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Synthesis of some new steroidal [16α,17α-d]-isoxazolines

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Abstract

Regioselective synthesis of novel steroidal anti-inflammatory ante drug analogues, viz., [16α,17α-d]-isoxazolines **1(a–h)** and **2(a–h)** prepared in a single step in good yield by the reaction of 16-dehydropregnenolone acetate (16-DPA) **1** or related 21-chloro-20-oxopregnane **2** with various aldoximes **(a–h)** in presence of chloramine-T in refluxing ethanol.

Keywords: 16-Dehydropregnenolone acetate; 21-Chloro-20-oxopregnane; Cycloaddition reactions; Steroidal [16,17-d]-isoxazolines; Topical anti-inflammatory agents

Inter- and intra-molecular cycloaddition reactions of nitrones are of great significance because of their potential flexibility to enter the complex molecular framework of many natural products [1]. This flexibility is further enhanced by using oximes as nitrone precursors which are potentially ambient nucleophiles with either nitrogen or oxygen acting as the reaction site depending on the other factors like reagents, solvents and pH of the reaction mixture [2]. Dipolar cycloaddition of nitrile oxides with olefinic compounds are of synthetic interest since the product isoxazolines are versatile intermediates for the synthesis of bifunctional compounds. The generation of nitrones leads to cycloaddition products like isoxazolines and isoxazolidines, which have further potential for synthetic manipulation. The chemistry of isoxazolines continues to attract the interest because of their ring functions as a masked aldol or unsaturated carbonyl group [3]. The isoxazoline derivatives could be utilized in order to regulate the stereo and regiochemistry in natural products synthesis [4–8]. Recent works on steroids reveal that many of the steroidal [16α,17α-d]-3′-carbethoxyisoxazolines have been found to be anti-inflammatory ante-drugs [9]. The earlier work of Green et al. [10] had also focussed on the topical anti-inflammatory activity of some steroidal [16α,17α-d]-isoxazolidines.

In steroid field there are two frequently utilized methods for generation of nitrile oxides for synthesizing steroid fused heterocycles. The Mukaiyama method [11] is based on the primary nitro-alkanes with phenyl isocyanate in presence of a base like triethylamine. But phenyl isocyanate being hazardous, the replacement of this method is desirable. The other most frequently used method is a base mediated dehydrohalogenation [12–14] of hydroxymoyl halides obtained by the reaction of aldoximes with NCS, NBS, halogens and 1-chlorobenzotriazole, etc. All these methods are tedious giving moderate yield of the isoxazolines. It was envisaged that 1,3-dipolar addition of fulminic acid to enone system yielded isoxazolines [15]. However, the generation of fulminic acid is often troublesome and leads to explosion if metal fulminates are used [1b]. 1,3-dipolar cycloaddition of carbethoxyformonitrileoxide (CEFNO) which is generated in situ by treatment of ethyl chloro oximido acetate with aqueous sodium bicarbonate has also been reported. Moerch et al. [16] had earlier investigated the reaction of 16-dehydropregnenolone acetate (16-DPA) with ethyl chloro oximido acetate and sodium bicarbonate and reported stereospecific formation of product giving [16α,17α-d]-isoxazoline derivatives.

