262. *Long-range Effects in Alicyclic Systems. Part III.*[1] *The Relative Rates of Condensation of Some Steroid and Triterpenoid Ketones with Benzaldehyde.*

By D. H. R. Barton, F. McCapra, P. J. May, and (in part) F. Thudium.

The rates of alkali-catalysed condensation of a series of steroidal 3-ketones with benzaldehyde to furnish the corresponding 2-benzylidene derivatives have been determined. As in the earlier work with triterpenoid ketones long-range effects produced by unsaturated substituents (especially the ethylenic linkage) and by other groups can be easily detected. There exists a quantitative relation between the rates for structurally analogous steroidal and triterpenoid ketones such that rates can be expressed in terms of the rate of a saturated reference ketone multiplied by a series of group rate factors (f) each of which is characteristic of the nature and position of the substituent group. The possible rôle of polar factors in influencing rates of condensation of carbonyl-substituted ketones is admitted, but the major importance of the new effects of conformational transmission is considered to have been again demonstrated for ketones having remotely placed ethylenic substitution.

A cursory investigation of derivatives of β-decalone has shown that, wherever structurally appropriate, the same effects can be recognised and are of the same quantitative magnitude as in corresponding steroid and triterpenoid ketones.

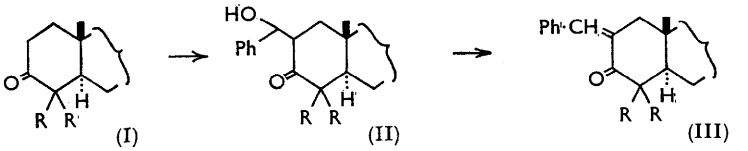
A preliminary account of this work has already been published.[2]

In the previous Part of this series [1] the rates of alkali-catalysed condensation of benzaldehyde with various triterpenoid ketones of partial structure (I; R = Me) to give benzylidene derivatives (as III; R = Me) were determined. It was demonstrated that, whilst polar factors may play some rôle in determining rate variation, there was in addition a more

[1] Part II, Barton, Head, and May, *J.*, 1957, 935.

[2] D. H. R. Barton, in the Kekulé Symposium, "Theoretical Organic Chemistry," Messrs. Butterworths Scientific Publications, London, 1959, p. 127.

important factor arising from the presence of unsaturated linkages, especially the ethylenic linkage, which caused marked long-range effects. The latter factor was associated with progressively varied angle strain through the molecule and given the name " conformational



transmission." We shall consider the results recorded in the earlier paper [1] at the same time as we discuss our new experimental work.

Another factor to which our attention has been directed is the possible incidence of " axial buttressing." According to this concept the influence of (say) a remotely placed linkage is due, not to the progressive deformation of angles, but to the altered interaction of axial substituents on the same side of the molecule. Thus lanost-8-enone (IV) (100 : standard rate as defined in earlier paper) would differ from lanostanone (V; R = Me, R′ = C_8H_{17}) (55) and from lanost-7-enone (VI; R = Me, R′ = C_8H_{17}) (17) because of the altered non-bonded interactions between the axial 4- and 10-methyl groups. In the present paper we report results with steroidal compounds, where the axial 4-methyl group has been removed, which show not only the same qualitative long-range effects but also the same *quantitative* relationship. We conclude therefore that axial buttressing is not a factor of major importance. It can, however, probably be detected in that lanostanone (V; R = Me, R′ = C_8H_{17}) (55) reacts more slowly than β-amyranone (VII; R = R′ = H) (88), presumably because of the extra axial methyl group at $C_{(8)}$ in the latter compound. The *trans*-fused five-membered ring D of lanostanone (angle strain) might, however, still be the more important factor.

Before we turn to the major substance of this paper, recently published work [3,4] demands a reappraisal of the mechanism of the alkali-catalysed reaction under study. The reaction sequence is as follows:

$$-CH_2-CO- + OH^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} -\bar{C}H-CO- + H_2O \quad . \; . \; . \; . \quad \text{(i, ii)}$$

$$-\bar{C}H-CO- + Ph\cdot CHO \underset{k_4}{\overset{k_3}{\rightleftharpoons}} Ph\cdot CH(-O^-)-\underset{|}{C}H\cdot CO- \quad . \; . \; . \quad \text{(iii, iv)}$$

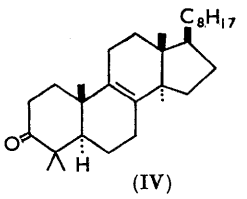
$$Ph\cdot CH(-O^-)-\underset{|}{C}H-CO- + H_2O \underset{k_6}{\overset{k_5}{\rightleftharpoons}} Ph\cdot CH(OH)-\underset{|}{C}H-CO- + OH^- \quad . \quad \text{(v, vi)}$$

$$Ph\cdot CH(OH)-\underset{|}{C}H-CO- + OH^- \underset{k_8}{\overset{k_7}{\rightleftharpoons}} Ph\cdot CH(OH)-\underset{|}{\bar{C}}-CO- + H_2O \quad \text{(vii, viii)}$$

$$Ph\cdot CH(OH)-\underset{|}{\bar{C}}-CO- \xrightarrow{k_9} Ph\cdot CH=\underset{|}{C}-CO- + OH^- \quad . \; . \; . \quad \text{(ix)}$$

The important papers by Noyce [3] and by Stiles [4] and their co-workers have shown that, except with methyl ketones, the rate-determining step for the formation of benzylidene ketone is not carbon–carbon bond formation [step (iii)] but the elimination of OH^- [step (ix)]. The formation of the final product is, in fact, controlled by the partition of the aldol intermediate between the regression step (iv) and the elimination step (ix). It can be shown that a scheme such as steps (i)—(ix) reduces to a kinetic form which is still of the

[3] Noyce and Reed, *J. Amer. Chem. Soc.*, 1959, **81**, 624.
[4] Stiles, Wolf, and Hudson, *J. Amer. Chem. Soc.*, 1959, **81**, 628.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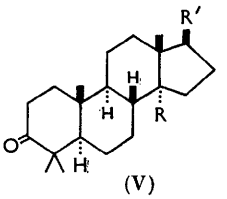
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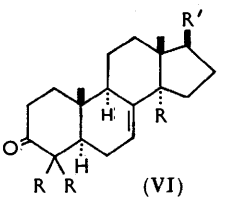
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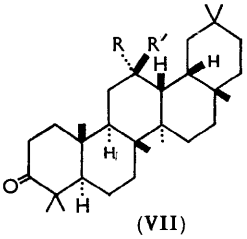
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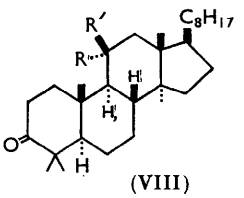
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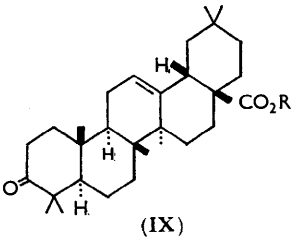

(IX)

first order in benzaldehyde, alkali, and ketone in agreement with experiment,[1] but the emphasis of interpretation is now transferred from the anion $-\bar{C}H\cdot CO-$, as in the earlier discussion, to the anion $Ph\cdot CH(OH)\cdot\bar{C}\cdot CO-$.

We have been able to secure direct experimental evidence for the partition of an intermediate aldol (as II) between starting materials and final product (benzylidene ketone). Thus cholestanone (V; R = H, R′ = C_8H_{17}), condensed with benzaldehyde in the minimum of 0·1N-ethanolic potassium hydroxide, gave the corresponding aldol [as (II; R = H)]. On treatment with alkali exactly as under the conditions of a kinetic run this aldol partitioned to furnish 90% of starting materials and only 10% of final product [as (III; R = H)]. The latter was shown to be completely stable to the same alkaline conditions and thus there is no reversibility from the benzylidene ketone.

