D-Homo-steroids. Part V.[1] A Study of the Mechanism of D-Homo-annulation of 17α-Hydroxypregnan-20-ones with Boron Trifluoride

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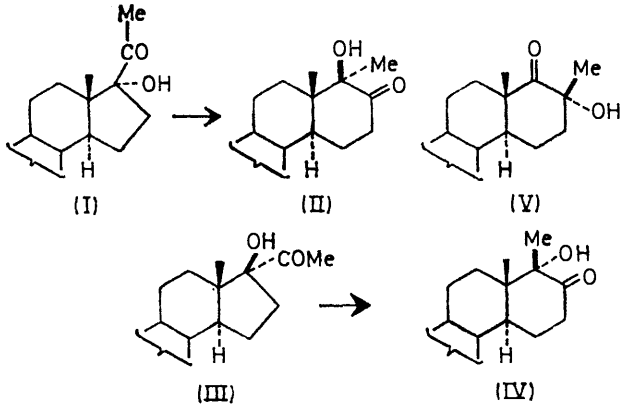
The rearrangement of 17α-hydroxypregnan-20-ones by boron trifluoride to give D-homo-ketols is retarded significantly by 16α-benzoyloxy-substituents, although variations in *p*-substitution in benzoyloxy-groups at C-16, and similarly in benzoates at C-11, had only slight effects on reaction rates. 16β-Methyl and 16-methylene substituents caused a marked acceleration and a slight retardation, respectively. Unsaturation at C(14)–C(15) caused a modest increase in reaction rate.

An n.m.r. study showed that a complex of boron trifluoride with the 17α-hydroxy-group is probably the main species present in the reacting solution, the postulated cyclic complex (XIII) having only transient existence as a highly reactive intermediate before undergoing rearrangement. These findings suggest that the rate of formation of a cyclic complex of type (XIII), as well as the rate of its rearrangement, is involved in the overall kinetics of D-homoannulation.

BASE-CATALYSED acyloin rearrangements of either 17α-hydroxypregnan-20-ones (I) [2-4] or 17β-hydroxy-17α-pregnan-20-ones (III) [2,3] give 17a-hydroxy-17a-methyl-D-homoandrostan-17-one derivatives (II) and (IV), respectively, by specific migration of the C(13)–C(17) bond. The same bond migrates when 17β-hydroxy-17α-pregnan-20-ones (III) are rearranged by Lewis acids (*e.g.* boron trifluoride or aluminium alkoxides). Unique in this series of reactions is the migration of the C(16)–C(17) bond when 17α-hydroxypregnan-20-ones (I) rearrange under the influence of Lewis acids. The major products



are then 17α-hydroxy-17β-methyl-17α-ketones (V), reportedly accompanied by minor amounts of the 17-ketones (IV). Reviews by Wendler,[2] and more recently by Kirk and Hartshorn,[3] have examined the reasons for the apparent abnormality of the latter reaction, but without reaching firm conclusions. It has been pointed out [5] that both isomers of a 17-hydroxypregnan-20-one react with Lewis acids mainly through transition states tending towards chair-like conformations of the D-homo-products, but Wendler [2] considered that evidence pointing to a preference for a skew or boat-like conformation of the ketol (V) considerably weakened this argument. The supposition that there should generally be an electronic preference for migration of the quaternary C-13 rather than the secondary C-16 has also been questioned,[3] and becomes even more doubtful when the ready migration of C-16 even in 16α-hydroxy-steroids [6] is taken into account.

Hoping to obtain a better understanding of the behaviour of 17α-hydroxypregnan-20-ones, we studied the Lewis acid-catalysed rearrangement of a series of substituted compounds in this series. N.m.r. spectroscopic analysis of samples withdrawn at intervals from reacting solutions provided comparisons of reaction rate amongst the various compounds, indicating the extent to which substituents assist or hinder the rearrangement. Analytical techniques are described in the Experimental section, and in Part II [4] of this series.

The reagent was a solution of boron trifluoride–ether complex in 1,2-dimethoxyethane. Reactions in this novel system took the normal path, and occurred at convenient temperatures (25 or 40 °C); all the steroids studied were sufficiently soluble in 1,2-dimethoxyethane, although sparingly soluble at these temperatures in other solvents examined.

[1] Part IV, I. Khattak, D. N. Kirk, C. M. Peach, and M. Wilson, *J.C.S. Perkin I*, 1975, 916.

[2] N. L. Wendler, in 'Molecular Rearrangements,' ed .P. de Mayo, Interscience, New York, 1964, vol. 2, pp. 1099—1101 and 1114—1121.

[3] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 294.

[4] D. N. Kirk and A. Mudd, *J. Chem. Soc.* (*C*), 1970, 2045.

