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SYNTHESIS OF α-CHLOROPYRIDINE-CONTAINING OXIMES OF 3β,5-DIHYDROXY-6-KETOSTEROIDS

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New derivatives of steroidal 6-ketoximes containing α-chloropyridine neonicotinoid groups characteristic of bioactive compounds were synthesized by formation of oximes of cholestane and stigmastane 3β,5-dihydroxy-6-ketosteroids with O*-(2-chloropyridin-5-ylmethyl)hydroxylamine in the presence of zinc or tin(IV) chloride.*

Keywords: 3β,5-dihydroxy-6-ketosteroids, steroidal 6-ketoximes, *O*-(2-chloropyridin-5-ylmethyl)hydroxylamine, synthesis.

Steroidal oximes represent a new class of biologically active compounds. It was found that several steroidal oximes exhibit gestagenic [1], antiviral [2], and cytotoxic [3] activity. Aromatase inhibitors have also been found among them [4]. Certain steroidal oximes are natural compounds. Thus, several steroidal oximes were recently isolated from marine sponges [2, 5].

One reason for our continuing interest in steroidal oximes is their great potential for biological activity. We have previously synthesized [6–8] oximes of stigmastane 6-ketosteroids including (24*R*,6*E*)-24-ethylcholest-6-hydroximino-4-en-3-one, which was isolated from *Cinachyrella* sponges. Herein we report the synthesis of *O*-substituted oximes of 3β,5-dihydroxy-6-ketosteroids containing an α-chloropyridine ring that is characteristic of neonicotinoid biologically active compounds such as the natural analgesic epibatidine from the frog *Epipedobates tricolor* [9] or the widely employed insecticide imidachloprid [10]. Therefore, we assumed that such chemical modification of 3β,5-dihydroxy-6-ketosteroids would increase their insecticidal activity. We synthesized previously [11, 12] derivatives of these steroids containing α-chloropyridine rings bonded to the 3-hydroxyl.

In order to prepare the target *O*-substituted 3β,5-dihydroxy-6-ketosteroid oximes, a synthetic method was required for the previously unknown *O*-(2-chloropyridin-5-ylmethyl)hydroxylamine (**3**), which we synthesized through a series of reactions including reaction of phthalic anhydride with hydroxylamine, subsequent alkylation of the resulting *N*-hydroxyphthalimide by 2-chloro-5-chloromethylpyridine (**1**) to form the phthalimide (**2**), and hydrazinolysis of it to give the target compound.

Our initial attempts to synthesize the corresponding *O*-substituted oxime via reaction of the 3β,5α-dihydroxy-6-ketone (**4**) with the *O*-substituted hydroxylamine (**3**) in the presence of acid catalysts were unsuccessful. It was found that this reaction did not occur in the presence of acetic acid. On the other hand, adding HCl to the reaction mixture produced three compounds: secosteroid **5**, 5-hydroxymethyl-2-chloropyridine (**6**), and the azomethine (**7**). These were isolated in yields of 70%, 63, and 25, respectively. The structures of the products were established using IR and NMR spectra. Furthermore, the structure of **7** was also confirmed by convergent synthesis using the reaction of 6-chloronicotinic aldehyde with substituted hydroxylamine **3**.

The structures of the products led directly to the conclusion that required oxime **8a** was in fact formed under these conditions. However, it underwent further Beckmann rearrangement to form first the 3β-hydroxy-5-keto-6-carbonitrile that then was dehydrated into enone **5** because the conditions were too harsh. 5-Hydroxymethyl-2-chloropyridine (**6**) was a