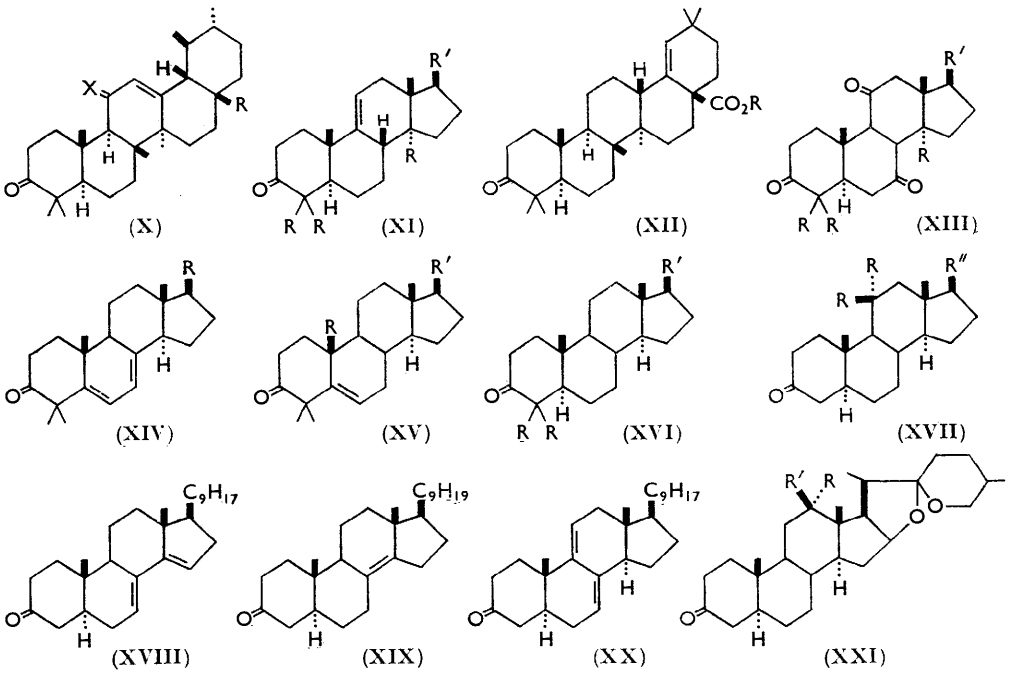
The evidence that justifies the formulation of the benzylidene ketone as a 2- rather than a 4-derivative must now be presented. All the steroid ketones that we have studied are of the *trans*-A/B type which, as is well known,[5] normally enolise towards $C_{(2)}$. A number of benzylidene ketones has been prepared and in each case they had the same ultraviolet absorption characteristics as the corresponding triterpenoid ketones [2] [as (III; R = Me)]. Representative benzylidene ketones were stable to attempted further condensation with benzaldehyde under the normal kinetic conditions. 2α-Methylcholestanone [6] did not condense at all with benzaldehyde under these conditions, indicating no tendency for $C_{(4)}$ condensation when $C_{(2)}$ is blocked. In the following cases the position of condensation was proved by degradation or by further reaction.

Stigmastanone gave only one crystalline monobenzylidene derivative which on ozonolysis afforded the known [7] 2,3-secostigmastane-2,3-dioic acid. Similarly β-decalone gave a single benzylidene derivative degraded by ozonolysis to the known [8,9] cyclohexane-*trans*-1,2-diacetic acid. As will be clear from the sequel the ketones where condensation at $C_{(4)}$ is most likely to be found are those that react slowly with benzaldehyde. In fact, it was important to prove specifically that ergosta-7,22-dienone (VI; R = H; R′ = C_9H_{17}) condensed at position 2 and not at position 4. This was shown as follows. 4,4-Dimethylergosta-5,7,22-trien-3-one (XIV; R = C_9H_{17}) was reduced with lithium–ethylamine [10] to 4,4-dimethylergosta-7,22-dien-3-one. With benzaldehyde this gave a

[5] For example, Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1954, **74**, 3852; (R. B.) Turner, Meador, and Winkler, *ibid.*, 1957, **79**, 4122.
[6] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[7] Heilbron, Coffey, and Spring, *J.*, 1936, 738; Larsen, *J. Amer. Chem. Soc.*, 1938, **60**, 2431.
[8] Kandiah, *J.*, 1931, 922.
[9] Ali and Owen, *J.*, 1958, 2111.
[10] Benkeser, Robinson, Sauve, and Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 3230, 3378.

crystalline 2-benzylidene derivative. Alternatively ergosta-7,22-dienone (VI; R = Me, R′ = C_9H_{17}) was condensed with benzaldehyde and the product then exhaustively methylated with potassium t-butoxide and methyl iodide [11] to furnish the same compound.

With these preliminaries completed it is now appropriate to discuss the new experimental data in more detail. Table 1 sets forth additional results (reported as in Part II [1])



with triterpenoid ketones, Table 2 does the same for steroidal ketones, whilst Table 3 presents pertinent data for decalin derivatives. We discuss first the triterpenoid data.

Table 1 gives results for two more triterpenoid acids. Together with the earlier data [2] we have the series: oleanonic acid (IX; R = H) (97), methyl ester (113); ursonic acid (X; R = CO_2H; X = H_2) (91), methyl ester (111); moronic acid (XII; R = H) (78), methyl ester (108). In each case the negative charge exerts a definite, but small, retarding effect as would be predicted on the basis of electrostatic theory. The data in no way suggest that electrostatic effects are of dominant importance (cf. Part II [1]). The addition of an 11-ketone group to lanostanone (V; R = Me, R′ = C_8H_{17}) (55) (Part II) causes a small decrease in rate (to 43). This is comparable to the decrease on going from α-amyrone (X; R = Me, X = H_2) (100) to 11-oxo-α-amyrone (X; R = Me, X = O) (75). We argued that if angle strain is the most important factor in this decrease then replacing the dipolar trigonal (>C=O) at $C_{(11)}$ by the non-polar, but equally trigonal, (>C=CH_2) group should give essentially the same rate decrease. In the event 11-methylene-α-amyrone (X; R = Me, X = CH_2) had a rate of 66 as expected.

The data for 11α- (35) and 11β-hydroxylanostanone (17) are of interest. The difference in rate, a factor of two, between the two compounds excludes any explanation based on bond induction for this would give the same rate in both cases. Both compounds differ from lanostanone (55). It may be that dipolar interactions are involved. A similar picture is presented by 12α- (53) and 12β-hydroxy-β-amyranone (89) compared with β-amyranone (88). The equatorial 12β-hydroxyl group does not alter the rate, but the axial 12α-hydroxyl group exerts a marked effect. Instead of exerting an effect by

[11] (W. S.) Johnson, *J. Amer. Chem. Soc.*, **1943**, **65**, 1317.

TABLE 1.

Compound	No. of runs	Average rate: % of lanost-8-enone rate	Limiting values
11β-Hydroxylanostanone (VIII; R = H, R′ = OH)	2	17	16·9—17·9
11α-Hydroxylanostanone (VIII; R = OH, R′ = H)	2	35	34·7—35·0
Lanostane-3,11-dione (VIII; R, R′ = 0)	2	43	43·0—43·0
12α-Hydroxy-β-amyranone (VII; R = OH, R′ = H)	2	53	51·7—53·6
11-Methylene-α-amyrone (X; R = Me, X = CH_2)	2	66	64·8—67·0
Lanost-9(11)-enone (XI; R = Me, R′ = C_8H_{17})	2	73	72·5—73·2
Moronic acid (XII; R = H)	2	78	77·2—78·5
β-Amyranone (VII; R = R′ = H)	2	88	88·2—88·5
12β-Hydroxy-β-amyranone (VII; R = H, R′ = OH)	2	89	86·8—92·0
Ursonic acid (X; R = CO_2H, X = H_2)	2	91	90·4—91·2
Lanostane-3,7,11-trione (XIII; R = Me, R′ = C_8H_{17})	2	92	90·7—94·1
Methyl ursonate (X; R = CO_2Me, X = H_2)	2	111	110—112
Lanostane-3,7-dione (XXII; R = Me, R′ = C_8H_{17}, X = O)	2	200	193—206

TABLE 2.

