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INTRAMOLECULAR CATALYSIS—V

LONG RANGE EFFECTS IN STEROIDS. ACETYLATION RATES OF SOME Δ^5-3β-HYDROXY STEROIDS

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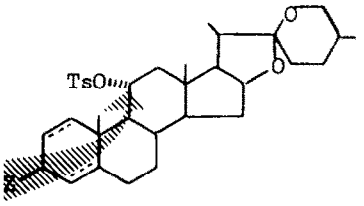
Abstract—A variety of solvolysis, addition, dissociation, reduction, oxidation, condensation, and enolization reactions are subject to long-range effects either in terms of reaction rate or product geometry. The effects, some of which operate over the entire steroid molecule, have been classified as inductive, electrostatic field, conformational transmission, and direct interaction. Significant long-range effects were found to be absent in the acetylation of a series of Δ^5-3β-ols whose rates were measured by following the change in optical rotation.

STEROIDS ARE A particularly favoured class of compounds for studying long-range effects because the rigid framework of the carbon skeleton permits reasonably precise knowledge about inter-group distances and spacial arrangements. Long-range effects have been classified by two groups of authors as: (1) inductive effects, (2) electrostatic field effects, and (3) conformational transmission.[1,2] To these may be added a fourth class of direct interaction between groups which, though remote in the sense of having more than a few carbons between their points of attachment, can nevertheless come close enough to interact with each other or with the reagent simultaneously.[3] It will be seen at once that there is no precise line of demarcation between this last class and the familiar neighbouring group effect,[4] although interactions of groups attached to the same ring clearly would not be considered "long-range," while interactions across several rings probably would.

The concept of long-range inductive effects represents a conundrum to the organic chemist, who traditionally expects to find significant inductive effects operating over short ranges only.[5] Peterson has shrewdly observed, however, that in calculating inductive effects in polycyclic systems *all possible routes* between the remote substituent and the reaction center should be summed,[6] and this approach was successfully employed to explain the decreases in acetolysis rates with increasing electronegative substitution in the A-ring of 11α-tosyloxy sapagenins (**1**).[7] Rates of addition to the Δ^5-double bond of **2** are lowered not only by nearby electronegative substituents at C-3, but also by distant electronegative substituents at C-17;[8] the data have been recalculated.[6] In a series of estrogens (**3**) substituents at C-17 were found to effect the pK_a values of the 3-phenolic hydroxyl group,[9] in fact, the earliest long-range effect noted was the observation that estriol exhibits a larger ionization constant than estrone.[10] Increasing the extent of conjugated unsaturated in ring A increases the rates of hydrolysis of 17-acetates and 17-benzoates (**4**)[11] and decreases the rate of



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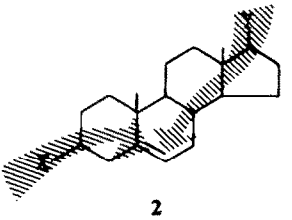

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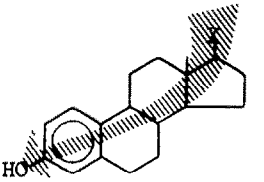

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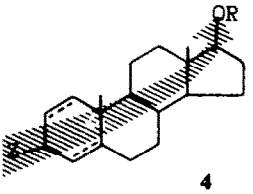

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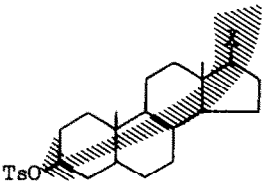

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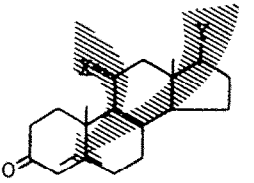

