Tetrahedron, 1966, Vol. 22, pp. 2039 to 2051. Pergamon Press Ltd. Printed in Northern Ireland

ACYLATION OF CYCLIC KETONES[1,2]

M. GORODETSKY, E. LEVY, R. D. YOUSSEFYEH and Y. MAZUR
Department of Organic Chemistry, Weizmann Institute of Science, Rehovoth, Israel

(*Received* 16 *November* 1965; *in revised form* 18 *January* 1966)

Abstract—Acylation of steroidal saturated ketones and their enol acetates with acetic anhydride and BF_3–etherate has been studied. α-Acylketones were obtained from 3-keto, 7-keto and 16-keto steroids (I, XII and IX) in the A/B *trans* series and from 3-ketone (VI) in the A/B *cis* series. The intermediate difluoroboron chelates (II and VII) were isolated and characterized. No C-acylation of tertiary carbon atom in steroids was observed.

The acylation of 2-methylcyclohexanone (XVI) and its enol acetates (XVII and XVIII) is described, and the relation between O-acylation and C-acylation is discussed.

Acylation of α,β-unsaturated ketones, testosterone (XXII) and 4-methyltestosterone (XXX) for a comparative short time results in C-6 derivatives (XXIII, XXV and XXXI, and over a longer period of time in difluoroboron chelates (XXVI and XXXIII).

The tautomeric equilibrium of the enolic β-diketones IV, XXVII, XXVIII, XXIX and XXXIV is also described.

RECENTLY, the conversion of enol acetates to the corresponding α-acetylketones by irradiation with UV light has been described.[3,4] Since some of the ketones had not been reported previously, their synthesis by more conventional routes was investigated. The most suitable method appeared to be the acid catalysed acylation of the ketones using acetic anhydride and boron trifluoride.[5–7] It has been suggested that these reagents first transfer the carbonyl group to an enolic derivative, (either enol acetate or BF_3–derivative of the enol) which is then further attacked by the acylating agent, the acylium cation.[6,7]

The reagent used was acetic anhydride and BF_3–etherate, and the reactions were done usually at room temperature. The BF_3–etherate proved more convenient than the BF_3 gas previously used.[5,6]

The acylation of 5α-androstan-3-on-17β-ol acetate (I), using acetic anhydride and BF_3–etherate, resulted in the difluoroboron chelate of the 2-acetyl-5α-androstan-3-on-17β-ol acetate (II)[3]. Compound II was recently reported as a product of acylation of I, using BF_3 gas.[8a] It has also been obtained by acylation of the ethylene ketal and the diethyl ketal of I[9]. Hydrolysis of II with a saturated solution of sodium acetate

[1] Taken in part from the Ph.D. thesis of M. Gorodetsky, submitted to the Senate of the Hebrew University, Jerusalem, December 1963.

[2] Presented in part at the 19th International Congress of Pure and Applied Chemistry, London 1962; Abstracts A, p. 341.

[3] A. Yogev, M. Gorodetsky and Y. Mazur, *J. Amer. Chem. Soc.* **86**, 5208 (1964).

[4] M. Gorodetsky and Y. Mazur, *J. Amer. Chem. Soc.* **86**, 5213 (1964).

[5] H. Meerwein and D. Vossen, *J. Prakt. chem.* **141**, 149 (1934).

[6] C. R. Hauser, F. W. Swamer and J. T. Adams, *Organic Reactions* Vol. 8, pp. 59–196. Refs. cited therein, Wiley, London (1954).

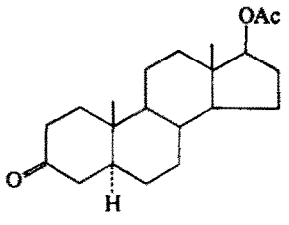
[7] D. P. N. Satchell, *Quart. Rev.* **17**, 160 (1963).

[8a] G. I. Fujimoto and R. W. Leedon, *J. Org. Chem.* **29**, 2058 (1964); [b] A. Manson, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler and R. O. Clinton, *J. Med. Chem.* **6**, 1 (1963).

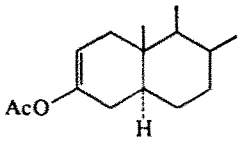
[9] R. Youssefyeh, *J. Amer. Chem. Soc.* **85**, 3901 (1963).

resulted in the 2-acetylketone (IV; R = CH_3)[3,8,9] Similar acylation of III gave in high yield the previously mentioned chelate II. Both the UV[10] and NMR spectra[11] of IV (R = CH_3) indicate that this compound is completely enolic. It is reasonable to assume that it exists in an equilibrium of the two possible enolic forms IVa (R = CH_3 and IVb (R = CH_3) with the first in preponderance. This assumption is made on the basis of analogy with the corresponding α-aldehydoketones (IV; R = H) which exists as a mixture of the two enols (IVa R = H and IVb R = H) the first being ca. 80% of the total.[12,13] The method used for the determination of this equilibrium in α-aldehydoketones cannot be applied with accuracy to the α-acetylketones. This method is based on the comparison of the chemical shifts of the vinylic or aldehydic protons of compounds existing in only one of the enolic forms with the chemical shift of the corresponding proton in the equilibrium mixture of the two enols.[12] In the α-acetylketones the difference in the chemical shift of the corresponding methyl protons of the two enolic forms i.e. IVa (R = CH_3) and IVb (R = CH_3) is expected to be too small for accurate determination of the weighted average of enols. Thus the

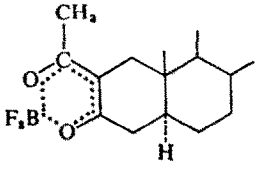
CHART I



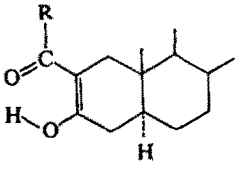
I



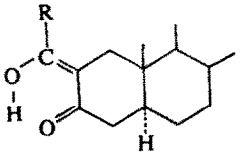
III



II



IVa



IVb

chemical shift in α-acetylcamphor (V) which is likely to exist in the exocyclic form only,[12] is at δ 1·83 ppm[14] and the corresponding signal in the enolic form of acetylacetone (1:1 average) is at 2·0 ppm, the difference being 0·17 ppm. The difference in the corresponding chemical shift in the protons in α-aldehydoketones is 1·25 ppm.[12] Nevertheless the value obtained for the methylprotones in IV (R = CH_3) δ 2·15 ppm, point to the preference for the enol (IVa; R = CH_3). It seems however that the structure of the difluoroboron chelate (II) features two equivalent oxygen atoms.

