Thermolysis and photolysis of two steroidal hydroxamic acid methanesulfonates

Oliver E. Edwards, Gunnar Grue-Sørensen, and Barbara A. Blackwell

Abstract: Thermolysis or photolysis of *N*-methanesulfonyloxy-4-aza-5α-cholestan-3-one gave derivatives of 4-azacholestan-3-one, 4-aza-A-nor-B-homocholestan-3-one, 3-aza-A-norcholestane, bis (4-aza-3-oxocholest-5-en-6-yl) methane, and bis(3-aza-A-norcholestan-3-yl) urea. The corresponding 5β-methanesulfonate gave the 5β (coprostane) analogues. Evidence for the mechanism of formation of these products, including a Favorski-like ring contraction and amide oxidation by methanesulfonic acid, is presented. Detailed ^{1}H and ^{13}C assignments are made for many of the products, and ultraviolet absorption for seven steroidal enamides is tabled. Long-range homo- and heteronuclear NMR connectivities were used to confirm the structure of three dimeric compounds and to assign the configuration of the methoxy function of 4-aza-5-methoxy-A-nor-β-homocholestan-3-one to be 5α.

Key words: steroidal enamides, 3-aza-A-norcholestanes, 4-aza-A-nor-B-homocholestanes, aza-Favorskii ring contraction.

Résumé : La thermolyse ou la photolyse de la *N*-méthanesulfonyloxy-4-aza-5α-cholestan-3-one fournit des dérivés de la 4-azacholestan-3-one, de la 4-aza-A-nor-B-homocholestan-3-one, du 3-aza-A-norcholestane, du bis(4-aza-3-oxocholest-5-én-6-yl)méthane et de la bis(3-aza-A-norcholestan-3-yl)urée. Le 5β-méthanesulfonate conduit aux analogues 5β (coprostane). On présente des données relatives au mécanisme de formation de ces produits, y compris une contraction de cycle de type Favorski et une oxydation d'amide par l'aide méthanesulfonique. On a effectué des attributions détaillées des spectres RMN du ^{1}H et du ^{13}C de plusieurs produits et on présente un tableau incorporant les absorptions ultraviolettes de sept énamides stéroïdaux. On a utilisé les connectivités RMN homo- et hétéronucléaires à longue distance pour confirmer les structures de trois composés dimères et pour conclure que la configuration de la fonction méthoxy de la 4-aza-5-méthoxy-A-nor-β-homocholestan-3-one est 5α.

Mots clés : énamides stéroïdaux, 3-aza-A-norcholestanes, 4-aza-A-nor-B-homocholestanes, contraction de cycle d'aza-Favorski.

[Traduit par la rédaction]

Introduction

Considerable interest has been shown in the potential of *N*-acyl imines (**1**) and related carbinolamides (**2**) as biochemical intermediates (1*a*), as possible biological alkylating agents with chemotherapeutic activity (1*b–d*), and as reagents for organic synthesis (1*e*). Three aliphatic *N*-acyl imines have been isolated in our laboratories (1*c*, 2) and showed moderate stability. Thus we were encouraged to attempt preparation of 4-azacholest-4-en-3-one (**3**) and related steroidal *N*-acyl imines.

Received January 15, 1997.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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Attempts to prepare 5α-azido-A-norcholestan-3-one **4** failed,[2] foiling attempts to prepare **3** by the photochemical route discovered in our laboratories (1*c*).

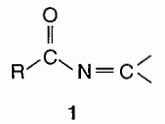
Thermolysis of keto acid **5** (R = H) in ammonia (3*a*) or exposure of the corresponding keto amide or enol lactone to ammonia gave enamide **17** or the corresponding carbinolamide (3*b*). Base-catalysed elimination of HCl from the *N*-chloro lactam **6** also gave **17** as major product[3] (see also recent work on photolysis of **6** by Back and Brunner (1*d*)). Thus it was evident that isomerization of **3** to **17** was facile.

This paper details attempts to observe or obtain **3** by rupture of the relatively weak N—O bond of hydroxamic acid methanesulfonates **13** and **14**. Since this work was initiated, Hoffman et al. (4) have shown that thermolysis of hydroxamic acid triflates gives transient *N*-acyl immonium salts.

Results

The desired methanesulfonates were prepared from keto acid **5** (R = H) as shown in Scheme 1. After the cyanoborohydride reduction of oximino acid **7** the cyclization to the hydroxamic

[2] Unpublished experiments by G. Grue-Sørensen, J.L. Douglas, and C. Grieco.
[3] Unpublished experiments with T.G. Back.



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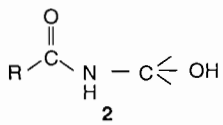

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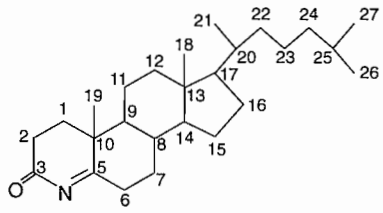

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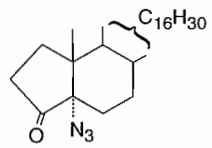

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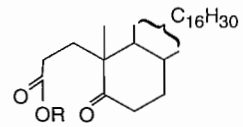

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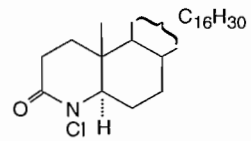

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Table 1. Steroidal enamides.

Enamide	λ_{max} (EtOH), nm	ε	Reference
8	238.5	14 400	—
15	234	13 500	—
16	240	9 100	—
17	232	13 000	3*a*
31	239	13 700	—
35	232	6 200	1*c*
36	240	6 600	6

acids **9** and **10** was spontaneous. The methyl ethers **11** and **12** were prepared for comparison with subsequent products. The properties and configurations as determined by the ^{1}H NMR signals for the 5-hydrogens agreed well with those reported by Edward and Morand (5) for samples prepared in other ways.

Finally, the methanesulfonates **13** and **14** were prepared using methanesulfonyl chloride in pyridine. Heating of **7** in vacuo gave the enamide *N*-hydroxycholest-5-en-3-one **8**.

Thermolysis of both mesylates **13** and **14** in dry tetramethylurea at 185°C under argon produced at least seven products (TLC), three of which were purified and characterized. The minor one (ca. 6%) was the hitherto unknown enamide 4-aza-A-nor-B-homocholest-5-en-3-one **15**. This had ν_{max} 1690 cm^{-1} (five-membered lactam), no NH, and two vinyl hydrogens. Its ultraviolet absorption (Table 1) indicated an enamide character. This, its chemistry, and the ^{13}C NMR spectrum (see Table 3) left no doubt that it had structure **15**.

A major product (52–57%) was 4-azacholest-5-en-3-one **17**, a known compound.[2] Another was the unexpected coupling product bis(4-aza-3-oxocholest-5-en-6-yl)-methane **16** (7–19%). This was a polar enamide (see Table 1) with NH absorption (ν_{max} 3390 cm^{-1}; δ 7.45). Its EI mass spectrum showed only very weak peaks above *m/z* 427, so it appeared to be a monomer. However a 2D NMR spectrum showed that an apparent one-hydrogen signal at δ 2.6 ppm was actually due to a methylene group, thus suggesting that it was linking two steroid units. The fact that none of the hydrogen or carbon signals were doubled indicated high symmetry. Since the general spectra were similar to those of **17** but the vinyl hydrogen was missing, the structure appeared to be **16**. Partial synthesis from **17** (see below) confirmed this.

To test if the methanesulfonic acid produced in the thermolysis was catalysing the isomerization of preformed **3**, powdered calcium carbonate was added to the reaction mixture before thermolysis. The results were erratic, but the yield of **17** increased at the expense of **16**, reaching as high as 84%. No *N*-acyl imine **3** was detected using ^{13}C NMR.

To reduce the effect of the methanesulfonic acid even further, the thermolysis was conducted in dry collidine. Yields of **17** of 73% (5α) and 80% (5β) were realized. No products derived from the A-nor base **24** were detected from **14** and no **3** was observed despite gentle work-up (expected ^{13}C NMR signals near 180 ppm and ν_{max} near 1700 cm^{-1}).

Thermolysis of **13** and **14** in dry methanol at 180°C in sealed tubes under argon again gave **15** and **17**, as well as **5** (R = CH_3), which undoubtedly arose by acid-catalysed methanolysis of **17** followed by hydrolysis during work-up. Indeed, treatment of **17** with acidic methanol did give **5** (R = CH_3). Additional products of the thermolysis were the methyl carbamates **18** and **19** (eqs. [1] and [2]). Since **19** formed excellent crystals it was submitted for X-ray crystallography. We are grateful to Prof. C. Bensimon for the structure and stereochemistry shown in formula **19**. The analogous spectra of **18** left no doubt as to its identity (Tables 2 and 3).

