TRANSFORMED STEROIDS.

COMMUNICATION 148. 1,3-CYCLOADDITION OF DIAZOMETHANE AND DIAZOACETATE TO Δ^{15}-17-KETOANDROSTANE AT NORMAL AND HIGH PRESSURES

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The Dields—Alder reaction of steroid Δ^{15}-17-ketones ad dienophiles with butadienes proceeds nonstereospecifically withthe formation of two diastereomeric 15α,16α- and 15β,16β-cycloadducts [1, 2]. The activity of these ketones in the diene reaction was found to be lower than that with the Δ^{16}-20-ketodienophiles of the pregnane series [3]. In the present work, we studied the 1,3-cycloaddition of diazomethane and ethyl diazoacetate to androsta-5,15-dien-3β-ol-17-one acetate (I) and also the stereochemistry and certain transformations of the adducts obtained.

The reaction of (I) with excess ethereal solution of CH_2N_2 at 20°C and normal pressure for 14 h led to the cycloaddition product, Δ^1-pyrazoline (II) in a ∿90% yield; its catalytic cleavage by BF_3 etherate in acetone gave the corresponding cyclopropane (IV). The structure of (II) and (IV) was established from the data of their physicochemical analysis, while the β-configuration of the cyclopropane ring in (IV), and hence also pyrazoline (II), follows from the PMR spectra (see below).

The 15β,16β-cyclopropane (IV) was also obtained by an alternative synthesis by the reaction of (I) with dimethylsulfoxonium methide, followed by acetylation of the intermediate 3β-hydroxycyclopropane (V). The last compound was also converted into the corresponding Δ^4-3-keto product (VI) by oxidation according to Oppenauer.

In contrast to diazomethane, ethyl diazoacetate does not react with (I) under normal conditions (atmospheric pressure and temperature up to 150°C). The 1,3-cycloaddition product, Δ^1-pyrazolinecarboxylic acid ester (III), could be obtained by the reaction of (I) with a 1.5-fold excess of ethyl diazoacetate in CH_2Cl_2 at 14 kbar and 20°C for 6 h. Under high pressure conditions, in analogy with [1], the formation of the two diastereomeric 15,16-cycloadducts could be expected. The possible formation of the isomeric Δ^1- and Δ^2-pyrazolines [4] should also not be excluded and the regiodirectivity of this reaction could not be predicted. Nevertheless, compound (III) was isolated as the only reaction product (in a yield of 60%). The presence of a band at 1545 cm^{-1} in the IR spectrum of (III) indicates the Δ^1-pyrazoline structure. The data of the ^{13}C and ^1H NMR spectra are discussed below (reaction flowchart).

Thus, in this case, a primary product of the cycloaddition of diazoacetate was obtained, and it was shown that (III) does not isomerize into the Δ^2-pyrazoline containing the =N—NH grouping under different conditions tried (heating in organic solvents, prolonged holding, contact with sorbents, etc.). Compound (III) thus sharply differs from the labile 16α,17α-Δ^1-pyrazolinecarboxylic acid ester of the pregnane series [4]. The corresponding cyclopropanecarboxylic acid ester (VII) was obtained by thermal decomposition of (III).

To establish the structure and the stereochemistry, we studied the ^{13}C and ^1H NMR spectra of the products (Tables 1 and 2). The presence of 3'-carbethoxy-15,16-pyrazoline ring in (III) is indicated by the presence in the ^{13}C NMR spectrum of not only signals of the carbethoxyl group, but also of three doublets at 35.5, 94.1, and 104.4 ppm with $^1J_{^{13}C,^1H}$ = 142, 145, and 153 Hz, respectively, instead of two triplets at 21.9 and 35.8 ppm of the C^{15} and C^{16} atoms of the unsubstituted analog, androst-5-en-3β-ol-17-one acetate [5]. The doublet at 91.4 ppm was assigned to the $C^{3'}$ atom and that at 104.4 ppm was assigned to C^{16}, based on the high descreening effect of the carbonyl group, compared with that of the ester group (a similar difference in the $\delta^{13}C$ of methyl carbon atoms is observed for MeCHO and $MeCO_2H$ [6]).

