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Ethyl Propenyl Ketone as a ψ-Diene in the Diels-Alder Reaction

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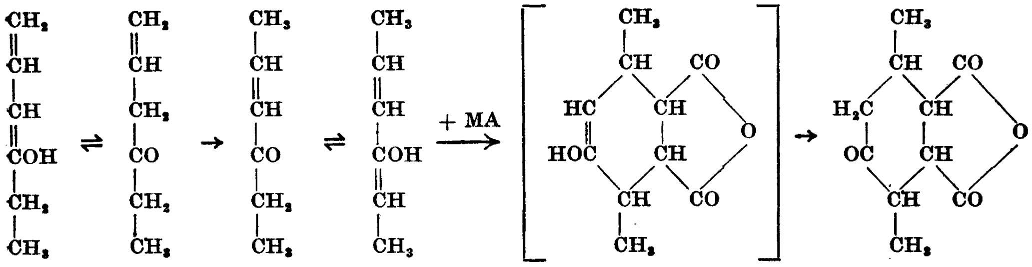
A crystalline adduct was formed by heating ethyl allyl ketone with maleic anhydride. The ψ-diene was, however, found to be ethyl propenyl ketone into which the ethyl allyl ketone isomerizes during the heating. The adduct by Clemmensen reduction gave a 3,6-dimethylhexahydrophthalic acid which could be resolved optically.

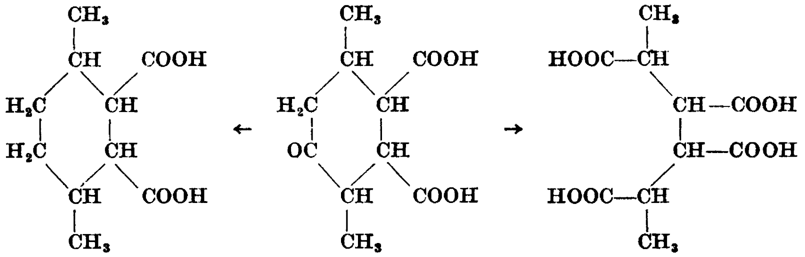
Some years ago the author[1] pointed out that a β-diketone might exist in a dienol form containing conjugated double bonds and accordingly ought to react with maleic anhydride and other dienophilic compounds. It was indeed found that acetylacetone reacted with maleic anhydride but the reaction proceeded in a way quite different from the expected one, an adduct being actually formed from two molecules of maleic anhydride and one of the diketone. Subsequently it was found that also citraconic anhydride reacted with acetylacetone, but neither in this case did the reaction proceed as expected, the reaction product being a furan derivative[2].

From the literature[3] some few examples are known showing that unsaturated aldehydes or ketones can react as ψ-dienes in Diels-Alder reactions. In the present case it was found of interest to investigate the behaviour of ethyl allyl ketone (I) as its enol (II) would contain a conjugated system. The ketone I actually reacted with maleic anhydride when heated for some days to 90°, but the crystalline adduct, although it had the calculated composition, did not behave as expected if the enol II had been the diene component. The adduct was thus completely saturated and had retained the carbonyl function of the ketone. The reason for this is that the ethyl allyl ketone on heating with the maleic anhydride did isomerize to ethyl propenyl ketone (III) the enol of which (IV) reacted with the maleic anhydride (MA) to give the adduct VI. The enolic form V is obviously an unstable intermediate. For the preparation of the adduct it was then of course found practical to isomerize the ethyl allyl ketone in a separate operation and then carry out the Diels-Alder reaction with the pure ethyl propenyl ketone.



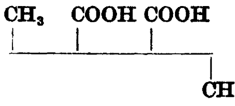
II I III IV V VI

The free dicarboxylic acid (VII) corresponding to the adduct could be resolved into optically active components. By reduction the same acid gave a hydroxy-acid which was easily transformed into a lactone. The acid VII further on Clemmensen reduction gave a 3,6-dimethylhexahydrophthalic acid (VIII) and on oxidation with nitric acid the open-chained hexane-2,3,4,5-tetracarboxylic acid (IX).