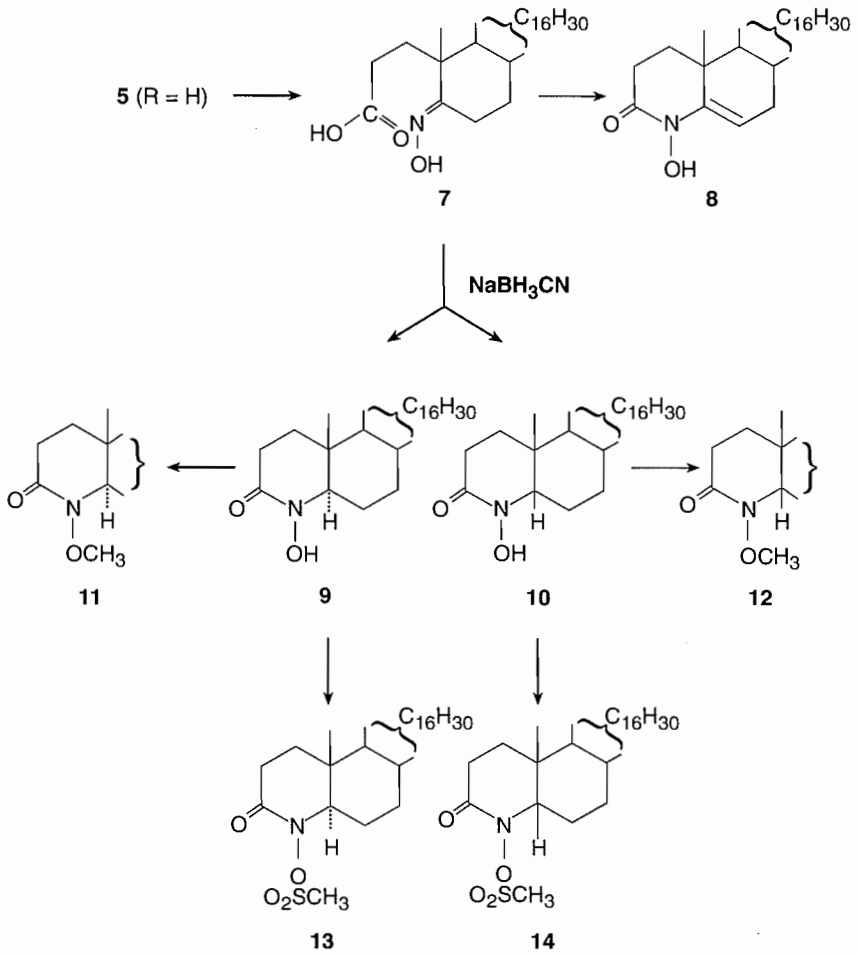
Photolysis of **13** and **14** in dry methanol gave enamide **17**, the carbamates **18** and **19**, respectively, and a new common product, the carbinolamide ether **20** clearly related to **15**. Indeed the two could be interconverted (see eq. [15]). Apparently pure samples of **20** slowly converted to a crystalline mixture containing **15** and **20** plus methanol, according to NMR results. Approximately 5% of the two lactams **21** and **22** (eqs. [3] and [4]) were formed from **13** and **14**, respectively.

In the hope of obtaining the bases corresponding to carbamates **18** and **19**, the mesylates **13** and **14** were photolyzed in aqueous tetrahydrofuran (eqs. [5] and [6]). The bases **23** and **24** were formed, and were characterized as their hydrochlorides and *N*-acetyl derivatives **27** and **28**. The yield of lactams **21** and **22** increased to 11%.

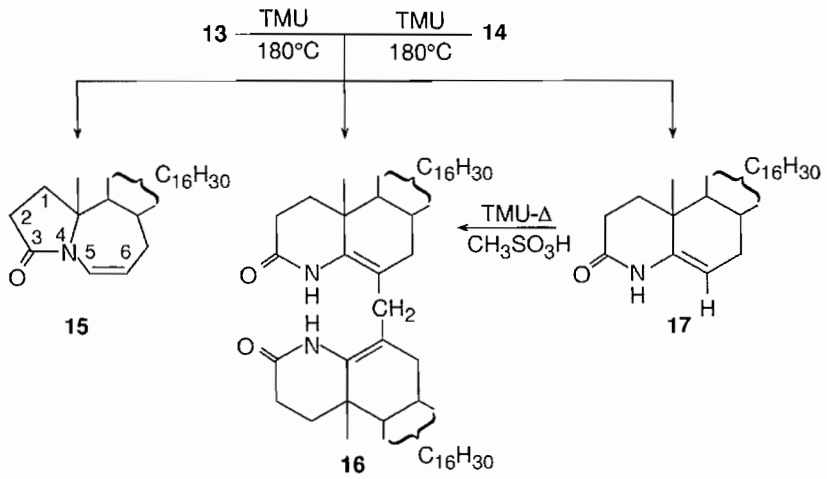
Photolysis of **13** and **14** in dichloromethane gave spectroscopic evidence for reactive intermediates with ν_{max} 1743 cm^{-1} (see Mechanism section). Depending on work-up conditions the products shown in eqs. [7]–[10] were formed. The reactive intermediates appeared to be the source of the carbamates **18** and **19**, the ureas **25** and **26**, and, as a consequence of traces of water (aqueous work-up), the bases **23** and **24**. The latter were subsequently acetylated, giving **27** and **28**.

In a last attempt to intercept the *N*-acylimine **3**, a small molar excess of triethylamine was added to a dichloromethane solution of **14** before photolysis. Again a transient species with ν_{max} 1743 cm^{-1} was formed. Treatment of the product with methanol, then acetic anhydride, gave a mixture of

Scheme 1.



Scheme 2.



5β-carbamate **19**, enamide **15**, and *N*-acetyl derivative **28**. No evidence for the presence of **3** or the related 5-methoxy or 5-acetoxy lactams **34** was found.

Since methoxy lactam **20** was moderately stable, attempts were made to prepare the 5-acetoxy-4-aza-A-nor-B-homo-cholest-3-one. However, the exposure of enamide **15** to an acetic acid – acetic anhydride mixture in the presence of *p*-toluenesulfonic acid at room temperature or at 68°C gave no isolable acetoxy compound.

Enamides **8**, **15**, **16**, and **17** deteriorated in air, especially in

Table 2A. 500 MHz ^{1}H NMR assignments of selected azasteroids (δ, ppm from TMS).

	Compound			
Position	**11**	**12**	**15**	**16**
1	1.30; 1.83	1.37; 1.76	1.82; 1.96	1.43; 1.87
2	2.42 (ddd 1.8, 7.0, 18.0)	2.31 (ddd 17.6, 6.0, 1.7)	2.37 (septet)	2.45 (m)
	2.49 (ddd 6.7, 12.7, 18.0)	2.39 (ddd 17.6, 13.6, 5.8)		
5	3.26 (dd 3.5, 12.4)	3.46 (t, 2.7)	6.34 (dd 9.0, 3.0)	—
6	1.45	1.60 (dd 14.7, 3.7);	5.25 (ddd 9.0, 9.1, 3.0)	—
	2.11 (dq 3.6, 7.0, 12.8)	2.12 (dq 14.7, 3.1)		
7	0.92	1.07	1.66	1.52
	1.77	1.46	2.24 (ddd 15.5, 9.1, 2.6)	1.87
8	1.30	1.35	1.38	1.02 (br m)
9	0.76	1.27	1.24	1.52 (br m)
11	1.31; 1.48	1.30	1.35; 1.64	1.40; 1.52
12	1.13; 1.98 (dt 3.4, 12.8)	1.12; 1.96 (dt 12.8; 3.4)	1.20; 1.95	1.15; 2.0 (dt)
14	1.06	1.00	1.09	0.98
15	1.24; 1.82	1.21; 1.81	1.25; 1.81	1.25; 1.83
16	1.05; 1.56	1.01; 1.54	1.09; 1.69	1.03; 1.52
17	0.98	1.02	1.03	1.07
18	0.65 (s)	0.63 (s)	0.65 (s)	0.67 (s)
19	0.81 (s)	1.00 (s)	1.12 (s)	1.03 (s)
NH				7.45
Me	3.68 (s)	3.71 (s)		
$-CH_2-$				2.59 (brs)
Position	**17**	**18**	**19**	**20**
1	1.44; 1.87	1.33; 1.62 (ddd 11.5, 6.2, 1.9)	1.38; 1.78	1.55; 2.28
2	2.44	3.40 (m)	3.36	2.30;
			3.46	2.41 (ddd 7.9, 12.8, 17.0)
5		2.84 (dd 12.3, 3.4)	3.24 (br s)	5.44 (dd 7.7, 10.1)
6	4.84 (dd 2.6, 5.0)	2.56 (brd)	1.45	1.65
		1.46	2.55 (br)	2.29
7	1.63 (dd 2.6, 17.0)	0.85	0.86	0.78 (dd)
	2.07 (dt 5.0, 17.0)	1.70 (dt 13.6, 3.1)	1.38	1.55
8	1.0	1.35	1.16	1.40
9	1.5	0.81	0.96	1.08
11	1.25; 1.40	1.32; 1.43 (ddd 12.7, 3.8)	1.33–1.45	1.40; 1.50
12	1.16; 2.01 (dt 12.7, 3.4)	1.14; 1.95 (dt 12.5; 3.4)	1.11; 1.97 (dt 12.6, 3.3)	1.15; 1.94 (dt 12.7, 3.4)
14	1.00	1.08	0.95-1.05	1.10
15	1.27; 1.82	1.23; 1.80	1.21; 1.80	1.25; 1.80
16	1.10; 1.57	1.04; 1.55	1.07; 1.56	1.10; 1.58
17	1.06	1.00	0.95–1.05	1.10
18	0.68 (s)	0.65 (s)	0.65 (s)	0.68 (s)
19	1.06 (s)	0.81 (s)	0.97 (s)	1.35 (s)
NH	8.0			
Me		3.63 (s)	3.64 (s)	3.22 (s)
$-CH_2-$				

solution. The melting points obtained in evacuated capillaries were higher and sharper than those taken in air.

Partial synthesis of enamide **16** was readily achieved by reaction of enamide **17** with formaldehyde using p-toluenesulfonic acid as catalyst. It was also possible to prepare 6-ethoxymethyl-4-azacholest-5-en-3-one **31** and react this with **17** to give the dimer **16** (eq. [11]).

Hydrogenation of **15** gave the parent lactam **32** (4-aza-A-nor-B-homocholestane-3-one).

Mechanism

The thermolysis of **13** and **14** in tetramethylurea or methanol is readily understood in ionic terms involving ion pair **A**

Table 2A. (*concluded*).

