Hyperacidic Media.† A Novel Route to 13α-Steroids

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Summary Treatment of pregnane-3,20-diones (**1**) by HF–SbF_5 or HSO_3F–SbF_5 leads to a mixture of compounds (**1**)—(**4**); the postulated intermediate is an opened ion due to a "β cleavage" of the C(13)–C(17) bond.

BECAUSE of their pharmacological interest[1] we have been looking for a new, less tedious synthesis of the 13α-pregnanes.

We now report a high-yield, one-step synthesis of these compounds. Treatment of compounds (**1a**) or (**1b**) with hyperacidic media (HF–SbF_5 or HSO_3F–SbF_5) gives an equilibrated mixture of compounds (**1**)—(**4**) (Table).

The isomers are separated by column chromatography on silica gel; isomers (**1a**) and (**2a**) are best separated as their 3-monoacetates.

Treatment of a mixture of the 17α and β isomers of (**5**) gave a mixture which had lost no deuterium.

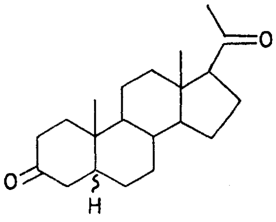
Thus the reaction does not appear to go through the intermediacy of a classical enol (cleavage of a C–H bond), but rather through an opened ion formed by a C–C bond cleavage[2] as shown in the Scheme. This opened ion may adopt several conformations leading, after reclosure, to the observed isomers. The proposed mechanism is consistent with the following observations:

(i) The kinetic study shows that each of the isomers formed is a primary product of the reaction.

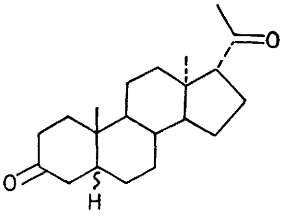
(ii) The triketone (**6**) is recovered under the usual reaction conditions in agreement with the fact that a positive charge in the 13 position is destabilized by the proximity effect of the protonated 11 keto-function.

This reaction is limited to the acyclic ketone of the pregnane dione system: because of the free rotation around the C(17)—C(20) bond, some appropriate conformations exist in which the π-orbital of the protonated carbonyl is properly eclipsed with the bond to be broken.

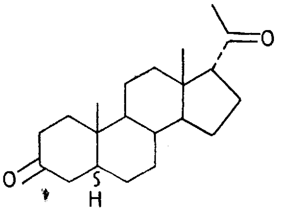
This unprecedented[3] reaction may be generalized to other flexible systems and permits, in a single step, isomerisations



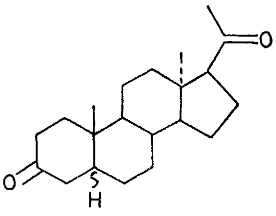
(1) a; 5α H
b; 5β H



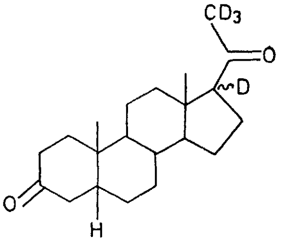
(2)



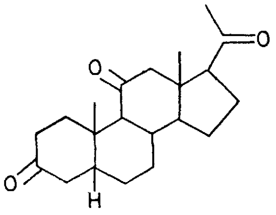
(3)



(4)



(5)



(6)

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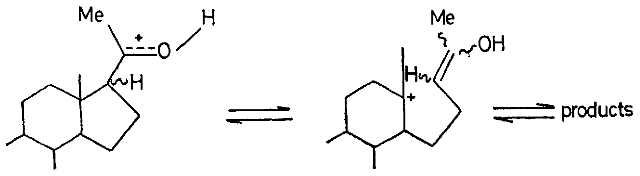
† For previous parts in this series see J. C. Jacquesy and J. P. Gesson, *Tetrahedron,* in the press.

TABLE

Starting material	Reaction conditions	Yield (%)			
(**1a**), (**2a**), or (**3a**)	HF–SbF_5;[a] 0 °C;7 h	(**1a**) 23·5	(**2a**) 67·5	(**3a**) 7·5	(**4a**) 1
"	HSO_3F–SbF_5;[b] 25 °C; 24 h	"	"	"	"
(**1b**) or (**3b**)	HF–SbF_5;[a] 0 °C; 7 h	(**1b**) 22	(**2b**) 69	(**3b**) 8	(**4b**) 1

[a] Molar ratio SbF_5 : substrate 14 : 1; molar ratio SbF_5 : HF 0·1 : 1. [b] 15% non-polar products are formed in this case.



SCHEME

in the α and/or β position of a carbonyl group without any exchange with the medium. New compounds described in this paper gave satisfactory elemental analyses.

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[1] T. Nambara and J. Goto, *Chem. Pharm. Bull.*, 1971, **19**, 1937; Jap. P. Appl. No. 15,864/1973; *Chem. Abs.*, 1973, **78**, 136,536.

[2] D. M. Brouwer and H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 1970, **89**, 211; D. M. Brouwer and J. A. Van Doorn, *ibid.*, 1971, **90**, 535.

[3] 13α-Methyl-D-homo-steroids were recently observed in the solvolysis of pregnane derivatives: F. B. Hirschmann and H. Hirschmann, *J. Org. Chem.*, 1973, **38**, 1270; I. Kattak, D. N. Kirk, C. M. Peach, and M. A. Wilson, *J.C.S. Chem. Comm.*, 1973, 341.