Aceton[9] ergeben 11β,17α-Dihydroxy-17β-acetoxymethyl-4-androsten-3-on (XII). Alkalische Hydrolyse von Verbindung XII führt schliesslich zu 11β,17α-Dihydroxy-17β-hydroxymethyl-4-androsten-3-on (XIII)[10].

Dass die 11-ständige Hydroxylgruppe von Verbindung XIII in β-Stellung orientiert ist, folgt aus der Bildung des Monoacetats XII unter milden Bedingungen sowie dem molaren Drehwertbeitrag der 11-Hydroxylgruppe von + 166°[11]. Durch Oxydation von XII mit Chrom-VI-oxid in wässriger Essigsäure entsteht 17α-Hydroxy-17β-acetoxymethyl-4-androsten-3,11-dion (XIV)[10].

Die nachstehende Tabelle enthält die Schmelzpunkte und optischen Drehwerte der im Text angeführten Verbindungen[12]. Weitere physikalische Daten, wie Elementaranalysen, UV- und IR-Spektren, stimmen mit den jeweils angegebenen Strukturen überein[13].

Verbindung	Fp.	$[\alpha]_D$
III	188–192°	+ 42,0°
V	202–205,5°	+ 32,0°
VI[a]	209–211°	+ 10,5°
VI[b]	207–211°	+ 9,0°
IX	229–231°	+ 188,0°
X	194–199,5°	− 5,5°[c]
XII	182–187°	+ 112,5°
XIII	156–158°	+ 122,0°
XIV	162–167°	+ 139,0°[d]

[a] Chemisch; [b] mikrobiologisch; [c] in Pyridin; [d] in Dioxan.

Summary. Starting from 17α-hydroxy-17β-hydroxymethyl-4-androsten-3-one, we synthesized 4-chloro-17α-hydroxy-17β-hydroxymethyl-4-androsten-3-one-17,20-acetonide and 17α-hydroxy-17β-hydroxymethyl-1,4-androstadien-3-one. 11β,17α-dihydroxy-17β-hydroxymethyl-4-androsten-3-one was obtained from cortisone via methyl-17α-hydroxy-3,11-dioxo-4-etienate.

A. Schubert und S. Schwarz

Wissenschaftliche Laboratorien des VEB Jenapharm, Jena (DDR), 9. Juni 1965.

[9] Zur Methode vgl. G. Rosenkranz, J. Pataki und C. Djerassi, J. org. Chem. *17*, 290 (1952).

[10] Im Niederl. Pat. 89348; Chem. Abstr. *54*, 8910 (1960) wird eine andere Synthese des 11β,17α-Dihydroxy-17β-hydroxymethyl-4-androsten-3-ons beschrieben. Physikalische Daten sind nicht angegeben. An gleicher Stelle wird auch eine Darstellung von 17α-Hydroxy-17β-acetoxymethyl-4-androsten-3,11-dion beschrieben; Fp. 161–164°; $[\alpha]_D$ + 140° (Dioxan).

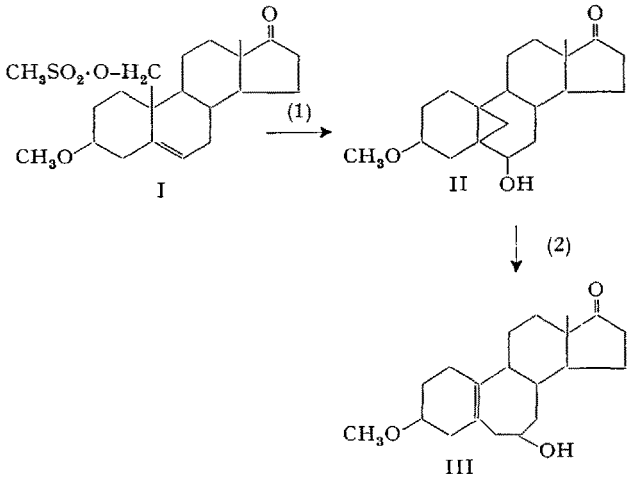
[11] Der Mittelwert aus den molaren Drehwertbeiträgen der 11β-Hydroxygruppe in Corticosteron, Hydrocortison, 11β-Hydroxyprogesteron und 11β-Hydroxytestosteron beträgt + 161°.

