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Solid-State Photodimerization of 16-Dehydroprogesterone

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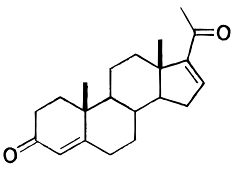
16-Dehydroprogesterone (**1**), a commercial steroid widely utilized in chemical[1] and biomedical research,[2] undergoes solid-state photodimerization to afford ring D−side-chain-connected dimer **2**.



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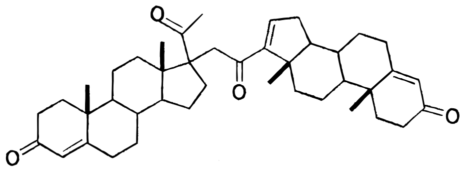

2

The dimerization was primarily observed when an aqueous suspension of **1** in a Pyrex flask was irradiated with fluorescent lamps. Under these conditions, **1** was slowly converted into **2**, which was formed in 20% yield after 10 days. The photodimerization was faster with a halogen lamp, and when solid **1** was irradiated for 10 h a 25% yield of **2** was obtained. The same amount of **2** was obtained after irradiation with a UV lamp for 1 h. On the contrary, no trace of **2** was detected when solutions of **1** in CH_3CN, dioxane, or CH_3OH were irradiated for the same period of time.

The attribution of structure **2** to the dimer derived from its physical features. It had a molecular peak in the EIMS spectrum at *m*/*z* 624 and showed a composition in the elemental analysis that agreed with the molecular formula $C_{42}H_{56}O_4$. Only 36 signals were present in the ^{13}C NMR spectrum. Six of them were integrated for two carbons in an inverse gated experiment. DEPT experiments showed the presence of only five methyls in addition to 16 methylene carbons and nine methine carbons, three of them vinylic. The remaining carbon signals could be attributed to four carbonyl carbons, three olefinic carbons, and five quaternary carbons. The ^1H NMR spectrum showed three olefinic protons, two as sharp singlets at δ 5.72 and 5.74 and one as a broad singlet at δ 6.70. In the spectrum were also detectable two methylene protons as two AB doublets at δ 2.92 and 3.39, a methylenic proton as a multiplet at δ 2.67, and five methyl singlets at δ 0.88, 0.91, 1.18, 1.20, and 2.08.

In the HMBC spectrum, the H-21 methyl protons at δ 2.08, linked to the carbon at δ 29.8, were heterocorrelated to the C-20 carbonyl at δ 212.2. The H-21′ proton at δ 2.92, linked to carbon at δ 45.8, was also related to the same carbon. Both the H-21′ protons at δ 2.92 and 3.39 gave cross-peaks with the C-17 carbon at δ 62.1, while only the latter gave a cross-peak with the quaternary carbon at δ 46.5, attributed to C-13. The correlation of the C-17 carbon to the methyl protons at δ 0.88 allowed these signals to be attributed to the H-18 methyl, and subsequently, the methyl protons at δ 0.91 were assigned to the C-18′ position. The H-21′ methylene protons were also heterocorrelated to the C-20′ carbonyl carbon at δ 197.5, and this carbon gave a further correlation with the olefinic H-16′ proton at δ 6.70. This latter along with the H-18′ methyl protons was correlated to both the C-17′ olefinic carbon at δ 154.9 and the C-13′ carbon at δ 46.5.

The configuration at C-17 derived from NOESY experiments. The H-21′ methylene proton at δ 2.92 gave NOE with the C-18 methyl protons at δ 0.88 while H-21′ methylene proton at δ 3.39 gave NOEs with the H-21 methyl protons at δ 2.08 and the H-16′ olefinic proton at δ 6.70. Furthermore, the H-21 methyl proton interacted with the C-18′ methyl protons at δ 0.91. These data unequivocally oriented α the acetyl group at C-17 and β the linkage between the two steroid moieties.

Formation of **2** might be justified through the H-21 hydrogen atom transfer from the first unit to the carbon C-16 of the second unit possessing the lowest (π,π*) triplet state and subsequent connection of the radicals at C-21 and C-17.

