residue 4.4 g was chromatographed on basic alumina and the fraction eluted with 3% ethyl acetate in cyclohexane gave 3.2 g of **3α-azido-5α-androstan-17-one 17-ethylene ketal** (XVa), after recrystallization from methanol: mp 162–165; $\nu_{max}^{KBr}$ 2113, 2085, 1170, 1122, 1110 $cm^{-1}$; nmr $\delta$ = 0.80 (s, C-18 methyl protons), 0.83 (s, C-19 methyl protons), and 3.92 ppm (C-3β proton plus ethylene ketal protons).

A solution of 3.2 g of the azido ketal XVa in 3 l. of anhydrous ether was treated with 3.2 g of lithium aluminum hydride under reflux overnight. The product (2.5 g) was isolated as the acetate salt of **3α-amino-5α-androstan-17-one 17-ethylene ketal** (XVb): mp 130–133°; TL-II, 0.50. To a solution of 1.0 g of the acetate salt (XVb) in 20 ml of methylene chloride was added 1.0 g of trichloroacetosiocyanate. The reaction mixture was allowed to stand overnight at room temperature. After evaporation of the solvent, the residue was extracted with benzene, which was washed with water and dried, and the solvent was evaporated. The residue was recrystallized from ethyl acetate to yield 0.83 g of **3α-(N-trichloroacetylureido)-5α-androstan-17-one 17-ethylene ketal** (XVc); mp 220–225°. A solution of 0.6 g of 3α-trichloroacetylureido derivative XVc in 7.0 ml of 1 *N* alcoholic hydrochloric acid was refluxed for 1.5 hr. The solution was extracted with chloroform at pH 8. The chloroform layer was dried and evaporated to dryness, and the residue (0.5 g) was crystallized from ethyl acetate to give **3α-ureido-5α-androstan-17-one** (XII): mp 184–186°; TL-II, 0.34; the infrared spectrum was identical with that synthesized by method A.

**Registry No.**—Ia, 2426-52-0; Id, 7794-95-8; Ic, 7794-96-9; Ib, 2426-33-7; IIId, 7794-98-1; IIIa, 7794-99-2; IIIc, 7795-00-8; IIIe, 10028-42-9; IVa, 4215-18-3; IVd, 7795-02-0; IVb, 7795-03-1; IVe, 7795-04-2; VI, 7795-05-3; IId, 7795-06-4; IIa, 2436-47-7; IIb, 2603-32-9; VIIa, 7795-09-7; XVIa, 7795-10-0; XVIb, 7795-11-1; VIIb, 7795-12-2; VIIc, 7795-13-3; XI, 7795-14-4; Xa, 7795-15-5; Xb, 7795-16-6; Xc, 7795-17-7; XIV, 7795-18-8; IXa, 7795-19-9; IXb, 7795-20-2; IXc, 10060-16-9; XIII, 7795-22-4; VIIIa, 4271-67-4; VIIIb, 7795-24-6; VIIIc, 7795-25-7; XII, 7795-26-8; XVa, 7795-27-9; XVb, 7795-28-0; XVc, 7795-29-1.

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# Spectral Properties and Reactions of 3β-Hydroxy-21-formyl-22-oximinopregn-5-en-20-one[1]

NORMAN J. DOORENBOS,[2a] LEON MILEWICH,[2b] AND DONALD P. HOLLIS

*Department of Pharmaceutical Chemistry, University of Maryland, School of Pharmacy, Baltimore, Maryland 21201, and Department of Physiological Chemistry, The Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205*

