

Potential Aldosterone Antagonists: Spiro-[androstane-17-yl-5'-oxazolidine] Derivatives and Their NMR Spectra

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Abstract □ The synthesis of some spiro-[androstane-17-yl-5'-oxazolidine] derivatives and their NMR spectra are described. Aldosterone antagonistic activity of some of the synthesized compounds is reported.

Keyphrases □ Spiro-[androstane-17-yl-5'-oxazolidine] derivatives—synthesis, NMR characterization, potential aldosterone antagonists □ Oxazolidine, steroidal derivatives—synthesis, NMR characterization, potential aldosterone antagonists □ Aldosterone antagonists, potential—spiro-[androstane-17-yl-5'-oxazolidine] derivatives □ NMR spectroscopy—analysis, structure, spiro-[androstane-17-yl-5'-oxazolidine] derivatives

In the search for drugs to counteract the clinical potassium excreting-sodium retaining effects of aldosterone, several investigators (1-4) reported the preparation of C₁₇ spiro compounds. So far, however, attention has been focused only upon synthesis of spiro-lactones or spiro-lactams. Accordingly, the authors undertook the preparation of compounds having both oxygen and nitrogen heteroatoms in the ring appended at C₁₇. Oxazolidine derivatives of this type were synthesized (5, 6) before but not for examination as potential antialdosterone agents.

The present study examines the effects upon the NMR spectra of a number of steroidal 17-oxazolidines caused by a change in substituents at either the nitrogen atom or the carbon atom situated between the oxygen and nitrogen of the oxazolidine ring.

DISCUSSION

The cyanohydrin of the 17-ketone (I) was prepared according to the modified method of Ercoli and De Ruggieri (7), giving mainly the 17 α -cyano-17 β -ol (II). Monitoring the reaction by TLC failed to detect any trace of the β -cyano isomer. The melting point of the crude cyanohydrin varied from batch to batch, but it could be raised to a constant value by exhaustive washing of the preparation with boiling methanol. The melting-point depression was due to the incomplete conversion of the ketone (I) to its cyanohydrin; this finding is in contrast to the observation reported earlier (7). The configuration assigned to Compound II was based on its conversions to the known (6) diacetate (III) and oxazolidine (IV). The diacetate (III) was prepared earlier by Heusser *et al.* (6), but a different method was used in the present study; *p*-toluenesulfonic acid was substituted for pyridine and refluxing was for 30 min. so that a purer product could be obtained in a shorter time. Again, monitoring of the reaction by TLC detected only a single isomer.

When Compound VI, prepared according to the method of Heusser *et al.* (6), was treated with lithium aluminum hydride, Compound VIII was obtained. A cyclic structure (5), rather than the open structure of VIIIa proposed by earlier workers (6), was determined previously for this product (5) and now confirmed by examination of its NMR spectrum. The NMR spectrum of Com-

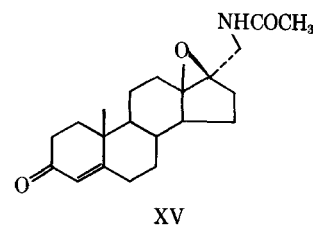
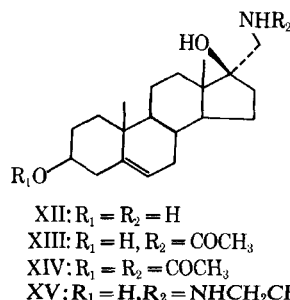
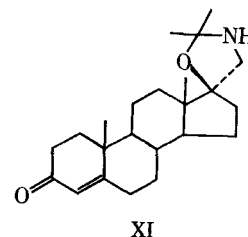
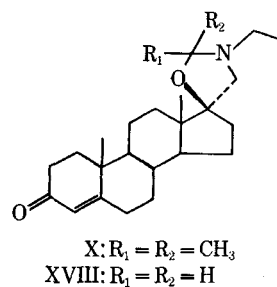
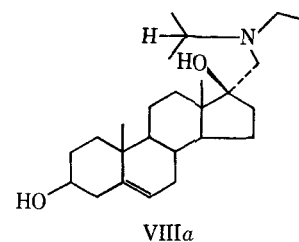
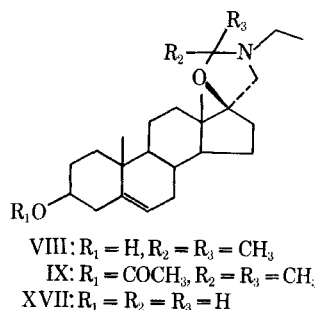
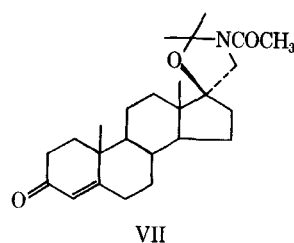
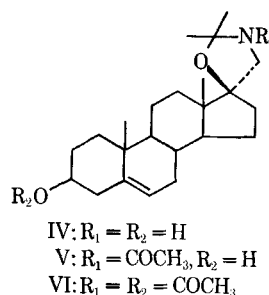
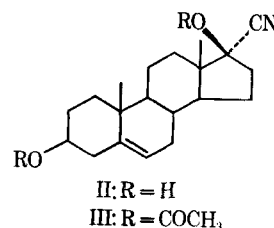
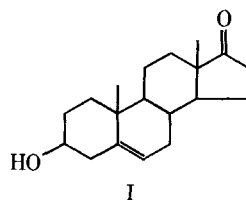


Table I—NMR Spectral Data: Chemical Shifts (δ , p.p.m.) and Coupling Constants (Hz.) of Protons of the Compounds