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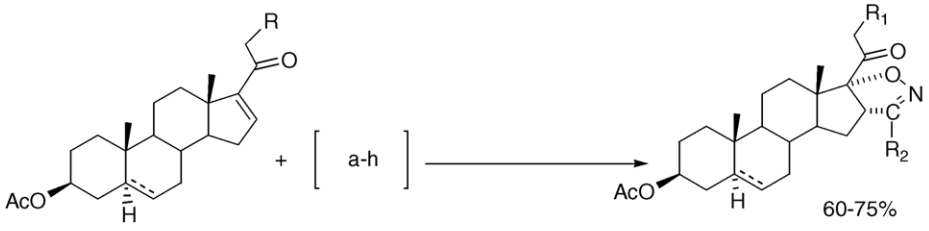
We investigated here 1,3-dipolar cycloaddition reaction of 16-dehydro-20-oxopregnanes [17–20], viz., 16-DPA 1 and related 21-chloro derivative 2 with the corresponding aldoxime by in situ generation of nitrile oxide [21] through the action of chloramine T (*N*-chloro-*N*-sodio-4-methyl benzene sulfonate) in ethanol to give their corresponding isoxazolines. The present method of synthesizing steroid-fused heterocycles through in situ generation of nitrile oxides from the reaction of aldoximes with chloramines-T is first of its kind to be reported in steroid field giving high yield of [16α,17α-d]-isoxazolines under simple reaction conditions. The reaction took place regioselectively at the α,β-unsaturated double bond at 16, 17 position to give only [16,17-d]-isoxazolines. Although earlier Culbertson et al. [22] reported the addition of C,*N*-diphenyl nitrone to 16-dehydropregnenolone acetate which gave both [16α,17α-d]- and [17α,16α-d]-isoxazolidines, the regiospecificity of 1,3 dipolar cycloaddition to α,β-unsaturated enone [10] and the stereo specificity of the cycloaddition to 16-ene steroid system with 17-acetyl side chain [16] are known and are generally reported to give their [16α,17α-d]-derivatives. Thus, both 16-DPA **1** and its 21-chloro derivative **2** furnished their [16α,17α-d]-isoxazolines **1(a–h)** and **2(a–h)**, respectively, in good yield (60–75%) when they were refluxed with different aliphatic and aromatic aldoximes **a–h** in ethanol. TLC and other analytical data confirmed the formation of only one regioisomer viz., [16,17-d]-isoxazolines in all the cases. In the ^{1}H NMR spectra of the isoxazolines formed, 16-vinyl hydrogen peak at 6.4 ppm disappeared with the appearance of a new methine hydrogen peak in the region 3.5–4.9 ppm for the C-16 proton. In the IR spectrum, the band for α,β-unsaturated carbonyl system appearing at 1675 cm^{-1} disappeared with the appearance of a band at 1700–1710 cm^{-1} for a normal carbonyl group. It is also pertinent to note that during the reaction in cases of 16-dehydro-21-chloro-20-oxopregnane **2**, chlorine atom was substituted by hydroxyl group under the basic reaction condition to give the corresponding 21-hydroxy-20-oxo pregnane **2(a–h)**. The reaction was also found to be selective as cycloaddition took place only at the α,β-unsaturated double bond at C-16 leaving the isolated double bond at C_5–C_6 unaffected as had been demonstrated by the substrate **1** as shown in Scheme 1.

The fast reaction of aldoximes with chloramine-T explains why the reaction proceeds in presence of olefinic double bond in spite of the fact that the later are known to react with chloramine-T [23]. The role of chloramine-T in these transformations may be chlorination of the aldoxime to a hydroxamic acid chloride followed by base catalyzed HCl elimination. It has been reported that chlorination of oxime to α-chloronitroso compounds could be accomplished under a variety of conditions [24] and formation of which is indicated by a blue colour [25] during the reaction. The various oximes **a–h** used in the reaction was prepared as per literature procedure [26]. The steric factor associated with the steroid molecules suggests that the product might be 16α,17α-d isoxazolines. Further work on biological activity evaluation of these new steroid-fused heterocycles is in progress and will be communicated in due course of time.



1. Δ^5, R=H
2. R=Cl

a. Benzaldoxime
b.Crotonaldoxime
c. p-Chlorobenzaldoxime
d. Cinnamaldoxime
e. p-Anisaldoxime
f. p-tolualdoxime
g. p-Nitrobenzaldoxime
h. Octanaldoxime

1a. Δ^5, R_1=H, R_2=Ph
1b. Δ^5, R_1=H, R_2=Me-CH=CH-
1c Δ^5, R_1=H, R_2=PhCl
1d.Δ^5, R_1=H, R_2= Ph-CH=CH-
1e. Δ^5, R_1=H, R_2=Ph-OMe
1f. Δ^5, R_1=H, R_2=Ph-Me
1g.Δ^5, R_1=H, R_2=Ph-NO_2
1h. Δ^5, R_1=H, R_2=CH_3-$(CH_2)_6$-

2a. R_1=OH, R_2=Ph
2b. R_1=OH, R_2=Me-CH=CH-
2c. R_1=OH, R_2=PhCl
2d.R_1=OH, R_2= Ph-CH=CH-
2e. R_1=OH, R_2=Ph-OMe
2f. R_1=OH, R_2=Ph-Me
2g.R_1=OH, R_2=Ph-NO_2
2h. R_1=OH, R_2=CH_3-$(CH_2)_6$-

Scheme 1.