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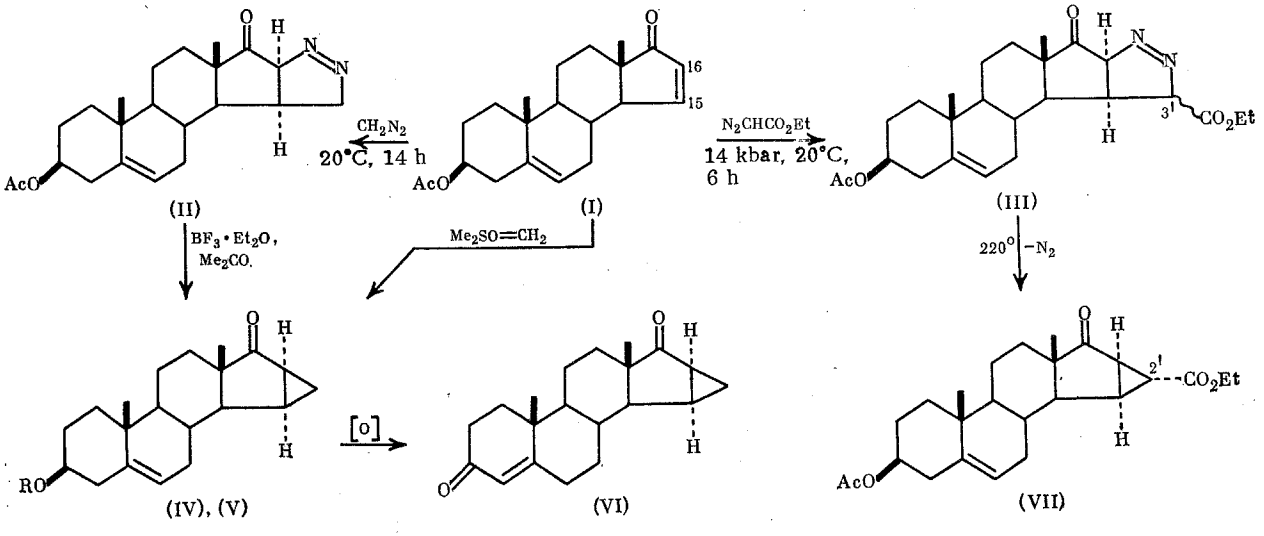

R = Ac (IV), H (V).

Reaction flowchart

TABLE 1. ^{13}C NMR Spectra of Compounds (III), (IV), and (VII) in $CDCl_3$ [δ, ppm (J, Hz)]

Carbon atom	Compound		
	III	(IV)	(VII)
1	36,83 t (128)	36,91t (127)	36,88 t (125)
2	27,56 t (129)	27,73 t (128)	27,70 t (129)
3	73,41d (148)	73,73 d (144)	73,64 d (149)
4	37,94 t (131)	38,17 t (129)	38,12 t (130)
5	140,26 s	140,52 s	140,57 s
6	121,18d (154)	121,78 d (156)	121,50 d (156)
7	30,42 t (125)	30,52 t (126)	30,50 t (126)
8	29,59d (127)	30,41 d (128)	30,21 d (128)
9	50,65 d (121)	50,11 d (122)	51,09d (123)
10	36,83 s	37,03 s	37,06 s
11	19,66t (124)	20,11 t (124)	20,03 t (127)
12	33,53 t (127)	35,49 t (129)	35,28 t (130)
13	47,80 s	42,11 s	42,70 s
14	49,13d (119)	52,23 d (123)	52,32 d (123)
15	35,48 d (142)	22,03d (169)	28,59d (177)
16	104,41 d (153)	25,77 d (176)	33,50d (180)
17	206,33s	216,10 s	212,88 s
18	16,15 q (131)	19,93 q (129)	19,78 q (127)
19	19,15 q (127)	19,18 q	19,17 q
2′ (IV), (VII) / 3′ (III)	94,06 d (145)	17,01 t (164)	28,95d (174)
CO_2Et	161,61 s, 62,33 t (149), 14,03 q (127)		170,35 s, 61,22 t (148), 14,15 q (128)
OCOMe	170,22 s, 21,18 q (130)	170,36 s, 21,33 q (130)	170,35 s, 21,32 q (129)