Compound	No. of runs	Average rate: % of lanost-8-enone rate	Limiting values
17β-Hydroxy-4,4-dimethyl-19-norandrost-5-en-3-one (XV; R = H, R′ = OH)	3	17	16·8—19·2
Ergosta-7,22-dienone (VI; R = H, R′ = C_9H_{17})	2	43	42·5—43·8
Ergost-7-enone (VI; R = H, R′ = C_9H_{19})	2	47	43·0—50·0
4,4-Dimethylergosterone (XIV; R = C_9H_{17})	2	50	52·0—48·0
4,4-Dimethylcholest-5-en-3-one (XV; R = Me, R′ = C_8H_{17})	1	51	—
17β-Hydroxy-4,4-dimethylandrost-5-en-3-one (XV; R = Me, R′ = OH)	2	57	55·0—58·0
17β-Hydroxy-4,4-dimethylandrostan-3-one (XVI; R = Me, R′ = OH)	1	58	—
11β-Hydroxyergost-22-en-3-one (XVII; R = H, R′ = OH, R″ = C_9H_{17})	2	68	67·2—68·8
Ergosta-7,14,22-trienone (XVIII)	2	62	60·0—63·5
Ergost-8(14)-en-3-one (XIX)	3	94	93·8—94·2
Ergosta-7,9(11),22-trien-3-one (XX)	2	99	95—102
3,11-Dioxobisnorallocholanic acid (XVII; R, R′ = O, R″ = $C_3H_5O_2$)	2	103	102—103
Ergost-22-ene-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{17})	2	110	109—110
Ergostane-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{19})	2	120	119—122
11α-Hydroxyergost-22-en-3-one (XVII; R = OH, R′ = H, R″ = C_9H_{17})	2	125	123—126
Tigogenone (XXI; R = R′ = H)	2	174	172—176
Stigmastanone (XVII; R = R′ = H, R″ = $C_{10}H_{21}$)	3	180	176—184
Cholestanone (XVII; R = R′ = H, R″ = C_8H_{17})	2	182	181—183
17β-Hydroxyandrostan-3-one (XVII; R = R′ = H, R″ = OH)	2	188	187—191
Ergostanone (XVII; R = R′ = H, R″ = C_9H_{19})	1	188	—
12β-Hydroxy-12α-methyltigogenone (XXI; R = Me, R′ = OH)	2	188	180—194
Ergost-22-en-3-one (XVII; R = R′ = H, R″ = C_9H_{17})	2	188	187—190
9(11)-Dehydrotigogenone (XXIII)	2	221	218—224
Ergost-14-en-3-one (XXIV)	2	223	220—226
12-Methylenetigogenone (XXI; R, R′ = CH_2)	2	218	218—218
Ergosta-8,22-dien-3-one (XXV)	1	280	—
11(12)-Dehydrotigogenone (XXVI)	2	380	358—400
Hecogenone (XXI; R, R′ = O)	2	328	327—331
Ergost-22-ene-3,7,11-trione (XIII; R = Me, R′ = C_9H_{17})	2	360	348—371
7-Methylenecholestanone (XXII; R = H, R′ = C_8H_{17}, X = CH_2)	3	365	356—375
Cholestane-3,7-dione (XXII; R = H, R′ = C_8H_{17}, X = O)	3	615	610—619
Cholest-6-enone (XXVII)	2	645	640—650

TABLE 3.

Compound	No. of runs	Average rate: % of lanost-8-enone rate	Limiting values
1,1,10-Trimethyl-Δ^6-*trans*-2-octalone (XXIX; R = R′ = Me)	2	8·1	8·0—8·1
trans-2-Decalone (XXVIII; R = R′ = H)	2	35	34·6—35·2
1,1,10-Trimethyl-*trans*-2-decalone (XXVIII; R = R′ = Me)	2	46	45·7—45·9
10-Methyl-Δ^6-*trans*-2-octalone (XXVIX; R = H, R′ = Me)	2	56	56·1—56·5
10-Methyl-*trans*-2-decalone (XXVIII; R = H, R′ = Me)	3	148	146·5—149·5

buttressing it is conceivable that axial substituents, for example OH, because of the repulsions exerted upon them distort the bond angles of the carbon atom to which they are attached and that this distortion is conformationally transmitted as discussed in our previous paper.[2]

The 9(11)-ethylenic linkage in lanost-9(11)-enone (XI; R = Me, R′ = C_8H_{17}) causes a significant (73) increase in rate not incompatible with that found earlier [1] for triterpenoid 9(11)-en-12-ones. We shall refer to the data for lanostane-3,7-dione and -3,7,11-trione in later discussion.

We now discuss the rate data for steroidal ketones (Table 2) as well as for a limited number of steroids with geminal methyl substitution at position 4. One can state at once that changes in the steroidal side chain have no effect upon condensation rates. Thus stigmastanone (XVII; R = R′ = H, R″ = $C_{10}H_{21}$) (180), cholestanone (XVII; R = R = H′, R″ = C_8H_{17}) (182), ergostanone (XVII; R = R′ = H, R″ = C_9H_{19}) (188), ergost-22-enone (XVII; R = R′ = H, R″ = C_9H_{17}) (188), and 17β-hydroxyandrostan-3-one R = R′ = H, R″ = OH) (189) all reacted at the some rate. Tigogenone (XXI; R = R′ = H_2) (174) and 12β-hydroxy-12α-methyltigogenone (XXI; R = Me, R′ = OH) (188) also showed unaltered rates.

The most striking fact that we have so for encountered in this work is the difference between ergosta-7,22-dienone (VI; R = H, R′ = C_9H_{17}) (43) and ergost-7-enone (VI; R = H, R′ = C_9H_{19}) (47) on the one hand and cholest-6-enone (XXVII) (645) on the other. Simply by moving the ethylenic linkage from the 6,7- to the 7,8-position the rates can be altered by a factor of 15. This is powerful evidence for conformational transmission effects. We have also studied the disturbance caused by ethylenic linkages placed in other positions. Relevant data are provided by ergost-8(14)-enone (XIX) (94), ergost-14-enone (XXIV) (223), ergosta-8,22-dienone (XXV) (280), 7-methylenecholestanone (XXII; R = H, R′ = C_8H_{18}, X = CH_2) (365), 9(11)-dehydrotigogenone (XXIII) (221), 11(12)-dehydrotigogenone (XXVI) (380), and 12-methylenetigogenone (XXI; R,R′ = CH_2) (218). In every case the presence of the ethylenic linkage causes a definite exaltation or depression in the rate due to conformational transmission. The same effect can be seen when two conjugated ethylenic linkages are present. Pertinent data are provided by ergosta-7,14,22-trienone (XVIII) (62) and ergosta-7,9(11),22-trienone (XX) (99). It was of some interest that, whilst 17β-hydroxy-4,4-dimethylandrostan-3-one (XVI; R = Me, R′ = OH) (58) was identical in rate with lanostanone (55), again showing that side-chain variation has no effect, 4,4-dimethylcholest-5-enone (XV; R = Me, R′ = C_8H_{17}) (51) and 17β-hydroxy-4,4-dimethylandrost-5-en-3-one (XV; R = Me, R′ = OH) (56·5) reacted at essentially the same rate. Thus a relatively close 5(6)-ethylenic linkage does not necessarily disturb the rate, whereas much more distant ethylenic linkages (see above) often do. The same applies for 4,4-dimethylergosterone (XIV; R = C_9H_{17}), which has a rate (50·0) close to that of lanostanone (55).

The influence of keto-groups at various positions in the steroid nucleus was investigated. It was, of course, established by preliminary experiments that only the 2-CH_2 in the polyketones was active in condensation. The 11-ketone group produced some depression in rate just as in triterpenoid compounds (Table 1 and Part II). One must note that ergost-22-ene-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{17}) had nearly the same rate (110) as 3,11-dioxobisnorallocholanic acid (103), again indicating the small effect of integral changes. Ergostane-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{19}) reacted at the same rate (120) as the analogue with the unsaturated side chain. Hecogenone (XXI; R, R′ = O) (328) and cholestane-3,7-dione (615) both showed much enhanced rates. The rate-enhancing 7-keto-group was clearly in competition with the relatively weak rate-depressing 11-keto-group in compounds such as ergosta-3,7,11-trione (XIII; R = Me, R′ = C_9H_{17}) (360). We can compare the cases of lanostane-3,7-dione, -3,11-dione, and -3,7,11-trione mentioned in an earlier paragraph. The influence of keto-groups on the rates is not due to bond induction, for one could not explain in this way, the weak effect of the proximate 11-ketone

but the powerful effect of the relatively remote 7-ketone. Ketone groups must affect rates either because of their dipoles or because of the angle distortion introduced by the trigonal carbonyl-carbon. One conceivable method of differentiation is, as already illustrated above, to replace $>C=O$ by $>C=CH_2$. We applied this test to the 7- and the 12-ketone group. 7-Methylenecholestane (XXII; R = H, R′ = C_8H_{17}, X = CH_2) reacted at a rate (365) which was much enhanced relative to all other compounds in Table 2 except two, but still less than that of cholestane-3,7-dione itself. 12-Methylenetigonenone (XXI; R,R′ = CH_2) showed a rate of 218 which was enhanced, but not so great as the enhancement of hecogenone (XXI; R, R′ = O) (328). The experiments of this kind appear to show that at least part of the effect of ketone groups is due to angle strain. All of the effect may be caused in this way because the grouping $>C=CH_2$ has, owing to the two C–H bonds, different steric requirements from the $>C=O$ grouping and thus the methylene ketones may receive extra distortion in this way which partly nullifies the principle of our method.