1. Experimental

1.1. General methods

Melting points were determined with an electro thermal melting point apparatus and are uncorrected. All the chemicals used were of reagent grade of Aldrich Chemical Co. and were used without further purification. Chloramine-T trihydrate used was purchased from Aldrich Chemical Co. Freshly distilled dichloromethane (DCM) was used. The progresses of the reactions were monitored by thin layer chromatography using silica gel (E Merck) and the plates were activated at 100 °C before use. Infrared spectra were recorded with a Perkin-Elmer model 2000 series FT-IR spectrometer for solutions in chloroform. Infrared absorbance is reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded on a Bruker DPX (300 MHz) spectrometer with tetra methyl silane (TMS) as internal standard on the ppm scale (δ). Multiplicity of the resonance peaks are indicated as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) and multiplet (m). Mass spectrometric analysis was performed by positive mode electro spray ionization with Bruker Esquire 3000 LC-MS instrument. Specific rotations (α_D) were recorded on a Perkin-Elmer Polarimeter 343 instrument. Elemental analysis was carried out in Varian CHN Analyzer.

1.2. Synthesis of steroidal [16,17-d] isoxazolines ***1(a–h)*** *and* ***2(a–h)***

1.2.1. General procedure

To a solution of a substrate (1.5 m mol) in 25 ml of EtOH, was added 2.0 m mol of aldoxime followed by chloramines-T (1.7 m mol). The mixture was heated to reflux with stirring for 3 h. The reaction was filtered and the filtrate was poured into cold water. The reaction mixture was then extracted with CH_2Cl_2 (2 × 100 ml) and the organic extract after drying over anhydrous $Na_2SO_4$was evaporated under reduced pressure to furnish a residue. The residue on purification by preparative TLC (ethyl acetate:petroleum ether: 12:1) and finally on crystallization from ethanol furnished the desired isoxazoline derivatives **1(a–h)** and **2(a–h)**.

1.2.1.1. 3β-Acetoxy-20-oxo-3′-(Benzo) isoxazolino [16,17-d] pregna-5-ene ***(1a)***. The reaction of 16-DPA **1** with benzaldoxime **a** according as per the general procedure which furnished the product **1a**.

Mp: 196–198 °C, α_D: (−)124° (C1, $CHCl_3$). IR (KBr): ν = 1735, 1710, 1588, 1450, 1200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.9 (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 4.26 (m, 2H, H-3 and H-16), 5.2 (m, 1H, H-6), 7.1–7.4 (m, 5H, Ph) ppm. Mass spectrum (*m*/*z*): 475 (M^+). Anal. Calcd. for $C_{30}H_{37}O_4N$: C, 75.79; H, 7.79; N, 2.95; Found: C, 75.48; H, 7.60, N, 3.13.

1.2.1.2. 3β-Acetoxy-20-oxo-3′-(prop-1-ene) isoxazolino [16,17-d] pregna-5-ene ***(1b)***. The reaction of 16-DPA **1** with crotonaldoxime **b** as per the general procedure furnished the product **1b**.

Mp: 206–208 °C, α_D: (−)122° (C1, $CHCl_3$). IR (KBr): 1730, 1710, 1590, 1445, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8 (s, 3H, Me), 1.1 (s, 3H, Me), 1.8 (s, 1H, Me under double bond), 1.9 (s, 3H, OAc), 2.0 (s, 3H, COMe), 3.9 (m, 1H, H-16), 4.5 (m, 1H, H-3), 5.3 (m, 1H, H-6), 5.9 (m, 2H, –CH=CH–) ppm. Mass spectrum (*m*/*z*): 439 (M^+). Anal. Calcd. for $C_{27}H_{37}O_4N$: C, 73.80; H, 8.43, N, 3.19; Found: C, 74.13; H, 8.60; N, 3.32.