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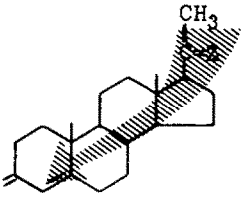
solvolysis of 17-tosylates (**4**).[12] The rates of solvolysis of 3-tosylates (**5**) are decreased by electronegative substituents at C-17.[13] Effects of substituents at C-11, C-17, and C-20 on the proportions of 5α and 5β steroids from hydrogenation of Δ^4-3-ketones (**6** and **7**) were observed by several groups.[14] Interpretations of these findings should perhaps be reexamined in the light of the observation that results differ depending on whether hydrogen or substrate is absorbed first on the catalyst.[15]

Long-range electrostatic field effects have been defined by Henbest in terms of the interaction of a dipole (C—Cl or C—O) with the transition state, and are illustrated by the observation that a 3-chloro substituent increases the proportion of 12α-ol in the hydride reduction of 12-oxotigogenins (**8**), and by the influence of 17-oxygenated substituents on the increase of α to β-epoxide formation from Δ^4-3-keto steroids (**9**).[16] Oxygenated side chains increase the rate of 4,5-epoxidation of **9** by alkaline



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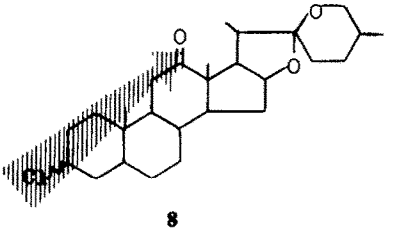

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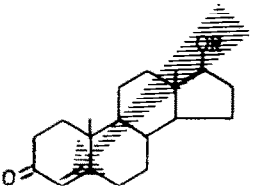

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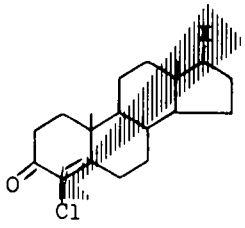
hydrogen peroxide,[17] but decrease the rate of 5,6-epoxidation of **12** by perbenzoic acid.[18] The faster methanolysis rates of 4-chloro steroids (**10**) with oxo and nitrate groups at C-17, compared with 17-OH, were shown to be an electrostatic field interaction and not inductive.[19] Rates of degradative oxidation of corticoid derivatives (**11**), some with 11-oxygen functions, were increased by conjugated unsaturation in the A-ring.[20] Comparing 3α- and 3β-chloro-5α-cholestan-6α-yl tosylate, the rate of solvolysis of the tosylate group is influenced by the configuration of the chlorine.[21] With 3α- and 3β-azido-5α-cholestan-6-one, electrostatic interactions between the 3-azide and 6-oxo groups effect the equilibrium between 5α- and 5β-isomers.[22]

The term as well as the concept of conformational transmission was first employed by Barton *et al.* to explain the variation in rates of condensation of benzadehyde with 3-oxo steroids and triterpenes (**13**) having double bonds at various positions.[23] The rigidity of the steroid skeleton requires that conformational changes produced in one ring, say by the introduction of a double bond, be transmitted to the adjacent fused ring, and possibly beyond.* In benzylidine formation double bonds in rings B, C and D operate to favour or hinder flattening of the A-ring at C-2, a critical feature of the rate determining step.[25]



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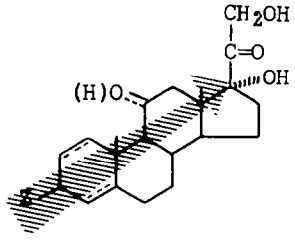

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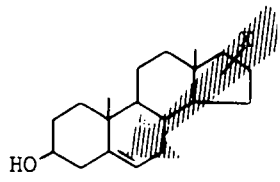

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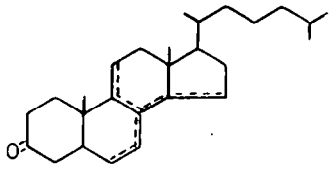

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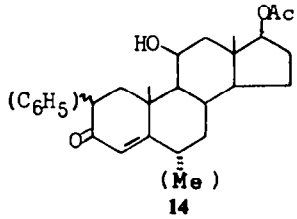

