Tetrahedron Vol. 28, pp. 135 to 153. Pergamon Press 1972. Printed in Great Britain

COTTON EFFECTS AND CONFORMATIONS OF SKELETALLY ISOMERIC SATURATED 3-OXO-STEROIDS

H. J. C. JACOBS and E. HAVINGA

Gorlaeus Laboratories, Department of Organic Chemistry, P.O. Box 75, State University, Leiden, The Netherlands

(*Received in the UK* 20 *August*; *Accepted for publication* 27 *August* 1971)

Abstract—The Cotton effects of a number of saturated 3-oxo-steroids, isomeric at one or more bridgehead C atoms of the steroid skeleton, are compared. The results are discussed in relation to the conformational aspects of differences in skeleton configuration. In several cases the Cotton effects point to specific non-all-chair conformations.

In the case of A/B-*cis*(ε)-connected 3-oxo-steroids a weak *anti*-octant contribution is assigned to CH_2-6, situated in a position β-axial to cyclohexanone ring A. Evidence is presented which suggests that the contribution of a β-axial substituent may vary in magnitude and even in sign according to the nature (detailed conformation, substituents) of the substituted cyclohexanone.

INTRODUCTION

IN 1956 Djerassi observed[1] that inversion of configuration at C-5 in the steroid skeleton is accompanied by a major change in the Cotton effect[2] associated with the 3-ketone group: the positive Cotton effect of a 3-oxo-5α-steroid (A/B-*trans*) contrasts with the weakly negative effect of a 3-oxo-5β-steroid (A/B-*cis*). This difference has since been frequently used for establishing the stereochemistry at C-5 in 3-oxo-steroids and related compounds.[2a] Most steroids investigated belong to the so-called natural (or normal) series (8β,9α,10β,13β,14α-configuration). In addition the chiroptical properties (ORD and CD) of a number of 3-oxo-steroids with unnatural (abnormal) configuration have been determined. A fairly comprehensive list is provided by Crabbé.[2d] A qualitative comparison of the ORD data was given in 1962 by Djerassi and Klyne.[3]

Studies on model compounds have shown[4] that rings C and D of the steroid do not contribute significantly to the Cotton effects of steroidal 3-ketones: sign, shape and generally also amplitude of the ORD curve are governed by the stereochemistry of rings A and B, and in particular by the nature of the ring junction (A/B-*trans* or -*cis*). These conclusions are completely in line with the generally accepted idea that the contribution of a group to the Cotton effect decreases rapidly with increasing distance to the carbonyl chromophore.[2a, 5]

From these results it may be anticipated that inversion of configuration at skeleton C atoms other than C-5 and C-10 will cause only a relatively small change (if any) in the intensity of the Cotton effect, provided the configurational change chiefly affects the relative position and orientation of the C and D rings with respect to the CO group. Consequently, if inversion at C-8, C-9, C-13 or C-14 is accompanied by a distinct change of the Cotton effect, this may be attributed rather safely to a more

or less drastic change in the conformation of rings A and/or B, connected with the alteration of configuration.

The purpose of the present study is to check these ideas and to consider the conformational information obtainable from a quantitative comparison and discussion of the ORD and CD data of skeletally isomeric 3-oxo-steroids.

RESULTS

From the theoretical point of view the rotational strength R_K of the Kth electronic transition is the appropriate quantity for describing and discussing the interaction of a symmetric chromophore with its chiral environment.[6] For practical reasons, however, it has become customary in organic chemistry to use either the differential dichroic absorption $\Delta\varepsilon_{max}$ (in CD) or the amplitude **a** (in ORD) for this purpose. In the latter case it is implicitly assumed that the value of the experimentally observed amplitude is not significantly influenced by contributions from other optically active transitions. In specific cases the comparison of the molecular rotations at

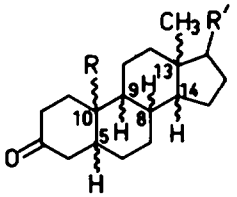


TABLE 1. COTTON EFFECTS OF SKELETALLY ISOMERIC 3-OXO-STEROIDS

A/B		Configuration*	R = CH_3 R'	ampl.	Δε	R = H R'	ampl.	Δε
	1	5α	OH	+55	+1·31	OH	+59	+1·48
	2	5α.13α	H	+60	+1·31			
	3	5α.9β	C_9H_{17}	+41	+1·00			
trans	4	5α.8α				OH		+1·69(E)[b]
	5	5β.10α				OH	−47(D)[c]	
	6	5β.9β.10α	OH	−55	−1·31	OH		−1·32[d]
	7	5β.8α.10α	C_9H_{17}	−52	−1·26	OH		−1·36(E)[b]
	8	5β	OH	−22	−0·45	OH	−25	−0·48
cis(a)	9	5α.9β.10α	OH	+23	+0·57	OH	+21[d]	+0·55[d]
	10	5α.8α.10α	C_9H_{19}	+50	+1·14	OH		+1·53(E)[b]
	11	5β.9β	C_9H_{17}	− 1	−0·05	β-OH. α-CH_3	−15[e]	−0·30[e]
cis(e)	12	5β.8α				OH		+0·11(E)[b]
	13	5α.10α	OH	+ 7	+0·11(D)	β-OH. α-CH_3	0[f]	+0·16[g]
cis(a) or *cis*(e)	14	5α.9β.10α.14β	C_9H_{19}	+22[a]				

* The configurations at ring junction positions 8, 9, 10, 13 and 14 are denoted only if different from the natural configuration (IUPAC rules on Nomenclature of Steroids. Information Bulletin No. 33. December 1968).

Solvent methanol, unless otherwise indicated; D = dioxan, E = ethanol. For the meaning of the designations *cis*(a) and *cis*(e), see Fig. 6 and footnote p. 142.

[a] Ref. 3. [b] Ref. 25. [c] M. Debono, E. Farkas, R. M. Molloy and J. M. Owen, *J. Org. Chem.* **34**, 1447 (1969). [d] Ref. 2*d* (solvent not specified). [e] Dr. E. Farkas, personal communication. [f] R. T. Rapala and E. Farkas, *J. Org. Chem.* **23**, 1404 (1958). [g] P. Witz, Thesis, Strassbourg 1964.

the extrema of the rotatory dispersion curves will provide information as to whether this assumption is justified.[7] The effect of "background rotation" will of course be more serious if the Cotton effect is small.

Circular dichroism data do not suffer from background effects and are more suitable for comparative purposes. In fact, it can be shown[8] that when comparing the CD spectra of a series of closely related compounds bearing the same chromophore, the value of $\Delta\varepsilon_{max}$ serves as a reliable measure of the rotational strength. This result is subject to the condition that the half-band width and the λ_{max} in the spectra under comparison are similar, a condition, that is frequently fulfilled if the Cotton effects are measured in the same solvent, and the compounds do not contain a second chromophore absorbing in the same spectral region.

The comparisons presented here have therefore been confined to isomeric steroids bearing as a chromophore the 3-carbonyl group only. Due precautions were taken to ensure the validity of quantitative comparisons (Experimental).

With the exception of two 19-nor steroids the compounds investigated all belong to the 10-methyl series. Detailed numerical results of the ORD and CD measurements are given in the Experimental (Table 5). The values of **a** and $\Delta\varepsilon_{max}$ are collected in Table 1, together with the data of one additional 10-methyl steroid **14** and of a number of skeletally isomeric 19-nor steroids reported in the literature. The literature values should be used for semiquantitative comparisons only.

Table 1 thus contains the information now available on the relationship between the Cotton effect associated with the 3-ketone chromophore and the configuration of the steroid skeleton.

For some skeletal configurations our values may be compared with those reported by other workers (the data refer to solvent methanol except where noted):

10-methyl steroids:

1 (R′ = OH): **a** + 55;[a] **1** (R′ = C_8H_{17}): **a** + 55 (mean of 15 determinations).[b] $\Delta\varepsilon$ + 1·32;[c] **2** (R′ = H): $\Delta\varepsilon$ + 1·03 (dioxan);[d] **3** (R′ = C_9H_{19}): **a** + 43;[e] **6** (R′ = C_9H_{19}): **a** − 52.[e] $\Delta\varepsilon$ − 1·12 (dioxan);[f] **8** (R′ = OH): **a** − 22.[g] $\Delta\varepsilon$ − 0·41;[h] **9** (R′ = C_9H_{19}): **a** + 16!;[i] **13** (R′ = C_9H_{19}): **a** + 12.[e]

19-nor steroids:

1 (R′ = OH): **a** + 57.[g] $\Delta\varepsilon$ + 1·37 (dioxan);[j] **8** (R′ = H): **a** − 24.[g]

[a] C. Djerassi, L. A. Mitscher and B. J. Mitscher. *J. Am. Chem. Soc.* **81**, 947 (1959).

