the bicyclic 1,4-butanediols, are structurally related to the anticancer drug Myleran. These dimesylates of established stereochemistry provide an opportunity to study the stereochemical influences upon physiological activity in compounds related to Myleran.

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[1] (a) Taken in part from a thesis submitted by L. A. Feliu-Otero to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree, 1965. (b) The support of this research in part by Research Grant CA-4298 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, and in part by funds from an American Cancer Society Institutional Grant to Duke University is gratefully acknowledged.

[2] P. Wilder, Jr., and C. F. Culberson, *J. Am. Chem. Soc.*, **81**, 2027 (1959).

[3] C. F. Culberson and P. Wilder, Jr., *J. Org. Chem.*, **25**, 1358 (1960).

[4] C. F. Culberson, J. H. Seward, and P. Wilder, Jr., *J. Am. Chem. Soc.*, **82**, 2541 (1960).

[5] C. F. Culberson and P. Wilder, Jr., *ibid.*, **82**, 4939 (1960).

[6] P. Wilder, Jr., and C. F. Culberson, *Chem. Ind.* (London), 1118 (1961).

[7] D. J. Cash, unpublished results, this laboratory.

[8] P. Wilder, Jr., and C. F. Culberson, *J. Org. Chem.*, **26**, 3556 (1961).