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THE KINETIC EFFECTS OF SUBSTITUTED BENZOATES ON THE WESTPHALEN REARRANGEMENT

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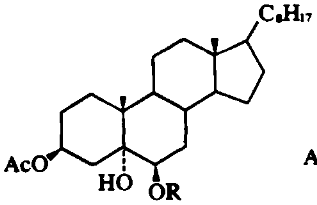
Abstract—The rate of the Westphalen rearrangement of 3β,6β-disubstituted 5α-cholestan-5-ols is influenced by substituted benzoates at the 6β position in a manner which can be correlated with Hammett substituent constants (σ), giving a reaction constant (ρ) of $-0{\cdot}35$.

The mechanism by which sulphuric acid-acetic anhydride promotes the Westphalen rearrangement of 3β,6β-disubstituted 5α-hydroxy steroids ($1\rightarrow2$) has been elucidated from kinetic studies.[1] All the evidence points to a transition state with carbonium ion-like character at C-5, resulting from heterolysis of an intermediate 5α-acetylsulphate. In particular, a Taft-type correlation of rate data for various substituents (H, Me, MeO, AcO, F and Cl) at the 6β-position afforded a ρ^* value near $-3{\cdot}5$; variations in the 3β-substituent[2] gave a similar ρ^* value, with the assumption that the electronic effect is attenuated by a factor of 1/2·8 due to the intervening carbon atom (C-4). Although the large value, $\rho^* = -3{\cdot}5$, corresponds to substantial carbonium ion character in the transition state, recent work with a 19-Me substituent (10β-Et) showed a rate enhancement (5·3 × rate for 10β-Me) consistent with some participation from the migrating alkyl group.[3] The rearrangement is specific to 5α-hydroxy steroids, suggesting that 10β-alkyl participation may be an essential requirement.



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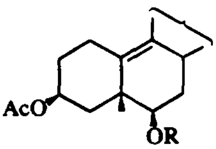

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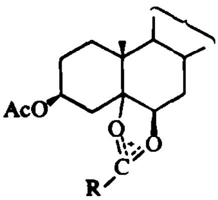

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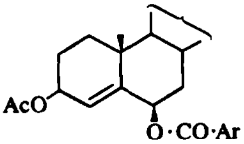

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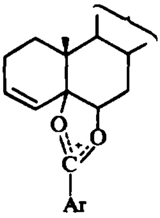

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The Westphalen rearrangement has now been studied for a series of derivatives of type **1**, with *m*- and *p*-substituted benzoate esters at the 6β-position. The primary purpose was to examine the suitability of a Hammett treatment of rate data for a reaction involving carbonium ion development in an alicyclic system, close to the site of the aromatic ester group, and in a fixed geometrical relationship to it. Although the effect of any substituent in the benzoate group must be attenuated by the intervening saturated aliphatic framework, the successful correlation with Hammett σ values reported below shows that the approach is a valid one for probing transition-state character in a rigid polycyclic structure. Other applications are envisaged.[4] Several workers have studied electronic effects of remote substituents in steroids,[5] but the compounds have generally included oxo groups and/or olefinic bonds which are known to distort polycyclic frameworks. It is then difficult to separate conformational from electrical effects. Steroid alcohols may generally be converted into a series of aromatic esters, without fear of the variations in skeletal strain and geometry which may result from the presence of substituents of more diverse character (halogens, OMe, Me, etc.).

It was also expected that this project would provide evidence either for or against involvement of the 6β-ester group, via a 5β,6β-acetoxonium ion (**3**),[6] in the formation of by-products during the Westphalen rearrangement. Earlier work has shown that an unusually high proportion of 5α-acetate is formed when the 6β-substituent is one capable of neighbouring-group participation to give a three-membered ring intermediate (6β-OMe, -Br, -I[1] and -N_3[7] compounds): Opening of the cyclic 'onium ion (**3**) by acetic acid, attacking at the 5α-position to give a diaxial product, would account for the formation of more 5-acetate than is usual during Westphalen rearrangements. Aromatic ester group participation should be minimal when a strongly electronegative substituent is present in the aromatic ring, but unsubstituted benzoates or those bearing electron-donating substituents are known to be capable of neighbouring-group participation,[8] and such participation might be expected to cause deviations from a linear Hammett plot, as well as significant changes in relative yields of products. No such deviations from normal were, however, observed.