[12] Schmelzpunkte sind unkorrigiert; optische Drehwerte in Chloroform, soweit nicht anders vermerkt.

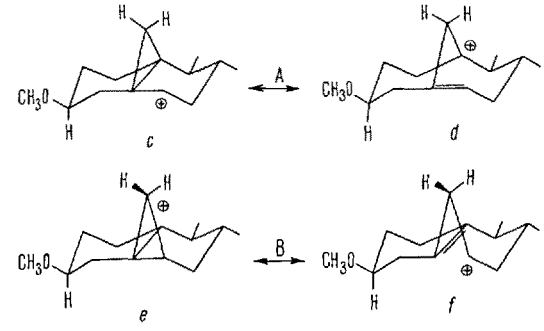
[13] Fräulein G. Kretzschmann hat uns in dankenswerter Weise bei der Durchführung der experimentellen Arbeiten unterstützt. Herrn Dr. K. Heller möchten wir für Aufnahme und Diskussion der IR-Spektren danken.

Isomeric Homoallylic Cations Formed from 19-Substituted Steroids[1]

The nature of the carbonium ion intermediates in the sequence I $\xrightarrow{(1)}$ II $\xrightarrow{(2)}$ III[2,3], involving hydrolysis (1) and acid-catalyzed rearrangement (2) has been investigated.



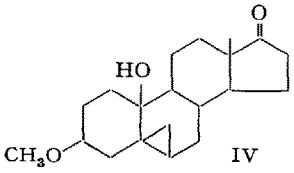
The products II and III suggested the intervention of two discrete carbonium ion intermediates: the first (A), a hybrid of the canonical structures *c* and *d*, which leads to the cyclopropylcarbinol, II, under conditions of kinetic control; and the second, B, a hybrid of *e* and *f*, formed from A under conditions of thermodynamic control, which leads to III.



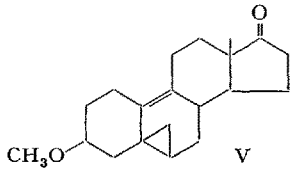
Consideration of an intermediate such as B suggested that buffered hydrolysis (kinetic control) of the methanesulfonate of III might lead to the cyclopropylcarbinol IV or a corresponding elimination product such as vinylcyclopropane V.

Attempted formation of the methanesulfonate of III employing methanesulfonyl chloride in anhydrous pyridine (3 h at room temperature) led to the isolation of an elimination product, m.p. 119–122°, $[\alpha]_D^{24}$ + 93°, the

spectral data[5] of which establish the structure as V. The nuclear magnetic resonance spectrum showed the absence of vinyl proton absorption and the presence of a complex absorption at 45 cps due to the cyclopropyl protons. The IR-spectrum confirmed the presence of the cyclopropyl ring[6] with ν_{max} 3067 cm^{-1}, while the UV-spectrum established the presence of the conjugated vinylcyclopropane chromophore[7] with λ_{max} 216 nm (ε 8400). Formation of V may be accounted for by the stereoelectronically favorable elimination of the 9α-axial proton from the intermediate B. The vinylcyclopropane, V, was smoothly converted back to the homoallylic alcohol, III, under conditions similar to those employed for the rearrangement of II to III.



IV

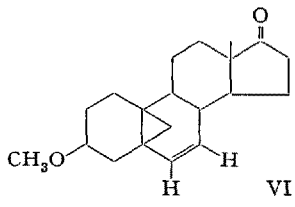


V

The interconversions of III and V provide chemical evidence that the alcohol III is homoallylic. Since the spectral data of III[2] and V show that neither has vinyl protons, the relationship of III to the cyclopropylcarbinol, II[2], and a tetrasubstituted vinylcyclopropane (V) provides convincing evidence for the structure of both III and V. The stereochemistry of III (7β-OH) is assigned[2] on the basis of its mode of formation by attack of water on the cation B *trans* to the partial bond broken in the transition state leading to product. This is analogous to the stereochemistry observed for a variety of cyclopropylcarbinyl-homoallylic conversions[8].