[b] C. Djerassi, P. A. Hart and E. J. Warawa. *Ibid.* **86**, 78 (1964).

[c] J. C. Jacquesy and J. Levisalles. *Bull. Soc. Chim. Fr.* 1538 (1965).

[d] M. Fétizon and J. C. Gramain. *Ibid.* 1003 (1967).

[e] Ref. 3.

[f] G. Snatzke and H. W. Fehlhaber. *Tetrahedron* **20**, 1243 (1964).

[g] Ref. 14.

[h] L. H. Zalkow, R. Hale, K. French and P. Crabbé. *Tetrahedron* **26**, 4947 (1970).

[i] W. T. Pike, G. H. R. Summers and W. Klyne. *J. Chem. Soc.* 7199 (1965) (second extremum not reached).

[j] P. Witz, H. Herrmann, J. M. Lehn and G. Ourisson. *Bull. Soc. Chim. Fr.* 1101 (1963).

DISCUSSION

A. *Configuration and conformation*

Unless heavily substituted, rings A, B and C of steroids with normal configuration (**1** and **8**) have a chair conformation. Inversion of configuration at one or more bridgehead C atoms changes the overall geometrical features of the steroid molecule with or

without preservation of the chair form of the individual rings. Inspection of Dreiding models gives a first impression of the conformational changes to be expected.

For reasons first outlined by Johnson[10] in the perhydrophenanthrene system, the *trans-cisoid-trans* fusion of the A,B,C-moiety in the 5β,10α-steroid **5** forces ring B to adopt the (twist)boat conformation. An analogous situation occurs in **3** and **4** (5α,9β and 5α,8α) where the *trans-cisoid-cis-transoid-trans* fusion of the four rings is possible only if at least one of rings B and C exists in the (twist)boat form (a more detailed discussion of the conformational aspects of **3**, **4** and **5** is given in part B).

For the other configurations of Table 1 all-chair models can be constructed without difficulty. Conformations in which one or more of the rings exist in a (twist)-boat form are also possible, but because of the relative instability of the (twist)boat conformation the all-chair arrangement will be the preferred conformation unless energetically important non-bonded interactions intervene. In **1**, **2**, **8** and **13** such interactions are precluded by virtue of the B/C-*trans*-8β,9α-fusion. However, when the junction between rings B and C is *cis*, serious steric interactions may occur, leading to destabilization of the all-chair form. In **6**, **9** and **11** (B/C-*cis*-8β,9β) C atom C-10 (together with its substituents) represents a t-butyl (R = Me) or an isopropyl group (R = H) in axial position relative to cyclohexane ring C (Fig. 1). This involves a strong repulsion between R (in **6** and **9**) or CH_2-1 (in **11**) and the axial H atoms on C-12 and C-14. In **7**, **10** and **12** (B/C-*cis*-8α,9α) the all-chair conformations are destabilized by the 1,3-diaxial interaction between CH_2-7 and CH_3-18. Configuration **10** shows an additional repulsion between CH_2-11 and the β-hydrogens of C-2 and C-4 of the type noted for **6**, **9** and **11** (Fig. 1, first row).

With the aid of Dreiding models it is easily seen that in the B/C-*cis*-8α,9α case the conversion of ring C and/or B into a (twist)boat form cannot significantly alter the relative position of C-7 and C-18, without simultaneously bringing C-10 (with its substituents) and C-18 very close together. On the other hand, a similar conversion in the B/C-*cis*-8β,9β systems might well occur, since it would effectively remove the non-

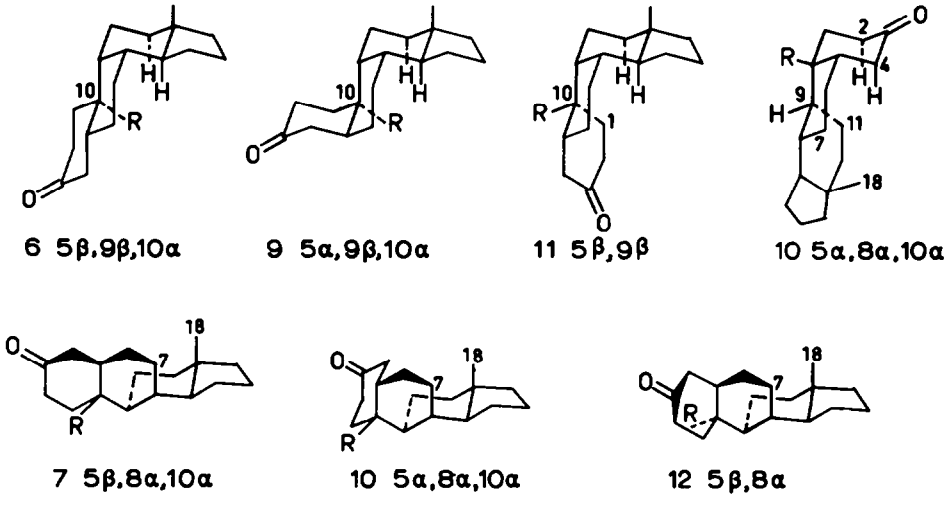


FIG 1. Stereoformulae of B/C-*cis*-connected 3-oxo-steroids.

bonded interactions noted above in **6**, **9** and **11**, at the expense, of course of the energy increase associated with the chair-(twist)boat conversion. X-ray analysis has shown,[11] however, that in 4-bromo-9β,10α-pregna-4,6-diene-3,20-dione, configurationally related to **6** and **9**, the steric interactions are actually relieved by a considerable decrease of the torsional angles φ(14-8-9-11) and φ(8-9-11-12), in connection with an enlargement of valency angle θ(9-11-12). These deformations have the effect that the 10 Me group is turned away from the α-side of ring C, while C itself remains in a (heavily distorted) chair conformation. The same conclusion can be drawn* from the X-ray data of 17β-hydroxy-9β,10α-androst-4-en-3-one bromoacetate.[12] A similar mechanism is probably operating in **6**, **9** and **11**, and presumably also in **7**, **10** and **12** in order to increase the distance between CH_2-7 and CH_3-18 (for **10**, however, see part C).

From these considerations it appears justified to assume all-chair conformations for the configurations mentioned (with the exception of **3**, **4** and **5**) as long as there is no contradictory experimental evidence. This holds also for **14**, which owing to the "all-*cis*" junctions of the rings can exist in two different all-chair conformations.[13]

B. A/B-trans *Steroids*

We will first consider the chiroptical data obtained with A/B-*trans* connected 3-oxo-steroids (Table 1. **1** to **7**).

As far as a quantitative comparison of the data is allowed, the Cotton effects of the 19-nor steroids† appear to be slightly larger than those of the steroids bearing the angular 10-Me group.‡ For steroids with normal configuration **1** this has previously been noted by Djerassi and Klyne *et al.*[3, 4c, 14] From its position in or near the vertical

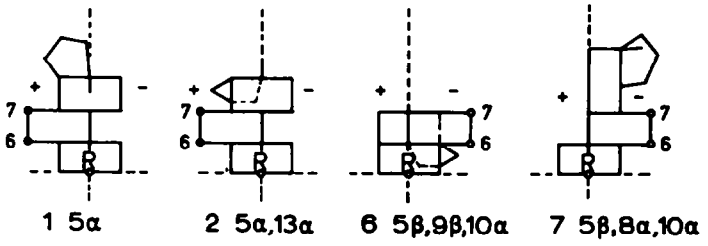


FIG 2. Octant projections of A/B-*trans*-connected 3-oxo-steroids.

symmetry plane of the CO group one would expect the direct contribution of the angular Me group to be zero. The actual non-zero contribution may tentatively be ascribed to a slight conformational distortion of rings A and B imposed by the 10-Me group. The relative decrease in ring valency angles at C-10, observed by Geise *et al.*[11b], as opposed to the increase of the other valency angles in rings A and B, points in the same direction.

* Dr. H. J. Geise, personal communication.

