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Thermal isomerization of steroid-boranes

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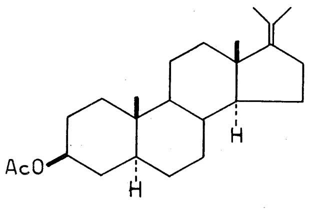
Chimica organica. — *Thermal isomerization of steroid-boranes* (*). Nota di Enrico Mincione (**) e Stefano Corsano (***), presentata (****) dal Socio L. Panizzi.

RIASSUNTO. — I composti organoboranici derivati dai due steroidi insaturi (I) e (II) sono stati sottoposti ad isomerizzazione termica.

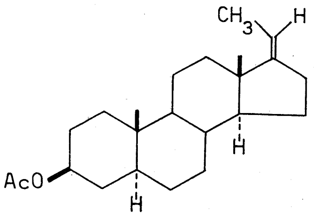
L'organoborano (III) derivante da (I) ha fornito esclusivamente, dopo ossidazione con H_2O_2, il 16-ossi-pregnano (VI).

L'organoborano (XX), derivante da (II) ha fornito come prodotto principale il 21-ossi-pregnano caratterizzato come acetil-derivato (XIII), oltre a piccole quantità del 16-ossi-pregnano (XV).

The thermal isomerization of organoborane compounds extensively studied by Brown and coworkers [1] has found so far only limited application in the steroid field [2, 3]. We report the results obtained in the hydroboration, followed by thermal isomerization, of compounds (I) and (II).



I



II

The pregnene (I) was treated at 0° with externally generated diborane; the initially formed borane (III) (hydroboration of hindered tetrasubstituted olefins like (I) proceeds with an excess of diborane to the monoalkylborane stage [4]), was oxidized with alkaline hydrogen peroxide: the diol (IV) obtained was directly converted by acetylation into the 3 acetate (V) m.p. 196–198°, identical with an authentic sample. Isomerization of the borane (III) in diglyme at 160° for 6 h, followed by oxidative work-up, gave with high yield only the diol (VI) which by acetylation afforded the diacetate (VII) m.p. 119–121° (1).

Evidence for the 16 position of the acetate group on ring D has been obtained as follows: chromic oxidation of diol (VI) yielded diketone (VIII) m.p. 115–117°. The presence of the IR band at 1740 cm^{-1} showed that one of the C=O groups of the diketone (VIII) must be on the ring D.

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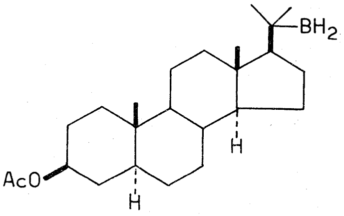
(****) Nella seduta del 15 novembre 1969.

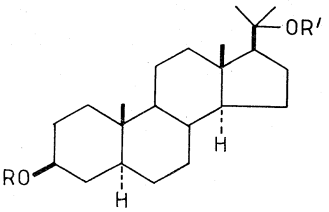
(1) Satisfactory analyses have been obtained for all new compounds reported.

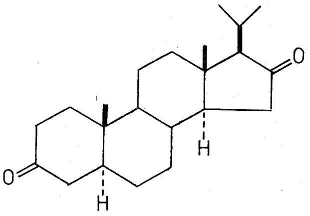
Selective reduction of (VIII) at C_3 with $NaBH_4$, followed by acetylation, afforded the keto-acetate (IX) m.p. 155–158°.

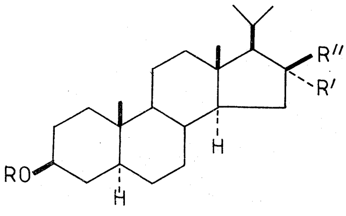
The D.O.R. curve of (IX) showed a very high *negative* Cotton effect (though at 324 mμ, Φ —11740°) specific for 16 ketosteroids [5] with the 17 β lateral chain (2).

The configuration at C_{16} of the acetate group of (VII) was shown to be α by the NMR spectra: the C_{18} methyl resonance of (VII) is at 0,69 δ and that of its 16 β epimer (X) m.p. 136–138°, obtained by reduction with an excess of $NaBH_4$ of diketone (VIII) (3), followed by acetylation, is at 0,81 δ, consistent with the deshielding effect of 16 β acetate group [7].