The rearrangement of II to III and the interconversions of III and V are analogous with regard to both structure and stereochemistry to the acid-catalyzed rearrangement of thujopsene to widdrol, the mechanism of which was recently elucidated by DAUBEN and FRIEDRICH[9].

In contrast to the behavior of III in anhydrous pyridine, treatment of the methanesulfonate (I) with refluxing pyridine for 18 h led to the isolation of the isomeric vinylcyclopropane, VI[10], m.p. 105–107°, $[\alpha]_D^{24}$ + 70° characterized by its spectral properties: ν_{max} 3025 cm^{-1} (vinyl)[11], 3063 cm^{-1} (cyclopropyl); λ_{max} 215 nm (ε 5780). The NMR-spectrum[12] exhibited the vinyl proton absorption as an AB-pattern with the low-field doublet showing additional splitting due to coupling with the proton at C_8. The peaks occurred at 315.5; 326.3: 347.3, 349.4; 357.0, 359.6 cps. The high-field cyclopropyl doublet was visible with peaks at 33.6 and 38.3 cps. Formation of VI may be accounted for by loss of a C_7-proton from the intermediate A. VI was recovered unchanged when subjected to the conditions employed for the conversion of II to III.



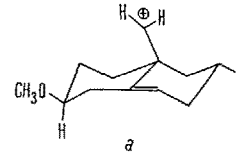
VI

Treatment of II with methanesulfonyl chloride in anhydrous pyridine (conditions identical to those employed with III) led to formation of a water-soluble product which is presumably the 5β,19-cyclo-6β-pyridinium salt (VII) formed from A. Continuous extraction of the aque-

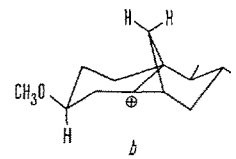
[1] This material was presented at the *Symposium on Steroids Made Through Intramolecular Functionalization on the C_{18}- and C_{19}-Methyl Groups*, at the 149th meeting of the American Chemical Society in Detroit (Michigan), on April 7, 1965.

[2] J. TADANIER and W. COLE, Tetrahedron Letters, No. 21, 1345 (1964).

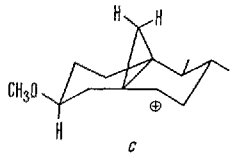
[3] The configuration at C_6 of the 5β,19-cyclo-6-ols has not yet been unequivocally established. Consideration of the canonical structures *a* through *d* of a non-classical ion formed by participation of the Δ^5-double bond indicates that to the extent that *b*, and thus 6β,19-bridging is important, the 6α-ol would be expected. This would require a short C_6-C_{19} distance, and the stabilization gained by delocalization would be offset by the strain of the resulting bicyclobutonium ion.



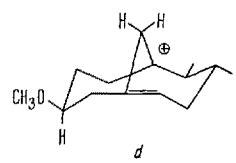
a



b

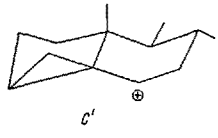


c

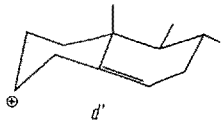


d

The canonical structures of *c* and *d* are analogous to the canonical structures *c'* and *d'* of the stable, homoallylic, 3α,5α-cyclo cation. Reactions of the latter intermediate at C_6 are known to occur stereospecifically with β attack of a nucleophile which preserves maximum overlap of the *p*-orbitals at C_5 and C_6 in the transition state leading to product[4]. A similar stereoelectronically controlled process operating on a cation with major contributions from canonical structures *c* and *d* would accordingly be expected to lead to the 5β,19-cyclo-6β-hydroxysteroid. A Dreiding model of *d*, used as an approximation to the geometry of the cation, indicates that β-attack of a nucleophile would also be favored sterically. The 6β-hydroxy orientation of the hydrolysis product, II, is in accord with the half-widths of the C_6-proton absorptions in the NMR-spectra of epimeric 6-hydroxy-5β,19-cyclosteroids provided the B-rings exist as half-chairs[2].