Compound	$C_{18}(\delta)$		$C_{19}(\delta)$		C_3	C_4	C_6	$C_{4'}$	$N_{3'}$	$C_{2'}$
	Calc.	Obs.	Calc.	Obs.						
IV	0.734	0.86	1.030	1.000	3.45	—	5.32	2.72 3.27 $J = 12$ Hz.	—	1.135 1.357
XI	0.770	0.90	1.210	1.170	—	4.67	—	2.73 3.26 $J = 12$ Hz.	—	1.315 1.350
V	0.734	0.90	1.030	1.010	3.45	—	5.32	3.20 3.68 $J = 10$ Hz.	2.02	1.555
VI	0.734	0.90	1.040	1.020	4.65	—	5.34	3.21 3.69 $J = 10$ Hz.	2.02	1.555
VII	0.770	0.930	1.210	1.170	—	4.68	—	3.21 3.67 $J = 10$ Hz.	2.02	1.55
VIII	0.734	0.850	1.030	1.000	3.45	—	5.32	2.37 3.05 $J = 9.0$ Hz.	1.06 CH ₂ nonequivalent	1.120 1.160
X	0.770	0.880	1.210	1.165	—	5.66	—	2.37 3.05 $J = 9.0$ Hz.	1.06	1.115 1.165
XIV	0.770	0.880	1.040	1.020	4.55 1.98 2.00	—	5.32	3.20 3.42 $J_{AX} = 7$ $J_{BX} = 4$ $J_{AB} = 14$	1.98 2.00	—
XVI	0.770	0.900	1.030	1.020	3.45	—	5.32	2.42 2.80 $J = 12$ Hz.	1.08 2.65 $J = 7$ Hz.	—
XVII	0.734	0.900	1.030	1.000	3.45	—	5.32	2.43 2.93 $J = 10$ Hz.	1.08 2.49 $J = 7$ Hz.	4.13 4.20 $J = 3$ Hz.
XVIII	0.770	0.930	1.210	1.170	—	5.68	—	2.43 2.93 $J = 10$ Hz.	1.08 2.49 $J = 7$ Hz.	4.17

pound VIIIa would be expected to show methyl resonances split by 5–7 Hz. due to the isopropyl group present in the molecule. However, in the NMR spectrum of the present sample, the gemdimethyl grouping caused two resonances that were magnetic field dependent; the spacing between these signals increased from 2.0 Hz. at 60 MHz. to 3.5 Hz. at 100 MHz. Furthermore, when the NMR sample solution was shaken with D₂O, an area corresponding to only one hydroxyl proton was seen to have undergone exchange; the NMR spectrum of the product obtained after acetylation of VIII showed a single acetyl peak and no hydroxyl proton capable of exchange with D₂O. Compound VIII was also synthesized by the action of acetone on 17 α -ethylaminomethyl-5-androsten-3 β ,17 β -diol (XVI) in the presence of a trace of acetic acid. The compounds obtained by these two synthetic procedures were identical according to melting-point determination, TLC, and IR and NMR spectroscopy. Finally, the IR spectrum of the α,β -unsaturated ketone (X), prepared by Oppenauer oxidation of VIII, showed no hydroxyl peak. These data are inconsistent with any alternatives to the proposed structure of VIII.

Oxazolidine (IV) was converted to its diacetate (VI) by the action of acetic anhydride and pyridine; VI was, in turn, saponified to its 3-hydroxy analog (V) with sodium carbonate solution. Oppenauer oxidation of V gave the α,β -unsaturated ketone VII.

Acetylation of Compound XII occurred on nitrogen and at the 3-hydroxyl position to yield XIV; the substitution pattern was established by elemental analysis, NMR spectroscopy [signals at δ 2.00 and 1.98 (3-OAc and NHAc, respectively)], and IR spectroscopy (3-OAc, 1735 cm.⁻¹; —NHAc, 1643 cm.⁻¹). Earlier work with related compounds showed that 17-OAc absorption in the IR occurs at 1752 cm.⁻¹, which was absent in this case. This is predictable since the 17-hydroxyl group is sterically hindered, favoring acetylation at the 3-hydroxyl position and at the amino group in Compound XII.

Selective hydrolysis of XIV yielded hydroxy Compound XIII, which, on Oppenauer oxidation, yielded the α,β -unsaturated ketone XV. Lithium aluminum hydride reduction of XIV yielded XVI, which, by treatment with formaldehyde and a catalytic

amount of acetic acid, yielded XVII. Oppenauer oxidation of XVII gave the corresponding α,β -unsaturated ketone (XVIII).

The preparation of Compounds VII and IX was reported previously (6).

NMR DISCUSSION

It is well known (8) that the resonance frequencies of C₁₈ and C₁₉ methyl group protons in NMR spectra provide a very sensitive probe for observing the nature and orientation of substituent groups in the steroidal skeleton. Also, the concept of additivity (9–13) of chemical shifts for these angular methyl groups due to diamagnetic shielding effects of various functions has been well established. However, the additivity rule does not hold (14, 15) in certain cases where there is a conformational change in a steroid ring or rings or an alteration in relative positions of two functional groups caused by a dipole interaction between them. The compounds examined in this study exhibit substitution at C₃, C₄, C₆, and C₁₇. The diamagnetic shielding effects upon C₁₈ and C₁₉ methyl protons due to the first three can be readily calculated according to the additivity rule (10). The following discussion will assay the effects of substitution at C₁₇.