Position	Compound 25	26	27	32
1	1.40; 1.60 (dd 7.2, 11.5)	1.43; 1.79	1.37; 1.68	1.59 (dt 12.6, 9.6); 2.08 (ddd 3.3, 12.6, 8.7)
2	3.13 (t, 9.4)	3.09 (br m)	3.43	2.23 (ddd 16.8, 3.0, 9.3)
	3.43 (dt 6.7, 10.4)	3.41	3.37	2.39 (dt 16.8, 9.1)
5	2.99 (dd 3.0, 11.7)	3.50 (br m)	2.90 (m)	2.95 (p 14.2, 7.2); 3.82 (p 14.2, 7.2)
6	1.22	1.42	1.45	1.48
	2.40 (dq 12.0, 3.1)	2.25 (br d 13.7)	2.24 (br d)	1.88
7	0.97	0.87	0.98	0.95
	1.65 (dq 13.3)	1.35	1.68	1.67
8	1.38	1.19	1.37	1.15–1.30
9	0.87	0.92	0.80	1.02–1.14
11	1.32; 1.43 (dd)	1.32–1.45	1.34; 1.43	1.37; 1.48
12	1.15; 1.95 (dd)	1.14; 1.98 (dt 12.6; 3)	1.15; 1.95	1.13; 1.94 (dt 12.7, 3.4)
14	1.09	1.10	1.10	1.02–1.14
15	1.21; 1.80	1.22; 1.79	1.22; 1.80	1.24; 1.80
16	1.02; 1.55	1.06; 1.56	1.07; 1.55	1.08; 1.67
17	1.00	0.97	0.98	1.02–1.14
18	0.65 (s)	0.66 (s)	0.65 (s)	0.66 (s)
19	0.86 (s)	1.01 (s)	0.82 (s)	1.20 (s)
NH				
Me				1.97 (s)
$-CH_2-$				

Table 2B. Selected ^1H NMR assignments of some azasteroids (δ, ppm from TMS).

Position	Compound 8	21	22	23	24	28	31
1	1.45; 1.87 (dt 12.8, 4.1)	1.86; ?	1.85; ?	1.5; 1.8	1.8; ?	1.83; ?	1.42; 1.82
2	2.58 (m)	2.42 (m)	2.3–2.4	3.38 (m)	3.27; 3.45	3.50 (m)	2.44 (m)
5	—	3.05 (dd)	3.3 (t, 3)	2.72 (m)	3.18 (m)	3.40 (br m)	—
6	5.48 (dd 5.2, 2.8)	1.72 (dq); ?	1.87; ?	2.04; ?	2.07; ?	2.6; ?	—
7	1.68 (ddd 2.8, 10.3, 17.0)	—	—	?	—	—	1.5
	2.22 (dt 5.4, 17.0)	—	—	1.80	—	—	2.0
12	1.18; 2.62 (dt 3.5, 12.7)	1.98 (dt); ?	2.00; ?	1.98; ?	1.94 (dt 12, 3); ?	2.0 (dt 12,3); ?	1.15; 2.03
15	1.27; 1.83	1.82; ?	1.82; ?	1.8; 1.2	1.78; ?	1.22; 1.80	1.20; 1.83
16	1.13; 1.58	1.58; ?	—	1.5; ?	—	1.07; 1.56	1.0; 1.5
18	0.69 (s)	0.65 (s)	0.64 (s)	0.64 (s)	0.64 (s)	0.65 (s)	0.67 (s)
19	1.08 (s)	0.89 (s)	1.00 (s)	0.98 (s)	1.03 (s)	0.99 (s)	1.08 (s)
NH	8.97	6.2	6.95	9.2; 10.0	9.05, 10.02		8.38
CH_3						2.14 (s)	1.21 (t)
OCH_2							3.45 (q)
$-CH_2-$							3.70; 4.05 (d 12.2)

Note: "?" denotes resonances where precise chemical shifts are not resolvable.

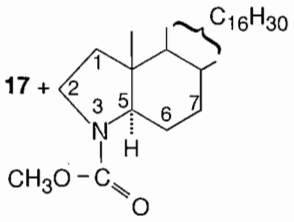
(Scheme 3). The high yield of **17** in collidine and the effect of calcium carbonate in the other solvents is consistent with a base-catalysed elimination involving the 5-hydrogen, leading to **3** as a metastable intermediate. This must rapidly rearrange to the more thermodynamically stable **17**.

However, since no *N*-methoxy compounds **11** or **12** were formed in methanol we conclude that free nitrenium ions **A** were not involved and that processes (a), (b), or (c) were synchronous with N—O bond rupture.

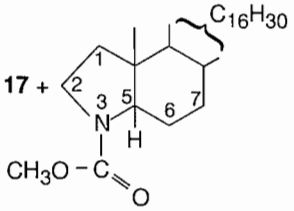
The formation of the A-nor amine derivatives could follow the ionic pathway (a) through ion pair **B**. However, an alternate ionic process involving an α-lactam could proceed as illustrated in eq. [12], although spectroscopic evidence for a reactive intermediate (ν_{max} 1743 cm^{-1}) in photolysis of **13** and

Table 3. ^{13}C NMR assignments of selected azasteroids (δ, ppm from TMS).

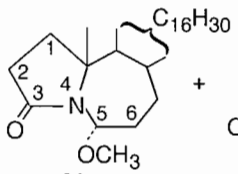
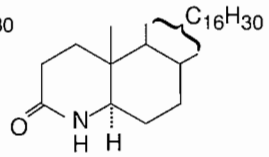
	Compound																		
Position	**8**	**11**	**12**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**31**	**32**
1	31.0	33.2	31.7	33.8	31.7	31.5	36.2	35.1	32.9	32.7	31.3	36.5	35.0	37.3	36.2	36.6	35.1	31.7	33.5
2	27.2	*29.5	29.0	28.8	28.2	28.3	46.0	45.6	29.5	29.6	28.2	43.4	41.2	48.7	48.2	47.3	47.2	28.2	29.3
3	161.0	168.6	168.1	175.0	169.6	169.8	—	—	176.7	173.6	174.5	—	—	—	—	—	—	169.0	174.4
5	138.2	69.1	66.3	125.1	135.5	139.9	68.0	65.3	82.3	61.1	59.5	67.5	65.2	68.6	65.0	69.0	66.2	138.1	37.5
6	103.9	23.3	23.1	116.3	109.3	103.9	24.9	23.6	32.7	27.2	25.2	22.9	22.5	25.0	23.7	25.2	23.0	107.9	25.2
7	29.7	*29.9	26.1	33.0	34.8	29.7	30.2	25.8	26.4	27.8	26.8	29.9	24.8	29.9	26.3	30.3	26.1	34.3	30.2
8	48.2	34.6	35.0	33.9	48.0	48.0	35.1	35.5	42.3	35.0	35.0	34.8	35.4	35.6	36.0	35.3	35.2	47.9	39.6
9	31.1	51.7	40.8	55.1	31.4	31.6	52.2	44.0	51.6	51.2	39.2	52.4	42.3	52.5	44.2	52.2	44.6	31.4	53.1
10	36.0	37.7	36.5	66.2	35.0	37.2	44.0	43.2	67.0	35.6	33.9	42.3	42.5	43.1	42.4	43.5	43.3	34.6	66.2
11	20.8	21.1	20.9	24.3	21.0	20.9	23.0	22.8	26.2	21.1	20.8	23.2	22.8	23.2	22.9	23.1	22.9	20.9	25.3
12	39.5	39.7	39.8	39.5	39.4	39.5	39.7	40.2	40.0	39.6	39.8	39.3	39.4	39.8	40.4	39.7	40.1	39.4	39.6
13	42.4	42.7	42.6	42.1	42.4	42.4	43.2	42.7	42.9	42.7	42.6	43.0	42.7	43.2	42.8	43.2	42.7	42.4	42.5
14	56.1	55.9	55.9	56.2	56.4	56.1	56.2	56.3	56.3	55.9	55.7	56.0	54.9	56.2	56.4	56.2	56.3	56.1	56.1
15	28.2	27.9	28.2	27.8	28.2	28.2	28.2	28.3	27.9	28.1	27.4	28.1	28.2	28.1	28.3	28.2	28.2	28.2	27.8
16	24.2	24.0	24.1	25.3	24.1	24.2	24.1	24.1	24.9	24.1	24.1	24.2	24.1	24.3	24.2	24.2	24.1	24.1	25.2
17	56.5	56.2	56.2	55.6	56.1	56.5	55.8	56.4	56.4	56.2	56.2	55.3	55.7	55.9	56.5	55.8	56.6	56.4	56.3
18	11.9	12.1	11.9	11.7	11.9	11.9	12.2	12.1	12.3	11.4	11.9	12.2	12.0	12.3	12.1	12.3	12.0	11.9	12.0
19	19.0	12.5	21.7	16.8	18.4	18.7	14.0	19.5	21.9	12.1	20.8	13.2	18.5	14.4	19.5	14.2	19.6	18.8	21.3
C=0							157.0	156.3						165.4	163.3	171.3	171.3		
OMe		62.7	61.1				51.7	51.9	55.2										
$-CH_2-$					31.5													71.2	
CH_3																23.6	22.8	15.1	
OCH_2																		66.1	

[1] **13** $\xrightarrow[180°C]{CH_3OH}$ **5** (R=CH_3) + **15** + **17** + 

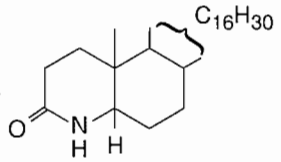
18

[2] **14** $\xrightarrow[180°C]{CH_3OH}$ **5** (R=CH_3) + **15** + **17** + 

19

[3] **13** $\xrightarrow[CH_3OH]{h\nu}$ **17** + **18** +  + 

20 **21**

[4] **14** $\xrightarrow[CH_3OH]{h\nu}$ **15** + **17** + **19** + **20** + 

22

14 in dichloromethane favors **C**[4] since an α-lactam would have absorption near 1850 cm^{-1} (7). Secondly, α-lactam formation as in eq. [12] and subsequent reaction would involve a 2-hydrogen. But thermolysis or photolysis of the mesylates in methanol-*d* gave no more than minor deuterium exchange on C-2 for **18** and **19**. Thirdly, photolysis or thermolysis of **13** and **14** in methanol (acidic) or photolysis in dichloromethane followed by treatment with acidic methanol gave none of the 2-methoxy-4-azacholest-3-one expected for an α-lactam intermediate (7*b*) and no acid **29** or its derivatives were observed[5] under more basic conditions.