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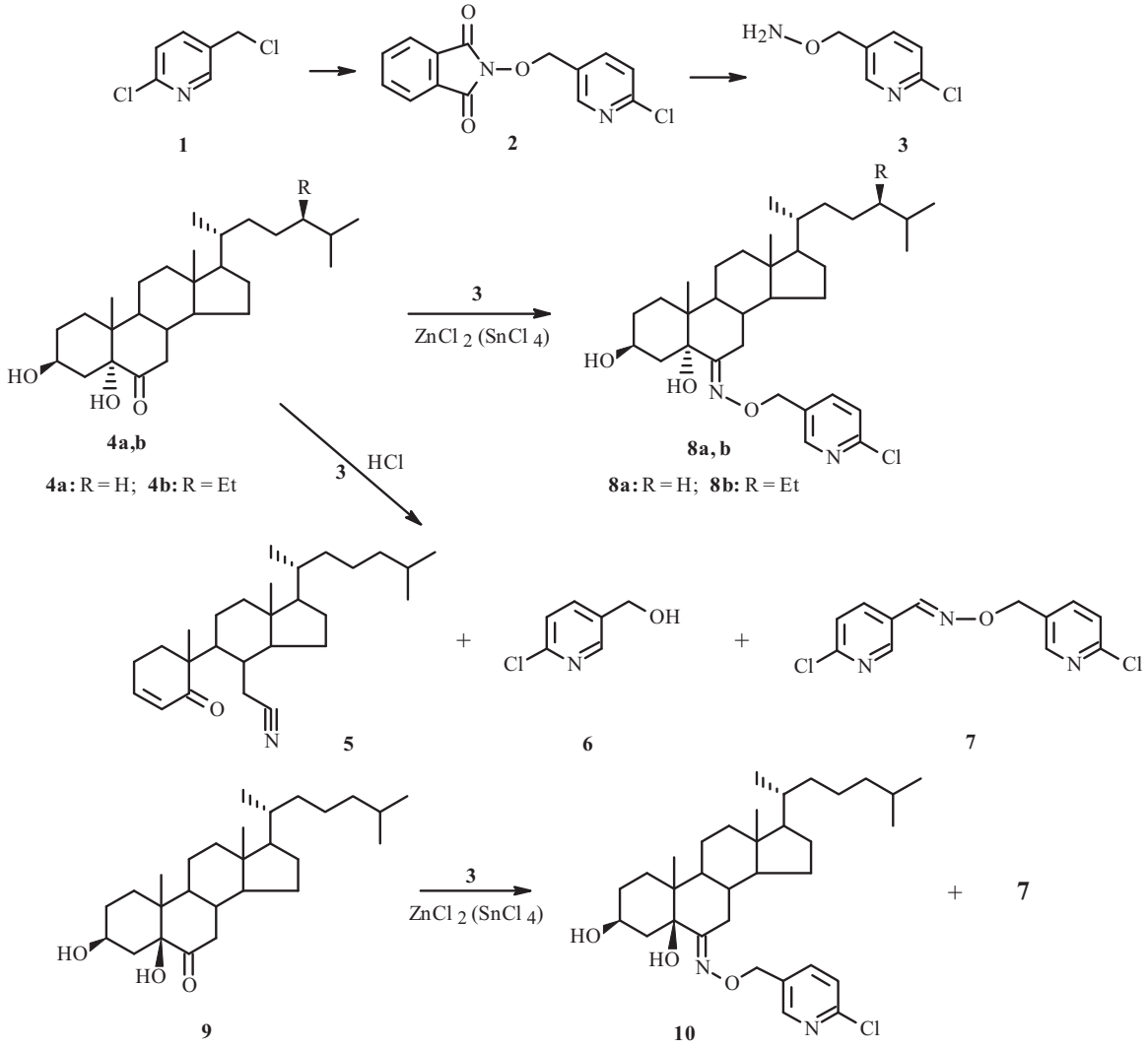
second product of Beckmann rearrangement of the intermediate oxime **8a**. Azomethine **7** was most probably formed by conversion of **3** under the reaction conditions into 6-chloronicotinic aldehyde and its further condensation with another molecule of **3**.



Next, we used Lewis acids to catalyze the reaction of the 3β,5-dihydroxy-6-ketosteroids with **3** in order to synthesize the steroidal *O*-substituted 6-ketoximes. Reaction of **4a** and **3** with heating in toluene in the presence of anhydrous $ZnCl_2$ catalyst formed the required oxime **8a**, which was isolated from the reaction mixture in about 70% yield. The structure of **8a** was elucidated unambiguously using spectral data. In particular, the IR spectrum of **8a** lacked a band for stretching vibrations of the 6-ketone and contained bands at 1618 and 1621 cm^{-1} that were characteristic of the C=N bond in an *O*-substituted oxime. PMR and ^{13}C NMR spectra of **8a** showed resonances for the H and C atoms of the steroidal part and resonances corresponding to the chloropyridine ring. Furthermore, resonances in the ^{13}C NMR spectrum of **8a** for C atoms of the steroidal ring had chemical shifts similar to those in spectra of steroidal 6-ketoximes [13]. This determined rather convincingly the site of attachment of the oxime.

