process. Due to the increased charge density on the pore wall, the diffusion of Cl^- is more restricted.

The increased transfer of calcium, seen under the same conditions as the decreased transfer of chloride, may have the same cause: the increase of negative charges in the pores caused by an increase in fixed anions in the pores. If the movement of calcium through membranes does not occur mainly by diffusion but involves intermediate reactions with fixed anionic groups in the walls of the pores (DUMONT et al.[39]), an increase in these fixed anionic groups by mersalyl could result in an increased transfer of calcium. Hydrochlorothiazide cannot act by the same mechanism, because the calcium absorption is inhibited, not activated. Apart from its interpretation regarding mode of action, the difference between mersalyl and hydrochlorothiazide may be helpful for further investigations.

Zusammenfassung. (1) Unter dem Einfluss von Mersalyl (5×10^{-4} *m*) und Hydrochlorothiazid (2×10^{-3} *m*) nimmt die Cl-Konzentration in der resorbierten Flüssigkeit ab, während die Na-Konzentration gleich bleibt und die Glucose-Konzentration ansteigt. Gleichzeitig kommt es zu einer osmotisch äquivalenten Einschränkung der Wasserresorption.

(2) Die prozentuale Hemmung der Wasserresorption durch Mersalyl nimmt zu bei höherer Cl^--Konzentration in der angebotenen Flüssigkeit und hängt zwischen pH 6,5 und 7,4 nicht von der H^+-Konzentration ab.

(3) Die Wirkung von Mersalyl lässt sich mit Cystein aufheben und ist auch *in vivo* an der abgebundenen Darmschlinge nachweisbar.

(4) Der Glucosetransport und die Calciumresorption werden durch Mersalylkonzentrationen, die die Wasser- und Natriumresorption um 30% hemmen, nicht beeinträchtigt. Der Durchtritt von Calcium durch die Darmwand ist auf das 1,5fache erhöht, es häuft sich dabei in der resorbierten Flüssigkeit an.

(5) *p*-Chloromercuribenzoat hemmt in Konzentrationen, die die Natrium- und Wasserresorption um 40% vermindern, den Glucosetransport ebenfalls um 40%. Im Unterschied zu Mersalyl setzt es die Cl^--Konzentration der resorbierten Flüssigkeit nicht herab.

[39] P. A. DUMONT, P. F. CURRAN, and A. K. SOLOMON, J. gen. Physiol. *43*, 1119 (1960).

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

Steroidal Cyclic Ketals[1]: The Preparation of Steroidal Δ^4-3-Ethyleneketals

Ketalization of steroidal Δ^4-3-ketones by the Salmi method[2] gives Δ^5-3-ethyleneketals[3–5]. We now describe a modification of this procedure which gives Δ^4-3-ethyleneketals.

When oxalic acid was substituted for *p*-toluenesulfonic acid as the catalyst in a series of ketalization reactions of Δ^4-3-ketones (see Table), the product was found to be either the Δ^4-3-ethyleneketal or a mixture of the Δ^4- and Δ^5-3-ethyleneketals. When the weaker adipic acid was used as the catalyst only the Δ^4-3-ethyleneketal was obtained. The presence of the Δ^4-3-ethyleneketal grouping was established when oxidation of 3,20-bis-ethylenedioxypregn-4-ene with osmium tetroxide in pyridine[6] gave 3,20-bis-ethylenedioxypregnane-4ξ,5ξ-diol from which the known[7] 4-hydroxyprogesterone was obtained by treatment with formic acid.

These Δ^4-3-ethyleneketals exhibit a sharp, weak band in the infrared at about 1668 cm^{-1} which is not shown by Δ^5-3-ethyleneketals. The Δ^4-3-ethyleneketals are stable to base but they are extremely sensitive to acid. In contrast to Δ^5-3-ethyleneketals, they are hydrolyzed almost quantitatively in benzene by magnesium sulfate, and, by comparison of the ultraviolet absorption before and after such treatment of a sample, this was found to be an excellent method of determining the proportions of Δ^4-3-ethyleneketal and Δ^5-3-ethyleneketal in a crude reaction mixture.

