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Thiosteroids. XXIII.[1] Diels Alder Reactions of 5′-Methylfuro-[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione

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5′-Methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione was treated with maleic anhydride, dimethyl acetylenedicarboxylate, dimethyl fumarate and benzyne, respectively, to yield the 1:1 adducts. The stereochemistry of these adducts was studied and the unexpected β-attack by the dienophiles was deduced from the NMR data.

In the previous paper[1] it was reported that treatment of 5′-methylfuro[4′,3′,2′,-4,5,6]-pregn-5-ene-3,20-dione (I) with one mole of maleic anhydride gave the 1:1 adduct (II). The present paper deals with the extension of this study, namely, the stereochemistry of this adduct as well as the adducts with some other dienophiles.

Whereas (I) was easily condensed with maleic anhydride to form the 1:1 adduct (II), no reaction of 5′-methylthieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione with the reagent occured. The adduct (II) was moderately stable but on treatment with acid or alkali the parent furo steroid (I) to be expected as product of a retro-Diels Alder reaction was obtained. Diazo-

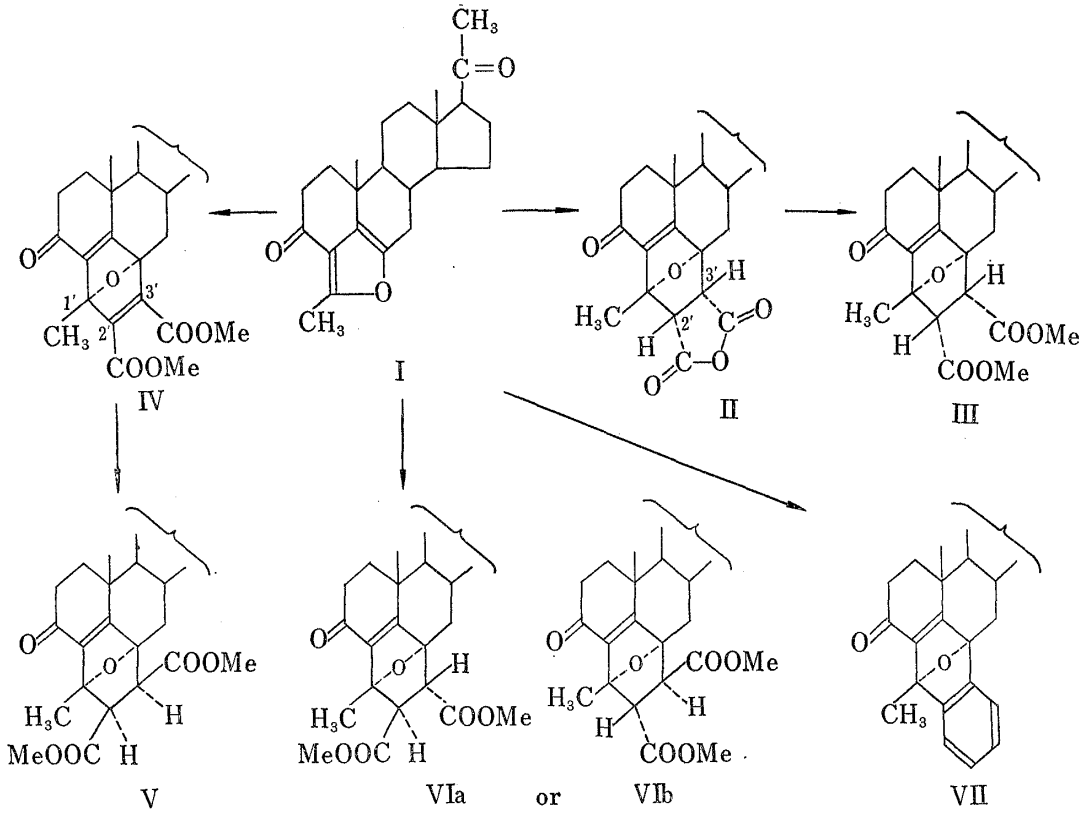


Chart 1

1) Part XXII: T. Komeno, S. Ishihara, K. Takigawa, H. Itani, and H. Iwakura, *Chem. Pharm. Bull.* (Tokyo), **17**, 2586 (1969).
2) Location: *Fukushima-ku, Osaka.*