Oxime **8b** was synthesized by reacting stigmastane derivative **4b** with **3** in pyridine in the presence of tin(IV) chloride catalyst. The target compound **8b** was obtained in >70% yield.

The effectiveness of the two aforementioned methods for forming the oxime was compared using **3** and a 3β,5β-dihydroxy-6-ketosteroid (**9**) as an example. It was found that using $ZnCl_2$ in toluene and $SnCl_4$ in pyridine as catalysts produced target oxime **10** in >90% yield based on starting steroid **9**. A side product that was isolated in low yield in both reactions was azomethine **7**. This indicated that both methods were approximately equally effective.

Thus, we developed synthetic methods for new oxime derivatives of the 6-ketone in steroidal 3β,5-dihydroxy-6-ketones that contain an additional α-chloropyridine moiety. Results from studies of the biological activity of the products will be reported separately.

EXPERIMENTAL

IR spectra were recorded on a Bomem-Michelson 100 FTIR spectrometer in the range 700–3600 cm^{-1}; UV spectra, in EtOH on a Specord M400 spectrophotometer. PMR and ^{13}C NMR spectra were taken on a Bruker Avance 500 NMR spectrometer (operating frequency 500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C). Chemical shifts are given vs. TMS as an internal standard. The course of reactions and purity of products were monitored using Kieselgel $60F_{254}$ plates (Merck). Melting points were determined on a Kofler block.

2-(2′-Chloropyridin-5′-ylmethyloxy)isoindol-1,3-dione (2). A suspension of *N*-hydroxyphthalimide (17.94 g, 0.11 mol) and anhydrous NaOAc (10.09 g, 0.123 mol) in DMF (100 mL) was stirred, heated to 70°C, treated over 1.5 h with a solution of 2-chloro-5-chloromethylpyridine (**1**, 20.0 g, 0.123 mol) (prepared by the literature method [14]) in DMF (25 mL), stirred at 70°C for 1 h 45 min, treated in one portion with anhydrous NaOAc (1.0 g, 0.0123 mol) and a solution of **1** (2.0 g, 0.0123 mol) in DMF (10 mL) over 15 min, treated after 1 h 35 min with another portion of anhydrous NaOAc (1 g, 0.0123 mol) and a solution of **1** (2 g, 0.0123 mol) in DMF (10 mL) over 15 min, stirred at 70°C for 1.5 h, cooled to room temperature, and poured in several portions with stirring into aqueous $NaHCO_3$ (1000 mL, 1.5%). The resulting precipitate was filtered off, washed with water (3 × 200 mL), and dried in air with gentle heating to afford **2** (26.67 g, 0.092 mol, 84%), mp 150–155°C (EtOH). IR spectrum (KBr, ν, cm^{-1}): 1725, 1780 (C=O). UV spectrum (λ_{max}, nm, ε): 221 (48,000), 265 (4,800), 296 (2,400).

PMR spectrum [$(CD_3)_2SO$, δ, ppm, J/Hz]: 5.24 (2H, s, CH_2), 7.59 (1H, d, J = 8, H-3′), 7.86 (4H, br.s, H-Ar), 8.05 (1H, dd, J_1 = 8, J_2 = 2, H-4′), 8.55 (1H, d, J = 2, H-6′).

