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Cycloaddition Reaction of Troponoids with Dimethyl Maleate

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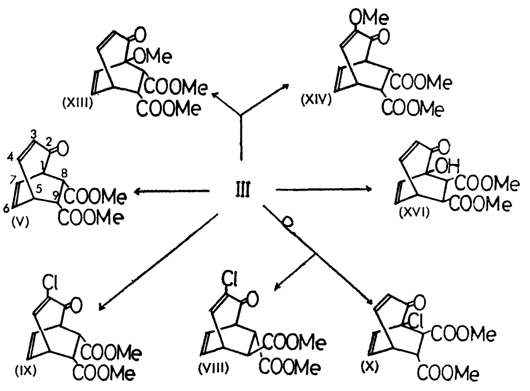
Synopsis. Thermal cycloaddition reaction of methyl maleate with tropone, 2-chloro-, 2-methoxytropone and tropolone was investigated. Each reaction yielded [4+2] type adducts with high peri- and stereospecificities but with less regioselectivity.

In a series of our studies on the Diels-Alder reaction of troponoids, it was shown[1,2] that maleic anhydride (I), a cyclic dienophile with symmetrical structure, yielded the *endo-cis*-adducts except in the case of tropolone(II), while acrylonitrile, an acyclic dienophile with unsymmetrical structure, yielded a mixture of *regio-* and *stereo* isomeric compounds.[3] The contrasting results there observed prompted us to investigate the reaction with another type of dienophiles, an acylic one with symmetrical structure. Thus, we have carried out the reactions with dimethyl maleate(III) for comparison.



When III was heated with tropone(IV), a single product, V, was obtained in 80% yield and its structure was established by direct comparison with the dimethyl ester of the hydrolysate of the adduct(VI) obtained from I and IV.[1]

The reaction of III with 2-chlorotropone(VII) afforded three 1 : 1-adducts, VIII, IX and X in 7, 11 and 7% yield, respectively. IX was shown to be identical with the corresponding dimethyl ester of the adduct(XI) derived from I and VII.[4] VIII exhibits three vinyl proton signals in its NMR spectrum (Table 1), indicating it be a 3-chloro-derivative. The configuration of the substituents was deduced as 8α, 9β-orientation on the basis of the observed coupling constants, $J_{1,8}=1.5$, and $J_{8,9}=6.0$ Hz.[5] Similarly X was identified as 1-chloro-8β,9α-isomer by the NMR evidences (four vinylic hydrogens (Table 1 and $J_{5,9}=2.0$, $J_{8,9}=4.5$ Hz).

Heating of III with 2-methoxytropone(XII), afforded two products, XIII and XIV, in 17 and 6% yield, respectively.[6] Since XIII was chemically correlated with the adduct(XV) obtained from I and XII,[2a] its structure was established to be 1-methoxy-8α,9α-derivative. On the other hand, XIV, having three vinyl proton signals and the coupling constants, $J_{1,8}=0$, $J_{8,9}=10.0$ Hz, in the NMR spectrum, was shown to be 3-methoxy-8α,9α-derivative.

Table 1. NMR Chemical shifts of the adducts[5]

	H_1	H_3	H_4	H_5	H_6	H_7	$H_{8\alpha}$	$H_{8\beta}$	$H_{9\alpha}$	$H_{9\beta}$	Me
V	3.95	5.80	7.05	3.70	6.53	6.22	COOMe	3.32	COOMe	3.60	3.61, 3.65
VIII	4.10	Cl	7.27	3.4—3.8	6.27	6.17	COOMe	3.4—3.8	3.4—3.8	COOMe	3.75, 3.75
IX	3.4—4.1	Cl	7.40	3.4—4.1	6.62	6.27	COOMe	3.4—4.1	COOMe	3.4—4.1	3.69, 3.72
X	Cl	6.05	7.03	3.77	6.53	6.13	4.03	COOMe	COOMe	3.40	3.73, 3.77
XIII	OMe	5.88	7.22	3.97	6.75	6.25	COOMe	3.35	COOMe	3.5—3.7	3.53, 3.61, 3.65
XIV	4.13	OMe	6.02	~3.9	6.52	6.22	COOMe	3.33	COOMe	~3.5	3.51, 3.65, 3.67
XVI	OH	5.98	7.32	3.9—3.5	6.53	6.15	3.5—3.9	COOMe	3.45	COOMe	3.65, 3.63

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The reaction of III with II was somewhat complicated yielding a mixture, and only the adduct XVI was isolated in 10% yield after the extensive silica-gel column chromatography. The NMR spectrum of XVI revealed the presence of four vinylic hydrogens and *exo-cis*-orientation for the ester groups.[7]

The present result revealed that the reaction of III with troponoids proceeded stereospecifically: All the adduct are free from their stereoisomers with opposite orientation of ester groups. This control of stereoselectivity of substituents on tropone ring is remarkable. Thus, the transition states leading to the *endo-cis* adducts are stabilized more than those to *exo-cis* products. The formation of *exo-cis* product XVI can be rationalized as the result of *endo* addition, followed by an isomerization, which are previously observed in the cycloaddition of tropolone.[2] In spite of the high stereospecificity, the regiospecificity is somewhat reduced: The formation of XIV as a minor adduct contrasts the case of maleic anhydride[1] and resembles with the case of acrylonitrile.[3]

