

PHOTOCHEMICAL REACTIONS OF 20-KETOSTEROIDS

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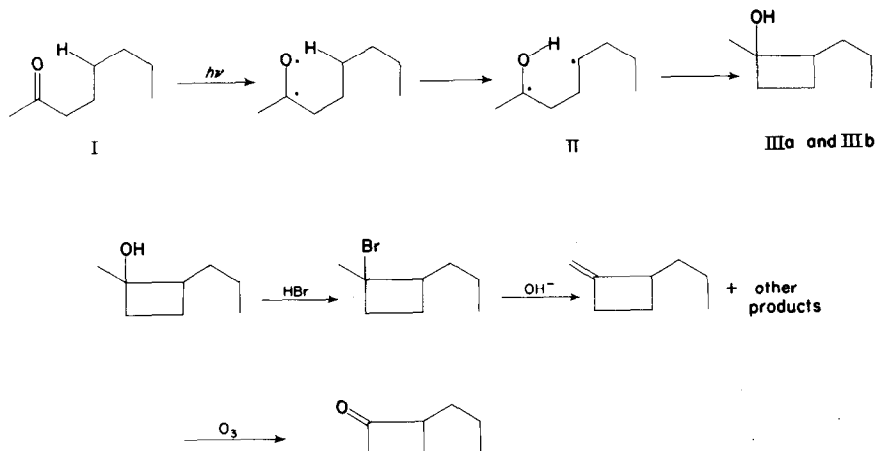
IN a previous communication from this laboratory,¹ it was shown that ketones having hydrogen atoms at γ -positions under the influence of ultraviolet light give, besides other products, cyclobutanols. Further investigations indicated that isomeric cyclobutanols were formed in these reactions. 2-Octanone (I) under previously reported conditions gave two isomeric 1-methyl-2-propylcyclobutan-1-ols (III): Compound IIIa, b.p. 67 - 68° (9 mm), n_D^{20} 1.4420, phenylurethane, m.p. 78°; Compound IIIb, b.p. 82° (38 mm), n_D^{20} 1.4402, phenylurethane, m.p. 102 - 103°. The structures of these isomers were established by chemical degradation. The cyclobutanols were converted to the corresponding bromides which were dehydrobrominated to mixtures of olefins. The mixtures of olefins showed infrared absorption at 1680 cm^{-1} and 880 cm^{-1} indicating the presence of a methylene cyclobutane.² Ozonization of these olefinic mixtures yielded 2-propylcyclobutanone, purified by distillation and gas chromatography, b.p. 73 - 75° (100 mm), ν_{max} 1780 cm^{-1} ,

¹ N.C. Yang and D.H. Yang, J.Amer.Chem.Soc. 80, 2913 (1958).

^{2a} J.D. Roberts and C.W. Sauer, J.Amer.Chem.Soc. 71, 3925 (1949).

^b R.C. Lord and F.A. Miller, Appl. Spectroscopy 10, 115 (1956).

and 2,4-dinitrophenylhydrazone, m.p. 116°.

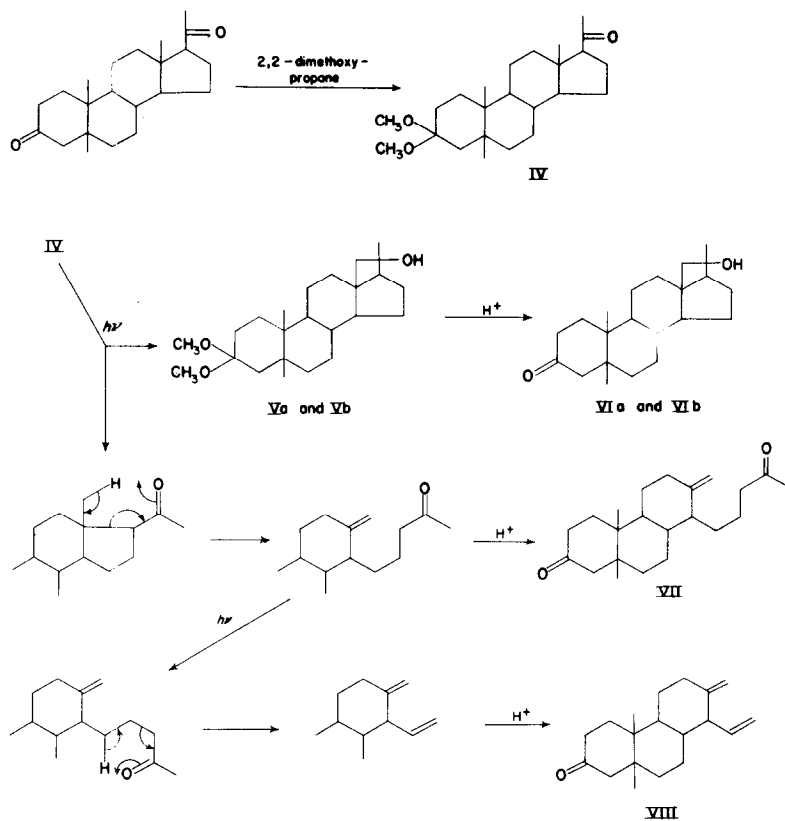


Recently, Jeger and coworkers³ reported the formation of single isomeric 20-hydroxy-18,20-cyclasteroids from the irradiation of 20-ketosteroids. Some of these cyclasteroids are intermediates in the synthesis of 18-oxygenated steroids. To explain the formation of only one isomeric 18,20-cyclasteroid, they postulated a "four-center" reaction mechanism. The results of independent investigation in this laboratory showed that two isomeric 20-hydroxy-18,20-cyclasteroids were actually formed in these reactions.