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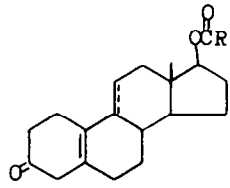

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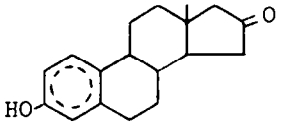
Conformational transmission (the Barton effect) has been employed to explain long distance effects in a number of other instances such as dissociation constants of cyanohydrins of **13**,[26] enol equilibria of 3-oxo steroids (**14**),[27]† acetolysis of 17-toxylates,[28]‡ composition of epimers from hydride reduction of the 3-ketones **15**,[29] enol acetate formation of 16-keto steroids (**16**),[30] configuration of B/C ring juncture in B-nor steroids (**17**),[31] hemiketal formation in di- and tetrahydrodigifologenins (**18**),[32] ORD curves of 3-oxo steroids (**19**),[33] and the effect of C-ring unsaturation on the equilibrium composition of 17-H–20-keto steroids.[34]



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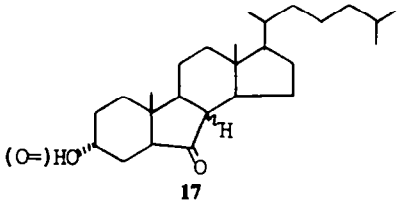

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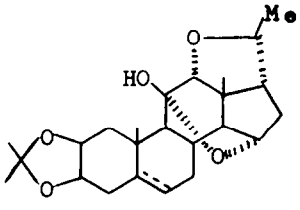

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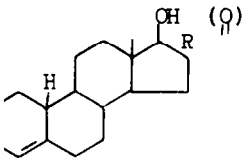
* Recently Altona *et al.* have observed that "transmission effects through the junctions are damped over short distances," ref. 24.

† In the last paper listed in ref. 27 these authors do not identify the effect observed (6α-methyl on direction of enolization) as conformational transmission; in addition, they point out that the enolization reactions previously studied are accompanied by C-acylation and dienone-phenol rearrangement.

‡ Takeda *et al.*[7] believe this is an inductive effect, however. These compounds are represented by **4**, $R = O_2SC_6H_4CH_3$.

It goes without saying that in many of the examples given of all three types, no effort was made to rule out rigorously alternative explanations, that more than one effect may be operating simultaneously, and that they would be difficult to examine individually. Furthermore, some long-range effects have been observed that remain unexplained: the type of substituent at C-17 influences the direction of homologation of 3-oxo steroids (**20**);[35] acetylation of the 3-hydroxyl of **21** alters the direction of dehydration of the 20-hydroxyl,[36] etherification of the phenolic hydroxyl of **22** increases the rate of oxidation of the 17-hydroxyl.[37]



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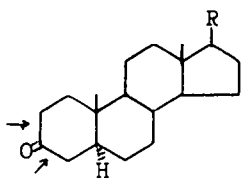

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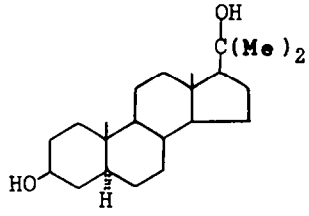

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The influence of remote groups on the wave length of Δ^4-3-keto absorption "by some type of long-range interaction" is well documented.[38] Hypsochromic shifts are observed by the introduction of double bonds (Δ^7, Δ^8, $\Delta^{8(14)}$, $\Delta^{9(11)}$, Δ^{11}, Δ^{14}), epoxides (9α11α, 11β12β, 14α15α), a ketone group at C-12, and a lactone or hemiacetal group (11β → 18). Bathochromic shifts are observed on addition of 11α-methyl or 9β, 11β-epoxide groups. Recent emphasis has been placed on the apparent interaction between remote chromophores in 4.16-pregnadiene-3.20-dione;[39] the sum of extinction coefficients for the individual chromophores is 26,500 (16-prenene-3,20-dione, 9,800;[40] progesterone, 16,700), while 4,16-pregnadiene-3,20-dione exhibits ε of only 24,100 suggesting a damping of 2,400.*