The formation of the cyclopropane fragment at C^{15} and C^{16} in (IV) is confirmed by the presence of two doublets at 22.0 and 25.8, and a triplet at 17.0 ppm with SSCC $J_{^{13}C,^1H}$ = 169, 176, and 164 Hz, respectively, which are characteristic of cyclopropanes. The doublets at 22.0 and 25.8 ppm are related to the C^{15} and C^{16} atoms, based on the experiment with the lanthanide shifting reagent (LSR) — $Eu(dpm)_3$. When an LSR is added in a ratio [LSR]/[substrate] = 0.3 for (IV) [0.35 for (VII)], the C^{15} and C^{16} signals are shifted by 0.6 and 1.4 ppm, respectively [for (VII) by 1.3 and 1.7 ppm]. A comparison of the ^{13}C NMR spectra of (IV) and (VII) (see Table 1) clearly shows that the cyclopropane fragment in (VII) includes a 2′-carboethoxyl group. This is indicated by the multiplicity of the cyclopropane ring signals (three doublets) and their shift, caused by the effect of the ester group: +12 ppm for $C^{2'}$ (the α-effect), +6.6 and +7.7 ppm for C^{15} and C^{16} (the β-effects), and −3.2 ppm for C^{17} (the γ-effect). The values of the SSCC $J_{^{13}C,^1H}$ of the cyclopropane fragment thus increase by 4-10 Hz.

The β-configuration of the cyclopropane rings in (IV) and (VII), and hence, the pyrazoline rings in (II) and (III) was ascribed on the basis of a comparison of the PMR spectral data (see Table 2) with those of the α- and β-series of certain 17-keto-15,16-methylenoandrostanes [7]. In the paper cited, the specificity of the values of δ of 18-Me protons for orientation of the cyclopropane ring was found. For compounds (IV) and (VII), the values of δ 18-Me, equal to 0.98 and 1.00 ppm, respectively, lie in the range of the chemical shifts characteristic of the 15β,16β-methyleno derivatives. However, as the result of cycloaddition, only one cycloadduct is formed, and the regions of the values of 15β,16β- and 15α,15α-methylenoandrostanes do not overlap, but differ little [7], and therefore the nuclear Overhauser effect (NOE) was used as an independent, more reliable proof of the stereochemistry of the products. It was found that during irradiation at the frequency of the 18-Me protons (δ 1.00 ppm), an increase in the intensity (by 4.8%) of the signal of only one proton at δ 2.69 is observed in the spectrum of compound (VII), and, conversely, irradiation at the frequency of this proton leads to increase in the intensity of the signal (by 10.4%) of the 18-Me group protons. It is clear that the signal at δ 2.69 ppm corresponds to the proton at $C^{2'}$. Hence, the 18-Me group and the $C^{2'}$ proton converge, which is possible only in the case of β-configuration of the cyclopropane ring, in which the H at $C^{2'}$ is trans-oriented with respect C^{15} and C^{16} protons (Fig. 1). Thus, by using the NOE method, not only the above orientation of the cyclopropane ring in relation to the plane of the steroid skeleton was determined, but also the α-orientation of the ester group at $C^{2'}$. The geometry of (VII) discussed here is also confirmed by analysis (see Table 2) of the values of vicinal SSCC: $^3J^{trans}_{H^{2'},H^{15}}$ = 3.5, $^3J^{trans}_{H_2',H^{16}}$ = 2.3, $^3J^{cis}_{H^{15},H^{16}}$ = 6.0 Hz, which corresponds well with the data in [8].

