

A NOVEL PHOTOCHEMICAL ADDITION REACTION OF
3 β -ACETOXPREGNA-5,16-DIEN-20-ONE

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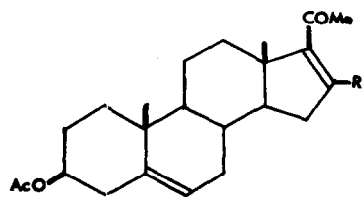
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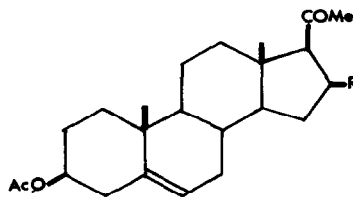
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The considerable interest shown recently in 16-alkylated steroids stems largely from the potent biological properties of dexamethasone (16 α -methyl-9 α -fluoroprednisolone)¹. The available methods for the introduction of 16-alkyl-substituents into the steroid nucleus have been usually based on the readily available Δ^{16} -20-oxosteroids, and proceed, for example, by addition of Grignard reagents², or by addition of diazomethane². We now wish to report a new method for the introduction of oxygen-bearing 16 α -alkyl substituents.

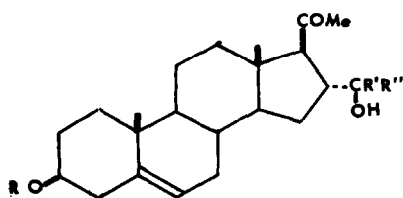
When 3 β -acetoxypregna-5,16-dien-20-one (Ia) in ethanol solution was irradiated with ultraviolet light, a rapid reaction (complete in 1.5 hr.) occurred and two crystalline products were isolated. The first was 3 β -acetoxypregn-5-en-20-one (IIa), formed by reduction of the Δ^{16} -double bond. The second, m.p. 199-203°, $[\alpha]_D - 59^\circ$, was formed by addition of the elements of ethyl alcohol to the steroid, and is assigned the structure, 3 β -acetoxy-16 α -(1'-hydroxyethyl)-pregn-5-en-20-one (IIIa), for the following reasons. It showed peaks in the infrared spectrum at 3695 and 3540 cm.⁻¹ indicative of the presence of a hydroxyl group, and on



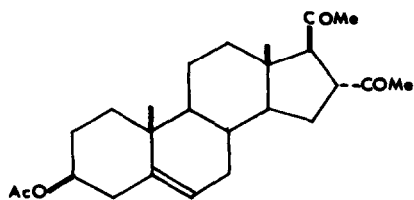
(Ia, R=H)
(Ib, R=Me)



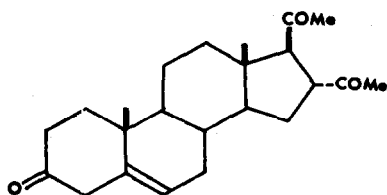
(IIa, R=H)
(IIb, R=Me)



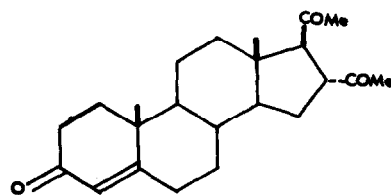
(IIIa, R=Ac, R'=H; R''=Me)
(IIIb, R=R'=H, R''=Me)
(IIIc, R=Ac, R'=R''=Me)
(III d, R=Ac, R'R''=cyclo(CH₂)₅)



(IV)



(V)



(VI)

