[Chem. Pharm. Bull. 27(7)1679—1682(1979)]

UDC 547.92.04.09 : 615.276.011.5.015.4

Photochemical Reaction of 21-Methyl-20,21-diketosteroids: The Formation of New 3′,4′,16α,17α-Tetrahydrocyclobut[16,17]androstanes

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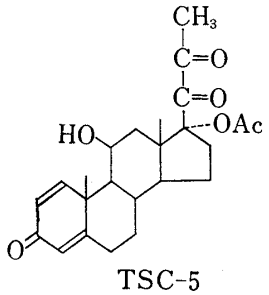
(Received October 23, 1978)

Exposure of 11β,17α-dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-acetate (Ia) and 17α-hydroxy-21-methylpregn-4-ene-3,20,21-trione 17-acetate (Ib) in EtOH to sunlight gave products having a new ring system in excellent yields, *i.e.*, 3′,4′,16α,17α-tetrahydro-4′ξ,11β,17α-trihydroxy-4′ξ-methylcyclobut[16,17]androsta-1,4,16-triene-3,3′-dione 17-acetate (IIa) and 3′,4′,16α,17α-tetrahydro-4′,17α-dihydroxy-4′ξ-methylcyclobut[16,17]androsta-4,16-diene-3,3′-dione 17-acetate (IIb). The structures of the products were assigned on the basis of spectral data.

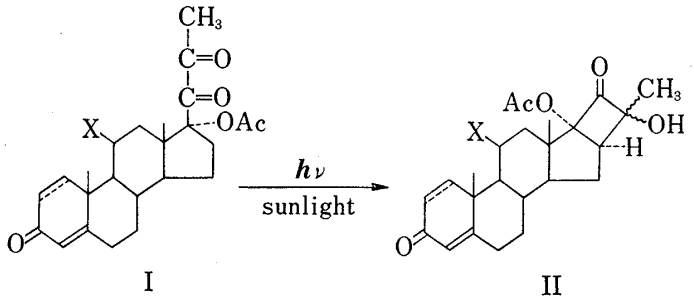
Keywords——photochemical cyclization; 20,21-diketocorticosteroid; cyclobut[16,17]-androstane; anti-inflammatory activity; ^{13}C NMR

In our previous papers,[2] we described the preparation of a series of 17α-hydroxy-21-methyl-20,21-diketocorticosteroid 17-acylates from the corresponding 21-hydroxymethyl-corticosteroids, of which 11β,17α-dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-acetate (TSC-5) showed potent anti-inflammatory activity.[3] In this paper, we report a photochemical reaction of 17α-hydroxy-21-methyl-20,21-diketocorticosteroid 17-acetates and give ^{13}C nuclear magnetic resonance (^{13}C NMR) data for the reaction products.



TSC-5

Chart 1



I
a: X=OH, Δ¹
b: X=H

II
a: X=OH, Δ¹
b: X=H

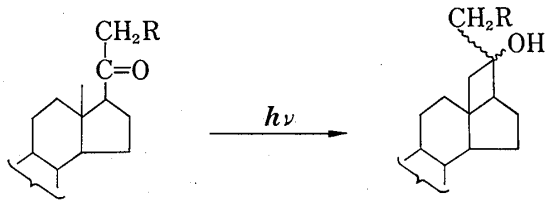
Chart 2

The yellow color of a solution of TSC-5 in EtOH faded rather rapidly when the solution was kept in the light, while the color did not fade in the dark. This finding prompted us to investigate the photochemical reaction of 17α-hydroxy-21-methyl-20,21-diketocorticosteroid 17-acetates (I). The starting materials in this study, 11β,17α-dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-acetate (Ia) and 17α-hydroxy-21-methylpregn-4-ene-3,20,21-trione 17-acetate (Ib), were synthesized according to the method[2] described by Noguchi *et al.* The materials were dissolved in EtOH in a glass flask and exposed to sunlight outdoors. The

1) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
2) *a*) S. Noguchi and K. Morita, *Chem. Pharm. Bull.* (Tokyo), **11**, 1235 (1963); *b*) S. Noguchi, F. Nakayama, and K. Morita, *ibid.*, **12**, 1180 (1964); *c*) S. Noguchi, H. Otsuka, M. Obayashi, M. Imanishi, and K. Takahashi, *Steroids*, **12**, 9 (1968).
3) K. Kawai, presented at the 32nd Kinki Meeting of the Pharmaceutical Society of Japan, Kyoto, April 7, 1967.

