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# SYNTHESIS, STRUCTURE AND REACTIONS OF SECO-STEROIDS CONTAINING A MEDIUM-SIZED RING—IX[1]

## REACTIONS OF $\Delta^{1(10)}$-UNSATURATED 5-OXO-5,10-SECO-STEROIDS WITH HYDROXYLAMINE AND N-METHYLHYDROXYLAMINE

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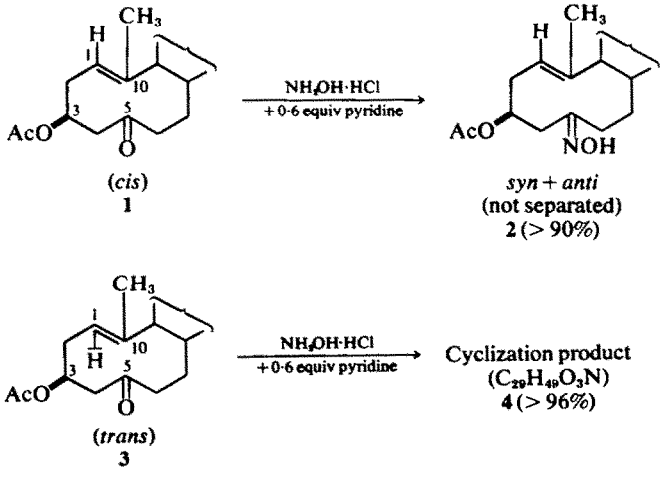
**Abstract**—When treated with hydroxylamine or N-methylhydroxylamine, in the presence of proton donor catalysts, *trans*-$\Delta^{1(10)}$-unsaturated 5-oxo-5,10-seco-steroids, such as **3** (but not the corresponding diastereomeric *cis*-compounds), are converted stereospecifically and in good yield to isoxazolidine derivatives (e.g. **4** and **13**), resulting from transannular 1,3-dipolar addition of the intermediately formed oximes and nitrones to the *trans*-double bond in the cyclodecene ring moiety of the seco-steroid system. Reactions are described and physical evidence is presented which establish the constitution and configuration of the isoxazolidine-containing cycloaddition products, and the mechanistic and steric course of this transannular ring closure process is discussed.

In one of our previous communications,[2] on the reactivity of the 1(10)-cyclodecen-5-one ring system in 5,10-seco-compounds prepared by the lead tetraacetate fragmentation of 5-hydroxysteroids, it was reported (in preliminary form) that in refluxing ethanolic solution, hydroxylamine hydrochloride in the presence of a 0·6 molar equivalent of pyridine (with respect to $NH_2OH \cdot HCl$) converted *cis*-3$\beta$-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (**1**) into a mixture of *syn*- and *anti*-oximes **2** (Scheme 1). With the corresponding *trans*-diastereomeric ketone **3** it reacted, under the same conditions, to give an intramolecular cyclization product **4** (isomeric with the oxime), in nearly quantitative yield.

For compound **4** four possible structures may be




SCHEME 1

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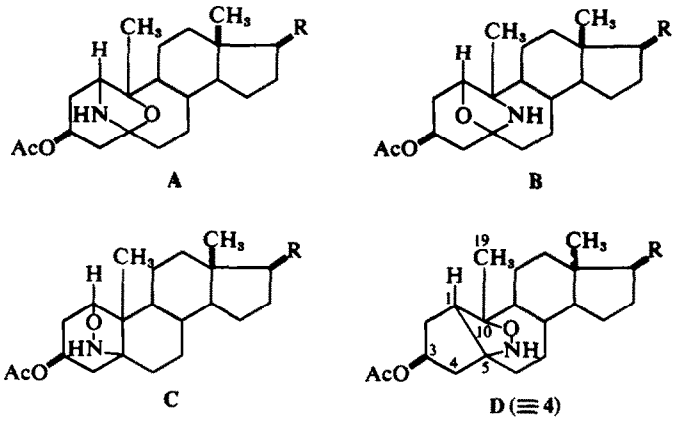



SCHEME 2

envisaged (Scheme 2, R = $CH(Me)CH_2CH_2CH_2$-$CHMe_2$), two of which (**A** and **B**) were considered in our previous paper.[2]

In the light of additional data we have now re-examined the reaction of **3** with hydroxylamine in more detail, in order to prove the constitution and configuration of the cyclization product **4**, and to study the mechanistic and steric course of this transannular addition process.

*For α-, β- and γ-alkyl protons in simple amino compounds Δδ values of (+0·7)–(+1·2) ppm, (+0·3)–(+0·5) ppm and +0·05 ppm, respectively, have been observed for the downfield signal displacement in acidic solution.[3a,b]

## RESULTS AND DISCUSSION

From NMR spectral data of product **4**, given in Table 1, and particularly from the downfield signal displacement of several protons (at C-1, C-3, C-4 and C-19) in acidic solution, it is possible to make a tentative choice between structures **A**, **B**, **C** and **D** (Scheme 2) for product **4**.

The paramagnetic signal displacement of the methyl protons at C-19 in acidic solution by only +0·15 ppm suggests that these hydrogens (like the proton at C-3 which shows the same signal displacement of +0·15 ppm) should be on carbon which is separated by two atoms (rather than one atom) from the amino-nitrogen,* thus making structure **B** improbable.

Table 1. NMR data (at 100 MHz) of products **4** and **17**

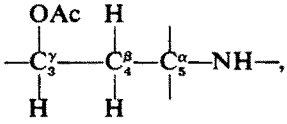
| Protons | Compound | Chemical shift (δ ppm)[a] $CDCl_3$ | | $CDCl_3+CF_3COOH$ | Displacement (Δδ ppm) |
|---|---|---|---|---|---|
| H—C(1)[b] | 4 | 2·84 | (*q*) | 3·19 | +0·35 |
| | 17 | 2·65 | | 3·02 | +0·37 |
| AcO—C(3) (β) | 4 | 2·06 | (*s*) | 2·17 | +0·11 |
| (α) | 17 | 2·04 | | 2·14 | +0·10 |
| H—C(3)[b] (α) | 4 | 5·23 | (*m*) | 5·38 | +0·15 |
| (β) | 17 | 5·22 | | 5·33 | +0·11 |
| $H_α$—C(4) | 4[c] | ~2 | (*m*) | 2·84 | ~+0·84 |
| | 17 | ~1·7 | | 2·40 | ~+0·7 |
| Me(19) | 4 | 1·21 | (*s*) | 1·36 | +0·15 |
| | 17 | 1·23 | | 1·40 | +0·17 |
| Me(18) | 4 | 0·72 | (*s*) | 0·72 | 0 |
| | 17 | 0·70 | | 0·70 | 0 |
| Me(21) | 4 | 0·87 | (*d*) | 0·87 | 0 |
| Me(26)\ | 17 | 0·89 | | 0·89 | 0 |
| C | 4 | 0·84 | (*d*) | 0·84 | 0 |
| Me(27)/ | 17 | 0·85 | | 0·85 | 0 |

[a]Abbreviations: *s* singlet, *d* doublet, *t* triplet, *q* quartet, *m* multiplet.