An alternative approach to an understanding of the effects of ketone groups is to make calculations of the maximum possible electrostatic effect upon the rate. To do this we calculate the interaction energy, ψ, in kcal./mole, between the carbonyl dipole and the integral charge of the enolate anion [see equation (ix)] from well-known expressions. This requires accurate molecular models [12] in order to determine the distances and angles involved. The anion of the ketone was assumed to have an ethylenic linkage between $C_{(2)}$ and $C_{(3)}$ and to have the negative charge on the oxygen atom. Placing the negative charge midway between $C_{(2)}$ and $C_{(3)}$ altered slightly the magnitude of the calculations but not their sign or relative order. The calculations are summarised in Table 4. The difference in activation energy between a saturated steroid ketone, for example, cholestanone, and a substituted derivative can, if entropy differences are constant, be set as equal to this electrostatic interaction energy, ψ. Table 4 shows good agreement between ψ and $\Delta\Delta E$, the latter being defined by the expression $R_s/R_0 = e^{-\Delta\Delta E/RT}$ where R_s is the rate for the substituted ketone, R_0 the rate for the standard saturated ketone, and the other symbols have their usual significance. The agreement is, of course, only satisfactory because a value of the effective dielectric constant of 10 was selected. Since a lower value could equally well have been accepted (making ψ greater) electrostatic interaction may, in principle, explain the observed effects with carbonyl groups with ease.

The calculations involving carboxylate anions present quite a different picture. A typical example is included in Table 4. Here the calculated interaction energy is much

TABLE 4.

Compound	ψ (kcal./mole)	$\Delta\Delta E$ (kcal./mole)
Cholestane-3,7-dione (XXII; R = H)	+0·33	+0·32
Hecogenone (XXI; R, R′ = O)	+0·17	+0·25
Ergost-22-ene-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{17}	−0·04	−0·32
Oleanonic acid (IX; R, H)	−2·8	−0·18

greater than the $\Delta\Delta E$ value. As yet no adequate explanation of this can be given unless, in fact, all polar effects are negligible and all rate variation is due to conformational transmission.

In so far as we have studied the effects of hydroxyl groups on the rates the results parallel those for triterpenoid ketones. Thus the axial 11β-hydroxyergost-22-en-3-one (XVII; R = H, R′ = OH, R″ = C_9H_{17}) showed a markedly depressed rate (67) whereas the rate for the equatorial 11α-epimer was only slightly depressed (125).

The results recorded above show that steroidal ketones can exhibit even more marked " conformational transmission " effects than triterpenoid ketones. The effects do not therefore depend in an obligatory manner upon the presence of an axial 4-methyl group.

[12] Barton, *Chem. and Ind.*, 1956, 1136.

Additional evidence that the rôle of the axial 4-methyl group is of minor importance was found in the study of (functional) group rate factors. Some relevant data are set out in

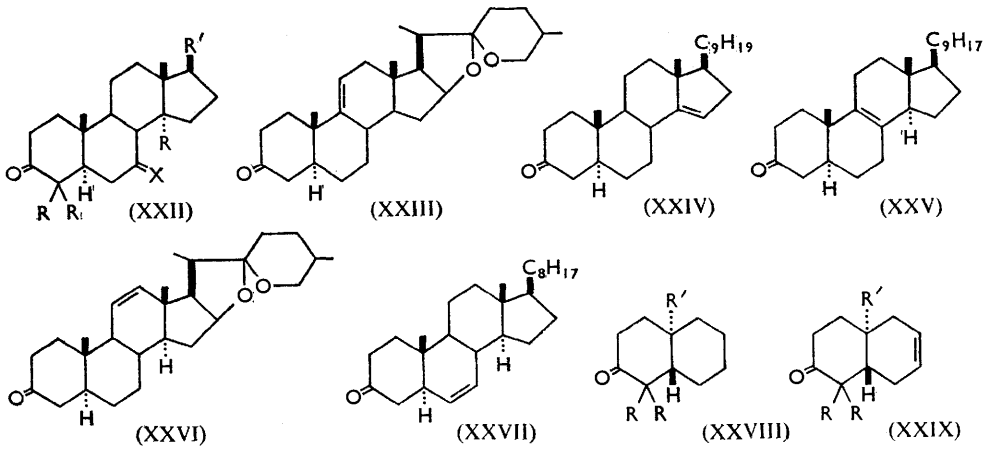


Table 5. We develop the concept that, if the rate of condensation of a parent unsubstituted ketone be represented as R_o, then the rate of condensation of a substituted derivative can be represented as:

$$R_s = R_o \prod_1^i f_i$$

where $f_1, f_2, f_3 \ldots f_i$ are group rate factors each characteristic of the substituent group. This is equivalent to the hypothesis that each separate group makes an independent contribution to the free energy of activation of the reaction. The various group rate factors can be determined from measurements on monosubstituted ketones and, as we shall discuss below, data for triterpenoid compounds can be transferred to steroid compounds without modification. The fact that this can be done on a more or less quantitative basis is strong evidence against the major importance of axial buttressing. The following example illustrates the type of procedure that may be employed. The rate data for ergostane-3,11-dione (XVII; R, R′ = O, R″ = C_9H_{19}) (120), compared with those for cholestanone (XVII; R, R′ = H, R″ = C_8H_{17}) (182), show that the 11-keto-group affects the rate by the factor (120/182) = 0·66. This then is the " group rate factor " for an 11-ketone. With this number we can then calculate the rate for lanostane-3,11-dione from the known rate for lanostanone (55). The calculated rate is 55 × 0·66 = 36·4. This compares closely with the observed value (Table 1) of 43. In general *gem*-dimethyl groups at $C_{(4)}$ reduce the rate of condensation of triterpenoids *versus* steroid by a factor of just over 3. Table 5 summarises a useful range of group rate factors which can be used to calculate rates for many ketones not yet studied experimentally. The agreement between *f* values for triterpenoids and for steroids is a measure of how conformational transmission operates irrespective of the presence or absence of the gem-dimethyl group at $C_{(4)}$. Further illustrative data have already been presented by us.[1]

The reduction in rate caused by gem-methyl groups at $C_{(4)}$ could possibly be explained mechanistically in terms of a reduction in the rate of step (iii) (see above scheme) or its reverse (iv), this pseudo-equilibrium appearing in the rate-constant expression. It was therefore of interest to discover that 17β-hydroxy-4,4-dimethyl-19-norandrost-5-en-3-one (XV; R = H, R′ = C_8H_{17}) (17) reacted more slowly than the 19-normal analogous steroid (XV; R = Me, R′ = OH) (55). This seems to imply that an axial 4-methyl group exerts a different influence from a 10-methyl group. We hope to discuss these results in more detail in a later paper.

The data of Table 3 show that the effects seen in steroids and triterpenoids can also be detected, where structurally appropriate, in simple decalin derivatives. In particular, *trans*-2-decalone (XXVIII; R = R′ = Me) (β-decalone), which condenses only at position 2 with benzaldehyde (see Experimental), reacts more slowly than 10-methyl-*trans*-2-decalone (XXVIII; R′ = Me) by the surprising factor of 148/35 = 4·2. An ethylenic linkage at the 7(8)-position in a β-decalone [compounds (XXIX; R = R′ = Me) and (XXIX; R = H, R′ = Me)] slows down the rate markedly, as in steroids and triterpenoids. The effects can be put on a quantitative basis as shown in Table 5. Gem-methyl groups at position 4 again reduce the condensation rate by a factor of about three.

TABLE 5.

	Group rate factors, *f*				Group rate factors, *f*		
Group	Steroid	Triterpenoid	Decalinoid	Group	Steroid	Triterpenoid	Decalinoid
7-Ketone	3·38	3·66	—	5(6)-Ethylenic linkage	1·0	1·0	—
11-Ketone	0·62	0·78	—	6(7)- ,,	3·55	—	—
12-Ketone	1·89	1·93	—	7(8)- ,,	0·24	0·31	0·23
11α-Hydroxyl	0·67	0·64	—	8(9)- ,,	1·49	1·82	—
11β-Hydroxyl	0·36	0·31	—	8(14)- ,,	0·50	—	—
10-Methyl	—	3·40	4·20	9(11)- ,,	1·27	1·33	—
4,4-Dimethyl	0·31	—	0·23	11(12)- ,,	2·18	—	—
				14(15)- ,,	1·19	—	—
				7(8),9(11)-Diene	0·53	0·80	—

Now that long-range effects have been placed on a firmly defined experimental basis, it is possible to consider their potential application in synthesis. We believe that the recent discovery [13,14] that cholest-7-enone is preferentially methylated at position 4, not at position 2 as is normally the case with *trans*-A/B steroids, is a reflection of the fact that the 7(8)-ethylenic linkage acts to induce preferential enolate formation at position 3,4 rather than 2,3. The geometrical relation between ethylenic 3,4- and 7,8-linkages is the same as that between 2,3- and 6,7-. From the very enhanced rate of condensation of cholest-6-enone (Table 2) it is known that the latter arrangement must be relatively preferred. It is this effect which Wells and Niederhiser,[13] without realising it, have been exploiting.