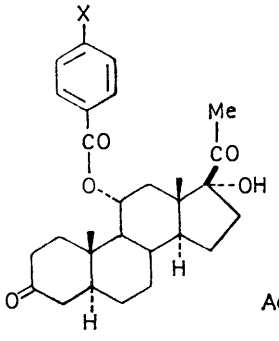
[5] I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. chim. France*, 1959, 742; N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, 1960, **11**, 163.

[6] L. L. Smith, M. Marx, J. J. Garbarini, T. Foell, V. E. Origoni, and J. J. Goodman, *J. Amer. Chem. Soc.*, 1960, **82**, 4616; N. L. Wendler and D. Taub, *ibid.*, p. 2836.

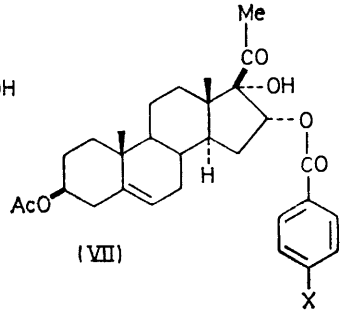
Other advantages of this solvent are the absence of n.m.r. signals in the region under study (thus traces remaining in samples after work-up were not detrimental) and solubility in water (permitting rapid quenching of the reaction when samples were taken).

17α-Hydroxypregnan-20-ones with various additional substituents were selected for study.[7]

(1) *p*-Substituted 11-benzoates (VI) derived from 11α,-17α-dihydroxy-5α-pregnane-3,20-dione, and a similar series of 16-esters (VII) derived from 3β-acetoxy-16α,17α-



(VI)



(VII)

dihydroxypregn-5-en-20-one were investigated. Several papers have described the application of Hammett–Taft relationships to probe long-range effects of polar substituents on reactions in steroids.[8,9] The rigidity of the steroid nucleus is assumed to validate such studies, although they are not applicable to aliphatic compounds in general. Recent work [9] has shown the possibility of using substituted benzoates to probe the charge character of the transition state in a suitable steroid reaction: the kinetics of the Westphalen rearrangement of 3,6-diesters of 5α-cholestane-3β,5,6β-triol, with substituted benzoate groups at C-6, exhibited an excellent Hammett correlation with the electronic effect of the aromatic substituent, the reaction constant (ρ −0.35) being consistent with the demonstrated rate-determining formation of a C-5 carbocation in the Westphalen rearrangement. The electronic effect of the aromatic substituent is transmitted effectively from the ester group to C-5, whether through two σ-bonds or across the intervening space. We therefore considered that variations in the rates of D-homoannulation of the benzoates of each series (VI) and (VII) should provide evidence as to the charge character of the transition state in this reaction. It even seemed that powerful electron withdrawal from C-16 might alter the path of reaction, leading to significant migration of C-13 instead of C-16.

The present results showed no such effect on product formation: C-16 migration, leading to ketols of the 17a-oxo-type (V), persisted throughout each series. Isomeric ketols, if present in the products, were below the limit of detection by the n.m.r. method employed (probably <2%), showing that C-16 migration is strongly favoured under kinetic control. The isomeric ketol (IV), with a 17-oxo-group, began to appear when reaction times were greatly prolonged, but this type of ketol equilibration has already been explained.[5,10]

The series of 11α-esters showed only slight variation in rates of reaction, the rates (relative to benzoate = 1.00) being: *p*-methoxybenzoate, 1.10; *p*-toluate, 1.06; *p*-nitrobenzoate, 0.81. A least-squares analysis of relative rates *vs.* Hammett σ values gave a regression line with a slope (ρ) −0.12, with a good correlation coefficient (0.99). The value of ρ suggests a transition state with moderate cationic character in the vicinity of C-17, allowing for attenuation of the effect of the 11α-substituent by three intervening C–C bonds.

The effects of benzoate substitution at the 16α-position were unexpectedly small. The relative rates determined experimentally covered a range hardly wider than those influenced by 11α-substituents, but the 16α-benzoate data did not fall on a straight line when plotted against σ values. Nevertheless, the 16-*p*-nitrobenzoate was again the slowest to react. The very low sensitivity to electronic effects of substituents seems to imply little positive charge on or near C-16 in the transition state, although the 16α-substituents as a group caused notable retardation of rearrangement compared with the 11α-benzoyloxy-series. No direct quantitative comparison of rates was made since the 11α-benzoyloxy- and 16α-benzoyloxy-series were differently substituted in rings A and B, but it was necessary to rearrange the 16α-substituted compounds at 40 °C, and with a four-fold increase in boron trifluoride concentration, in order to obtain rates comparable with those for the 11α-derivatives at 25 °C. The retardation by 16α-substituents may be mainly of steric rather than electronic origin (see below).