[b]In both compounds **4** and **17** the H—C(1) proton is coupled to the two H—C(2) protons ($J$ = 7–11 Hz), while the H—C(3) proton is coupled to the two H—C(2) and the two H—C(4) protons ($J$ = 1–11 Hz).

[c]In compound **4** proton $H_{α(eq)}$ attached to C-4 is coupled to $H_α$—C(3) by about 6 Hz (as shown by double resonance), and exhibits also a geminal coupling of 18 Hz.

It was shown by double resonance technique that the proton exposed to the strongest paramagnetic influence in acidic solution (and exhibiting a signal displacement of about +0·8 ppm) is coupled to the proton at C-3 and represents one of the C-4 hydrogens, whereby it should be located on carbon which is $\beta$ with respect to nitrogen,* i.e. incorporated in the partial structure



and, in addition, in a specific steric orientation allowing direct field influence of the amino-nitrogen.†‡ All three structures **A**, **C** and **D** contain such a grouping, but in **A** carbon C-1 is directly bound to nitrogen and one would expect its proton to exhibit a larger downfield displacement of chemical shift in acidic solution than actually observed ($\Delta\delta = +0{\cdot}35$ ppm).* Therefore structure **A** is improbable, and cyclization product **4** should have one of the remaining isoxazolidine structures **C** or **D**, in which the $C_1$—H grouping is separated by one atom from nitrogen.

From the facts that the signal position of the methyl protons at C-19 ($\delta = 1{\cdot}21$ ppm) is characteristic for methyl groups attached to a saturated carbon atom bearing an oxygen,[3a] and that the proton at C-1 has a signal value (of 2·84 ppm) in the region where one observes chemical shifts for such C-1 protons in other 5(10 → 1)*abeo*-steroid systems,[2,4] it appears that the polycyclic structure **D** (Scheme 2) for product **4**, in which the isoxazolidine ring is incorporated in the 5(10 → 1)*abeo*-cholestane system, is in better agreement with NMR data and therefore more probable than structure **C**.

That constitution **D** (and not **C**) corresponds to compound **4** was confirmed by the chemical transformations shown on Scheme 3.

The keto-carbonyl band at 1754 $cm^{-1}$ in the IR spectrum of compound **7** indicates the presence of a five-membered rather than a six-membered cyclic ketone.[5] On the other hand, hydrogenolysis (either catalytic or with zinc and acetic acid) of **4** opens the isoxazolidine ring to give an amino-alcohol **8** which was converted to its N-acetyl derivative **9**. When treated with Kiliani's solution (chromic acid in acetone) this product (**9**) remained unchanged, thus indicating that compounds **8** and **9** contained a tertiary hydroxyl group. (Structure **C** for product **4** would give a secondary alcohol and, upon oxidation, a 2-keto-derivative.)

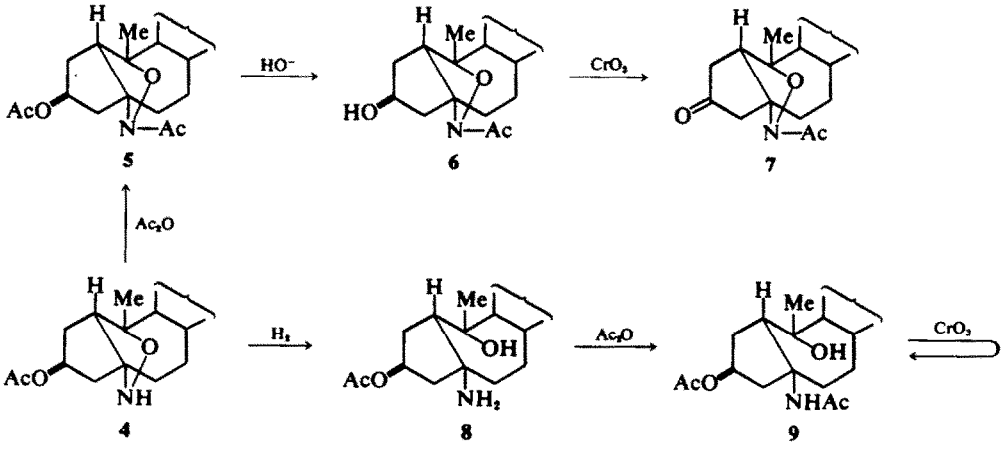
When the *trans*-seco-ketone **3** (Scheme 4) was treated with hydroxylamine hydrochloride and a large *excess* of pyridine in refluxing ethanol, the major reaction products, obtained in about 80% yield, were the *syn*- and *anti*-oximes **10** (which were separated but not configurationally defined), whereas the isoxazolidine derivative **4** was formed in minor amount (10–15%).

Either of these stereoisomeric oximes (**10a** or **10b**), upon refluxing in ethanolic solution in the presence of hydroxylamine hydrochloride + pyridine (molar ratio 1:0·4), were quantitatively isomerized to the isoxazolidine derivative **4** (Scheme 4), and the same conversion was also achieved by using other acid catalysts, such as hydroxylamine hydrochloride alone, pyridine hydrochloride alone, ammonium chloride (requires longer heating) or

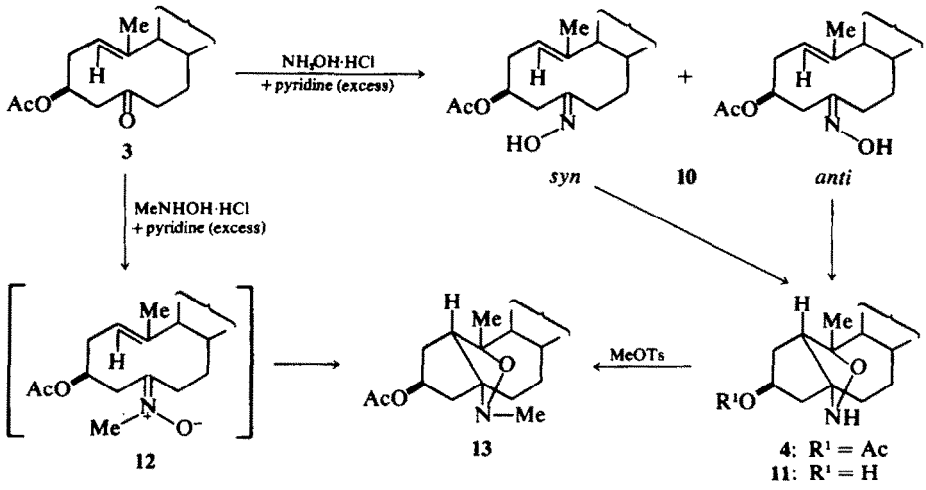
*See footnote* on preceding page.