[10] UV spectra were determined on a Cary 14 spectrophotometer.

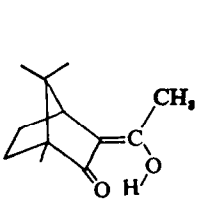
[11] The NMR spectra were taken in $CDCl_3$ on an A-60 Varian spectrometer, tetramethylsilane serving as internal reference. The peak positions are reported in ppm (δ), downfield from tetramethylsilane.

[12] E. W. Garbisch, *J. Amer. Chem. Soc.* **85**, 1696 (1963).

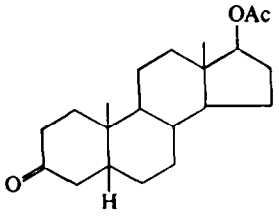
[13] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* pp. 95–96. Holden-Day, San Francisco (1964).

[14] To be published at a later date.

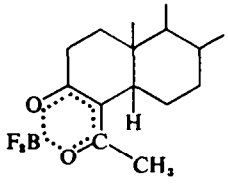
CHART II



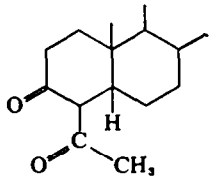
V



VI



VII



VIII

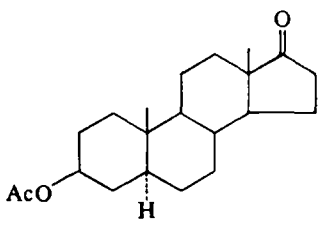
The acylation of 5β-androstan-3-on-17β-ol acetate (VI) gave the difluoroboron chelate of 4-acetyl-5β-androstan-3-on-17β-ol acetate (VII). The sodium acetate hydrolysis of this compound led to the non-enolic 4β-acetyl-5β-androstan-3-on-17β-ol acetate (VIII), in which the acetyl group has the 4β-equatorial configuration, as shown previously.[4] The equatorial configuration of the 4-acetyl group may also be deduced from its NMR spectrum. The hydrogen at C-4 in VIII appeares as a doublet with $J = 12{\cdot}5$ c/s at δ 3·86 ppm. This high coupling constant indicates the *trans* diaxial relation between the hydrogen at C-4 and at C-5, similar to that found previously in the isomeric 4α-acetyl-5α-androstan-3-on-17β-ol acetate.[4]

The formation of the 4-acetylketone (VIII) involves an attack of the acylating agent on the primarily formed Δ^3-enol derivative of the C-3 ketone (VI). The possibility exists that the attack of the acylating agent on the olefinic carbon atom, C-4, proceeds axially from the α-side of the molecule, and is then followed by the loss of the equatorial, β-hydrogen at C-4, with the formation of the difluoroboron chelate (VII). The latter gives on hydrolysis VIII which is not enolic since its axial hydrogen at C-4, hindered by the hydrogens at C-7 and C-9, cannot be removed with ease. On the other hand, a β-side attack at C-4 can also be envisaged, with direct formation of VIII. Although the latter does not form an enol easily, but exists in its ketonic form in neutral solution, it reacts with BF_3–etherate and acetic anhydride, and forms VII.

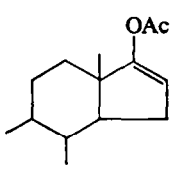
The necessity for a primary formation of an enol derivative in the reaction of the ketones with BF_3 and acetic anhydride, is exemplified by the behaviour of 17-ketosteroids. It is known that this type of ketone undergoes enol acetylation only under forcing conditions, such as prolonged boiling with isopropenyl acetate and sulphuric acid.[15] Our attempts to C-acylate 5α-androstan-17-on-3β-ol acetate (IX) using standard conditions, merely resulted in the unchanged starting material. On the other

[15] N. S. Leeds, D. K. Fukushima and T. G. Gallagher, *J. Amer. Chem. Soc.* **76**, 2943 (1954).

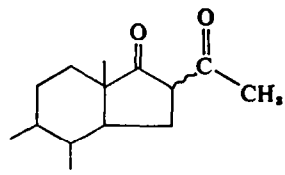
CHART III



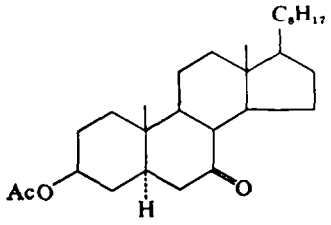
IX



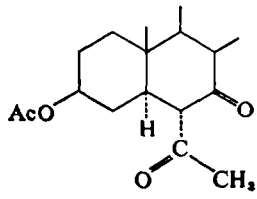
X



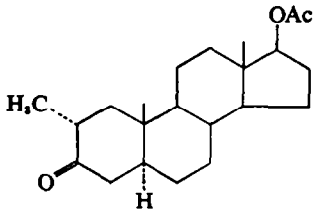
XI



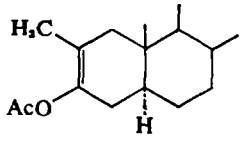
XII



XIII



XIV



XV

hand, the corresponding enol acetate (X) could be converted to the 16-acetylketone (XI). This compound was obtained as a mixture of enol and ketone tautomers, in approximately equal proportions,[16] and was identified as its copper complex.[3]