DJERASSI and GORMAN[8] proposed a mechanism for the formation of Δ^5-3-ethyleneketals in which an intermediate 3,5-dienol ether I is formed which ring-closes by 1,2-addition to the 3,4-double bond to give the Δ^5-3-ethyleneketal II. Similarly, the preparation of Δ^4-3-ethyleneketals IV probably involves the formation of an intermediate

[1] Paper XXIV; paper XXIII see S. BERNSTEIN and R. LITTELL, J. org. Chem. *26*, 3610 (1961).

[2] E. SALMI, Ber. dtsch. chem. Ges. *71*, 1803 (1938).—E. SALMI and V. RANNIKKO, Ber. dtsch. chem. Ges. *72*, 600 (1939).

[3] R. ANTONUCCI, S. BERNSTEIN, R. LITTELL, K. J. SAX, and J. H. WILLIAMS, J. org. Chem. *17*, 1341 (1952).

[4] E. FERNHOLZ, U.S.P. 2356154/1944 and U.S.P. 2378918/1945.—E. FERNHOLZ and H. E. STAVELY, Amer. chem. Soc. Meeting, Atlantic City (Sept. 1941), Abs. Papers, 39M.

[5] G. I. POOS, G. E. ARTH, R. E. BEYLER, and L. H. SARETT, J. Amer. chem. Soc. *75*, 422 (1953).

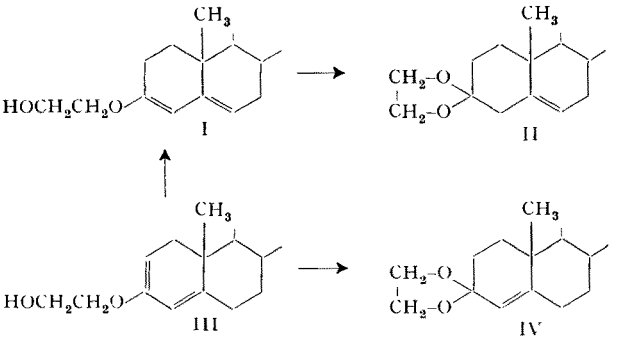
[6] J. S. BARAN, J. org. Chem. *25*, 257 (1960).

[7] R. H. BIBLE, Jr., C. PLACEK, and R. D. MUIR, J. org. Chem. *22*, 607 (1957).

[8] C. DJERASSI and M. GORMAN, J. Amer. chem. Soc. *75*, 3704 (1953).

2,4-dienol ether III with subsequent ring-closure by 1,2-addition to the 2,3-double bond[9].

It is possible that the intermediate III is also involved in the preparation of Δ^5-3-ethyleneketals. By analogy to the isomerization[10] of cholesta-2,4-diene to cholesta-3,5-diene by mineral acids in either polar or non-polar solvents, the intermediate 2,4-dienol ether III could rearrange to the intermediate 3,5-dienol ether I under the influence of the *p*-toluenesulfonic acid[11] used as the catalyst in the reaction. Thus the formation of a Δ^4-3-ethyleneketal or of a Δ^5-3-ethyleneketal would depend on the rate of ring-closure of the 2,4-dienol ether III *versus* the rate of isomerization of the double bonds. This possibility is being examined further.