†Which would account for the rather large paramagnetic displacement of a proton attached to a $\beta$-carbon.

‡Actually, this hydrogen at C-4 is $\alpha$-oriented (quasi-equatorial; see Fig 1).




SCHEME 3

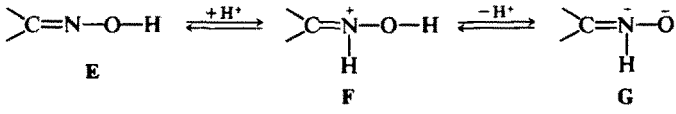



SCHEME 4

hydrochloric acid.* However, in the absence of these acid catalysts, oximes **10** remained unchanged upon heating in ethanol for four to ten hours. The oximes **2** of the *cis*-seco-ketone **1** (Scheme 1) do not undergo intramolecular cyclization (and remain unchanged) when treated with three acid catalysts.

Similar results were also observed in the androstane series. Thus, with hydroxylamine *cis*-3β,17β-dihydroxy-5,10-seco-androst-1(10)-en-5-one diacetate gives always and only the corresponding *syn*- and *anti*-oximes, whereas the *trans*-diastereomeric ketone, depending upon reaction conditions, affords either the oxime or the bridged 5,10-iminoöxy-5(10 → 1)*abeo*-androstane derivative with structure **D** (Scheme 2, R = OAc).

Inter- and intramolecular 1,3-dipolar additions of oximes to double and triple bonds in which one or both reacting centres are activated by adjacent groups take place thermally without the aid of catalysts.[6,7] In contrast, the present transannular oxime addition to a non-activated *trans*-ethylenic linkage in a ten-membered ring requires the presence of a proton donating catalyst, probably because it facilitates intramolecular 1,3-dipolar cycloaddition by protonating the nitrogen of the oxime grouping (**E**). This then reacts as a mesomeric polar species, either in the O-protonated (**F**) or more probably in the free nitronic form (**G**).[6,7]




**E** **F** **G**

N-Methylhydroxylamine, in the form of its hydrochloride and in the presence of excess pyridine (i.e. under conditions used for preparing the oximes **10** from **3**), also reacts (in refluxing ethanol) with the *trans*-seco-ketone **3** (but not with the *cis*-ketone **1**) to give the non-isolable nitrone **12** (Scheme 4) as intermediate, which undergoes spontaneous transannular cycloaddition of the intramolecular nitrone-olefin type,[7–10] with formation of the N-methylisoxazolidine derivative **13** in over 60% yield.† The constitutional and configurational identity of the isoxazolidine ring system in both compounds **4** and **13** was established by treating **4** with methyl *p*-toluenesulfonate, whereby the N-methyl derivative **13** was obtained (Scheme 4).

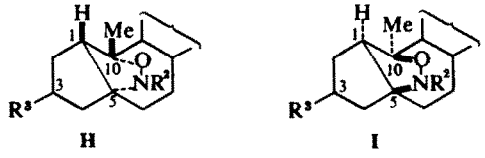
As to the stereochemistry of these transannular cycloadditions, it should be noted that in the isoxazolidine compounds with constitution **D** (Scheme 2), such as products **4** and **13** (and also **17**, Scheme 6), the five-membered A-nor-ring must be 1,5-*trans*-fused to the seven-membered B-homo-ring in

*With hydrochloric acid as catalyst, internal cycloaddition took place in 88% yield, but with simultaneous hydrolysis of the 3-acetate group, affording the 3β-hydroxy-isoxazolidine derivative **11**.

†When ketone **3** was treated with free N-methylhydroxylamine, under conditions often applied for effecting intramolecular nitrone-olefin cycloadditions,[7–10] it remained either unchanged (in boiling ether or in ethanol at room temperature) or underwent thermal intramolecular cyclization[4] to the previously described 5(10 → 1βH)*abeo*-5α-cholest-10(19)-ene-3β,5-diol 3-acetate[2,4] (in refluxing ethanol or toluene).

The presence of an acid-containing catalyst in the above mentioned reaction with N-methylhydroxylamine is probably necessary in order to facilitate, in the first step, the formation of the (intermediate) nitrone **12**.

order to permit bridging of carbons C-5 and C-10 by the imino-oxy (—$NR^2$—O—) grouping with minimum strain. (The corresponding isoxazolidine structures with a *cis* A-nor/B-homo 1,5-ring junction would be too strained to be formed under these reactions conditions.) Hence, only two stable configurations for the isoxazolidine products of type **D** (**4**, **13**, **17**, etc.) are possible (Scheme 5), one in which the 5,10-iminoöxy (—$NR^2$—O—) bridge is α- (i.e. under the general plane of the A-nor-B-homo-bicyclic system) and the hydrogen at C-1 β-oriented (**H**), and the other with a β-oriented



**H** **I**

**4**: $R^2 = H$, $R^3 = \beta$-OAc
**13**: $R^2 = Me$, $R^3 = \beta$-OAc } Cholestane series
**17**: $R^2 = H$, $R^3 = \alpha$-OAc

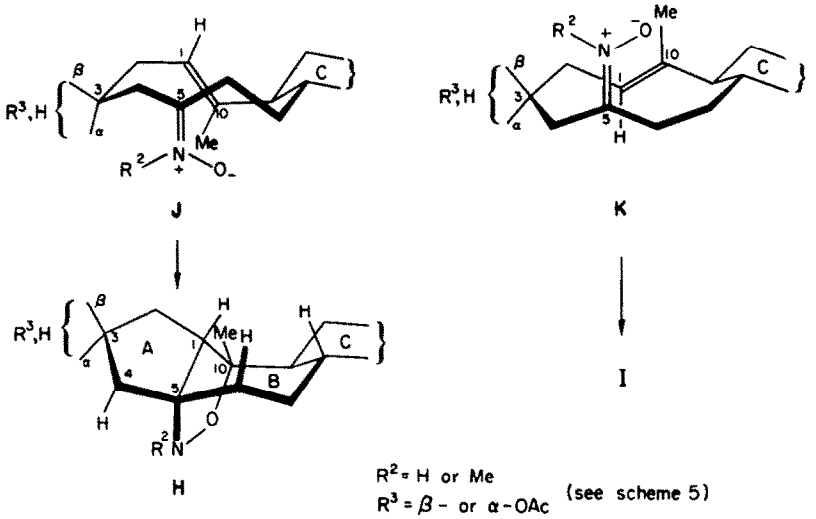
**25**: $R^2 = H$, $R^3 = \beta$-OAc } Androstane series

SCHEME 5

5,10-iminoöxy (—$NR^2$—O—) bridge and α-hydrogen at C-1 (**I**).