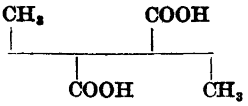


VIII VII IX

As the hexahydrophthalic acid VIII could be resolved optically and the carboxyl groups, due to their origin from maleic anhydride, must be *cis* to each other the methyl groups can only be in *trans* position to each other. The acid VIII ought therefore to be identical with the $3^c,6^t$-dimethyl*cyclo*hexane-$1^c,2^c$-dicarboxylic acid prepared by Alder and Vogt[4] by hydrogenating the adduct of *cis-trans*-1,4-dimethylbutadiene and maleic anhydride. These authors, designating the acid according to their scheme as the Bα-form (X), gave the m. p. as 134°, while we have found 121° for the inactive acid. The discrepancy may most probably be due to dimorphism. It could also be due to a partial spontaneous resolution taking place during the crystallization (we have found m. p. 138° for the active acid), but we have on crystallizing the acid repeatedly from the same solvent as used by Alder and Vogt never observed any deviation of the m. p. from 121°. That the acids m. p. 121° and 134° are identical is, however, evident from the fact that both on isomerization by heating with concentrated hydrochloric acid procured the all-*trans* form XI (Bβ) for which we found the m. p. 185°, while Alder and Vogt gave m. p. 183°.

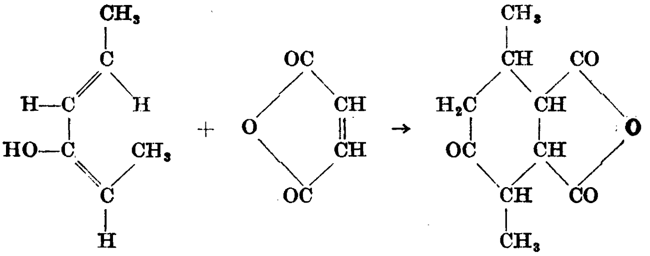


X (Bα)



XI (Bβ)

From the configuration of the acid VIII and the general rules set up by Alder and Schumacher [5], 1) that the diene component reacts according to the "*cis*-principle", 2) that an acyclic diene reacts in its quasi-cyclic form, and 3) that the orientation-complex has maximum congestion of the double bonds, it can be concluded that the enol IV taking part in our reaction must have the configuration *cis-trans* (*cis* referring to the position of the methyl group at the double bond formed by the enolization). The formation of the adduct, which may be designated as the anhydride of 2,5-dimethyl-3,4-dicarboxy*cyclo*hexanone, can therefore be written



IV VI

However, from the experimental data available it is not possible to decide whether the methyl group in position 2 or that in 5 (CO = 1) is the one being in *trans* position to the three other substituents.

EXPERIMENTAL

(Melting points not corrected)

Ethyl allyl ketone and maleic anhydride. Ethyl allyl ketone (25 g), prepared according to Blaise [6], and maleic anhydride (25 g) were mixed and heated for 4 days to 90°, the colour in the end becoming brownish red. After cooling to room temperature the mixture was inoculated with crystals obtained by a preliminary experiment. Next day the adduct was filtered off by suction and washed thoroughly with ethanol when it became practically colourless. It weighed 15.2 g. The mother liquor from this first fraction after heating for three more days gave 4.8 g crystalline adduct. Yield in all 40 %. Recrystallized from ethyl acetate. M. p. 146°. (Found: C 61.38, 61.25; H 6.19, 6.16. Calc. for $C_{10}H_{12}O_4$ (196.2): C 61.21; H 6.17.)