yellow color of the solution faded under sunlight within 3 hr. Removal of EtOH by evaporation, followed by recrystallization afforded 3′,4′,16α,17α-tetrahydro-4′ξ,11β,17α-trihydroxy-4′ξ-methylcyclobut[16,17]androsta-1,4,16-triene-3,3′-dione 17-acetate (IIa) and 3′,4′,16α,17α-tetrahydro-4′ξ,17α-dihydroxy-4′ξ-methylcyclobut[16,17]androsta-4,16-diene-3,3′-dione 17-acetate (IIb) from Ia and Ib, respectively, almost quantitatively.

The structure (II) of the reaction products was assigned on the basis of their physicochemical properties. Elemental analysis of IIa and IIb gave satisfactory values for $C_{24}H_{30}O_6$ and $C_{24}H_{32}O_5$, respectively. Conversion of the C-21 carbonyl group in I to a hydroxyl group was suggested by the infrared (IR) and NMR spectral data. An absorption band due to a hydroxyl group was observed at 3550 cm^{-1} in IIa and 3510 cm^{-1} in IIb in the IR spectra. NMR spectra showed a signal due to the hydroxyl group at 4.70 ppm in IIa and at 4.64 ppm in IIb, which disappeared on treatment with D_2O. In addition, the conversion of the C-21 carbonyl group into a hydroxyl group was confirmed by an upfield shift of the signal due to the C-21a methyl group from 2.31 ppm to 1.42 ppm in IIa and from 2.32 ppm to 1.41 ppm in IIb. The fact that II failed to undergo acetylation but was recovered unchanged under usual reaction conditions using Ac_2O–pyridine shows that the newly formed hydroxyl group was tertiary.



R=H, OAc

Chart 3

The presence of a cyclobutane ring in II was suggested by the IR spectra, which showed an absorption band ascribable to cyclobutanone at 1790 and 1786 cm^{-1} in IIa and IIb, respectively. As noted in the experimental section, NMR and IR spectral data showed that the ring A system, 18- and 19-methyl groups, and 17α-acetoxyl group in both IIa and IIb and the 11β-hydroxyl group in IIa remained unchanged.

It has been reported[4] that the irradiation of 20-ketopregnane derivatives leads to the formation of 20-hydroxy-18,20-cyclopregnanes. However, the present study clearly showed that 21-methyl-20,21-diketocorticosteroids underwent cyclization upon irradiation between C-16 and C-21, not between C-18 and C-20. In particular, the retention of the C-18 methyl group in II shown in the NMR spectrum [1.19 ppm (3H, s) in IIa and 0.88 ppm (3H, s) in IIb] and the presence of cyclobutanone shown in the IR spectrum excluded the possibility of the formation of a C–C bond between C-18 and C-20.

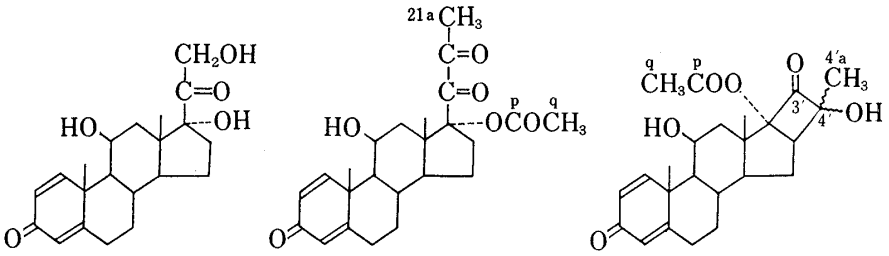
Further support for the structure II was obtained from ^{13}C NMR data. Assignment of the signals of Ia and IIa was made by comparison with those of 11β,17α-dihydroxypregna-1,4-diene-3,20-dione (prednisolone) and other steroids.[5] The data obtained are collected in Table I.