***O*-(2-Chloropyridin-5-ylmethyl)hydroxylamine (3).** A solution of **2** (26.56 g, 0.092 mol) in CH_2Cl_2 (170 mL) and MeOH (5 mL) was treated in one portion with a solution of hydrazine hydrate (4.48 mL, 0.092 mol) in MeOH (10 mL), stirred for 3.5 h at room temperature, treated with aqueous ammonia (100 mL, 10%), and stirred for 5–10 min until the precipitate dissolved completely. The organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), adding additional water (150 mL). The combined organic extracts were dried over K_2CO_3. The desiccant was filtered off and washed with CH_2Cl_2 (100 mL). The CH_2Cl_2 was evaporated at reduced pressure. The residue was vacuum distilled (1 mm Hg). Fractions with bp 90–99°C were collected to obtain **3** (12.21 g, 0.077 mol, 84%), mp 47–60°C. IR spectrum (KBr, ν, cm^{-1}): 3320 (NH). UV spectrum (λ_{max}, nm, ε): 215 (10,000), 267 (3,600).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 4.59 (2H, s, CH_2), 6.17 (1H, br.s, NH), 7.51 (1H, d, J = 8.5, H-3), 7.81 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4), 8.37 (1H, d, J = 2.5, H-6).

Oxidation of 3β,5-Dihydroxy-5α-cholestan-6-one (4a). A. A solution of **4a** (0.42 g, 1 mmol) (prepared by the literature method [15]) and **3** (0.17 g, 1.1 mmol) in EtOH (20 mL) was refluxed for 2 h, treated with acetic acid (1 mL), and refluxed for another 2 h. The reaction mixture was treated after 18 h with HCl (1 mL, 36%), refluxed for another 9.5 h, and evaporated to half the volume. The solution was poured into saturated $NaHCO_3$ solution (30 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with water (2 × 30 mL) and dried over K_2CO_3. The desiccant was removed. The solvent was evaporated in vacuo. The residue was evaporated together with benzene (2 × 20 mL) and chromatographed over a column of silica gel with elution by mixtures of petroleum ether (70–90°C) and EtOAc with increasing polarity (20:1 to 2:1) to afford the following three fractions.

Fraction 1: amorphous 5,6-secocholest-3-en-5-on-6-carbonitrile (**5**, 0.28 g, 0.704 mmol, 70%). IR spectrum (film, ν, cm^{-1}): 1674, 1678 (C=O), 2243 (C≡N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.69 (3H, s, 18-Me), 0.86 (3H, d, J = 6.5, 26-Me), 0.87 (3H, d, J = 6.5, 27-Me), 0.90 (3H, d, J = 6.5, 21-Me), 1.06 (3H, s, 19-Me), 2.11 (1H, dd, J_1 = 17.5, J_2 = 3.5, CH_2–CN), 2.22 (1H, br.d, J = 20, H-2α), 2.43 (1H, m, W/2 = 39, H-2β), 2.75 (1H, dd, J_1 = 17.5, J_2 = 3.5, CH_2CN), 6.06 (1H, dd, J_1 = 10, J_2 = 2, H-4), 6.84 (1H, m, W/2 = 20, H-3).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.82 (C-18), 17.27 (C-19), 18.51 (C-21), 19.47 (C-11), 22.56 (C-26), 22.80 (C-27), 23.28 (CH), 23.69 (C-23), 24.48 (C-15), 24.60 (CH_2), 27.69 (C-16), 28.00 (C-25), 35.15 (C-20), 35.67 (CH), 35.67 (CH_2), 35.90 (C-22), 39.35 (C-12), 39.45 (C-24), 41.31 (C-9), 42.23 (C-13), 47.49 (C-10), 53.40 (C-14), 56.07 (C-17), 118.30 (C-6), 128.76 (C-4), 147.48 (C-3), 208.86 (C-5).

Fraction 2: 1,4-di-(2-chloropyridin-5-ylmethyl)-2-aza-3-oxabut-1-ene (**7**, 0.04 g, 0.14 mmol, 25% calculated for starting **3**), mp 133–134°C (petroleum ether 70–90°C). The PMR spectrum of the isolated compound agreed with that of **7** obtained by convergent synthesis.

Fraction 3: 5-hydroxymethyl-2-chloropyridine (**6**, 0.1 g, 0.697 mmol, 63% calculated for starting **3**), mp 47–49°C (petroleum ether:EtOAc) (lit. [16] mp 39–40°C).

