

SKELETAL REARRANGEMENTS OF 4,4-DIMETHYL- $\Delta^{5,8(9)}$ STEROIDAL AZOESTER ADDUCTS.

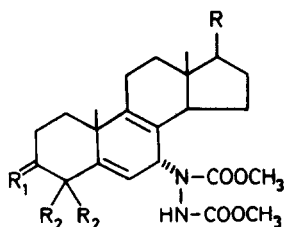
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Steroid al azoester adducts Ia,b have been found to undergo readily anthra-steroid rearrangement upon treatment with acid¹⁾. In this communication new synthetic and mechanistic results on the previously unknown 4,4-dimethyl-adducts Ic-Ig are reported emphasizing thereby the potential hazards of using NOE techniques in structural assignments to the rearranged systems.



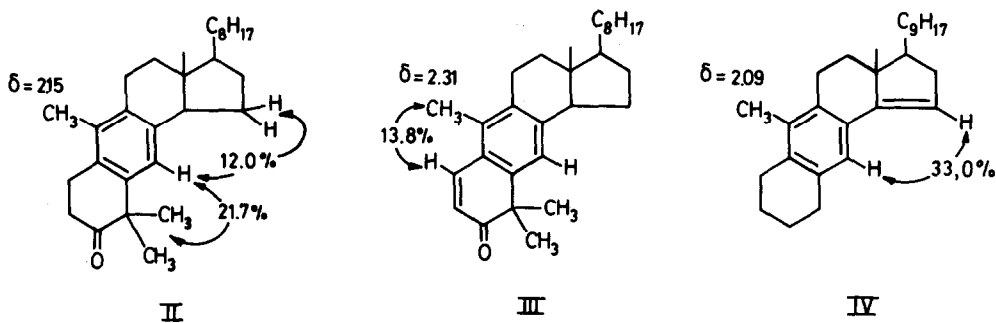
I	R ₁	R ₂	R
a	β -OAc,H	H	C ₈ H ₁₇
b	β -OAc,H	H	C ₉ H ₁₇
c	O	CH ₃	C ₈ H ₁₇
d	β -OH,H	CH ₃	C ₈ H ₁₇
e	β -OAc,H	CH ₃	C ₈ H ₁₇
f	O	CH ₃	COCH ₃
g	O	CH ₃	OAc

Adducts Ic,f,g were prepared via ene addition of dimethyl azodicarboxylate to the corresponding 4,4-dimethyl- $\Delta^{5,7}$ -steroids²⁾. Compound II [m.p. 80-81°C ; $\bar{\nu}_{\text{KBr}}^{\text{cm}^{-1}}$ 1710 (C=O), 879 (Ar-H) ; $\lambda_{\text{max}}^{\text{EtOH}}$ 225 (11.860), 272 (970), 282 (815) ; $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.58 (s, 3H, C₁₈), 1.40 (s, 6H, C₄-methyls), 2.15 (s, $W_{\frac{1}{2}}=2\text{Hz}$, 3H, C₁₉), 6.86 (s, 1H, C₇-H)] was obtained in 90% yield upon treatment of Ic with BF₃-Et₂O in benzene, which proved to be a highly effective reagent to induce specific rearrangements in this type of adducts. In order to establish the structure of II NOE experiments were carried out in CDCl₃, which showed an increase of the Ar-H absorption (21.7%) upon irradiation of the six-proton singlet at $\delta=1.40$; however, irradiation of the Ar-CH₃ singlet ($\delta=2.15$) also caused a 12.0% increment of the Ar-H absorption³⁾. Comparable results were found in C₆D₆ as the solvent⁴⁾. Analogous effects were noted in the rearranged products of 4,4-dimethyl-adducts If and Ig. This evidence seemed to suggest a series of methyl shifts leaving the steroid skeleton intact^{5,6)}, rather than occurrence of the expected anthra-

steroid structure.