No acylation on a tertiary carbon atom was observed, when the 7-ketone (XII)[17] was subjected to standard acylating conditions, the only product isolated after sodium acetate hydrolysis was the 6-acetyl-7-ketone (XIII). This compound had the thermodynamically more stable ketonic structure, as evident from its IR and UV spectra (λ_{max}^{KBr} 5·77 and 5·80 μ; λ_{max}^{EtOH} 286 mμ, ε 84), and its NMR spectrum. In the latter spectrum the signal due to the proton at C-6 appears as a doublet at δ 3·33 ppm (J = 12·5 c/s). This coupling pattern is similar to that observed previously in both 4α-acetyl-5α-androstan-3-on-17β-ol acetate,[4] and in 4β-acetyl-5β-androstan-3-on-17β-ol acetate (VIII). In the ethanolic sodium hydroxide solution the UV spectrum of XIII does not change, indicating the additional difficulty in removing the β-axial hydrogen at C-6.

[16] It is pertinent to note that a 16-acetyl-17-ketone was previously described in the 5β-11-ketone series: N. L. Wendler, *Tetrahedron* **11**, 213 (1960).

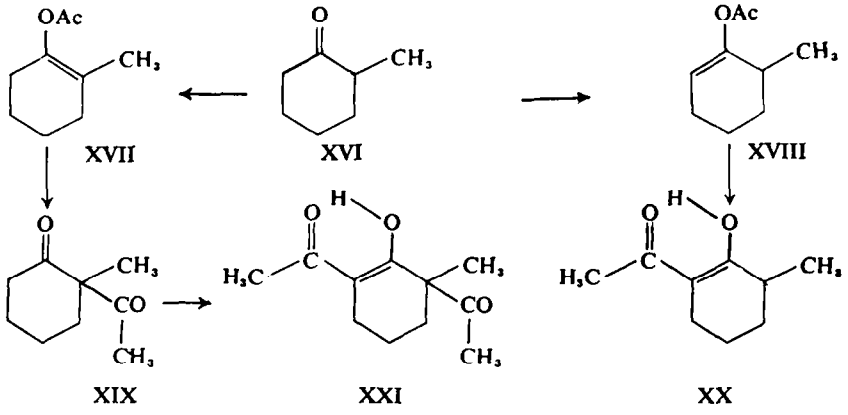
[17] The O-acylation of XII was described by E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.* 907 (1959).

No C-acylation was observed when 2α-methyl-5α-androstan-3-on-17β-ol acetate (XIV) was treated with acetic anhydride and BF_3–etherate. These reagents however converted XIV in good yield to the corresponding enol acetate (XV). The latter was recovered unchanged even after prolonged treatment with the same reagents.

The inability of the acylating agent to attack the fully substituted olefinic carbon atom in steroids may be attributed to both steric and electronic factors.

It appears that suitable compounds for the comparison of the relative composition of O-acylation and C-acylation products would be the 2-methylcyclohexanone (XVI). This ketone gives a mixture of the two enol acetates (XVII and XVIII). When the O-acylation is done with acetic anhydride and strong acid, an equilibrium mixture of the two enol acetates is obtained, in which the relative composition of the two products is ca. 9:1.[18] On the other hand, the relative composition of the enol acetates (XVII and XVIII) from O-acylation of XVI with isopropenyl acetate and sulphuric acid is ca. 2:1.[18]

CHART IV



In the reaction of acetic anhydride and BF_3–etherate on XVI,[19] the main compound was the enol acetate XVII (ca. 80% of the isolated products) which was free from its isomer XVIII. In addition, the two isomeric acetyl-methylcyclohexanones XIX and XX (ca. 10% of the isolated products each) were isolated. The 2-acetyl-2-methylcyclohexanone (XIX) was identified by comparison with an authentic sample,[3,20] and the structure of the 6-acetyl-2-methylcyclohexanone (XX) was deduced from its physical properties. The UV spectrum of XX was similar to that of 2-acetylcyclohexanone,[3] and in the NMR spectrum of XX both the doublet due to the methyl proton at C-2, and the singlets of the acetyl protons and of the enolic hydrogen [at δ 1·28 (J = 7 c/s), 2·11 and 16·0 ppm] were observed. The fourth product of the reaction, the 2,6-diacetyl-2-methylcyclohexanone (XXI; less than 5%) was not isolated in its pure form but only as a mixture with XX. Its presence was deduced from the NMR spectra of the mixture which showed in addition to the signals due to XX, sharp signals assigned to the protons at C-2, C-6 and to the enolic hydrogen (at δ 1·23

[18] H. O. House and V. Kramar, *J. Org. Chem.* **28**, 3362 (1963).

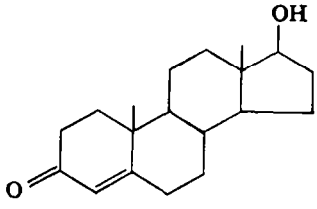
[19] The C-acylation of XVI with Ac_2O and BF_3 gas was reported previously; the compounds isolated were not defined unequivocally, cf. C. R. Hauser and J. T. Adams, *J. Amer. Chem. Soc.* **74**, 345 (1944).

[20] G. B. Payne, *J. Org. Chem.* **26**, 4793 (1961).