Isomerization of ethyl allyl ketone. Ethyl allyl ketone was mixed with twice its volume of 20 % sulphuric acid and refluxed for one hour. The ketone was taken up in ether and the solution dried with sodium sulphate. After removing the ether the residue was fractionated twice. The fraction boiling at 137—138° consisted of the ethyl propenyl ketone which gave a semicarbazone with m. p. 160° (Blaise [6] found 157°).

Ethyl propenyl ketone and maleic anhydride. The ketone (13.5 g) and maleic anhydride (13.5 g) were heated for 3 days to 90° when a first fraction of adduct (6.0 g) was obtained.

Further heating for 3 days of the mother liquor gave a second fraction of 5.2 g adduct, both fractions washed with ethanol. Yield in all 41.5 %. After recrystallization from ethyl acetate, m. p. as above 146°.

Investigation of the adduct. The adduct could be sublimated unchanged in a high vacuum, after which it had m. p. 145°, recrystallized from ethyl acetate m. p. 146°. A solution of the adduct in chloroform did not add bromine, nor did an aqueous solution react with bromine-water.

The free acid (VII) was obtained by dissolving the adduct in N sodium hydroxide and adding an excess of 2 N sulphuric acid. On standing hard crystals separated which after recrystallization from water had m. p. 206—207°. The same acid was obtained by dissolving the adduct in boiling water and evaporating the solution or by dissolving it in conc. sulphuric acid and pouring the solution on ice. (Found: C 55.93, 55.89; H 6.63, 6.54; M by titration 216.4. Calc. for $C_{10}H_{14}O_5$ (214.4): C 56.07, H 6.59.)

The original adduct was recovered from the acid VII by dehydration. For this purpose the acid (0.5 g) was pulverized and refluxed for 2 hours with acetyl chloride (5 ml). The solution on evaporation in a vacuum desiccator above potassium hydroxide gave a crystalline residue which after recrystallization from ethyl acetate had m. p. and mixed m. p. 145°.

The methyl ester of the acid VII was prepared by means of diazomethane. After evaporating the ethereal solution the ester crystallized spontaneously. It had m. p. 52—53° but was not recrystallized owing to its great solubility in most solvents. For preparation of the hydrazone a solution of 2,4-dinitrophenylhydrazine in hydrochloric acid was added to the ester dissolved in ethanol. The hydrazone separated immediately as an oil which crystallized on scratching. Recrystallized from ethanol, m. p. 177°. (Found: C 51.30; H 5.25; N 13.26. Calc. for $C_{18}H_{22}O_8N_4$: C 51.18; H 5.25; N 13.26.)

Optical resolution of the acid VII. Preliminary experiments gave crystalline salt of the acid with strychnine when used in the molecular ratio 1:1. The acid (2.7 g) and strychnine (4.2 g) were dissolved in water (50 ml) at room temperature and the solution inoculated. The strychnine salt (2.1 g) which had separated during the night was decomposed by adding 10 ml N hydrochloric acid. After removing the strychnine hydrochloride by filtration the active acid was extracted with ether and was obtained as a crystalline mass (0.35 g) which melted at 195—199° and had $[\alpha]_D^{20} = -21.5°$ (water, *c* 3).

Oxidation of the acid VII with nitric acid. To a solution of the adduct (2 g) in water (60 ml) was added conc. nitric acid of sp. gravity 1.4 (11 ml) and the solution heated on the steam-bath. In a few minutes the solution became light blue, the colour soon changing into greenish and then yellow and an evolution of nitric oxide set in. After heating for 20 min. the solution was evaporated slowly at room temperature. The crystalline residue was washed with a small amount of water and crystallized twice from water. A final recrystallization from 2 N hydrochloric acid gave beautifully developed hexagonal prisms, M. p. 202°. (Found: C 45.81; H 5.31. Calc. for $C_{10}H_{14}O_8$ (262.2): C 45.80; H 5.38.)