Finally, had proton elimination as in eq. [12] been the source of the A-nor derivatives, a base such as collidine for thermolysis, or triethylamine for photolysis in dichloromethane, should have increased the yield of these. Actually the A-nor derivatives could not be detected in thermolysis in collidine and the yields in the photolysis did not change.

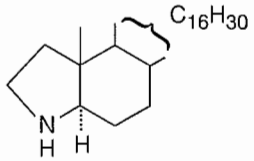
We conclude that the mechanisms in Scheme 3 are essentially correct. The formation of the A-nor derivatives is a new type of ring contraction. Since the reaction is closely analogous to the Favorskii-type ring contraction observed in deamination of α-amino ketones when cyclopropanone formation was impossible (8), it can be called an aza-Favorskii reaction.

The high energy available in the photolyses (ca. 250 nm) means that a homolytic fission of the N—O bond as a first step (eq. [13]) is possible. Cadogan and Rowley have produced evidence for such fission for hydroxamic acid toluenesulfonates (9). The only direct evidence for nitrogen-centered radicals in our work is the isolation of lactams **21** and **22** (eqs. [3] and [4]). As expected, the yields of these were highest in the best hydrogen atom donor tetrahydrofuran, lower in methanol, and near zero for dichloromethane.[6] Since most of our

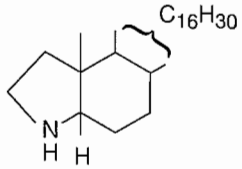
[4] Attempts to make a simple analogue of C failed.

[5] The base-promoted opening of *N-tert*-butyl phenylaziridinones are cases of C—C bond cleavage of α-lactams (7*c*).

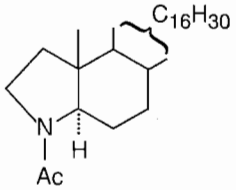
[6] The high yield of parent lactams in the photolysis of *N*-chlorolactams (1*d*) contrasts with our experience with the mesylates.

[5] **13** $\xrightarrow[\text{aq THF}]{h\nu}$ **15** + **17** + **21** + 

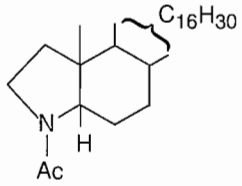
23

[6] **14** $\xrightarrow[\text{aq THF}]{h\nu}$ **15** + **17** + **22** + 

24

[7] **13** $\xrightarrow[(2)\ CH_3OH\ (3)\ Ac_2O]{(1)\ h\nu\ in\ CH_2Cl_2\ (H_2O)}$ **15** + **17** + **20** + 

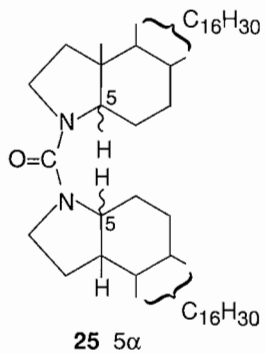
27

[8] **14** $\xrightarrow[(2)\ Ac_2O,\ pyridine]{(1)\ h\nu\ in\ CH_2Cl_2\ (H_2O)}$ **15** + **26** + 

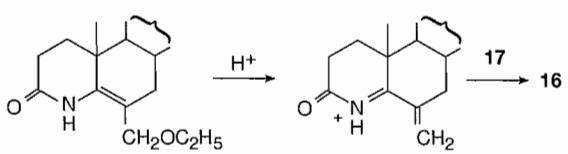
28

[9] **13** $\xrightarrow[(2)\ Ac_2O,\ pyridine]{(1)\ h\nu\ in\ CH_2Cl_2}$ **15** + **25** + **27**

[10] **14** $\xrightarrow[(2)\ CH_3OH\ (3)\ Ac_2O]{(1)\ h\nu\ in\ CH_2Cl_2}$ **15** + **19**+ **28**



25 5α
26 5β

[11] 

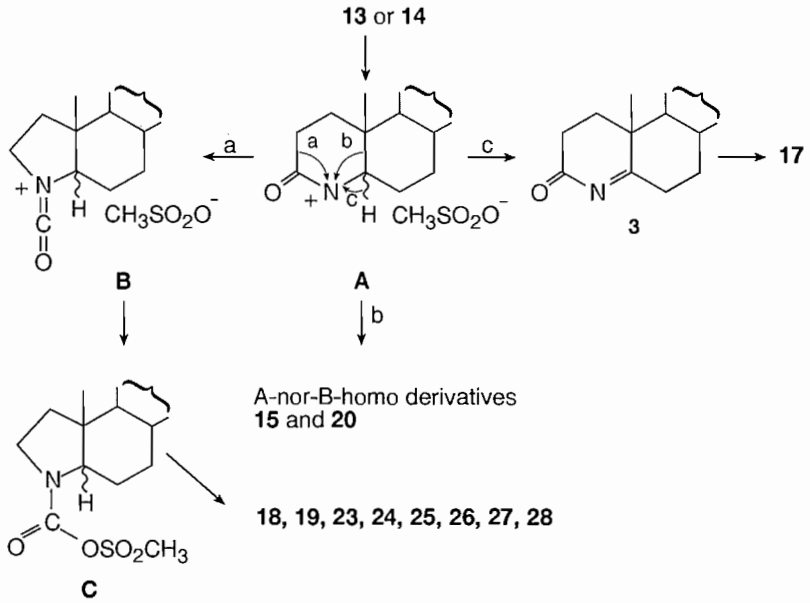
31

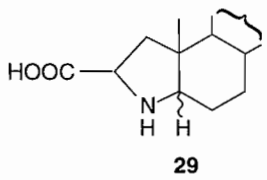
products seem to be of ionic origin, electron transfer to ion pair **A** would have to occur as a major step (eq. [13]). For similar electron transfer, see ref. 10*a* (see, however, ref. 10*b*).

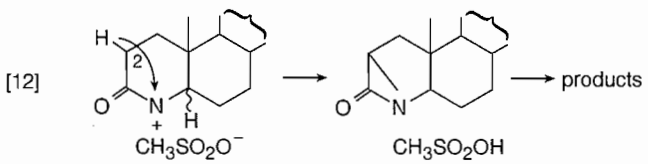
The rearrangement of the proposed *N*-acyl nitrenium ion **A** to the A-nor-B-homo derivatives **15** and **20** (path b, Scheme 3) is plausible. It gave a modest yield of **15** (maximum observed 30% in aqueous tetrahydrofuran). Recently a preparation of 2-alkylated steroids with this skeleton was developed by Back et al. (11).

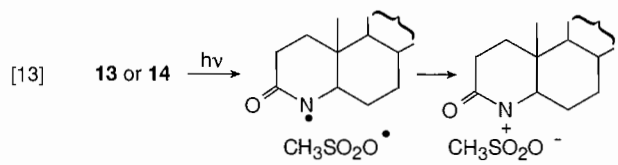
A most surprising result in the photolyses in tetramethyl urea was the formation of the methylene-bridged dimer **16**. When TMU containing methanesulfonic acid was heated at 180°C neither formaldehyde nor trimethyl urea could be detected among the products. However, the formaldehyde required to form the methylene bridge must have arisen from a methyl group of the TMU (eq. [14]). Heating **17** with tetramethyl urea under argon at 180°C gave no **16**, but if methanesulfonic acid was included a 50% yield of **16** was obtained. Thus the methanesulfonic acid formed from the mesylates is the oxidant. The occurrence of products containing both methylamido and steroid units was evident from ^{1}H NMR spectra, but none were characterized. These must arise from reaction

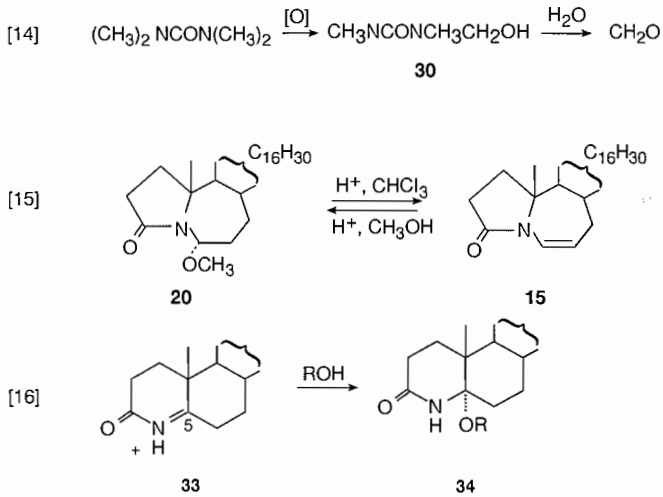
Scheme 3.











of carbinolamides such as **30** with enamides such as **17**. The acid-catalysed formation of **16** from **17** and formaldehyde or from **17** and the ethoxymethylene compound **31** (eq. [11]) shows the electron-donating potential of enamides. The addition of methanol to enamide **15** undoubtedly involves the same phenomenon: i.e., protonation on C-6 to give the immonium salt, then methanol attack on C-5 (eq. [15]). Attempts to convert **17** to the immonium salt **33** and then to neutralize this using weak base to obtain **3** failed. Acid-catalysed addition of methanol or acetic acid to **17** to give the 5-methoxy or 5-acetoxy compounds **34** (R = OCH_3 or $OCOCH_3$) also failed, probably due to the steric crowding at C-5.

Spectra

Table 1 lists the characteristic ultraviolet absorption spectra of the known steroidal enamides. Detailed NMR spectral assignments for the C-1 to C-19 nuclei of many of the compounds discussed are presented in Tables 2A, 2B, and 3. These constitute either full chemical shift assignments of known compounds or those of the new compounds to determine their structures. Other NMR data to confirm known structures are reported in the Experimental. The assignments reported in Table 2A result from a combination of homo- and heteronuclear correlation experiments so that, even if the multiplets themselves cannot be resolved in the overlapped portion of the proton spectrum (0.8–1.8 ppm), the centres of AB systems can be determined. Selected proton chemical shift assignments for other compounds are reported in Table 2B where more detailed information was not available (i.e., no 2D experiments were performed). The ^{13}C chemical shift assignments were determined from direct and long-range (HMBC) $^{1}H/^{13}C$ correlation experiments for critical or new structures (i.e., **12**, **15**, **16**, **18**, **24**, **26**, and **32**), while assignments for others were made by comparison of related spectra (e.g., **27** and **33** compared to **18** and **25**, **28** and **24** compared to **19** and **26**, etc.). Tables 2 and 3 show that the chemical shifts of positions C-11

Table 4. ^{13}C and ^{1}H NMR assignments for the C_8H_{17} moiety.