PMR spectrum [$(CD_3)_2SO$, δ, ppm, J/Hz)]: 4.53 (2H, d, J = 6, CH_2), 5.42 (1H, t, J = 6, OH), 7.48 (1H, d, J = 8, H-3), 7.79 (1H, dd, J_1 = 8, J_2 = 2, H-4), 8.35 (1H, d, J = 2, H-6).

B. A solution of **4a** (0.42 g, 1 mmol) and **3** (0.17 g, 1.1 mmol) in toluene (20 mL) was refluxed for 3 h, treated with anhydrous $ZnCl_2$ (0.15 g, 1.1 mmol), refluxed for another 14 h 45 min, treated with additional **3** (0.17 g, 1.1 mmol) and $MgSO_4$ (0.12 g, 1 mmol), and refluxed for another 20.5 h. The precipitate was filtered out of the hot reaction mixture and washed twice with small portions of toluene with heating and then CH_2Cl_2. The filtrate was evaporated in vacuo. The solid was dissolved in CH_2Cl_2 (50 mL), washed successively with aqueous $NaHCO_3$ (5%, 30 mL) and water (2 × 30 mL), and dried over anhydrous $MgSO_4$. The desiccant was filtered and washed on the filter with CH_2Cl_2. The filtrate was evaporated in vacuo. The resulting oil was chromatographed over a column of silica gel with elution by mixtures of CH_2Cl_2 and MeOH of increasing polarity (40:1 to 35:1) to afford amorphous **8a** (0.39 g, 0.697 mmol, 70%). Recrystallization from EtOH (5 mL) afforded crystalline **8a** (0.28 g, 50%), mp 93–96°C (EtOH). IR spectrum (KBr, ν, cm^{-1}): 1621, 1618 (C=N–).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.64 (3H, s, 18-Me), 0.76 (3H, s, 19-Me), 0.86 (3H, d, J = 6.5, 26-Me), 0.86 (3H, d, J = 6.5, 27-Me), 0.90 (3H, d, J = 6.5, 21-Me), 4.04 (1H, m, W/2 = 25, H-3α), 5.01 (2H, s, =N–O–CH_2–), 7.28 (1H, d, J = 8, H-3_{Py}), 7.64 (1H, dd, J_1 = 8, J_2 = 2, H-4_{Py}), 8.35 (1H, br.s, W/2 = 4.8, H-2_{Py}).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 12.12 (C-18), 14.39 (C-19), 18.61 (C-21), 21.39 (C-11), 22.56 (C-26), 22.82 (C-27), 23.86 (C-23), 24.07 (C-15), 25.90 (C-7), 28.01 (C-25), 28.17 (C-16), 29.82 (C-1), 30.62 (C-2), 34.87 (C-8), 35.77 (C-20), 36.13 (C-22), 38.30 (C-4), 39.49 (C-24), 39.71 (C-12), 41.02 (C-10), 42.99 (C-13), 44.68 (C-9), 56.12 (C-17), 56.17 (C-14), 67.42 (C-3), 71.87 (CH_2O), 123.94 (C-3_{Py}), 132.98 (C-5_{Py}), 139.20 (C-4_{Py}), 149.72 (C-6_{Py}), 150.53 (C-2_{Py}), 162.40 (C-6).

Further elution afforded starting **4a** (0.07 g, 0.167 mmol, 17%). The PMR spectrum of the sample isolated from the reaction was identical to that of the authentic compound.