On the basis of these configurational conditions for the isoxazolidine products and from inspection of Dreiding models it follows that there are only two possible conformational types (**J** and **K**, Fig 1) for the *trans*-cyclodecene ring of the 5,10-seco-steroid substrate undergoing internal cyclization, in which the reacting sites, i.e. the nitrone grouping at C-5 and the *trans*-$\Delta^{1(10)}$-carbon-carbon double bond, are suitably disposed to undergo transannular 1,3-dipolar cycloaddition* (whether synchronously as a supra-supra-facial [4 + 2]-process[9–11] or, less likely, as a two-step combination *via* a dipolar intermediate with positive charge at the tertiary C-10 carbon), whereby the more stable conformation **J** would lead to the product with the α-oriented iminoöxy bridge **H**, and conformation **K** would afford the corresponding β-oriented stereoisomer **I**.

That in the isoxazolidine compound **4**, and therefore also in products **13** and **17**, the imino-oxy bridge has the 5α,10α-stereochemistry (**H**, Scheme 5 and Fig. 1), which results from stereospecific intramolecular cycloaddition involving, at least in



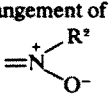
**J** **K**

**H** **I**

$R^2$ = H or Me
$R^3$ = β- or α-OAc (see scheme 5)

Fig 1.

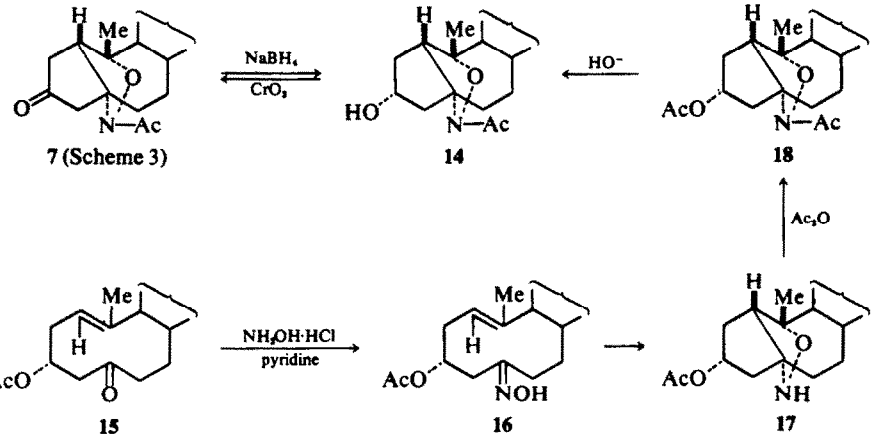
*This also implies the additional prerequisite of an *anti*-stereoisomeric arrangement of the



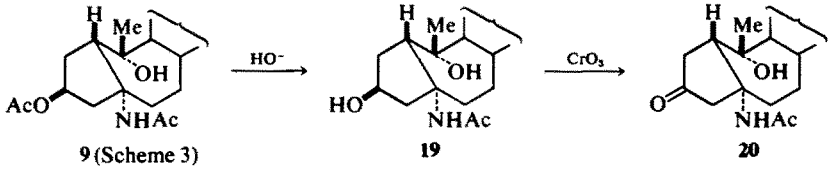
($R^2$ = H or Me) system in the course of reaction (corresponding to the configuration of the oxime group in *anti*-**10** and the nitrone group in **12**). However, under the reaction conditions employed, it appears that the *syn* ⇄ *anti* interconversion of such systems is rapid,[12] since, as described above, both geometrical forms (**a** and **b**) of the oxime **10** are readily converted, by transannular cycloaddition, to the same isoxazolidine product **4** (Scheme 4).

the transition state, a conformation of type **J**, was established on ground of the following chemical and physical evidence.

When the N-acetyl 3-ketone **7**, obtained by oxidation of the corresponding 3β-ol **6** (Scheme 3), was reduced with sodium borohydride (Scheme 6), it afforded as sole product the epimeric 3α-ol **14**, thus indicating that the hydride ion attacks the 3-keto group from the less hindered β-side, i.e. that the 5,10-iminoöxy bridge (which prevents approach of the reducing agent) must be α-oriented. The same 3α-hydroxy-isoxazolidine compound **14**




SCHEME 6




SCHEME 7

was also synthesized by the oxime-olefin transannular cycloaddition, starting from *trans*-3α-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (**15**) and by the reaction sequence shown on Scheme 6. The cycloaddition product **17** has similar NMR characteristics (Table 1) to those of its 3β-epimer **4**.

Conclusive evidence in favour of configuration **H** for product **4** (and therefore also for **13** and **17**) was obtained from CD measurements (Table 2) performed on the 3-ketone **7** (Schemes 3 and 6) and its hydrogenolysis derivative, the 3-ketone **20**, which was prepared by the reactions shown on Scheme 7.

Table 2. CD data of ketones **7** and **20** (in acetonitrile)

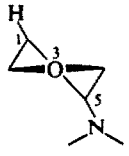
| Compound | λ(nm) ($\Delta\epsilon_{max}$) |
|---|---|
| **7** | 312 *sh* (+1·33), 301 (+2·72), 291 (+3·12), 285 (+2·68), 245 (−7·0), 217 (+17·1) |
| **20** | 311 (+2·60), 302 (+4·57), 293 (+4·68), 283 *sh* (+3·53), 228 (−1·04), 203 (+8·5) |

*The weaker positive CD value at 300 nm for ketone **7** may be attributed to the fact that the —NH—O— bridge either deforms somewhat the A-nor-cyclopentanone ring or has some (possibly "anti-octant") influence on the 3-keto-carbonyl group.

The strong CD band at 245 nm found for ketone **7** appears to arise from the presence of the N-acetyl iminoöxy grouping, —N(Ac)—O—, since it was also observed for the N-acetyl-iminoöxy-3β-ol **6** (λ = 242 nm, $\Delta\epsilon_{max}$ = −8·29), but not for products **20**, **13** and **4**.

Both compounds should have the same configurations at C-1, C-5 and C-10, whereby in ketone **7** the A-nor-B-homo system, because of additional bridging, is more rigid and strained than in ketone **20**.

As can be seen from Table 2, the CD of the ketone band at about 300 nm is strongly positive for **20**, somewhat weaker and positive for ketone **7**, indicating that in both cases the A-nor-cyclopentanone ring has P-helicity (**L**).[4,*] This is possible only if the heterocyclic ring is formed under the steroid system, namely when the 5,10-iminöxy bridge has the α-configuration, as shown by **H** (Scheme 5 and Fig 1).