(2) The rates of reaction of the 16β-methyl-substituted ketol (VIII; R = Me) and the corresponding unsubstituted compound (VIII; R = H) were compared. A 16β-methyl group is reported [11] to facilitate D-homoannulation, such compounds rearranging rapidly even on neutral alumina. A 16α-methyl compound, while undergoing D-homoannulation,[12] apparently does not show this unusually high reactivity, which has been attributed to relief of β-face strain when the 16β-methyl compound rearranges, the 16β-methyl group becoming equatorial in the product (IX; R = Me).[11]

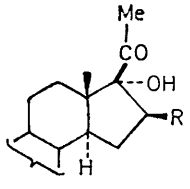
Our findings confirm the very high reactivity of the 16β-methyl compound. Its rate of reaction differed so much from that of the reference compound (VIII; R = H) that no single set of experimental conditions was

[7] A. Mudd, Ph.D. Thesis, London, 1970.
[8] R. A. Sneen, *J. Amer. Chem. Soc.*, 1958, **80**, 3977, 3982; P. E. Peterson, *Tetrahedron Letters*, 1963, 181; K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, 1966, **31**, 734.
[9] D. N. Kirk, *Tetrahedron*, 1975, **31**, 1299.
[10] R. B. Turner, M. Perelman, and K. T. Park, *J. Amer. Chem. Soc.*, 1957, **79**, 1108.
[11] D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012; N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, 1959, **7**, 173.
[12] P. J. May, F. A. Nice, and G. H. Phillipps, *J. Chem. Soc.* (*C*), 1966, 2210.

convenient for a direct kinetic comparison (see Experimental section). Again exclusive C-16 migration was found.

(3) The rearrangement of 17α-hydroxy-16-methyleneprogesterone was compared directly with that of 17α-hydroxyprogesterone. Here the rates differed only by a factor of 2, the 16-methylene compound reacting the more slowly. The only product found was that derived from C-16 migration, as reported elsewhere for a related 16-methylene derivative.[12]

(4) The effect of unsaturation at C(14)–C(15) was studied by comparing the rates of reaction of 17α-hydroxyprogesterone and its Δ^{14}-analogue (X). The latter compound does not appear to have been examined before. It was chosen in order to test the assumption [13] that the driving force for the known D-homoannulations comes in part from the relief of strain when a *trans*-fused hexahydroindane derivative rearranges into a *trans*-decalin. Various cholestenes are known to rearrange under acidic conditions to give cholest-14-ene,[14] so we may infer that 14,15-unsaturation relieves some of the strain in the *trans*-CD-ring junction. The stability



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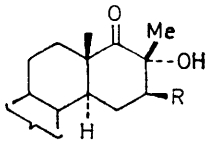

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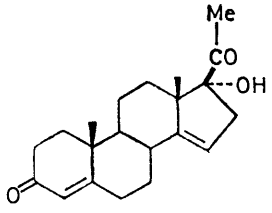

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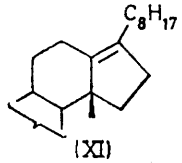


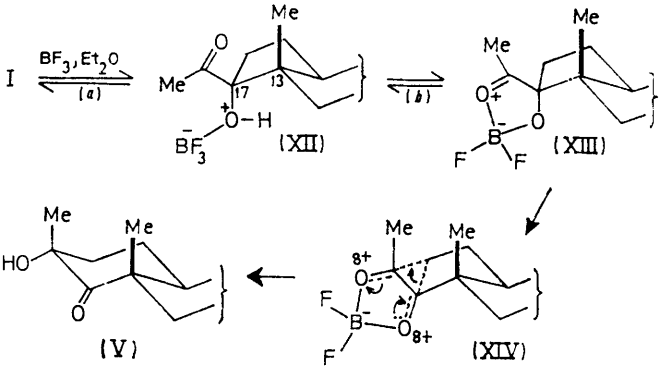
(XI)

of 'back-bone rearranged' cholest-13(17)-enes (XI) [15] supports this conclusion. The cyclopentene unit in both these classes of ring-D-unsaturated compounds is able to assume a near-planar conformation, with the 14,15- and 13,17-bonds almost eclipsed in each series. Such eclipsing is apparently energetically favourable when one of the bonds concerned is ethylenic.[16]

Despite these considerations, the Δ^{14}-compound (X) was found to react *ca.* 4.5 times *faster* than its saturated analogue, though once again with exclusive involvement of the C(16)–C(17) bond.

DISCUSSION

There seems little doubt that Turner's interpretation [2,3,13] of the stereochemistry of Lewis acid-catalysed D-homoannulation in terms of the formation of a cyclic complex of type (XIII) (Scheme) is correct. Our own observation that even the base-catalysed rearrangement may be subject to stereochemical control by complexing of the metal cation with both the 17α- and the 20-oxygen



SCHEME Steps in the D-homoannulation process

atom in a solvent of low polarity [4] provides additional support for the concept of a cyclic intermediate as the active species, which undergoes rearrangement to give D-homo-ketols with the hydroxy-group specifically in the α-configuration.