To achieve further support for this dimerization scheme, the X-ray crystal structure analysis of 16-dehydroprogesterone was carried out. Both Cu and Mo Kα radiations were suitable for data collection as no damage to crystals was observed. The scrutiny of intermolecular contacts in the crystal packing reveals a head-to-head contact between the reference molecule (unprimed unit) and the molecule at $0.5 + x$, $0.5 - y$, $1 - z$ (primed unit), which really fulfills the conditions required by the proposed mechanism. In fact, as shown in Figure 1, the methyl carbon C-21′ is 4.14 and 4.05 Å, respectively, from the olefinic C-16 and C-17, and its hydrogen atoms can attain the distance of about 3.4 Å from C-16. This value is only

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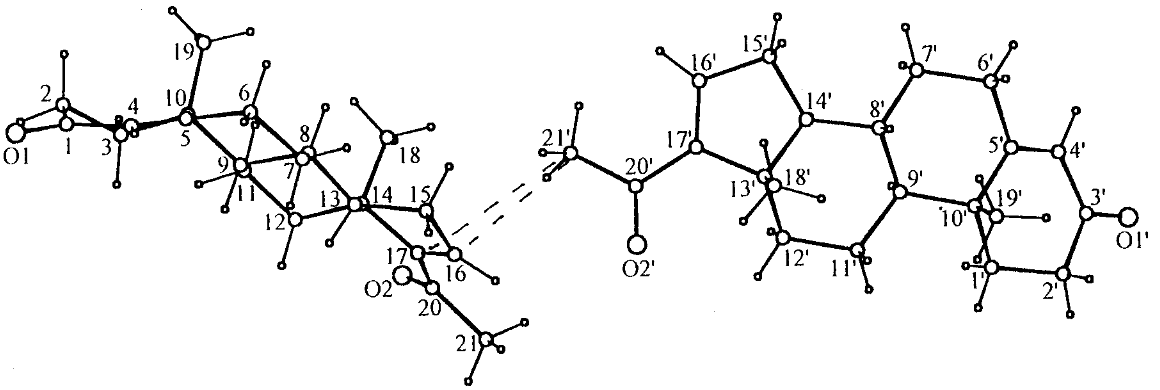

Figure 1.

0.5 Å larger than the sum of van der Waals radii of the two atoms and is compatible with a dimerization mechanism which demands, in the crystalline state, a minimum of molecular motion.

To test whether the photoreaction is topotactic, that is, with a substantial maintenance of crystalline organization, the crystal used for the X-ray data was exposed for 1 h to radiation active in the photodimerization. The experiment resulted in a partial destruction of the crystal. The remaining part, corresponding to about a tenth of the original crystal, was used for a recollection of the X-ray data. The subsequent analysis showed the preservation of diffration pattern. The agreement between old and new intensity data, properly scaled, was about 5%. This result indicates that the active radiation in the photoreaction is not simply a trigger but a quantitative participant of process.

Dimeric steroids are emerging as a class of compounds that have potential applications in pharmacology[3] as well as in other fields such as detergents,[4] liquid crystals,[5] and catalysis.[6] These compounds have been obtained by chemical couplings[7] as well as photochemical[8] and microbial[9] processes. Photochemical dimerization of unsaturated ketosteroids in solution has been extensively studied and dimers of 3-keto and 7-ketosteroids formed through [2 + 2] cycloaddition have been described.[10,11] The photodimerization of norethisterone in the solid state has been reported[12] to occur through side chains to give a seco dimer product.