**L**

In conclusion it can be pointed out that the stereospecific oxime-olefin and nitrone-olefin transannular cycloadditions starting from *trans*-$\Delta^{1(10)}$-unsaturated 5-oxo-5,10-seco-steroids (e.g. **3** and **15**) are consistent with previously reported results, which show that the geometry of the *trans*-cyclodecenone ring in these modified steroid compounds is favourable to transannular reactions and that it corresponds preferably to conformations of

type J.[4,13,*] The fact that oximes of the diastereomeric *cis*-$\Delta^{1(10)}$-unsaturated 5-ketones (e.g. **2**) do not undergo such intramolecular 1,3-dipolar additions to the double bond is also in agreement with our previous observations that in the stable conformations of the *cis*-cyclodecenone ring in these systems the 1(10)-olefinic group and the trigonal C-5 carbon are too far apart to permit internal cyclization reactions with transannular bond formation.[2,4,13]

## EXPERIMENTAL†

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln. CD measurements were carried out with a Roussel-Jouan Dichrographe Model 185 in acetonitrile soln at 20° and concentrations less than 0·1%, using cells of pathlengths of 0·01 to 0·1 cm. NMR spectra were obtained at 100 MHz with a Varian HA-100 spectrometer in $CDCl_3$ soln at room temp using TMS as internal standard (chemical shifts are reported in δ values).‡ IR spectra were determined on Perkin-Elmer instruments, Model 221 and Model 337, in KBr, $CCl_4$ and/or $CH_2Cl_2$. UV absorption spectra were recorded in 95% EtOH with a Perkin-Elmer 137 UV spectrophotometer. The separation of products was monitored by TLC on silica gel G (Stahl) with benzene-AcOEt (9:1, 7:3 or 1:1), detection being effected with 50% $H_2SO_4$. Silica gel 0·05–0·2 mm was used for column chromatography. Light petroleum refers to the fraction b.p. 40–60°.

*Oxime* **2** *of* cis-3β-*hydroxy*-5,10-*seco*-*cholest*-1(10)-*en*-5-*one acetate* (**1**). A. The preparation of **2** (as a mixture of *syn*- and *anti*-forms), m.p. 158–159°, in 90% yield, from **1**[2] and $NH_2OH \cdot HCl$ + pyridine (molar ratio 1:0·6) in refluxing EtOH, was described previously.[2] (Found: C, 75·63; H, 10·53; N, 3·37. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).§

B. A soln of 100 mg **1** and 100 mg $NH_2OH \cdot HCl$ in 5 ml EtOH and 5 ml pyridine was heated for 2 h on a steam bath. The cooled reaction mixture was poured into water, the resulting crystalline product filtered off and thoroughly washed with water, to give 90 mg (87%) of **2**, m.p. 158–159° (from MeOH).

5α,10α-*Iminoöxy*-5(10 → 1β*H*)abeo-5α-*cholestan*-3β-*ol acetate* (**4**) *from* trans-3β-*hydroxy*-5,10-*seco*-*cholest*-1(10)-*en*-5-*one acetate* (**3**). The preparation of **4**, m.p. 141–142°, in 97% yield, from **3**[2] and $NH_2OH \cdot HCl$ + pyridine (molar ratio 1:0·6) in refluxing EtOH, was reported previously;[2] NMR: see Table 1. (Found: C, 75·88; H, 10·91; N, 3·34. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).§

*N*-*Acetyl*-5α,10α-*iminoöxy*-5(10 → 1β*H*)abeo-5α-*cholestan*-3-*one* (**7**) *from* **4** (*via* **5** *and* **6**). A soln of **4** (160 mg) in pyridine (0·75 ml) and $Ac_2O$ (0·75 ml) was left 12 h at room temp. After addition of water the mixture was extracted with ether-$CH_2Cl_2$, the organic layer washed with dilute $H_2SO_4$, water, aq$NaHCO_3$, and water, and dried over $Na_2SO_4$. Evaporation *in vacuo* afforded **5** (172 mg) as an oily residue; IR (KBr): $\nu_{max}$ = 1745, 1631, 1235 $cm^{-1}$.

Without further purification, **5** (160 mg) was treated with 2 ml of 2% methanolic KOH and the resulting soln heated with stirring at 70° for 2·5 h. Upon cooling, the mixture was diluted with water, extracted twice with ether-$CH_2Cl_2$, and the organic layer worked up as usual. The solid product (107 mg) was recrystallized from ether-light petroleum to give 91 mg (62%) of **6**, m.p. 141–143°; $[\alpha]_D^{20} = +45°$ ($c$ = 1·0); UV: $\lambda_{max}$ = 234 nm (ε 4360); IR (KBr): $\nu_{max}$ = 3440, 1650, 1630, 1120 $cm^{-1}$; NMR: δ = 0·69 (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·88 (Me-21, *d*), 1·27 (Me-19, *s*), 2·02 (Ac-N, *s*), about 3·2 (HC-1, *q*), 4·42 (HC-3, *m*). (Found: C, 75·64; H, 10·80; N, 3·28. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

Kiliani's chromic acid soln[15] (0·1 ml of 8N) was added (in 1 min) with swirling to a cooled (0°) soln of **6** (87 mg) in 4 ml acetone (distilled over $KMnO_4$). After 5 min at 0°, water was added and the reaction mixture extracted with ether-$CH_2Cl_2$. The organic layer was washed with saturated $NaHCO_3$ aq and water, dried ($Na_2SO_4$) and evaporated in vacuo. Crystallization of the solid residue (68 mg) from ether-light petroleum afforded 51 mg (58·6%) of **7**, m.p. 142–144°. By further recrystallization, the m.p. was raised to 152–153°; $[\alpha]_D^{20} = +169° \pm 5°$ ($c$ = 0·26); UV: $\lambda_{max}$ = 236 nm (ε ≠ 4550); IR ($CH_2Cl_2$): $\nu_{max}$ = 1754, 1650 $cm^{-1}$; NMR: δ = 0·68 (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·88 (Me-21, *d*), 1·27 (Me-19, *s*), 1·94 (Ac-N, *s*), 2·85 (HC-1, *q*); CD: see Table 2. (Found: C, 76·35; H, 10·07; N, 3·10. $C_{29}H_{47}O_3N$ requires: C, 76·10; H, 10·35; N, 3·06%).