In a further search for ester participation, a series of 3-acetate 6-benzoates (**4**) of cholest-4-ene-3β,6β-diol was prepared by dehydration of the corresponding 5α-hydroxy compounds (**1**) with thionyl chloride-pyridine. The 3α,6β- and 3β,6β-diacetates are known to equilibrate readily at C-3 in strongly acidic solutions in acetic acid-acetic anhydride.[9] An intermediate allyl carbonium ion might be stabilised by transient formation of the 5β,6β-acetoxonium ion (**5**); comparable behaviour has been observed during the solvolysis of 3β-acetoxy-6β-halogenocholest-4-enes, when a 3β,4β-acetoxonium ion is generated as the key intermediate.[10] The present series of substituted benzoates at C-6, however, showed no significant deviations from a linear Hammett plot when rates of equilibration at C-3 were compared, suggesting that participation by the 6β-ester groups occurs either uniformly in all cases or in none: the latter seems the more likely.

Kinetics. Westphalen reactions were followed polarimetrically as in earlier work, optical rotation data obtained from the recorder chart being analysed essentially as before.[1] A plot of $\log k_{rel}$ against Hammett's σ values was linear within the limits of experimental error (k_{rel} = first-order rate constant for substituted benzoate relative to that of the unsubstituted benzoate taken as unity). The regression line from a least-squares analysis of data had a slope (ρ) of $-0{\cdot}348$, with a correlation coefficient of 0·995.

The value of ρ is in good agreement with the concept of a well-developed carbonium ion at C-5, separated from the benzoate oxygen atom by two saturated sigma bonds which attenuate the electronic influence of the aromatic substituent.

Isomerisation at C-3 in the 4,5-unsaturated 3,6-diesters (**4**) was followed in essentially the same way, but with a 10-fold increase in the concentration of sulphuric acid (0·01 M) to secure convenient rates of reaction. Relative initial rates of isomerisation were obtained from the recorder charts, with the assumption that each 3β,6β-diester reacted to give a similar equilibrium mixture of 3α- and 3β-acetoxy-6β-aroyloxy compounds. TLC and IR examination of products, and the similarity of optical rotation data throughout the set of 6β-esters, indicated that this was approximately true, although no attempt was made to analyse each product mixture precisely. Again a plot of $\log k_{rel}$ vs σ was reasonably close to linear, with $\rho = -0{\cdot}496$, although the correlation coefficient (0·97) was less satisfactory than for the Westphalen reaction. Assuming ionisation at C-3 to be rate-determining in the equilibration, the value of ρ indicates that the transition state carries a formal positive charge in the vicinity of C-5 which is slightly larger than that in the Westphalen reaction. This seems reasonable for a well-developed allylic cation embracing C-3, C-4 and C-5, with the tertiary C-5 carrying a major proportion of the charge. The transition state may well be more cationic in character than that in the Westphalen reaction, because of the lesser effectiveness of acetate compared with acetylsulphate as a leaving group. Again there is no indication that 6β-ester participation makes any major contribution to the rate determining step.