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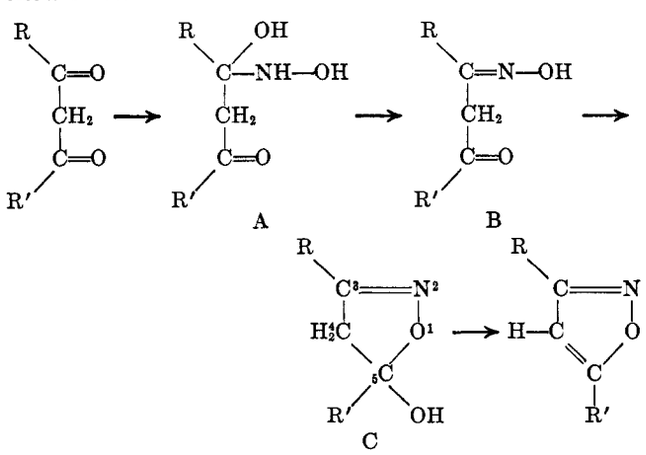
The reaction of 3β-hydroxy-21-formylpregn-5-en-20-one sodium enolate (**7**) with hydroxylamine hydrochloride, in ethanol–water, gave 3β-hydroxy-21-formyl-22-oximinopregn-5-en-20-one (**8**), as shown by its spectral and chemical characteristics. An attempted Beckmann rearrangement resulted in 3β-chloro-17β-(5-isoxazolyl)-5-androstene (**9**) as the sole product; this reaction seems to indicate that the formation of a nitrogen–oxygen bond is involved in the synthesis of the isoxazole ring.

The reaction of β-dicarbonyl compounds with hydroxylamine give rise to isoxazole derivatives, which are postulated to be formed according to the sequence shown below.




We reported earlier[3] that the reaction of 3β-hydroxy-21-formylpregn-5-en-20-one (**1**) with hydroxylamine hydrochloride in acetic acid yielded a mixture of 17β-(5-isoxazolyl)-5-androsten-3β-ol acetate (**2**) and 17β-(3-isoxazolyl)-5-androsten-3β-ol acetate (**3**). Treatment of this mixture with base allowed the isolation of 17β-(3-isoxazolyl)-5-androsten-3β-ol (**4**) and of 3β-hydroxy-21-cyanopregn-5-en-20-one sodium enolate (**5**). When β-ketoaldehyde **1** was treated with hydroxylamine hydrochloride in acetic acid buffered with sodium acetate, only 17β-(5-isoxazolyl)-5-androsten-3β-ol (**6**) was obtained; isoxazole **6** was also the only product when 3β-hydroxy-21-formylpregn-5-en-20-one sodium enolate (**7**) was treated with hydroxylamine in acetic acid (see Scheme I).

There have been reports on the isolation of 5-hydroxy-$\Delta^2$-isoxazoline derivatives of type C as intermediates in the synthesis of 3,4- and 4-5-dialkyl-substituted isoxazoles.[4] We were unable, however, to find any mention of intermediates isolated in the preparation of 5-alkyl monosubstituted isoxazoles. We wish to report on the isolation, characterization, and chemical reactivity of an intermediate of type B, an