*N*-*Acetyl*-5α-*amino*-5(10 → 1β*H*)abeo-5α-*cholestane*-3β,10α-*diol* 3-*acetate* (**9**) *from* **4** (*via* **8**). Hydrogenolysis of **4** to **8** was brought about in two ways. (1). To a stirred soln of **4** (5 g) in 30 ml of 9:1 AcOH—$H_2O$ was added 10 g of Zn-dust. After heating for 8 h at 70°, excess Zn was separated by filtration from the cooled reaction mixture and washed with 5% HCl. The filtrate was made basic by addition of 10% aqueous NaOH and extracted with ether from which, after evaporation to dryness, 4·8 g of crude **8** was obtained. (2). A soln of **4** (145 mg) in EtOH (20 ml) was hydrogenated at room temp and atmospheric pressure in the presence of 100 mg of 10% Pd/C. After the reduction was complete (about 2 h), the mixture was filtered off and evaporated, affording 140 mg of crude **8**, which crystallized slowly; IR (KBr): $\nu_{max}$ = 3635, 1739, 1235 $cm^{-1}$.

Without purification, crude **8** (135 mg) dissolved in 1·5 ml $Ac_2O$ was left for 12 h at room temp. The reaction mixture was diluted with water, extracted with ether-$CH_2Cl_2$, and the organic layer washed with $NaHCO_3$ aq and water, dried ($Na_2SO_4$) and evaporated to dryness *in vacuo*. The oily product (140 mg), which solidified upon addition of light petroleum, was recrystallized 3 times from ether-light petroleum (or acetone-light petroleum), to give 80 mg of pure **9**, m.p. 117–119°; $[\alpha]_D^{20} = +28° \pm 2°$ ($c$ = 0·69); IR ($CH_2Cl_2$): $\nu_{max}$ = 3676, 3446, 1739, 1678, 1242 $cm^{-1}$; NMR: δ = 0·66 (Me-18, *s*), 0·84 (Me-26 and Me-27, *d*), 0·88 (Me-21, *d*), 1·16 (Me-19, *s*), 1·85 (Ac-N, *s*), 1·98 (AcO, *s*), 3·12 (HC-1, *q*), 4·98 (HC-3, *m*). (Found: C, 74·11; H, 10·39; N, 2·85. $C_{31}H_{53}O_4N$ requires: C, 73·91; H, 10·61; N, 2·78%).

When **9** (26 mg) in acetone (1 ml) was treated with

*Although other conformations are also possible[2,13] and have to be considered in certain transannular reactions.[2,4,14]

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‡For abbreviations see Table 1.

§For additional physical data see Ref. 2.

0·015 ml of 8N Kiliani's chromic acid soln[15] at 0°, only unchanged **9** (22 mg) was isolated from the reaction mixture.

*Oximes* **10a** *and* **10b** (*geometrical isomers of the* syn-anti *type*) *of* trans-3β-*hydroxy*-5,10-*seco*-*cholest*-1(10)-*en*-5-*one acetate* (**3**). A soln of **3** (700 mg) and $NH_2OH \cdot HCl$ (700 mg) in EtOH (35 ml) and excess pyridine (35 ml) was refluxed for 2 h, and then poured into water. After cooling, the solid product was separated by filtration, washed thoroughly with water and recrystallized twice from MeOH and once from acetone, to give 372 mg of oxime **10a** (one geometrical form, *anti* or *syn*), m.p. 154–156°; $[\alpha]_D^{20} = -26° \pm 1°$ ($c = 0·69$); IR (KBr): $\nu_{max} = 3280$, 1725, 1720, 1240 $cm^{-1}$; NMR: δ = 0·71 (Me-18, *s*), 0·85 (Me-26 and Me-27, *d*), 0·87 (Me-21, *d*), 1·75 (Me-19, *d*), 2·03 (AcO, *s*), about 5·20 (HC-1 and HC-3, *m*), over 8·5 (=N—OH, broad signal). (Found: C, 75·77; H, 10·79; N, 3·35. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%). From the combined mother liquors of the above crystallizations, after evaporation to dryness and chromatography of the residue (about 350 mg) on 18 g silica gel using benzene–ether (95:5) as eluent, an additional amount (106 mg) of the same oxime **10a**, m.p. 154–155°, was obtained (total yield: 478 mg, 66%).

Further elution with benzene–ether (85:15) afforded the diastereomeric oxime **10b** (other geometrical form, *syn* or *anti*), which was recrystallized from MeOH (yield: 80 mg, 11%), m.p. 146–148°; $[\alpha]_D^{20} = 0° \pm 2°$ ($c = 0·41$); IR (KBr): $\nu_{max} = 3300$, 1728, 1250 $cm^{-1}$; NMR: δ = 0·69 (Me-18, *s*), 0·84 (Me-26 and Me-27, *d*), 0·86 (Me-21, *d*), 1·70 (Me-19, *s*), 2·01 (AcO, *s*), about 5·10 (HC-1 and HC-3, *m*), over 8 (=N—OH, broad signal). (Found: C, 75·59; H, 10·77; N, 3·39. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

Finally, elution with ether gave 108 mg (15%) of the isoxazolidine product **4** (identified by m.p., mixed m.p. and IR).

*Isoxazolidine product* **4** (*or* **11**) *by internal cycloaddition of oximes* **10a** *and* **10b**. A soln of **10a** or **10b** (70 mg), $NH_2OH \cdot HCl$ (70 mg) and pyridine (0·032 ml) (molar ratio of the latter two reagents being 1:0·4) in 5 ml EtOH was refluxed for 5 hr. Addition of water and cooling caused precipitation of product **4** in quantitative yield.

Similar results with **10a** or **10b** (70 mg) were obtained by using as proton donors: $NH_2OH \cdot HCl$ (70 mg) alone (yield of **4**: 75%); pyridine (0·15 ml) + HCl (0·15 ml) (yield of **4**: 80%); $NH_4Cl$ (70 mg) (yield of **4** from **10a** after refluxing for 10 hr: about 50%); conc HCl (0·15 ml) which afforded (from **10a**) 67% of 5α,10α-*iminoöxy*-5(10 → 1β*H*)abeo-5α-*cholestan*-3β-*ol* (**11**), m.p. 176–177° (from MeOH). This compound (**11**) was compared and found to be identical with authentic **11**, prepared (in 82% yield) by hydrolysis of **4** (200 mg) with 10 ml of 5% methanolic KOH at room temp for 2 hr and recrystallization of the precipitate (obtained upon addition of a little water and cooling at 0°) from MeOH, m.p. 178–179°; $[\alpha]_D^{20} = +76° \pm 3°$ ($c = 1·0$); IR (KBr): $\nu_{max} = 3390$, 3220, 1638 $cm^{-1}$. (Found: C, 77·75; H, 11·40; N, 3·55. $C_{27}H_{47}O_2N$ requires: C, 77·64; H, 11·34; N, 3·35%).