† The amplitude of the 5β,10α-19-nor compound **5**, $a = -47$ in dioxan, which as judged from the molecular rotations at the extrema represents a *lower* limit, corresponds to a value of about −56, calculated for solvent methanol[7].

‡ The enhancement of the amplitude of **2** is due to background effects (see p. 135 and ref. 7).

Table 1 further shows that, with exception of the compound with 5α,9β-configuration **3**, the A/B-*trans* 10-Me steroids exhibit Cotton effects of nearly identical intensity. The absolute values of the amplitude and the dichroic absorption amount to about 55 and 1·30 respectively. A comparison of the octant projections (Fig. 2), based on all-chair conformations, shows that the immediate vicinity of the ketone groups is identical (or mirror-image identical) the diagrams differing only from ring C on. This indicates that the intensity of the Cotton effect is essentially determined by the position of C-6 and C-7 with respect to the CO chromophore, and that the orientation of rings C and D exerts little or no influence, in agreement with the concept noted in the Introduction. Furthermore, manipulation of Dreiding models of **6** and **7** demonstrates that closure of the torsional angles at the B/C ring junction in order to relieve the non-bonded interactions, does not influence the position of C-6 and C-7; in contrast, conversion of ring B into a (twist)boat conformation would drastically alter the position of C-7 relative to the CO group.

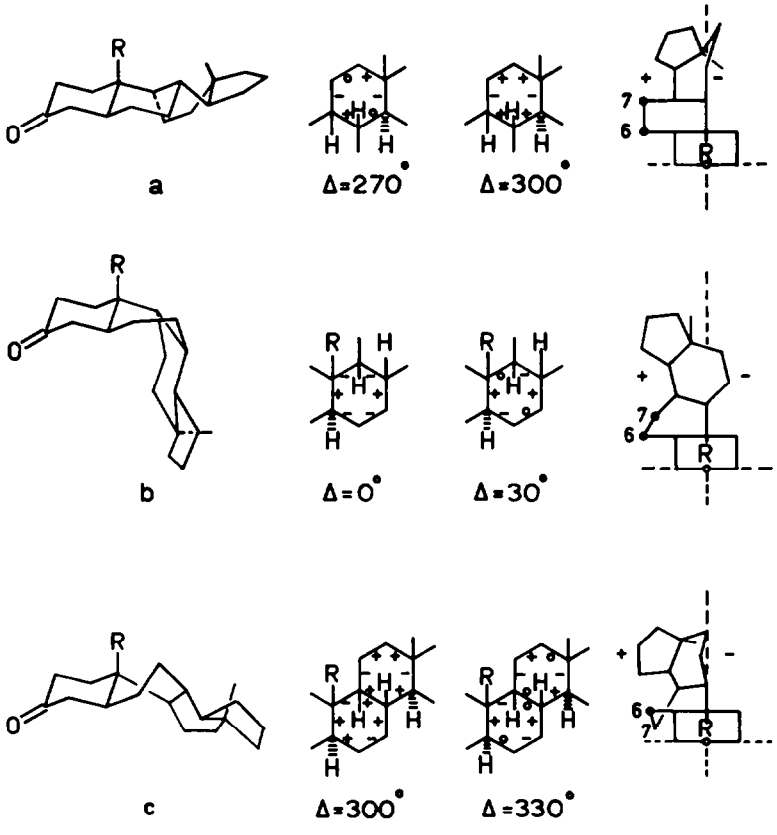


FIG 3. Possible conformational combinations and octant projections of a 5α,9β-steroid (configuration 3): **a**. B-chair/C-(twist)boat; **b**. B-(twist)boat/C-chair; **c**. B-(twist)boat/C-(twist)boat.

(The sign convention for torsional angles is that of Klyne and Prelog;[16] Δ is the phase angle of pseudo-rotation as defined by Buys and Geise[17]).

The steroid with 5α.9β-configuration **3** shows a significant decrease in the intensity of the Cotton effect as compared to the other A/B-*trans*-connected steroids. In **3** the A/B- and C/D-*trans*-connections require relatively large torsional angles φ_B(5–10) and φ_C(13–14) (positive and negative respectively). The B/C-*cis* junction demands about equal values of the torsional angles around the C-8/C-9 bond. in addition to identity of sign. These requirements can be met by the conformational combinations B-chair/C-(twist)boat. B-(twist)boat/C-chair and B-(twist)boat/C-(twist)boat. The first two combinations have been discussed by Bucourt.[15] As to the B-chair/C-(twist)boat case he arrives at the conclusion that the energetically favoured form of ring C is intermediate between the classical boat and the twist conformation (Fig. 3a), designated by $\Delta = 270°$ and $\Delta = 300°$ respectively. and probably nearer to the latter. As to the combination B-(twist)boat/C-chair (Fig. 3b) Bucourt's conclusions favour a form of ring B which is intermediate between the twist conformation. $\Delta = 0°$, and the classical boat. $\Delta = 30°$. probably close to the former. From the octant projections based on these conformations it is clear that the position of C-6 and C-7 does not differ appreciably from that in **1**. **2**. **6** and **7**. Consequently one would expect a Cotton effect similar in magnitude to that of the latter compounds instead of the decreased intensity actually observed.

Considering the third possibility—both rings (twist)boat—we may rule out conformations having negative torsional angles around the C-8/C-9 bond. on the assumption that closure of the torsional angle φ_B(5–10). opposite to the *trans*-connected 6-membered ring A. is energetically preferred to closure of φ_C(13–14). opposite to the *trans*-connected 5-membered ring D. This leads to a geometry of **3** that can be depicted (Fig. 3c) as intermediate between both rings having a twist conformation ($\Delta = 300°$) and both rings being classical boats ($\Delta = 330°$). The steric interaction between CH_3-19 and 7β-H probably causes it to come quite close to the former extreme. In this conformation the position of C-7 has changed considerably. The octant projection shows that C-7 is in or near the horizontal symmetry plane of the carbonyl chromophore and accordingly the intensity of the Cotton effect should be reduced.

Thus. contrary to the two chair/(twist)boat combinations the twist/twist conformation can account for the decrease in the intensity of the Cotton effect observed with steroid **3**. Of course. a conformational equilibrium of the twist/twist and one or both of the chair/twist forms cannot be excluded. It should be noted that X-ray analysis of a configurationally related steroid possessing the 3-oxo-4-ene moiety has demonstrated the presence of twist conformations in both rings B and C.[18]

As pointed out in part A. configurations **4** and **5** likewise require the presence of at least one (twist)boat form in the B/C ring system. In view of the deviating intensity

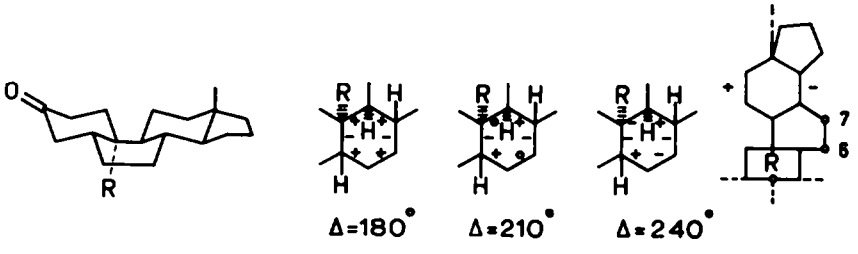


FIG 4. Conformation and octant projection of a 5β,10α-steroid (configuration **5**).

shown by the 10-Me steroid **3**, it is interesting to note that the 19-nor steroids **4** and **5** (see footnote† on p. 139) do not show a decrease in intensity of the Cotton effect. In **5** the *trans* fusion to rings A and C requires relatively large torsional angles at the ring junctions within ring B (negative and positive, respectively). The form of ring B which best accomodates these demands is the classical boat conformation, having C-5 and C-8 at the bowsprit and flagpole positions (Fig. 4, $\Delta = 210°$). The inherent eclipsed interactions may be relieved by pseudorotation towards one of the twist conformations characterized by $\Delta = 180°$ and $\Delta = 240°$ respectively. This leaves the position of C-6 and C-7 practically unchanged. The octant diagram clearly shows that the position of C-6 and C-7 is similar to that in **1**, **2**, **6**, and **7** (Fig. 2). Accordingly an important change in the intensity of the Cotton effect is not to be expected.