C₁₈ Methyl Proton—The signal of this angular methyl group occurs in the NMR spectrum of 5-androsten-3 β -ol and 4-androsten-3-one at δ 0.734 and 0.770, respectively. In the present compounds, which have a spiro-oxazolidine ring at C₁₇, the chemical shift of the C₁₈ methyl groups ranges between δ 0.850 and 0.900 for alcohols and between 0.880 and 0.930 for ketones. Since the change in chemical shifts of 0.03–0.04 p.p.m. between alcohols and ketones is quite consistent with the additivity rule, attention may be limited to the C₁₈ methyl resonance of alcohols.

The diamagnetic shielding of the oxazolidine ring upon the C₁₈ methyl protons may be studied by comparing the chemical shifts of

¹ The NMR spectral data were obtained by running 5–6% solutions of the compounds on a Varian HR-100 NMR spectrometer.

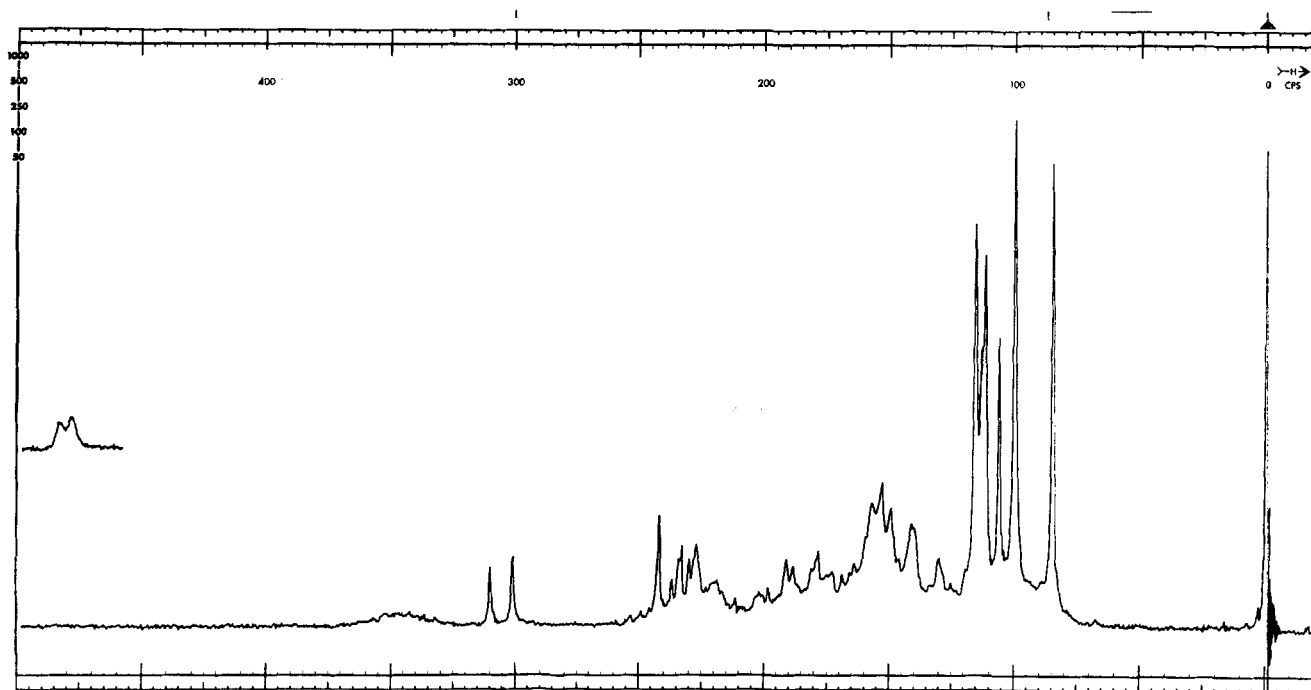


Figure 1—NMR spectrum of *spiro*-[5-androsten-3 β -ol-17-yl-5'-(N-ethyl-2',2'-dimethyloxazolidine)] (VIII).

the C₁₈ methyl group in Compounds XVI and XVII. In XVI, the C₁₈ methyl group would experience effects due to the 3 β -hydroxyl, Δ 5, 17 β -hydroxyl, and 17 α -ethylaminomethyl functions. The calculated chemical shift, using the additivity value for the first three groups, would be δ 0.770 p.p.m. for the C₁₈ methyl resonance. The observed value for this angular methyl group in XVI is δ 0.900. Thus, the remaining downfield shift of 0.13 p.p.m. is attributable to the 17 α -ethylaminomethyl function. It is known that 17 β -C₂H₅, 17 β -C₃H₇, and 17 β -C₄H₉ groups produce *upfield* shifts of 0.140, 0.050, and 0.033 p.p.m., respectively, in C₁₈ methyl resonances. Therefore, the downfield shift of 0.13 p.p.m. must be caused by an inductive effect, transmitted through space, of the nitrogen atom present in the side chain. The C₁₈ methyl resonance in the spectrum of XVII also occurs at δ 0.90, an observation that is not too surprising, since the orientation of the C₁₇ substituents in relation to the C₁₈ methyl groups in the two compounds is quite similar. The C₁₈ methyl resonance of VIII occurs at δ 0.850, 0.050 p.p.m. upfield compared to the corresponding signal of XVII. This effect may be attributable to introduction of the gem-dimethyl group at C₂'. The substitution of an acetyl group in place of the ethyl function in V produces partial double-bond character of the nitrogen-acetyl bond and its greater electron-withdrawing power, causing the C₁₈ methyl signal to appear at δ 0.900. In Compound IV, the C₁₈ peak appears at δ 0.860, which means that hydrogen substitution at the nitrogen atom in place of the ethyl group produces very little change in the C₁₈ methyl resonance.

