Evidence is produced to the effect that in mass spectrometry a quasi-thermal retro-Diels-Alder decomposition does not occur. This reaction has to be triggered by the positive charge in the molecule.

The retro-Diels-Alder (RDA) decomposition of compounds containing a cyclohexene ring is one of the most characteristic fragmentation reactions in mass spectrometry [2]. Regarding its mechanisms two aspects have been the subject of much controversy, viz. (a) whether it is a two-step or a concerted process (in the latter case it should obey the same orbital symmetry rules as the thermal RDA), and (b) whether it occurs only if the positive charge is localized at the cyclohexene π-bond (which would exclude a so-called quasi-thermal decomposition). Over the years a wealth of information has been accumulated pertinent to these two questions (see Refs. [2-4] and literature cited there) the corollaries of which will be summarized below.

1) Both cis- and trans-octalene and hydrindene systems yield RDA-fragments (see, e.g., Fig. 1 for 5β-androst-2-en-17-one and Ref. [3] for the 5α-isomer). Since a concerted process is symmetry-forbidden, for the latter a two-step mechanism has to be assumed.

2) Comparison of the relative abundances of the RDA fragments for isomeric cis- and trans-systems does not give a consistent picture.

3) From the fact that the [M-butadiene]+ fragment of 5α-androst-2-en-17β-ol showed the typical ring D-fragmentation it was inferred [5] that in the decomposing M+ the charge was localized at C-13 (a) and hence that RDA of the (trans-fused) ring A occurred without participation of the charge. This conclusion was invalidated by the observation that (a) 4,4-dimethyl-5α-androst-2-en-17-one yields ionized 4-methyl-pentadiene-1,3 and hence the charge has to reside in ring A during the RDA process, and (b) that ions of the type b where there is a potential minimum for the positive charge at the C-17 substituent do not decompose further by RDA (in contrast to, e.g., the [M – ring D]-fragments of 17-keto steroids [3].

4) From the observations with 17-amino steroids yielding b it was concluded that RDA would be observed only when the charge was localized in the cyclohexene ring [3]. It has, however, been objected [4] that only 5α-compounds had been investigated where a “quasi-thermal” RDA should be symmetry-forbidden.

5) From his studies with 5α- and 5β-β-steroids Djerassi concluded [4] that if ionization occurred by removal of an electron from the cyclohexene π-bond and subsequent allylic cleavage were possible only

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by formation of an ion where the stereochemistry of
the 2-octene system has been destroyed (e.g., c),
RDA will proceed by a two-step mechanism. If,
however, allylic cleavage is possible without af-
fected the octene stereochemistry (e.g., d), con-
certed RDA will occur when symmetry-allowed
(5ß, but not 5a). He suggested that RDA should,
therefore, be observed also for the 5ß-isomers of b
(b').

To check this point and thus to settle finally the
question whether RDA may occur even if the
positive charge is localized at a site remote from the
cyclohexene double bond (so-called quasi-thermal
RDA) 17ß-n-propylamino-5ß-androst-2-ene has
been synthesized.

gave 5ß-androst-2-en-17-one (7, Fig. 1). Formation
of a Schiff base with n-propylamine and subsequent
reduction with NaBH₄ [3, 13] finally yielded 1. The
17ß-orientation of the propylamino group fol-

gows (a) from the general steric course of the
hydrolysis reduction of Schiff bases [14, 15] at C-17,
(b) the chemical shift of the C-17 proton (δ =
2.61 ppm; δ = 2.57 ppm has been reported [16] for
17ß-aminosteroids, 2.83 ppm for their 17α-isomers)
and (c) most conclusively from the different splitting
[17] of the 17α- and 17ß-proton signals. Since
J (16α, 17α), J (16ß, 17α) and J (16ß, 17ß) are large
and J (16α, 17β) ~ 0 Hz a C-17α-H can be recog-
nized by a (more or less well resolved) double
doublet (occasionally referred to in the literature as
multiplet or triplet), a C-17β-H by sharp doublet.
This behavior has been confirmed with 17α- and
17ß-aminosteroids [16]. In the case of 1 the C-17-H
signal appears as a double doublet and hence oc-

cupies an α-position, the amino substituent has to
be β-oriented.