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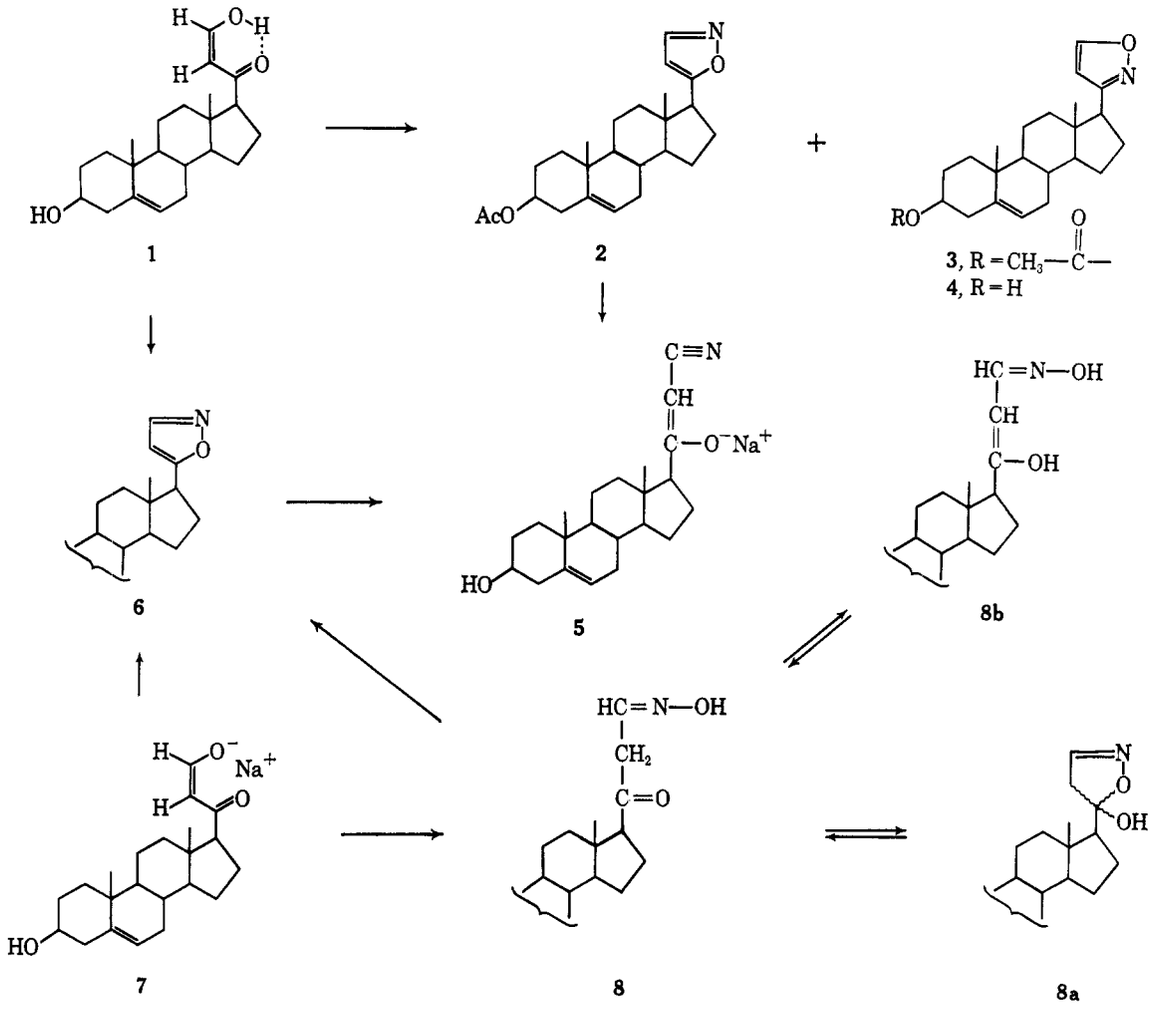
(2) (a) School of Pharmacy, University of Mississippi, University, Miss. 38677; (b) School of Medicine, The Johns Hopkins University, Departments of Obstetrics and Gynecology and Pathology, Baltimore, Md. 21205.

(3) N. J. Doorenbos and L. Milewich, *J. Org. Chem.*, **31**, 3193 (1966).

(4) (a) K. Brückner, K. Irmscher, F. v. Werder, K. Bork, and H. Metz, *Ber.*, **94**, 2897 (1961); (b) J. A. Vida and M. Gut, *Steroids*, **2**, 499 (1963); (c) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963); (d) R. E. Schaub, and J. H. v. d. Hende, *J. Org. Chem.*, **30**, 2234 (1965).

SCHEME I




α-unsubstituted β-oximino ketone in which R is hydrogen and R′ is the steroidal nucleus.

The reaction of the sodium enolate **7** with hydroxylamine hydrochloride in a solvent mixture of ethanol–water gave a compound which proved to be 3β-hydroxy-21-formyl-22-oximinopregn-5-en-20-one (**8**) as discussed below.