The *trans*-adducts, VIII and X, whose formation apparently conflicts with the general rule of concerted cycloaddition, should be regarded as the adducts of not III but dimethyl fumarate (XVII), since the recovered unsaturated ester fraction in this particular case was consisted of XVII and no trace of III was detected. Some amounts of hydrogen chloride liberated by the decomposition of VII should be sufficient for this isomerization.[8,9]

Experimental

The Reaction of Dimethyl Maleate (III) with Tropone(IV). Formation of endo-cis-*Adduct(V).* IV(2 g) and III (4 g) were heated in a sealed tube(glass) for 18 hr at 130—140 °C. From the reaction mixture, III was removed by distillation *in vacuo*, and the residual mass was sublimed on a cold finger at 120 °C/2 mmHg to give V (3.6 g), colorless crystals, mp 86—88 °C(lit,[1] 83—87 °C), whose identity was confirmed by a direct comparison with the authentic sample.

*The Reaction of III with 2-Chlorotropone (VII). Formation of 3-Chloro-*endo-cis-*adduct(IX), 3-Chloro-*$8\alpha,9\beta$-trans-*adduct (VIII) and 1-Chloro-*$8\beta,9\alpha$-trans-*adduct(X).* VII(415 mg) and III(1.10 g) were heated in a similar manner for 20 hr at 150 °C. The reaction mixture was sublimed on a cold finger at 70 °C/2 mmHg to separate dimethyl fumarate (XVII), 870 mg. The residue was further distilled at higher temperature(120—140 °C/2 mmHg) to give a colorless liquid, 230 mg, which was then chromatographed on silica gel column to obtain VIII(a colorless liquid, 50 mg) (Found: C, 58.94; H, 4.46%. Calcd for $C_{13}H_{13}O_5Cl$: C, 58.87; H, 4.60%. ν: 1740, 1640, 1610 cm^{-1}), IX (colorless crystals, mp 172—173 °C (lit,[4] mp 172—173 °C), 90 mg, ν 1740, 1642, 1612 cm^{-1}), and X (colorless crystals, mp 177—179 °C, 50 mg) (Found: C, 59.01; H, 4.70%. ν: 1745, 1690 cm^{-1}).

*The Reaction of III with 2-Methoxytropone(XII). Formation of 1-Methoxy-*endo-cis-*adduct(XIII) and 3-Methoxy-*endo-cis-*adduct(XIV).* XII(400 mg) and III(1.0 g) were heated in a similar manner as the above for 15 hr at 150 °C. The reaction mixture was distilled *in vacuo* to remove unreacted III (620 mg). The residue was then distilled on a cold finger to give a colorless semi-soild, from which, a major component, XIII, was obtained by a filtration as colorless crystals (140 mg, mp 148—149 °C) (Found: C, 60.11; H, 5.67%. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75%. ν: 1750, 1675 cm^{-1}). The mother liquor of the above was then chromatographed on silica gel to give XIV (colorless crystals, mp 141—142 °C, 50 mg) (Found: C, 60.37; H, 5.60%. ν: 1747, 1680, 1635, 1617 cm^{-1}).

*The Derivation of 1-Methoxy-*endo-cis-*Adduct(XIII) from the adduct(XV) of I and XII.* XV (75 mg) was suspended in distilled water (3 ml) and heated for 30 min at 95—100 °C. After coling, separated colorless crystals were collected by filtration. Weight; 60 mg, mp 184—184.5 °C (Found: C, 57.16; H, 4.84%. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80%). The esterification of this specimen by diazomethane gave colorless crystals (mp 148—149 °C, 40 mg), whose identity with XIII has been established by a direct comparison.

*The Reaction of III with Tropolone(II). Isolation of 1-Hydroxy-*exo-cis-*Adduct(XVI).* II(400 mg) and III (1.0 g) were heated in a sealed tube for 15 hr at 145 °C and the reaction mixture was then distilled *in vacuo* to remove the unreacted III. The residue was fractionated by repeated column chromatography to yield XVI, colorless crystals, mp 95—101 °C, 45 mg (Found: C, 58.54; H, 5.22%. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30%. ν: 3450, 1745, 1685 cm^{-1}).

References and Footnotes

1) a) T. Nozoe, T. Mukai, T. Nagase, and Y. Toyooka, This Bulletin, **33**, 1147 (1960). b) S. Itô, H. Takeshita, Y. Shoji, Y. Toyooka, and T. Nozoe, *Tetrahedron Lett.*, **1968**, 3215.

2) S. Itô, A. Mori, Y. Shoji, and H. Takeshita, *ibid.*, **1972**, 2685.

3) S. Itô, H. Takeshita and Y. Shoji, *ibid.*, **1969**, 1815.

4) T. Nozoe and Y. Toyooka, This Bulletin, **34**, 623 (1961).

5) All NMR spectra were determined in deuteriochloroform solutions and parameters were obtained by first-order analysis.

6) The formation of third product was recognized, but due to a limited quantity available, no characterization was made.

7) Chemical correlation of XVI with the *exo-cis*-adduct of I and II was not attempted, since the latter is known to cause lactonization under a hydrolysis condition. see Ref. 1b.

8) A. Kekule and O. Strecker, *Ann. Chem.*, **183**, 170 (1884).

9) The reaction of XVII with the troponoids is a subject of the independent paper which will be published in due course.