1.2.1.3. 3β-Acetoxy-20-oxo-3′-(4-chloro benzo) isoxazolino [16,17-d] pregna-5-ene ***(1c)***. The reaction of 16-DPA **1** with 4-chloro benzaldoxime **c** as per the general procedure furnished the product **1c**.

Mp: 114–116 °C; α_D: (−)111° (C1, $CHCl_3$). IR (KBr): 1730, 1710, 1590, 1450, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8 (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 4.1–4.3 (m, 2H, H-3 and H-16), 5.1 (m, 1H, H-6), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 509 (M^+), 511 (M^++2). Anal. Calcd. for $C_{30}H_{36}O_4NCl$(%): C, 70.73; H, 7.07; N, 2.75; Found: C, 70.84; H, 7.20; N, 2.93.

1.2.1.4. 3β-Acetoxy-20-oxo-3′-(2-phenyl ethylene) isoxazolino [16,17-d] pregna-5-ene ***(1d)***. The reaction of 16-DPA **1** with cinnalmaldoxime **d** as per the general procedure furnished the product **1d**.

Mp: 225–228 °C, α_D: (−)102° (C1, $CHCl_3$). IR (KBr): 1730, 1710, 1588, 1400, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.9 (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 4.24 (m, 2H, H-3 and H-16), 5.3 (m, 1H, H-6), 6.3 (m, 2H, –CH=CH–Ph), 7.1–7.4 (m, 5H, Ph) ppm. Mass spectrum (*m*/*z*): 501 (M^+). Anal. Calcd. for $C_{32}H_{39}O_4N$: C, 76.65; H, 7.78; N, 2.79; Found: C, 76.79; H, 7.87, N, 2.95.

1.2.1.5. 3β-Acetoxy-20-oxo-3′-(4-methoxy benzo) isoxazolino [16,17-d] pregna-5-ene ***(1e)***. The reaction of 16-DPA **1** with *p*-anisaldoxime **e** as per the general procedure furnished the product **1e**.

Mp: 119–121 °C, α_D: (−)116° (C1, $CHCl_3$). IR (KBr): 1734, 1710, 1587, 1443, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.9 (s, 3H, Me), 1.1 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 3.4 (s, 3H, OMe), 4.3 (m, 2H, H-3 and H-16), 5.2 (m, 1H, H-6), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 505 (M^+). Anal. Calcd. for $C_{31}H_{39}O_5N$: C, 73.66; H, 7.72; N, 2.77; Found: C, 73.51; H, 7.90, N, 2.82.

1.2.1.6. 3β-Acetoxy-20-oxo-3′-(4-methyl benzo) isoxazolino [16,17-d] pregna-5-ene ***(1f)***. The reaction of 16-DPA **1** with *p*-tolualdoxime **f** as per the general procedure furnished the product **1f**.

Mp: 121–123 °C, α_D: (−)114° (C1, $CHCl_3$). IR (KBr): 1735, 1710, 1589, 1445, 1200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8 (s, 3H, Me), 1.1 (s, 3H, Me), 1.9 (s, 3H,

OAc), 2.2 (bs, 6H, Me and COMe), 4.25 (m, 2H, H-3 and H-16), 5.3 (m, 1H, H-6), 7.1–7.5 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 489 (M^+). Anal. Calcd. for $C_{31}H_{39}O_4N$: C, 76.07; H, 7.98; N, 2.86; Found: C, 76.19; H, 7.84, N, 2.93.

*1.2.1.7. 3β-Acetoxy-20-oxo-3′-(4-nitro benzo) isoxazolino [16,17-d] pregna-5-ene **(1g)***. The reaction of 16-DPA **1** with *p*-nitrobenzaldoxime **g** as per the general procedure furnished the product **1g**.