**Spectral Properties of β-Oximino Ketone 8.**—This compound had a very low chloroform solubility and therefore the infrared and nmr spectra were determined in solutions containing pyridine as solvent or cosolvent. The infrared spectrum in pyridine showed the characteristic bands for an oxime (3.00 μ) and for the carbonyl group (5.80 μ). However, when the infrared spectrum was carried out in a potassium bromide pellet, or in a Nujol mull, the carbonyl stretching appeared as a very weak band; in addition, a splitting was observed in the hydroxy stretching region (stong absorptions at 2.85 and 3.05 μ) and also a very weak band at 6.18 μ (C=N). These findings suggest that in the solid state compound **8** could exist in the 5-hydroxy-$\Delta^2$-isoxazoline form (**8a**) or as enol oxime **8b** (see Scheme I). The infrared spectra in potassium bromide and Nujol are consistent with the presence of enolic structure **8b**.

The presence of some enolic form in solution is supported by a positive ferric chloride test (see the Experimental Section), since it is known that 5-hydroxy-$\Delta^2$-isoxazolines do not give a positive reaction.[4c]

The nmr spectrum was determined in a mixture of deuteriochloroform and $d_5$-pyridine. In addition to the methyl and other resonances ascribable to the steroidal skeleton, the spectrum showed signals at δ 3.49 (doublet, $J$ = 5.0 cps, C-21 methylene) and 7.03 (triplet, $J$ = 5.0 cps, $C_{22}$-H). Double irradiation experiments showed unequivocally that the protons at C-21 and C-22 were coupled.

The ultraviolet spectrum showed $\lambda_{max}^{EtOH}$ 289 mμ (ε 140).[5] When base was added, a new band of high intensity appeared immediately at $\lambda_{max}^{EtOH,\ NaOH}$ 334 mμ (ε 12,600); its intensity began to decrease rapidly, while another band at 264 mμ started to develop. This latter band reached the maximum intensity (ε 11,200) after approximately 2.5 hr, during which time the 334-mμ band had disappeared; the ultraviolet spectra did not display isosbestic points. The 334-mμ band apparently decreased according to first-order kinetics. Applying the optical density values to a first-order formula,[6] as shown in Table I, the value of the reaction constant was calculated to be $k \sim 2.8 \times 10^{-2}$ min$^{-1}$.

(5) This band is assigned to the n → π* transition of the Cβ-carbonyl group. It shows an exalted intensity value which is probably due to interaction between the C=N and C=O chromophores. This effect seems to be similar to the one observed with nonconjugated β,γ-unsaturated ketones. See A. I. Scott, "Interpretation of Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 75.

(6) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1963, p 38.

TABLE I[a]

DETERMINATION OF THE REACTION CONSTANT OF THE SPECIES ABSORBING AT 334 mμ[b]

| Time, (min) | OD (334 mμ) | OD (corrected), [c] $(D_t - D_\infty)$ | $D_{t_0}/D_t$ | $k = 2.303/t \times \log D_{t_0}/D_t$ |
|---|---|---|---|---|
| 0 | 0.77 | 0.64 | 1 | |
| 10 | 0.56 | 0.43 | 1.4883 | 0.0397 |
| 20 | 0.48 | 0.35 | 1.8285 | 0.0328 |
| 30 | 0.40 | 0.27 | 2.3703 | 0.0287 |
| 40 | 0.33 | 0.20 | 3.2000 | 0.0290 |
| 50 | 0.29 | 0.16 | 4.0000 | 0.0276 |
| 60 | 0.25 | 0.12 | 5.3333 | 0.0282 |
| 70 | 0.22 | 0.09 | 7.1111 | 0.0280 |
| 90 | 0.19 | 0.06 | 10.6666 | 0.0262 |
| 100 | 0.17 | 0.04 | 16.0000 | 0.0277 |
| 120 | 0.15 | 0.02 | 32.0000 | 0.0287 |
| 160 | 0.13 | 0 | | |

[a] Experimental conditions were as follows: 0.04 ml of 1 *N* sodium hydroxide solution was added to the ultraviolet cell containing 3 ml of the β-oximino ketone solution ($2.2 \times 10^{-2}$ g/l. in 95% ethanol), and to the reference cell; temperature 35°; cell path, 1 cm. [b] Reference 6. [c] $D_\infty = 0.13$; $D_t$ = OD at time $t$; $D_{t_0}$ = OD at time $t = 0$.