The conformational possibilities of the 5α,8α-configuration **4** are analogous to those of the 5α,9β-configuration **3**. Again three combinations are possible: B-(twist)boat/C-chair, B-chair/C-(twist)boat and B-(twist)boat/C-(twist)boat. The second and third possibility can be ruled out on account of serious steric crowding on the β-side of ring C, inherent to the (twist)boat situation. The first-mentioned combination, already proposed by Jones *et al.*[19] in 1953, is illustrated in Fig. 5. We suppose the actual geometry to be intermediate between the twist form with $\Delta = 0°$ and the classical boat, $\Delta = 30°$, probably considerably shifted towards the former in order to relieve the steric interactions between CH_3-18 and CH_2-7. From the octant projection it is seen that again there is no reason to expect a decrease in the intensity of the Cotton effect similar to that occurring in compound **3**.

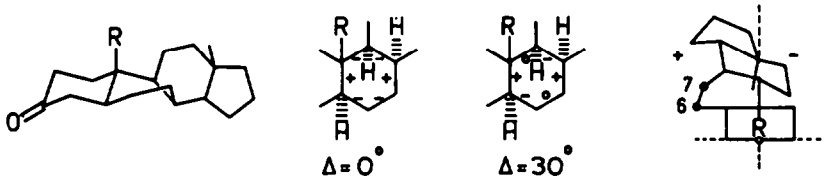


FIG 5. B-(twist)boat/C-chair conformation and octant projection of a 5α,8α-steroid (configuration **4**).

C. A/B-cis *Steroids*

A/B-*cis*-connected 3-oxo-steroids may be considered as derivatives of *cis*-2-decalone **15**. This compound can exist in two different chair/chair conformations, designated in Fig. 6 as *cis*(e) and *cis*(a).*

Owing to its junction to rings C and D the decalone moiety of a 3-oxo-steroid usually can adopt only one of these conformations. For the A/B-*cis* steroids in Table 1 (**8** to **14**) the relevant conformation is indicated. Compound **14** can exist in both conformations by virtue of the all-*cis* junction of the rings.

* The letters (e) and (a) refer to the equatorial or axial orientation (relative to the cyclohexanone ring) of the H atom or substituent at the bridgehead C atom nearest to the CO group. The terms most frequently used to distinguish between the two conformations are non-steroid (NS) and steroid (S) conformation. These are based on the (non)similarity of the conformations to that of the A/B-*cis* steroid of normal configuration. In a discussion of the conformation of steroids with abnormal configuration this nomenclature might lead to confusion. The symbols *cis*(e) and *cis*(a) were introduced by Klyne[20] and defined in an equivalent way.

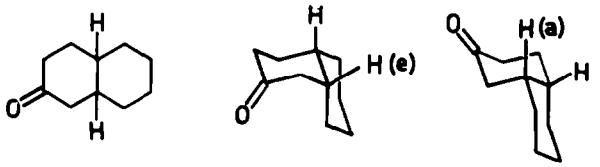


FIG 6. Chair/chair conformations of *cis*-2-decalone.

From the data in Table 1 it appears that the difference in conformation is reflected in the intensity of the observed Cotton effects. The *cis*(e) steroids exhibit very weak Cotton effects (**a** from 0 to 10 or 15, $\Delta\varepsilon$ from 0 to 0·2 or 0·3), while the values obtained with the *cis*(a) steroids—with the notable exception of configuration **10**—are slightly larger (**a** from 20 to 25, $\Delta\varepsilon$ about 0·50). If we accept this as a tentative rule then the amplitude of compound **14** points to the *cis*(a)-conformation; this agrees with the conformation assigned to the corresponding 3β-hydroxy-compound on chemical and infrared absorption evidence[13] (*cf* Ref. 3).

The octant projections of the *cis*(a) steroids **8** and **9** are shown in Fig. 7. Again, the immediate vicinity of the ketone groups is identical, suggesting that the intensity of the Cotton effect is essentially determined by the contribution of CH_2-6, while the influence of the more remote rings C and D is negligible. In agreement with this view the **a** and $\Delta\varepsilon$ values recorded for **8** and **9** are about equal to the contribution of a Me group in β-position to the CO group and equatorially oriented to the cyclohexanone ring. This group contribution is reported[14,21] to be about 25 in amplitude units, equivalent to an increment of $\Delta\varepsilon$ by about 0·6.

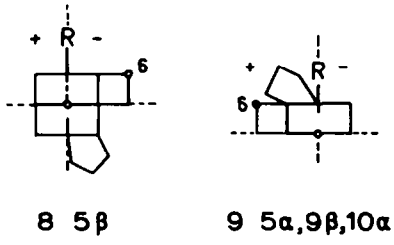


FIG 7. Octant projections of A/B-*cis*(a)-connected 3-oxo-steroids.

The strongly deviating Cotton effect of the steroids with configuration **10** suggests a major change of the all-chair conformation pictured in Fig. 1. As discussed in part A, in compounds with 9β,10α-configuration the steric interactions caused by the presence of an axial "t-butyl" group are relieved by closure of the relevant torsional angles rather than by chair-(twist)boat conversion. In **10** this preference may well be less pronounced or even reversed, owing to the decreased difference in energy content of chair and (twist)boat conformation of cyclohexanone compared with cyclohexane[22]. A twist conformation of ring A (Fig. 8) (Δ between 240° and 270°, probably close to 240°) seems an attractive possibility: C-2 is moved well away from C-11, while the decrease in torsional angle φ_A(5–6) leads to a concomitant decrease of torsional angle

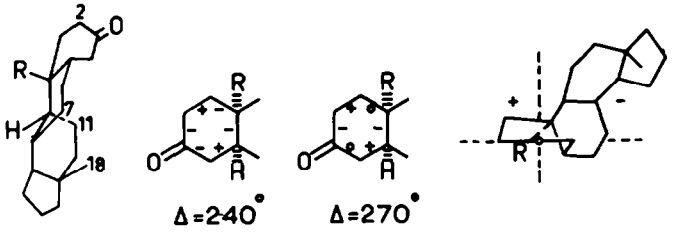


FIG 8. Conformation and octant projection of a 5α,8α,10α-steroid (configuration **10**).

φ_B(5–6). and to a less extent also of φ_B(8–9) and φ_C(8–9).[23] thereby flattening ring B and increasing the distances C-4/C-11 and C-7/C-18. The octant projection based on this conformation predicts a rather strong positive Cotton effect. the intensity of which depends on the skewness of ring A.[24] Of course a conformational equilibrium involving the all-chair form and the twist form would equally well account for the observed Cotton effect. Clearly the interesting conformational aspects of this type of steroid deserve further investigation. It should be noted that Bucourt *et al.*[25] likewise suggested the twist conformation of ring A in order to explain the observed enhanced circular dichroism of the 19-nor steroid **10**.

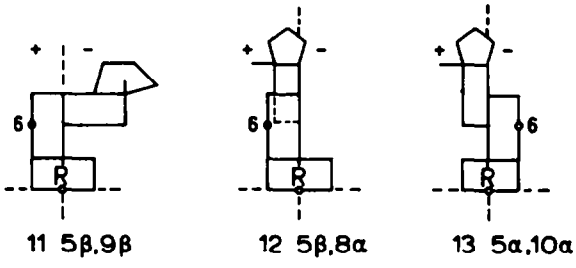
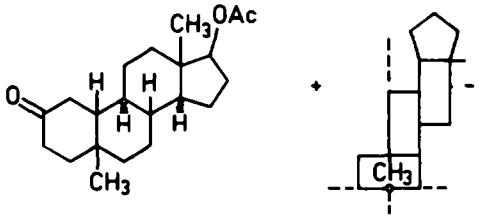


FIG 9. Octant projections of A/B-*cis*(e)-connected 3-oxo-steroids.

Neglecting the influence of rings C and D the octant projections of the *cis*(e) steroids (Fig. 9) predict Cotton effects of equal magnitude. positive for **11** and **12**. and negative for **13**. The intensity should be about equal to the contribution of an axial Me group in β-position with respect to the CO group. This is variously estimated to be about 20.[4c,26] 24.[14] 33 or more[27] and even 55[28] in amplitude units (in $\Delta\varepsilon$ increments: 0·5. 0·6. 0·8 and 1·4 respectively). Evidently these predictions do not fit in with the ORD and CD values actually observed (Table 1); the Cotton effects of the *cis*(e) steroids are. in fact. very weak. and for **11** and **13** even the sign appears to be wrong. From a consideration of the octant projection of **12** it is apparent that the discrepancy cannot be explained by an unexpectedly large contribution of rings C and D. which might offset the influence of CH_2-6 in **11** and **13**. This is confirmed by the very weak Cotton effect ($\Delta\varepsilon = -0{\cdot}05$ in dioxan) reported[29] for the conformationally closely related 2-oxo-steroid **16**.