Mp: 109–111 °C, α_D: (−)108° (C1, $CHCl_3$). IR (KBr): 1730, 1710, 1590, 1528, 1450, 1347, 1245, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 4.31 (m, 2H, H-3 and H-16), 5.3 (m, 1H, H-6), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 520 (M^+), 521 (M^++1). Anal. Calcd. for $C_{30}H_{36}O_6N_2$: C, 69.23; H, 6.92; N, 5.38; Found: C, 69.08; H, 6.85, N, 5.23.

*1.2.1.8. 3β-Acetoxy-20-oxo-3′-(n-heptyl) isoxazolino [16, 17-d] pregna-5-ene **(1h)***. The reaction of 16-DPA **1** with octanaldoxime **h** as per the general procedure furnished the product **1h**.

Mp: 224–226 °C, α_D: (−)118° (C1, $CHCl_3$). IR (KBr): 1730, 1710, 1593, 1443, 121 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 3.4 (m, 1H, H-16), 4.3 (m, 1H, H-3), 5.3 (m, 1H, H-6) ppm. Mass spectrum (*m*/*z*): 497 (M^+). Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.85; H, 9.46; N, 2.82; Found: C, 74.96; H, 9.54, N, 2.89.

*1.2.1.9. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (benzo) isoxazolino [16,17-d] pregna-5-ene **(2a)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with benzaldoxime **a** as per the general procedure furnished the product **2a**.

Mp: 212–214 °C, α_D: (+)12° (C1, alc). IR (KBr): 3300, 1735, 1710, 1590, 1444, 1210, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.1 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 3.4 (d, $J = 19$ Hz, H-21), 3.7 (d, $J = 19$ Hz, H-21), 4.4 (m, 1H, H-3), 4.9 (m, 1H, H-16), 7.1–7.4 (m, 5H, Ph) ppm. Mass spectrum (*m*/*z*): 493 (M^+). Anal. Cacld. for $C_{30}H_{39}O_5N$: C, 73.02; H, 7.91; N, 2.84; Found: C, 73.29; H, 7.61, N, 3.05.

*1.2.1.10. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (prop-1-ene) isoxazolino [16,17-d] pregna-5-ene **(2b)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with crotonaldoxime **b** as per the general procedure furnished the product **2b**.

Mp: 227–229 °C, α_D: (+)11° (C1, alc). IR (KBr): 3303, 1734, 1710, 1590, 1445, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.8$ (s, 3H, Me), 1.1 (s, 3H, Me), 1.8 (s, 1H, Me under double bond), 1.9 (s, 3H, OAc), 2.0 (s, 3H, COMe), 3.4 (d, $J = 19$ Hz, H-21), 3.7 (d, $J = 19$Hz, H-21), 3.9 (m, 1H, H-16), 4.5 (m, 1H, H-3), 5.9 (m, 2H, –CH=CH–) ppm. Mass spectrum (*m*/*z*): 457 (M^+). Anal. Calcd. for $C_{27}H_{39}O_5N$: C, 70.90; H, 8.53, N, 3.06; Found: C, 71.03; H, 8.66; N, 3.19.

*1.2.1.11. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (p-chlorobenzo) isoxazolino [16,17-d] pregna-5-ene **(2c)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with *p*-chlorobenzaldoxime **c** as per the general procedure furnished the product **2c**.

Mp: 139–141 °C; α_D: (+)5° (C1, alc). IR (KBr): 3300, 1736, 1710, 1590, 1450, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.8$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 3.2 (d, $J = 19$ Hz, H-21), 3.6 (d, $J = 19$Hz, H-21), 4.5 (m, 1H, H-3), 4.9 (m, 1H, H-16), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 527 (M^+), 529 (M^++2). Anal. Calcd. for $C_{30}H_{38}O_5NCl$(%): C, 68.31; H, 7.21; N, 2.66; Found: C, 68.54; H, 7.39; N, 2.51.