*N-Methyl*-5α,10α-*iminoöxy*-5(10 ⟶ 1β*H*)abeo-5α-*cholestan*-3β-*ol acetate* (**13**) *from ketone* **3** (*via nitrone* **12**). A soln of **3** (400 mg) and MeNHOH·HCl[16] (400 mg) in 20 ml EtOH and 20 ml pyridine was refluxed for 48 h, then poured into water and extracted with ether. The organic layer was repeatedly washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on 20 g silica gel. Elution with benzene–ether (98:2) and (95:5) gave starting **3** (12 mg, 3%) and 5(10 → 1β*H*)*abeo*-5α-cholest-10(19)-ene-3β,5α-diol 3-acetate (21 mg, 5%), m.p. 109° (from MeOH) (previously described product, resulting from acid-catalyzed or thermal intramolecular cyclization of **3**).[2,4]

With benzene–ether (80:20) as eluent, 278 mg (65%) of **13** was obtained, which upon recrystallization from MeOH (yield 220 mg) melted at 104°; $[\alpha]_D^{20} = +49·4° \pm 3°$ ($c = 0·85$); IR: $\nu_{max} = 1738$, 1238 $cm^{-1}$; NMR: δ = 0·72 (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·89 (Me-21, *d*), 1·22 (Me-19, *s*), 2·05 (AcO, *s*), 2·58 (Me-N, *s*), 2·94 (HC-1, *m*), 5·25 (HC-3, *m*). (Found: C, 76·34; H, 10·95; N, 3·32. $C_{30}H_{51}O_3N$ requires: C, 76·06; H, 10·85; N, 2·96%).

*N-Methyl-isoxazolidine product* **13** *by methylation of* **4**. A soln of **4** (918 mg, 2 mmoles) and methyl *p*-toluenesulfonate (186 mg, 1 mmole) in 10 ml benzene was refluxed for 4 h. After cooling and addition of ether, the mixture was washed with aq$NaHCO_3$ and water, dried over $MgSO_4$ and evaporated. The residue (about 900 mg) was chromatographed on 45 g silica gel, whereby benzene–ether (80:20) eluted 440 mg of product which was recrystallized from MeOH to give 380 mg (80·3% yield based on methyl tosylate) of **13**, m.p. 104°; $[\alpha]_D^{20} = +51·1° \pm 3°$ ($c = 0·90$); IR and NMR identical to above.

With benzene–ether (10:10) as eluent, 380 mg of starting **4** was recovered.

*N-Acetyl*-5α,10α-*iminoöxy*-5(10 ⟶ 1β*H*)abeo-5α-*cholestan*-3α-*ol* (**14**) *by sodium borohydride reduction of ketone* **7**. A soln of **7** (360 mg) in 25 ml MeOH was reduced with 300 mg $NaBH_4$ at 10° for 45 min. The usual work-up gave **14**, as a semi-solid product (but which, according to TLC, was pure and free of its 3β-epimer **6**); $[\alpha]_D^{20} = +82° \pm 3°$ ($c = 1·0$); IR ($CCl_4$): $\nu_{max} = 3450$, 1640 $cm^{-1}$; NMR: δ = 0·69 (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·89 (Me-21, *d*), 1·29 (Me-19, *s*), 2·04 (Ac-N, *s*), 2·76 (HC-1, *q*), 4·30 (HC-3, *m*). (Found: C, 75·61; H, 10·86; N, 3·31. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

5α,10α-*Iminoöxy*-5(10 → 1β*H*)abeo-5α-*cholestan*-3α-*ol acetate* (**17**) *from* trans-3α-*hydroxy*-5,10-*seco*-*cholest*-1(10)-*en*-5-*one acetate* (**15**) (*via oxime* **16**). A soln of 500 mg of **15*** in 25 ml EtOH was treated with $NH_2OH \cdot HCl$ (600 mg) + pyridine (0·35 ml) (molar ratio 1:0·5), and refluxed for 14 h. After addition of water, the mixture was extracted with ether, the organic phase was washed repeatedly with water, dried over $Na_2SO_4$ and evaporated *in vacuo*, leaving a residue (about 500 mg) which was chromatographed on 15 g silica gel. Elution with benzene–ether (95:5) gave the oxime **16** (140 mg, 27%), m.p. 204–205° (twice from MeOH); $[\alpha]_D^{20} = +43° \pm 2°$ ($c = 0·56$); IR (KBr): $\nu_{max} = 3250$, 1740, 1245 $cm^{-1}$; NMR: δ = 0·68 (M-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·87 (Me-21, *d*), 1·65 (Me-19, *d*), 2·10 (AcO, *s*), 5·10 (HC-1 and HC-3, *m*), between 8 and 10 (=N—OH, broad signal). (Found: C, 75·55; H, 10·82; N, 3·37. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

Elution with benzene–ether (80:20) afforded first a complex mixture (40 mg) and then 200 mg (38·7%) of **17**, m.p. 135–136° (recrystallized twice from acetone-MeOH); $[\alpha]_D^{20} = +76° \pm 2°$ ($c = 0·4$); IR (KBr): $\nu_{max} = 3260$, 1730, 1260 $cm^{-1}$; NMR: see Table 1. (Found: C, 75·94; H,

*This ketone, m.p. 118–119°, $[\alpha]_D^{20} = +13° \pm 2°$ ($c = 0·86$), was obtained by treating cholestane-3α,5β-diol 3-acetate[17] with lead tetraacetate (to be published).

10·66; N, 3·35. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

*N-Acetyl product* **14** *from* **17** (*via* **18**). A soln of **17** (100 mg) in pyridine (0·5 ml) and $Ac_2O$ (0·5 ml) was left 12 h at room temp. After dilution with MeOH and evaporation to dryness, the residue was chromatographed on 5 g silica gel. Elution with benzene–ether (90:10) gave 91 mg (83·5%) of **18**, as a semi-solid product (but, according to TLC, free of impurities); $[\alpha]_D^{20} = +73° \pm 3°$ ($c = 0·62$); IR (KBr): $\nu_{max} = 1745$, 1650, 1245 $cm^{-1}$; NMR: $\delta = 0·69$ (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·89 (Me-21, *d*), 1·28 (Me-19, *s*), 2·00 (Ac-N, *s*), 2·05 (AcO, *s*), 2·84 (HC-1, *q*), 5·12 (HC-3, *m*). (Found: C, 74·32; H, 10·36; N, 2·89. $C_{31}H_{51}O_4N$ requires: C, 74·21; H, 10·25; N, 2·79%).

A soln of **18** (80 mg) in 2 ml of 2% methanolic KOH was left 12 h at room temp. After addition of water extraction with ether and usual work-up, 64 mg (87·6%) of **14** was obtained, which was identical with the above described $NaBH_4$ reduction product of ketone **7**; $[\alpha]_D^{20} = +81° \pm 3°$ ($c = 0·71$).

*Oxidation of* **4** *to* **7**. A soln of **4** (48 mg) in 4 ml acetone (distilled over $KMnO_4$) was treated at 0° with 0·1 ml of a 8*N* Kiliani's chromic acid soln.[15] After the usual work-up and crystallization from acetone-MeOH, 40 mg (83%) of **7**, m.p. 152–154°, was obtained (identical with **7** prepared as described above from the 3β-ol **6**).