Inspection of the data shows that the singlet signal at 197.2 ppm due to the C-21 carbonyl carbon in Ia was replaced by the singlet signal at 85.4 ppm in IIa, which is ascribable to a carbon having a hydroxyl group. This supports the conversion of the C-21 carbonyl group in Ia into a hydroxyl group in IIa. The formation of a four-membered ring was also strongly suggested by the observation that a triplet signal at 33.5 ppm due to C-16 was converted into a doublet signal at 57.3 ppm. Furthermore, signals at 194.8 ppm due to the C-20 carbonyl carbon in Ia and at 210.7 ppm due to the C-3′ carbonyl carbon in IIa are in good agreement

4) *a*) P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959); *b*) M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *ibid.*, **46**, 354 (1960); *c*) H. Wehrli, M. Cereghetti, K. Schaffner, and O. Jeger, *ibid.*, **47**, 367 (1960).

5) *a*) H.H. Reich, M. Jautelat, M.T. Messe, F.J. Weighert, and J.D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969); *b*) G.C. Levy and F.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, 1972.

TABLE I. ^{13}C Chemical Shifts of Prednisolone, 11β,17α-Dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-Acetate (Ia) and 3′,4′,16α,17α-Tetrahydro-4′ξ,11β,17α-trihydroxy-4′ξ-methylcyclobut[16,17]androsta-1,4,16-triene-3,3′-dione 17-Acetate (IIa)



prednisolone Ia IIa

Position	Compounds		
	Prednisolone[a]	Ia[a]	IIa[a]
1	156.2(d)	156.0(d)	156.0(d)
2	126.4(d)[b]	127.6(d)[b]	127.6(d)[b]
3	185.5(s)	186.2(s)	186.2(s)
4	121.1(d)[b]	122.2(d)[b]	122.2(d)[b]
5	169.9(s)	169.7(s)	169.5(s)
6	33.4(t)[c]	33.9(t)[c]	34.0(t)
7	31.3(t)	31.9(t)	31.8(t)
8	30.6(d)	31.4(d)	31.2(d)
9	54.8(d)	55.0(d)	55.1(d)
10	43.5(s)	43.9(s)	44.0(s)
11	68.6(d)	70.0(d)	70.1(d)
12	38.5(t)	41.1(t)	41.9(t)
13	46.7(s)	47.8(s)	44.7(s)
14	50.6(d)	53.0(d)	55.6(d)[c]
15	23.2(t)	24.1(t)	29.6(t)
16	33.1(t)[c]	33.5(t)[c]	57.3(d)[c]
17	87.9(s)	94.5(s)	102.7(s)
18	16.4(q)	17.1(q)	16.5(q)
19	20.2(q)	21.0(q)	20.9(q)
20	211.5(s)	194.8(s)[d]	(3′) 210.7(s)
21	66.1(t)	197.2(s)[d]	(4′) 85.4(s)
		(21a) 24.6(q)	(4′a) 17.8(q)
		(p) 171.8(s)	(p) 171.0(s)
		(q) 21.0(q)	(q) 20.6(q)

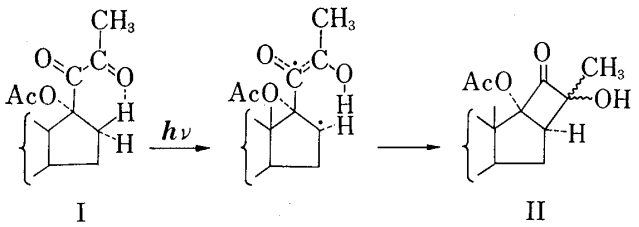
a) Letters in parentheses indicate the multiplicity: s, singlet; d, doublet; t, triplet: q, quartet.
b), *c*), *d*) These assignments may be reversed, although those given here are preferred.

with the reported signals due to carbonyl carbons for α-diketone and cyclobytanone groups,[5b] respectively. Downfield shifts by 5.5 ppm and 8.2 ppm of C-15 and C-17, respectively, coincide with the known[5b] downfield shifts of carbons adjacent to a carbon into which an alkyl group is introduced. No other significant shift was noted except for the upfield shift of C-13 by 3.1 ppm and the downfield shift of C-14 by 2.6 ppm, both of which might reflect the steric influence of the four-membered ring thus formed.

II was assigned as having the *R* configuration at C-16, since C–C bond formation between C-16 and C-21 was considered to be possible only from the β-side. The stereochemistry at C-4′ could not be definitely assigned from the spectral data so far obtained.

Several reports[6] have described the formation of a hydroxycyclobutanone ring by the photochemical reaction of alkyl α-diketones possessing a γ-carbon bearing a hydrogen. In

6) N.J. Turro and T.J. Lee, *J. Am. Chem. Soc.*, **91**, 5651 (1969) and references cited therein.