C₁₉ Methyl Protons—The chemical shifts of this tertiary methyl in the spectrum of 5-androsten-3 β -ol and 4-androsten-3-one are δ 1.030 and 1.210, respectively. In the present compounds, having a spiro-oxazolidine ring at C₁₇, the C₁₉ methyl resonance occurs near δ 1.00 for alcohols and at δ 1.170 for ketones. Since the change in the chemical shift of the C₁₉ methyl group of from 0.170 to 0.180 p.p.m. in passing from alcohols to ketones is also consistent with the additivity rule, only the C₁₉ methyl resonances of alcohols will be discussed.

The diamagnetic shielding effect of the oxazolidine ring upon the C₁₉ methyl protons may be studied similarly by comparing the chemical shifts of the C₁₉ methyl resonances of XVI and XVII. The C₁₉ methyl group in XVI may be affected by four functional units: the hydroxyl 3 β -, Δ 5, 17 β -hydroxy, and 17 α -ethylaminomethyl groups. Unlike the C₁₈ methyl resonance, the C₁₉ methyl signal experiences no effect from the 17 β -hydroxyl group. Hence, the total predicted value for the C₁₉ methyl resonance of XVI is 1.030 p.p.m., the same as in 5-androsten-3 β -ol; the observed chemical

shift of the C₁₉ methyl signal in XVI is δ 1.02. Therefore, the contribution due to the 17 α -ethylaminomethyl group is very slight. In XVII, the observed shift is δ 1.00. Therefore, the slight upfield shift of the C₁₉ methyl resonance must be due to the entire oxazolidine ring or to the ring nitrogen. This effect is somewhat similar to the upfield shift (0.020 p.p.m.) produced upon the C₁₉ methyl resonance by a C₈H₁₇ or C₉H₁₉ group attached at the 17 β -position.

NMR of Protons Associated with Oxazolidine Ring Protons at C₄'—The chemical shifts and coupling constants of these two protons are influenced by the character of the nitrogen atom in the ring and, to a much lesser extent, by the substituent at C₂'. Since the two methylene protons see the nitrogen atom differently (one is closer to the lone pair of electrons on the nitrogen atom than the other), these protons are magnetically as well as chemically non-equivalent. Naturally, the proton closer to the lone pair of electrons is less shielded, and its signal appears at lower field. In IV, these two protons resonate at δ 2.720 and 3.270 ($\Delta\delta$ 0.550), while in VIII the methylene hydrogens appear at δ 2.370 and 3.050 ($\Delta\delta$ 0.680). The upfield shift for the two protons in the latter compound can be explained by the presence of an ethyl group on the nitrogen atom; this alkyl group, in turn, contributes a different degree of shielding to the two methylene hydrogens. The chemical shift of the two methylene protons at C₄' in V is to a much lower field (δ 3.200 and 3.680) than the two earlier compounds. As mentioned in the section on C₁₈ methyl resonances, the nitrogen atom in V assumes certain *sp*² character, and the π -electron redistribution therein causes a downfield shift in the methylene signals.

The effect caused by the substituent at C₂' can be observed by comparing the chemical shifts of the two methylene protons in VIII and XVII, where the protons in question resonate at δ 2.370 and 3.05 and 2.43 and 2.93, respectively. This effect is somewhat indirect. The elimination of the gem-dimethyl group at C₂' increases the inversional freedom of the amine nitrogen and, thereby, changes the character of the ethyl group. In VIII, the methylene protons of the ethyl group are nonequivalent because the bulky gem-dimethyl group hinders rapid interconversion of the nitrogen position; in XVII, the gem-dimethyl function is replaced by hydrogen atoms which permit rapid flipping of the amine nitrogen and, consequently, cause equivalence of the methylene protons of the ethyl group (Table I and Figs. 1 and 2).

The coupling constants of the two methylene protons attached to C₄' also vary due to the change in the character of the nitrogen atom (Table I).