Although satisfactory as an explanation of stereochemistry, the rearrangement of a cyclic complex of the type (XIII) fails to meet all the requirements for the rate-determining step, when present data are considered. In particular, the migration of C-16, although retarded by the 16α-benzoyloxy-substituents, shows almost no sensitivity to aromatic substitution as would be expected of a transition state (XIV) with partial cationic character delocalised over C-16, C-17, and C-20.

Additional evidence against rate determination by the rearrangement step came from an n.m.r. study of the reacting solution, by which we hoped to detect intermediate species. When the overall reaction sequence was considered, it was evident that rearrangement *via* a cyclic transition state (XIV) must be preceded by two preliminary steps, each likely to be an equilibrium process (Scheme): (*a*) transfer of the Lewis acid (BF_3) from co-ordination with a molecule of ether (or with the solvent, in this case dimethoxyethane) to the 17α-hydroxy-group of the steroid to give a complex of type (XII) (the oxygen atom of the OH group is more basic than that of the carbonyl group); (b) rotation of the 17β-side-chain away from its preferred conformation, with the carbonyl oxygen atom in the vicinity of C-16,[17] into the conformation with *syn*-oxygen functions, to permit complexing between the boron and the carbonyl oxygen [if the cyclic complex is correctly represented as (XIII), the carbonyl oxygen atom must displace F^- from the OBF_3^- group, but the exact state of co-ordination of boron is not critical in the present discussion: the BF_2^- group in diagram (XIIII) could be replaced by a non-commital 'X',

[13] R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484.
[14] J. C. Eck and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986.
[15] Ref. 3, pp. 291—293.
[16] A. A. Bothner-By, C. Naar-Colin, and H. Günther, *J. Amer. Chem. Soc.*, 1962, **84**, 2748; W. J. Hehre and L. Salem, *J.C.S. Chem. Comm.*, 1973, 754 and references therein.
[17] N. L. Allinger, P. Crabbe, and G. Pérez, *Tetrahedron*, 1966, **22**, 1615.

to represent any Lewis-acidic species capable of holding the oxygen atoms to form the cyclic complex].

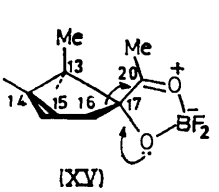
Both equilibria (*a*) and (*b*) would need to lie substantially to the right if rearrangement of the cyclic complex (XIII) were to be wholly or largely rate-determining. The cyclic complex (XIII) would then necessarily reach an appreciable concentration in the solution. It should be detectable by a change in the n.m.r. spectrum of the reactant following the addition of boron trifluoride, but preceding the spectral changes associated with molecular rearrangement. When boron trifluoride–ether complex was added to a solution of 17α-hydroxyprogesterone in deuteriochloroform, the only immediate change in the n.m.r. spectrum of the steroid was the disappearance of the signal (τ 6.72) due to the 17α-hydroxylic proton. The 20-methyl signal at τ 7.7 was unaffected, although complexing of the carbonyl group with boron would have been expected to cause a shift to lower field,[18] as a consequence of reduced electron density of C-20. This expectation was confirmed in a separate experiment when 5α-pregnan-20-one in deuteriochloroform was treated with boron trifluoride gas: the 20-methyl signal, initially at τ 7.83, was shifted to τ 7.33 by formation of the ketone–boron trifluoride complex (the corresponding shift for acetone was 0.32 p.p.m. downfield [18a]). There was also a small shift of the 13-methyl signal (from τ 9.36 to 9.30) and other minor changes in the methylene envelope. The use of boron trifluoride gas was dictated by the failure of the ether complex to form a complex with the steroid, owing to the relatively low basicity of the carbonyl oxygen compared with the ether).

The spectrum of the 17α-hydroxyprogesterone solution containing boron trifluoride underwent a gradual change over 15 min to the spectrum of a solution of the D-homo-ketol (V) containing boron trifluoride. Repetitive scans during the change gave no evidence of any other species accumulating in detectable amount. The 20-methyl signal, in particular, remained unmoved while it diminished in size until it had finally disappeared at the completion of the rearrangement.