On the other hand, when NOE was applied to the Ar-CH₃ signal of a series of normal anthra-steroids of unambiguously established structure ⁸⁾, similar data were obtained for the Ar-H of 14 α - (13.4%) and 14 β -anthraergosta-5,7,9,22-tetraen-3 α -ol (15.5%); pentaene IV, however, failed to give an enhancement of the Ar-H area. The neighbouring position of C₁₅-H and Ar-H was shown by a NOE of 33.0%.

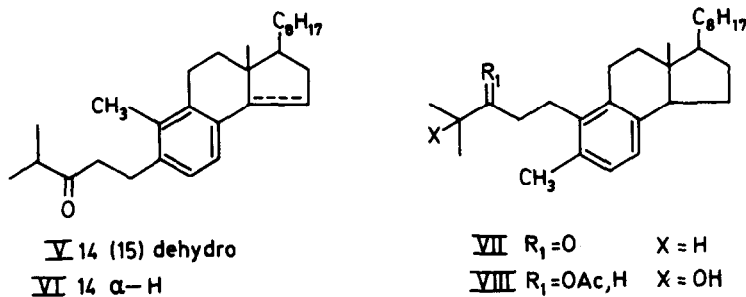
Therefore the A-ring unsaturated isomer III - prepared via bromination-dehydrobromination of II - was investigated. Upon irradiation of the Ar-CH₃ signal at δ =2.31, the Ar-H absorption remained unaffected, while the area of the vinylic proton (δ =7.82) increased (CDCl₃; 13.8%). This observation proved the anthra-steroid structure of II, the misleading results most probably being explained by absorption of one of the C₁₅ protons in a region close to the aromatic methyl ⁹⁾.



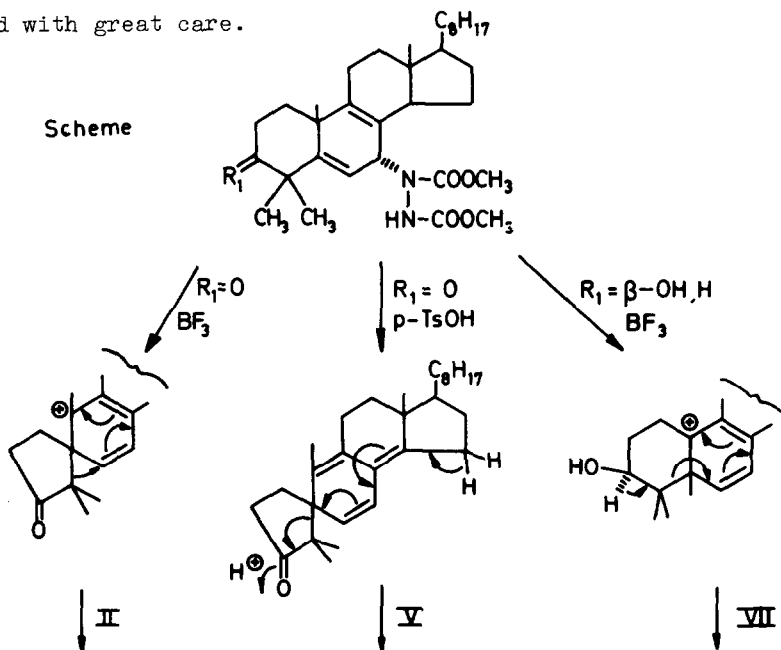
Reaction of Ic with p-TsOH in benzene afforded inter alia the A-ring opened tetraene V¹⁰ [m.p. 97-100°C; $\nu_{\text{KBr}}^{\text{cm}^{-1}}$ 1700 (C=O), 810 (Ar-H); $\lambda_{\text{max}}^{\text{EtOH}}$ 217 (21.300), 267 (18.200); $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.89 (s, 3H, C₁₈), 1.06 (d, 6H, C₄-methyls, J=7Hz), 2.15 (s, 3H, C₁₉), 5.96 (q, 1H, C₁₅-H), 6.93 and 7.35 (AB pattern C₆, C₇-H's, J=8Hz)], hydrogenation (Pd-H₂) of which gave the 14 α -ketone VI [$\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.55 (s, 3H, C₁₈), 1.05 (d, 6H, C₄-methyls, J=7Hz), 2.13 (s, W₂=2Hz, 3H, C₁₉), 6.79 and 6.91 (AB pattern C₆, C₇-H's, J=8Hz)].