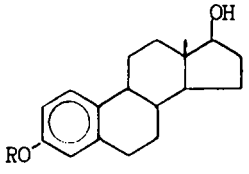
In some instances long-range effects were found to be absent: equilibria between AB-*cis* and AB-*trans* isomers (with C=O adjacent to ring juncture) are unaffected by expansion of ring D,[42] or by substituents at C-17 or unsaturation in ring D,[43] equilibria between 17-epimers is not influenced by alterations to rings A and B;[44] rates of reactions of Δ^4-3-oxo steroids with thiosemicarbazide[45] or with cyanide ion[46] are not influenced by remote groups.

An effect that is long-range in a different sense is represented by the $Pb(OAc)_4$–I_2 oxidation of friedelan-3β-ol.[47] Not only is the expected oxide (**23**) obtained, but also an iodinated derivative (**24**) resulting from two *consecutive* 1,5-hydrogen shifts. Somewhat similarly, photolysis of **25** gives rise to a C-18 free radical which then attacks the C-20 cyanohydrin resulting ultimately in **26**.[48]

A remarkable series of remote oxidations represent the final class of long-range reactions. Photolysis of ω-(*p*-benzoylphenyl)alkanoic esters of 5α-cholestan-3α-ol (**27a**) induces hydrogen abstraction from C-12, C-14, or C-17, degradation of the

* This conclusion is weakened by the fact that the value for the first of these steroids was obtained in water, while values for the last two were obtained in EtOH. Using values obtained only in EtOH (16-pregnene-3,20-dione, 9,800; progesterone, 17,000; 4,16-pregnadiene-3,20-dione, 25,200[41]) the difference is only 1,600. Using values obtained in ether (5,16-pregnadiene-3β-ol-20-one acetate, 9,600; progesterone, 17,300; 4,16-pregnadiene-3,20-dione, 26,100[40]) the difference is only 800.

intermediates formed giving rise to ketones or olefins.[3] Although the non-steroidal moiety obviously can assume many nonproductive conformations, a folded back conformation brings the ketone group close to particular hydrogens (depending partly on the value of *n*) giving rise to a considerable degree of specificity. The attacking group need not be attached to the steroid by a covalent bond, as photolysis of the acid dimer type of complex (**27b**) results in attack at C-16.[4c] This highly promising approach has recently been extended to functionalization at positions 7, 9, 11, 15, and 16.[49] Another example in this general class is the $NaBH_4$ reduction of the Diels–Alder adduct **28a** to give exclusively lactone **28b**, the influence of the 3-acetoxy group.[50]



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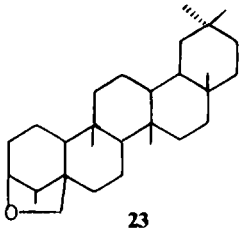

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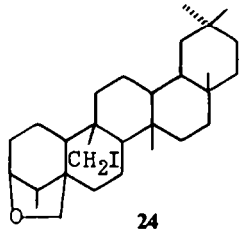

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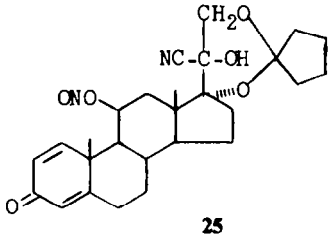

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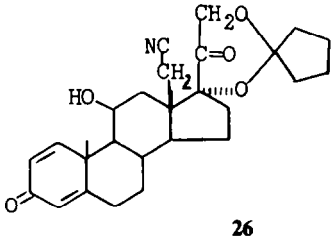

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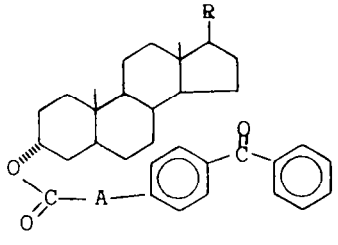