Esterification: A solution of the acid m. p. 202° (0.2 g) in 20 ml methanol containing 4 % hydrogen chloride was refluxed for 7 hours. A part of the methanol (15 ml) was distilled off and replaced by new methanol containing hydrogen chloride. The refluxing was continued for 4 hours after which most of the methanol was evaporated. The residue was neutralized with sodium carbonate and the ester taken up in ether. From the ethereal solution the ester was obtained as an oil (0.17 g) which after some time crystallized. Recrystallized from dilute methanol. M. p. 50°. (Found: C 52.59; H 7.05; OCH_3 38.90. Calc. for $C_{14}H_{22}O_8$ (318.3): C 52.82; H 6.97; OCH_3 39.00.)

Reduction of the acid VII with sodium amalgam. The adduct (2 g) dissolved in 0.5 N sodium hydroxide (40 ml) was treated with 4 % sodium amalgam at 50—60° until a sample did not give precipitate with dinitrophenylhydrazine. The solution was neutralized and concentrated somewhat on the water-bath. After adding 10 ml 5 N sulphuric acid and standing over night the hydroxy-acid had separated (1.7 g). Recrystallized from water. M. p. 196—197°. (Found: C 55.55; H 7.47. Calc. for $C_{10}H_{16}O_5$ (216.2): C 55.54; H 7.46.)

On refluxing the above 2,5-dimethyl-3,4-dicarboxy*cyclo*hexanol with five times its weight of acetic anhydride for 2 hours it was converted into a lactone. The lactone after being isolated by evaporating the solution in a vacuum was recrystallized twice from benzene. M. p. 135°. Dissolved in dilute ethanol it could be titrated as a monobasic acid. (Found: C 60.52; H 7.14; M 200.0. Calc. for $C_{10}H_{14}O_4$ (198.2): C 60.59; H 7.12.)

Clemmensen reduction of the acid VII. Pieces of zinc sheet (10 g) were treated for half an hour at room temperature with a 5 % solution of mercuric chloride. After washing the zinc with water 15 % hydrochloric acid (20 ml) and adduct (4 g) were added and reduction effected by refluxing for 3 hours. The dimethylhexahydrophthalic acid separated as an oil which crystallized on standing. It was isolated by extraction with ether. Yield 3.0 g. The acid after crystallization from water had m. p. 120°. On recrystallization from acetonitrile the m. p. rose to 121° and this m. p. remained unchanged on recrystallizing the acid repeatedly from the same solvent. (Found: C 59.95, 59.84; H 8.10, 8.07; M by titration 203.7. Calc. for $C_{10}H_{16}O_4$ (200.2): C 59.98; H 8.06.)

Resolution of the acid m. p. 121°. Strychnine and cinchonine did not give crystalline salts. Brucine, however, when used in the ratio 2 moles alkaloid to 1 mole acid was effective. The acid (1 g) and brucine (3.4 g) were dissolved in ethanol (10 ml) by heating gently. On standing at room temperature for 5 days 1.2 g brucine salt had separated. It was dissolved in 2 N hydrochloric acid and the active acid (0.23 g) isolated by extraction with ether. This crude acid which in ethanol had $[\alpha]_D^{20} = -13.0°$ was recrystallized from a small amount of water. The first fraction consisted of practically inactive acid, m. p. 120–121° and $[\alpha]_D^{20} = -1.6°$. Evaporation of the mother liquor gave a laevorotatory acid with m. p. 138° and $[\alpha]_D^{20} = -29.3°$ (ethanol, c 2.5). The filtrate from the 1.2 g brucine salt gave a crude dextrorotatory acid with $[\alpha]_D^{20} = +4.2°$.

Isomerization of the acid m. p. 121°. The acid (0.4 g) was heated to 180° in a sealed tube with conc. hydrochloric acid (5 ml) for 5 hours. After diluting with water extraction with ether gave a partly crystallized residue which on a porous tile left 0.2 g crystalline acid. Recrystallized several times from acetonitrile, m. p. 185°.

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