We must now discuss why, if this prefered enolisation towards $C_{(4)}$ produced by a 7,8-ethylenic linkage be granted, yet benzaldehyde condenses with ergosta-7,22-dienone at position 2, not at position 4 (see above). We consider that this follows from the nature of the mechanism. Thus benzaldehyde does condense first at $C_{(4)}$, but the reverse step (iv) is probably even more favourable than at $C_{(2)}$, because $C_{(4)}$ is subject to extra hindrance by the 6-methylene group, and thus the net rate for formation of the 4-benzylidene derivative is very low. This allows condensation at position 2 to be consummated, not because enolate anion formation [steps (i) and (ii)] is favoured, but because the elimination step (ix) is relatively favoured over the reversed aldol step (iv). The situation is, in fact, comparable to that pertaining to the reactions of the anions of cholest-4-enone. Irreversible alkylation of the anion with methyl iodide proceeds at position 4.[15] Reaction of the anion with ethyl formate gives the 2-derivative.[6,16] Again we believe that the formylation occurs rapidly at position 4 but is reversed and so ends up ultimately at position 2 where the final elimination step is more favoured.

In a recent paper Djerassi, Halpern, Halpern, and Riniker [17] have discussed the possible relation of conformational transmission as revealed by benzaldehyde condensation rates with variation in optical rotatory dispersion curves. The shift of an ethylenic linkage

[13] Wells and Neiderhiser, *J. Amer. Chem. Soc.*, 1957, **79**, 6569; *Arch. Biochem.*, 1959, **81**, 300.
[14] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906.
[15] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131.
[16] Burr, Holton, and Webb, *J. Amer. Chem. Soc.*, 1950, **72**, 4903; Weisenborn, Remy, and Jacobs, *ibid.*, 1954, **76**, 552; Quartey, *J.*, 1958, 1710.
[17] Djerassi, O. Halpern, V. Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001; see also Djerassi, Osiecki, and Closson, *ibid.*, 1959, **81**, 4587.

from the 7,8- to the 8,9-position in a triterpenoid 3-ketone inverts the sign of the Cotton effect. In steroidal 3-ketones the analogous structural change has little influence on the dispersion curve. On this basis the rates of benzaldehyde condensation for 7,8- and 8,9-unsaturated steroidal ketones should be similar. In fact, they are as markedly different as the structurally analogous triterpenoid compounds. We feel, therefore, that, as yet, a close parallel between the two series of investigations has not been established in every case.

Experimental

For general experimental details see earlier work.[18] Rotations refer to $CHCl_3$ solution unless specified to the contrary. Ultraviolet absorption spectra were determined with a Unicam S.P. 500 Spectrophotometer. Absolute ethanol was used except for the kinetic runs. These were made in 99% v/v aqueous ethanol, as in our previous work.[1] For runs with carboxylic acids the appropriate additional amount of alkali was, of course, added to neutralise the carboxyl group. Light petroleum refers to the fraction of b. p. 40—60°. Rate measurements were made at 25·0° ±0·03° with flasks protected from light. Ketones were thoroughly dried *in vacuo* before being weighed for rate measurements. Benzylidene derivatives were prepared essentially as outlined earlier.[1]

Derivatives of Lanostane-3,11-dione.—Lanostane-3,11-dione (1·16 g.), ethylene glycol (0·22 ml.), toluene-*p*-sulphonic acid (10 mg.), and dry benzene (50 ml.) were refluxed in a Dean and Stark apparatus for 18 hr. The solution was then poured into saturated aqueous sodium carbonate, and the benzene layer was separated. Removal of the solvent and crystallisation from benzene–methanol gave *lanostane-3,11-dione 3-(ethylene ketal)* (1·13 g.), m. p. 140—141°, $[\alpha]_D$ +31° (*c* 1·37) (Found: C, 79·15; H, 11·2. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%).

The ketal (150 mg.) in refluxing propan-1-ol (10 ml.) was treated during 1 hr. with diced sodium (1·0 g.). Propanol (7 ml.) was added to destroy excess of sodium, and the solvent removed *in vacuo*. Working up in the usual way and crystallisation from methanol gave *11α-hydroxylanostan-3-one ethylene ketal* (131 mg.), m. p. (prisms) 165—166°, $[\alpha]_D$ 0° (*c* 1·88) (Found: C, 78·9; H, 11·75. $C_{32}H_{56}O_3$ requires C, 78·65; H, 11·55%).

Hydrolysis of the hydroxy-ketal (180 mg.) in acetic acid (12 ml.) and water (3·5 ml.) on the steam-bath for 10 min. gave *11α-hydroxylanostan-3-one* (150 mg.), crystallising from aqueous methanol as prisms, m. p. 151—152°, $[\alpha]_D$ −6° (*c* 1·66) (Found: C, 81·1; H, 11·5. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Lanostane-3,11-dione 3-(ethylene ketal) (200 mg.) in dry ether (50 ml.) was refluxed with lithium aluminium hydride (220 mg.) for 16 hr. The excess of reducing agent was destroyed by ethyl acetate. Working up in the usual way and crystallisation from methanol afforded *11β-hydroxylanostan-3-one ethylene ketal* (165 mg.), m. p. 143—144°, $[\alpha]_D$ +30° (*c* 2·00) (Found: C, 78·8; H, 11·4. $C_{32}H_{56}O_3$ requires C, 78·65; H, 11·55%). This hydroxy-ketal (270 mg.) in acetic acid (35 ml.) and water (5 ml.) was heated on the steam bath for 10 min., to give *11β-hydroxylanostan-3-one* (157 mg.) as plates (from light petroleum), m. p. 188—189°, $[\alpha]_D$ +28° (*c* 1·49) (Found: C, 81·05; H, 12·0. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Lanost-9(11)-en-3-one.—11β-Hydroxylanostan-3-one ethylene ketal (see above) (279 mg.) was treated with aqueous 60% perchloric acid (12 drops) in acetic acid (15 ml.) at room temperature for 15 min. Careful dilution with water gave *lanost-9(11)-en-3-one* (211 mg.). Recrystallised from chloroform–methanol this had m. p. 113—114°, $[\alpha]_D$ +65° (*c* 2·67), +68° (*c* 1·70) (Found: C, 84·3; H, 11·6. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%).

11-Methylene-α-amyr-12-en-3-one and 11-Methyl-α-amyra-9(11),12-dien-3-one.—3β-Hydroxy-α-amyr-12-en-11-one (1·50 g.) in dry benzene (100 ml.) was added dropwise with good stirring to an ethereal (200 ml.) solution of methylmagnesium iodide (from 6·5 g. of magnesium and 8 ml. of methyl iodide).[19] Then the ether was boiled off and the benzene solution refluxed for 55 hr. Excess of saturated aqueous ammonium chloride was added and the benzene layer separated and washed with water. After removal of the benzene, the product was treated with pyridine (10 ml.) and acetic anhydride (10 ml.) overnight at room temperature and then chromatographed over alumina (Grade I; 150 g.). Elution with 1 : 99 benzene–light petroleum gave, in the later fractions, 11-methylene-α-amyr-12-enyl acetate (752 mg.), m. p. (from chloroform–methanol)

[18] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.

[19] See Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767; Seymour, Sharples, and Spring, *J.*, 1939, 1075.

229—232°, $[\alpha]_D$ +143° (*c* 1·95), $\lambda_{max.}$ 246 mμ (ε 19,700). Hydrolysis to the corresponding alcohol and oxidation with pyridine–chromium trioxide afforded 11-*methylene*-α-*amyr*-12-*en*-3-*one* as needles (from aqueous methanol), m. p. 146—147°, $[\alpha]_D$ +208° (*c* 1·20), $\lambda_{max.}$ 247 mμ (ε 19,700) (Found: C, 85·5; H, 11·3. $C_{31}H_{48}O$ requires C, 85·25; H, 11·1%).