I II

Chart 4

the present reaction, the product (II) was considered to be produced by the abstraction of 16β-hydrogen by the C-21 carbonyl group, followed by intramolecular cyclization as shown below.

The selective formation of II in this study might be due to the facile formation of the six-membered cyclic transition state (I) for hydrogen transfer.

IIa and IIb did not show any significant anti-inflammatory activity in the carrageenin edema test in rats.

Experimental[7]

3′,4′,16α,17α-Tetrahydro-4′ξ,11β,17α-trihydroxy-4′ξ-methylcyclobut[16,17]androsta-1,4,16-triene-3,3′-dione 17-Acetate (IIa)——A yellow solution of 2.0 g of 11β,17α-dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-acetate (Ia) in 200 ml of EtOH was placed in a glass flask (not necessarily of Pyrex) and exposed to sunlight outdoors at around 25°. The yellow color of the solution faded completely within 3 hr. The solution was concentrated to dryness to give a white residue, which was crystallized from CH_2Cl_2–EtOH to afford 1.6 g (80%) of white crystals, mp 270°, $[\alpha]_D^{24}$ −186.5° (c=1.0, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3550, 3500, 1790, 1730, 1660. NMR ($CDCl_3$): 1.19 (3H, s, 18-CH_3), 1.42 (3H, s, 4′-CH_3), 1.50 (3H, s, 19-CH_3), 2.12 (3H, s, 17-$OCOCH_3$), 4.70 (1H, s, D_2O-exchangeable, 4′-OH), 6.04 (1H, s, 4-H), 6.25 (1H, q, J=10 Hz, 2 Hz, 2-H), 7.33 (1H, d, J=10 Hz, 1-H). Mass spectrum m/e: 372, 354, 343, 311. *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.26; H, 7.84.

3′,4′,16α,17α-Tetrahydro-4′ξ,17α-dihydroxy-4′ξ-methylcyclobut[16,17]androsta-4,16-diene-3,3′-dione 17-Acetate (IIb)——Two g of 16-hydroxy-21-methylpregn-4-ene-3,20,21-trione 17-acetate (Ib) was treated in the same way as for Ia. Crude IIb was crystallized from CH_2Cl_2–MeOH to afford 1.6 g (80%) of white crystals, mp 223—225°. $[\alpha]_D^{24}$ −179.4° (c=1.0, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3510, 1786, 1721, 1670, 1619. NMR ($CDCl_3$): 0.88 (3H, s, 18-CH_3), 1.22 (3H, s, 19-CH_3), 1.41 (3H, s, 4′-CH_3), 2.16 (3H, s, 17-$OCOCH_3$), 4.64 (1H, s, D_2O-exchangeable, 4′-OH), 5.74 (1H, s, 4-H). Mass spectrum m/e: 372, 358, 340, 329, 311. *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.22; H, 8.13.

Acetylation of IIa and IIb——Acetic anhydride (1 ml) was added to a solution of 0.5 g of IIa or IIb in 5 ml of pyridine, and the solution was left to stand at room temperature overnight. The resulting solution was poured into ice-water and the precipitates were collected by filtration, washed with water, and dried. Elemental analysis and IR and NMR spectra showed the product to be identical to the starting material IIa or IIb. From IIa: mp 268—269°. *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.46; H, 7.77. From IIb: mp 222—223°. *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.15; H, 8.22.

Acknowledgement The authors are grateful to Dr. E. Ohmura, Managing Director and Director of the Central Research Division, Takeda Chemical Industries, Ltd. for his encouragement and advice and to Dr. K. Morita, Director of the Medicinal Research Laboratories of the Central Research Division for fruitful discussions throughout the work.

7) Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Hitachi EPI-S2 spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were determined on a Varian XL-100-12 Fourier transform spectrometer operating at 25.2 MHz with proton noise decoupling and off-resonance decoupling techniques. The spectral width was 240 ppm and 8192 data points were used for 12000—20000 accumulations. The samples, Ia (200 mg) and IIa (180 mg), were dissolved in $CDCl_3$ (3 ml), and prednisolone (200 mg) in $CDCl_3$–d_6-DMSO (50: 50). The ^{13}C-shifts were measured relative to the ^{13}C signal of $CDCl_3$ and converted to ppm from TMS using δ ($CDCl_3$)=76.9.