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THE 5β-CHOLAJERVENES[1] ISOMERIC AT C-13

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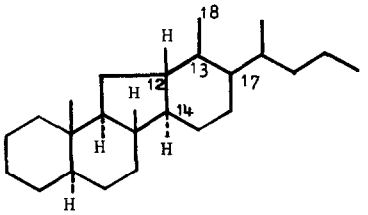
Recently we reported (1) that the epimeric 12-cholanol mesylates and 12-oxocholane tosylhydrazone all undergo rearrangement reactions to yield Δ^{12}-5β-cholajervene[1] (I) as the major rearrangement product.

Further efforts to separate products of the reactions by chromatography on silver nitrate-impregnated alumina have been rewarded by the isolation of two more compounds, olefins II and III. We will present here evidence that II and III are other Δ^{13}-isomers of I, and describe some interconversions among the three olefins.

Olefins II ($C_{24}H_{40}$, M^+ 328, mp. 36.0-37.2°, α_D +57°)[2], isolated and purified by repeated column chromatography, gives a positive tetranitromethane test, has

[1] The official IUPAC nomenclature for C_{24}-C-nor-D-homo steroids is cumbersome, and adaptation of etiojervane as parent compound leads to other complications. We propose "cholajervane" for the C_{24} compounds to accompany the trivial names jervane (C_{27}) and etiojervane (C_{19}) which are generally in accepted use (2), and define for it the following configuration and numbering:



The proposed configuration follows the prior convention of Kupchan [J. Org. Chem., 33, 647 (1968)] at C-12 and C-13 for etiojervane, with the normal cholestane configuration at other centers.

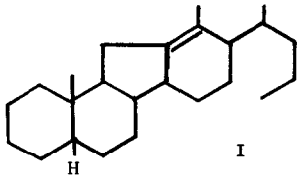
Drs. W. F. Johns (Searle) and T. Masamune (Hokkaido) in the interests of a uniform nomenclature have expressed a willingness to subscribe to this convention, which would automatically define etiojervane and jervane, and other potential homologs. In addition, other investigators who have previously published in this area, Drs. J. Fried (Chicago), J. Huffman (Clemson), W. S. Johnson (Stanford), H. Mitsuhashi (Hokkaido) and S. M. Kupchan (Wisconsin) endorse this proposal (private communications).

It has been suggested further that a similar trivial name be adopted for the C_{21} analog; "pregnajervane" would be a logical choice (as a substitute for 17-ethyletiojervane).

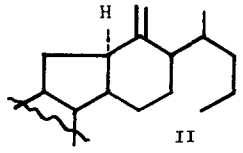
[2] Satisfactory elemental analyses have been obtained for all new compounds. Optical rotations were determined in $CHCl_3$ at 25°; NMR spectra in $CDCl_3$, except where stated, with Me_4Si as internal standard.

a strong infrared absorption band at 11.23μ, and exhibits NMR signals at 4.83 and 5.30τ [each a slightly perturbed 1H singlet (3)] and at 8.93τ (sharp singlet, ~3H, C-19 Me); properties consistent for an exocyclic olefin of structure II.

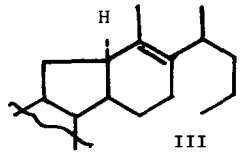
Olefin III ($C_{23}H_{40}O$; M^+ 328, α_D -76°), although obtained homogeneous by TLC and GLC, has so far resisted attempts at crystallization. It also gives a positive tetranitromethane test, but shows no olefinic characteristics in its IR spectrum. In its NMR spectrum, resonance in the olefin region is absent, but 3-proton sharp singlets are present at 8.37 (vinyl Me) and 9.15τ (C-19 Me). A broad quadruplet centered at 7.43τ (1H, C-20, allylic) is shown by double irradiation to be coupled with a doublet centered at 9.08τ (3H, J=7 cps, C-21 Me), indicative that the C-17 side chain is attached to the double bond.



I



II



III

Characterization of the corresponding diol and ketone derived from each olefin confirms that II and III are $\Delta^{13(18)}$- and $\Delta^{13(17)}$-cholajervene[3], respectively. Each olefin on dihydroxylation (OsO_4) yielded a single product, which in turn was oxidized to a ketone.

II-diol, $C_{24}H_{42}O_2$; M-18[4], 344; mp. ca. 121° (dec.); α_D +37°; λmax(CS_2) 2.78, 2.88 and 9.67μ; NMR (CCl_4): quadruplet[5] centered at 6.46τ (J=11cps, 2H, C-18), singlet[6] at 9.09τ. II-mono ketone, $C_{23}H_{38}O_2$; M^+ 330; mp. 39.8-41.0°; α_D +14°; λmax(CS_2) 5.83μ (6-ring C=O); NMR: singlet[6] at 9.11τ.