The ultraviolet spectrum of β-oximino ketone **8** in acidic medium showed $\lambda_{max}^{EtOH,\ HCl}$ 217 mμ (ε 7600).

The mass spectrum did not show a molecular ion peak but had peaks corresponding to the loss of one and two water molecules.

**Reactions of β-Oximino Ketone 8.**—When compound **8** was dissolved in acetic acid, isoxazole **6** [$\lambda_{max}^{EtOH}$ 217 mμ (ε 7600), $\lambda_{max}^{MeOH,\ NaOMe}$ 264 mμ (ε 13,000)[3]] was obtained as the sole product.

On treatment with an ethanol–water solution of sodium hydroxide at room temperature for 2.5 hr, compound **8** gave 3β-hydroxy-21-cyanopregn-5-en-20-one sodium enolate (**5**), $\lambda_{max}^{EtOH,\ NaOH}$ 264 mμ (ε 11,200), which on acidification yielded 3β-hydroxy-21-cyano-5-pregnen-20-one.

An attempted Beckmann[7] rearrangement, with thionyl chloride in dioxane, gave 3β-chloro-17β-(5-isoxazolyl)-5-androstene[8] (**9**) as the only product, without any evidence of the expected 21-formamido-20-keto derivative.

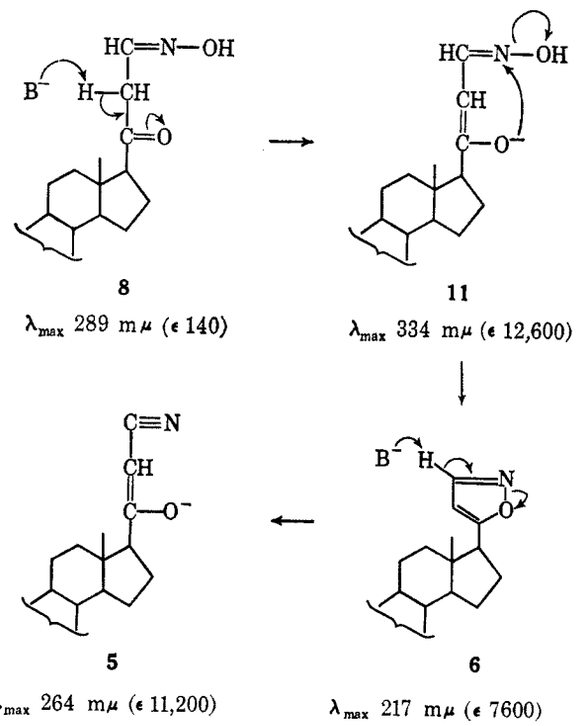
Acetylation of compound **8** in pyridine and chromatography on alumina gave isoxazole **2**.

The reaction of β-oximino ketone **8** with phenylhydrazine hydrochloride, in ethanol–water at room temperature for 2 hr, gave a mixture of isoxazole **6** and 17β-[5-(1-phenylpyrazolyl)]-5-androsten-3β-ol[3] (**10**).

**Interpretation of the Experimental Results.**—The products obtained in the reactions of the β-oximino ketone with acetic acid and with base partially explain the behavior of this compound in the ultraviolet region under acid and basic conditions; as noted, the 217-mμ band arises from isoxazole **6**, while the band at 264 mμ is due to cyano ketone enolate **5**.[9]

The 334-mμ band evidently arises from a transient intermediate, which seems to be the enolate anion (**11**) obtained by α-hydrogen abstraction (Scheme II).