On the other hand, the occurrence of (twist)boat conformations which could produce the observed Cotton effects seems equally improbable (see part A). In the 5α,10α-configuration **13** particularly it is hardly possible to perceive any steric interaction important enough to compensate for the increase in energy associated with the chair-(twist)boat conversion. Moreover, NMR evidence directly points to the all-chair *cis*(e) conformation of **13**. From the Me-19 chemical shifts of 17β-hydroxy-5α,10α-androstan-3-one (Experimental) and of 5α,10α-androstane[30] we conclude that the additional chemical shift of the 10-Me protons due to the CO group amounts to 0·24 ppm* ($CDCl_3$, 60 Mcs). This value is characteristic of the mutual position and orientation of the CO function and the 10-Me group as present in the *cis*(e) conformation, and is inconsistent with the *cis*(a) or (twist)boat conformation of ring A.[33]



16

For configurations **11** and **12** the reference compounds needed to construct similar arguments are not available as yet. In the case of **11**, however, the chemical shift of the C-18 protons indicates that at least ring C exists in the chair conformation. This may be argued as follows. Normally, inversion at C-5 has little or no influence on the chemical shift of Me-18.[31] The 10-Me steroids 5α,9β- and 5β,9β-ergost-22-en-3-one (**3** and **11**) do however show a considerable difference in Me-18 shift: 5α,9β: 0·88 ppm.[32] 5β,9β: 0·69 ppm (Experimental) ($CDCl_3$, 60 Mcs). From the NMR data of a number of skeletally isomeric steroids[32] it appears that in compounds with 5α,9β- and with Δ^4,9β-configuration the C-18 protons are generally shifted downfield in comparison to the corresponding compounds of the other isomeric series. The difference noted in **3** and **11** is therefore to be ascribed to the unusual downfield shift in the 5α-isomer. We are inclined to associate the downfield shift of Me-18 with ring C having a (twist)boat conformation. Table 2 shows the Me-18 shifts of the isomeric androstanes having C/D-*trans* ring junction. The conformations indicated are the ones discussed above in relation to the Cotton effects of the saturated 3-oxo-steroids. Obviously, a δ value of about 0·70 ppm is indicative of a chair conformation of ring C. 5β,8α,10α-Androstane (configuration **7**) constitutes a special case, due to the 1,3-diaxial interaction of CH_2-7 with Me-18; as is well known[34] a substituent in this relationship causes a downfield shift of the Me protons.

Taking into account the additional chemical shifts of Me-18 due to 17β-C_9H_{17} (invariably −0·03 ppm in C/D-*trans* compounds[32]) and to the 3-oxo-function (between −0·03 and +0·04 in all configurations known[30–32]) one arrives at a calculated value

* This figure includes the increment due to the 17β-OH group, which, however, is very small,[31] irrespective of the configuration at C-10.[32]

for the 5β.9β-andostrane skeleton ranging from 0·68 to 0·75 ppm. This result compares favourably with the δ values. noted in Table 2 for androstanes having ring C in a chair conformation.

A Dreiding model of **11** shows that forms in which ring C has a chair conformation but rings A or B or both adopt a (twist)boat conformation should be energetically unfavourable when compared with the all-chair conformation.

TABLE 2. CHEMICAL SHIFT (IN PPM) OF Me-18 IN SOME SKELETALLY ISOMERIC C/D-*trans* ANDROSTANES ($CDCl_3$, 60 Mcs)

Configuration	Conformation of ring C	δ_{CH_3-18}	Ref.
1: 5α	chair	0·69	31
8: 5β	chair	0·69	31
13: 5α.10α	chair	0·69	30
6: 5β.9β.10α	chair	0·72	32
9: 5α.9β.10α	chair	0·71	*
7: 5β.8α.10α	chair	0·84	32
3: 5α.9β	(twist)boat	0·90	32

* This work; measured at 100 Mcs.

We may conclude that the observed Cotton effects of the *cis*(e) steroids when interpreted in the light of the octant rule are not consistent with the exclusive presence of the all-chair *cis*(e) conformation; that. on the other hand. consideration of the energies involved virtually excludes the presence of an appreciable amount of a (twist)boat form. whereas the available NMR evidence strongly points to the all-chair *cis*(e) conformation. especially in the case of **13**.

This situation is strongly reminiscent of the controversy with respect to the preferred conformation of *cis*-10-methyl-2-decalone and some of its derivatives. Again. NMR evidence[33a, b, 35] and energy considerations[20, 36, 22b] designate the *cis*(e) conformation as being predominant in the conformational equilibrium, while application of the octant rule predicts Cotton effects opposite in sign to those actually observed.[4b, 37, 33a] The values of the ORD amplitudes closely resemble the ones obtained in the case of the *cis*(e) steroids.

In our opinion in both cases there is little room to doubt the validity of the conclusions from NMR measurements and energy considerations; the observed Cotton effects of the *cis*(e) steroids as well as of the *cis*-10-Me-2-decalones are best explained* by assigning a very weak Cotton effect contribution to that part of the *cis*(e) conformation that may be regarded as a β-axial alkyl substituent to the cyclohexanone

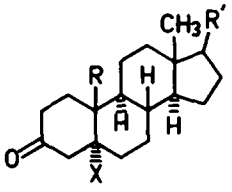
* In the case of the decalones the conclusion was advanced[37, 33a] that the sign of the Cotton effect must be controlled by a conformer present in minor amounts and having an extremely powerful rotational strength. This explanation seems less satisfactory to us, considering that, in the presence of a conformer having a relatively large rotational strength, even a small shift in equilibrium composition—as is to be expected with change of solvent or temperature—will drastically change the observed Cotton effect. However, the changes actually observed with change of solvent are reported[33a] to be insignificant, while lowering the temperature resulted[37] in only a small increase of the Cotton effect in the "wrong" direction.

moiety of the molecules. The sign of this group contribution is rather uncertain in some compounds but definitely opposite to the prediction of the octant rule in other cases.

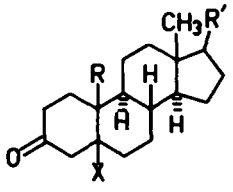
This conclusion is considerably strengthened by the recent findings of Snatzke *et al.*[38] who observed a very small contribution of the β-axial Me group in 2ᵃ-methyladamantanone-4. consistent in sign with the octant rule prediction. when determined in iso-octane, but showing "anti-octant behaviour" for solutions in ethanol and dioxan. Here the rigidity of the adamantane skeleton ensures the chair conformation of the cyclohexanone ring.

D. *Varying group contributions of β-axial substituents*

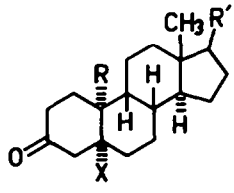
The small anti-octant contribution of a β-axial Me substituent. first observed by Snatzke *et al.*[38] and now also found in the compounds discussed above. sharply contrasts with the medium size contribution of normal sign. established by Klyne[4c, 26a,b] and confirmed again recently.[14, 26c] Reconsidering the literature data we notice that the octant rule behaviour is inferred mainly from the data of *trans*-connected decalone derivatives in which the substituent is located at one of the bridge-head C atoms. as e.g. in a 3-oxo-5α-steroid **17** (X = Me). If however the data of A/B-*cis*-connected 3-oxo-5β-steroids are examined the contribution of the 5β-Me group.



