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TRANSFORMED STEROIDS.

141. IODOSOBENZENE DIACETATE FOR THE α-HYDROXYLATION OF [17,16a]-2'-METHYLOXAZOLINE DERIVATIVES OF 20-KETOSTEROIDS

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Using the [17,16a-d]-2'-methyloxazoline derivatives of 3β-hydroxypregn-5-en-20-one (I) as an example, the α-hydroxylation reaction has been studied with the use of rodosobenzene diacetate in a methanolic solution of NaOH as the α-hydroxylating reagent. The reaction took place successfully through the stage of the formation and isolation of the corresponding [17,16a-d]-2'-methyloxazoline derivative of 20, 20-dimethylpregn-15-ene-3β,21-diol (II), the dimethyl acetal protection of which was eliminated by acid hydrolysis in methanol. The results of physicochemical investigations and biological trials of the [17,16a-d]-2'-methyloxazoline derivatives of 21-hydroxy-21-acetoxy-20-ketosteroids obtained are given.

The hydroxylation of position 21 of 16,17-substituted steroids is a complex task which sometimes cannot be resolved by ordinary methods. Iodosobenzene diacetate (IBD) has recently been proposed as a 21-hydroxylating reagent for 3β-hydroxypregn-5-en-20-one [1]. We have used this reagent successfully in the reaction with the [17,16a-d]-2'-methyloxazoline derivatives of 3β-hydroxypegn-5-en-20-one (I), after the methods of constructing the corticoid side chain usually used has proved unsuccessful.

The reaction of (I) with IBD in methanolic NaOH solution at 20°C took place through the formation of the 20-(dimethyl acetal) (II), the acetal group in which was eliminated by acid (HCl) hydrolysis in methanol, giving the 21-hydroxy derivative of the [17,16a-d]-2'-methyloxazoline compound (IV). The selective acetylation of the 21-hydroxy group of (IV) with acetic anhydride in pyridine at a low temperature (−30°C) gave the 21-acetoxy derivative (V), which was oxidized by the Oppenhauer method to the Δ^4-3-ketone (VI). The latter was converted by alkali ($KHCO_3$)saponification in methanolic solution into the 2-hydroxy-Δ^4-3-ketone (VII), which cannot be obtained by the selective oxidation of the diol (IV).

The structures of the products obtained were shown by a combination of physicochemical methods. The mass spectra of all the compounds represented in the scheme had molecular peaks. Arguments in favor of the presence of a methyloxazoline ring in each of compounds (II-VII) are the characteristic absorption of the C=N band at ν 1650-1670 cm^{-1} observed in the IR spectra, and the resonance signal of the methyl group in an oxazoline ring δ 1.85-1.92 ppm in the PMR spectra. The fact, not without interest, of the splitting of the carbonyl band in the IR spectrum of (IV) with ν 1700 and 1720 cm^{-1} is apparently due to the formation of an intramolecular hydrogen bond with the 21-hydroxy group. It follows from the PMR spectra that the protons of the 21-methylene group for each of the products obtained are either chemically equivalent (compounds (II), (V), and (VI)) or nonequivalent (compounds (III), (IV), and (VII)). In the latter case they exhibit the geminal coupling that is characteristic for

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an AB system with the constant J = 9-18 Hz with only small differences in the chemical shifts (0.04-0.25 ppm).

It is known that corticosteroids with methyloxazoline rings E exhibit high antiinflammatory activity, sometimes exceeding those of dexamethasone and of triamcinolone [2, 3]. In view of this, the compounds obtained, (IV,VII), were subjected to the corresponding tests by a method described previously [4]. Such testing was all the more of interest since it has recently been shown [5] that steroidal [16,17a-d]-2'-methyloxazolines even without 11- and 21-hydroxy groups may exhibit antiinflammatory action.

It was found, however, that not one of the compounds tested exerted an appreciable effect on the granulema of adrenalectomized rats when administered four times in daily doses of 10 and 20 mg/kg. At the same time, for compounds (VI) and (VII), in doses of 20 mg/kg a significant thymolytic activity of 30% and 25%, respectively, was detected, which is considered as a sign of glucocorticoid action [6].

EXPERIMENTAL

Melting points were determined on a Koffler block. IR spectra were taken on a UR-20 instrument in KBr tablets, and PMR spectra on a Tesla BS-497 (100 MHz) spectrometer in $CDCl_3$ solution with hexamethyldisilane as internal standard. Mass spectra were recorded on a MAT CH-6 instrument with direct introduction of the sample into the ion source.