TABLE 2. PMR Spectra (250 MHz) of Compounds (III), (IV), and (VII) in $CDCl_3$ [δ, ppm ($^3J_{HH}$, Hz)]

Group	Compound		
	(III)	(IV)	(VII)
18-Me	0,69 s	0,92 s	1,02s
19-Me	1,10 s	1,00 s	1,07 s
$MeCH_2O$	1,40t (7,0)		1,28 t (7,0)
MeCO	2,07 s	1,98 s	2,06 s
$MeCH_2O$	4,37 q (7,0)		4,15 q (7,0)
HC^3	4,63 m	4,55 m	4,52 m
HC^6	5,50m (5,0)	5,39 m	5,46 m
$HC^{2'}$	5,42 d.d (5,6; 3,5)		2,60 d.d (3,5; 2,3)
HC^{15}	3.10m		2,37 m
HC^{16}	5,63 d.d (8,8; 3,5)		2,19 d.d (6,0; 2,3)

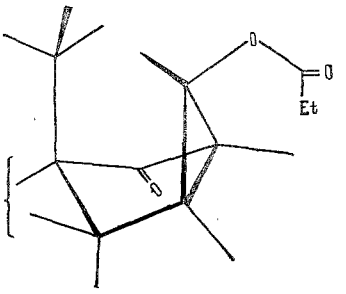

Fig. 1. Steric structure of the D and D' rings of compound (VII).

It is interesting to note that in the PMR spectrum (see Table 2) of pyrazoline (III), a homoallylic $^5J_{H^{3'},H^{16}}$ = 3.5 Hz via the N=N bond, and a vicinal SSCC $J_{H_3',H^{15}}$ = 5.6 Hz are observed. However, there is no confirmation of an unequivocal conclusion on the configuration of the carboethoxyl group.

Thus, the 1,3-cycloaddition of diazomethane (at 1 bar) and ethyl diazoacetate (at 14 kbar) to Δ^{15}-17-ketoandrostane (I) proceeds regio- and stereospecifically from the β-region of the stereoid ring. This can probably be explained by the fact that 18β-methyl group that usually creates hindrances to approach of the reagent from the β-region is remote from the reaction centers in (I), but on the other hand, the α-approach can be completely hindered because of the 1,2-interaction between 14α-H and the carbon terminal of the dipole.

EXPERIMENTAL

The melting points were determined on a Kofler block. The IR spectra were measured on a UR-20 spectrophotometer in KBr tablets, the ^1H and ^{13}C NMR spectra on a Bruker WM-250 spectrometer. The nuclear Overhauser effect (NOE) was measured by the TOE procedure [truncated driven nuclear Overhauser effect] [9], using an original program for a Aspect-2000 computer applied to a spectrometer. The mass spectra were measured on a Varian MAT CH-6 spectrometer. The TLC was carried out on microplates with brand L SiO_2 (5-40 μm). An iron-free KSK silica gel (200-250 mesh) was used for the columns.

3'-H-Androst-5-en-3β-ol-17-one[15β,16β-d]pyrazole Acetate (II). A 40-ml portion of an ethereal solution of CH_2N_2 (∿20 mmoles) was added to a solution of 0.5 g (1.4 mmoles) of (I) in 20 ml of ether, and the reaction mixture was held for 14 h at ∿20°C. The crystalline residue obtained after removal of solvent was washed with hexane and dried in air. Yield 0.48 g (86%) of compound (II), mp 178-180°C (acetone–hexane). IR spectrum (ν, cm^{-1}): 1545, 1735. PMR spectrum (δ, ppm): 0.66 s (3H, 18-Me), 1.01 s (3H, 19-Me), 1.99 s (3H, 3-OAc), 5.38 m (1H, $H-C^6$). Mass spectrum, m/z: 370 (M^+).

15β,16β-Methylenoandrost-5-en-3-β-ol-17-one Acetate (IV). A solution of 0.3 ml of BF_3 etherate in 3 ml of acetone was added dropwise, with vigorous stirring and external water cooling, to a solution of 0.58 g (1.6 mmoles) of (II) in 50 ml of acetone, and the mixture was allowed to stand for 1 h at ∿20°C. The solution was poured onto ice, the oil that

separated was extracted by $CHCl_3$, and the organic layer was washed with water and dried over $MgSO_4$. The residue after removal of solvent was chromatographed on 40 g of SiO_2. Elution by a heptane–ether mixture (9:1) gave 0.12 g (23%) of (IV), mp 144-145°C (ether–hexane). IR spectrum (ν, cm^{-1}): 1245, 1710, 1735. PMR spectrum (see Table 2). Found, %: C 77.45; H 9.16. Mass spectrum, m/z 283 $[M - AcOH]^+$. $C_{22}H_{30}O_3$. Calculated, %: C 77.15; H 8.88. Mol. wt. 342.6.