17



18



19

which should be negative according to the octant rule. turns out to be +7 and +8 for 10-Me steroids[14, 39] (**18**. R = Me). and +6 for 19-nor steroids[14] (**18**. R = H) in amplitude units. In view of the background effect on amplitude values we measured the CD of some suitably substituted A/B-*cis*(a) 3-oxo-steroids. The results, given in Table 3, qualitatively agree with the literature ORD data and clearly show that the

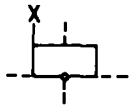
TABLE 3. CONTRIBUTION OF A 5-Me SUBSTITUENT TO THE COTTON EFFECT OF SOME A/B-*cis*(a) 3-OXO-STEROIDS (SOLVENT METHANOL)

	R	R'	X	Δε	Δ(Δε)	
					Exp.	Octant rule prediction
18a	H	OH	H	−0·48	+0·09	—
18b	H	OAc	CH_3	−0·39		
18c	CH_3	OH	H	−0·45	+0·20	—
18d	CH_3	OAc	CH_3	−0·25		
19a	CH_3	OH	H	+0·57	−0·47	+
19b	CH_3	OAc	CH_3	+0·10		

contribution of the Me group is opposite to the prediction of the octant rule. The behaviour of the β-axial Me group in this class of compounds thus presents a third example of the anti-octant contribution shown by a nonpolar β-axial substituent.

Polar substituents in β-axial position similarly may exhibit anti-octant contributions. as has been demonstrated conclusively by the work of Snatzke *et al.* on adamantanones.[40] Using literature data we compare in Table 4 the behaviour of the Me group with that of some conically symmetric polar groups in the three types of compounds mentioned above. The range in Δa values reflects the sometimes large numerical differences in literature data. In spite of this Table 4 shows that the contribution of a substituent in β-axial position to a cyclohexanone may vary considerably according to the nature of the compound of which the cyclohexanone moiety forms a part. In addition to the Me substituted compounds the change of sign only occurs in the fluoro compounds.

TABLE 4. CONTRIBUTIONS Δa OF β-AXIAL SUBSTITUENTS TO THE COTTON EFFECT IN DIFFERENT TYPES OF CYCLOHEXANONES



Octant rule: +

X	Adamantanones	A/B-*trans* (17)	A/B-*cis* (*ent*-18, 19)
CH_3	− 4 a	+ 7 to +18 c.d.e.f	−19 to −4 c.d.n.o
CN		−10 to + 3 c.g.h.i.j	− 8 to 0 c.i.p.q
F	+ 2 b	−17 to −14 k.l.m	−18 m
Cl	−17 b	−34 to −31 h.k.l	
Br	−23 b	−40 h.k	

Solvents: ethanol (adamantones). methanol or dioxan (steroids).

The Δa values of the steroids have been calculated using as reference values the amplitudes of the corresponding unsubstituted 3-oxo-steroids (Table 1). corrected, if necessary, for difference of solvent. Δε values have been converted into amplitudes by means of the equation $a = 40{,}28\ \Delta\varepsilon$.[41]

Ent-**8** denotes the enantiomer of compound **18**: the three columns thus refer to the same absolute configuration of the substituted cyclohexanone.

[a] Ref. 38. [b] Ref. 40. [c] Ref. 39. [d] W. Nagata. S. Hirai. H. Itazaki and K. Takeda. *Ann. Chem.* **641**. 196 (1961). [e] J. C. Jacquesy and J. Levisalles, *Bull. Soc. Chim. Fr.* 1866 (1962). [f] W. G. Dauben and E. J. Deviny, *J. Org. Chem.* **31**. 3794 (1966). [g] Ref. 2c. [h] J. C. Jacquesy and J. Levisalles. *Bull. Soc. Chim. Fr.* 1538 (1965). [i] A. D. Cross and I. T. Harrison. *J. Am. Chem. Soc.* **85**. 3223 (1963). [j] A. T. Glen. W. Lawrie and J. McLean. *J. Chem. Soc.* (C) 661 (1966). [k] C. S. Barnes and C. Djerassi. *J. Am. Chem. Soc.* **84**. 1962 (1962). [l] N. L. Allinger. J. G. D. Carpenter and M. A. da Rooge. *J. Org. Chem.* **30**. 1423 (1965). [m] J. C. Jacquesy. R. Jacquesy and J. Levisalles, *Bull. Soc. Chim. Fr.* 1649 (1967). [n] Ref. 14. [o] See Table 3. [p] A. Bowers, *J. Org. Chem.* **26**, 2043 (1961). [q] R. Jacquesy and J. Levisalles, *Bull. Soc. Chim. Fr.* 1642 (1967).

Leaving aside the theoretical implications of anti-octant behaviour* it is clear. that the variation in group contribution of a β-axial substituent has important bearing on the conformational aspects of ORD and CD studies. in particular if a change of sign is involved. Among the conformational features that should be considered are

* A survey and discussion of the relevant theories is given by Snatzke *et al.*[38, 40] For later papers dealing with anti-octant behaviour, see Refs 26*c* and 42.

the geometry of the cyclohexanone ring. the position and orientation of the substituent with respect to the CO chromophore. and. as far as non-conically symmetric groups are involved. the conformation of the substituent itself.

From electron diffraction measurements[43] and from calculations[44] it is known that the valency and torsional angles of *cis*-decalin are significantly different from those in *trans*-decalin. in particular at the bridgehead C atoms. Starting from the perfect chair model the rings of *cis*-decalin are considerably more flattened than those of the *trans*-isomer. In the case of adamantane X-ray analysis[45] has shown that the geometry of the 6-membered rings is very near to the perfect chair conformation. An analogous difference may be expected in the geometry of the three corresponding CO compounds. and this will result in a different position and orientation of a β-axial substituent with respect to the CO chromophore. Conversely. the distortion of the cyclohexanone moiety by the presence of a β-axial substituent will vary from one type of compound to another.

The observed group contribution will be the joint result of the change in cyclohexanone geometry and the direct contribution of the β-axial substituent. In comparing the group contributions in different types of cyclohexanones a possible difference in substituent conformation should also be taken into account. On the assumption that the difference in group contribution is primarily the result of a change in the direct contribution of the substituent. we may conclude that the contribution of a β-axial substituent is very sensitive to changes in the position and orientation of the substituent with respect to the CO chromophore. This might reasonably be explained by the existence of an additional nodal surface in the immediate vicinity of the β-axial substituent. as suggested by Pao and Santry[46] (see also Ref. 26*c*).

The sensitivity of the group contribution to the relative disposition of substituent and CO group would also explain the differences observed in the Cotton effects of the *cis*(e) steroids (Table 1). The presence or absence of the angular 10-Me group in conjunction with the different connections between rings B and C will presumably result in slightly different geometries of ring A with the concomitant difference in position of the β-axially oriented CH_2-6.

SYNTHESES

Using conventional methods the following novel unnatural steroids have been prepared: 17β-hydroxy-5α,9β,10α-androstan-3-one (**9**), 5α,8α,10α-ergostan-3-one (**10**). 5β,9β-ergost-22-en-3-one (**11**), 17β-hydroxy-5α,10α-androstan-3-one (**13**) and 5α,9β. 10α-androstane. Details are reported in the Experimental.

CONCLUSION

The comparison of the Cotton effects of skeletally isomeric 3-oxo-steroids has been shown to give important information on the conformational differences connected with differences in skeleton configuration. In addition it has lead to the suggestion that the contribution of β-axial substituent to the Cotton effect is very sensitive to relatively small changes in its position and orientation relative to the carbonyl chromophore.

EXPERIMENTAL

A. *ORD and CD measurements*

The spectropolarimeter used is described in detail by Emeis.[47] CD was measured with a Dichrographe Roussel-Jouan (Paris).

Care was taken to ensure the same experimental conditions in all measurements. With one exception the measurements were all performed in MeOH as a solvent, giving Cotton effect curves without fine structure. The instruments were operated such as to keep the half-intensity bandwidth below or equal to 2 nm. The determinations were made at room temp (22–25°), using 2 cm sample cells; concentrations were approximately 1 mg/ml. The presence of impurities—e.g. the C-5 epimer—may considerably affect the intensity of the Cotton effect actually measured. The purity of the samples was therefore carefully checked (TLC. GLC). If necessary. the compounds were repeatedly subjected to column chromatography and recrystallization.

The results of the ORD and CD measurements are given in Table 5.

