

A NOVEL REDUCTIVE AROMATIZATION OF 4,4-DIMETHYL-STEROIDS.

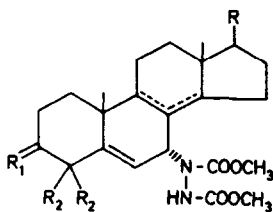
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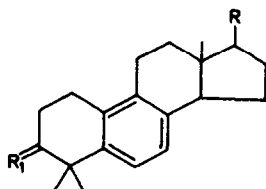
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In contrast to the multitude of acid-catalysed and pyrolytic steroidal aromatizations, only a few examples of reductive aromatization reactions have been described¹⁾. During our studies on the chemical properties of 4,4-dimethyl- $\Delta^{5,8(9)}$ -steroidal azoester adducts²⁾ a novel highly selective ring B aromatization was discovered, which occurred in good yield upon treatment of 1a,b,d with LiAlH_4 (LAH). In addition formation of 7 α ,7' α -bis-steroids was detected³⁾. The latter type of dimerization was found to be the exclusive process in the LAH reaction of $\Delta^{5,8(14)}$ -adducts 2a,d.

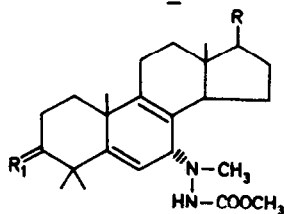


1 : $\Delta^{8(9)}$
2 : $\Delta^{8(14)}$

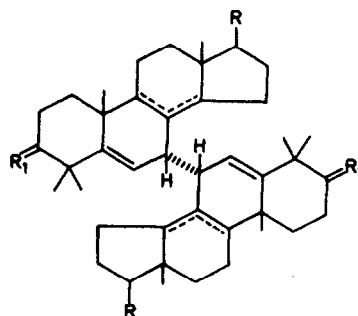
	R ₁	R ₂	R
a.	O	CH ₃	C ₈ H ₁₇
b.	β -OH, H	CH ₃	C ₈ H ₁₇
c.	β -OAc, H	CH ₃	C ₈ H ₁₇
d.	O	CH ₃	OAc
e.	β -OAc, H	CH ₃	OAc
f.	β -OAc, H	H	C ₈ H ₁₇
g.	(OCH ₂) ₂	H	C(OCH ₂) ₂ CH ₃
h.	O	H	COCH ₃



3



6



4 : $\Delta^{8(9)}$
5 : $\Delta^{8(14)}$

Thus, on refluxing 1a with an excess of LAH in THF for 15 mn the ring B aromatic steroid 2b was obtained in 66% yield, which was acylated with AcCl-pyridine to afford 2c, m.p. 133-135°C; $\lambda_{\max}^{\text{EtOH}}$ 220 (10.965), 268 (710), 275 (infl. 614); $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.58 (s, 3H, C₁₈), 1.27 (s, 6H, C₄-CH₃'s), 2.03 (s, 3H, OAc) 4.95 (q, 1H, C₃-H), 7.01 (AB pattern, $\Delta_{\text{AB}}=23\text{Hz}$, $J=8\text{Hz}$, C_{6,7}-H's)⁴). LAH treatment of 1b (C₃-H, $W_{\frac{1}{2}}=16\text{Hz}$), prepared via NaBH₄ reduction of 1a, gave after acylation the identical product 2c. The latter result demonstrated the neosteroid structure of 2c⁵).

Formation of a 4,4-dimethyl-neosteroid under such mild conditions is unprecedented. Therefore some experiments were carried out to obtain some insight in the course of the reaction. Firstly, it was established that no detectable aromatization occurred on refluxing 1a and 1b in a strongly alkaline medium (10% KOH-CH₃OH-2 hr). Secondly, when the LAH-reaction was carried out at r.t. (2 hr), spectral analysis revealed the presence of a new instable compound. As its main PMR characteristic a 3H-signal was found at $\delta 2.50$ (N-CH₃), which absorption replaced one of the original N-COOCH₃ signals. Treatment of this crude compound with 10% KOH-CH₃OH led to the formation of 2b in addition to other products.

As LAH reduction of azoester adducts is known to occur firstly at the ester group of the tertiary nitrogen⁶), a possible structure for the intermediate can be formulated as 6b. The aromatization then may proceed via abstraction of the N-proton from 6b, followed by elimination of the partly reduced azoester moiety under expulsion of a Li-coordinated methyl carbanion from the steroid skeleton⁷).

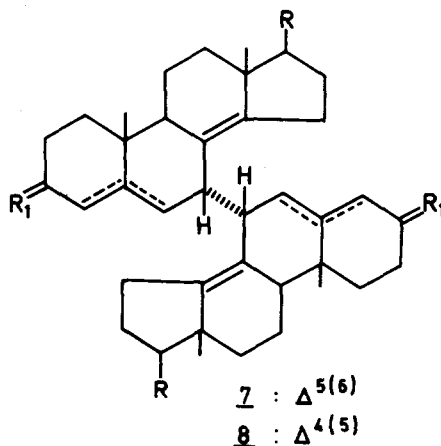
On the other hand, the intermediacy of a radical can not be excluded, 7 α ,7' α -bis-steroid 4b being obtained as a minor product (10%) in the reaction of 1a with LAH-THF; m.p. 161-162°C; $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.68 (s, 3H, C₁₈), 1.06 (s, 6H, C₄-CH₃'s), 1.17 (s, 3H, C₁₉) 3.00 (s, $W_{\frac{1}{2}}=3\text{Hz}$, 1H, C₇-H), 3.07 (m, 1H, C₃-H), 5.32 (s, $W_{\frac{1}{2}}=4\text{Hz}$, 1H, C₆-H). The possibility of 4b being a precursor of 2b was ruled out by the observation that 2b could not be detected upon refluxing 4b in THF⁸).