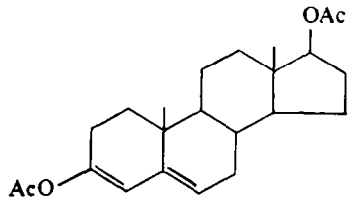
2·11, 2·20 and 15·9 ppm). When the previously described mixture of enol acetates XVII and XVIII (2:1) obtained by action of isopropenyl acetate on XVI was treated under similar conditions, the relative proportion of the products varied: the yield of XX increased (25%), and the yield of XVII decreased (ca. 60%). On the other hand, treatment of the equilibrium mixture of XVII and XVIII (9:1) under similar conditions, resulted mainly in the unchanged XVII (ca. 80%) and XX was formed only in traces.

It may be therefore assumed that of the two enol acetates (XVII and XVIII) the latter is converted to the monoacetyl derivative XX, while the former is mainly regenerated unchanged. However, this fully substituted XVII may have reacted to a small extent with the acylating agent to give XIX. This ketone (XIX) undergoes probably further enolization and subsequent acylation at C-6, to yield XXI. The direct acylation of XVI may also proceed through a primarily formed mixture of XVII and XVIII whose composition approaches that of the equilibrium mixture. Hence the relative small yield of XX in this reaction.

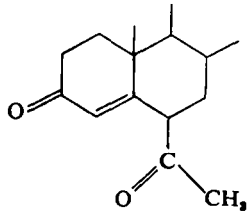
CHART V



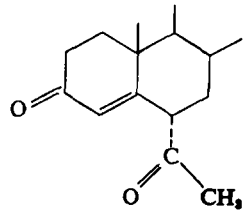
XXII



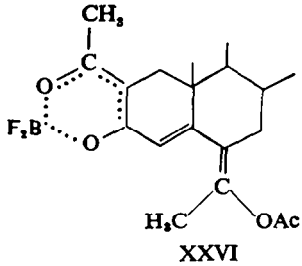
XXIV



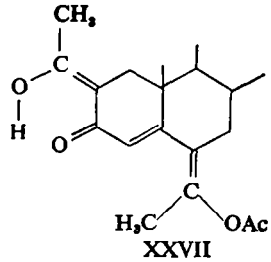
XXIII



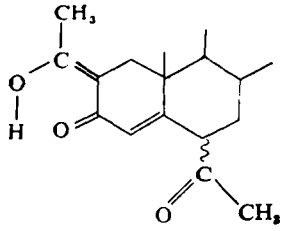
XXV



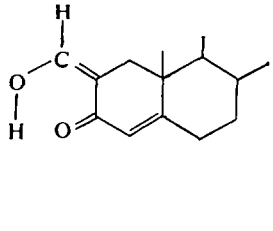
XXVI



XXVII



XXVIII



XXIX

The steroidal Δ^4-3-ketones also underwent C-acylation with the same reagent. Thus treatment of testosterone (XXII) with acetic anhydride and BF_3–etherate for 15 min at 0°, and then for 5 min at room temperature, resulted in 6β-acetyltestosterone acetate (XXIII).[4,21] When the reaction was done for 10 min at 0° the main product isolated was the dienol acetate (XXIV). Higher yields of the 6β-acetyltestosterone acetate (XXIII) were obtained when XXIV was directly reacted with these reagents for 4 min at room temperature. Chromatographic separation of the reaction products revealed in addition the 6α-acetyltestosterone acetate XXV.[4] It appears that testosterone is converted primarily to XXIV which is directly attacked at the olefinic C-6 carbon atom with concurrent loss of the O-acetyl group at C-3. As expected, this electrophilic substitution proceeds mainly axially. However, the formation of XXV may indicate some α-side attack at C-6, though a partial epimerization at C-6 during the reaction is not excluded. It is noteworthy that no 4-acetyltestosterone derivative could be identified among the reaction products. Thus the substitution pattern of XXIV resembles that of the corresponding enol and not that of the enolate.[22]

When testosterone (XXII), or its dienol acetate (XXIV) is treated with the same reagent for 3 h at room temperature, a high melting yellow compound is obtained. Its analytical data and physical properties (Table 1 and 2) suggest its being a difluoroboron chelate of a polyacetylated testosterone (XXVI). The difluoroboron group in XXVI was removed by hydrolysis with sodium acetate solution to give the β-diketone (XXVII). Treatment of the latter with hydrochloric acid yielded an equilibrium mixture of the two isomeric 6-acetyl derivatives (XXVIII) obtained as an amorphous powder which could not be separated.

TABLE 1. UV SPECTRUM DATA OF THE 2-SUBSTITUTED TESTOSTERONE DERIVATIVES[10]

Compound		Absorption maxima in ethanol		Absorption maxima in ethanolic sodium hydroxide	
		λ_{max}	ε	λ_{max}	ε
2-aldehydo-	XXIX[23]	252	11500	248	16000
		307	5000	355	10000
2,6-diacetyl	XXVIII	249	7200	239	11200
		334	5100	363	7100
2,6-diacetyl-4-methyl	XXXIV	260	8000	255	10600
		343	7200	363	11200
enol acetate of 2,6-diacetyl	XXVII	243	8200		
		281	5500		
		351	8300		
difluoroboron chelate	XXVI	250	6500		
		271	5000		
		377	11500		
difluoroboron chelate	XXXIII	257	11200		
		272	10900		
		364	10900		

[21] B. C. Elmes, M. P. Hartshorn and D. N. Kirk, *J. Chem. Soc.* 2285 (1964), describe analogous reaction in cholestane series.

[22] S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.* **86**, 1997 (1964); *Ibid.* **85**, 1538 (1963).

The UV absorption maxima of the polyacetylated testosterone derivatives are recorded in Table 1. The 2,6ξ-diacetyltestosterone acetate (XXVIII) shows two maxima, the one at higher wavelength associated with the conjugated-β-diketone chromophore (in its enolic form), and one at lower wavelength with conjugated carbonyl group. Two comparable electronic transition maxima are also observed in 2-hydroxymethylene-testosterone (XXIX),[23] possessing somewhat similar chromophores (Table 1).[24] The UV spectrum of XXVII shows a third maximum at λ_{max} 281 mμ which may be related to the additional exocyclic double bond at the C-6 position. Three comparable maxima are also observed in the UV spectrum of the difluoroboron chelate XXVI (Table 1).

