[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY CHEMISTRY LABORATORY]

DIELS-ALDER REACTIONS OF 2-METHOXY-1,3-BUTADIENE

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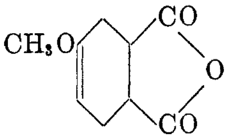
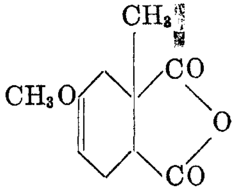
The work herein reported was undertaken in order to obtain information on the behavior of 2-methoxy-1,3-butadiene in Diels-Alder reactions with certain dienophiles. This information was desired because of the possibility of synthesis of steroid compounds containing a ketonic group in position 11 by suitable Diels-Alder reactions followed by further synthetic operations.

2-Methoxybutadiene has been shown to react with maleic anhydride (1) to yield a product which on hydrolysis was converted to 4-ketohexahydrophthalic acid. However, the experiments were not described and no properties of the adduct or ketoacid were given. The reactions of methoxybutadiene with acrolein and crotonaldehyde (2) to give products having the structure predicted on the basis of the electronic polarization theory of the Diels-Alder reaction (3) are reported.

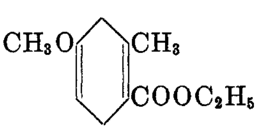
We have studied the reactions of 2-methoxybutadiene (I) with maleic anhydride (II), citraconic anhydride (III), and ethyl 2-butynoate (IV) to yield the adducts, V, VI, and VII respectively.



V



VI



VII

The structure V was supported by hydrolysis (alkaline and acid) to 4-ketohexahydrophthalic acid (probably *trans*) and reduction to the known (4) *trans*-hexahydrophthalic acid. It is likely that the original adduct was *cis* but the isomerization to *trans* took place during alkaline hydrolysis.

The structure of VI was not established and rests on analogy (3). There was evidence that the keto-methylhexahydrophthalic acid produced on hydrolysis was a mixture which, however, was predominantly one isomer.

The structure of VII was established by converting VII to Hagemann's ester (5), ethyl 2-methyl-4-ketocyclohexenecarboxylate (Δ^1 or Δ^2). This provides an interesting new route to Hagemann's ester and to variations thereof in which the alkyl group in the 2-position may be varied by varying the alkynoate originally used.

EXPERIMENTAL[2]

2-Methoxybutadiene was prepared by pyrolysis of 1,3,3-trimethoxybutane (6) and was stored over hydroquinone in an ice box. *Maleic anhydride* and *citraconic anhydride* were

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[1] The material herein presented was taken from the Ph.D. thesis of H.A.L., Ohio State University, 1951. Present address of H.A.L., National Heart Institute, Bethesda, Maryland.

[2] All melting points are corrected.

freshly distilled before use. *Ethyl 2-butynoate*, b.p. 97–98° at about 65 mm., was prepared in 85% yield by esterification of the acid using the benzene-ethanol-water azeotrope method. The required *2-butynoic acid* was prepared as follows. A propyne solution (7) in liquid ammonia was prepared from sodium acetylide (1.1 moles of sodium in 500 cc. of liquid ammonia) and 95 g. of methyl bromide and was cooled by a Dry Ice-acetone bath. To this was added a suspension of the sodium amide prepared (8) from 1.1 moles of sodium in 500 cc. of liquid ammonia followed by 250 cc. of dry benzene. The cooling bath and reflux condenser were removed and most of the ammonia allowed to evaporate overnight. More benzene (250 cc.) was added and the remaining ammonia removed by stirring and warming under a stream of dry nitrogen for four hours. About 500–600 g. of powdered solid carbon dioxide was added slowly to the stirred mixture which was then allowed to stand overnight. A saturated solution of 200 g. of potassium bisulfate in water was added slowly with vigorous stirring. The acid was isolated by ether extraction and distillation in a yield of 50% based on methyl bromide (42 g., b.p. 90–98° at about 18 mm.). This crude acid was used directly for esterification.

TABLE I

REACTIONS OF 2-METHOXYBUTADIENE WITH CITRACONIC ANHYDRIDE

TIME OF REFLUX	DISTILLED ADDUCT[a]	YIELD[b]
hrs.	*g.*	%
5	0.5	10.9
10	1.2	26.1
22	2.0	43.5
30	2.4	52.2
45	2.9	63.0
56	3.25	70.7
73	3.75	81.5
146	4.35	94.5[c]

[a] B.p. 105–110° at 1 mm. [b] Calculated on diene.

[c] Distillation of the remaining reaction mixture afforded the adduct in 95% yield.

Reaction of 2-methoxybutadiene (I) *with maleic anhydride* (II). In the best of several experiments a solution of 11 g. of I in 100 cc. of benzene[3] was added to a solution of 19.2 g. of maleic anhydride in 100 cc. of benzene. A slight rise in temperature was noted. After standing overnight the mixture was refluxed for four hours. After filtration from a small amount of colorless solid (when necessary) the solvent was removed and the residue distilled to yield 21.1 g. (93.5%) of a colorless liquid adduct, V, b.p. 123–125° at 1 mm. About 1 g. of brittle resin remained. Four grams of V was dissolved by refluxing with a solution of 2 g. of sodium hydroxide in 10 cc. of water. The hot solution was decolorized with charcoal (Darco G-60), made acidic with hydrochloric acid, boiled a few minutes, and taken to dryness under reduced pressure. After drying in a vacuum-oven at 80°, 6.8 g. of solid was obtained. This was extracted with dry acetone in a Soxhlet to yield 3.95 g. (96.5%) of yellowish crystals, m.p. 154–158°. Two recrystallizations from acetic acid afforded colorless crystals of 4-ketohexahydraphthalic acid, m.p. 160.2–161.2°, with little loss.