SCHEME II

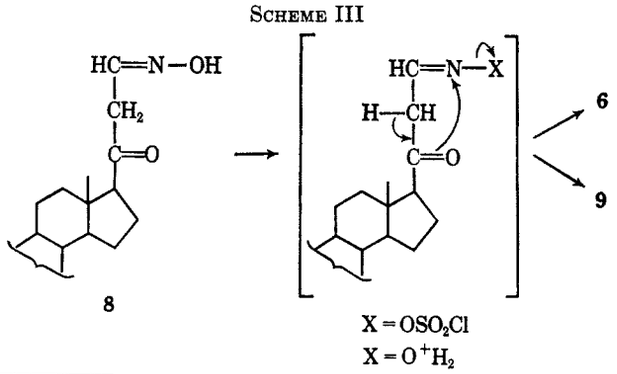



It is generally accepted that the nitrogen–oxygen bond in the isoxazole ring is already preformed in one of the reactants, *e.g.*, $HONH_2$, rather than being formed in the course of the reaction.[10]

As noted above, the species absorbing at 334 mμ (**11**) disappeared, apparently according to first-order kinetics; a mechanism involving an internal SNi attack by the enolate anion on the oxime–nitrogen atom was thus suggested (Scheme II). This mechanism implies the formation of a nitrogen–oxygen bond to give isoxazole **6**; this compound, however, is not detected in basic medium owing to its conversion to the cyano ketone enolate **5**.[3,11]

The nitrogen–oxygen bond appears to be formed in the reaction with thionyl chloride; formation of an electron-deficient nitrogen atom and the simultaneous intramolecular nucleophilic attack by the carbonyl oxygen would produce isoxazole **9** (Scheme III). It seems that isoxazole formation is the normal reaction

SCHEME III




(7) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(8) The configuration at C-3 is retained in this reaction. See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 321.

(9) When the base was an ethanolic or aqueous solution of sodium hydroxide, the final intensity obtained on reaction with isoxazole **6** (ε 11,200) was lower than when sodium methoxide in methanol was used (ε 13,000). It was noted that with sodium hydroxide solution there was a slow but steady decrease of the 264-mμ band after the maximum intensity was reached. This probably suggests a hydrolytic process involving the cyano group.

(10) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1960, p 272.

(11) The fact that the ultraviolet spectra (334 → 264 mμ) do not show isosbestic points characteristic of a two-component system supports Scheme II.

product when a β-oximino ketone is subjected to the conditions of the Beckmann rearrangement.

In acidic medium, the β-oximino ketone gives isoxazole **6**. This compound could, in principle, be formed by two different mechanism: (a) the classical one involving formation of intermediate **8a**, and dehydration, and (b) protonation of the oximinohydroxy group followed by nucleophilic attack on the electron-deficient nitrogen atom by the carbonyl oxygen (Scheme III).

The products obtained in the reaction of β-oximino ketone **8** with phenylhydrazine hydrochloride arise from the nucleophilic attack of the β-nitrogen atom of phenylhydrazine on C-22; after elimination of hydroxylamine, cyclization, and dehydration, pyrazole **10**[3] is obtained. The conditions of the experiment also favors the formation of isoxazole **6**.

In addition to the classical mechanism of isoxazole synthesis involving a 5-hydroxy-$\Delta^2$-isoxazoline intermediate, the findings described above suggest that the isoxazole ring may arise also through a different pathway which involves the nitrogen–oxygen bond formation.