TABLE 2. NMR RESONANCE DATA OF THE POLYACETYLATED TESTOSTERONE DERIVATIVES[11]

Compound	CH_3 at C-18	CH_3 at C-19	CH_3–C at C-6	CH_3–C at C-2	AcO at C-17	AcO at C-6	H at C-4
XXVII	0·83	1·01	2·0	2·1	2·06	2·17	5·85
XXVI	0·83	1·06	2·01	2·30	2·05	2·15	6·03 singlet
XXVIII							
6β-$COCH_3$	0·80	0·91	2·22	2·1	—	—	6·15 singlet
6α-$COCH_3$	0·80	1·11	2·27	2·1	—	—	5·50 doublet (J = 2 c/s)
XXXIII	0·83	1·0	2·13	2·27	2·01	2·22	1·76

In Table 2 the major signals of the NMR spectra of the three polyacetylated steroids (XXVI, XXVII and XXVIII) are compared. The mixture of the epimeric 2,6ξ-diacetyltestosterone (XXVIII) shows single peaks which may be assigned to both epimers (methyl protons at C-18 and at C-2), and signals assigned separately to the 6β- and 6α-acetyl derivatives. The latter assignment was done by a comparison with the respective signals of 6β-acetyl and 6α-acetyltestosterone acetate (XXIII and XXV).[25]

The formation of this mixture of epimers at C-6 which is an equilibrium mixture (the relative proportion of both 6-epimers does not change on further boiling with acid) indicates a comparable thermodynamic stability of these two isomers XXVIII with that of 6-acetyltestosterones (XXIII and XXV).

The polyacetylated steroids (XXVII and XXVIII) may exist in one of the two possible enolic forms or as a fast equilibrium between the two. We assume however

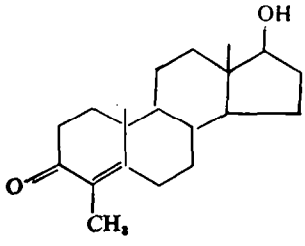
[23] R. O. Clinton, A. J. Mason, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson and C. Carabaeas, *J. Amer. Chem. Soc.* **83**, 1478 (1961).

[24] As seen from Table 1 a substitution of the vinylic hydrogen of the hydroxymethylene with a methyl group gives a bathochromic shift of the higher wavelength maximum. This red shift is observed also when the UV spectra of 2-aldehydoandrostan-3-on-17β-ol (λ_{max} 282 mμ, ε 9000) is compared with that of its 2-acetyl analog II (λ_{max} 289 mμ, ε 9000); Refs. 3 and 24.

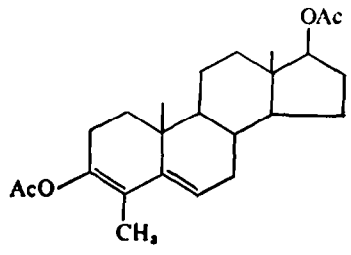
[25] M. Gorodetsky, D. Amar and Y. Mazur, *J. Amer. Chem. Soc.* **86**, 5218 (1964).

that the predominant form is the one indicated in the formulae, having an exocyclic double bond at C-2. This reasoning is based on an assumed similarity with the 2-aldehydo-testosterone (XXIX). The latter showed a signal in its NMR spectrum assigned to the C—H proton at C-2 at δ 7·38 ppm.[14] This value points to an equilibrium of the two enolic forms of XXIX, the one having an exocyclic double bond at C-2 in ca. 77%.[12] It is of interest to remark that in the saturated analog of XXIX, namely in the aldehydo-ketone (IV; R = H); the proportion of the two enols is reversed.

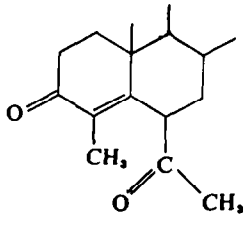
CHART VI



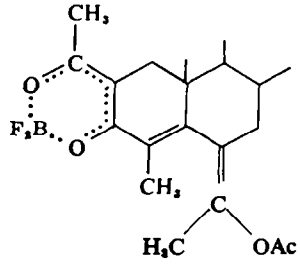
XXX



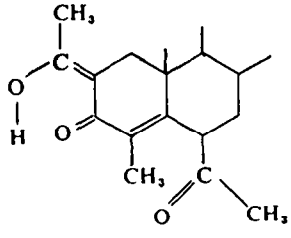
XXXII



XXXI



XXXIII



XXXIV

The C-acylation of 4-methyltestosterone (XXX) also resulted in C-6 substitution to give the 6β-acetyl-4-methyl-testosterone acetate (XXXI). The latter could also be obtained from the corresponding dienol acetate (XXXII). Both 4-methyl derivatives (XXX and XXXII) were less reactive than the analogous compounds (XXII and XXIV) lacking the 4-methyl group. The comparative reaction periods for C-6 acylation in the former compounds were longer and the yields were smaller. It is also significant that no 6α-acetyl derivative of 4-methyltestosterone could be isolated from the reaction mixture, and no epimerization at C-6 occurred when XXXI was heated

with acid. A reason for this behaviour may be the "peri" steric effect of the 4-methyl group which hinders the equatorial approach of the attacking reagent.[26]

Prolonged action of acetic anhydride and BF_3–etherate (20 hr at room temp) on XXX gave a yellow high melting compound. Its structure, (XXXIII), was implied by analogy with the chelate (XXVI) due to its similarity in the UV spectrum (Table 1) and NMR spectrum (Table 2). As previously mentioned, XXX is less reactive than XXII. Thus treatment of the former for 1 hr with the reagent mixture resulted mainly in XXXI. On the other hand, treatment of XXII under similar conditions produced the polyacetylated derivative (XXVI), and not the monoacetyl derivatives (XXIII and XXV).