3'ξ-Carboethoxy-3'-H-androst-5-en-3β-ol-17-one[15β,16β-d]pyrazole Acetate (III). A solution of 0.3 g (0.98 mmole) of (I) and 0.15 ml (1.4 mmoles) of ethyl diazoacetate in 2.5 ml of CH_2Cl_2 was allowed to stand for 6 h in a thin-walled ampule at 20°C and 14 kbar. The crystalline residue obtained after the evaporation of the solvent was suspended in a hexane–ether mixture (2:1). The precipitate was filtered and dried in air. Yield 0.23 g (56%) of (III), mp 149-154°C. IR spectrum (ν, cm^{-1}): 1545, 1730-1740. PMR spectrum (see Table 2). Mass spectrum, m/z: 383 $[M - AcOH]^+$.

2'α-Carboethoxy-15β,16β-methylenoandrost-5-en-3β-ol-17-one Acetate (VII). A 0.38 g portion of pyrazoline (III) was heated for 30 min at 210-220°C up to cessation of nitrogen evolution (∿1 h), and the residue was chromatographed on 40 g of SiO_2, using a heptane–ether mixture (94:6) as eluent. Yield 0.06 g (17%) of (VII), mp 128-130°C (ether–petroleum ether). IR spectrum (ν, cm^{-1}): 1245, 1715-1740. PMR spectrum (see Table 2). Mass spectrum, m/z: 355 $[M - AcOH]^+$.

15β,16β-Methylenoandrost-5-en-3β-ol-17-one (V). A 22-mg portion (0.9 mmole) of NaH was added at 20°C in an Ar atmosphere to a solution of 0.13 g (0.58 mmole) of trimethylsulfoxonium iodide [10] in 15 ml of DMSO, stirred at 20°C, and stirring was continued to the cessation of evolution of H_2. Then, 0.14 g (0.42 mmole) of (I) was added to the reaction mixture, which after 2 h was decomposed by 5% AcOH. The oil that separated was extracted by $CHCl_3$. The subsequent usual treatment and chromatography of the product on 20 g of SiO_2 with elution by a hexane–acetone mixture (17:3) gave 0.05 g (38%) of (V), mp 241-244°C (acetone–hexane). IR spectrum (ν, cm^{-1}): 1700, 3460. PMR spectrum (δ, ppm): 0.97 s (3H, 18-Me), 1.02 s (3H, 19-Me), 5.40 m (1H, H-C^6), Mass spectrum, m/z: 300 M^+.

Saponifaction of (IV) by aqueous-alcoholic alkali under standard conditions gave alcohol (V), mp 240-243°C.

15β,16β-Methylenoandrost-4-ene-3,17-dione (VI). A solution of 0.39 g (0.77 mmole) of (V) and 2 ml of cyclohexanone in 50 ml of toluene was boiled with a slow distillation until a transparent distillate was obtained, and then a solution of 0.7 g (3.4 mmoles) of $(i\text{-}PrO)_3Al$ in 25 ml of toluene was added to the reaction mixture, and the boiling was continued for 6 h. When cool, the mixture was acidified by 5% AcOH, the organic solution was separated, washed with a dilute solution of $NaHCO_3$ and water, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on 50 mg of SiO_2. Elution by a hexane–acetone mixture (17:3) gave 0.19 g (50%) of (VI), mp 188-191°C (acetone–hexane). IR spectrum (ν, cm^{-1}): 1665, 1720. PMR spectrum (δ, ppm): 1.02 s (3H, 18-Me), 1.22 s (3H, 19-Me), 5.82 br. s (1H, H-C^4). Mass spectrum, m/z: 298 M^+.

CONCLUSIONS

1,3-Cycloaddition of diazomethane and ethyl diazoacetate to Δ^{15}-17-ketoandrostane proceeds regio- and stereospecifically from the β-region of the steroid molecule. The pyrazolinoandrostanes obtained were converted into the corresponding 15β,16β-cyclopropane derivatives.

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