The Photochemical Synthesis of A-Nor-5α,10α-steroids

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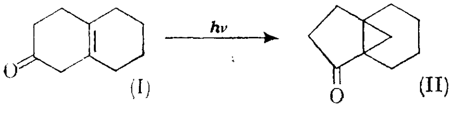
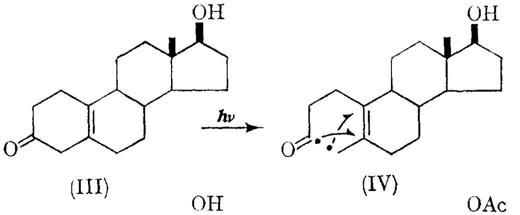
THE recent and growing importance of A-nor-steroids has prompted us to examine whether the recently reported[1] photochemical rearrangement of the $\beta\gamma$-unsaturated ketone (I) to the "conjugated" cyclopropyl ketone (II) could be employed in the preparation of A-nor-steroids. An investigation of the irradiation of (+)-17β-hydroxyœstr-5(10)-en-3-one (III) has shown that this rearrangement can be used for the preparation of A-nor-steroids and furthermore that the rearrangement is stereospecific, *i.e.*, only one of the two possible cyclopropyl ketones is formed. Unexpectedly, the ring is 5α,10α and therefore is convertible into the hitherto difficultly accessible 10α-methyl-A-nor-steroids.



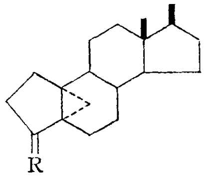
(I) (II)

Irradiation† of a solution of (III) [λ_{max} (MeOH) 280—287 mμ, ε 34] in t-butyl alcohol yielded the photo-product (Va) with the same molecular formula‡ as the starting material in 55% yield.§ Further spectral data [λ_{max} (MeOH) 210·5 mμ, ε 4600; 282 mμ, ε 120; and ν_{max} 3030 and 1705 cm.$^{-1}$] correspond closely to those reported for (II),[1] and are consistent with the structure (Va). The n.m.r. spectrum of (Va) showed no absorption upfield from δ 0·65, and absence of vinyl protons. The presence of the cyclopropane ring in (Va) was confirmed by Wolff–Kishner reduction to yield (Vb), the n.m.r. of which showed an AB quartet centred at δ 0·27 (Δν 29·5 c./sec., J = 4·5 c./sec.) due to the nonequivalent protons of the cyclopropyl methylene group. The cyclopropyl protons in (Va) are shifted downfield as a result of conjugation with the carbonyl group as noted previously in (II).[1]

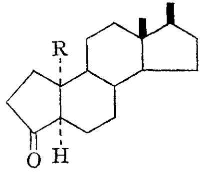
The cyclopropane ring of (Va) was easily opened by heating the compound under reflux with HBr in glacial acetic to yield the bromo-compound (VIa). Its n.m.r. spectrum showed an AB quartet centred at δ 3·42 (Δν 24·0 c./sec., J = 11·0 c./sec.) due to a bromomethylene group on a quaternary carbon atom, along with two singlets at δ 2·04 (3H, acetate) and δ 0·83 (3H, C-18 methyl), and an apparent triplet at δ 4·56 (1H, C-17 hydrogen). The γ-bromo-ketone (VIa) could be recyclized to (Va) by treatment with alkali, demonstrating that no rearrangement had occurred during the acid treatment. Hydrogenolysis of the bromine in (VIa), using Pd/$CaCO_3$, yielded the keto-acetate (VIb) whose n.m.r. spectrum showed the presence of a new methyl group on C-10 at δ 0·99 along with the C-18 methyl at δ 0·83, and acetyl at δ 2·06. The i.r. spectra of (VIa) and (VIb) (ν_{max} 1742, 1732 cm.$^{-1}$; and 1735 and 1727 cm.$^{-1}$, respectively) confirmed the presence of the cyclopentanone system. The above results prove the presence in the photo-product of a cyclopentanone conjugated with a cyclopropane ring, the β-carbon of which is quaternary. These results together with the similarity in the mode of formation of (II) leads directly to the structure 17β-hydroxy-5α,10α-methylene-A-norœstran-3-one (Va) for the photo-product. The assignment of the cyclopropane



(III) (IV)


(V)

a, R=O
b, R=H_2


(VI)

a, R=CH_2Br
b, R=Me

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† The photolysis was carried out under nitrogen with a high-pressure mercury lamp (Hanovia, 450w) using a Pyrex filter.

‡ Satisfactory analyses were obtained for all new compounds reported. The n.m.r. spectra were determined in $CDCl_3$ with Me_4Si (δ = 0·0 p.p.m.) as an internal standard. The i.r. spectra were determined in $CHCl_3$.

§ No trace of the 5β,10β-methylene isomer was found among the side-products formed in low yields.

ring as α is based on the following evidence. Firstly, the assignment can be made on the basis of the optical rotatory dispersion curve (o.r.d.) of (Va). It has been shown[2] that the sign of the o.r.d. curve of a conjugated cyclopropyl ketone is governed by a modified octant rule in which the cyclopropane ring outweighs all other substituents. The observed large negative Cotton effect of (Va) (MeOH, $\Phi_{300}-15{,}700°$, $\Phi_{260}+30{,}500°$) requires the cyclopropane ring to be α. Secondly, (VIb) (shown to be stable to alkali, *i.e.* *cis*-A/B ring-junction) is not identical with the known 17β-acetoxy-A-nor-5β,10β-androstan-3-one. The melting points of (VIb) (m.p. 114·5—115·5°) and the corresponding 17β-alcohol (m.p. 127—128·5°) are different from those reported for 17β-acetoxy-A-nor-5β,10β-androstan-3-one (m.p. 139—140°) and the corresponding 17β-alcohol[3] (m.p. 156—157°) and also the o.r.d. of (VIb) ($\Phi_{304}-715°$, $\Phi_{264}+639°$) is of opposite sign to that reported for the 5β,10β-steroid ($\Phi_{302}+7600°$, $\Phi_{264}-1560°$),[4] further suggesting a mirror-image relationship.

The nature of the reactive excited species has not been completely defined, although the reaction probably proceeds *via* α-cleavage as shown in (IV). If the irradiation is carried out in the presence of piperylene the reaction is greatly retarded, as would be expected for a triplet intermediate. When benzophenone was used as a sensitizer, (III) was rapidly destroyed and only a trace of (Va) was observed.¶

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¶ The reaction was monitored by gas chromatography. A separate irradiation experiment indicated that (Va) was only slowly rearranged in the presence of the sensitizer, benzophenone.

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[2] C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 1965, **21**, 163.
[3] T. Rull and G. Ourisson, *Bull. Soc. chim. France*, 1958, 1573.
[4] B. Camerino and U. Valcavi, *Gazzetta*, 1963, **93**, 723.