Treatment of the difluoroboron chelate (XXXIII) with a solution of sodium acetate resulted in hydrolysis of both difluoroboron and enol acetate groups. Although this compound was obtained in amorphous form, the structure XXXIV was assigned to it through its physical properties (Table 1).

EXPERIMENTAL[10,11]

All m.ps were taken in capillaries and were uncorrected. The IR spectra were determined on a Perkin-Elmer infracord spectrophotometer, and the rotations were done in $CHCl_3$ solution.

C-Acylation of 5α-androstan-3-on-17β-ol acetate (I)

The ketone I (5·0 g) was treated at room temp with Ac_2O (75 ml) and then with BF_3–etherate (12 ml). After being left at room temp for 15 min, the crystalline precipitate was filtered off and washed with ether (25 ml). Recrystallization from ether yielded 5·04 g (80%) of II, m.p. 282–283°, $[\alpha]_D$ + 36°, λ_{max}^{KBr} 5·76, 6·28, 6·63 and 8·12 μ; λ_{max}^{EtOH} 301 mμ (ε 9600); lit.[8a]; m.p. 265–277°, $[\alpha]_D$ +38·7°; lit.[9], m.p. 262–265°, $[\alpha]_D$ +48°.

A solution of II (2 g) in MeOH (50 ml) was treated with a sat AcONa aq (5 ml), then heated under reflux for 2 hr, and evaporated to dryness. The residue was extracted with ether, the solution washed with water and the isolated material recrystallized from ether–pentane to give IV (1·5 g; 85%), m.p. 179–180°, $[\alpha]_D$ +42°; lit.[3] m.p. 178–179°, $[\alpha]_D$ +41°; lit.[8a] m.p. 180–181°, $[\alpha]_D$ +43·3°; lit.[9] m.p. 180–183°, $[\alpha]_D$ +52°.

C-Acylation of 5α-androst-2-en-3,17β-diol diacetate (III)

Treatment of III (3·0 g) at room temp with Ac_2O (50 ml) and BF_3-etherate (8 ml) for 15 min, and similar workup as above resulted in II (3·1 g; 93%), m.p. 282–283° identical with the compound obtained by C-acylation of I.

C-Acylation of 5β-androstan-3-on-17β-ol acetate (VI)

The ketone VI (0·12 g) was treated at room temp with Ac_2O (1 ml) and BF_3–etherate (0·3 ml). The solution was allowed to stand for 3 hr at room temp, and was then poured into ice and water The precipitated material was filtered off after 2 hr, and recrystallized from ether to give VII (0·125 g; 82%), m.p. 215–217°, $[\alpha]_D$ + 101°; λ_{max}^{KBr} 5·76, 6·36, 6·70 and 8·02 μ; λ_{max}^{EtOH} 302 mμ (ε 9400). (Found: C, 65·37; H, 7·86; B, 2·59. Calc. for $C_{23}H_{33}O_4BF_2$: C, 65·41; H, 7·88; B, 2·56%.)

A solution of VII (0·5 g) in MeOH (10 ml) was treated with a sat. AcONa aq (2 ml), then heated under reflux for 2 hr and evaporated to dryness. The product was isolated with ether and recrystallized from ether–pentane to give VIII (0·3 g; 85%), m.p. 180–182, $[\alpha]_D$ +33°, λ_{max}^{KBr} 5·77, 5·84 and 8·04 μ; λ_{max}^{EtOH} 289 mμ (ε 110); λ_{max} in ethanolic NaOH 313·5 mμ (ε 11500). (Found: C, 74·00; H, 9·06. Calc. for $C_{23}H_{34}O_4$; C, 73·76; H, 9·15%.)

Compound VIII (0·1 g) was reconverted to VII by treatment with Ac_2O (1 ml) and BF_3–etherate (0·2 ml) for 3 hr at room temp, yield of VII was 75% (0·85 g).

[26] A similar steric interference of the 4-methyl group is probably responsible for the reported formation of the 2-bromo derivative and not the expected 6-bromo derivative, when 4-methyltestosterone XXX is brominated; C. W. Shoppee, G. A. R. Johnston and R. E. Lack, *J. Chem. Soc.* 3604 (1962).

C-*Acylation of* 5α-*androst*-16-*ene*-3β,17-*diol diacetate* (X)

Compound X (1 g) was treated at room temp with Ac_2O (5 ml) and then with BF_3–etherate (1 ml). The solution was allowed to stand for 2 hr and was then poured into ice and water and the material isolated from ether. Chromatography on alumina (30 g) and elution with pentane–ether (10:1) yielded XI (0·22 g; 22% yield) which showed a coloration with FeCl aq. This compound was identical with XI obtained previously[8] by IR and NMR comparison.

This mixture of isomers, XI (0·2 g) was dissolved in MeOH (5 ml) and treated with a sat. solution of cupric acetate (2 ml). After heating on water bath for 5 min, the copper chelate of XI was isolated with ether. Recrystallization from benzene–hexane yielded a sample m.p. 300–302°, λ_{max}^{EtOH} 260 and 308 mμ (ε 12000 and 20000), identical with a sample described previously.[8]

C-*Acylation of cholestan*-3β-*ol*-7-*one acetate* (XII)

The ketone XII (0·5 g) was treated at room temp with Ac_2O (5 ml) and then with BF_3–etherate (1 ml). After being left at room temp overnight, the reaction mixture was poured into ice and water, left for 2 hr, and the material isolated from ether. The residue was dissolved in MeOH (25 ml) and heated for 2 hr under reflux with a sat AcONa aq (5 ml). The material isolated from ether was chromatographed on alumina (15 g). The first fraction eluted with pentane–ether (10:1) gave 0·02 g (4%) of the starting material. The next fraction eluted with pentane–ether (5:1), was recrystallized from ether–MeOH to yield XIII (0·12 g; 22%), m.p. 150–151°, $[\alpha]_D$ −42°, λ_{max}^{KBr} 5·77 and 5·80 μ; λ_{max}^{EtOH} 286 mμ (ε 84), unchanged in ethanolic NaOH aq. (Found: C, 76·42; H, 10·35. Calc. for $C_{31}H_{50}O_4$: C, 76·50; H, 10·36%.)