It seems clear from this evidence that the main unrearranged species present was a complex (XII) between the hydroxy-group of the steroid and the boron trifluoride [step (*a*)], and that the cyclised complex (XIII) is never present in any detectable concentration. It follows that the rate of rearrangement of the cyclic complex is at least comparable with the rate of its formation, and that equilibrium (*b*) [and possibly also (*a*)] plays a major role in the kinetics of the rearrangement process. Assuming that a large excess of boron trifluoride ensures substantial conversion of the 17α-hydroxypregnan-20-one into its hydroxy–boron trifluoride complex [step (*a*)], the free energy of activation for rearrangement must then be acquired in two further stages. The energetics of the first stage [step (*b*)] will be decided by the ability of the carbonyl group to participate in ring-closure with the hydroxy–boron trifluoride complex: the energy requirements here should be largely subject to steric factors. Any substituent at C-16 would be expected to exert some blocking effect, by interfering either with the 20-methyl group (16β-substituent [17]) or with the oxygen–boron system (16α-substituent). The almost uniform retardation by *p*-substituted 16α-benzoyloxy-groups can be interpreted in this way, with the assumption that the cyclic complex (XIII), once formed, need acquire only modest further activation to rearrange to the boron complex of the corresponding D-homo-ketol. The 16β-methyl derivative requires substantially more conformational free energy to attain the *syn*-arrangement of oxygen functions necessary for simultaneous complexing to boron, when the 13-, 20-, and 16β-methyl groups become closely compressed.[17] In comparison with compounds lacking the 16β-methyl substituent, proportionately more of the total free energy of activation must be acquired during the initial cyclisation step, but there would be a corresponding decrease in the further activation required for rearrangement of the cyclic complex, since the extra compression is relieved as the transition state is reached. The unusually fast reaction observed for the 16β-methyl compounds implies a total activation energy which is unusually low; elevated ground-state energy [17] due to unavoidable interaction of the 16β-methyl group with the 17β-side-chain probably helps in this respect.

Migration of the vinylic C-16 in 17α-hydroxy-16-methyleneprogesterone is only slightly slower than for the corresponding unsubstituted compound. The propensity of unsaturated carbon atoms to migrate has been much discussed in connection with the Beckmann rearrangement of αβ-unsaturated oximes,[19] and despite an earlier suggestion to the contrary there now seems to be no general reason why unsaturation should hinder such reactions. The slight retardation could be of steric origin (see above), but the evidence is inconclusive.

Accelerated reaction of the Δ^{14}-compound, despite the low strain in this CD-ring system, may result from a combination of at least two factors. A Dreiding model shows that the tilt of ring D imposed by the trigonal C-14 slightly lessens compression between the 13- and 20-methyl groups in the cyclic complex (XV), compared



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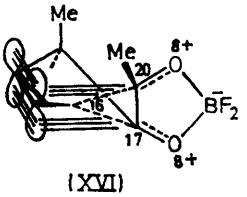

(XVI)

with the saturated analogues, and should therefore be favourable to the cyclisation process. Moreover C-16 is now allylic, and its migration may be facilitated by interaction between the π orbital of the C(14)–C(15) bond and

[18] (*a*) M. F. Lappert, *J. Chem. Soc.*, 1961, 817; (*b*) A. Fratiello, G. A. Vidulich, and Y. Chow, *J. Org. Chem.*, 1973, **38**, 2309.

[19] C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J. Chem. Soc.*, 1962, 1050; C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, *ibid.*, 1965, 5868; F. Kohen, *Chem. and Ind.*, 1966, 1378; T. Sato, H. Wakatsuka, and K. Amano, *Tetrahedron*, 1971, **27**, 5381.

an orbital involved in the electron-deficient cyclopropane-like bonding of C-16, C-17, and C-20 in the transition state (XVI). The spatial disposition of orbitals is suitable for a stabilizing overlap of this nature.

The present studies cast no further light on the main outstanding problem in this field, namely the preference for migration of C-16 rather than C-13, throughout the series, under catalysis by Lewis acids. Further work is in progress with the aim of explaining this pecularity.

EXPERIMENTAL

Boron trifluoride–ether was repeatedly distilled under reduced pressure until free from traces of coloured impurities. Solvents for n.m.r. spectra in kinetic studies were [$^2H_6$]dimethyl sulphoxide and in [$^2H_5$]pyridine as described before:[4] n.m.r. spectra for pure compounds mentioned below were recorded for solutions in $CDCl_3$ at 60 MHz with Me_4Si as internal standard. M.p.s. were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded for KBr discs. C.d. curves (solvent methanol) were determined by Mrs. W. P. Mose.