## Experimental Section[12]

**3β-Hydroxy-21-formyl-22-oximino-pregn-5-en-20-one (8).**—A solution of hydroxylamine hydrochloride (25.0 g) in water (250 ml) was added to a solution of 3β-hydroxy-21-formylpregn-5-en-20-one sodium enolate (7 100.0 g) in 60% ethanol (2500 ml), while stirring. A white precipitate formed immediately; on further stirring, this solid dissolved and a new precipitate appeared. The reaction mixture was left at room temperature overnight. After filtration, washing with water, and drying, compound **8** (63.4 g) was obtained. It migrated as one spot on tlc and gave a very intense green color with ethanolic ferric chloride. It had mp 151–158° and decomposed with evolution of gas. After one recrystallization from acetonitrile, the melting point was 153–156° dec. When this compound was recrystallized a second time, it acquired a dark brownish color with an increase of the melting point range (145–156° dec). β-Oximino ketone **8** showed $[\alpha]^{25}D$ −12° (*c* 1.0, $CHCl_3$–EtOH, 9:1); $\lambda_{max}^{EtOH}$ 289 mμ (ε 140); $\lambda_{max}^{EtOH, NaOH}$ 334 mμ (ε 12,600, obtained immediately after adding base), $\lambda_{max}^{EtOH, NaOH}$ 264 mμ (ε 11,200, obtained 2.5 hr after adding base); $\lambda_{max}^{EtOH, HCl}$ 217 mμ (ε 7600); $\lambda_{max}^{pyridine}$ 3.00 (vs, oxime), 5.80 μ (s, C=O); $\lambda_{max}^{KBr}$ 2.85–3.05 (s, broad, hydroxy), 5.83 (vw, C=O), 6.18 μ (vw, C=N); nmr (in a mixture of deuteriochloroform and pyridine-$d_5$) δ 3.49 (doublet, *J* = 5.0 cps, C-21 methylene), 7.03 (triplet, *J* = 5.0 cps, $C_{22}$-H); mass spectrum, no molecular ion peak ($M^+$ calcd for $C_{22}H_{33}NO_3$, 359), mass peaks at *m/e* 341 (18%, $M^+ - H_2O$), 323 (50%, $M^+ - 2H_2O$), 308 [50%, $M^+ - (2H_2O + CH_3)$], base peak at *m/e* 70.

**Reactions of the β-Oximino Ketone. A. With Acetic Acid.**—The solution of compound **8** (40.0 g) in glacial acetic acid (250 ml) was obtained by gently warming on the steam bath. After staying overnight at room temperature, crystalline isoxazole **6** (32.0 g) separated; it was identified by melting point, mixture melting point, and comparison of spectral and chromatographic data with an authentic sample.[3]

**B. With Acetic Anhydride in Pyridine.**—A solution of compound **8** (12.0 g) in a 1:1 mixture (80 ml) of pyridine and acetic anhydride was left overnight at room temperature. After evaporation at room temperature and drying for 48 hr *in vacuo*, the acetylated product showed three spots on tlc. An attempted separation by column chromatography on neutral alumina (activity grade III) using benzene as eluent yielded isoxazole **2** (7.0 g) exclusively. The identity of **2** was established by comparison of physical constants with an authentic sample.[3]

**C. With Thionyl Chloride.**—Thionyl chloride (10 ml) was added dropwise to a solution of β-oximino ketone **8** (10.0 g) in dioxane (200 ml) while stirring. The reaction was exothermic and the temperature of the mixture reached 40°. After the addition was complete, the mixture was stirred for 15 min and then poured into a 5% solution of sodium bicarbonate (400 ml). Water (2000 ml) was added and a precipitate separated. After filtration, washing with water, and drying, the product was chromatographed on alumina using benzene as the eluent; 3β-chloro-17β-(5-isoxazolyl)-5-androstene (**9**, 5.0 g) was obtained. Three recrystallizations from methanol afforded the analytical sample: mp 169.5–171°; $[\alpha]^{25}D$ −30°; $\lambda_{max}^{EtOH}$ 217 mμ (ε 8600); $\lambda_{max}^{CHCl_3}$ 6.28 μ (m, 5-monoalkyl substituted isoxazole);[3] nmr δ 8.12 (d, *J* = 1.5, C-3), 5.97 (d, *J* = 1.5, C-4).