Oximation of (24*R*)-3β,5-Dihydroxy-5α-stigmastan-6-one (4b). A solution of **4b** (0.45 g, 1 mmol) (prepared by the literature method [17]) and **3** (0.48 g, 3 mmol) in Py (4 mL) was treated with $SnCl_4$ (two drops) and refluxed for 23.5 h. Additional **3** (0.16 g, 1 mmol) was added during the refluxing. The mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (50 mL, 30 mL). The organic extract was washed with HCl (2 N, 20 mL) and water (30 mL) and dried over K_2CO_3. The desiccant was filtered off and washed with CH_2Cl_2 (50 mL, 20 mL). The extract was evaporated in vacuo. The resulting solid was treated with EtOAc (5 mL). The resulting precipitate was filtered off. The filtrate was evaporated in vacuo. The solid was dissolved in dichloroethane and filtered through a layer of silica gel with elution first by dichloroethane and then mixtures of dichloroethane and MeOH of increasing polarity (50:1 to 30:1) to afford **8b** (0.6 g) that was recrystallized from EtOH to afford the final product (0.42 g, 0.72 mmol, 72%), mp 96–99°C (EtOH). IR spectrum (KBr, ν, cm^{-1}): 1637, 1631 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.64 (3H, s, 18-Me), 0.76 (3H, s, 19-Me), 0.81 (3H, d, J = 6.8, 26-Me), 0.83 (3H, d, J = 6.8, 27-Me), 0.84 (3H, t, J = 7.6, 29-Me), 0.90 (3H, d, J = 6.4, 21-Me), 4.05 (1H, m, W/2 = 25, H-3α), 4.99 (1H, d, J_{AB} = 13, =N–O–CH_2), 5.02 (1H, d, J_{AB} = 13, =N–O–CH_2), 7.27 (1H, d, J = 8, H-3′), 7.65 (1H, dd, J_1 = 8, J_2 = 2, H-4′), 8.33 (1H, d, J = 2, H-6′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.98 (C-18), 12.11 (C-29), 14.39 (C-19), 18.66 (C-21), 19.02 (C-26), 19.83 (C-27), 21.38 (C-11), 23.03 (C-28), 24.07 (C-15), 25.90 (C-7), 26.09 (C-23), 28.19 (C-16), 29.10 (C-25), 29.82 (C-1), 30.61 (C-2), 33.88 (C-22), 34.86 (C-8), 36.15 (C-20), 38.29 (C-4), 39.70 (C-12), 41.02 (C-10), 43.00 (C-13), 44.68 (C-9), 45.81 (C-24), 56.03 (C-17), 56.18 (C-14), 67.42 (C-3), 71.86 (CH_2O), 123.95 (C-3_{Py}), 132.99 (C-5_{Py}), 139.28 (C-4_{Py}), 149.73 (C-6_{Py}), 150.52 (C-2_{Py}), 162.40 (C-6).

Oximation of 3β,5-Dihydroxy-5β-cholestan-6-one (9). A. A solution of **9** (0.42 g, 1 mmol) (prepared by the literature method [11]) and **3** (0.24 g, 1.5 mmol) in toluene (20 mL) was treated with anhydrous $ZnCl_2$ (0.2 g, 1.5 mmol) and refluxed for 67 h. Additional portions of **3** (0.24 g, 1.5 mmol; 0.16 g, 1 mmol) and anhydrous $ZnCl_2$ (0.07 g, 0.5 mmol) were added during the refluxing. The precipitate was filtered off and washed with toluene (30 mL) with heating. The toluene filtrate was evaporated in vacuo. The solid was treated with CH_2Cl_2 (30 mL) and water (20 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were added to the solid obtained after evaporation of the toluene, washed with water (2 × 20 mL), and dried over $MgSO_4$. The desiccant was filtered off and washed with CH_2Cl_2. The filtrate was evaporated in vacuo. The solid was chromatographed over a column of silica

gel with elution first by dichloroethane and then by mixtures of dichloroethane and MeOH of increasing polarity (200:1 to 80:1) to afford two fractions.

Fraction 1: 1,4-di-(2-chloropyridin-5-ylmethyl)-2-aza-3-oxabut-1-ene (**7**, 0.05 g, 0.18 mmol).