Kinetics.—Reactions were carried out (in duplicate) by adding boron trifluoride–ether to a solution of the steroid in anhydrous 1,2-dimethoxyethane, in a flask held at the required temperature (±0.1°). Samples were withdrawn at timed intervals over a period of 20—50 min depending upon the reactant, quenched in aqueous sodium hydrogen carbonate, and analysed by the n.m.r. method described previously.[4] To provide an internal reference standard for quantitative measurement of peak areas, 3β-acetoxyandrost-5-en-17-one was added to each reaction mixture in the same molar concentration as the steroid under study. The area under the acetate proton peak (τ 7.96) was used as the standard for measurement, after calibration by comparison with the peak area of the signal due to the 20-methyl protons in the 17α-hydroxypregnan-20-one. The benzoates (VII) of the 16α-hydroxy-series were the only exception to the use of 3β-acetoxyandrost-5-en-17-one as internal standard, the 3β-acetate signal of each compound (VII) itself being used as internal standard. The probable error in this method of measurement of the concentration of unchanged steroid is considered to be within ±4%. Pseudo-first-order rate constants were evaluated from the slope of the essentially linear plot of $\log_{10}[a/(a-x)]$ *vs.* time [a is the initial concentration of reactant steroid, and $(a-x)$ the concentration remaining after time t].

Experimental Conditions and Results of Kinetics.—(a) *Substituted benzoates* (VI) *of* 11α,17α-*hydroxy*-5α-*pregnane*-3,20-*dione*. Steroid (0.6 mmol), 1,2-dimethoxyethane (25 ml), BF_3, Et_2O (0.5 ml), 25 °C.

11α-*p*-Nitrobenzoate	$k = 3.8 \times 10^{-5}$ s^{-1}
11α-Benzoate	$k = 4.55 \times 10^{-5}$ s^{-1}
11α-*p*-Toluate	$k = 4.8 \times 10^{-5}$ s^{-1}
11α-*p*-Methoxybenzoate	$k = 4.9 \times 10^{-5}$ s^{-1}

(b) *Substituted benzoates* (VII) of 3β-*acetoxy*-16α,17α-*dihydroxypregn*-5-*en*-20-*one*. Steroid (0.6 mmol), 1,2-dimethoxyethane (25 ml), BF_3,Et_2O (2 ml), 40 °C.

16α-*p*-Nitrobenzoate	$k = 1.1 \times 10^{-4}$ s^{-1}
16α-Benzoate	$k = 1.2 \times 10^{-4}$ s^{-1}
16α-*p*-Toluate	$k = 1.4 \times 10^{-4}$ s^{-1}
16α-*p*-Methoxybenzoate	$k = 1.1 \times 10^{-4}$ s^{-1}

(c) 3β,17α-*Dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (VIII; R = Me). Steroid (0.3 mmol), 1,2-dimethoxyethane (25 ml), BF_3,Et_2O (0.125 ml), 25 °C.

$k = 4.1 \times 10^{-4}$ s^{-1} ($t_{\frac{1}{2}}$ *ca.* 28 min)

3β,17α-Dihydroxy-5α-pregnan-20-one (VIII; R = H) showed no reaction after 50 min under these conditions.

(d) 17α-*Hydroxy*-16-*methylenepregn*-4-*ene*-3,20-*dione*, 17α-*hydroxypregna*-4,14-*diene*-3,20-*dione and* 17α-*hydroxyprogesterone*. Conditions as (a) (25 °C).

16-Methylene compound	$k = 3.85 \times 10^{-5}$ s^{-1}
Δ^{14}-Compound	$k = 35 \times 10^{-5}$ s^{-1}
17α-Hydroxyprogesterone	$k = 7.75 \times 10^{-5}$ s^{-1}

Preparation of Reactants.—11α-*Benzoates* (VI) *from* 11α,17α-*dihydroxy*-5α-*pregnane*-3,20-*dione*. Benzoates were prepared by reactions of the dihydroxy-dione with the stoicheiometric amount of the appropriate substituted benzoyl chloride in pyridine, overnight at room temperature. The products crystallised from aqueous acetone: 11α-*p*-*nitrobenzoate*, m.p. 235—236°, τ 7.73 (21-H_3), 8.83 (10β-Me), and 9.13 (13β-Me); Δε +4.13 (296 nm) and 1.27 (252 nm) (Found: C, 67.1; H, 7.2; N, 2.7. $C_{28}H_{35}NO_7$ requires C, 67.6; H, 7.1; N, 2.8%); 11α-*benzoate*, m.p. 258—261°, τ 7.73 (21-H_3), 8.83 (10β-Me), and 9.13 (13β-Me); Δε +3.65 (296 nm) and 3.44 (228 m) (Found: C,74.7; H, 8.1. $C_{28}H_{36}O_5$ requires C, 74.3; H, 8.0%); 11α-p-*Toluate*, m.p. 234—235°, τ 7.56 (*p*-Me), 7.75 (21-H_3), 8.55 (10β-Me), and 9.15 (13β-Me); Δε +2.74 (300 nm) and 3.98 (236 nm) (Found: C, 74.8; H, 8.2. $C_{29}H_{38}O_5$ requires C, 74.7; H, 8.2%); 11α-p-*methoxybenzoate*, m.p. 215—217°, τ 6.15 (*p*-MeO), 7.73 (21-H_3), 8.83 (10β-Me), and 9.13 (13β-Me); Δε +4.42 (295 nm) and 3.16 (242 nm) (Found: C, 72.1; H, 8.1. $C_{29}H_{38}O_6$ requires C, 72.2; H, 7.9%).