III


IV R=R′=H
V R=Ac R′=H


VIII


VI R=R″=H ; R′=OH
VII R=Ac ; R′=OAc ; R″=H
IX R=Ac; R′=R″= >O
X R=Ac ; R′=H ; R″=OAc

Migration of the boron atom of the organoborane (III) to position 16 was unexpected since Krubiner *et al.* [3] have observed that the thermal isomerization of borane (XI) involves even at 160° only a shift from position 20 to 21. Moreover there is a tendency for the boron atom, even for alkylcyclopentylboranes, to accumulate in the exocyclic positions [8].

In order to obtain more information on the thermal isomerization of boranes derived from steroids with an unsaturated lateral chain, the olefin (II) was hydroborated at 0°.

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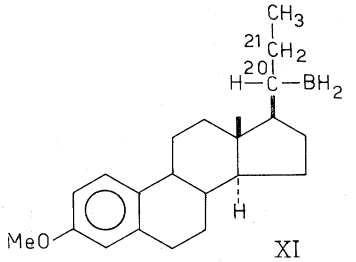
(2) 15 ketosteroids with a 13 β–14 α junction show a *positive* Cotton effect [5].

(3) Reduction by metal hydrides of 16 ketosteroids affords mainly the 16 β hydroxy epimer [6].

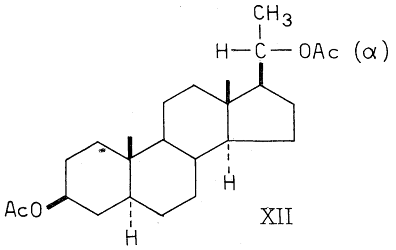
Oxidative work-up followed by acetylation afforded the 3–20 diacetate (XII), identical with an authentic sample, according to the diborane approach from the bottom side. The organoborane (XX) derived from (II) (4) was heated at 160° for 20 h (its isomerization occurred at a slower rate than for (III)). Oxidative work-up followed by acetylation afforded two products in the ratio of 85 : 15.

The main product was the 3–21 diacetate (XIII) m.p. 127–130° $[\alpha]_D+4{,}5°$; (reported m.p. 132–133° $[\alpha]_D+2{,}5°$ [9]); NMR spectrum: triplet at 4,05 δ; J = 7 c.p.s. 2 H, —CH_2—O—Ac.

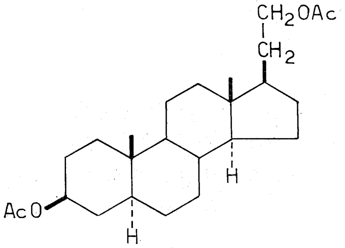
The minor component m.p. 151–153°, was demonstrated to be the 3–16 α diacetate (XIV) by the same way used for compound (VII): (XIV) was reduced with $LiAlH_4$ to diol (XV) m.p. 254–258° which by oxidation with CrO_3 to the diketone (XVI) and subsequent selective reduction by $NaBH_4$ yielded ketol (XVII) m.p. 174–178° (IR spectrum ν max 1740 cm^{-1}). Its D.O.R. curve showed a negative Cotton effect. (Though at 324 mμ Φ —10470°).



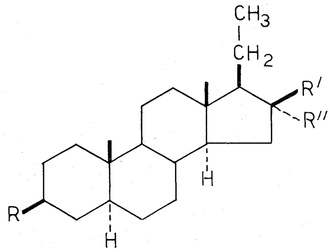
XI



XII



XIII



XIV R = R'' = OAc ; R' = H
XV R = R'' = OH ; R' = H
XVI R = >O ; R' = R'' = >O
XVII R = OH ; R' = R'' = >O
XVIII R = R' = OAc ; R'' = H

Since in the NMR spectrum of the 16 β epimer (XVIII) m.p. 169–173° obtained by reduction with an excess of $NaBH_4$ of diketone (XVI) and subsequent acetylation, the C_{18} methyl resonated at lower fields (0,72 δ) than the corresponding signal of (XIV) (0,68 δ), the acetate group of (XIV) must have an α configuration.