Synthesis of
17ß-n-propylamino-5ß-androst-2-ene (1)
The synthesis started from testosterone (2) which
upon hydrogenation [6] yielded mainly 17ß-
hydroxy-5ß-androstan-3-one (3) (the stereo-
chemistry of 3 is confirmed by the abundant
[M–C₆H₄O]⁺ ion in its mass spectrum [7]; the 5α-
isomer does not show this fragment to any extent).
Treatment [8] of 3 with ethyl formate/NaH gave
17ß-hydroxy-2-hydroxymethylene-5ß-androst-3-
one (4), from which by reaction [9, 10] with N-
bromosuccinimide (5) and subsequent selective
reduction [11] with NaBH₄ a mixture of the
stereoisomeric 2ß-bromo-3ß-hydroxy-5ß-androstan-
17-ones (6) was obtained. Treatment with Zn [12]

Discussion
The fragmentation pattern of 7 differs only in the
relative abundance of several fragments from that
of the 5α-isomer [3]. The somewhat more pronounced
RDA-product ([M–C₆H₄]⁺, m/z 218) does not
necessarily reflect the occurrence of a different
(concerted) mechanism. It may as well be a conse-
quence of the higher strain of the A/B-cis system
(cf. the observation that 3 loses C-1 to C-4
[M–70]⁺ – while this fragment is not observed for
the 5α-isomer; see also Ref. [7]). More revealing in
this context is the mass spectrum of 1-hydro-
chloride (Fig. 2): The main fragments are b', c and
def in the case of the 5α-isomer [3]. There is a
minute (0.1% rel. int.) ion due to the RDA starting
from M⁺ (m/z 261), but no RDA starting from b'
(m/z 232)! Hence, even if symmetry allowed a
quasi-thermal RDA does not occur in mass spectro-
metry. RDA fragments will, therefore, only be
observed when triggered by the positive charge
located in the cyclohexene ring.
This conclusion can be confirmed by the CI (isobutane) spectra of 7 and 1-hydrochloride: 7 yields by charge transfer \( M^+ \) (12\% rel. int.) which as in the EI spectrum (Fig. 1) loses \( C_4H_6 \) (m/z 218), and by \( H^+ \)-transfer \([M + H]^+\) (100\%) which does not decompose by RDA. As protonation occurs at the C-17 carbonyl group (as evidenced by the formation of \([M + H - H_2O]^+\)) localisation of the positive charge away from the cyclohexene ring again prevents RDA. Analogously, 1-hydrochloride does not show RDA starting from \([1 + H]^+\). Thus, the results by Djerassi [4] regarding stepwise and concerted RDA pertain only to ions where the charge is localised in the cyclohexene \( \pi \)-system.

**Experimental**

**Instruments.** Mass spectra: MAT CH7-A (3) or Finnigan 3200 (all other compounds). NMR: Varian EM 300. Solvent CDCl\(_3\) or (for 1-hydrochloride) CD\(_3\)OD; TMS as internal standard; \( \delta \)-values (ppm) UV: Beckmann Model 25. IR: Perkin Elmer 283 (KBr). Melting points: Kofler (uncorrected). Column Chromatography: Silicagel 60 (0.06–0.2 mm); Macherey & Nagel.

**17ß-Hydroxy-5ß-androstan-3-one** (3) was obtained from testosterone (2) as described in Ref. [6]. The raw reduction product was purified by chromatography (CHCl\(_3\) with increasing – up to 5\% – amounts of CH\(_3\)OH). M. p. (from acetone/petrol ether) 138 °C (lit. [6] 139–140 °C). IR: 1709 (\( v_{co} \)) cm\(^{-1}\). NMR: \( CH_3-18 \ 0.77 \) (calc’d according to Zürcher [18] 0.77); \( CH_3-19 \ 1.03 \) (calc’d 1.04); H-17 3.70 (t, 9 Hz). MS: m/z 290 (82\%): \( M^+ \), 220 (59\%): \([M-C_4H_6O]^+\).