*1.2.1.12. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (phenyl ethylene) isoxazolino [16,17-d] pregna-5-ene **(2d)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with cinnamaldoxime **d** as per the general procedure furnished the product **2d**.

Mp: 248–250 °C, α_D: (+)7° (C1, alc). IR (KBr): 3350, 1730, 1710, 1588, 1400, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 3.3 (d, $J = 19$ Hz, H-21), 3.6 (d, $J = 19$Hz, H-21), 4.4 (m, 1H, H-3), 4.8 (m, 1H, H-16), 6.3 (m, 2H, –CH=CH–Ph), 7.1–7.4 (m, 5H, Ph) ppm. Mass spectrum (*m*/*z*): 519 (M^+). Anal. Calcd. for $C_{32}H_{41}O_5N$: C, 73.99; H, 7.90; N, 2.70; Found: C, 74.12; H, 7.77, N, 2.92.

*1.2.1.13. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (4-methoxybenzo) isoxazolino [16,17-d] pregna-5-ene **(2e)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with *p*-anisaldoxime **e** as per the general procedure furnished the product **2e**.

Mp: 144–146 °C, α_D: (+)3° (C1, alc). IR (KBr): 3305, 1734, 1710, 1587, 1443, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.1 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 3.2–3.4 (m, 4H, H-21 and OMe), 3.6 (d, $J = 19$ Hz, H-21), 4.5 (m, 1H, H-3), 4.8 (m, 1H, H-16), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 523 (M^+). Anal. Calcd. for $C_{31}H_{41}O_6N$: C, 71.13; H, 7.84; N, 2.68; Found: C, 71.34; H, 7.95, N, 2.75.

*1.2.1.14. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (p-methylbenzo) isoxazolino [16,17-d] pregna-5-ene **(2f)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with *p*-tolualdoxime **f** as per the general procedure furnished the product **2f**.

Mp: 142–144 °C, α_D: (+)8° (C1, alc). IR (KBr): 3300, 1735, 1710, 1589, 1445, 1200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.8$ (s, 3H, Me), 1.1 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (bs, 6H, Me and COMe), 3.4 (d, $J = 19$ Hz,

H-21), 3.7 (d, $J = 19$Hz, H-21), 4.4 (m, 1H, H-3), 4.9 (m, 1H, H-16), 7.1–7.5 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 507 (M^+). Anal. Calcd. for $C_{31}H_{41}O_5N$: C, 73.37; H, 8.09; N, 2.76; Found: C, 73.54; H, 8.22, N, 2.85.

*1.2.1.15. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (p-nitrobenzo) isoxazolino [16,17-d] pregna-5-ene **(2g)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with *p*-nitrobenzaldoxime **g** as per the general procedure furnished the product **2g**.

Mp: 133–136 °C, α_D: (+) 2.5° (C1, alc). IR (KBr): 3313, 1730, 1710, 1590, 1528, 1450, 1347, 1245, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.2 (s, 3H, COMe), 3.3 (d, $J = 19$ Hz, H-21), 3.7 (d, $J = 19$Hz, H-21), 4.5 (m, 1H, H-3), 4.9 (m, 1H, H-16), 7.1–7.4 (m, 4H, Ph) ppm. Mass spectrum (*m*/*z*): 538 (M^+), 539 (M^++1). Anal. Calcd. for $C_{30}H_{38}O_7N_2$: C, 66.91; H, 7.06; N, 5.20; Found: C, 67.09; H, 6.91, N, 5.38.

*1.2.1.16. 21-Hydroxy-3β-acetoxy-20-oxo-3′- (octanal) isoxazolino [16,17-d] pregna-5-ene **(2h)***. The reaction of 21-chloro-16-dehydro-5, 6-dihydro pregnenolone acetate **2** with octanaldoxime **h** as per the general procedure furnished the product **2h**.