[17,16a-d]-2'-Methyloxazoline Derivative of 20,20-Dimethoxypregn-5-ene-3β,21-diol (II). At 20°C, 1.28 g of (I) [7] was added to a solution of 1.96 g of NaOH in 19 ml of CH_3OH. The resulting suspension was treated with 1.2 g of $C_6H_5I(OAc)_2$ [8, 9], and the reaction mixture was stirred for 3.5 h. The solvent was evaporated off, washed with water, and recrystallized from aqueous CH_3OH. This gave 0.8 g of (II) with mp 196-201°C. IR spectrum, cm^{-1}: ν_{max}^{KBr} 955, 1050, 1085, 1675, 3405. PMR spectrum, δ, ppm: 0.9 s (18-CH_3); 0.96 s (19-CH_3); 1.91 s (2'-CH_3); 3.26 s (20-OCH_3); 3.32 s (20-OCH_3); 3.78 s (21-CH_2); 5.06 m (16-H); 5.26 m (6-H). Mass spectrum (m/z): 443 (M^+); 402 ($M^+ - OCH_3$); 388, 373, 358, 320.

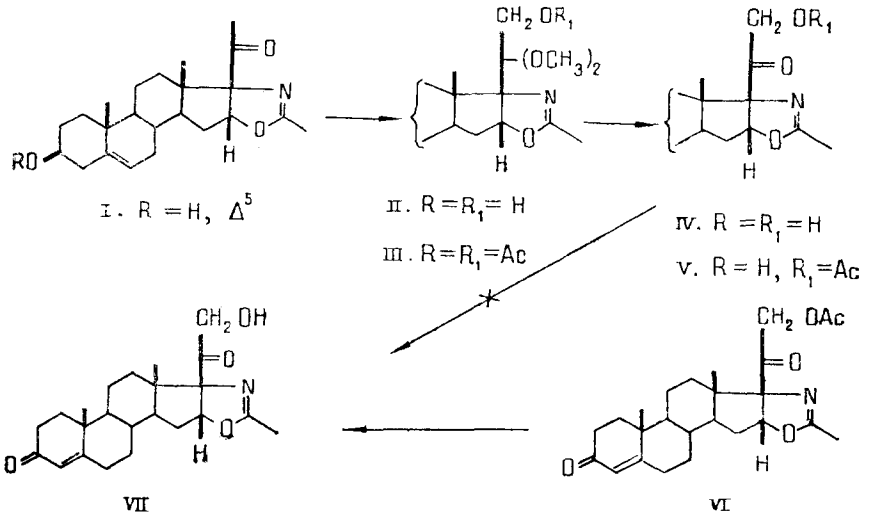
[17,16a-d]-2'-Methyloxazoline Derivative of 3β,21-Diacetoxy-20,20-dimethoxypregn-5-ene. A solution of 0.03 g of (II) in 3 ml of C_5H_5N and 0.3 ml of Ac_2O was kept at 20°C for 24 h and evaporated to dryness in vacuum by an azeotropic distillation with heptane, and the resulting residue was purified by TLC (SiO_2, ether). This gave 0.025 g of (III) with mp 145-150°C (from CH_3OH). IR spectrum, cm^{-1}, ν_{max}^{KBr}: 1025, 1035, 1240, 1250, 1263, 1380, 1670, 1732, 1745. PMR spectrum, δ, ppm: 0.93 s (18- and 19-CH_3); 1.85 s (2'-CH_3); 1.94 s (3-OAc); 1.98 s (21-OAc); 3.23 (s, 20-OCH_3); 3.42 s (20-OCH_3); 4.27 and 4.31 dd, J = 8.83 Hz (21-CH_2); 4.91 m (16-H); 5.26 m (6-H). Mass spectrum (m/z): 517 (M^+), 486 ($M^+ - OCH_3$), 444 ($M^+ - OCH_3 - COCH_2$).

[17,16a-d]-2'-Methyloxazoline Derivatives of 3β,21-Dihydropregn-5-en-20-one (IV). A solution of 0.47 g of (II) in 20 ml of CH_3OH containing 3 ml of 1 N HCl was boiled for 3 h. The solvent was evaporated off, the residue was dissolved in water, the solution was neutralized with aqueous NH_4OH, and the resulting precipitate was filtered off, washed with water, dried, and recrystallized from CH_3OH. This gave 0.34 g of (IV) with mp 210-220°C. IR spectrum, cm^{-1}, ν_{max}^{KBr}: 1660, 1700, and 1720; (C=O doublet); 3260, 3375, 3500. PMR spectrum, δ, ppm: 0.6 s (18-CH_3); 0.9 s (19-CH_3); 1.91 s (2'-CH_3); 3.4 m (3-H); 4.25 and 4.5 dd, J = 18 Hz (21-CH_2); 5.25 m (6-H, 16-H). Mass spectrum (m/z): 387 (M^+), 329 ($M^+ - NHAc$).