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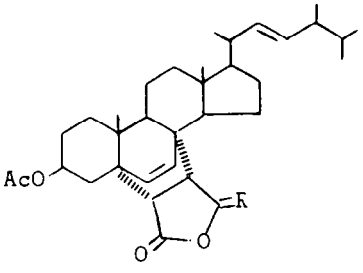
a: A = $(CH_2)_n$, R = C_8H_{17}

b: A = $-CH_2CH_2C(=O\cdots HO)-C(=O\cdots HO)-$, R = H



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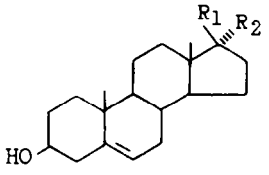
a: R = O

b: R = H_2



29

a: R_1R_2 = O

b: R_1 = Ac, R_2 = H

c: R_1 = OH, R_2 = CH_3

d: R_1 = R_2 = H

e: R_1 = $CH(CH_3)CO_2CH_3$, R_2 = H

f: R_1 = $C_{10}H_{21}$, R_2 = H

g: R_1 = $OC(O)C_6H_5$, R_2 = H

As part of our continuing interest in long-range effects in steroids,[51] we studied the influence of substituent groups at C-17 on the rate of acetylation of steroids containing the Δ^5-3β-hydroxy grouping (**29**). The pyridine-catalyzed acetylation of alcohols is generally believed to proceed by nucleophilic attack of the alcohol on an

N-acetylpyridinium ion, which is formed in a rapidly established equilibrium (eq. 1).[52] The influence of steric factors on acetylation rates of cyclic alcohols has been examined,[53] but inductive substituent effects appear not to have been studied.

$$Py + Ac_2O \rightarrow AcO^- + AcPy^+ \xrightarrow{ROH} ROAc + PhH^+ \quad (1)$$

TABLE 1. RATES OF ACETYLATION WITH ACETIC ANHYDRIDE AND PYRIDINE AT ROOM TEMPERATURE[a]

Compound	
29a 3β-Hydroxy-5-androsten-17-one	$1{\cdot}73 \times 10^{-4}$, $1{\cdot}55 \times 10^{-4}$
29b 3β-Hydroxy-5-pregnen-20-one	$1{\cdot}67 \times 10^{-4}$, $1{\cdot}54 \times 10^{-4}$
29c 3β-Hydroxy-17α-methyl-5-androsten-17β-ol	$1{\cdot}65 \times 10^{-4}$
29d 3β-Hydroxy-5-androstene	$1{\cdot}60 \times 10^{-4}$
29e Methyl 3β-Hydroxy-5-bisnorcholenate	$1{\cdot}16 \times 10^{-4}$, $1{\cdot}28 \times 10^{-4}$
29f 3β-Hydroxy-5-stigmastene[b]	$1{\cdot}15 \times 10^{-4}$
29g 3β-Hydroxy-5-androsten-17β-yl benzoate	$1{\cdot}04 \times 10^{-4}$

[a] Steroid (0·37 M), Ac_2O (1·065 M), 25·6° ± 0·8°. [b] Run at lower concentration because of poor solubility: steroid (0·25 M), Ac_2O (0·75 M).

A new method was developed for determining rates of acetylation of hydroxy steroids by monitoring the change in optical rotation.* Second order rate constants given in Table 1 were calculated from the expression

$$k = \frac{2{\cdot}303}{t(b-a)} \log \frac{a(b-x)}{b(a-X)}$$

where a = starting concentration of steroid, b = starting concentration of acetic anhydride, and x = concentration of each having reaction at time t. It is readily seen that the compounds studied have similar rates, the fastest having a rate constant only 1·7 times that of the slowest. We conclude that, while these rate differences are as large as some of those long range effects referred to earlier, they are not large enough to allow mechanistic interpretation.