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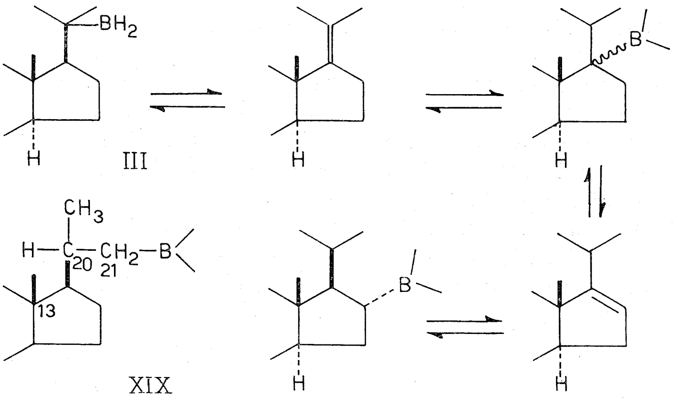
(4) Hydroboration of the trisubstituted olefins like (II) affords dialkylboranes.

Thus the organoborane derived from olefin (II) places likewise, although with lower field, the boron atom (oxygen precursor) at position 16.

A possible isomerization path of borane (III) according to the mechanism proposed by Brown *et al.* [10] is reported in chart 1.

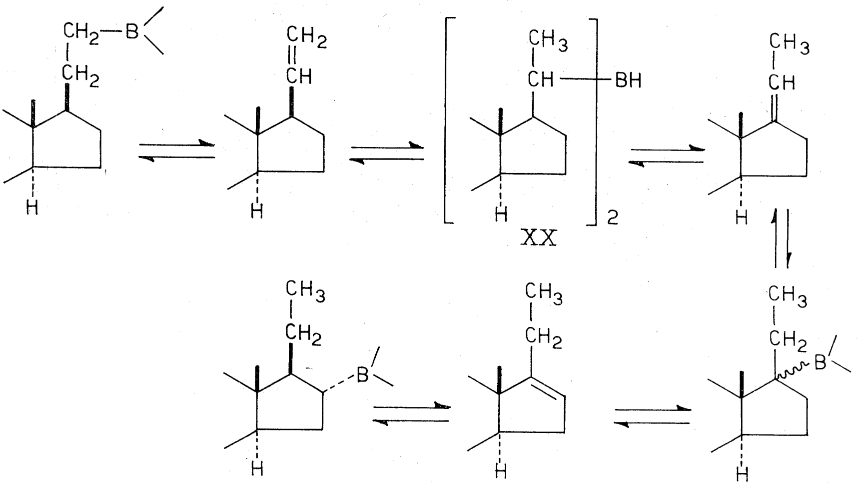
CHART 1.



Since the boron atom prefers the less hindered positions [10], the absence of the organoborane (XIX) at the primary C_{21} position could be attributed to the great steric crowding produced by the two methyls at C_{20} and at C_{13}.

A probable isomerization sequence for the organoborane (XX) derived from (II) is reported in chart 2.

CHART 2.



In this case boron atom clearly prefers the less hindered primary position at C_{21}.

The results so far obtained show that in the thermal isomerization of steroid-boranes like (III) and (XX) the boron atom prefers between position 15 and 16 on ring D the 16 α position.

New investigations are in progress in this interesting area of study.

These thermal isomerizations could be an useful tool for the synthesis of steroids substituted at position 16.

REFERENCES.

[1] H. C. BROWN, «Hydroboration», Benjamin N. Y. 1962, pp. 136–149.
[2] J. E. HERZ, L. MARQUEZ and E. GONZALES, «Chem. Comm.», *1095* (1967).
[3] A. M. KRUBINER, N. GOTTFRIED and E. P. OLIVETO, « J. Org. Chem. », *33*, 1715 (1968).
[4] H. C. BROWN, «Hydroboration», Benjamin, N. Y. 1962, pp. 164–167 and p. 174.
[5] C. DJERASSI, *Optical Rotatory Dispersion*, Mc Graw–Hill N. Y., 1960, p. 44.
[6] S. BERNSTEIN, M. HELLER and M. S. STOLLER, « J. Am. Chem. Soc. », *77*, 5327 (1955).
[7] A. D. CROSS and P. G. CRABBÉ, « J.A.C.S. », *86*, 1221 (1964).
[8] H. C. BROWN and G. ZWEIFEL, « J.A.C.S. », *89*, 561 (1967).
[9] CH. MEYSTRE and K. MIESCHER, «Helv. Chim. Acta», *27*, 1153 (1944).
[10] H. C. BROWN, «Hydroboration», Benjamin N. Y. 1962, p. 143.