LAH-reaction of $\Delta^{5,8(14)}$ -adduct 2a (THF, reflux) afforded the

7 α ,7' α -bis-steroid 2b as the single product in 74% yield, m.p. 165-171°C (decomp.) $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.88 and 0.90 (s, 3H, C₁₈ and C₁₉), 1.05 and 1.12 (s, 3H, C₄-CH₃'s), 3.15 (m, 1H, C₃-H), 3.22 (s, $W_{\frac{1}{2}}=6\text{Hz}$, 1H, C₇-H), 5.43 (s, $W_{\frac{1}{2}}=4\text{Hz}$, 1H, C₆-H). Dimers 4b and 5b were tentatively assigned a 7 α ,7' α -structure on the basis of the narrow band width of the respective C₁₈ and C₁₉ PMR signals. This latter observation indicated symmetric structures for 4b and 5b.

Analogous aromatization and dimerization reactions were found in the 4,4-dimethyl-androstane series (1d and 2d) to yield after acylation 3e, m.p. 187-189°C, and 5e, m.p. 190-195°C (dec.) respectively.

The C₄-unsubstituted $\Delta^{5,8(9)}$ -adduct 2f gave on LAH treatment a complex reaction mixture even at low temperature (-10°C). However, the corresponding $\Delta^{5,8(14)}$ -adduct 2g reacted readily to give dimer 7g in 50% yield, m.p. 217-219°C; $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.85 (s, 3H, C₁₉), 0.96 (s, 3H, C₁₈), 1.33 (s, 3H, C₂₁), 3.20 (s, $W_{\frac{1}{2}}=6\text{Hz}$, 1H, C₇-H), 3.90 (s, 8H, (OCH₂)₂'s), 5.15 (s, $W_{\frac{1}{2}}=6\text{Hz}$, 1H, C₆-H)⁹, which on hydrolysis (HCl - acetic acid) afforded 8h, m.p. 263-264.5°C; $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.87 (s, 3H, C₁₈), 1.10 (s, 3H, C₁₉), 2.13 (s, 3H, C₂₁), 2.68 (s, $W_{\frac{1}{2}}=6\text{Hz}$, 1H, C₇-H), 5.82 (s, $W_{\frac{1}{2}}=2\text{Hz}$, 1H, C₄-H).



Although dimers 4b, 5b, 5e, 7g and 8h failed to show a M^+ peak in the mass spectrum as a consequence of thermolytic instability, evidence for the dimeric character was obtained from the observed F^+ peaks; for instance, 5b showed peaks at m/e 412 and m/e 410 indicating a thermolytic disproportionation process and a peak at m/e 411, formed via direct cleavage of the dimer. Analogous mass spectra were found for 4b, 5e, 7g and 8h (cf. table 1). Application of the refocussing technique¹¹⁾ upon fragment m/e 311 in the mass spectrum of dimer 8h showed this fragment to originate from m/e 622, corresponding with the M^+ -ion of 8h.

TABLE 1.

Compound	Highest m/e values in the mass spectrum.
<u>2c</u>	M^+ : 438 (9.5%).
<u>2e</u>	M^+ : 384 (14%).
<u>4b</u>	F^+ : 410 (5%), 396 (35%).
<u>5b</u>	F^+ : 412 (60%), 411 (57%), 410 (100%).
<u>5e</u>	F^+ : 400 (22%), 399 (44%), 398 (13%).
<u>7g</u>	F^+ : 400 (12%), 398 (11%).
<u>8h</u>	F^+ : 312 (46%), 311 (100%), 310 (24%).

ACKNOWLEDGEMENT

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REFERENCES AND FOOTNOTES

- 1a. R.H. Shapiro, "Steroid Reactions" (C. Djerassi, ed.), Holden-Day, Inc., San Francisco, 1963, p.371.
- b. D.N. Kirk and M.P. Hartshorn, Steroid Reaction Mechanisms, Elsevier, Amsterdam, 1968, p.277.
2. H. de Nijs and W.N. Speckamp, Tetrahedron Letters, 813 (1973).
3. E. Mosettig and I. Scheer, J.Org.Chem., 17, 764 (1952).
4. The C_6^- and C_7-H 's of neocholesteryl acetate absorbed as a singlet at $\delta 6.70$. A. van der Gen, J. Lakeman, M.A.M.P. Gras and H.O. Huisman, Tetrahedron, 20, 2521 (1964).
5. S.G. Levine and A.C. Ghosh, Tetrahedron Letters, 39 (1969).
6. R. Huisgen, F. Jakob, W. Siegel and A. Cadus, Liebigs Ann., 590, 1 (1954).
7. H.L. Dryden, Jr., G.M. Webber and J.J. Wieczorek, J.Am.Chem.Soc., 86, 742 (1964).
8. Ref. 1a, p.391 and ref. cited.
9. The PMR data of 5b, 5e and 7g showed close resemblance with those reported for one of the photodimers of ergosterol, to which a $7\beta,7'\beta-\Delta^{5,8(9)}$ structure was assigned¹⁰). However, especially the positions of the C_{18}^- and C_{19}^- methyl signals suggest strongly a $\Delta^{5,8(14)}$ -structure for this bis-steroid.
10. P. Crabbé and K. Mislow, Chem.Comm., 657 (1968).
11. K.R. Jennings in "Some Newer Physical Methods in Structural Chemistry" (R. Bonnett and J.G. Davis, ed.), United Trade Press Ltd., London, 1967, p.105.