methane in methanol transformed (II) into the dimethyl ester (III), mp 158°, in good yield. On the other hand (I) with dimethyl acetylenedicarboxylate in boiling benzene gave the 1:1 adduct (IV). The ultraviolet (UV) spectrum of (IV) exhibits the absorption maximum at 244.5 mμ (ε 14,920). Hydrogenation of (IV) over palladium–calcium carbonate gave the dihydro–dimethyl ester (V), mp 135°, which contains α,β-unsaturated ketone, λ_{max} 255 mμ (ε 9280). These two dimethyl ester, (III) and (V), show quite different properties. Since the dienophiles, maleic anhydride and dimethyl acetylenedicarboxylate, attack the furan ring from the same side, the difference expected should be in the orientation of the dimethyl ester groups. Woodward established *exo* configuration for the anhydride ring in the reaction product of furan with maleic anhydride by chemical means.[3,4] Hence the dimethyl ester (III) was also expected to have *exo* configuration. Then the dimethyl ester (V) should have *endo* configuration which meets the preferential *exo* attack of hydrogen on catalytic hydrogenation. It is also well known that the reaction of furan with maleic imide and maleic acid affords an *endo–exo* pair of adducts.[5] However, the reaction of the furo compound (I) with dimethyl maleate did not take place and (I) was recovered. The furo compound (I) was treated with dimethyl fumarate to give the 1:1 adduct (VI), mp 142°, dimethyl ester groups of which should be *trans*.

Table I. The UV and NMR Data of the Adducts of 5′-Methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione

Compound	UV: λ_{max}^{EtOH} mμ (ε)	NMR (τ) (in $CDCl_3$)						
		(18-H)	(19-H)	(21-H)	(1′-CH_3)	(COOMe)	(H)	(Ph-H)
II	250.5 (11,070)	9.28	8.82	7.88	8.14		6.77 s	
III	251 (10,830)	9.31	8.83	7.87	8.17	6.34	7.03 s	
IV	244.5 (14,920)	9.28	8.92	7.87	8.11	6.21		
V	255 (9280)	9.29	8.83	7.87	8.25	6.43 6.39	6.65 s	
VI	252 (9150)	9.27	8.68	7.85	8.09	6.37 6.23	6.92[a] 6.57[a]	
VII	227~231 (12,970) 297 (3230)	9.26	9.18	7.85	7.94			2.87 m

a) AB type quartet J_{AB}=4.0 cps

The nuclear magnetic resonance (NMR) and UV data of these five compounds are summarized in the Table I. In the NMR spectra of bicyclo[2,2,1]heptane derivatives it has been observed[4,6] that an *endo* proton appears at higher field than an *exo* proton does. This relationship is well maintained in the case of the *cis* dimethyl esters (III) and (V). Now a remaining problem to be clarified is the direction from which the dienophiles attack the furan ring. The 19-methyl in the adduct with dimethyl acetylenedicarboxylate (IV) was found to be more shielded by 0.09 ppm than in the adducts (II), (III), and (V). Since the signals of 19-methyl for (II), (III) and (V) have almost same value, 8.83 τ, the effect of *cis* dimethyl ester groups on the chemical shift of the 19-methyl seems to be negligibly small. A similar result was reported by Jones[7] in the adduct of ergosterol with dimethyl maleate. Consequently, this shielding effect was attributable to the diamagnetic anisotropy of the double bond at $C_{2'}$ and $C_{3'}$. Calculation by Nakagawa's equation,[8] using the parameters determined directly from

3) R.B. Woodward and H. Bear, *J. Am. Chem. Soc.*, **70**, 1161 (1948).
4) F.A.L. Anet, *Tetrahedron Letters*, **1962**, 1219.
5) J.A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **75**, 1721 (1953).
6) R.R. Fraseri, *Can. J. Chem.*, **40**, 78 (1962); S.W. Wong and C.C. Lee, *ibid.*, **42**, 1245 (1964) and cited ref.
7) R.N. Jones, *J. Chem. Soc.* (*C*), **1964**, 5206.
8) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).

a Cenco–Petersen model shows that the value of this shielding is 0.124 ppm in the β- and -0.013 ppm in the α-adduct.