**17-Hydroxy-2-hydroxymethylene-5ß-androstan-3-one** (4) was obtained from 3 as described in Ref. [8]. M. p. (from acetonitril) 164–167 °C (lit. 157–163 °C). IR: 3444 \( (v_{OH}) \) cm\(^{-1}\), 1640 and 1629 (intramolecularly H-bonded enol), 1586 (\( v_{c=c} \)) cm\(^{-1}\). UV (EtOH): 282 nm (\( e \sim 8300 \)) (lit. [8] 284; 7900). NMR: \( CH_3-18 \)

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Fig. 2. Mass spectrum (EI) of 17ß-n-propylamino-androst-2-ene (1) (introduced as hydrochloride) Finnigan 3200, direct, 70 eV, probe temperature 100 °C.
0.73; CH3-19 1.07; H-17 3.63 (t, 8 Hz); bonded enolic H 8.33 (s). MS: m/z 318 M+

2-ß-Bromo-5ß-androstan-3ß,17-dione (5) (cf. Refs. [9, 10]). 2.15 g of 3 in 30 ml dioxan, 8 ml HClO4 (0.46 N) and 1.74 g N-bromosuccinimide were stirred at room temperature. Further portions of N-bromosuccinimide were added after 2 h. (0.45 g), 1.5 h (0.45 g) and 75 min (0.2 g). After 75 min a 10% aqueous solution of Na2SO3 is added until all bromine is destroyed (care pH stays acidic). Work-up by shaking with ice/water, extraction with CHCl3 etc.) and purification by chromatography (CHCl3 with 0.5% CH3OH) with 0.5% methanol and ether and dried at 110°C. Afterwards with H2O until a pH 6.5 was reached, the aqueous solution was kept for 20 min at room temperature, the residue diluted with 5 ml H2O and extracted with ether. From the ether phase 1.67 g (61%) 5. M.p. 186-187°C (decomp.) [9] 201-202°C (decomp.) [10].

5ß-Androst-3ß-en-17-one (7) (cf. Refs. [11, 12]). To a stirred suspension of 1.2 g of 5 in 26 ml CH3OH 39 mg NaBH4 were added in portions. The resulting solution was kept for 20 min at room temperature, acidified with acetic acid to pH 5, diluted with H2O and extracted with ether. From the ether phase 1.2 g of a mixture of epimeric 2ß-; bromo-3ß-hydroxy-5ß-androst-17-ones (6) was obtained. 750 mg of 6 without further purification were dissolved in 112 ml ethanol and refluxed for 3 h with 3 g of activated Zn powder (washed several times with 5% HCl, afterwards with H2O until a pH 6.5 was reached, methanol and ether and dried at 110°C). After removal of the Zn and evaporation of the solvent 530 mg of an oil were obtained which upon chromatography (CHCl3) gave 278 mg of 7 (50%). M.p. 112-114°C. IR: 1727 (vw) cm−1. NMR: CH3-18 0.86 calc’d 0.86); CH3-19 1.00; H-2/H-3 5.20; 5.58, 5.62, 6.07 (AB-system intensity ratio 0.95:4.3:10:0.48). MS: see Fig. 1.

7ß-n-propylaminoandrost-2-ene (1) (cf. Ref. [13]). A suspension of 120 mg 7 in 3.5 ml methanol and 1 ml n-propylamine was heated to 50°C under argon for 6 h. After cooling to room temperature and addition of 40 mg NaBH4 in portions the mixture is stirred over night. Then the solvent is removed i.v. at room temperature, the residue diluted with 5 ml H2O and extracted with 40 ml ether. From the concentrated ether phase 1-hydrochloride was precipitated with 15 ml 5 N HCl. Yield (after thorough washing with ether) 110 mg (71%). M.p. (from H2O) 195-210°C (decomp.). IR: 2934 (broad), 1447 and 664 cm−1. NMR: Hydrochloride: CH3-18 0.90; CH3-19 1.01; propyl-CH2-1.01 (t, 9.5 Hz); collapses to a s upon irradiation at 1.81 ppm); -NH2—CH2— 3.00 (br. t, 9 Hz; collapses to a broad s upon irridiation at 1.81 ppm); H2/H3 5.59, 5.63 (br. d). Free 1: CH3-18 0.79, CH3-19 0.98, H-17 2.61 (dd 8.9 and 11.2 Hz); –NH–CH2— 2.7 (t, 9 Hz); H-2/H-3 5.63 br. s. MS: see Fig. 2.

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