Position	^{1}H	^{13}C
20	1.35 (m)	35.7
21	0.88 (d, 6.6)	18.6
22	0.98; 1.31	36.1
23	1.15; 1.30	23.8
24	1.04–1.17 (br m)	39.4
25	1.49 (dq, 6.6)	28.0
26,27	0.840; 0.836 (d, 6.6)	22.5, 22.8

to C-17 are relatively constant for all compounds, but that positions C-8 and C-9 are strongly influenced by the nature of the B ring (six- or seven-membered, presence of a 5,6 double bond, etc.).

There is some ambiguity regarding the assignment of resonances due to C-14 and C-17. Although similar in chemical shift, these may be distinguished as long as the corresponding proton resonances are resolved. Thus for compounds **12**, **15**, **16**, **18**, **25**, and **26** these resonances may be distinguished by correlation to their respective protons and the proton coupling of H-14 to H-15 or that of H-17 to H-16 and H-20 as seen in the COSY spectrum. However, for compounds such as **19**, **20**, and **32**, where H-14 and H-17 are coincident, the identity of the carbon resonances is not confirmed.

For simplicity, the chemical shift assignments for the C_8H_{17} side chain for all compounds are summarized in Table 4. These figures represent an average of all compounds characterized. Variability between compounds was very slight, amounting to only ± 0.1 ppm for ^{13}C and ± 0.02 ppm for ^{1}H. This indicates that the overall molecular configuration for all compounds studied was very similar, in spite of changes in the A and B rings.

Interesting differences show up between the spectra of the members of the 5α and 5β series of compounds, especially for the A-nor series. Comparison of the ^{13}C chemical shifts of the 5α A-nor compounds (**18**, **23**, **27**, and **25**) with the 5β analogues (**19**, **24**, **28**, and **26**) shows that C-5, C-7, and C-9 are shifted upfield by ca. 3, 3–4, and 8 ppm, respectively, in the 5β compared to the 5α compounds. C-6, however, is unaffected, while the methyl function C-19 is shifted downfield by 5 ppm in the β series. A similar comparison of the spectra of the 6,6-nucleus analogues (**11**, **21** (5H-α) and **12**, **22** (5H-β) yields the same qualitative effects although shift differences are larger for C-9 and C-19 (11 ppm upfield and 8 ppm downfield, respectively). The shift of the C-5 resonance is the same (ca. 3 ppm upfield). Both C-6 and C-7 are relatively unaffected in these compounds by the orientation of the H-5 proton. Concomitant but much smaller shift effects are seen in the proton spectra for all of these compounds. The effects observed in the ^{13}C spectra may be due to a marked increase in the strain of ring A (according to Dreiding models) in the 5α, as compared to the 5β, configurations. There is no evidence for such strain in the 6,6 series. However, for the 5β compounds **12** and **22**, the H-9 and C-9 are in the shielding cone of the amide. In all cases, the 5α proton is distinguished from the 5β proton by the presence of a large *trans* diaxial coupling (ca. 12 Hz) to one of the hydrogens at position 6.

The dimeric compounds **16**, **25**, and **26** yield deceptively simple NMR spectra, in that identical ^{1}H and ^{13}C shifts are observed for both steroid nuclei in these structures. In the absence of clear mass spectrometric evidence (see above), the only clue to the presence of a dimer rather than a monomer for these compounds is the appearance of a carbonyl resonance of reduced intensity in the ^{13}C spectra of **25** and **26** (at 165.4 and 163.3 ppm, respectively) and of an extra methylene carbon (again reduced in intensity) at 31.5 ppm in the spectrum of **16**, which in turn was correlated to a broad singlet at 2.59 ppm in the proton spectrum. The location of this methylene bridge at position C-6 was confirmed by the HMBC experiment, which showed coupling of the methylene singlet at 2.56 ppm in the proton spectrum to C-6 at 109.3 ppm in the carbon spectrum. Weaker couplings were also observed between this proton signal and C-5 and C-7 at 135.5 and 34.8 ppm, respectively. Similarly, couplings were observed between the H-5 protons at 3.0 and 3.5 ppm and H-2 protons at 3.4 and 3.1 ppm in the spectra of **25** and **26** to the carbonyl carbons at 165.4 and 163.3 ppm, respectively, thus supporting other spectroscopic and chemical evidence for the urea structures.

Two explanations are possible for the simplicity of the NMR spectra: either that rotation about the bonds of the bridging function is sufficiently fast on the NMR time scale to average out any effects or that the barrier to rotation is high and only one rotamer exists — one that has a plane of symmetry. The former explanation is preferred in the case of compound **16**, since free rotation about the bridging methylene function would be expected. In the case of the ureas **25** and **26**, the overlap of the two nitrogen lone pairs with the carbonyl function predicts that there is less double bond character than in an ordinary amide and therefore the barrier to rotation should also be relatively low. This is consistent with the fact that tetramethyl urea gives a single signal for both ^{1}H and ^{13}C at room temperature while for the classical example of dimethyl formamide, where the barrier to rotation is quite high, there is doubling of signals (12).

Other motional effects are observed when the spectra of the A-nor series of compounds are compared. In the ^{13}C spectra of the carbamates **18** and **19**, the resonances due to C-2, C-6, and C-10 of the A ring are broadened and reduced in intensity. The C-5 resonance is also affected but to a lesser extent. In the proton spectrum of **19**, the resonance due to H-6α is only barely visible and shifted to 2.6 ppm and the resonances of H-5 and H-2 are also broadened. These effects are also seen in the spectra of **18**. The broadening of these particular resonances was also observed for the *N*-acetyl derivatives **27** and **28** but is not so pronounced, less so for the ureas **25** and **26**, and absent for the salts **23** and **24**. In all cases the effect is more pronounced in the 5β compounds than the 5α. This behavior may be accounted for by the presence of two rotamers with restricted rotation on the NMR time scale. This restricted motion would be maximum in the carbamates, less for the *N*-acetyl compounds, and least for the ureas and the salts. This is supported by the infrared spectra, in which the carbamate frequencies are high (ca. 1695 cm^{-1}) with little overlap while the frequencies for the ureas are low (1626 cm^{-1}). Therefore, the energy required to stretch the C=O bond is lowest in the ureas, where the amount of the double-bond character is the least. The restricted rotation is greater in the 5β compounds since the nonbonded interactions are also maximized.

Long-range couplings, both homonuclear ($^1H/^1H$) and heteronuclear ($^1H/^{13}C$), that occurred through the nitrogen atom in ring A were observed in several cases in COSY and HMBC spectra. These long-range *J* values are likely enhanced by the partial C=N double-bond character of the amide system. In particular, long-range couplings were observed in the spectra of compounds **32** and **20** that permit the determination of configuration of C-5 in the latter. In the COSY spectrum of **32**, a homoallylic coupling ($^5J_{HH}$) was observed between H-2β at 2.25 ppm and H-5β at 2.95 ppm. Homoallylic coupling is often observed in aromatic systems where the π orbitals of the double bond system are parallel and overlap with the CH bond (13). This would favour a conformation in which the 5β hydrogen is axial. In the spectra of compound **20**, no allylic coupling was observed but NOE measurements show a positive effect both between H-2 at 2.30 ppm and H-5 at 5.44 and H-5 and CH_3-19 at 1.35 ppm. Thus the methoxy function has an α configuration and the conformation of ring β is such that the 5β proton is axial and proximate to the CH_3-19. This conformation minimizes the nonbonded interaction of the 5α methoxy group with the carbonyl function.

The correct assignment of the C-2 proton of the A-nor compounds was critical to the determination of mechanism for the aza-Favorskii reaction (see mechanism section). Integration of the H-2 signals at ca. 3.4 ppm from samples of **18** and **19** formed from methanol-*d* showed that less than 5% exchange of these hydrogens had occurred. As expected (see eq. [15]), both enamides **15** and **17** produced in these reactions showed partial exchange of the C-6 hydrogens (at 5.25 ppm and 4.24 ppm, respectively), while no reduction in the intensity of the H-2 signals at ca. 2.4 ppm was observed.

Summary

Attempts to prepare *N*-acyl imine **3** failed, but it was implicated as a transient intermediate in reactions of hydroxamic acid methanesulfonates **13** and **14**. A new aza-Favorskii reaction was observed, leading to a new route to 3-aza-A-nor steroids. A new preparation of 4-aza-A-nor-B-homocholestane derivatives and a high-yielding synthesis of the enamide 4-azacholest-5-ene-3-one (**17**) were described. Both homolytic and heterolytic reactions were implicated in the photochemistry of the methanesulfonates.

Experimental

Infrared spectra were for dichloromethane solutions, unless otherwise indicated, on a Perkin–Elmer model 683 grating spectrometer, and ultraviolet spectra were taken for 95% ethanol solutions unless otherwise indicated. Routine ^1H NMR spectra were taken on a Varian Gemini instrument at 200 MHz and ^{13}C spectra at 50 MHz. High-resolution ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) at 500.13 and 125.18 MHz, respectively, on a Bruker AM500 NMR spectrometer operating at 303 K. A 5 mm normal geometry $^{13}C/^1H$ probe was used (90° ^{13}C = 18 μs, 90° ^1H = 7 μs). Chemical shifts were referenced to $CDCl_3$ at 77.0 ppm (^{13}C) and 7.24 ppm (^1H) and are reported relative to TMS. The resonance assignments for known compounds were elaborated and for new compounds were determined using a combination of $^1H/^1H$ correlation (COSY, TOCSY), DEPT, ID NOE, and $^1H/^{13}C$ correlation (HETCOR, HMBC) experiments using standard Bruker pulse sequences.