Derivatives of β-*Amyrane*-3,12-*dione*.—β-Amyrane-3,12-dione (1·7 g.) in redistilled ethylene glycol (160 ml.) containing toluene-*p*-sulphonic acid (60 mg.) was slowly distilled at 1·5 mm. over a period of 2 hr.[20] until only 15—20 ml. of the glycol remained. Addition of dilute aqueous potassium hydroxide gave, after crystallisation from benzene–methanol, β-*amyrane*-3,12-*dione* 3-(*ethylene ketal*) (1·59 g.), m. p. 279—281°, $[\alpha]_D$ −45° (*c* 1·64) (Found: C, 79·55; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

The ketal (150 mg.) in refluxing propan-1-ol (10 ml.) was treated in 1 hr. with an excess (1·0 g.) of diced sodium. The excess of sodium was destroyed by addition of further propanol (5 ml.), and the solution worked up in the usual way. Crystallisation of the product from benzene–methanol furnished 12β-*hydroxy*-β-*amyran*-3-*one ethylene ketal* (121 mg.) as plates, m. p. 272—274°, $[\alpha]_D$ −12° (*c* 2·28), −14° (*c* 1·59) (Found: C, 78·7; H, 11·35. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%). Treatment of this hydroxy-ketal (167 mg.) with 90% acetic acid (5 ml.) at 100° for 5 min. furnished 12β-*hydroxy*-β-*amyran*-3-*one* (87 mg.); recrystallised from aqueous methanol this had m. p. 210—213°, $[\alpha]_D$ +39° (*c* 1·54) (Found: C, 81·45; H, 11·25. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Reduction of β-amyrane-3,12-dione 3-(ethylene ketal) (474 mg.) with lithium aluminium hydride (900 mg.) in refluxing ether (150 ml.) gave, on chromatography of the product over alumina (Grade III) and elution with (1 : 1) benzene–light petroleum, 12α-*hydroxy*-β-*amyran*-3-*one ethylene ketal* (254 mg.). Recrystallised from benzene–methanol this had m. p. 261—263°, $[\alpha]_D$ +16° (*c* 2·13) (Found: C, 78·7; H, 11·2. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%). Elution with benzene gave the 12β-hydroxy-epimer (see above) (123 mg.). Treatment of the 12α-hydroxy-ketal with aqueous acetic acid as above furnished 12α-*hydroxy*-β-*amyran*-3-*one*. Recrystallised from chloroform–methanol this had m. p. 252—255°, $[\alpha]_D$ +81° (*c* 1·11) (Found: C, 81·7; H, 11·15. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

β-*Amyran*-3-*one*.—Wolff–Kishner reduction of 12-oxo-β-amyranyl acetate (1·9 g.) under forcing conditions [21] gave, after reacetylation, β-amyranyl acetate (1·24 g.). Alkaline hydrolysis and oxidation with pyridine–chromium trioxide furnished β-amyran-3-one. Crystallised from chloroform–methanol, this had m. p. 200—201°, $[\alpha]_D$ +41° (*c* 0·97) (Found: C, 84·8; H, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·45; H, 11·8%). Jeger and Ruzicka [22] gave m. p. 194—195°.

7-*Methylenecholestanone*.—7-Oxocholestanyl acetate was converted into 7-*methylenecholestanyl acetate* (80%), m. p. (leaflets from ethanol) 72—73°, $[\alpha]_D$ −43° (*c* 0·95), $\nu_{max.}$ (in Nujol) 890 and 1650 cm.$^{-1}$ (>C=CH$_2$) (Found: C, 81·5; H, 11·65. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%), by the general procedure of Sondheimer and Mechoulam.[23] Refluxing with 3% methanolic potassium hydroxide for 30 min. gave 7-*methylenecholestanol*, m. p. (from light petroleum) 115°, $[\alpha]_D$ −31° (*c* 1·14) (Found: C, 84·15; H, 12·2. $C_{28}H_{48}O$ requires C, 83·95; H, 12·1%).

7-Methylenecholestanol (560 mg.) in " AnalaR " acetone (60 ml.) was treated with a standard solution (0·5 ml.) of chromium trioxide (26·72 g.) in concentrated sulphuric acid (23 ml.) made up to the mark (100 ml.) with water at 20°, under nitrogen with shaking for 3 min. Excess of saturated sodium hydrogen carbonate solution was added and the ketone extracted into ether. Crystallisation from aqueous ethanol gave 7-*methylenecholestanone* (530 mg.), m. p. (plates) 104—106°, $[\alpha]_D$ −11° (*c* 0·94), $\nu_{max.}$ 1700 (ketone), and 890 and 1650 (>C=CH$_2$) cm.$^{-1}$ (Found: C, 84·55; H, 11·7. $C_{28}H_{46}O$ requires C, 84·25; H, 11·65%).

12-*Methylenetigogenone*.—Hecogenin acetate (1·5 g.) in dry benzene (20 ml.) was treated with ethereal methylmagnesium iodide, prepared from magnesium (0·53 g.) and methyl iodide (3·13 g.) in ether (16 ml.), for 1 hr. at room temperature and then for 45 min. at 40° (infrared control of disappearance of the 12-ketone band). The product, crystallised from ether, gave 12β-*hydroxy*-12α-*methyltigogenin* (910 mg.), m. p. 197—199°, $[\alpha]_D$ −37° (*c* 1·00) (Found: C, 75·4; H, 10·45. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%). This alcohol (720 mg.) in " AnalaR " acetone (70 ml.) was treated at 0° with standard oxidation mixture (0·65 ml.; preparation

[20] Allen, Bernstein, and Littell, *J. Amer. Chem. Soc.*, 1954, **76**, 6116.
[21] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[22] Jeger and Ruzicka, *Helv. Chim. Acta*, 1941, **24**, 1178.
[23] Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.

described under 7-methylene cholestanone) for 7 min. to give 12β-*hydroxy*-12α-*methyltigogenone* (600 mg.). Recrystallised from ether–light petroleum this had m. p. (plates) 228—243°, but it crystallised from aqueous ethanol in prisms, m. p. 241—243°. The two forms were interconverted by change of solvent. The compound had $[\alpha]_D$ −21° (*c* 1·06) (Found: C, 75·55; H, 9·95. $C_{28}H_{44}O_4$ requires C, 75·65; H, 9·95%).

12β-Hydroxy-12α-methyltigogenone (245 mg.) in dry pyridine (12 ml.) was treated with redistilled phosphorus oxychloride at room temperature for 16 hr. and then at 55° for 2½ hr. The solvents were removed *in vacuo* at <50° and the product chromatographed over alumina (grade III). Elution with 1 : 1 light petroleum–benzene gave 12-*methylenetigogenone*, m. p. (from light petroleum) 219—221°, $[\alpha]_D$ −5° (*c* 0·88), $\nu_{max.}$ 890 and 1650 (>C=CH_2) cm.$^{-1}$ (Found: C, 78·75; H, 10·2. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%).

12-Methylenetigogenone (49 gm.) in methylene dichloride (50 ml.) was ozonised at −80° for 60 min. The excess of ozone was removed with dry nitrogen. The product, crystallised from methanol–benzene, was shown to be hecogenone (12 mg.) by m. p., mixed m. p., and infrared spectrum.

11-*Dehydrotigogenone* (XXVI).—11-Dehydrotigogenin [24] was oxidised with chromium trioxide as for 12β-hydroxy-12α-methyltigogenin (see above). The resultant 11-*dehydrotigogenone*, recrystallised from methanol as irregular plates, had m. p. 169—174°, $[\alpha]_D$ −20° (*c* 1·13) (Found: C, 78·55; H, 9·5. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·75%).

9(11)-*Dehydrotigogenone* (XXIII).—9(11)-Dehydrotigogenin [25] was oxidised as for 11-dehydrotigogenone (see above), to 9(11)-*dehydrotigogenone*, m. p. (from methanol) 195—196·5°, $[\alpha]_D$ −45° (*c* 0·98) (Found: C, 78·7; H, 10·0. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·75%).

Ergosta-7,14,22-*trien*-3-*one*.—Ergosta-7,14,22-trienol (ergosterol B_3) (prepared by the method of Barton and Brooks [26]) (250 mg.) in dry benzene (38 ml.), acetone (10 ml.), and redistilled aluminium isopropoxide (2·0 g.) were refluxed for 8 hr. Working up in the usual way and crystallisation from methanol gave *ergosta*-7,14,22-*trien*-3-*one* (70 mg.), m. p. 150—152°, $[\alpha]_D$ −220° (*c* 0·96), $\lambda_{max.}$ 242 mμ (ε 9800) (Found: C, 84·6; H, 10·55. $C_{28}H_{42}O$ requires C, 85·2; H, 10·75%). This ketone was also prepared by chromic acid–acetone–sulphuric acid oxidation [27] of ergosterol B_3, but the yield was low (20%).