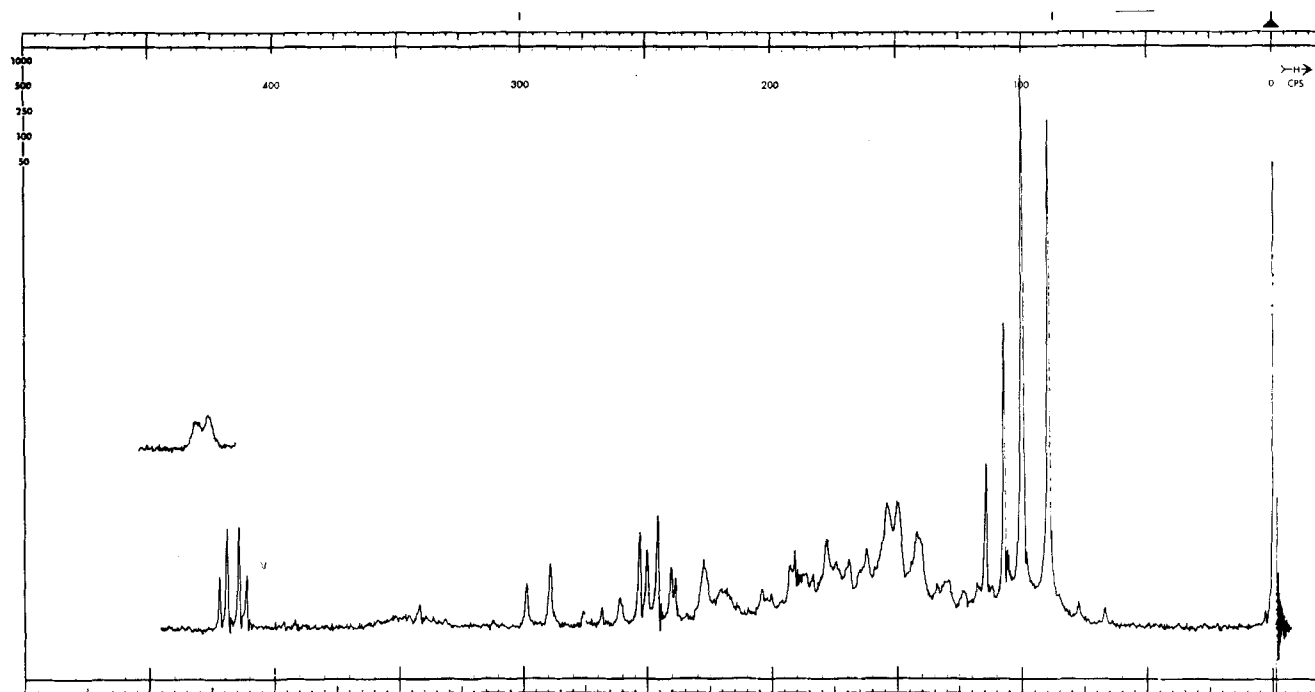


Figure 2—NMR spectrum of spiro-[5-androsten-3 β -ol-17-yl-5'-(N-ethyloxazolidine)] (XVII).

Protons at N $_3$ '—Aliphatic NH protons usually occur at δ 1–2 and are often not discernible from the other high field signals in the spectrum unless the NMR sample solution is heated or shaken with D $_2$ O. (In the latter case, an area corresponding to the amine hydrogen disappears from the spectrum.) The N-acetyl group hydrogens of the compounds reported here appear at the characteristic position, δ 2.00. The nonequivalence of the methylene protons of the ethyl groups on the nitrogen atoms in VIII and XVII was already discussed.

Methyl Protons at C $_2$ '—The methyl protons of the gem-dimethyl group exhibit two signals in IV at δ 1.315 and 1.360 for the same reason as in the case of methylene protons at C $_4$ '. Since these gem-dimethyl protons are one more σ -bond away than the methylene protons at C $_4$ ', the effect of the nitrogen is much less pronounced; consequently, the chemical shift difference between these gem-dimethyl signals is much smaller. In VIII, these methyl resonances appear at higher fields, δ 1.120 and 1.160, which are also consistent with the introduction of an ethyl group on the nitrogen atom. However, in VII the resonance due to gem-dimethyl protons appears as a singlet at δ 1.550. This may be explained by the fact that the nature of the nitrogen atom here is no longer the same as in the two earlier compounds but possesses a certain double-bond character, which makes the N $\equiv$ C(=O) bond planar. In this configuration, the N-acetyl group bisects the gem-dimethyl groups, thereby providing them with almost equal shielding.

In XVII, the methylene protons at C $_2$ ' appear at δ 4.130 and 4.200 as an AB quartet, having a geminal coupling constant of 3 Hz. The magnitude of this coupling constant is quite in harmony with similar values reported in the literature (16). However, these protons appear as a singlet at δ 4.170 in the 3-oxo- Δ 4-derivative of V, an observation that would suggest some type of long-range effect caused by the addition of the two substituents to the steroid skeleton.

Compounds VII, X, XI, XIII, and XVII were tested for aldosterone antagonistic activity (Table II) in the adrenalectomized rat. The dose of each compound was 800 mcg./rat. None of the compounds displayed appreciable antagonistic activity.

EXPERIMENTAL

17 α -Cyano-5-androstene-3 β ,17 β -diol (II)—To 15.84 g. of 5-androsten-3 β -ol-17-one (I) was added 22 ml. of freshly prepared acetone cyanohydrin (17). The mixture was warmed at 50° for 5 min. and then allowed to remain at room temperature for 2 hr. The product was washed with petroleum ether (30–60°) and then

with boiling methanol and finally was dried *in vacuo* to yield 16 g., m.p.² 206°, $\nu_{\text{max}}^{\text{KBr}}$ 2260 cm.⁻¹ (17 α -C $\equiv$ N).

Anal.—Calc. for C $_{20}$ H $_{29}$ NO $_2$: C, 76.20; H, 9.26; N, 4.44. Found: C, 76.84; H, 9.43; N, 4.76.

17 α -Cyano-5-androstene-3 β ,17 β -diol Diacetate (III)—To 2 g. cyanohydrin (II) was added 68 mg. of *p*-toluenesulfonic acid and 16 ml. of acetic anhydride. The mixture was heated at water bath temperature for 30 min. and then cooled over an ice bath and diluted with cold water. The precipitate was collected by filtration, washed with water, and recrystallized from chloroform-methanol, yielding 1.6 g. as white prisms, m.p. 204.5–205.5° [lit. (6) m.p. 203–206° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 1725 cm.⁻¹ (3-OAc) and 1752 cm.⁻¹ (17-OAc). The NMR spectrum showed two acetate peaks at δ 3.39 and 3.52.

Anal.—Calc. for C $_{24}$ H $_{35}$ NO $_4$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.90; H, 8.58; N, 3.61.

Spiro-[5-androsten-3 β -ol-17-yl-5'-(2',2'-dimethyloxazolidine)] (IV)—This compound was prepared according to the method of Heusser *et al.* (6), m.p. 199–201° [lit. (6) m.p. 189–190° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 1370 cm.⁻¹ split peak (gem-dimethyl). The NMR spectrum showed two methyl singlets at δ 1.315 and 1.357 (2',2'-gem-dimethyl) and a pair of doublets at δ 2.73 and δ 3.26 (J = 12 Hz.; 4'—CH $_2$ —).

