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ADDITION TO STEROID POLYENES—V*

REACTION OF 7-DEHYDROPROGESTERONE-DIKETAL WITH DIMETHYL DIAZODICARBOXYLATE

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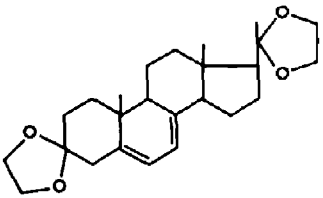
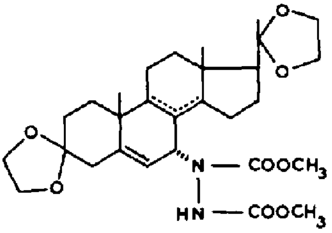
Abstract—Dimethyl diazodicarboxylate reacts with 7-dehydroprogesterone-diketal (I) by nucleophilic addition at C_7. Two products are obtained, resulting from subsequent hydrogen abstraction from C_9 (III) and C_{14} (IV) respectively. Acid hydrolysis of adduct IV results in the formation of 1,2-dicarbomethoxy-hydrazine and 6,8(14)-bisdehydroprogesterone (VII) in nearly quantitative yield.

7-Dehydrocholesteryl acetate has been found to react with dimethyl diazodicarboxylate by addition at C_7, preceded by hydrogen abstraction from C_9.[2] Abstraction of the proton at C_{14} instead of the proton at C_9 was not observed, probably due to the occurrence of a "long-range" conformational transmission effect of the side-chain, which, on steric grounds, renders the removal of the proton at C_{14} less likely.

Dimethyl diazodicarboxylate (II) reacts with 7-dehydroprogesterone-diketal (I)† with formation of the addition-abstraction products III and IV. In view of the absence of a long side-chain, the abstraction of the proton at C_9 is no longer preferred and consequently both types of adducts have to be expected. According to NMR spectroscopy the abstraction of the proton at C_{14}—leading to the 8(14)-isomer IV—is even more favoured in the reaction with the progesterone derivative (I) than removal of the proton at C_9.



I



III 8,(9) dehydro
IV 8,(14) dehydro

Structure assignments were made on the basis of NMR evidence. While in the presence of a 8(9)-dehydrosystem the signal of the C_{19} Me group is shifted towards

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* Part IV of this Series. J. Lakeman, W. N. Speckamp and H. O. Huisman, Tetrahedron Letters, 3699 (1967).

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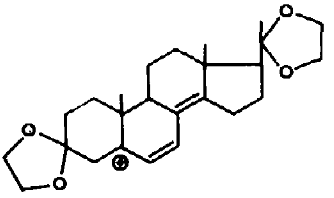
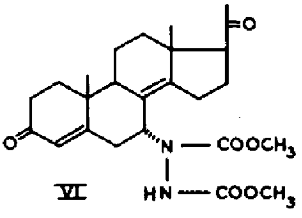
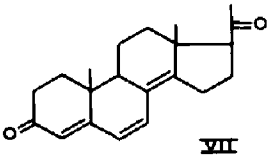
higher field, and the corresponding signal of the C_{18} Me group towards lower field, shifts in opposite directions are observed when the the 8(14)-dehydrosystem is present. A consideration of the chemical shift differences of the C_{18} and C_{19} Me absorptions in the starting diene (I) and the 8(14)-dehydroproduct (IV), based on similar experience in the ergosterol and cholesterol series,[3] leads to predicted values of 0·96 and 0·95 ppm respectively, while in the 8(9)-dehydrostructure (III) the C_{18} and C_{19} signals are expected at 0·72 and 1·22 ppm. The observed values—0·88 and 0·98 ppm for compound IV; 0·72 and 1·17 ppm for compound III*—agree well with the expected ones.

Corroborative evidence with regard to the structure assignments is found in the different solvent effects. Whereas the C_{18} Me signal is hardly influenced upon change of solvent from deuterochloroform to benzene, the C_{19} Me signal in 8(14)-dehydrosteroids shifts to higher field ($\delta_{CDCl_3} - \delta_{C_6H_6} = +0{\cdot}20$ ppm), while the corresponding signal in the 8(9)-dehydrostructure expresses a downfield shift ($\delta_{CDCl_3} - \delta_{C_6H_6} = -0{\cdot}16$ ppm).† The observed effect constitutes another aid in the structure determination of the addition-abstraction products of the reaction of 5,7-bisdehydrosteroids with dienophiles.