16α-*Benzoates* (VII) *from* 3β-*acetoxy*-16α,17α-*dihydroxypregn*-5-*en*-20-*one*. The 16α,17α-dihydroxy-compound was prepared by a modification which we found more reproducible than the published procedure.[20] Two solutions were prepared: (*a*) 3β-acetoxypregna-5,16-dien-20-one (10 g) in acetone (500 ml) and formic acid (2.4 ml); (*b*) potassium permanganate (6.07 g) in water (110 ml), diluted to 500 ml with acetone. Solutions (*a*) and (*b*) were cooled to −5 °C and mixed with vigorous swirling in a 3 l conical flask for exactly 5 s, then aqueous sodium hydrogen sulphite (10%; 40 ml) was added to stop the reaction. Precipitated MnO_2 was filtered off, and the filtrate was concentrated under reduced pressure to the point of crystallisation. On cooling, the 16α,17α-diol (7.8 g) was obtained as rods, m.p. 194—196° (lit.,[20] 193—195°).

The 16-benzoates were prepared from the 16α,17α-diol as above: 16α-p-*nitrobenzoate*, m.p. 224—226°, τ 4.0 (16β-H), 4.6 (6-H), 6.65 (17α-OH), 7.64 (21-H_3), 7.98 (3β-OAc), 8.96 (10β-Me), and 9.16 (13β-Me); Δε +2.21 (298 nm) (Found: C, 66.0; H, 6.8; N, 2.5. $C_{30}H_{37}NO_8$ requires C, 66.8; H, 6.9; N, 2.6%); 16α-*benzoate*, m.p. 233—234°, τ 4.0 (16β-H), 4.6 (6-H), 6.72 (17α-OH), 7.68 (21-H_3), 7.98 (3β-OAc), 8.96 (10β-Me), and 9.18 (13β-Me); Δε +2.75 (298 nm) (Found: C, 73.0; H, 7.7. $C_{30}H_{38}O_6$ requires C, 72.9; H, 7.7%); 16α-p-*toluate*, m.p. 197—198°, τ 4.0 (16β-H), 4.6 (6-H), 6.71 (17α-OH), 7.66 (*p*-Me), 7.68 (21-H_3), 7.98 (3β-OAc), 8.96 (10β-Me), and 9.16 (13β-Me); Δε +2.66 (299 nm) (Found: C, 72.9; H, 7.8. $C_{31}H_{40}O_6$ requires C, 73.2; H, 7.9%); 16α-p-*methoxybenzoate*, m.p. 184—186°,

[20] A. E. Hydorn, J. N. Korzun, and J. R. Moetz, *Steroids*, 1964, **3**, 493.

τ 4.02 (16-H), 4.6 (6-H), 6.15 (*p*-MeO), 6.68 (17α-OH), 7.70 21-H_3), 7.98 (3β-AcO), 8.96 (10β-Me), and 9.18 (13β-Me); Δε +2.80 (298 nm) (Found: C, 70.9; H, 7.7. $C_{31}H_{40}O_7$ requires C, 71.0; H, 7.7%).

17α-*Hydroxypregna*-4,14-*diene*-3,20-*dione* (X). This was prepared from 14α,17α,21-trihydroxypregn-4-ene-3,20-dione *via* 14α,17α-dihydroxypregn-4-ene-3,20-dione essentially as described,[31] but with particular care in the final selective dehydration step. The dihydroxy-dione (1 g) in benzene (200 ml) was heated under reflux with a Dean–Stark water separator. Toluene-*p*-sulphonic acid (250 mg) in benzene (25 ml) was then added, and heating was continued for 1 h. The cooled solution was washed (aq. NaOH and water), dried, and evaporated. The residue crystallised from acetone–hexane to give 17α-hydroxypregna-4,14-diene-3,20-dione as rods (520 mg), m.p. 193—195° (lit.,[21] 194°).

D-*Homo-compounds*.— 17α-Hydroxy-17β-methyl-D-homoandrostan-17a-one (V) derivatives resulting from boron trifluoride-catalysed D-homoannulation were isolated from reaction media after completion of the kinetic experiments. The following compounds were obtained.