Ergost-22-*ene*-3,11-*dione* 3-(*Ethylene Ketal*).—Ergost-22-ene-3,11-dione [28] (720 mg.) in ethylene glycol (200 ml.) containing toluene-*p*-sulphonic acid (60 mg.) was slowly distilled at 63°/1·5 mm. during 5 hr. until the residual volume was 10 ml. (cf. Allen, Bernstein, and Littell [20]). Working up after addition of sufficient ethanolic potassium hydroxide to make it alkaline gave *ergost*-22-*ene*-3,11-*dione* 3-(*ethylene ketal*) (640 mg.), m. p. (plates from methanol) 153—154°, $[\alpha]_D$ +19° (*c* 2·02) (Found: C, 78·9; H, 10·7. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

11α-*Hydroxyergost*-22-*en*-3-*one*.—The ketal (see above) (200 mg.) in refluxing propan-1-ol (15 ml.) was treated with sodium (1·5 g.). Working up gave 11α-*hydroxyergost*-22-*en*-3-*one ethylene ketal* (180 mg.), m. p. (needles from methanol) 184—185°, $[\alpha]_D$ −23° (*c* 1·50) (Found: C, 78·55; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). The ketal (150 mg.) was hydrolysed by 80% aqueous acetic acid on the steam-bath for 10 min. to 11α-*hydroxyergost*-22-*en*-3-*one* (100 mg.), m. p. [needles from light petroleum (b. p. 60—80°)] 142—144°, $[\alpha]_D$ −19° (*c* 1·58) (Found: C, 81·25; H, 11·2. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

11β-*Hydroxyergost*-22-*en*-3-*one*.—The diketone 3-ketal (see above) (150 mg.) was reduced with excess of lithium aluminium hydride in ethereal solution, to give 11β-*hydroxyergost*-22-*en*-3-*one ethylene ketal* (120 mg.), m. p. (needles from aqueous methanol) 155—156°, $[\alpha]_D$ ±0° (*c* 1·60) (Found: C, 78·8; H, 10·6. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Hydrolysis with aqueous acetic acid as above furnished 11β-*hydroxyergost*-22-*en*-3-*one* (60 mg.), m. p. (needles from light petroleum) 170—172°, $[\alpha]_D$ +12° (*c* 2·00) (Found: C, 81·15; H, 11·1. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

Ergostane-3,7,11-*trione and Ergost*-22-*ene*-3,7,11-*trione*.—3β-Acetoxyergostane-7,11-dione [29] was hydrolysed in the usual way to 3β-*hydroxyergostane*-7,11-*dione*, m. p. (needles from methanol) 177—179°, $[\alpha]$ −6° (*c* 2·73) (Found: C, 77·9; H, 11·0. $C_{28}H_{46}O_3$ requires C, 78·1;

[24] Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[25] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278; Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 3252.
[26] Barton and Brooks, *J.*, 1951, 257.
[27] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.
[28] Heusser, Anliker, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1537.
[29] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.

H, 10·75%). Oxidation with chromium trioxide in acetic acid–benzene afforded *ergostane*-3,7,11-*trione*, m. p. 186—188°, $[\alpha]_D$ +16·7° (*c* 1·92) (Found: C, 78·5; H, 10·6. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Similar oxidation of 3β-hydroxyergost-22-ene-7,11-dione [30] furnished *ergost*-22-*ene*-3,7,11-*trione*, m. p. (plates from methanol) 194—195°, $[\alpha]_D$ −9° (*c* 2·28) (Found: C, 78·75; H, 9·85. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%).

Ergosta-8,22-*dienone*.—Ergosta-8,22-dienol [31] was oxidised with chromium trioxide in pyridine to *ergosta*-8,22-*dienone*, m. p. (plates from methanol) 168—170°, $[\alpha]_D$ +47° (*c* 0·30) (Found: C, 85·25; H, 10·9. $C_{28}H_{44}O$ requires C, 85·2; H, 10·75%).

17β-*Hydroxyandrostan*-3-*one*.—This compound was prepared by a new procedure. 17β-Hydroxyandrostan-3-one hexahydrobenzoate (800 mg.) in benzene (10 ml.) and methanol (10 ml.) was treated with toluene-*p*-sulphonic acid (5 mg.), and the solution slowly distilled. The residue crystallised from methanol, to give 3,3-*dimethoxyandrostan*-17β-*yl hexahydrobenzoate* (500 mg.), m. p. (needles) 130—132°, $[\alpha]_D$ +12° (*c* 2·03) (Found: C, 75·3; H, 10·4. $C_{28}H_{46}O_4$ requires C, 75·5; H, 10·35%). This compound was reduced with lithium aluminium hydride in the usual way, to furnish 3,3-*dimethoxyandrostan*-17β-*ol* (300 mg.). Recrystallised from aqueous methanol this had m. p. 180—182°, $[\alpha]_D$ +14° (*c* 1·68) (Found: C, 74·95; H, 10·8. $C_{21}H_{36}O_3$ requires C, 74·95; H, 10·8%). The ketal (300 mg.) in methanol (10 ml.) and 4N-sulphuric acid (2 ml.) was left for 1 hr. at room temperature. Pouring into water, extraction into ether, and processing in the usual way afforded 17β-hydroxyandrostan-3-one (200 mg.), m. p. (from aqueous methanol) 178—179°, $[\alpha]_D$ +32° (*c* 1·91). Serini and Köster [32] give m. p. 176—177°. This procedure gives a better yield than hydrolysis of the hexahydrobenzoate in the presence of the 3-ketone.

3,11-*Dioxobisnorallocholanic Acid*.—3β-Hydroxy-11-oxobisnorallocholanic acid [33] (800 mg.) in benzene (50 ml.), oxidised with a slight excess of chromic acid in aqueous acetic acid, gave 3,11-*dioxobisnorallocholanic acid* (600 mg.). Recrystallised from ethanol this formed plates, m. p. 258—261°, $[\alpha]_D$ +52° (*c* 2·54) (Found: C, 73·5; H, 9·05. $C_{22}H_{32}O_4$ requires C, 73·35; H, 8·95%).

2-*Benzylidenestigmastanone*.—Stigmastanone (500 mg.) in 0·1N-ethanolic potassium hydroxide (50 ml.) was treated with benzaldehyde (500 mg.) at room temperature in the dark for 24 hr. The crystalline 2-*benzylidenestigmastanone* that separated (310 mg.) was filtered off. It formed needles (from methanol–benzene), m. p. 151—152°, $[\alpha]_D$ −108° (*c* 1·46), $\lambda_{max.}$ 294 mμ (ε 16,200) (Found: C, 86·2; H, 10·5. $C_{36}H_{54}O$ requires C, 86·0; H, 10·85%). Addition of water to the filtrate, ether-extraction, and washing with sodium metabisulphite furnished additional material (80 mg.) with identical properties. No trace of an isomeric benzylidene derivative could be found.

2-Benzylidenestigmastanone (563 mg.) in chloroform (100 ml.) at −60° was ozonised until the absorption band at 294 mμ had disappeared (20 mins.). Water (5 ml.) was added and the chloroform removed *in vacuo*. The resulting oil was dissolved in 2% aqueous potassium hydroxide and washed with ether. Acidification and further ether-extraction gave 2,3-seco-stigmastane-2,3-dioic acid (50%), m. p. (plates from benzene) 230—232°, $[\alpha]_D$ +33° (*c* 0·98), undepressed in m. p. on admixture with an authentic specimen of identical properties.

2-*Benzylidene*-*ergost*-22-*ene*-3,11-*dione*.—Ergost-22-ene-3,11-dione (300 mg.) in 0·1N-ethanolic potassium hydroxide (25 ml.) was treated with benzaldehyde (300 mg.) for 24 hr. at room temperature in the dark. The crystalline 2-*benzylidene derivative* (190 mg.) deposited had m. p. (plates from ethanol) 191—192°, $[\alpha]_D$ −7° (*c* 1·52), $\lambda_{max.}$ 294 mμ (ε 17,000) (Found: C, 83·65; H, 9·65. $C_{35}H_{48}O_2$ requires C, 84·0; H, 9·65%). Working up the solution as detailed above gave a further quantity of benzylidene derivative (55 mg.) but no indication of an additional isomer.

2-*Benzylidene*-3,11-*dioxobisnorallocholanic Acid*.—3,11-Dioxobisnorallocholanic acid (200 mg.) in 0·1N-ethanolic potassium hydroxide (25 ml.) was treated with benzaldehyde (300 mg.) as above. Pouring into water, acidification, and extraction as in the earlier examples gave 2-*benzylidene*-3,11-*dioxobisnorallocholanic acid* (150 mg.) as needles (from methanol–benzene),

[30] Chamberlin, Ruyle, A. E. Erickson, Chemerda, Aliminosa, R. L. Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396.
[31] Henbest, Hallsworth, and Wrigley, *J.*, 1957, 1969.
[32] Serini and Köster, *Ber.*, 1938, **71**, 1766.
[33] Chamberlin *et al.* (as in 30), *J. Amer. Chem. Soc.*, 1953, **75**, 3477; Cameron, Hunt, Oughton, Wilkinson, and Wilson, *J.*, 1953, 3864.

m. p. 268—270°, $[\alpha]_D$ −24° (*c* 2·28), $\lambda_{max.}$ 294 mμ (ε 16,800) (Found: C, 77·6; H, 7·95. $C_{29}H_{36}O_4$ requires C, 77·65; H, 8·1%).