Acid hydrolysis. In agreement with earlier observations[2] 1,2-dicarbomethoxyhydrazine was isolated when adduct IV was hydrolysed in refluxing methanol containing hydrochloric acid. The loss of the hydrazine moiety can initiate the formation of several anthrasteroids via the occurrence of an intermediate carboniumion at C_5 (V). With structure IV one can expect such a rearrangement only to occur when the protonation of the hydrazine nitrogen is faster than the protonation and subsequent cleavage of the ketal function at C_3. In the reversed situation the formation of the C_5 carboniumion and correspondingly also the anthrasteroid rearrangement are not possible because of the hydrolysis of the ketal at C_3 and the following rearrangement of the 5(6) double bond into the stable 4(5) position (VI). Loss of 1,2-dicarbomethoxyhydrazine will lead to the introduction of a C_6—C_7 double bond. After column


V


VI


VII

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* Although the pure adduct III could not be obtained, the position of its C_{18} and C_{19} methyl signals could be established from the NMR spectrum of a 1:1 mixture of III and IV.

† A discussion of the solvent effects in 8(9)- and 8(14)-dehydrosteroids will be given in a separate communication.

chromatography of the crude reaction mixture, a sole product is obtained in 65% yield, the structure of which proved to be 6,8(14)-bis-dehydroprogesterone (VII). Its structure is in agreement with the following spectral characteristics: The UV spectrum shows a characteristic absorption at 348 nm ($\varepsilon = 26{,}500$)[4]; the NMR spectrum possesses a singlet (δ 5·72) and a quartet (δ 6·33) assigned to the olefinic protons at C_4 and $C_{6,7}$; the mass spectrum shows a molecularion peak at *m/e* 310. Furthermore, the aforementioned data correspond closely with those of the recently synthesized 19-nor analogue.[5]

The aforementioned reactions constitute a potential and highly selective method for the introduction of additional double bonds in steroid dienes. Experiments are currently directed to obtain an estimation of its general value.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured on A Zeiss RPQ 20 C spectrophotometer. IR spectra were taken on a Unicam SP-200 spectrophotometer. The NMR spectra have been recorded on a Varian HR-60 spectrometer, using solutions in $CDCl_3$ containing 5% tetramethylsilane as an internal standard. Mass spectra were taken on a AEI-MS 9 mass spectrometer.

Dimethyl diazodicarboxylate. The hydrazoester was prepared according to the method of Rodgman and Wright.[6] When oxidation was carried out as described[6] the results were unsatisfactory. Application of the method of Diels[7] did not exclude the possibility of an explosion. Therefore a mixture of conc and fuming HNO_3 of 2:3 was added to a solution of hydrazoester in chloroform at a temp below − 5°. When the temp raised to 2° the oxidation started. Cooling of warming up controlled the reaction rate, yield 55% (lit. 52%[6,7]) azoester. (NMR: liq. 4·07 ppm (Me)).

7α-(1′,2′-*Dicarbomethoxyhydrazo*)3,3;20,20-*bisethylenedioxy-pregna*-5,8-*diene* (IV). Compound I (5 g: 0·014 mole) was dissolved in 50 ml benzene. To this solution dimethyl diazodicarboxylate (5 g; 0·034 mole) was added and the mixture was refluxed during 8 hr. After removal of the solvent with the aid of a rotatory evaporator under reduced press, the residue was dissolved in chloroform and washed with a Na_2SO_3 aq to remove the excess ester. Additional washings with water, evaporation of the organic solvent and recrystallization from pet ether 60/80 gave the adduct IV in 60% yield (m.p. 115-119°). (Found: C, 64·0; H, 7·9; N, 5·1. $C_{29}H_{42}O_8N_2$ requires: C, 63·71; H, 7·74; N, 5·13%). The NMR spectrum shows absorptions at δ 7·03 (m, 1p, N—H), δ 5·18 (m, 1p, C_6—H), δ 3·93 (s, 8p, ketal), δ 3·73 and δ 3·66 (s, 3p, ester), δ 1·30 (s, 3p, C_{21}—Me), δ 0·98 (s, 3p, C_{19}—Me), and δ 0·88 (s, 3p, C_{18}—Me).

Pregna-4,6,8(14)-*triene*-3,20-*dione* (VII). Adduct IV (3 g; 0·006 mole) was refluxed for 1 hr in 150 ml MeOH containing 30 ml HCl. The solvent was evaporated under reduced press and the residue dissolved in chloroform. After several washings (water, $NaHCO_3$ aq) and drying with $CaCl_2$ the solvent was evaporated and the residual oil (1·65 g) chromatographed over Florisil after taking up in benzene. Eluation with 200 ml benzene, 400 ml benzene/EtOAc 19:1, 200 ml 5:1, 200 ml 7:3, 200 ml 3:2 and 300 ml pure EtOAc. The benzene/EtOAc fractions gave VII in 65% yield. Recrystallization from MeOH delivered the pure triene; m.p. 133–135°. (Found: C, 81·1; H, 8·6. $C_{21}H_{26}O_2$ requires: C, 81·25; H, 8·44%). The NMR spectrum possesses absorptions at δ 6·33 (quartet, 2p, $C_{6,7}$—H); δ 5·72 (s, 1p, C_4—H), δ 2·16 (s, 3p, C_{21}—Me) δ 0·99 (s, 3p, C_{19}—Me) and δ 0·93 (s, 3p, C_{18}—Me).

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