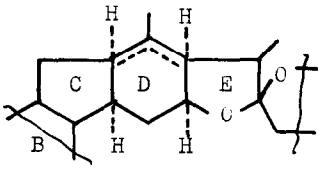
III-diol, $C_{24}H_{42}O_2$; M^+ 362; mp. 166.2-167.0°; α_D -3.5°; λmax(CS_2) 2.75μ; NMR: singlet at 8.77 (3H, C-18 Me) and 9.05τ (3H, C-19 Me), no resonance below 7.4τ. III-dione, $C_{24}H_{40}O_2$, M^+ 360; mp. 68.0-68.6°, α_D -49°; λmax(CS_2) 5.8μ (6-ring or aliphatic C=O); NMR: singlets at 7.83 (3H, Me alpha to C=O) and 9.07τ (3H, C-19 Me).

3 Tentative assignment of 12α-H to II and III, in analogy with sapogenin results.
4 M^+ nearly absent; characteristic of tertiary alcohols [R. A. Friedel, J. L. Shultz, and A. G. Sharkey, Anal. Chem., 28, 926 (1956)].
5 Due to non-equivalence of the two C-18 protons of the hydroxymethyl group (R. H. Bible, Guide to NMR Empirical Method, p. 225, Plenum Press, N. Y., 1967).
6 Each singlet of the II-diol and II-one represents about 8 protons (integration), and is assigned to C-19 methyl and contributions from C-21 and C-24 methyl.

Two additional sets of evidence afford further support for the structural assignments: olefins II and III are aromatized by palladium-cymene treatment (4) to the same[7] aromatic compound derived from I, a derivative shown by NMR to have two aromatic protons (1); and I by formic acid equilibration of 62° is converted to III, while II at 25° is isomerized to a mixture of I and III[8].

Isolation of the three olefins isomeric at C-13, and isomerization of I and II into III are of special interest in relation to the findings in the analogous sapogenin rearrangements (5,6). In that work, repeated in several laboratories, only two rearranged olefins were found: One (IIa[9]) had an exocyclic double bond corresponding to structure II; the other, originally (5) considered to be IIIa has been proved to be Ia (6). Acid equilibration of IIa yielded Ia in good yield (5a); the $\Delta^{13(17)}$-isomer is unknown.

With the cholajervenes, exo to endo isomerization under equilibrating conditions would be expected (7), and of the two endo possibilities, I with the double bond exocyclic to the 5-membered ring, should be less stable than III. Rationalization of the results of equilibration in the sapogenin series is more speculative. The stabilities of the two possible endo olefins represented by the partial formula,



predicted on the basis of steric strain, or degree of substitution (7), should not be substantially different, and any difference should be in favor of the olefin exocyclic to ring E, which is held less rigidly than the one exocyclic to the C ring (fused to the A and B ring). One might expect both isomers to be present in equilibrium[10].

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7 Confirmed by TLC and GLC, and isolation.
8 Confirmed by TLC, and conversion to and isolation of diols I and III.
9 Ia, IIa, IIIa are used to designate the sapogenin compounds corresponding in double bond positions to I, II and III.
10 A polar effect of the oxygen atom of the E ring could conceivably be operative [$HOCH_2$-CH=CH_2 was reported to be 1.2 Kcal more exothermic than CH_3CH_2-CH=CH_2 in hydrogenation (R.W. Taft, Jr. and M. M. Kreevoy, J. Am. Chem. Soc., 79, 4011, 1957]

The 12α-mesylate and 12-oxo tosylhydrazone reactions yield the same products, 11-cholene, I and III, but in different proportions, whereas 12β-mesylate yields I, II and III. Discussion of possible mechanistic implications from these results are reserved for a full paper; Table I is a summary of the results:

TABLE I

5β-Cholane Derivative	Reaction		% Yield[12] of Olefinic Products			
	Reagent	Duration[11] in minutes	11-cholene	I	II	III
12α-mesylate	Collidine (1)	180	40	32	0	15
12β-mesylate	Collidine (1)	60	0	35	30	25
12-oxo tosylhydrazone	Na-ethylene glycol (5b)	60	24	26	0	8

[11] Prolonged reflux produced only trace changes in the proportions of the main products (other unidentified olefins were present in minor amounts).
[12] Estimated by GLC and TLC (precision ±5% of values given).

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