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STEROID ALKALOIDS CLXX (1). BACKBONE REARRANGEMENT XV (2). ON THE 1,2 HYDRIDE SHIFTS.

J. Thierry, F. Frappier, M. Païs and F.-X. Jarreau

Institut de Chimie des Substances Naturelles du CNRS, 91190-Gif/Yvette (France)

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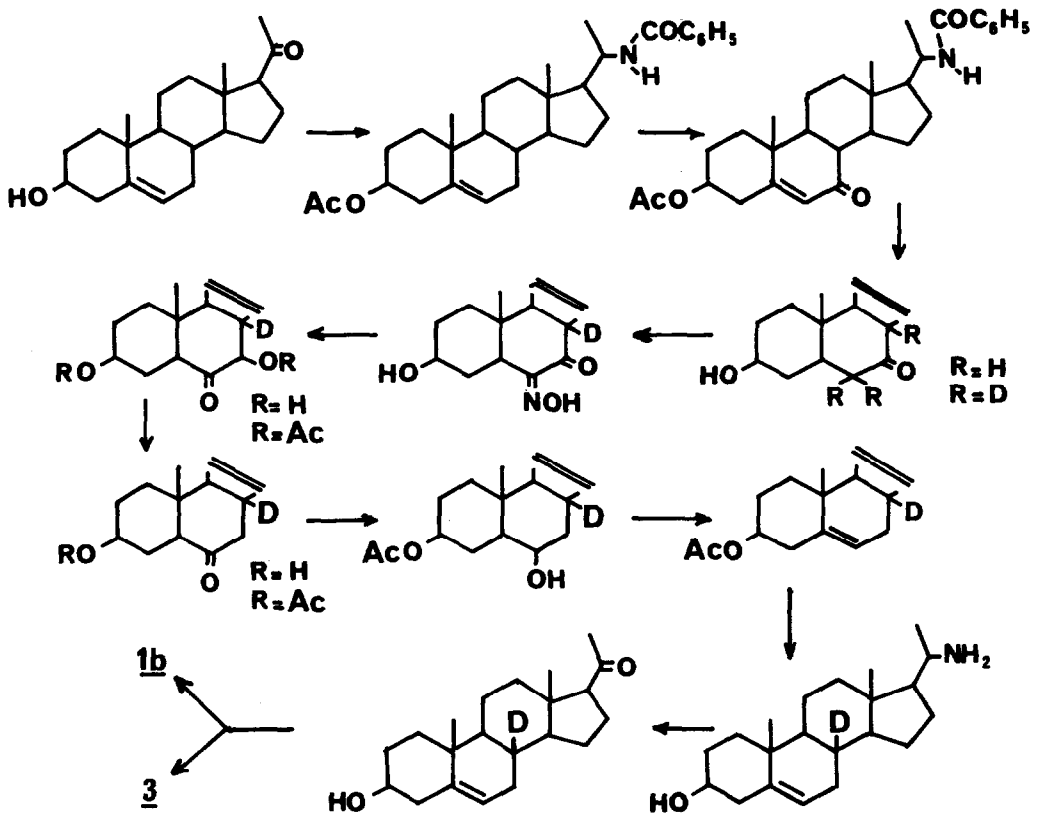
Since Kirk reported a backbone rearrangement in the steroid series[3], this reaction has been a subject of considerable studies[4]. The isomerization is initiated by the attack of a double bond or an O-containing function in acidic conditions.

Currently, almost all results are interpreted in terms of ionization followed by a set of sequential 1,2 shifts, proceeding via discrete carbonium ion intermediates. Levisalles's studies on a Des-A steroid model seemed to support this hypothesis[5].

However, it has been proved both in the triterpene[6] and steroid series[7,8] that deprotonation and reprotonation were operating in various media (AcOD-TsOH, DF, D_2SO_4). Thus, in their experiments, Ourisson et al.[6] have shown that little "non-stop" reaction occurred (the rearranged product is 10% d_1), but no evidence was given concerning the migration process at the tertiary carbon atoms bearing hydrogens.

In a previous paper, we reported the backbone rearrangement of holamine (3α-aminopregn-5-en-20-one) 1a in D_2SO_4 yielding polydeuterated isoholamine 2[8]. A subsequent careful analysis of the ^{13}C NMR spectrum of 2 showed that a deuterium atom had been introduced on at least one of the spinal carbons (C_8, C_9, C_{10}). This experimental fact cannot be explained without assuming the intermediacy of a tetrasubstituted olefin.

In order to study the real mechanism of the mutual interconversion of the carbonium ions, 8β-d_1-holamine 1b and 8β-d_1-methylholaphylline (8β-d_1-3β-methylaminopregn-5-en-20-one) 3 were prepared. The localization and the stereochemistry of the deuterium atom were secured by the following reaction sequence[9].