The range of electronic effects available from ester substituents is greatly extended by use of the 6β-trifluoroacetate (**1**; R=$COCF_3$) and 6β-acetate in the Westphalen reaction. The trifluoroacetate group has a retarding effect greater than that of any of the aromatic esters, the rate of reaction being only about one-seventh of that observed from the 6β-*m*-nitrobenzoate. The retarding effect of the trifluoroacetate is equivalent to that of a benzoate with a hypothetical substituent having a σ value of about $+3{\cdot}2$, far exceeding that available from any aromatic derivative. Similarly, the 6β-acetate, which exhibited a rate 20-fold greater than that of the trifluoroacetate,[1] may be allotted a substituent constant equivalent to an effective σ value of $-0{\cdot}65$, being *less* retarding than the 6β-*p*-methoxybenzoate.

EXPERIMENTAL

Solvents were purified as described previously.[1] Thionyl chloride was distilled first from linseed oil and then from quinoline. "Deactivated alumina" refers to P. Spence, Grade H, deactivated by mixing with 5% of aqueous 10% acetic acid.

The 6β-benzoate and substituted benzoates were prepared from 5α-cholestane-3β,5,6β-triol 3-monoacetate by reaction with the appropriate acid chloride (1·25 mol) in pyridine at 0°, followed by chromatographic purification (deactivated alumina) and crystallisation from methanol or methanol-acetone mixtures. The Table records m.ps; all derivatives gave satisfactory elemental analyses.

The 3,6-diesters of cholest-4-ene-3β,6β-diol were prepared from the corresponding triol diesters by Darzens' dehydration ($SOCl_2$-pyridine[9]). Products were decolourised by passage through a short column of deactivated alumina, and crystallised from methanol, ethanol or acetone-methanol. M.ps are recorded in Table 1: all products gave satisfactory elemental analyses.

Westphalen reactions were carried out as previously described,[1] using each steroid at 0·005 M concentration in AcOH–Ac_2O (4:1) containing H_2SO_4 (0·001 M), at 30°. Rearranged Δ^9-compounds

Table 1. Esters of 3β-acetoxy-5α-cholestane-5,6β-diol and 3β-acetoxycholest-4-en-6β-ol, and kinetic data for Westphalen rearrangement and equilibration at C-3, respectively.

Ester	3β-Acetoxy-5α-cholestane-5,6β-diol derivative		Westphalen rearrangement product	3β-Acetoxycholest-4-en-6β-ol derivative	
	m.p.	Relative rate (6β-benzoate = 1.000)	m.p.	m.p.	Relative rate (6β-benzoate = 1.00)
6β-Acetate	168-169°	1.718	127-128°	134-136°	1.863
6β-p-Methoxybenzoate	90-104° (amorph.)	1.330	gum	-	-
6β-m-Toluate	114-116°	1.068	147-148°	90.5-92.5°	1.223
6β-Benzoate	159-160°	1.000	157-158°	gum	1.000
6β-m-Methoxybenzoate	106-108°	0.929	133-135°	101-103°	0.927
6β-p-Chlorobenzoate	145-147°	0.869	143-143.5°	120-121°	0.857
6β-m-Chlorobenzoate	-	-	-	92-94°	0.761
6β-m-Nitrobenzoate	129-133°	0.590	179-180°	133-135°	0.476
6β-trifluoroacetate	151-151.5°[1]	0.086	-	-	-

generally crystallised directly after conventional work-up of mixtures, or were isolated by chromatography on deactivated alumina. Yields were in the range 50–60%; m.ps are listed in the Table: satisfactory elemental analyses and NMR and IR spectra were obtained for all crystalline products (the 6β-*p*-methoxybenzoate, a gum, was characterised only from its spectroscopic characteristics).

Equilibrations of diesters of cholest-4-ene-3β,6β-diol were followed polarimetrically[9] under similar conditions to the Westphalen rearrangement,[1] but with a sulphuric acid concentration of 0·01 M. Relative rates of reactions were evaluated from the initial slopes of the recorder traces of optical rotation as a function of time, because darkening of the solutions by side reactions prevented accurate measurements of optical rotations at equilibrium; this probably accounts for the somewhat lower correlation coefficient compared with that for data from the Westphalen reaction.

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