11-*Benzoates of* 11α-17α-*dihydroxy*-17β-*methyl*-D-*homo*-5α-*androstane*-3,17a-*dione*: 11α-p-*nitrobenzoate*, m.p. 225—227°, τ 4.39 (11β-H), 8.56 (17β-Me), 8.73 (10β-Me), and 8.83 (13β-Me) (Found: C, 67.3; H, 7.3; N, 2.8. $C_{28}H_{35}NO_7$ requires C, 67.6; H, 7.1; N, 2.8%); 11α-*benzoate*, m.p. 219—220°, τ 4.42 (11β-H), 8.56 (17β-Me), 8.73 (10β-Me), and 8.85 (13β-Me); Δε +1.88 (293 nm) and +3.24 (299 nm) (Found: C, 74.1; H, 8.0. $C_{28}H_{36}O_5$ requires C, 74.3; H, 8.0%); 11α-p-*toluate*, m.p. 201—203°, τ 4.42 (11β-H), 7.56 (*p*-Me), 8.56 (17β-Me), 8.73 (10β-Me), and 8.85 (13β-Me); Δε +1.36 (293 nm) and 3.38 (226 nm) (Found: C, 74.4; H, 8.1. $C_{29}H_{38}O_5$ requires C, 74.7; H, 8.2%); 11α-p-*methoxybenzoate*, m.p. 159—161°, τ 4.45 (11β-H), 6.09 (*p*-MeO), 8.57 (17β-Me), 8.75 (10β-Me), and 8.85 (13β-Me); Δε +1.11 (298 nm) and 2.76 (242 nm) (Found: C, 72.1; H, 7.8. $C_{29}H_{38}O_6$ requires C, 72.2; H, 7.9%)

16-*Benzoates of* 3β-*acetoxy*-16α,17α-*dihydroxy*-17β-*methyl*-D-*homoandrost*-5-*en*-17a-*one*: 16α-p-*nitrobenzoate*, m.p. 115—116°, τ 4.45 (16β-H), 4.66 (6-H), 6.00 (17α-OH), 7.98 (3β-AcO), 8.43 (17β-Me), 8.79 (10β-Me), and 8.96 (13β-Me); Δε +2.86 (295 nm) (Found: C, 66.1; H, 6.8; N, 2.3. $C_{30}H_{37}NO_8$ requires C, 66.8; H, 6.9; N, 2.6%); 16α-*benzoate*, m.p. 222—225°, τ 4.50 (16β-H), 4.66 (6-H), 6.08 (17α-OH), 7.98 (3β-AcO), 8.43 (17β-Me), 8.79 (10β-Me), and 8.96 (13β-Me); Δε +2.50 (299 nm) (Found: C, 72.2; H, 7.7. $C_{30}H_{38}O_6$ requires C, 72.9; H, 7.7%); 16α-p-*toluate*, m.p. 192—194°, τ 4.52 (16β-H), 4.69 (6-H), 7.61 (*p*-Me), 7.98 (3β-AcO), 8.43 (17β-Me), 8.79 (10β-Me), and 8.96 (13β-Me); Δε +2.29 (289—299 nm) (Found: C, 72.9; H, 8.0. $C_{31}H_{40}O_6$ requires C, 73.2; H, 7.9%); 16α-p-*methoxybenzoate*, m.p. 198—200°, τ 4.50 (16β-H), 4.69 (6-H), 6.15 (*p*-MeO), 7.98 (3β-AcO), 8.43 (17β-Me), 8.79 (10β-Me), and 8.96 (13β-Me); Δε +2.75 (286—296 nm) (Found: C, 70.1; H, 7.5. $C_{31}H_{40}O_7$ requires C, 71.0; H, 7.7%.)

3β,17α-*Dihydroxy*-16β-17β-*dimethyl*-D-*homo*-5α-*androstan*-17a-*one*, m.p. 175—176°, τ 8.78 (17β-Me), 8.97 (d, *J* 6 Hz, 16β-Me), 8.96 (10β-Me), and 9.20 (13β-Me) (Found: C, 75.8; H, 10.4. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%).

17α-*Hydroxy*-17β-*methyl*-16-*methylene*-D-*homoandrost*-4-*ene*-3,17a-*dione*, m.p. 164—165°, τ 4.28 (4-H), 4.75 and 5.1 [C(16)=CH_2], 6.12 (17α-OH), 8.48 (17β-Me), and 8.78 (6H, s, 10β-Me and 13β-Me) (Found: C, 77.4; H, 8.8. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%).

17α-*Hydroxy*-17β-*methyl*-D-*homoandrosta*-4,14-*diene*-3,17a-*dione*, m.p. 154—156°, τ 4.25 (4-H), 4.6 (15-H), 6.00 (17α-OH), 8.53 (17β-Me), 8.67 (10β-Me), and 8.74 (13β-Me) (Found: C, 77.0; H, 8.7. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%).

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[21] B. M. Bloom, E. J. Agnello, and G. D. Laubach, *Experientia*, 1956, **12**, 27; G. Cooley, B. Ellis, and V. Petrow, *Tetrahedron*, 1966, Suppl. 7, 325.