Anal.—Calc. for C $_{24}$ H $_{37}$ NO $_2$: C, 76.83; H, 10.36; N, 3.89. Found: C, 76.61; H, 10.41; N, 3.69.

Spiro-[5-androsten-3 β -ol-17-yl-5'-(N-acetyl-2',2'-dimethyloxazolidine)] (V)—To a solution of 1 g. of N-acetyl oxazolidine acetate (VI) in 30 ml. methanol was added 8 ml. of a 6% solution of sodium carbonate. The mixture was stirred for 2 hr., poured into 100 ml. water, filtered, dried, and crystallized from methanol, yielding 0.7 g. prisms, m.p. 231–233° [lit. (6) m.p. 230–232° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 3450 cm.⁻¹.

Anal.—Calc. for C $_{26}$ H $_{39}$ NO $_3$: C, 74.77; H, 9.79; N, 3.61. Found: C, 75.00; H, 9.97; N, 3.80.

Spiro-[5-androsten-3 β -ol-yl-5'-(N-acetyl-2',2'-dimethyloxazolidine)] Acetate (VI)—One gram of oxazolidine (IV) was dissolved in a mixture of 50 ml. pyridine and 20 ml. acetic anhydride. The mixture was stirred overnight at room temperature and poured into ice-cold water. The precipitate was collected by filtration, dried, and recrystallized from acetone, yielding 0.7 g. of white needles, m.p. 162–163° [lit. (6) m.p. 162–163° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 1720 cm.⁻¹ (3-OAc) and 1643 cm.⁻¹ (—NHAc). The NMR spectrum showed two methyl singlets at δ 4.65 and 2.02 [3—O—C(=O)—CH $_3$ and 3'—N—C(=O)—CH $_3$].

² When the product was washed with further quantities of methanol, the melting point of the product was raised to 227–228°.

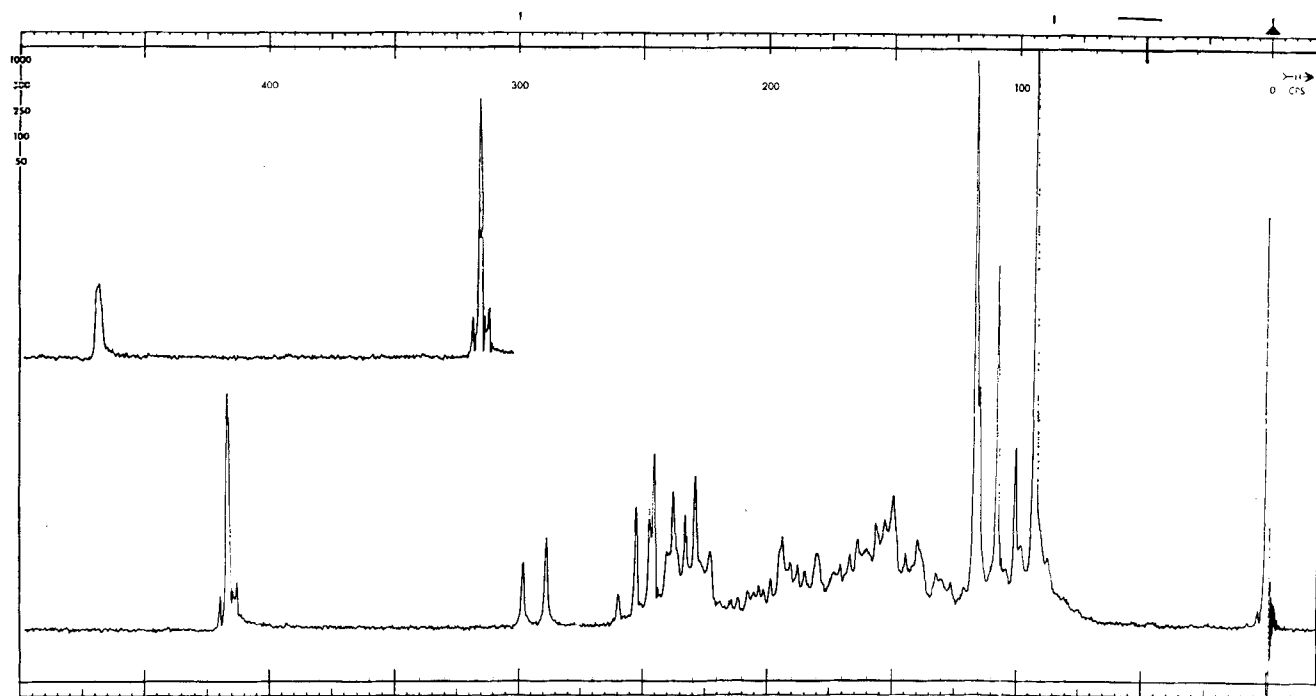


Figure 3—NMR spectrum of spiro-[4-androsten-3-one-17-yl-2'-(N-ethyloxazolidine)] (XVIII).

Spiro-[4-androsten-3-one-17-yl-5'-(N-acetamido-2',2'-dimethyloxazolidine)] (VII)—A solution of 500 mg. of *N*-acetyloxazolidine (V) in 5 ml. of cyclohexanone and 20 ml. of toluene was azeotroped under a Dean-Stark head for 1 hr. A solution of 500 mg. of aluminum-*tert*-butoxide in toluene was added, and the mixture was refluxed for 8 hr. The reaction mixture was cooled to room temperature, treated with 3 ml. of water, filtered, and concentrated under reduced pressure and finally under high vacuum. Addition of 10 ml. of *n*-hexane yielded 350 mg. of white needles. Recrystallization from acetone-hexane gave the analytical sample, m.p. 221–223° [lit. (6) m.p. 212–214° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 1665 cm^{-1} .