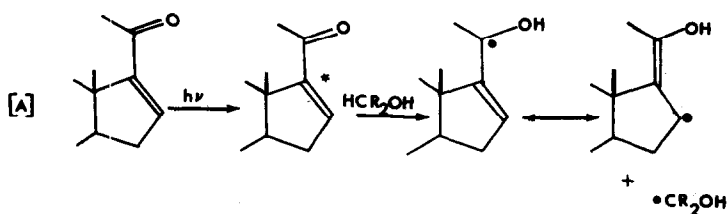
oxidation with chromic acid in acetone it gave the diketone (IV), m.p. 181.5-184°, $[\alpha]_D + 7.2^\circ$. The nuclear magnetic resonance spectrum of this last compound showed the presence of two C-acetyl groups (peak at 7.86 τ , area \equiv 6 protons) in addition to the 3-acetate group (peak at 7.99 τ , area \equiv 3 protons). The product (IIIb) of saponification of the photo-addition product (IIIa) on oxidation with the same reagent gave the triketone (V), which was not isolated but was isomerised by aqueous sulphuric acid in methanol to 16 α -acetyl-pregesterone (VI), m.p. 171-175°, $[\alpha]_D + 158^\circ$, identical in all respects (I.R., N.M.R., mixed m.p.) with an authentic sample³. This correlation proves in particular that the entering group in the photo-chemical reaction has the α -configuration. The photo-addition product (IIIa) is probably a mixture of two compounds stereoisomeric at position 1', although thin layer chromatography did not reveal any inhomogeneity.

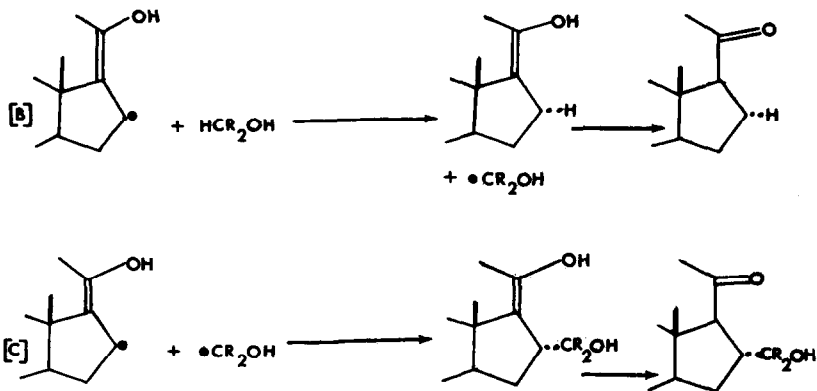
By using secondary alcohols (e.g. isopropanol, cyclohexanol) as solvents in this novel photochemical reaction, other addition products were formed e.g. 3 β -acetoxy-16 α -(1'-hydroxy-1'-methylethyl)-pregn-5-en-20-one, (IIIc), m.p. 186-189°, $[\alpha]_D + 7.25^\circ$; and 3 β -acetoxy-16 α -(1'-hydroxy-cyclohexyl)-pregn-5-en-20-one, (IIId), m.p. 206-209.5, $[\alpha]_D + 0.8^\circ$, the yield in all cases being 30-40%. Pregnenolone acetate (IIa) was again formed in 40-50% yield. With tert-butanol as solvent, the overall rate of the photochemical reaction was much less, and pregnenolone acetate was the

only identifiable product. A similar slow reaction occurred in dioxan when pregnenolone acetate was accompanied by a small yield of a bi-steroid derivative.

When 3β -acetoxy-16-methyl-pregna-5,16-dien-20-one (Ib) was irradiated in ethanol or isopropanol solution, no addition of the solvent took place, but the disappearance of the 252 m μ peak in the ultraviolet spectrum was rapid, and almost quantitative yields of the reduction product, 3β -acetoxy-16 β -methylpregn-5-en-20-one (IIb), m.p. 147-148°, $[\alpha]_D - 22.2^\circ$ were obtained.

Previous records of photochemical addition of alcohols to olefines are rare. Urry, Stacey, Huyser and Juveland⁴ reported the addition of ethanol to hex-1-ene and of isopropanol to oct-1-ene to yield octan-2-ol and 2-methyldecan-2-ol respectively. These, in contrast to the reactions reported here, proceeded slowly and in poor yield, and are addition reactions of hydroxyalkyl radicals formed in inefficient photo-activation steps. The present reaction probably proceeds by the following steps:-





Reactions [A] and [B] lead to the reduction products while [A] and [C] give photo-addition products. It must be supposed that steric effects prevent reaction [C] when there is a 16 α -methyl group present. These mechanisms find analogies in the well known pinacol formation reactions or aromatic ketones⁵.

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