Upon treatment of alcohol Id - obtained from Ic via NaBH₄ reduction - with BF₃-Et₂O in benzene a dramatic change in reaction type led to a quantitative formation of the A-ring opened product VII, which differed from V in its spectral properties: $\nu_{\text{CHCl}_3}^{\text{cm}^{-1}}$ 1710 (C=O), 830 (Ar-H); $\delta_{\text{CDCl}_3}^{\text{TMS}}$ 0.55 (s, 3H, C₁₈),

1.10 (d, 6H, C_4 -methyls, $J=7\text{Hz}$), 2.27 (s, $W_{\frac{1}{2}}=3\text{Hz}$, 3H, C_{19}), 6.81 and 6.95 (AB pattern C_6 , C_7 -H's, $J=8\text{Hz}$). The corresponding acetate **Ie** reacted in the same way to give **VIII** (m.p. 100-101°C)¹¹. Irradiation of the Ar- CH_3 signal of **VII** enhanced the low-field Ar-H absorption ($CDCl_3$, 15.0%); no effect was found in **V**, which confirmed the structural assignments.



Thus it appeared that while **Ib** underwent exclusive anthrasteroid formation via cleavage of the C_1 - C_{10} bond upon BF_3 treatment, corresponding reactions of alcohol **Id** and acetate **Ie** resulted in exclusive migration of the 19-methyl¹²⁾. The above findings are summarized in the scheme below. The mechanistic implications will be discussed in our full paper. From the results it is evident that application of NOE as a structure proof in ring B aromatic steroids has to be used with great care.



ACKNOWLEDGEMENT

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REFERENCES AND FOOTNOTES.

- 1a. A. van der Gen, J. Lakeman, M.A.M.P. Gras and H.O. Huisman, Tetrahedron, 20, 2521 (1964).
- b. K. Tsuda, R. Hayatsu, J.A. Steele, O. Tanaka and E. Mosettig, J.Am.Chem.Soc., 85, 1126 (1963).
2. H. de Nijs, forthcoming thesis 1973, University of Amsterdam.
3. NOE's were measured on a Varian HA 100 spectrometer in carefully degassed solutions of $4 \cdot 10^{-4}$ moles in 0.5 ml $CDCl_3$ or C_6D_6 ; signals were integrated at 250 Hz/500 s (integrals $\pm 2\%$), $\frac{\nu H_2}{2\pi} = 5\text{Hz}$.
4. C_6D_6 : irradiation of Ar- CH_3 ($\delta=1.91$) gave 11.8% enhancement of Ar-H ; irradiation of C_4 -methyls ($\delta=1.45$) 24.6%.
5. M. Fukuoka and S. Natori, Tetrahedron Letters, 4867 (1970).
6. In 9-methyl-s-octahydro-phenanthrene synthesized as a model compound⁷⁾, NOE of the same magnitude of the Ar-H absorption was found upon irradiation of the Ar- CH_3 singlet, whereas the phenomenon was absent in the corresponding anthracene derivative.
- 7a. G.M. Badger, W. Carruthers, J.W. Cook and R. Schoental, J.Chem.Soc., 169, (1949).
- b. G.M. Badger, W. Carruthers, J.W. Cook, J.Chem.Soc., 2044 (1949).
8. A.W. Burgstahler and E. Mosettig, J.Am.Chem.Soc., 81, 3697 (1959).
9. Irradiation in the region ($\delta=2.21$) next to the Ar- CH_3 of II gave a small but definite NOE of 6.9%.
10. To be published in our full paper.
11. BF_3 -treatment of the desmethyladduct Ib gave quantitatively 14 α -H-anthra-steroid.
12. Compare: T.G. Halsall, E.R.H. Jones, E.L. Tan and G.R. Chaudhry, J.Chem.Soc. (C), 1374 (1966);
J.W. Blunt and M.P. Hartshorn, D.N. Kirk, J.Chem.Soc.(C), 635 (1968).