TABLE 5. ORD AND CD DATA OF 3-OXO-STEROIDS

	Compounds	Source	ORD					CD	
			λ_1	$[\varphi]_1$	λ_2	$[\varphi]_2$	a	λ_{max}	$\Delta\varepsilon_{max}$
1	17β-hydroxy-5α-androstan-3-one	*a*	308	+2670	267	−2830	+55	289	+1·31
1	17β-hydroxy-5α-estran-3-one	*b*	309	+3300	269	−2650	+59	289	+1·48
2	5α,13α-androstan-3-one	*c*	308	+1720	264	−4240	+60	290	+1·31
3	5α.9β-ergost-22-en-3-one	*d*	309	+2740	271	−1350	+41	289	+1·00
6	17β-hydroxy-5β.9β.10α-androstan-3-one	*d*	309	−2510	268	+2990	−55	289	−1·31
7	5β.8α.10α-ergost-22-en-3-one	*d*	309	−2240	268	+2980	−52	289	−1·26
8	17β-hydroxy-5β-androstan-3-one	*e*	309	− 340	266	+1840	−22	289	−0·45
8	17β-hydroxy-5β-estran-3-one	*b*	308	+ 10	264	+2470	−25	289	−0·48
9	17β-hydroxy-5α.9β.10α-androstan-3-one	*f*	308	+1330	266	− 970	+23	289	+0·57
10	5α.8α.10α-ergostan-3-one	*f*	308	+1710	267	−3320	+50	289	+1·14
11	5β.9β-ergost-22-en-3-one	*f*	310	− 340	280	− 240	− 1	~290	−0·05
13	17β-hydroxy-5α.10α-androstan-3-one	*f*	308	+ 90	257	− 660	+ 7	293	+0·11(D)
18*b*	17β-acetoxy-5-methyl-5β-estran-3-one	*b*						289	−0·39
18*d*	17β-acetoxy-5-methyl-5β-androstan-3-one	*g*						289	−0·25
19*b*	17β-acetoxy-5-methyl-5α.9β.10α-androstan-3-one	*h*						288	+0·10

Solvent methanol. except for CD of compound **13**. where dioxan was used.

In ORD the wavelengths (in nm) and molecular rotations at the extrema are given. together with the value of the amplitude a.

[a] Ref. 9. [b] S. J. R. Rinses. Thesis. Leiden. to be published. [c] J. Pot. Thesis. Leiden. 1964. [d] Ref. 32. [e] E. Merck. A. G. Darmstadt. [f] This work. [g] J. W. J. Gielen and H. J. C. Jacobs. unpublished. [h] P. Westerhof. unpublished.

B. *Syntheses*

(with the assistance of Mr. J. Brussee and Drs. J. Veltmeijer).

M.ps were taken in evacuated capillary tubes and are corrected. UV absorption spectra were measured in MeOH soln with a Cary recording spectrophotometer M14. IR spectra (in KBr discs. unless otherwise indicated) were obtained with a Unicam spectrophotometer SP 100 or SP 1200 or with a Beckman IR-10

instrument. NMR spectra were recorded in $CDCl_3$ (10% w/w solns); the 100 Mcs were run on a Jeol JNM-PS-100, the 60 Mcs spectra on a Varian A-60 spectrometer; chemical shifts are reported in ppm downfield from TMS as internal reference. Mass spectra were taken with a GEC-AEI Mass spectrometer, type MS 902, at ion source temps between 150° and 185°. GLC was performed on a Hewlett-Packard High Efficiency gas chromatograph F + M Model 402, using U-shaped glass columns packed with 1% SE-30 or 1% XE-60 on GasChrom Q (80–100 mesh).

a. 17β-*Hydroxy*-5α,9β,10α-*androstan*-3-*one* (**9**). 17β-Hydroxy-9β,10α-androst-4-en-3-one* (100 mg) was dissolved in AcOH (20 ml) and hydrogenated over 10% Pd-C (100 mg) at 3 atm. After 30 min the catalyst was removed by filtration and the soln worked up as usual. As judged from GLC the mixture contained the A/B-*cis* and -*trans* saturated ketones in about 4:1 ratio. Chromatography on silicagel (eluent: benzene-acetone) and crystallization from cyclohexane-ether gave pure 17β-hydroxy-5α,9β,10α-androstan-3-one, m.p. 122–125°; $[\alpha]_D^{21}$ + 15° (*c* 0·10 in MeOH); UV: ε_{275} 24; ORD and CD, see Table 5; IR: 3400, 1710 and 1035 cm^{-1}; NMR (100 Mcs): 0·80/s (3) Me_3-18, 1·14/s (3) Me_3-19, 3·67/t (1) CH-17; MS: calc. for $C_{19}H_{30}O_2$ 290·2246, found *m/e* 290·2243.

b. 5α,9β,10α-*Androstane*. 17β-Hydroxy-5α,9β,10α-androstan-3-one (1·2 g) was dissolved in acetone and titrated with 8N chromic acid soln[48] at room temp. After oxidation the mixture was diluted with water and extracted with ether. The ethereal soln was washed successively with water, saturated $NaHCO_3$ aq and water, and dried over Na_2SO_4. After removal of the solvent 900 mg of crystalline 3,17-dione were obtained, m.p. 95–100°, showing IR absorption bands at 1730 and 1705 cm^{-1} (no OH absorption). Without further purification the dione was dissolved in diethylene glycol, 4 g KOH pellets and 6 ml hydrazine hydrate were added, and the soln was heated at 145° for 90 min, followed by another 90 min at 210°. After this the mixture was poured into water, neutralized with 2N HCl and extracted with ether. The ethereal soln was washed and dried and the ether evaporated. The yellowish oily residue was chromatographed on silica-gel (eluent: hexane). The first few fractions contained the hydrocarbon 5α,9β,10α-androstane, obtained as a colourless oil in 64% yield; n_D 1·5246; $[\alpha]_D^{22}$ + 3° (*c* 0·47 in $CHCl_3$); IR (pure): 1450 and 1375 cm^{-1}; NMR (100 Mcs): 0·71/s (3) Me-18, 1·04/s (3) Me-19; MS: calc. for $C_{19}H_{32}$ 260·2504, found *m/e* 260·2499.

c. 5α,8α,10α-*Ergostan*-3-*one* (**10**). 8α,10α-Ergosta-4,22-dien-3-one[49] (600 mg) in AcOH (25 ml) was hydrogenated in the presence of catalyst (150 mg), as described under a. Crystallization from acetone-MeOH and chromatography of the mother liquors on silicagel (eluent: cyclohexane) afforded 400 mg of 5α,8α,10α-ergostan-3-one, slightly contaminated with the 5β-isomer (GLC). Repeated recrystallization from acetone-MeOH proved necessary to remove the last traces of 5β-compound; m.p. 98–99°; $[\alpha]_D^{21}$ − 5° (*c* 0·13 in MeOH); ORD and CD, see Table 5; IR: 1710 cm^{-1}; NMR (100 Mcs): 0·78/s (3) Me-18, 1·10/s (3) Me-19; MS: calc. for $C_{28}H_{48}O$ 400·3705, found *m/e* 400·3663.

d. 5β,9β-*Ergost*-22-*en*-3-*one* (**11**).† This compound was formed as a byproduct in the earlier reported[32] lithium-liquid ammonia reduction of 9β-ergosta-4,22-dien-3-one, which lead predominantly to the A/B-*trans* isomer **3**. The 5β,9β-isomer was isolated in 20% yield, m.p. 88·5 90° (from acetone; $[\alpha]_D^{22°}$ − 21° (*c* 0·53 in $CHCl_3$); UV: ε_{282} 32; ORD and CD, see Table 5; IR: 1720 and 972 cm^{-1}; NMR (60 Mcs): 0·69 s (3) Me-18, 1·29/s (3) Me-19, 5·18/m (2) CH-22 + CH-23; MS: calc. for $C_{28}H_{46}O$ 398·3549, found *m/e* 398·3541.

e. 17β-*Hydroxy*-5α,10α-*androstan*-3-*one* (**13**).† 17β-Acetoxy-10α-androst-4-en-3-one[50] was subjected to lithium-liquid ammonia reduction according to the procedure described.[32] The A/B-*cis* compound 17β-hydroxy-5α,10α-androstan-3-one was obtained in 25% yield, the remaining 75% being mainly unchanged starting material; m.p. 178·5–179·5° (from ether–hexane); $[\alpha]_D^{21}$ − 10° (*c* 0·51 in $CHCl_3$); UV: ε_{280} 22; ORD and CD, see Table 5; IR: 3450, 1707 and 1070 cm^{-1}; NMR (60 Mcs): 0·73/s (3) Me-18, 1·27/s (3) Me-19, 1·82/s (1) 17–OH, 3·63/m (1) CH-17; (Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4. Found: C, 78·8; H, 10·5%).