All preparative thin-layer chromatography was done on 20 × 20 cm glass plates with fluorescent indicator and column chromatography on 100–200 mesh silica gel or Woelm neutral alumina. Melting points were corrected using standards. Tetramethyl urea and 2,4,6-collidine were distilled from calcium hydride, tetrahydrofuran from lithium aluminum hydride, methanol from magnesium methoxide, and dichloromethane from phosphorus pentoxide. Yields were calculated based on unrecovered starting material.

Unless otherwise noted, the NMR spectral assignments, both ^1H and ^{13}C, of the following compounds are documented in Tables 2 and 3.

3,5-Seco-A-nor-5-oxocholestan-3-oic acid 5 (R = H)

A modified procedure of Singh and Paul (14) was used to prepare **5** (R = H).

To a stirred solution of 13 g of 4-cholesten-3-one in 600 mL of *tert*-butyl alcohol was added 7 g of potassium carbonate in 150 mL of water, then 45 g of sodium periodate in 350 mL of water, followed by 100 mg of potassium permanganate in 10 mL of water. A cold water bath was used to keep the temperature below 38°C. After 3 h the solid (mostly inorganic) was removed by filtration. Solid sodium hydrogen sulfite was added to the filtrate until only a pale yellow color persisted. The two phases were separated. The aqueous phase was extracted with dichloromethane. The phase rich in *tert*-butyl alcohol was evaporated to a volume of 150 mL. This was made strongly acid using dilute sulfuric acid, then extracted with dichloromethane. The combined dichloromethane extracts were washed with water, dried, and concentrated. Addition of hexane resulted in crystallization of 7.7 g of desired acid with mp as high as 145°C. On recrystallization from methanol this gave 6.9 g (50%), mp 147–152°C (lit. (13) mp 154–154.5°C). A purified specimen had mp 151–153°C, ν_{max}: 1703 cm^{-1}, and ^1H NMR signals at δ 1.13 (3H), 0.93, 0.89, 0.85 (methyl resonances), and 0.73 (3H).

Methyl 3,5-seco-A-nor-5-oxocholestan-3-oate 5 (R = CH_3)

This ester, prepared by action of diazomethane on a methanol solution of **5** (R = H), remained amorphous. It has ν_{max} 1732 and 1700 cm^{-1} and gave ^1H NMR signals at δ 3.66 (3H), 1.12 (3H), 0.93, 0.89, 0.85 (methyl resonances), and 0.73 (3H). ^{13}C NMR: 214.7, 174.3, 56.0, 55.7, 51.5, 50.3, 47.8, 42.5, 39.4, 38.1, 36.1, 35.9, 35.7, 31.3, 29.5, 29.1, 28.0, 24.4, 24.2, 23.8, 22.5, 21.4, 20.5, 18.6, and 12.0 ppm.

3,5-Seco-A-nor-5-oximinocholestan-3-oic acid 7

Acid **5** (2.0 g) and hydroxylamine hydrochloride (2.5 g) were dissolved in 30 mL of ethanol, then 2.0 g of anhydrous sodium acetate was added. The mixture was heated under reflux for 3 h, cooled, then filtered from inorganic salts. The filtrate was evaporated to dryness. The residue was dissolved in 100 mL of dichloromethane. This solution was washed with 1 M sulfuric acid, then water, dried over sodium sulfate, then concentrated (care; the oxime may crystallize at any stage). Three crops of crystals totalling 1.8 g (87%), mp 181°C, were collected. These were purified on 55 g of "flash" silica gel using 5% methanol in chloroform (a red zone just precedes the main eluate, probably an iron chelate) raising the mp to 183–185°C.

This gave ν_{max}: 3580, 3260, and 1703 cm^{-1} and ^1H NMR signals at δ 3.35 (1H, br d), 1.09, 0.88, 0.85, and 0.69 (sharp methyl signals).

***N*-Hydroxy-4-aza-cholestane-3-ones (hydroxamic acids)**

The oximino seco acid **7** (2.35 g) was dissolved in 45 mL of hot acetic acid. The solution was cooled to room temperature, then 1.1 g of sodium cyanoborohydride was added in portions with stirring during 7 min. Hydrogen was steadily evolved. After 0.5 h a further 250 mg of cyanoborohydride was added. After warming gently to dissolve all solids, the mixture was stirred for 1 h. The acetic acid was then removed on a rotating evaporator under 1 Torr (133.3 Pa), leaving a froth. This was dissolved in dichloromethane and the solution washed with water (emulsion). The dichloromethane layer gave 2.5 g of colorless froth. This was separated on 100 g of flash silica gel using chloroform. The lower melting isomer (5β) eluted first, followed by a sharp orange band (a small amount of iron chelate) and then the higher melting isomer (5α). Both isomers crystallized from ethyl acetate. The yield of **9** (5α) was 402 mg (18%) and of **10** (5β), 608 mg (27%).

***N*-Hydroxy-4-aza-5α-cholestane-3-one 9**

The higher melting isomer after recrystallization from ethyl acetate formed shimmering needles with mp 195°C (lit. (5) mp 185–187°C). It had ν_{max}: 3390, 3250, and 1625 cm^{-1} and gave ^1H NMR signals at δ 8.5 (OH), 3.33 (1H dd, J = 11.6, 3.3 Hz), 2.52 (2H m), 2.25 (1H, m), 0.97, 0.92, 0.88, 0.85, and 0.67 (sharp methyl signals). ^{13}C NMR: 165.6, 68.0, 56.1, 55.9, 51.4, 42.7, 39.6, 39.5, 37.5, 36.1, 35.7, 34.4, 32.6, 29.3, 28.2, 28.0, 27.8, 24.0, 23.8, 23.1, 22.8, 22.5, 21.0, 18.6, 12.5, and 12.1 ppm. Anal. calcd. for $C_{26}H_{45}NO_2$: C 77.36, H 11.24, N 3.47; found: C 77.23, H 11.37, N 3.49.

***N*-Methanesulfonyloxy-4-aza-5α-cholestan-3-one 13**

A solution of 402 mg of hydroxamic acid **9** and 0.3 mL of methanesulfonyl chloride in 2 mL dry pyridine was left at room temperature for 16 h. A crystalline solid separated. The mixture was cooled with ice, then 1 mL of water was added. After 50 min much of the pyridine and water was removed under reduced pressure. The residue was distributed between dichloromethane and dilute sulfuric acid. The dichloromethane yielded 466 mg of light brown gum, which crystallized from ethyl acetate. The product was purified by passage of a dichloromethane solution through a column of 6 g of neutral alumina, activity 1, giving 350 mg of **13**. This crystallized from ethyl acetate as fine needles, mp 158–159°C. It had ν_{max}: 1692, 1373, and 1183 cm^{-1} and gave ^1H NMR signals at δ 3.45 (1H dd, J = 13, 4 Hz), 2.62 (2H m), 1.06, 0.91, 0.88, 0.85, and 0.67 (sharp methyl signals). ^{13}C NMR: 169.5, 71.9, 56.2, 55.8, 51.7, 42.6, 40.3, 39.7, 39.5, 39.2, 36.1, 35.7, 34.4, 33.3, 30.5, 29.3, 28.2, 28.0, 24.5, 24.0, 23.8, 22.8, 22.6, 21.2, 18.7, 12.5, 12.1. Anal. calcd. for $C_{27}H_{47}NO_4S$: C 67.25, H 9.77, N 2.91; found: C 67.40, H 9.89, N 3.08.

***N*-Hydroxy-4-aza-5β-cholestan-3-one 10**

This crystallized from ethyl acetate, mp 125–126°C (lit. (5) mp 122–124°C), recrystallizing and melting at 131°C if heating was very slow. It had ν_{max}: 3670, 3390, 3240, and 1014 cm^{-1} and gave ^1H NMR signals at δ 8.65 (OH), 3.51 (1H s), 2.40 (3H m), 1.04 (3H s), 0.91, 0.88, 0.85 (sharp methyl signals), 0.67 (3H s). ^{13}C NMR: 164.9, 66.0, 56.2, 55.8, 42.6, 41.0, 39.9, 39.5, 36.4, 36.1, 35.8, 35.0, 31.3, 28.2, 28.0, 26.8, 25.7, 24.1, 23.9, 23.1, 22.8, 22.6, 21.4, 21.1, 18.7, 12.0 ppm. Anal. calcd. for $C_{26}H_{45}NO_2$: C 77.36, H 11.24, N 3.47; found: C: 77.18, H 11.40, N 3.53.

***N*-Methanesulfonyloxy-4-aza-5β-cholestan-3-one 14**

The 126°C hydroxamic acid **5** (218 mg) was treated with methanesulfonyl chloride in pyridine as for the 192°C isomer. The product was purified by passage through a column of 4 g of neutral alumina, activity 1. Hexane eluted 31 mg of mesylate containing a small amount of higher R_f impurities (TLC). A 30% ethyl acetate in hexane mixture eluted 211 mg of pure mesylate. This did not crystallize readily, but finally separated from hexane as fine needles, mp 87–88°C. Methanol proved to be the solvent of choice for recrystallization. The crystals had ν_{max}: 1678, 1372, and 1182 cm^{-1} and gave ^1H NMR signals at δ 3.80 (1H, br s), 3.45 (3 H, s), 2.5 (2H, m), 1.07, 0.91, 0.88, 0.85, and 0.67 (sharp methyl signals). ^{13}C NMR: 167.9, 71.2, 56.2, 55.8, 42.6, 40.8, 40.7, 39.8, 39.5, 37.8, 36.1, 35.8, 35.0, 31.2, 29.2, 28.2, 28.0, 25.5, 24.1, 23.8, 23.6, 22.8, 22.6, 21.5, 20.9, 18.7, 12.0. Its CI mass spectrum gave *m/z*: 482(81), 388(100), 387(44), and 386(75); calcd. for $C_{27}H_{47}NO_4S$: 481.