Experimental Section

An aqueous suspension (50 mL) of 16-dehydroprogesterone (**1**) (100 mg) in a Pyrex flask was irradiated with fluorescent lamps (Philips, TLD 30w/55) under magnetic stirring at 24 °C for 10 days. EtOAc extraction and flash chromatography (silica gel, EtOAc−hexane 3:2) followed by preparative TLC gave **2** (20 mg) as a colorless oil: ^{1}H NMR (CDCl$_3$) 6.70 (1H, brs, H-16′), 5.72 (1H, s, H-3 or H-3′), 5.74 (1H, s, H-3′ or H-3), 3.39 (1H, d, J = 18.0 Hz, H-21′), 2.92 (1H, d, J = 18.0 Hz, H-21′), 2.08 (3H, s, H-21), 1.20 (3H, s, H-19), 1.18 (3H, s, H-19′), 0.91 (3H, s, H-18′), 0.88 (3H, s, H-18); ^{13}C NMR (CDCl$_3$) 35.6 and 35.7 (C-1 and C-1′), 34.0 (C-2 and C-2′), 199.1 (C-3 and C-3′), 124.7 (C-4 and C-4′), 170.6 (C-5 and C-5′), 32.7 and 32.8 (C-6 and C-6′), 31.9 and 32.0 (C-7 and C-7′), 36.2 (C-8), 53.3 (C-9), 38.5 and 38.7 (C-10 and C-10′), 20.7 and 20.9 (C-11 and C-11′), 34.4 (C-12 and C-12′), 46.5 (C-13 and C-13′), 50.0 (C-14), 25.4 (C-15), 32.1 (C-16), 62.1 (C-17), 16.2 (C-18), 17.2 and 17.4 (C-19 and C-19′), 212.2 (C-20), 29.8 (C-21), 33.9 (C-8′), 54.1 (C-9′), 55.7 (C-14′), 32.4 (C-15′), 142.7 (C-16′), 154.9 (C-17′), 15.9 (C-18′), 197.5 (C-20′), 45.8 (C-21′); IR (CHCl$_3$) 1662, 1616, 1589 cm^{-1}; UV (λ_{max}, ϵ) 239, 4729. Anal. Calcd for C$_{42}$H$_{54}$O$_4$: C, 80.71; H, 9.04. Found: C, 80.63; H, 9.12.

Irradiation by Solar and UV Lamps. 1 (100 mg), solidified onto the surface of a Pyrex flask from a CH$_3$CN solution, was irradiated with a halogen superphot lamp (Osram, 650 W) for 10 h to give **2** (25 mg). **1** (100 mg), solidified onto the surface of a Pyrex flask from a CH$_3$CN solution, was irradiated with a Hanovia 450 W lamp for 1 h to give **2** (25 mg).

Crystal Data of 1. Crystal suitable for X-ray analysis were obtained in the darkness from methanol−acetone solutions: C$_{21}$H$_{28}$O$_2$, orthorhombic, $P2_12_12_1$, a = 6.384(2) Å, b = 11.708(3) Å, c = 23.575(5) Å, V =1762(1) Å^3, Z = 4, F(000) = 680, D_c = 1.18 g/cm^3. X-ray data were collected on an Enraf-Nonius CAD4-F diffractometer using the Cu Kα graphite-monochromated radiation (λ = 1.54056 Å), operated in the ω/θ scan mode. θ_{max} = 75°, μ = 0.69 cm^{-1}. The unit cell parameters were obtained by a least-squares fitting of the setting values of 25 strong reflections in the θ range $23 < \theta > 29°$. Three monitoring reflections, measured every 500, warranted stability conditions. A total of 2101 independent reflections were collected, of which 1877 were above $3\sigma(I)$. The structure was solved by direct methods.[13] The full-matrix least-squares refinement minimized the quantity $\Sigma w(\Delta F)^2$ with $w^{-1} = [\sigma^2(F_o) + (0.02F_o)^2 + 1.5]$ where σ is derived from counting statistics. All non-hydrogen atoms were refined anisotropically. The H atoms were added at calculated positions, also taking into account the indications of the difference electron density map for the methyl groups, with isotropic thermal parameters equal to those of the carrier atoms and held fixed during the refinement. The final refinement cycles included a secondary extinction parameter that converged to a value of 1.27(2) × 10^{-5}. The final values of R and R_w were 0.056 and 0.072, respectively. The final Fourier difference map was within 0.3 e Å^{-3}. All calculations were performed with the Enraf-Nonius (SDP) set of programs.[14] Complete lists of atomic positional and thermal parameters and bond distances and angles have been deposited as Supporting Information.

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Supporting Information Available: Crystallographic data of **1**, and ^{1}H- and ^{13}C-, COSY, HMQC, HMBC, and NOESY spectra of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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