Acknowledgement—We thank Professor P. Crabbé and Dr. E. Farkas for exchange of information. We are indebted to Drs. C. Altona, H. J. P. M. Dekkers, C. A. Emeis and S. J. Halkes for helpful comments and criticisms.

* We acknowledge a generous gift of this material and of a sample of compound **19b** by Mr. P. Westerhof (Research Laboratories Philips-Duphar, Weesp).

† In collaboration with Dr. S. J. Halkes.

REFERENCES

[1] C. Djerassi and W. Closson. *J. Am. Chem. Soc.* **78**. 3761 (1956)

[2] [a] C. Djerassi. *Optical Rotatory Dispersion: Applications to Organic Chemistry*. McGraw-Hill. New York (1960);
[b] L. Velluz. M. Legrand and M. Grosjean. *Optical Circular Dichroism: Principles. Measurements. and Applications*. Verlag Chemie. Weinheim; Academic Press. New York (1965);
[c] P. Crabbé. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Holden-Day. San Fransisco (1965);
[d] P. Crabbé, *Application de la Dispersion Rotatoire Optique et du Dichroisme Circulaire Optique en Chimie Organique*. Gauthier-Villars, Paris (1968)

[3] C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962)

[4] [a] C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.* **78**, 6362 (1956);
[b] C. Djerassi and D. Marshall. *Ibid.* **80**. 3986 (1958);
[c] W. Klyne. *Experientia* **20**. 349 (1964)

[5] [a] W. Moffitt. R. B. Woodward. A. Moscowitz. W. Klyne and C. Djerassi. *J. Am. Chem. Soc.* **83**. 4013 (1961);
[b] A. Moscowitz. *Tetrahedron* **13**. 48 (1961)

[6] A. Moscowitz. Chapter 12 in Ref 2*a*

[7] H. J. C. Jacobs. in preparation

[8] H. J. C. Jacobs. Thesis. Leiden. to be published

[9] S. J. Halkes. Thesis. Leiden (1964)

[10] W. S. Johnson. *Experientia* **7**. 315 (1951)

[11] [a] C. Romers. B. Hesper. E. van Heykoop and H. J. Geise. *Acta Cryst.* **20**. 363 (1966);
[b] H. J. Geise. C. Altona and C. Romers. *Tetrahedron* **23**. 439 (1967)

[12] W. E. Oberhänsli and J. M. Robertson. *Helv. Chim. Acta* **50**. 53 (1967)

[13] J. Castells. G. A. Fletcher. E. R. H. Jones. G. D. Meakins and R. Swindells. *J. Chem. Soc.* 2627 (1960)

[14] D. N. Kirk. W. Klyne and S. R. Wallis. *Ibid.* (C) 350 (1970)

[15] R. Bucourt. *Bull. Soc. Chim. Fr.* 2080 (1964)

[16] W. Klyne and V. Prelog. *Experientia* **16**. 521 (1960)

[17] H. R. Buys and H. J. Geise. *Tetrahedron Letters* 5619 (1968)

[18] B. Hesper. H. J. Geise and C. Romers. *Rec. Trav. Chim.* **88**. 871 (1969)

[19] R. B. Clayton. H. B. Henbest and E. R. H. Jones. *J. Chem. Soc.* 2015 (1953)

[20] W. Klyne. *Experientia* **12**. 119 (1956)

[21] C. Djerassi. E. Lund and A. A. Akhrem. *J. Am. Chem. Soc.* **84**. 1249 (1962)

[22] [a] E. L. Eliel. N. L. Allinger. S. J. Angyal and G. A. Morrison. *Conformational Analysis* p. 115. Interscience. New York (1965);
[b] N. L. Allinger. J. A. Hirsch. M. A. Miller and I. J. Tyminski. *J. Am. Chem. Soc.* **91**. 337 (1969)

[23] R. Bucourt. *Bull. Soc. Chim. Fr.* 1262 (1963)

[24] C. Djerassi and W. Klyne. *Proc. Nat. Acad. Sci. U.S.* **48**. 1093 (1962)

[25] R. Bucourt. D. Hainaut. J. C. Gasc and G. Nominé, *Bull. Soc. Chim. Fr.* 1920 (1969)

[26] [a] W. Klyne and W. Robertson. *Experientia* **18**. 413 (1962);
[b] M. P. Hartshorn. D. N. Kirk and W. Klyne. *Tetrahedron Letters* 89 (1965);
[c] C. Coulombeau and A. Rassat. *Bull. Soc. Chim. Fr.* 516 (1971)

[27] K. M. Wellman. P. H. A. Laur. W. S. Briggs. A. Moscowitz and C. Djerassi. *J. Am. Chem. Soc.* **87**. 66 (1965)

[28] J. C. Tai and N. L. Allinger. *Ibid.* **88**. 2179 (1966)

[29] J. Frei. C. Gauter. D. Kägi. K. Kocsis. M. Miljlovic. A. Siewinski. R. Wenger. K. Schaffner and O. Jeger. *Helv. Chim. Acta* **49**. 1049 (1966)

[30] M. Fétizon and J. C. Gramain. *Bull. Soc. Chim. Fr.* 3444 (1966)

[31] R. F. Zürcher. *Helv. Chim. Acta* **46**. 2054 (1963)

[32] S. J. Halkes and E. Havinga. *Rec. Trav. Chim.* **84**. 889 (1965)

[33] [a] W. G. Dauben. R. M. Coates. N. D. Vietmeyer. L. J. Durham and C. Djerassi. *Experientia* **21**. 565 (1965);
[b] K. L. Williamson and T. A. Spencer. *Tetrahedron Letters* 3267 (1965);
[c] M. Gorodetsky and Y. Mazur. *Ibid.* 227 (1964);
[d] K. L. Williamson. L. R. Sloan. T. Howell and T. A. Spencer. *J. Org. Chem.* **31**. 436 (1966)

[34] K. Tori and K. Kuriyama. *Chem. and Ind.* 1525 (1963)

[35] D. R. Elliott. M. J. T. Robinson and F. G. Riddell. *Tetrahedron Letters* 1693 (1965)
[36] W. D. Cotterill and M. J. T. Robinson. *Tetrahedron* **20**. 777 (1964)
[37] C. Djerassi. J. Burakevich. J. W. Chamberlin. D. Elad. T. Toda and G. Stork. *J. Am. Chem. Soc.* **86**. 465 (1964)
[38] G. Snatzke. B. Ehrig and H. Klein. *Tetrahedron* **25**. 5601 (1969); see also M. E. Herr. R. A. Johnson. W. C. Krueger. H. C. Murray and L. M. Pschigoda. *J. Org. Chem.* **35**. 3607 (1970)
[39] C. Djerassi and W. Klyne. *J. Chem. Soc.* 2390 (1963)
[40] [a] G. Snatzke and G. Eckhardt. *Tetrahedron* **24**. 4543 (1968);
[b] G. Snatzke and G. Eckhardt. *Ibid.* **26**. 1143 (1970)
[41] S. F. Mason. *Quart. Rev.* **17**. 20 (1963)
[42] [a] J. Hudec. *Chem. Comm.* 829 (1970);
[b] L. Bartlett. D. N. Kirk. W. Klyne. S. R. Wallis. H. Erdtman and S. Thorén. *J. Chem. Soc.* (C) 2678 (1970);
[c] R. R. Gould and R. Hoffman. *J. Am. Chem. Soc.* **92**. 1813 (1970);
[d] A. H. Beckett. A. Q. Khokhar. G. P. Powell and J. Hudec. *Chem. Comm.* 326 (1971)
[43] M. I. Davis and O. Hassel. *Acta Chem. Scand.* **18**. 813 (1964)
[44] R. Bucourt and D. Hainaut. *Bull. Soc. Chim. Fr.* 501 (1966)
[45] J. Donohue and S. H. Goodman. *Acta. Cryst.* **22**. 352 (1967)
[46] Y. H. Pao and D. P. Santry. *J. Am. Chem. Soc.* **88**. 4157 (1966)
[47] C. A. Emeis. Thesis. Leiden (1968)
[48] A. Bowers. T. G. Halsall. E. R. H. Jones and A. J. Lemin. *J. Chem. Soc.* 2548 (1953)
[49] P. Westerhof and A. Smit. *Rec. Trav. Chim.* **80**. 1048 (1961)
[50] R. van Moorselaar. S. J. Halkes and E. Havinga. *Ibid.* **84**. 841 (1965)