O-*Acylation of* 2-*methyl*-5α-*androstan*-17β-*ol*-3-*one acetate* (XIV)

The ketone XIV (1 g) was treated at room temp with Ac_2O (10 ml), and then with BF_3–etherate (2 ml). After being left at room temp for 1 hr, the reaction mixture was poured into ice and water for 2 hr, and the material isolated from ether. Recrystallization from ether–pentane gave XV, (0·9 g; 80%), m.p. 91–92°; $[\alpha]_D$ +66°, identical with an authentic sample.[27]

Treatment of XV with the same reagent mixture for 24 hr at room temp, led to the unchanged starting material.

Acylation of 2-*methylcyclohexanone* XVI

The ketone XVI was treated at room temp with Ac_2O (80 ml) and then slowly with BF_3–etherate (20 ml). After standing at room temp for 30 min, the reaction mixture was poured into ice and water, left for 2 hr and the material isolated from ether. It was then dissolved in EtOH (100 ml), treated with a sat AcONa aq (50 ml), heated under reflux for 3 hr and extracted with ether. The ether solution (λ_{max}^{EtOH} 289 mμ, ε 1000) was extracted with cold 10% NaOH aq. The ethereal extract (24 g) was distilled *in vacuo*. The first fraction (12 g; b.p. 95–110°/28 mm) was redistilled to give 10·5 g of XVII, b.p. 95–96°/28 mm, identical with an authentic sample.

The second fraction from the distillation of the neutral material (2·4 g; b.p. 115–120°/28 mm) was redistilled to give additional 1·3 g of XVII and 1·1 g of XIX, b.p. 60–62°/0·5 mm, n_D^{20} 1·4660, identified by comparison with an authentic sample.[3,20]

The NaOH solution was acidified and extracted with ether. The ether extract (5 g; λ_{max}^{EtOH} 289 mμ, ε 4000) was distilled *in vacuo*, the fraction, b.p. 130–132°/28 mm, was identified as XX, 1·2 g; n_D^{20} 1·4809; λ_{max}^{EtOH} 289 mμ (ε 9000). (Found: C, 70·35; H, 8·20. Calc. for $C_9H_{14}O_2$: C, 70·10; H, 7·95%.)

The second fraction from the distillation of the acidic material (0·7 g; b.p. 145–160°/28 mm) consisted of a mixture of XX, and an additional product to which the structure XXI was assigned (see text).

O-*Acylation of* 2-*methylcyclohexanone* (XVI)

a. The ketone XVI (5 g) was treated with isopropenyl acetate (25 ml) and 2 drops of conc. H_2SO_4. The reaction mixture was heated under reflux overnight and the product isolated from ether and distilled *in vacuo*. The fraction boiling at 89–90°/25 mm (3 g); n_D^{25} 1·4570 consisted of a mixture of XVII and XVIII as found from the NMR spectrum.[18] The relative proportion of XVII and XVIII was 2:1 as determined by integration of the NMR spectrum.[18]

[27] R. Mauli, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 5488 (1960).

b. The ketone XVI (5 g) was dissolved in Ac_2O (20 ml) and treated with *p*-toluensulfonic acid (0·2 g). The mixture was heated under reflux for 3 hr, poured into ice and water and extracted with ether. Distillation gave the mixture of XVII and XVIII (4 g), b.p. 88–90°/25 mm. The ratio of XVII and XVIII was found to be ca. 9:1 (see a.)

C-Acylation of the enol acetates XVII *and* XVIII

a. The mixture of XVII and XVIII obtained from the reaction of XVI with isopropenyl acetate, (0·87 g), was treated with Ac_2O (10 ml) and BF_3–etherate (2 ml). After being left for 1½ hr at room temp, the reaction mixture was poured into ice and water and after 2 hr the material was isolated from ether. The residue was dissolved in MeOH (20 ml), treated with a sat. AcONa aq (5 ml) and extracted with cold 10% NaOH. The neutral ether extracts were distilled *in vacuo*. The fraction boiling at 95–97°/28 mm (0·3 g) consisted of XVII, identified by comparison with an authentic sample.

The second fraction of this distillation was the mixture of XVII and XIX, (1:1) as established by comparison of the NMR spectrum with the spectrum of the pure component.

The NaOH extract was acidified with 10% HCl and then extracted with ether. Distillation *in vacuo* yielded a first fraction, b.p. 130–132°/28 mm (0·11 g), identified as XX. The second fraction, b.p. 145–160°/28 mm (0·05 g) consisted of a mixture of XX and XXI (see text).

b. The mixture of XVII and XVIII obtained from the reaction of XVI with Ac_2O and *p*-toluensulfonic acid (1·0 g) was treated with Ac_2O and BF_3–etherate as described under a. The neutral material obtained was distilled *in vacuo* to give XVII (0·5 g) and XIX (ca. 0·05 g) both identified by comparison with authentic samples. The acidic material (0·1 g) had an NMR spectrum corresponding to the one of a mixture of XX and XXI.