2-Benzylidene-7-methylenecholestanone.—This *derivative* was prepared from 7-methylenecholestanone (100 mg.) as in the above examples. From methanol–benzene, it formed needles (65 mg.), m. p. 145—147°, $[\alpha]_D$ −178° (*c* 1·16), $\lambda_{max.}$ 294 mμ (ε 17·700) (Found: C, 85·75; H, 10·5. $C_{35}H_{52}O$ requires C, 86·0; H, 10·7%).

2-Benzylidene-ergost-8(14)-*en*-3-*one.*—This was prepared from ergost-8(14)-enone by the method used above. From benzene–methanol it formed needles, m. p. 162—163°, $[\alpha]_D$ −18° (*c* 2·40), $\lambda_{max.}$ 294 mμ (ε 17,000). The m. p. in the literature is 161—162.[34]

2-Benzylidene-17-hydroxyandrostan-3-one.—17-Hydroxyandrostan-3-one (65 mg.) was treated with benzaldehyde as above, to give *2-benzylidene-17-hydroxyandrostan-3-one* (50 mg.), needles (from methanol), m. p. 190—191°, $[\alpha]_D$ −140° (*c* 1·80), $\lambda_{max.}$ 294 mμ (ε 16,600) (Found: C, 82·5; H, 9·05. $C_{26}H_{34}O_2$ requires C, 82·8; H, 9·0%).

2-Benzylidene-17β-hydroxy-4,4-dimethylandrost-5-en-3-one.—17β-Hydroxy-4,4-dimethylandrost-5-en-3-one (100 mg.) was converted into the *2-benzylidene* derivative as above. Recrystallised from methanol–benzene this (50 mg.) formed prisms, m. p. 159—161°, $[\alpha]_D$ −148° (*c* 1·45), $\lambda_{max.}$ 294 mμ (ε 16,500) (Found: C, 83·35; H, 9·05. $C_{28}H_{36}O_2$ requires C, 83·1; H, 8·95%).

2-Benzylidene-4,4-dimethylergosta-7,22-dien-3-one.—4,4-Dimethylergosterone[35] (300 mg.) in tetrahydrofuran (50 ml.) and ethylamine (100 ml.) at 0° was treated with lithium until the blue colour persisted. Solid ammonium chloride was added and the ethylamine and tetrahydrofuran were removed *in vacuo*. The residue, which showed no selective ultraviolet absorption, was oxidised at 0° with chromium trioxide in acetone,[27] and the product chromatographed over alumina (grade III; 15 g.). Elution with light petroleum gave fractions (150 mg.) with m. p. 176—180°, after crystallisation from methanol–benzene, $[\alpha]_D$ −33° (*c* 1·36), giving a negative Fieser test with selenium dioxide.[36] These fractions were not investigated further. Further elution with light petroleum furnished, after crystallisation from methanol, *4,4-dimethylergosta-7,22-dien-3-one* (100 mg.), m. p. (needles) 143—145°, $[\alpha]_D$ −37° (*c* 1·36) (Found: C, 84·60; H, 11·45. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%), giving a strongly positive Fieser test. This ketone (50 mg.) was treated with benzaldehyde according to the general procedure described earlier.[1] Recrystallisation of the product from methanol–benzene afforded *2-benzylidene-4,4-dimethylergosta-7,22-dien-3-one* (25 mg.), m. p. (needles) 133—135°, $[\alpha]_D$ −111° (*c* 1·90), $\lambda_{max.}$ 289 mμ (ε 17,300) (Found: C, 86·2; H, 10·7. $C_{37}H_{54}O$ requires C, 86·3; H, 10·53%). The compound having the same m. p., mixed m. p., rotation {($[\alpha]_D$ −114° (*c* 1·10)} and ultraviolet and infrared spectra was obtained from ergosta-7,22-dien-3-one in the following way.

Benzaldehyde was condensed with ergosta-7,22-dien-3-one as in earlier experiments, to give an oily derivative (800 mg.) with $\lambda_{max.}$ 294 mμ (ε 13,500). This was taken into benzene (10 ml.) and a solution of potassium (200 mg.) in t-butyl alcohol (10 ml.) was added. The solution was refluxed with methyl iodide (5 ml.) for 14 hr. Working up gave a product which crystallised from methanol–benzene to furnish 2-benzylidene-4,4-dimethylergosta-7,22-dien-3-one (250 mg.) as already stated.

2α-Hydroxybenzylcholestanone.—Cholestanone (100 mg.) in 0·1N-methanolic potassium hydroxide (*ca.* 20 ml.) was treated with benzaldehyde (100 mg.) at room temperature. Immediately, on scratching, needles (80 mg.) of *2α-hydroxybenzylcholestanone*[37] were deposited. Recrystallised from methanol–benzene this had m. p. 188—190°, $[\alpha]_D$ −71° (*c* 1·12) (Found: C, 82·85; H, 11·2. $C_{34}H_{54}O_2$ requires C, 82·55; H, 11·0%). On treatment with ethanolic potassium hydroxide under the conditions of a kinetic run this afforded, in <5 min., benzaldehyde plus cholestanone (90%) and 2-benzylidenecholestanone (10%), as determined by ultraviolet absorption. Treatment of the ketol (50 mg.) with refluxing N-ethanolic hydrogen chloride (20 ml.) for 15 min., followed by pouring the mixture into water and working up as usual, produced the amorphous benzylidene derivative, $\lambda_{max.}$ 294 mμ (ε 16,000).

3-Benzylidene-trans-β-decalone.—*trans*-β-decalone (700 mg.) in 0·1N-ethanolic potassium hydroxide (25 ml.) was treated with benzaldehyde (2·6 g.) and left in the dark at room temperature for 30 hr. Working up as in earlier examples and trituration with light petroleum

[34] Heilbron, Simpson, and Wilkinson, *J.*, 1932, 1699.
[35] Cooley, Ellis, and Petrow, *J.*, 1955, 2998.
[36] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4395; Nakaniski, Bhattacharyya, and Fieser, *ibid.*, p. 4415.
[37] Cf. Goldberg and Kirschsteiner, *Helv. Chim. Acta*, 1943, **26**, 288.

gave 3-*benzylidene*-trans-β-*decalone* (405 mg.) as prisms, m. p. (from light petroleum) 92—93°, $\lambda_{max.}$ 292 mμ (ε 17,400) (Found: C, 85·1; H, 8·35. $C_{17}H_{20}O$ requires C, 84·95; H, 8·4%).

This benzylidene derivative (351 mg.) in chloroform (100 ml.) was ozonised at −20° until the absorption at 292 mμ had essentially disappeared (30 min.). The solution was worked up as for the corresponding experiment on 2-benzylidenestigmastanone (see above), to give *trans*-cyclohexylidene-1,2-diacetic acid (250 mg.). This formed prisms (from benzene), m. p. 164—165°, undepressed on admixture with authentic material kindly supplied by Dr. L. N. Owen.[9]

Treatment of Benzylidene Ketones with Excess of Benzaldehyde.—The benzylidene derivatives of stigmastanone (21·2 mg.), ergost-8(14)en-3-one (19·8 mg.), and *trans*-β-decalone (10·4 mg.) were treated with a 10-molar excess of benzaldehyde in 0·1N-ethanolic potassium hydroxide (10 ml.). In 20 hr. there was no change in the intensity of the ultraviolet absorption and no increase in the 330 mμ region of the spectrum characteristic [38] of 2,6-bisbenzylidenecyclohexanones.

Treatment of 2α-Methylcholestanone with Benzaldehyde.—2α-Methylcholestanone (19·8 mg.) was treated with benzaldehyde in ethanolic potassium hydroxide under the conditions of a kinetic run. There was no change in ultraviolet absorption after 18 hr. and the 2α-methylcholestanone was recovered unchanged (12·0 mg.; identified by m. p., mixed m. p., and rotation).

Treatment of Miscellaneous Ketones with Benzaldehyde.—The following ketones were treated under the conditions of a kinetic run: 3-Hydroxycholestan-7-one, hecogenin, 3β-hydroxyergost-22-ene-7,11-dione and 3β-hydroxyergost-22-en-11-one. In each case there was no appearance of ultraviolet absorption and the ketone was recovered unchanged.

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[38] For example, Burnell, *J.*, 1958, 1307.