***N*-Methoxy-4-aza-5α-cholestan-3-one 11**

A solution of sodium methoxide in 3 mL of dry methanol was prepared using 104 mg of sodium hydride. To this was added 95 mg of hydroxamic acid **9** and 90 μL of methyl iodide in 5 mL of methanol. After 2 h refluxing a further 80 μL of methyl iodide was added, then the refluxing continued for an extra 2 h. The mixture was evaporated under reduced pressure, water was added, and then the product was extracted into dichloromethane. The 70 mg of **11** recovered from the dichloromethane was recrystallized from hexane. It had mp 146°C and ν_{max} 1668 cm^{-1}.

***N*-Methoxy-4-aza-5β-cholestan-3-one 12**

This was prepared from hydroxamic acid **10** as described for **11**. It crystallized from aqueous methanol as thin plates with mp 115°C (Lit. (5) mp 115°C). It had ν_{max} 1655 cm^{-1}.

***N*-Hydroxy-4-azacholest-5-en-3-one 8**

Oximino acid **7** in an evacuated (0.2 Torr) flask was placed in a bath at 185°C for 20 min. The melt bubbled vigorously. After cooling, the product was dissolved in dichloromethane. After addition of ethyl acetate the bulk of the dichloromethane was evaporated. A gel formed that was slowly transformed into balls of extremely fine needles, mp 196–198°C, in an evacuated capillary (immersed at 180°C). Chromatography over silica gel with chloroform eluant gave an orange zone followed by **8**. Its mp remained the same. It had ν_{max}: 3660, 3380, 3230, and 1617 cm^{-1} and λ_{max} 238.5 nm (Table 1).

Thermolysis of 13

(a) In tetramethyl urea

The 5α mesylate **13** (77 mg) in 2 mL of dry tetramethylurea (TMU) was heated in a bath at 180°C under argon for 5 h. The solvent was then removed at 100°C under 0.5 Torr pressure. A dichloromethane solution of the residue was washed with aqueous sodium carbonate. The 65 mg recovered from the

dichloromethane crystallized in part from an ethyl acetate – hexane mixture giving 30 mg of enamide **17**. The mother liquor was separated on a 1 mm SiO_2 plate using 80% ethyl acetate – 20% hexane. Of the seven zones visible under UV light, three were characterized as enamide **15** (R_f 0.5, 3 mg, 5%), enamide **17** (R_f 0.33, 4 mg), and dimeric enamide **16** (R_f 0.14, 8 mg, 7%). The total yield of enamide **17** was 34 mg (57%). The yield of **17** and products related to it with the 4-azacholest-5-ene skeleton was 71% (calculated as monomer).

(b) In TMU with $CaCO_3$

For details see the comparable experiment with **14**: 71 mg of **13** and 158 mg of $CaCO_3$ in 2 mL of dry TMU under argon were stirred at 180°C for 3 h. Mesylate (3 mg) was recovered. Crystalline **17** (42 mg, 77%) was obtained, along with small amounts of **15** and **16**.

(c) In collidine

A solution of 5α-mesylate **13** in 0.8 mL of dry 2,4,6-collidine under argon was placed in a bath at 145°C. The temperature was raised to 175°C (1 h), then maintained at that temperature for 2.5 h. The bulk of the collidine was removed under 0.5 Torr pressure, and then the residue was dissolved in dichloromethane. This solution was washed with 1 N sulfuric acid, then with aqueous sodium carbonate. The 65 mg of brown residue recovered from the dichloromethane crystallized from ethyl acetate – hexane mixture, giving 40 mg of enamide **17**. Separation of the contents of the mother liquor as for (*c*) gave 8 mg of **17**; total yield 48 mg (73%).

Thermolysis of 5β-mesylate 14

(a) In tetramethylurea (TMU)

A flask containing 180 mg of mesylate **14** and 4 mL of dry TMU was flushed with argon, then heated in a bath at 180°C for 3 h. The solvent was removed under 0.5 Torr pressure, the residue dissolved in dichloromethane, then this was washed with saturated aqueous sodium bicarbonate. The aqueous layer was evaporated, finally at 60°C under 0.5 Torr pressure, leaving 179 mg of gum. This crystallized in part from 1:1 ethyl acetate/hexane giving 38 mg of **17**. Again the solvents were removed, finally at 120°C, 0.5 Torr. A ^{13}C NMR spectrum of the residue showed the presence of **17** (140.0, 103.4 ppm), **15** (135.3, 109.6 ppm), and **16** (125.1, 116.3 ppm) with carbonyl carbons at 169.7 and 169.6 ppm. No signal corresponding to an *N*-acyl imine was present.

The residue (121 mg) was separated on a 1 mm plate of C-18 coated silica gel using 30% benzene – 70% acetonitrile. The products, in order of decreasing R_f, were **15** (9 mg, 7%), unchanged mesylate (25 mg), unknown (9 mg), **17** (15 mg), and dimer **16** (47 mg, 19%). The total yield of crystalline **17** was 50 mg (41%) but the yield of products with the 4-azacholest-5-ene skeleton was 79%.

(b) In TMU with $CaCO_3$

A solution of 161 mg of **14** in 4 mL of dry TMU and 373 mg of powdered $CaCO_3$ in a flask fitted with a sintered glass funnel was flushed with argon, then heated at 180°C for 3.5 h. The cooled suspension was diluted with dichloromethane, then filtered under pressure. The solid was washed twice with dichloromethane. The filtrate was evaporated, finally at 75°C, 0.5 Torr pressure. The residue crystallized in part from dichloromethane–hexane, giving 88 mg of **17**. The products recovered from the filtrate were separated on a 1 Torr SiO_2 plate using 1:1 ethyl acetate/hexane giving, in order of decreasing R_f, recovered mesylate, 9 mg; enamide **15**, 6 mg (5%), enamide **17**, 7 mg; and enamide **16**, 12 mg (5%). The total yield of crystalline **17** was 95 mg (78%). A zone just ahead of **16** contained 9 mg of a mixture giving two main N-CH_3 or N-CH_2 signals near δ 3.0 and the steroid CH signals, i.e., these were coupling products of **17** with products such as **30**. None of these was characterized further. The use of higher ratios of $CaCO_3$ produced yields of **17** as high as 88%. A ^{13}C NMR spectrum of the total chloroform-soluble product before plating showed only low-field signals due to **17**.

(c) In 2,4,6-collidine

This was carried out as for the 5α-mesylate **13**. The yield of **17** was 80%, averaged over three runs.

(d) In methanol with $CaCO_3$

A mixture of 90 mg of **14**, 273 mg of $CaCO_3$ powder, and 5 mL of dry methanol was sealed in a tube under argon. This was heated at 190 ± 5°C for 3 h. The cooled suspension was filtered and the solid washed with methanol. The filtrate was evaporated in vacuo, finally at 60°C, 0.5 Torr pressure. The residue was suspended in dichloromethane, then filtered, giving 11 mg of insoluble solid. The filtrate yielded 74 mg of gum. The ^1H NMR and ^{13}C NMR of this residue showed only the main products described below. These were separated on a 1 mm SiO_2 plate using 1:1 ethyl acetate/hexane. The products identified were, in order of decreasing R_f, methyl keto ester **5** (R = CH_3), 12 mg (16%); carbamate **19**, 12 mg (15%); enamide **15**, 22 mg (30%); methoxy lactam **20**, 5 mg (6%); enamide **17**, 9 mg (16%).

(e) In methanol-d *with $CaCO_3$*

A solution of 116 mg of **14** in 4 mL of methanol-*d* and 244 mg of $CaCO_3$ was heated as for (*d*) but at 175°C for 4 h. The yields were **5** (R = CH_3), 9 mg (9%); **19**, 24 mg (18%); **15**, 48 mg (38%); **17**, 11 mg (12%).

The ^1H NMR spectrum of carbamate **19** showed less than 5% exchange of the hydrogens on C-2. Both enamides **15** and **17** showed approximately 50% exchange of the 6-hydrogens for deuterium (see the NMR section).

Irradiation of 13

(a) In methanol

A solution of 189 mg of 5α mesylate **13** (warming) in 55 mL of dry methanol was irradiated for 5.5 h using 254 nm Rayonet lamps (cold finger at 15°C). The bulk of the methanol was removed on a rotating evaporator, the residue was dissolved in dichloromethane, and then this solution was washed with 5% sodium carbonate. The organic layer yielded a gum that was separated on two 1 mm plates using 30% hexane – 70% ethyl acetate. The products identified were methyl keto ester **5** (R = CH_3, 4%); carbamate **18**, 57 mg (35%); methoxy lactam **20**, 42 mg (25%); enamide **17**, 12 mg (8%); and lactam **21**, 8 mg (5%).

(b) In methanol-d

A solution of 103 mg of **13** in 42 mL of methanol-*d* was irra-

diated as for (*a*) with the cold finger at 23°C. The main products and yields were the same as for the photolysis in methanol. Enamide **17** had partial exchange of the vinyl hydrogen (H-6) (see NMR section)

(c) In aqueous tetrahydrofuran

A solution of 114 mg of **13** in 50 mL of tetrahydrofuran and 5 mL of water was flushed with argon. This was irradiated for 4.5 h with the cold finger at 5°C, with mixing at half-hour intervals. The solvent was evaporated on a rotating evaporator, then the product was distributed between 5% sodium carbonate and chloroform. The mixture recovered from the chloroform was dissolved in methanol, then this was titrated to pH 2 with hydrochloric acid in methanol. The solvent was evaporated to dryness and the residue suspended in ethyl acetate. This was filtered, giving 56 mg of solid (mainly **23** hydrochloride). The products in the filtrate were separated on a 0.5 mm plate using 10% ethanol in chloroform. The products identified were: **15**, 27 mg (30%); **17**, 3 mg (5%); **21**, 10 mg (11%); and **23** hydrochloride, 5 mg. The total yield of pure **23** hydrochloride was 34%.