Acylation of testosterone (XXII)

a. Compound XXII (1 g) was treated with Ac_2O (15 ml) and BF_3–etherate (3 ml) at 0°, and then left for 15 min at this temp, and an additional 5 min at room temp. The reaction mixture was poured into ice and water and the precipitate produced filtered off. Recrystallization from ether gave XXIII (0·25 g; 20%), m.p. 165–166°; $[\alpha]_D$ −306°; λ_{max}^{EtOH} 246·4 mμ (ε 13000)[4]; identical with an authentic sample.

b. Similar treatment of XXII (1·0 g) with the same reagent as under a, but at 0° for 10 min only, gave XXIV 0·7 g, (54%) which after recrystallization from pentane–ether melted at 149–152°.

Acylation of the dienol acetate (XXIV)

A solution of XXIV (1 g) in Ac_2O (15 ml) was treated with BF_3–etherate (3 ml) at room temp. After being left for 4 min, the solution was poured into ice and water, the crystalline precipitate filtered off, and recrystallized from ether to give XXIII (0·425 g; 42%), m.p. 165–166°, identical with an authentic sample.[4]

The mother liquor from recrystallization was evaporated to dryness, and chromatographed on alumina (15 g). The fraction eluted with benzene–ether (9:1) was recrystallized from ether to give XXV (0·1 g–10%), m.p. 150–152°, $[\alpha]_D$ +66°, λ_{max}^{EtOH} 238 mμ (ε 13500), identical with an authentic sample.[4]

Polyacetylated chelate of testosterone (XXVI)

Compound XXII (5 g) was dissolved in Ac_2O (50 ml) and treated with BF_3–etherate (10 ml) at room temp. After being left for 3 hr, the solution was poured into ice and water, left for 2 hr, and the oily precipitate triturated with ether. The crystals thus produced, which showed a negative reaction with $FeCl_3$ aq were recrystallized from ether to give XXVI, 3 g, (34%), m.p. 281–282°, $[\alpha]_D$ +636°, λ_{max}^{KBr} 5·69, 5·77, 6·16, 6·34, 6·61 and 8·04 μ. (UV see Table 1). (Found: C, 64·70; H, 6·75. Calc. for $C_{27}H_{35}O_6BF_2$: C, 64·30 H, 6·95%.)

Enol acetate of 2,6-*diacetyltestosterone acetate* (XXVII)

A solution of XXVI (0·5 g) in MeOH (50 ml) was treated with sat. AcONa aq (10 ml). The reaction mixture was heated under reflux for 2 hr, the solvent evaporated, and the material isolated from ether. Recrystallization from ether–pentane gave XXVII (0·32 g; 71%), m.p. 156–157°, $[\alpha]_D$ +486°, λ_{max}^{KBr} 5·69, 5·74, 6·00, 6·16, 8·05 and 8·24 μ (UV see Table 1). (Found: C, 71·37 H, 7·64. Calc. for $C_{27}H_{36}O_6$. C, 71·02; H, 7·95%.)

2,6-Diacetyltestosterone acetates (XXVIII)

The solution of XXVII, (0·35 g) in MeOH (50 ml) was treated with 20% H_2SO_4 (3 ml). The reaction mixture was heated under reflux for 4 hr, and then poured into water and the material isolated from ether. The residue was dissolved in a small volume of ether and precipitated by addition of pentane, to give an amorphous yellow powder, m.p. 120–180°, of the isomeric mixture of diacetyl testosterone acetates (XXVIII) which gave a positive $FeCl_3$ reaction. λ_{max}^{KBr} 5·84, 6·19 μ. (UV spectra see Table 1).

6β-Acetyl-4-methyltestosterone acetate (XXXI)

a. A solution of XXX (1·0 g) in Ac_2O (25 ml) was treated with BF_3–etherate (5 ml) at room temp. After being left for 1 hr, the solution was poured into ice and water, and after 2 hr extracted with ether. The ether residue was dissolved in MeOH (20 ml) and treated with sat. AcONa aq (5 ml) and heated under reflux for 2 hr. The solvent was evaporated to dryness *in vacuo*, and the residue dissolved in a mixture of benzene–pentane (1:1) and chromatographed on alumina (15 g). Elution with benzene–pentane (4:1) and recrystallization from CH_2Cl_2–hexane gave XXXI, (0·14 g; 13%), m.p. 187–190°, $[\alpha]_D$ −201°, λ_{max}^{EtOH} 252 mμ (ε 13500), identical with an authentic sample.[4]

b. Treatment of XXXII (0·5 g) under similar conditions with the same reagents resulted also in XXXI, (0·08 g; 14%).

Enol acetate of 2,6-diacetyl-4-methyltestosterone acetate (XXXIII)

A solution of XXX (0·35 g) in Ac_2O (10 ml) was treated with BF_3–etherate (3 ml) at room temp. After being left for 20 hr, the solution was poured into ice and water, left for 2 hr and the material isolated with ether. The crystalline product obtained from the ether gave XXXIII (0·13 g; 22%), m.p. 227–229°, $[\alpha]_D$ +390°, λ_{max}^{KBr} 5·69, 5·76, 6·24, 6·37, 6·62, 8·04 μ. (UV spectra see Table 1). (Found: C, 64·66; H, 7·19; B, 2·15. Calc. for $C_{28}H_{37}O_6BF_2$. C, 64·87; H, 7·20; B, 2·09%.)

2,6-Diacetyl-4-methyltestosterone acetate (XXXIV)

A solution of XXXIII (0·1 g) in MeOH (20 ml) was heated under reflux with sat AcONa aq (5 ml) for 3 hr. The solvent was evaporated to dryness, and the material isolated with ether. Chromatography of the product on alumina (5 g) and elution with benzene–ether (1:1) gave an amorphous yellow powder (0·035 g) to which we assigned the structure, XXXIV. $\lambda_{max}^{CHCl_3}$ 5·86, 6·24 μ (UV spectra see Table 1).