This argument was further confirmed by cycloaddition of the furo steroid (I) with benzyne. The reaction of (I) with benzyne generated from *o*-azobenzoic acid[9] afforded the adduct (VII), mp 252°, in 75% yield. The structure was supported by the infrared (IR) and UV spectrum. In the NMR spectrum of this adduct four benzene protons appear centered at 2.87 τ and the 19-methyl protons are observed at 9.18 τ. Calculation according to the method of Johnson and Bovey[10] in a similar manner as above indicates that the value of shielding due to the benzene ring is 0.348 ppm in the β- and zero in the α-adduct. (Observed value: *ca.* 0.35 ppm)

An attempt was unsuccessful to convert the dimethyl maleate adduct to benzenosteroid by treatment with conc. sulfuric acid[11] or poly-phosphoric acid.[12]

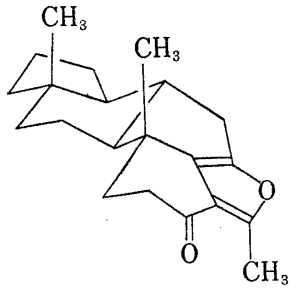
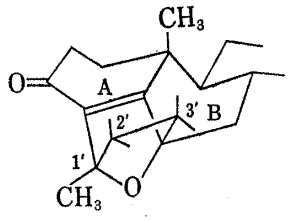
In the Diels–Alder reaction with steroidal 5,7-,[13] 2,4-,[14] and 16,20-diene,[15] it has been observed that dienophiles attack the molecule predominantly from the α-side owing to the steric hindrance caused by the angular methyl group. In this case, an examination with a Dreiding model indicates that the ring A and B of the furo steroid give rise to some distorsion due to the fusion with the furan ring. As the result thereof, the approach of the dienophile from the β-side should be facilitated. Finally for the dimethyl fumarate adduct, structure (VIa) is favored over (VIb) on account of the following consideration. Because of steric interaction with the 19-methyl group the transition state leading to (VIb) appears to be more crowded than the one for the formation of (VIa). The UV maximum of (VI) is similar to that of the adduct (III), which contains *cis exo* dimethyl ester groups. The bathochromic shift (4 mμ) observed in the UV spectrum of the *cis endo* dimethyl ester (V) may be caused by interaction between the α,β-unsaturated ketone and the *endo* $C_{3'}$-ester moiety because of the spacial proximity.

Experimental[16]

Esterification of the Maleic Anhydride Adduct (II)——To a solution of 132 mg of the maleic anhydride adduct (II) in 2 ml of MeOH a CH_2N_2–ether solution was added until evolution of N_2 ceased. The resulting mixture was kept standing at room temperature for 16 hr. The solvent was removed by distillation under reduced pressure. The residue was recrystallized from acetone–hexane to yield 142 mg (84.5%) of (III), mp 156—158°, $[\alpha]_D^{27.5}$ +22.0±2° (c=1.003). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1748, 1710, 1675, 1630, 1178. *Anal.* Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68. Found: C, 69.82; H, 7.77.

The Dimethyl Acetylene Dicarboxylate Adduct (IV)——A solution of 617 mg of 5′-methylfuro[4′,3′,2′-4,5,6]pregnene-3,20-dione (I) and 495 mg of dimethyl acetylenedicarboxylate in 7 ml of benzene was kept standing at room temperature for 10 days and the mixture was evaporated to dryness *in vacuo*. The residue

9) L. Friedman and F.M. Lognello, *J. Am. Chem. Soc.*, **85**, 1549 (1963); M. Stiles, R.G. Miller, and U. Burckhardt, *ibid.*, **85**, 85 (1963).
10) C.E. Johnson, Jr. and F.A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
11) W. Treibs, *Ann.*, **630**, 120 (1960).
12) W. Tochtermann, *Chem. Ber.*, **97**, 1329 (1964).
13) A. Windaus and A. Lüttringhaus, *Ber.*, **64**, 850 (1931); O. Tanaka and E. Mosettig, *J. Am. Chem. Soc.*, **85**, 1131 (1963).
14) P.N. Rao and H.R. Gollberg, *Chem. Ind.* (London), **1961**, 1317.
15) F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959); R.H. Mazur and G.P. Mueller, *Chem. Ber.*, **51**, 270 (1957); R.H. Mazur, *ibid.*, **51**, 4436 (1957); S.G. Levine, M.E. Wall, and N.H. Eudy, *J. Org. Chem.*, **28**, 1936 (1963); J.E. Pike, M.A. Rebenstorf, G. Slomp, and F.A. MacKeller, *ibid.*, **28**, 2499 (1963); V. Georgian and L.T. Georgian, *ibid.*, **29**, 58 (1964).
16) All melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined in 1% EtOH–$CHCl_3$ with a Perkin–Elmer Polarimeter, type 141. IR spectra were recorded with a Nihon Bunko Infrared Spectrophotometer Model DS-201B and UV spectra were measured with a Hitachi Recording UV Spectrophotometer, EPS-2. The NMR spectra were run in $CDCl_3$ solutions on a Varian A-60 spectrometer, tetramethylsilane serving as internal standard. For preparative TLC silica gel G (Merck Co.) was used as an adsorbent.