EXPERIMENTAL

All compounds were commercial samples except **29d** which was reported previously,[51a] and **29e**, prepared by refluxing the corresponding acid in MeOH and conc HCl for a day: m.p. 140–142° (lit.[55] 142–143·7°). Polarimetric measurements were taken on an instrument manufactured by Dr Steeg & Reuter, Bad Homburg, and available from E. H. Sargent & Co.

Kinetic measurements by optical rotation. Ac_2O (2·50 ml, 26·6 mmole) was added to a solution of 9·25 mmole of steroid in pyridine (which had been dried over molecular sieve type 4A) in a 25 ml volumetric flask. The volume was quickly made up to 25 ml with pyridine;† the solution was mixed and transferred to a 20 cm polarimeter tube.‡ The first reading usually could be taken 3 min after addition of the anhydride.

* Polarimetry was used to follow the first reaction to be studied kinetically, the inversion of sucrose (ref. 54).

† At this concentration 5,20α,22α,25D-spirosten-3β-ol (diosgenin) was soluble, but its acetate pptd out in the polarimeter tube during the reaction.

‡ The tube was kept in the polarimeter during the run, where the temperature was 25·6° ± 0·8° in the cell compartment.

The zero time value was obtained by extrapolation of readings taken during the first 20–30 min, and the reaction was followed until constant readings were obtained, usually 24–36 hr (about 18 half-lives).* Data from a typical run with pregnenolone (**29b**) are presented in Table 2; a plot of log $[a(b-x)/b(a-x)]$ vs. t gave a least squares line with a slope of 0·1676, giving $k = 0{\cdot}555\ M^{-1}H^{-1}$ or $k = 1{\cdot}54 \times 10^{-4}\ M^{-1}\ sec^{-1}$.

TABLE 2. KINETIC RUN OF THE ACETYLATION OF 3β-HYDROXY-5-PREGNEN-20-ONE, (PREGNENOLENE) WITH ACETIC ANHYDRIDE AND PYRIDINE

Time, hr	α	$\log \frac{a(b-x)}{b(a-x)}$	Time, hr	α	$\log \frac{a(b-x)}{b(a-x)}$
0·083	+7·65	0·019	3·00	+3·80	0·503
0·117	7·50	0·027	3·50	3·65	0·553
0·167	7·30	0·039	4·08	3·40	0·656
0·25	7·10	0·052	4·50	3·25	0·734
0·33	6·70	0·080	5·00	3·15	0·797
0·50	6·35	0·108	5·50	3·00	0·915
1·00	5·35	0·208	6·00	2·90	1·020
1·50	4·85	0·278	8·00	2·70	1·380
2·00	4·45	0·346	12·00	2·55	—
2·58	4·00	0·446	24·00	2·55	—

* Extrapolation of the first 5 readings gives a value of 8·00° for t_0.

This method has the advantage over GLPC,[51a] UV,[51a] and radioisotope methods[51b] in that it is not necessary to remove aliquots. It suffers from the disadvantage that large quantities of steroid are required. In order to compare this method directly with the GLPC method, methyl lithocholate was acetylated in a benzene medium (steroid 0·37 M; Ac_2O, 1·065 M; pyridine, 1·24 M), the procedure being otherwise identical to that described above. Duplicate runs gave values of $k = 59{\cdot}2 \times 10^{-6}$ and $60{\cdot}7 \times 10^{-6}\ M^{-1}\ sec^{-1}$; the GLPC method gave $k = 55{\cdot}6 \times 10^{-6}\ M^{-1}\ sec^{-1}$.[51a]

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* This part of the procedure was validated by comparing initial and final values with optical rotations of pseudo acetylation mixtures: (pseudo initial) steroid (**29b**, 0·37 M) in pyridine; (pseudo final) steroid (acetate of **29b**, 0·37 M), AcOH (0·37 M), Ac_2O (0·695 M) in pyridine. In most runs the rotation changed rapidly at first, then slowly leveled off; unexplicably, with **29g** the rotation became more positive for the first 10 min, then became more negative for the rest of the reaction.

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