c'



d'

[4] This type of stereoelectronic control is discussed by WHITHAM in regard to solvolytic formation of 6β-hydroxy-3β,5β-cyclosteroids from the corresponding homoallylic cation. G. H. WHITHAM and (in part) J. A. F. WICKRAMASINGHE, J. chem. Soc. *1964*, 1655.

[5] IR-spectra were determined with carbon tetrachloride solutions, UV-spectra were determined in absolute methanol, and optical rotations were determined with 1% solutions in chloroform. The NMR-spectra were determined with a Varian A-60 spectrometer with solutions in deuteriochloroform using tetramethylsilane as an internal reference. All compounds reported had satisfactory analyses for carbon and hydrogen.

[6] M. HORÁK, J. ŠMEJKAL, and J. FARKAS, Coll. Czech. chem. Comm. *28*, 2280 (1963).

[7] J. W. ROWE, A. MALERA, D. ARIGONI, O. JEGER, and L. RUZICKA, Helv. chim. Acta *40*, 1 (1957).

[8] E. M. KOSOWER and S. WINSTEIN, J. Am. chem. Soc. *78*, 4347 (1956). – W. F. JOHNS, J. org. Chem. *29*, 1490 (1964).

[9] W. G. DAUBEN and L. E. FRIEDRICH, Tetrahedron Letters, No. 38, 2675 (1964).

[10] Formation of 5β,19-cyclo-6-enes from Δ^5-19-sulfonate esters in refluxing pyridine has been previously reported by (a) J. J. BONET, H. WEHRLI, and K. SCHAFFNER, Helv. chim. Acta *45*, 2615 (1962) and (b) O. HALPERN, P. CRABBÉ, A. D. CROSS, I. DELFIN, L. CERVANTES, and A. BOWERS, Steroids *4*, 1 (1964).

[11] K. NAKANISHI, *Infrared Absorption Spectroscopy – Practical* (Holden-Day Inc., San Francisco 1962), p. 24.

[12] Compare reference [10b].

ous solution with chloroform led to the isolation of VI. Formation of VI from VII most probably occurs via a Hofmann-type elimination.

These data conclusively demonstrate the existence of two discrete carbonium ion intermediates under conditions of the elimination reaction and provide strong evidence for their intervention under the solvolysis conditions in the sequence I → II → III. The difference between these two intermediates must lie in their different internuclear distances and in the orientation of the C_{19}-methano bridge[13].

Zusammenfassung. Die Existenz von zwei verschiedenen isomeren Homoallylkationen in der Umlagerung von Steroid-Δ^5-19-Methansulfonsäure-Estern zu 5β,19-cyclo-6-hydroxylierten Steroiden und deren Umlagerung zu $\Delta^5(^{10})$-B-homo-7-hydroxylierten Steroiden wurde bewiesen, und eine neue Art der Homoallylumlagerung eines $\Delta^5(^{10})$-B-homo-7-hydroxylierten Steroids zum 5β,6β-Methano-9-en und zum 5β,6β-Methano-10β-ol wurde beobachtet.

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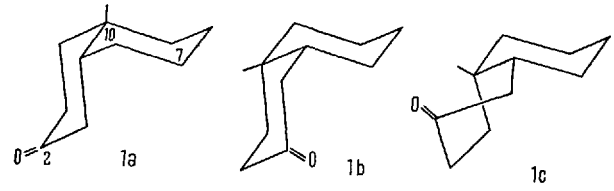
Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago (Illinois USA), May 31, 1965.