was subjected to chromatography over 20 g of neutral Al_2O_3 (Grade II). The eluate with pet. ether–benzene (3:1—2:1) was crystallized from pet.ether to give 583 mg (67.5%) of the adduct (IV), which was further recrystallized from acetone–hexane to yield the pure sample, mp 167—168°, $[\alpha]_D^{23.5}$ +33.0±2° (c =1.064). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1739sh, 1713, 1708, 1672, 1624, 1258. *Anal.* Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31; O, 22.55. Found: C, 70.43; H, 7.39; O, 22.65.

Hydrogenation of the Dimethyl Acetylenedicarboxylate Adduct (IV)——The adduct (IV) (500 mg) was dissolved in 24 ml of AcOEt and was hydrogenated over 50 mg of pre-reduced 10% Pd–$CaCO_3$. After 21.5 ml (1.1 equivalent) of H_2 was adsorbed, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from acetone–hexane to give 470 mg (90.4%) of (V), mp 138—140°, $[\alpha]_D^{27.5}$ −33.0±2° (c=1.109). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1764, 1740sh, 1710, 1674, 1641, 1204. *Anal.* Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68. Found: C, 69.69; H, 7.75.

The Dimethyl Fumarate Adduct (VI)——A solution of 202 mg of (I) and 174 mg of dimethyl fumarate in 2.4 ml of benzene was allowed to stand at room temperature overnight. The mixture was evaporated to dryness and the residue was submitted to the preparative TLC using cyclohexane–AcOEt (1:1) as developing solvent. The more mobile fraction yielded 63 mg of (I) recovered. The less mobile fraction gave 242 mg of crystals which upon recrystallization from acetone–hexane yielded 221 mg of (VI), mp 140—142°, $[\alpha]_D^{22.5}$ +52.1±2° (c=0.963). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1736, 1700, 1676, 1643, 1164. *Anal.* Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68. Found: C, 70.12; H, 7.77.

The Benzyne Adduct (VII)——A solution of 240 mg of anthranilic acid in 1.5 ml of tetrahydrofuran was added with stirring during 3 hr to a refluxing mixture of 300 mg of (I) and 222 mg of amyl nitrite in 5 ml of CH_2Cl_2. The resulting mixture was heated to 60—70° for an additional 1 hr, cooled, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue, dissolved in pet. ether–benzene (9:1), was chromatographed over 10 g of neutral Al_2O_3. The fractions eluted with pet. ether–benzene (9:1—7:3) were recrystallized from acetone–hexane to yield 272 mg (74.5%) of (VII), mp 250—252°, $[\alpha]_D^{27}$ +50.3±2° (c=1.025). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1703, 1658, 1602sh. *Anal.* Calcd. for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.95; H, 8.09.

Attempt to Convert (II) or (III) to a Benzenosteroid——a) The adduct, (II) or (III), (10 mg) was treated with 0.03 ml of conc. H_2SO_4 at room temperature for 1 hr, poured into ice water, and the mixture was extracted with CH_2Cl_2. After usual working up, the furo steroid (6 mg) was recovered.

b) The adduct (III) (20 mg) was treated with poly-phosphoric acid prepared from 507 mg of P_2O_5 and 0.6 ml of H_3PO_4 at room temperature for 15 min and the mixture was heated to 70—75° for an additional 1.5 hr. Working up afforded 13 mg of (I).

c) The adduct (III) (20 mg) was treated with 0.02 ml of $BF_3 \cdot OEt_2$ in 1 ml of tetrahydrofuran at room temperature for 65 hr. No change was observed on TLC and the usual working up gave 18 mg of the recovered adduct (III).

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