The resulting 1b and 3 were analysed by mass spectrometry :

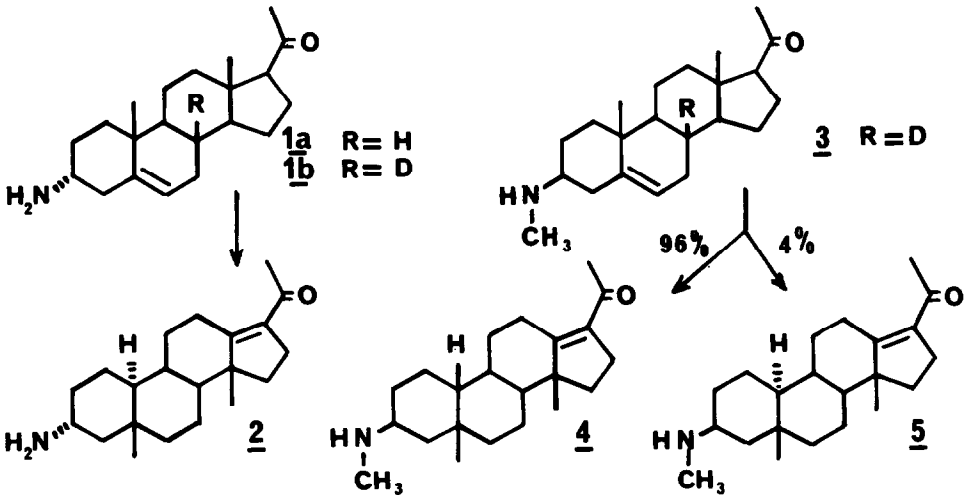
d_o = 3.5% d_1 = 96.5%

Bearing in mind the margin of error in mass spectral measurements ($\pm$ 3%) this leads to the conclusion that deuterium incorporation is very satisfactory.

These two amino-Δ^5-steroids, the backbone rearrangement of which is well known[10], were treated with H_2SO_4 and the two spinal isomers so obtained were analysed by mass spectroscopy. The formation of 2 and 4 respectively from 1b and 3 is accompanied by high loss of deuterium.

	% d_1	% retention
Isoholamine, 2	19	20
Isomethylholaphylline, 10β-H, 4	8	8.5
Isomethylholaphylline, 10α-H, 5	76	80

It is important to note that 2, treated by D_2SO_4 under the same conditions remains unchanged ; no deuterium is incorporated.



Thus, it appears that the reaction of C_9^+ to give C_8^+ proceeds unequally by two routes :

Path 1 : hydrogen shift from C_8 to C_9
Path 2 : formation of an olefin $\Delta^{8,9}$ followed by reprotonation on C_9.

The deprotonation-reprotonation pathway prevails in the two cases.

The formation of the 3β-10α isomer 5, obtained in 4% yield is an exception since the rearrangement proceeds by path 1 to the extent of 80%. Because of metadiaxial interaction between the 3β-amino function and the 5β-methyl, it is likely that in this case the formation of an olefin $\Delta^{8,9}$ is energetically unfavourable, while this interaction is less important for the 8,9 hydrogen shift.

These preliminary results lead to the conclusion that hydrogen shift from C_8 to C_9 is not the normal way in the backbone rearrangement of the steroid skeleton.

It is clear that the situation may be different for the other tertiary carbon atoms involved in this rearrangement and each individual case needs to be studied separately.

This work is now in progress in our Laboratory.

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References :

(1) Alcaloïdes CLXIX. J.-P. Alazard, B. Khemis and X. Lusinchi, Tetrahedron, to be published.

(2) Backbone Rearrangement XIV. J. Thierry, F. Frappier, M. Pais, F.-X. Jarreau and R. Goutarel, Bull. Soc. Chim. France, 4753 (1972).

(3) J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 2125 (1966) ; Tetrahedron, 22, 3195 (1966).

(4) D.N. Kirk in Specialist Periodical Reports ed. by the Chemical Society. Terpenoids and Steroids, vol. 2, 300 ; vol. 3, 378.

(5) J.P. Berthelot and J. Levisalles, Bull. Soc. Chim. France, 1888 (1971).

(6) Y. Nakatani, G. Ponsinet, G. Wolff, J.L. Zundel and G. Ourisson, Tetrahedron, 28, 4249 (1972).

(7) J. Barbier, C. Berrier, J.C. Jacquesy and R. Jacquesy, Tetrahedron, 1047 (1973).

(8) M.-M. Janot, F. Frappier, J. Thierry, G. Lukacs, F.-X. Jarreau and R. Goutarel, Tetrahedron Letters, 3499 (1972).

(9) To be published in a following paper.

(10) F. Frappier, Q. Khuong-Huu and F.-X. Jarreau, Bull. Soc. Chim. France, 3265 (1969).