Mp: 249–251 °C, α_D: (+)9° (C1, alc). IR (KBr): 3310, 1730, 1710, 1593, 1443, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.9$ (s, 3H, Me), 1.0 (s, 3H, Me), 1.9 (s, 3H, OAc), 2.1 (s, 3H, COMe), 3.3–3.5 (m, 2H, H-21 and H-16), 3.6 (d, $J = 19$Hz, H-21), 4.5 (m, 1H, H-3) ppm. Mass spectrum (*m*/*z*): 515 (M^+). Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.23; H, 9.51; N, 2.72; Found: C, 72.07; H, 9.34, N, 2.59.

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References

[1] (a) Padwa A. 1,3-Dipolar cycloaddition chemistry, vol. 2. New York: John Wiley & Sons; 1984. p. 83;
(b) Torsell KGB. Nitrile oxides, nitrones and nitronates in organic synthesis. Weinheim: VCH; 1988.
[2] Dondas HA, Grigg R, Hadjisoteriou M, Markandu J, Thomas WA, Kennewell P. Tetrahedron 2000;56:10087.
[3] (a) Kozikowski AP. Acc Chem Res 1984;17:410;
(b) Curran DP, Kim BH. Synthesis 1986:312.
[4] Stevens RV, Beaulieu N, Chan WH, Daniewski AR, Tanaka T, Waldner A, et al. J Am Chem Soc 1986;108:1039.
[5] Asaoka M, Abe M, Takei H. Bull Chem Soc Jpn 1985;58:2145.
[6] Ko SS, Confalone PN. Tetrahedron 1985;41:3511.
[7] Jager V, Muller I. Tetrahedron 1985;41:3519.
[8] Kozikowski AP, Stein PD. J Org Chem 1984;49:2301.
[9] Kwon T, Heimann AS, Oriaku ET, Yoon K, Lee HJ. J Med Chem 1995;58:1048.
[10] Green MJ, Tiberi RL, Friary R, Lutsky BN, Berkenkoph J, Fernendez X, et al. J Med Chem 1982;25:1492.
[11] Mukayama T, Hashino T. J Am Chem Soc 1984:291.
[12] Gi H-J, Xiang Y, Shiazi RF, Zhao K. J Org Chem 1997;62:88.
[13] (a) Eibler E, Kasbauer J, Pohl H, Sauer J. Tetrahedron Lett 1987;28:1097;
(b) Corbett DF. J Chem Soc Perkin Trans I 1986;421.
[14] (a) Kim JN, Ryu EK. Synth Commun 1990;20:1373;
(b) Brandi A, De Sarlo F, Guama A, Speroni G. Synthesis 1982:719.
[15] (a) Beckmann E. Chem Ber 1886;19:993;
(b) Lobry CA. Chem Ber 1886;19:1370.
[16] (a) Moerch GW, Wittle EL, Neuklis WA. J Org Chem 1965;30:1272;
(b) Moerch GW, Wittle EL, Neuklis WA. J Org Chem 1965;30:1387.
[17] Chowdhury PK, Bordoloi MJ, Baruah NC, Sharma HP, Goswami PK, Sharma RP, et al. US Patent No. 5,808,117. Chem Abs 1998;29: 230884e.
[18] Borah P, Ahmed M, Chowdhury PK. J Chem Res (S) 1998:236–7.
[19] Borah P, Ahmed M, Chowdhury PK. J Chem Res (M) 1998:1173.
[20] Borah P, Chowdhury PK. Ind Pat (Filed) No. NF 267/95-Pat.
[21] Armstrong SK, Collington EW, Knight JG, Naylor A, Warren S. J Chem Soc Perkin Trans I 1993:1433.
[22] (a) Culbertson TP, Moerch GW, Neuklis NA. J Heterocycl Chem 1963;1:280;
(b) Ius A, Parinic C, Sportoletti G, et al. J Org Chem 1971;36:3470;
(c) Tetrahedron Lett 1975:3235.
[23] Campbell MM, Johnson G. Chemistry 1978;78:65.
[24] Diekmann H, Luttke W. Angew Chem Int Ed 1968;7:387.
[25] Corey EJ, Estreicher H. Tetrahedron Lett 1980;21:1117.
[26] Vogel AI. Vogel's text book of practical organic chemistry, 4th ed. Longman; 1946.