3,3-Dimethoxypregnan-20-one (IV), prepared by selective ketal interchange between 3,20-pregnanedione and 2,2-dimethoxypropane, was irradiated

³ O. Jeger et al., Helv. Chim. Acta 42, 2122 (1959).

in methanol by means of an immersion apparatus⁴ for 16 - 24 hr. Two isomeric 3,3-dimethoxy-18,20-cyclapregnan-20-ols (Va and Vb) were separated from the reaction medium by crystallization and chromatography. Compound Va was isolated in 24 - 35% yield, m.p. 168°, $[\alpha]_D^{25} = +29.0^\circ$ (CHCl₃); and Compound Vb was isolated in 8 - 12% yield, m.p. 111 - 112°, $[\alpha]_D^{25} = +33.9^\circ$ (CHCl₃). These compounds may be hydrolyzed readily to the corresponding 3-ketones, Compound VIa, m.p. 85 - 86° and Compound VIb, m.p. 175°. In addition to



⁴ M.S. Kharasch and H.N. Friedlander, J. Org. Chem. 14, 245 (1949)

these cyclasteroids, two by-products were isolated as their respective 3-ketones (VII and VIII). Compound VII, $C_{21}H_{32}O_2$, m.p. 88 - 89°, is an unsaturated ketone isomeric with pregnanedione with a vinylidene type of unsaturation ν_{\max} at 885 and 1640 cm^{-1} ⁵ which may be derived from a Type II photochemical cleavage⁶ of IV involving the 20-ketone function. Compound VIII, $C_{18}H_{26}O$, m.p. 97 - 99°, is a diene with both vinyl and vinylidene types of unsaturation ν_{\max} at 885 and 910 cm^{-1} ⁵ which may be derived from an additional Type II cleavage of the unsaturated ketone VII.

TABLE 1. Nuclear magnetic resonance spectra of 18,20-cyclasteroids

Compound	Methoxyl (3-CH ₃ O)	C ₂₁ -CH ₃ (CH ₃ CO)	C ₂₁ -CH ₃	C ₁₉ -CH ₃	C ₁₈ -CH ₃
3,3-Dimethoxypregnan-20-one (IV)	6.97,7.07	8.00		9.15	9.55
3,3-Dimethoxy-18,20-cyclapregnan-20-ol (Va)	6.93,7.03		8.85	9.05	
Vb	6.69,6.87		8.85	8.97	
18,20-Cyclapregnan-20-ol-3-one (VIa)			8.85	9.02	
VIb			8.85	9.02	

⁵ L.J. Bellamy, The Infrared Spectra of Complex Molecules (2nd Ed.) p.34. John Wiley, New York (1958).

^{6a} C.H. Bamford and R.G.W. Norrish, J.Chem.Soc. 1938, 1544;

^b W. Davis, Jr. and W.A. Noyes, Jr., J.Amer.Chem.Soc. 69, 2153 (1947).

⁷ The NMR spectra were measured with a Varian 40 mc High Resolution NMR spectrometer with superstabilizer. The unit given is according to G.V.D. Tiers, J.Phys.Chem. 62, 1151 (1958). The unit of cps with benzene as external reference may be converted to (p.p.m. with Me₄Si as internal reference) by the following formula:

$$\tau = 3.60 + \frac{\text{cps}}{40}$$

The structures of 18,20-cyclasteroids V and VI are supported by NMR spectrometry. The NMR spectrum of 3,3-dimethoxypregnan-20-one shows peaks of methyl groups at 6.97 τ , 7.07 τ (methoxyl), 8.00 τ (C₂₁ acetyl methyl), 9.15 τ (C₁₉ methyl) and 9.55 τ (C₁₈ methyl).^{7,8} The disappearance of methyl peaks in 9.50 region in Compounds Va, VIa, and VIb is indicative of the participation of C₁₈ methyl group in these photochemical reactions. The shifting of methyl peak from 8.00 to 8.55 (singlet) shows that the C₂₁ methyl is no longer adjacent to a carbonyl group but is attached to a tertiary carbon atom in these compounds.

Isomeric 18,20-cyclasteroids (IX) were also formed from the photolysis of pregnenolone in ethanol, Compound IXa, m.p. 236°, [α]_D²⁵ = -27.5° (abs. ethanol) and Compound IXb, m.p. 190°, [α]_D²⁵ = -24.2° (abs. ethanol). These isomeric cyclasteroids (IX) may be oxidized with aluminium isopropoxide and cyclohexanone to the corresponding isomeric 18,20-cyclasteroids (X), Compound Xa, m.p. 204 - 205° and Compound Xb, m.p. 163 - 165°. The structures of these compounds are supported by spectroscopic evidence.

The formation of isomeric cyclobutanols in these photochemical reactions are in agreement with the stepwise mechanism postulated earlier. The excited carbonyl function abstracts a hydrogen atom from the γ -position to give a diradical (II) which then cyclizes to give isomeric cyclobutanols. The detail mechanism of this reaction and the relative configuration of these alcohols are currently being investigated.

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⁸ J.N. Shoolery and M.T. Rogers, J.Amer.Chem.Soc. 80, 5121 (1958).