[17,16a-d]-2'-Methyloxazoline Derivative of 21-Acetoxy-3β-hydroxypregn-5-en-20-one (V). A solution of 0.13 ml of Ac_2O in 1 ml of C_5H_5N was added to a solution of 0.05 g of (IV) in 4 ml of C_5H_5N at −30°C. The reaction mixture was kept at the given temperature for 25 h. Then the acetic anhydride was decomposed with methanol and the solvent was eliminated by azeotropic distillation in vacuum with heptane. The residue was recrystallized from CH_2Cl_2–hexane, giving 0.03 g of (V) with mp 226-231°C. IR spectrum, cm^{-1}; ν_{max}^{KBr}: 1075, 1230, 1650, 1725, 1750, 3355. PMR spectrum, δ, ppm: 0.67 s (18-CH_3); 0.93 s (19-CH_3); 1.92 s (2'-CH_3); 2.09 s (21-OAc); 3.42 m (3-H); 4.9 s (21-CH_2); 5.25 m (6-H and 16-H). Mass spectrum (m/z): 429 (M^+), 414 ($M^+ - CH_3$), 386 ($M^+ - Ac$), 328 ($M^+ - COCH_2OAc$), 310 ($M^+ - COCH_2OAc - H_2O$).

[17,16a-d]-2'-Methyloxazoline Derivative of 21-Acetoxy-pregn-4-ene-3,20-dione (VI). A solution of 0.4 g of $Al(iOPr)_3$ in 4 ml of absolute toluene was added to a solution of 0.29 g of (V) in 9 ml of absolute toluene. After it has been boiled for 20 min, the reaction mixture was treated with Rochelle salt and was washed with water, the toluene solution was separated off and evaporated in vacuum, the residue was triturated with hexane, and the insoluble

residue was filtered off and recrystallized from a mixture of acetone and hexane. This gave 0.162 g of (VI) with mp 206-210°C. IR spectrum, cm^{-1}, λ_{max}^{KBr}: 1235, 1615, 1660, 1680, 1725, 1750. PMR spectrum, δ, ppm: 0.70 s (18-CH_3); 1.10 s (19-CH_3); 1.90 s (2'-CH_3); 2.08 s (21-OAc); 4.86 s (21-CH_2); 5.7 m (16-H); 5.64 (4-H). UV spectrum, $\lambda_{max}^{C_2H_5OH}$: 240 nm (log ε 4.11). Mass spectrum (m/z): 427 (M^+), 384 (M^+ − Ac), 367 (M^+ − HOAc), 326 (M^+ − $COCH_2OAc$), 315.4 ($426^{\pm} \rightarrow 367$), 284.



[17,16a-d]-2'-Methyloxazoline Derivative of 21-Hydroxypregn-4-ene-3,20-dione (VII). A solution of 0.18 g of (VI) in 18 ml of CH_3OH containing 3.6 ml of 5% $KHCO_3$ was kept at 20°C for 24 h. The solvent was distilled off, the residue was diluted with water, and the resulting precipitate was filtered off, washed with water, dried, and crystallized from aqueous acetone. Yield 0.155 g of (VII), mp 196-200°C. IR spectrum, cm^{-1}, λ_{max}^{KBr}: 1618, 1670, 1720, 3450. PMR spectrum, δ, ppm: 0.95 s (18-CH_3); 1.12 s (19-CH_3); 1.92 s (2'-CH_3); 4.33 and 4.42 dd, J = 15 Hz (21-CH_2); 5.42 m (16-H); 5.65 (4-H). UV spectrum, $\lambda_{max}^{C_2H_5OH}$: 242, 291 nm (log ε 4.26, 2.27). Mass spectrum (m/z): 385 (M^+), 370 (M^+ − CH_3), 367 (M^+ − H_2O), 327 (M^+ − NHAc), 312 (M^+ − NHAc − CH_3), 297, 285, 270.

SUMMARY

[17,16a-d]-2'-Methyloxazoline derivatives of 21-hydroxy- and 21-acetoxy-20-ketosteroids have been synthesized and subjected to biological tests.

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