Anal.—Calc. for $\text{C}_{25}\text{H}_{37}\text{NO}_3$: C, 75.15; H, 9.93; N, 3.51. Found: C, 75.16; H, 9.49; N, 3.54.

Spiro-[5-androsten-3 β -ol-17-yl-5'-(N-ethyl-2',2'-dimethyloxazolidine)] (VIII)—A solution of 500 mg. of *N*-acetyloxazolidine acetate (VI) in a mixture of 10 ml. benzene and 20 ml. anhydrous ether was added dropwise, with constant stirring, to a suspension of 500 mg. of lithium aluminum hydride in 30 ml. anhydrous ether. After addition was complete, the reaction mixture was stirred for 30 min. and refluxed for an additional 30 min. The slurry was decomposed with ether-water and filtered; evaporation of the solvent under vacuum produced a residue which was mixed with the dried precipitate and extracted with *n*-hexane for 72 hr. Evaporation of the solvent under vacuum and crystallization from acetone yielded 400 mg. of white crystals, m.p. 145–146°. It was also possible to synthesize this compound in the following way: 250 mg. of the amine (XVI) was extracted with 20 ml. acetone containing 0.005 ml. of acetic acid for 72 hr. Filtration and removal of the solvent gave a solid which was recrystallized from acetone, m.p. 143–145°. The NMR spectrum showed two methyl singlet peaks at δ 2.37 and 3.05 (2',2'-gem-dimethyl) and a triplet δ 1.06 ($J = 7 \text{ Hz.}, 4' - \text{N} - \text{CH}_2$).

Anal.—Calc. for $\text{C}_{25}\text{H}_{41}\text{NO}_2$: C, 77.47; H, 10.66; N, 3.61. Found: C, 77.27; H, 10.56; N, 3.61.

Spiro-[4-androsten-3-one-17-yl-5'-(N-ethyl-2',2'-dimethyloxazolidine)] (X)—A 500-mg. sample of *N*-ethyl-2',2'-dimethyloxazolidine (VIII) was dried by azeotropic distillation with 25 ml. of benzene under a Dean-Stark head. After distillation of 5 ml. of benzene, a solution of 500 mg. of aluminum-*tert*-butoxide in benzene and 10 ml. of absolute acetone was added. The reaction mixture was refluxed 24 hr., cooled to room temperature, diluted with 3 ml. of distilled water, and filtered. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on grade I neutral alumina³. Elution

with *n*-hexane gave the crude α,β -unsaturated ketone X which, after crystallization from acetone, yielded 240 mg. of white needles, m.p. 117–119°, $\nu_{\text{max}}^{\text{KBr}}$ 1670 cm^{-1} . The NMR spectrum showed a vinyl proton peak at δ 5.66.

Anal.—Calc. for $\text{C}_{25}\text{H}_{39}\text{NO}_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.57; H, 10.63; N, 3.74.

Spiro-[4-androsten-3-one-17-yl-5'-(2',2'-dimethyloxazolidine)] (XI)—A solution of 0.5 g. of 3 β -ol-17-yl-dimethyloxazolidine (IV) in 19 ml. of toluene was refluxed under a Dean-Stark head for 1 hr. A solution of 0.53 mg. aluminum-*tert*-butoxide in 10 ml. of toluene and 6 ml. of absolute acetone was added and refluxed for 37 hr. The reaction mixture was cooled to room temperature, and 1 ml. of distilled water was added. Filtration and removal of the solvent under reduced pressure gave a residue which was triturated with 5 ml. of *n*-hexane, yielding white crystals. The product was chromatographed over grade II neutral alumina³. Elution with *n*-hexane-benzene (9:1) gave the desired product, which was recrystallized from acetone, yielding 100 mg. of white needles, m.p. 179–180° [lit. (6) m.p. 179–180° dec.], $\nu_{\text{max}}^{\text{KBr}}$ 1670 cm^{-1} , λ_{max} 241 nm. The NMR spectrum showed a vinyl proton peak at δ 5.66.

Table II—Aldosterone Antagonistic Activity of the Compounds Tested^a

Compound	Percent Block of a 12-mcg. Deoxycorticosterone Acetate ^b Dose
Aldactone	95
VII Spiro-[4-androsten-3-one-17-yl-5'-(<i>N</i> -acetamido-2',2'-dimethyloxazolidine)]	24
X Spiro-[4-androsten-3-one-17-yl-5'-(<i>N</i> -ethyl-2',2'-dimethyloxazolidine)]	22
XI Spiro-[4-androsten-3-one-17-yl-5'-(2',2'-dimethyloxazolidine)]	15
XIII 17 α -Acetamidomethyl-5-androsten-3 β ,17 β -diol	0
XVII Spiro-[5-androsten-3 β -ol-17-yl-5'-(<i>N</i> -ethyl-oxazolidine)]	13

^a Results are expressed in terms of the percent block of a 12-mcg. dose of deoxycorticosterone acetate by a dose of 800 mcg./rat. ^b Doca.₄

³ E. Merck.

Anal.—Calc. for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87; N, 3.92. Found: C, 77.22; H, 10.08; N, 3.83.