[13] Acknowledgment: The author is indebted to Mr. W. WASHBURN for the IR-spectra, Dr. R. W. MATTOON for NMR-spectra, Mr. J. SUTHERLAND for UV-spectra, and Mr. O. KOLSTO for analyses.

Conformational Studies of *cis*-10-Methyl-2-decalones

In the past eight years, the conformation equilibrium of *cis*-10-methyl-2-decalone (1) has been evaluated by conformational concepts[1] and by ORD measurements[2]. On the basis of the conformational postulates it was suggested that such a ketone would assume the *non-steroidal* conformation 1b, but subsequently the *steroidal* conformation 1a was indicated on the basis of ORD studies. Recently, this problem was reinvestigated[3] and ORD and temperature dependent circular dichroism measurements were performed on *cis*-7,7,10-trimethyl-2-decalone and on *cis*-7α-isopropyl-10β-methyl-2-decalone. These studies led the investigators to the conclusion that in these substituted *cis*-10-methyl-2-decalones the *non-steroidal* all-chair conformation 1b probably played an unimportant role in the conformational equilibrium and a twist conformation (for example 1c) was favored. It was also suggested that the only other and rather remote possibility was that the 'non-steroid' conformer 1b was indeed predominant and the Cotton curve was controlled by a smaller amount of a conformer with an extremely powerful amplitude. This possibility has now been evaluated and, indeed, shown to be correct.



In conformations 1a, 1b, and 1c, the relative position of the C-10 methyl group with respect to the carbonyl group is different and the position of the methyl group should be indicated by its chemical shift in its NMR-spectrum. For example, in the steroids it has been found that when the C-19 methyl group is axial to the ring (in a chair conformation) having a carbonyl group at C-3 (i.e. A/B-*trans*-3-keto-steroid) its resonance band is shifted downfield by 0.22 ppm as compared to the chemical shift of the C-19 methyl group in the parent hydrocarbon[4-6]. When the C-19 methyl group is equatorial to the ring (in a chair conformation) the downfield shift is only 0.11 ppm. On the other hand, in a *twist* conformation the C-19 methyl group is diamagnetically shielded by the C-3 carbonyl group and its resonance band is approximately at the same position as in the parent hydrocarbon[6].

In order to employ this method of analysis in the *cis*-10-methyl-2-decalone series, it was first necessary to see if these simple models of steroids followed the downfield paramagnetic shift. The data obtained are summarized in the Table.

Chemical shifts of C_{10}-methyl protons[a]

Compound	τ (ppm)	Δ ppm (one-ane)	Compound	τ (ppm)	Δ ppm (one-ane)
A/B-*trans*			A/B-*cis*		
Cholestane	9.23		Coprostane	9.08	
3-keto	9.01	−0.22	3-keto	8.97	−0.11
10-Methyl-decalin	9.17		10-Methyl-decalin	9.05	
2-keto	8.97	−0.20	2-keto	8.83	−0.22
4-keto	8.93	−0.24	4-keto	8.83	−0.22
			2-keto-7,7-dimethyl	8.76	−0.29
			7α-Isopropyl-10β-methyl-decalin	9.05	
			2-keto	8.78	−0.27

[a] The spectra were obtained with carbon tetrachloride solutions and calibrated with tetramethylsilane as an internal standard.

[1] W. KLYNE, Exper. *12*, 119 (1956).
[2] C. DJERASSI and D. MARSHALL, J. Am. chem. Soc. *80*, 3986 (1958).
[3] C. DJERASSI, J. BURAKEVICH, J. W. CHAMBERLIN, D. ELAD, T. TODA, and G. STORK, J. Am. chem. Soc. *86*, 465 (1964).
[4] R. F. ZÜRCHER, Helv. chim. Acta *44*, 1380 (1961).
[5] E. R. MALINOSKI, M. S. MANHAS, G. H. MÜLLER, and A. K. BOSE, Tetrahedron Letters *1963*, 1161.
[6] M. GORODETSKY and Y. MAZUR, Tetrahedron Letters *1964*, 227.