Compound	Catalyst	Product	% yield[a]
Reichstein's Substance S	A[b]	Δ^4-3-ethyleneketal	74
	O[c]	Δ^4-3-ethyleneketal	(24)
		Δ^5-3-ethyleneketal	45(72)
Progesterone	A	Δ^4-3-ethyleneketal	10
	O	Δ^4-3-ethyleneketal	6
		Δ^4-3,20-bisethyleneketal	30
		20-ethyleneketal	21
Testosterone	A	Δ^4-3-ethyleneketal	64
	O	Δ^4-3-ethyleneketal	59
		Δ^5-3-ethyleneketal	28
6-Dehydrotestosterone	A	$\Delta^{4,6}$-3-ethyleneketal	14(55)
Androst-4-ene-3,17-dione	A	no reaction	—
	O	Δ^4-3-ethyleneketal	30–40
		Δ^4-3,17-bisethyleneketal	10
Hydrocortisone 21-acetate	A	Δ^4-3-ethyleneketal	70
	O	Δ^4-3-ethyleneketal	(55)
		Δ^5-3-ethyleneketal	23(27)
Cortisone 21-acetate	A	Δ^4-3-ethyleneketal	74
	O	Δ^4-3-ethyleneketal	28
		Δ^5-3-ethyleneketal	67
21-Acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione	A	Δ^4-3-ethyleneketal	77
	O	Δ^4-3-ethyleneketal	65
16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-pregn-4-ene-3,20-dione	A	Δ^4-3-ethyleneketal	50

[a] Figures in parenthesis are based on ultraviolet absorption data
[b] A = adipic acid
[c] O = oxalic acid

Zusammenfassung. Ersatz von *p*-Toluolsulfosäure durch Oxal- oder, bevorzugt, Adipinsäure in Salmis Methode für die Synthese von Δ^5-3-Äthylendioxysteroiden führt zu Δ^4-3-Äthylendioxysteroiden.

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Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River (New York, U.S.A.), March 7, 1962.

[9] G. J. FONKEN, J. org. Chem. *26*, 2549 (1961), suggested a similar mechanism for the formation of the $\Delta^{4,6}$-3-ethyleneketals of cholesta-4,6-dien-3-one and ergosta-4,6,22-trien-3-one using *p*-toluenesulfonic acid as catalyst.

[10] H. E. STAVELY and W. BERGMAN, J. org. Chem. *1*, 575 (1936).

[11] However, we have found that ketalization of 6α,17β-diacetoxy-androst-4-en-3-one using *p*-toluenesulfonic acid as catalyst gives the corresponding Δ^4-3-ethyleneketal in high yield.

Liberation of Mechanical Tension by Heating of Collagen Fibres

Collagen fibres (such, for example, as the isolated fibres from the rat's tail tendons) show a shrinkage of 70–75% above 58°C ('thermic contraction'). This can be inhibited by weights, the size of which is related to the age of the animal[1].

It was observed that if the thermic contraction of a fibre is inhibited by a certain load, the fibre does not lose the capacity of thermic contraction, inspite of the high temperature.

If such a fibre with a contraction-inhibiting load of several g is transferred from 65°C to 20°C (in Ringer's solution), the load can be taken off and the fibre still keeps its original length. If then without a load (or with only 0.1 g load for stretching) it is heated again to above 58°C, a maximal thermic contraction occurs.

Such observations may lead to the surprising conclusion that the influence of heat on the crystalline structure of the collagen macromolecule can be inhibited by mechanical stretching.

Instead of using the estimation of the load which inhibits thermic contraction ('isotonic method'), we have evolved a method for measuring the tension at constant length ('isometric method')[2].

Fibres of 5 cm length from the rat's tail tendon were placed in Ringer's solution, and their tension was continuously registered while they were heated in a water bath. It was seen that the maximal tension is evolved at the point at which relaxation begins. If the heating of the fibre is interrupted at a lower temperature (62–65°C), only a *partial tension* is liberated. Such fibres can be cooled to 20°C and their tension brought back to 0. A second heating above 58°C then liberates the *remaining tension*, which will be reached at the point at which relaxation begins. The Table shows examples with tendons of animals of different ages. The sum of tension at the first and second heatings is identical with the *maximal tension*, which can,

[1] F. VERZÁR, Helv. physiol. Acta *13*, 64 (1955); *14*, 207 (1956); Gerontologia *1*, 363 (1957).

[2] J. BROCAS and F. VERZÁR, Gerontologia *5*, 223 (1961).