*N-Acetyl-5α-amino-10α-hydroxy-5*(10 → 1β*H*)*abeo-5α-cholestan-3-one* (**20**) *from* **9** (*via* **19**). A soln of **9** (200 mg) in 5 ml of 3% methanolic KOH afforded, after standing for 12 h at room temp and then cooling, a solid product (180 mg, 98%) which was filtered off and recrystallized from ether-light petroleum, to give 154 mg (84%) of **19**, m.p. 236°; $[\alpha]_D^{20} = +28° \pm 2°$ ($c = 0·5$); IR (KBr): $\nu_{max}$ = 3440, 3350, 1660, 1545 $cm^{-1}$; NMR: $\delta = 0·67$ (Me-18, *s*), 0·86 (Me-26 and Me-27, *d*), 0·87 (Me-21, *d*), 1·19 (Me-19, *s*), 1·89 (Ac-N, *s*), 3·15 (HC-1, *q*), 4·30 (HC-3, *m*). (Found: C, 75·31; H, 11·20; N, 3·22. $C_{29}H_{51}O_3N$ requires: C, 75·45; H, 11·15; N, 3·03%).

A soln of **19** (200 mg) in 30 ml acetone was oxidized at 0°, with Kiliani's chromic acid soln, as described above for **6** → **7**, to give, after crystallization from ether-light petroleum, 179 mg (90%) of **20**, m.p. 106°; $[\alpha]_D^{20} = +48° \pm 2°$ ($c = 1·0$); IR (KBr): $\nu_{max} = 3370$, 1760, 1660, 1530 $cm^{-1}$; NMR: $\delta = 0·69$ (Me-18, *s*), 0·88 (Me-26 and Me-27, *d*), 0·89 (Me-21, *d*), 1·21 (Me-19, *s*), 1·93 (Ac-N, *s*), 3·00 (HC-1, *q*); CD: see Table 2. (Found: C, 75·62; H, 10·60; N, 3·24. $C_{29}H_{49}O_3N$ requires: C, 75·77; H, 10·74; N, 3·05%).

*Oxime* **22** *of* cis-*5-oxo-5,10-seco-androst-1*(10)*-ene-3β,17β-diol diacetate* (**21**). This oxime* **22** was obtained in 77–80% yield from the corresponding ketone† **21** by the same procedures A[2] and B used for the preparation of oxime **2** from ketone **1** in the cholestane series (see above); m.p. 195° (from MeOH); $[\alpha]_D^{20} = +59° \pm 1°$ ($c = 0·66$); IR (KBr): $\nu_{max} = 3400$, 1740, 1710, 1240 $cm^{-1}$; NMR: $\delta$ = 0·80 (Me-18, *s*), 1·68 (Me-19, *d*), 2·01 (two AcO, *s*), 4·66 (HC-17, *m*), about 5·3 (HC-1 and HC-3, *m*), above 7·9 (=N—OH). (Found: C, 68·44; H, 8·86; N, 3·84. $C_{23}H_{35}O_5N$ requires: C, 68·15; H, 8·81; N, 3·47%).

*Oxime* **24** *of* trans-*5-oxo-5,10-seco-androst-1*(10)*-ene-3β,17β-diol diacetate* (**23**). This oxime* **24** was obtained in 85–90% yield from the corresponding ketone† **23** by the procedure (i.e. using an excess of pyridine) used for the preparation of oxime **10** from ketone **3** in the cholestane series (see above); m.p. 204–205° (from MeOH); $[\alpha]_D^{20} = -37° \pm 2°$ ($c = 0·54$); IR (KBr): $\nu_{max} = 3450$, 3260, 1730, 1720, 1248 $cm^{-1}$; NMR: $\delta = 0·82$ (Me-18, *s*), 1·72 (Me-19, *d*), 2·01 (two AcO, *s*), 4·58 (HC-17, *m*), 5·13–5·40 (HC-1 and HC-3, *multiplets*), over 8·0 (=N—OH). (Found: C, 68·21; H, 8·86; N, 3·80. $C_{23}H_{35}O_5N$ requires: C, 68·15; H, 8·81; N, 3·47%).

*5α,10α-Iminoöxy-5*(10 → 1β*H*)*abeo-5α-androstane-3β,17β-diol diacetate* (**25**) (*structure* **D**, $R = OAc$; *config.* **H**, $R^2 = H$, $R^3 = \beta$-$OAc$). (1). *From the* trans-*seco-ketone* **23**. A soln of **23** (200 mg) in EtOH (10 ml) was treated with $NH_2OH \cdot HCl$ (200 mg) + pyridine (0·13 ml) (molar ratio 1:0·6), refluxed for 7 h, diluted with water, extracted with ether and the organic layer worked up as usual. After removal of solvent, the resulting product (200 mg) was chromatographed on 10 g silica gel. Elution with benzene-EtOAc (7:3) afforded first 52 mg (25%) of oxime **24** (of the starting ketone **23**) and then a (not further investigated) complex mixture (about 50 mg). With EtOAc as eluent, 105 mg (50%) of the cycloadduct **25** was obtained, m.p. 142–143° (from light petroleum); $[\alpha]_D^{20} = +47° \pm 2°$ ($c = 0·58$); IR (KBr): $\nu_{max} = 3440$, 3230, 1730, 1720, 1240 $cm^{-1}$; NMR: $\delta = 0·84$ (Me-18, *s*), 1·18 (Me-19, *s*), 2·00 and 2·04 (AcO at C-3 and C-17, two *singlets*), 2·82 (HC-1, *q*), 4·60 (HC-17, *m*), 5·23 (HC-3, *m*). (Found: C, 68·27; H, 8·81; N, 3·66. $C_{23}H_{35}O_5N$ requires: C, 68·15; H, 8·81; N, 3·47%).

(2) *From the* trans-*seco-ketone oxime* **24**. A soln of oxime **24** (50 mg) in EtOH containing conc HCl (0·1 ml) + pyridine (0·1 ml) was refluxed for 7 h, then cooled, poured into water and worked up as usual. The resulting oily product was chromatographed on silica gel, whereby benzene-EtOAc (7:3) eluted less polar compounds (about 11 mg) while EtOAc as eluent afforded the cycloadduct **25** (37 mg, 71%).

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*According to NMR data probably a mixture of *syn*- and *anti*-forms.

†Seco-ketones **21** (*cis*-1(10)-unsaturated) and **23** (*trans*-1(10)-unsaturated) of the androstane series were obtained by the lead tetraacetate oxidation of androstane-3β,5α,17β-triol 3,17-diacetate (to be published).

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