Anal. Calc'd for $C_8H_{10}O_5$: C, 51.6; H, 5.4; N.E., 93.1.

Found:[4] C, 51.5; H, 5.4; N.E., 94, 92.

Attempts to prepare the 2,4-dinitrophenylhydrazone of this ketoacid were unsuccess-

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[3] The benzene used in these experiments was dry and free of thiophene.

[4] All analyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

ful. However, after esterification with methanolic hydrogen chloride, the derivative of the dimethyl ester was formed readily. After recrystallization from methanol it formed yellow-orange crystals, m.p. 120.5–123.5°.

Anal. Calc'd for $C_{16}H_{18}N_4O_8$: C, 48.7; H, 4.6; N, 14.2.

Found: C, 48.6; H, 4.4; N, 14.4.

The ketoacid (2.4 g.) was reduced (9) to yield 2 g. (90%) of slightly yellow crystals of *trans*-hexahydrophthalic acid. After recrystallization from water colorless crystals, m.p. 215–221° w. decomp., were obtained which did not depress the melting point of an authentic sample (4).

Reaction of 2-methoxybutadiene (I) *with citraconic anhydride* (III). A solution containing 21 g. (0.25 mole) of I, 56 g. (0.50 mole) of III, 0.2 g. of pyrogallol, and 300 cc. of benzene[3] was refluxed in an all-glass apparatus. After various intervals 35 cc. of the solution (homogeneous at all times) was removed for analysis by distillation under reduced pressure. The results are summarized in Table I. Other conditions which included heating the components without solvent at 80° or in refluxing xylene were considerable less effective in producing the desired reaction, considerably more polymeric product being formed in each case. As the adduct, VI, could not be crystallized it was hydrolyzed with about 16% sodium hydroxide by short heating. The solution was decolorized with charcoal (Darco G-60), acidified, heated a few minutes, and taken to dryness under reduced pressure. The residue was continuously extracted with dry acetone in a Soxhlet. Removal of the solvent afforded a partly crystalline syrup which represented a quantitative yield of acid if calculated as ketomethylhexahydrophthalic acid. On recrystallization from glacial acetic acid-petroleum ether (b.p. 35–40°, Skellysolve F) colorless crystals, m.p. 145.2–146.4°, were obtained in high but not exactly determined yield.

Anal. Calc'd for $C_9H_{12}O_5$: C, 54.0; H, 6.0; N.E., 100.1.

Found: C, 54.3; H, 6.0; N.E., 100.9, 100.0.

Reaction of 2-methoxybutadiene (I) *with ethyl 2-butynoate* (IV). In the best of several experiments 21.7 g. (0.194 mole) of IV, 7 g. (0.0834 mole) of I, 0.2 g. of pyrogallol, and 40 cc. of benzene[3] were sealed in a Carius tube and heated at 200° for 3.5 hours. Rectification of the mixture afforded 13.2 g. of IV, 8.4 g. of VII (51.5% of the expected adduct calculated on I; b.p. 85–90° at 1 mm.), and 6–7 g. of polymeric residue. When a solution of 2 g. of VII in 10 cc. of alcohol containing a drop of hydrochloric acid was kept a few minutes and then treated in the usual way there was obtained 2.2 g. (90%) of crude semicarbazone. Two recrystallizations from alcohol afforded 1.4 g. (57%) of the *semicarbazone* of Hagemann's ester, m.p. and mixture m.p. with authentic sample,[5] 164–166°.

Anal. Calc'd for $C_{11}H_{17}N_3O_3$: C, 55.2; H, 7.2; N, 17.6.

Found: C, 55.6; H, 7.1; N, 17.5.

The adduct, VII, was further characterized by hydrolysis and decarboxylation to 3-methyl-2-cyclohexenone (10). Both the pure red *2,4-dinitrophenylhydrazone*,[6] m.p. 178.2–179.0°, and the colorless semicarbazone,[6] m.p. 193–194°, were obtained in 68% and 65% yields, respectively from the crude ketone obtained by hydrolysis of VII as described below. A mixture of 4 g. of VII and 40 cc. of 10% sulfuric acid was refluxed for 10 hours (5), the mixture becoming homogeneous after 5 hours. Evolution of carbon dioxide commenced soon after reflux started. The mixture was then made alkaline with excess solid potassium carbonate and extracted continuously with ether. On removal of solvent there remained 2 g. (89% if all pure ketone) of a pale yellow oil. This was diluted with 20 cc. of alcohol and aliquots were used to make the derivatives above mentioned.

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[5] We wish to thank Dr. John Hogg, the Upjohn Company, for an authentic sample of Hagemann's ester from which we prepared the semicarbazone.

[6] The melting points were not depressed by addition of pure authentic samples kindly furnished by Dr. G. F. Woods.

SUMMARY

Conditions have been found under which 2-methoxy-1,3-butadiene reacts with maleic anhydride and citraconic anhydride to form Diels-Alder adducts in almost quantitative yields.

The condensation of this diene with ethyl 2-butynoate occurs less rapidly and in somewhat poorer yield to produce an adduct which on mild acid hydrolysis affords Hagemann's ester. Thus, a new route to Hagemann's ester and related compounds is at hand.

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