17 α -Aminomethyl-5-androstene-3 β ,17 β -diol (XII)—This compound was prepared according to the modified method of Heusser *et al.* (6). Oxazolidine (IV) (100 mg.) was dissolved in 0.5 ml. of acetic acid and diluted with 10 ml. of water. The amine was precipitated out by the addition of 15% sodium hydroxide and collected by filtration. The dried residue was extracted with methanol-acetonitrile (1:1) for 72 hr. to yield 70 mg. of white needles, m.p. 222–223° [lit. (6) m.p. 222–223° dec.].

17 α -Acetamidomethyl-5-androstene-3 β ,17 β -diol (XIII)—To a solution of 0.5 g. of XIV in 15 ml. methanol was added 8 ml. of 6% sodium carbonate. The mixture was stirred for 2 hr. and poured in water. The precipitate was collected by filtration, dried, and recrystallized from methanol-acetonitrile to yield 0.3 g. of white platelets, m.p. 240.5–241.5°.

Anal.—Calc. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.29; H, 9.90; N, 3.90.

17 α -Acetamidomethyl-5-androstene-3 β ,17 β -diol, 3-Acetate (XIV)—A solution of 0.5 g. of XII in 28 ml. pyridine and 12 ml. acetic anhydride was stirred overnight. The solution was poured into cold water, filtered, and crystallized from methanol, yielding 0.45 g. of crystalline XIV, m.p. 227–228°, $\nu_{\text{max}}^{\text{KBr}}$ 1643 cm^{-1} (—NHAc), 1730 cm^{-1} .

Anal.—Calc. for $C_{24}H_{37}NO_4$: C, 71.43; H, 9.24; N, 3.47. Found: C, 71.18; H, 9.11; N, 3.29.

17 α -Acetamidomethyl-17 β -hydroxy-4-androsten-3-one (XV)—A solution of 500 mg. of XIII in 5 ml. of cyclohexanone and 100 ml. of toluene was refluxed under a Dean-Stark head for 1 hr. A toluene solution containing 500 mg. of aluminum-*tert*-butoxide was added, and reflux was resumed for 12 hr. The reaction mixture was cooled to room temperature, and 3 ml. of water was added; filtration and removal of the solvent under reduced pressure and finally under high vacuum gave a crude α,β -unsaturated ketone which was precipitated by the addition of *n*-hexane and collected by filtration. Chromatography on grade IV neutral alumina³ and elution with benzene and benzene-chloroform (9:1) gave the desired product. The analytical sample was obtained by crystallization from acetone-*n*-hexane, yielding 100 mg., m.p. 199–201°, $\nu_{\text{max}}^{\text{KBr}}$ 1670 cm^{-1} .

Anal.—Calc. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.45; H, 9.17; N, 3.95.

17 α -Ethylaminomethyl-5-androstene-3 β ,17 β -diol (XVI)—A solution of 400 mg. of XIV in 40 ml. of tetrahydrofuran was added dropwise, with constant stirring, to a suspension of 500 mg. of lithium aluminum hydride in 40 ml. of tetrahydrofuran. After addition was complete, the reaction mixture was refluxed for 24 hr. and then decomposed with tetrahydrofuran-water and filtered. After most of the tetrahydrofuran was distilled off *in vacuo*, the crude amine was precipitated out by the addition of 6% NaOH solution. The residues were combined and extracted for 72 hr. with petroleum ether (30–60°), yielding 250 mg. of prisms. Recrystallization from petroleum ether afforded the analytical sample, m.p. 128–129°. The NMR spectrum showed a 3-proton triplet signal at δ 1.08 (—NHCH₂—CH₃).

Anal.—Calc. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 76.01; H, 10.79; N, 3.89.

Spiro-[5-androsten-3 β -ol-17-yl-5'-(*N*-ethylloxazolidine)] (XVII)—To a solution of 200 mg. of *N*-ethylamine (XVI) in 10 ml. methanol was added 0.047 ml. of 37% formaldehyde solution and 0.01 ml. of glacial acetic acid. The reaction mixture was stirred at room temperature for 15 min. and then refluxed for 30 min. The mixture was cooled on an ice bath and treated with 6 ml. of distilled water and 6 ml. of 6% sodium hydroxide solution. The precipitated ethyloxazolidine was collected by filtration, dried, and recrystallized from methanol-acetonitrile (1:4), yielding 150 mg. of white

needles, m.p. 155–157°. The NMR spectrum showed a pair of doublets at δ 4.13; 4.20 ($J = 3\text{Hz.}$; 2'-CH₂).

Anal.—Calc. for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.64; H, 10.50; N, 4.10.

Spiro-[4-androsten-3-one-17-yl-2'-(*N*-ethylloxazolidine)] (XVIII)—A solution of 500 mg. of *N*-ethylloxazolidine (XVII) in 25 ml. of benzene was refluxed under a Dean-Stark head. After 5 ml. of benzene was distilled out, a solution of 500 mg. of aluminum-*tert*-butoxide in benzene and 6 ml. of absolute acetone was added. The reaction mixture was refluxed for 24 hr., cooled to room temperature, diluted with 3 ml. of distilled water, and filtered. Concentration of the filtrate *in vacuo* and chromatography of the residue on grade I neutral alumina³, using *n*-hexane as the eluant, gave the α,β -unsaturated ketone. Crystallization from *n*-hexane yielded 250 mg. of white needles, m.p. 120–121°, $\nu_{\text{max}}^{\text{KBr}}$ 1670 cm^{-1} . The NMR spectrum showed a vinyl proton peak at δ 5.68 (Fig. 3).

Anal.—Calc. for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.08; H, 9.90; N, 3.91.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 22, 1971, from the *Department of Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677 and the †Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803

Accepted for publication July 8, 1971.

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