Fraction 2: amorphous 6-(2′-chloropyridin-5′-ylmethyloximino)-5β-cholestan-3β,5-diol (**10**, 0.51 g, 0.91 mmol). IR spectrum (film, ν, cm^{-1}): 1589, 1568 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.64 (3H, s, 18-Me), 0.74 (3H, s, 19-Me), 0.86 (3H, d, J = 6.4, 26-Me), 0.87 (3H, d, J = 6.5, 27-Me), 0.90 (3H, d, J = 6.5, 21-Me), 4.01 (1H, br.s, W/2 = 13, H-3α), 4.26 (1H, s, 5β-OH), 4.49 (1H, br.d, J = 8.5, 3β-OH), 5.09 (2H, s, =N–O–CH_2), 7.33 (1H, d, J = 8, H-3′), 7.63 (1H, dd, J_1 = 8, J_2 = 2, H-4′), 8.37 (1H, d, J = 2, H-6′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 12.04 (C-18), 16.82 (C-19), 18.62 (C-21), 21.45 (C-11), 22.56 (C-26), 22.81 (C-27), 23.81 (C-23), 24.13 (C-15), 24.69 (C-1), 27.16 (C-2), 27.84 (C-7), 28.02 (C-25), 28.09 (C-16), 34.91 (C-8), 35.70 (C-20), 36.12 (C-22), 38.87 (C-4), 39.49 (C-24), 39.63 (C-12), 42.31 (C-10), 42.59 (C-9), 44.97 (C-13), 56.09 (C-17), 56.74 (C-14), 66.45 (C-3), 72.57 (CH_2O), 77.63 (C-5), 124.08 ($C\text{-}3_{Py}$), 132.07 ($C\text{-}5_{Py}$), 138.61 ($C\text{-}4_{Py}$), 149.38 ($C\text{-}6_{Py}$), 151.06 ($C\text{-}2_{Py}$), 161.75 (C-6).

B. A solution of **9** (0.42 g, 1 mmol) and **3** (0.48 g, 3 mmol) in Py (4 mL) was treated with $SnCl_4$ (two drops), refluxed for 5 h, diluted with water (50 mL), and etracted with CH_2Cl_2 (70 mL, 30 mL). The organic extract was washed successively with HCl (1 N, 2 × 20 mL) and water (30 mL) and dried over K_2CO_3. The desiccant was filtered off and washed with CH_2Cl_2 (50 mL, 20 mL). The filtrate was evaporated in vacuo. The resulting solid was chromatographed over a column of silica gel with elution first by dichloroethane and then mixtures of dichloroethane and MeOH of increasing polarity (100:1 to 40:1) to afford two fractions.

Fraction 1: **7** (0.03 g, 0.11 mmol).

Fraction 2: **10** (0.53 g, 95%).

1,4-Di-(2-chloropyridin-5-ylmethyl)-2-aza-3-oxabut-1-ene (7). 6-Chloronicotinic aldehyde (0.14 g, 1 mmol) [16] and **3** (0.16 g, 1 mmol) were dissolved in EtOH (5 mL) and left for 20 h at 5°C. The resulting precipitate was filtered off to afford **7** (0.14 g). The filtrate was evaporated. The solid was recrystallized from petroleum ether (70–100°C) to afford additional **7** (0.06 g). Total yield 0.2 g (0.71 mmol, 71%), mp 134–136°C (EtOH), 133–134°C (petroleum ether 70–100°C). IR spectrum (KBr, ν, cm^{-1}): 1585, 1568 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 5.20 (2H, s, CH_2), 7.34 (1H, d, J = 8, $H\text{-}3_{Py}$), 7.35 (1H, d, J = 8.5, $H\text{-}3_{Py'}$), 7.70 (1H, dd, J_1 = 8, J_2 = 2.5, $H\text{-}4_{Py}$), 7.92 (1H, dd, J_1 = 8.5, J_2 = 2, $H\text{-}4_{Py'}$), 8.10 (1H, s, CH=N), 8.43 (1H, d, J = 2.5, $H\text{-}6_{Py}$), 8.47 (1H, d, J = 2, $H\text{-}6_{Py'}$).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 77.17 (C-4), 124.20 ($C\text{-}3_{Py}$), 124.57 ($C\text{-}3_{Py'}$), 126.87 ($C\text{-}5_{Py}$), 131.66 ($C\text{-}5_{Py'}$), 135.91 (C-1), 138.96 ($C\text{-}4_{Py'}$), 145.68 ($C\text{-}4_{Py}$), 148.68 ($C\text{-}6_{Py'}$), 149.70 ($C\text{-}6_{Py}$), 151.33 ($C\text{-}2_{Py'}$), 152.74 ($C\text{-}2_{Py}$).

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