*Anal.* Calcd for $C_{22}H_{30}ClNO$: C, 73.41; H, 8.40; Cl, 9.85; N, 3.89. Found: C, 73.12; H, 8.55; Cl, 9.76; N, 3.86.

**D. With Sodium Hydroxide.**—A solution of sodium hydroxide (1.0 g) in water (15 ml) was added to a solution of compound **8** (2.3 g) in 95% ethanol (500 ml) at room temperature. After 2.5 hr the ultraviolet spectrum showed only $\lambda_{max}^{EtOH, NaOH}$ 264 mμ, corresponding to cyano ketone enolate **5**. This solution was evaporated to dryness *in vacuo*, at 40°. Water and chloroform were added and the suspension was shaken until solution occurred. The chloroform layer was discarded. The aqueous layer was extracted again with chloroform and the organic layer was again discarded. The aqueous solution was acidified with 2 *N* hydrochloric acid and then extracted with chloroform. The organic extract was washed with water, dried, and evaporated *in vacuo* to give a gum. After chromatography on neutral alumina (activity grade I), using ethyl acetate as the eluent, 3β-hydroxy-21-cyanopregn-5-en-20-one was obtained. Two recrystallizations from acetonitrile gave 477 mg: mp 182–184°; $\lambda_{max}^{MeOH, NaOMe}$ 264 mμ (ε 13,000); $\lambda_{max}^{CHCl_3}$ 4.39 (w, C≡N), 5.75 μ (s, C=O); nmr δ 3.45 (singlet, two protons, C-21 methylene), 0.69 (C-18), 1.01 (C-19).

**E. With Phenylhydrazine Hydrochloride.**—A solution of phenylhydrazine hydrochloride (2.0 g) in water (100 ml) was added to the solution of β-oximino ketone **8** (5.0 g) in 95% ethanol (500 ml) at room temperature. After 2 hr, the solution was evaporated to dryness *in vacuo*. Vapor phase chromatography of the product showed that two compounds were present: isoxazole **6** and pyrazole **10**.[3] Acetylation of the product (3.5 g) with acetic anhydride and pyridine (180 ml, 1:1 mixture) was accomplished by heating gently on the steam bath until solution occurred, and then leaving it overnight at room temperature. Evaporation *in vacuo* gave a product which by vpc was shown to consist of isoxazole **2** and 17β-[5-(1-phenylpyrazolyl)]-5-androsten-3β-ol acetate.[3] This fact was confirmed when the mixture of the acetylated product was dissolved in ether (50 ml) and treated with a 5% solution of methanolic potassium hydroxide (50 ml) at room temperature for 2.5 hr; after evaporation *in vacuo*, water and ether were added to the residue. The ethereal layer was separated and washed with water, dried, and evaporated to give pyrazole **10**, mp 222–224°. The physical constants of this compound matched that of an authentic sample.[3] The aqueous layer showed absorption in the ultraviolet region at 264 mμ, this corresponding to cyano ketone enolate **5**.

(12) Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured in chloroform solution (*c* 1.0) except when otherwise stated. The nmr spectra were obtained with a Varian A-60 and an HA-100 spectrometer, using tetramethylsilane as internal standard; chemical shifts (ppm) are expressed as δ values and coupling constants are given in cycles per second (cps). The mass spectrum was obtained by direct insertion into the ion source of a A.E.I. MS-9 double-focusing mass spectrometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer and ultraviolet spectra were obtained with a Beckman Model DB spectrophotometer. The chromatographic procedures used (tlc and vpc) were described previously.[4]

**Registry No.**—**8**, 7732-54-9; 3β-chloro-17β-(5-isoxazolyl)-5-androstene, 7732-55-0; 3β-hydroxy-21-cyanopregn-5-en-20-one, 7732-56-1.

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