(d) In dichloromethane

13 (103 mg) in 50 mL of dry dichloromethane was irradiated for 4 h with the cold finger at −5°C. The solvent was evaporated (bath at 40°C), then 2 mL of dry dichloromethane was added. This solution had ν_{max}: 1750 (str), 1696 (med), 1625 (wk), and 1215 (str) cm^{-1}. Methanol (2 mL) was added, then the mixture was heated for 10 min, distilling off the dichloromethane. The methanol was removed in a rotating evaporator, dichloromethane was added, then this was shaken with sodium carbonate solution. The organic layers yielded 94 mg of neutral and basic products. Acetic anhydride (1 mL) was added. After 20 h at room temperature the anhydride was removed in vacuo, the residues were heated with methanol, and then the mixture was evaporated again. A dichloromethane solution of the residue was washed with sodium carbonate solution, dried, and then the solvent was distilled, giving 86 mg of gum. This was separated on a 1 mm plate using 10% hexane – 80% ethyl acetate giving, in order of decreasing R_f, carbamate **19**, 21 mg (24%); unknown, 4 mg; unknown, 6 mg; *N*-acetyl derivative **27**, 10 mg (12%); unknown (origin), 11 mg. The estimated yield of products having the A-nor skeleton **23** was 36%.

(e) In moist dichloromethane

A dichloromethane solution (70 mL) of **13** (243 mg) was irradiated (cold finger at 15°C, stirring at intervals) for 5 h. The solution was washed with aqueous sodium carbonate, dried, and evaporated. The residue in 1 mL of acetic anhydride and 1 mL of pyridine was heated to give a clear solution. After 18 h at room temperature the mixture was worked up as in (*d*), giving 228 mg of product. This was separated on three 1 mm plates as for (*d*,) giving in order of decreasing R_f: urea **25**, 30 mg (9%); unchanged **13**, 28 mg; enamide **15**, 29 mg (16%); unknown, 12 mg; an unknown, 10 mg; and *N*-acetyl derivative **27**, 50 mg (29%). The yield of products with the A-nor skeleton **23** was 29% + (2 × 9%) = 47%.

Irradiation of 14

(a) In methanol

Mesylate **14** (188 mg) in 45 mL of dry methanol was irradiated under argon with the cold finger at 10°C for 4.5 h, with mixing at 1 h intervals. The methanol was evaporated and the residue dissolved in dichloromethane, then this solution was washed with aqueous sodium bicarbonate. The 165 mg of colorless oil was separated on two 1 mm plates using 30% hexane – 70% ethyl acetate. Recovered mesylate **14** (17 mg) was followed in order of decreasing R_f by carbamate **19**, 56 mg (38%); methoxy lactam **20**, 47 mg (32%); and enamide **17**, 14 mg (10%).

(b) In methanol-d

A solution of **14** (122 mg) in 30 mL of methanol-*d* was irradiated (cold finger at 23°C) for 4 h. Work-up and separation as for (*a*) gave 14 mg of unchanged **14**; carbamate **19**, 35 mg (32%); enamide **15**, 4 mg (5%); methoxy lactam **20**, 11 mg (12%); and **17**, 9 mg (10%). ^1H NMR spectra of **15** and **17** showed partial exchange of H-6 for deuterium. Carbamate **19** showed less than 5% exchange of the 2-hydrogens (see NMR section).

(c) In aqueous tetrahydrofuran

A solution of 212 mg of **14** in 100 mL of tetrahydrofuran and 10 mL of water was irradiated in two equal portions as for **13**. In the work-up, ether was used to precipitate the hydrochloride (50 mg). The filtrate was evaporated and the residue separated on two 1 Torr plates using 15% hexane – 75% ethyl acetate. The products characterized in order of decreasing R_f were enamide **15**, 48 mg (28%); enamide **17**, 11 mg (6%); and lactam **22**, 19 mg (11%). The low R_f zone was extracted with hot methanol in chloroform. After evaporation of the solvent the extract was treated with 1:1 acetic anhydride/pyridine, giving *N*-acetyl derivative **28**, 9 mg (5%). The total yield of products related to A-nor base **24** was 33%.

(d) In dichloromethane

1. Dry, methanol work-up: Following irradiation of 102 mg of **14** as for **13** but at 15°C, 10 mL of methanol was added. After 0.5 h the solvents were evaporated under reduced pressure. The residue was dissolved in dichloromethane, then the solution was washed with aqueous sodium carbonate. The dried solution was evaporated. The residue was suspended in chloroform, filtered from a small amount of inorganic solid, and then separated on a 1 mm plate using 30% hexane – 70% ethyl acetate. The products characterized were carbamate **19**, 15 mg (19%); recovered **14**, 10 mg; and enamide **15**, 9 mg (12%). The low R_f zone was treated as in (*c*) yielding **28**, 8 mg (10%).

2. Dry dichloromethane (55 mL) containing 118 mg of **14** was irradiated for 4 h with the cold finger at 5°C. Moisture was probably introduced during stirring. The solution was shaken with aqueous sodium carbonate, dried, and distilled. The residue was acetylated using acetic anhydride and pyridine (20 h). The product after removal of the reagents under 1 Torr pressure was dissolved in dichloromethane. This solution was washed with 1 N sulfuric acid, then with 5% sodium carbonate. The dried solution gave 100 mg of gum, which was separated on a 1 mm plate using 2% methanol in chloroform. The products identified were urea **26**, 10 mg (6%); recovered mesylate, 11 mg; enamide **16**, 15 mg (17%); and *N*-acetyl derivative **28**, 16 mg (19%).

(e) In dichloromethane with triethylamine

Mesylate **14** (58 mg) and triethylamine (20 mg) in 50 mL of

dry dichloromethane were irradiated under argon with the cold finger at 20°C for 3 h. The solvent was evaporated on a rotating evaporator in a bath at 40°C, then the residue put under 0.5 Torr pressure at 40°C. The residue had ν_{max}: 1743, 1686, 1614, and 1037 cm^{-1}. Its ^{13}C NMR spectrum (500 MHz) had the olefinic and carbonyl peaks of **15** as dominant, but also minor ones of unknown origin at 175.5, 162.9, 146.3, 144.8, and 136.6. A signal at 89.05, corresponding to a carbon carrying two hetero atoms, is also unassigned.

The product recovered from the $CDCl_3$ was heated briefly in methanol, then left in solution for 2 h at room temperature. After removal of the methanol the infrared spectrum was retaken. The 1743 cm^{-1} band was completely gone but the 1686 and 1614 cm^{-1} peaks remained. A dilute dichloromethane solution was shaken with aqueous sodium carbonate. The organic layer gave 55 mg of brown gum. This was acetylated using acetic anhydride. The neutral products were then separated on a 1 Torr plate using 30% hexane – 70% ethyl acetate. The major components were carbamate **19**, 13 mg (28%); recovered **14**, 4 mg; enamide **15**, 6 mg (14%); and *N*-acetyl derivative **28**, 6 mg (13%).

*Enamide **15***: This crystallized from ethyl acetate – hexane as fine needles, mp 134°C. For its UV spectrum, see Table 1. It gave ν_{max}: 1690 and 1180 cm. Its EI mass spectrum had peaks at *m/z* 385.3345 (M^+), 370, 272, 173, and 137 (base peak); calcd. for $C_{26}H_{43}NO$: 385.3344. Its CI mass spectrum had peaks at *m/z* 386 ($M^+ + 1$) and 370 ($M^+ - CH_3$).

*Bis(4-aza-3-oxocholest-5-en-6-yl)-methane **16***: This remained amorphous. Its UV absorption is listed in Table 1. It had ν_{max}: 3390 and 1667 cm.

*4-Azacholest-5-en-3-one **17***: This crystallized from dichloromethane – ethyl acetate as short needles, mp 253°C (immersed at 243°C), 258–260°C (immersed at 230°C in an evacuated capillary (lit. (3*a*) mp 256°C). Its ultraviolet spectrum is listed in Table 1. It had ν_{max}: 3380, 3185, 1681 (med), and 1661 (str) cm^{-1}.

N-*Methoxycarbonyl 3-aza-A-nor-5α-cholestane **18***: This formed fine needles from methanol, mp 128–129°C. It had ν_{max}: 1695 and 1124 cm^{-1}. The mass spectrum in CI mode showed a strong $M^+ + 1$ ion at *m/z* 418 and in EI mode an M^+ ion at *m/z* 417.

N-*methoxycarbonyl-3-aza-A-nor-5β-cholestane **19***: This crystallized from aqueous methanol as hexagonal plates with mp 88°C. It had ν_{max}: 1691, 1135, and 1105 cm^{-1}. Its CI mass spectrum had peaks at *m/z* 418 ($M^+ + 1$), 402 ($M^+ + 1$) – CH_4), and 386 ($M^+ + 1 - CH_3OH$). Its structure was determined by X-ray crystallography (unpublished work by Professor C. Bensimon, University of Ottawa).

*4-Aza-5-methoxy-A-nor-B-homocholestan-3-one **20***: This crystallized as rods from cold hexane, mp 82–83°C. It had ν_{max}: 1682 and 1089 cm^{-1}. Its CI mass spectrum gave *m/z* 387 ($M - 31 + H^+$).

*4-Aza-5α-cholestan-3-one **21***: This crystallized from methanol as short needles, mp 250–252°C (lit. (5) mp 252°C) and had ν_{max}: 3380, 3190, and 1659 cm^{-1}.

*4-Aza-5β-cholestan-3-one **22***: This crystallized from ethyl acetate, mp 189–190°C, which disagrees with the literature value of 151–155°C (5) (dimorphic ?). It had ν_{max}: 3380 and 1658 cm^{-1}.

*3-Aza-5α-A-norcholestane hydrochloride (**23** hydrochloride)*: The hydrochloride of **23** crystallized as fine needles from dichloromethane – ethyl acetate, mp 262°C (dec.) when heating was started at 245°C.

*3-Aza-5β-A-norcholestane hydrochloride (**24** hydrochloride)*: The hydrochloride of **24** crystallized from methanol – ethyl acetate as small plates or needles, mp 258°C (dec.) when heated from 245°C.

*Urea **25***: After purification using a preparative plate and 1:1 dichloromethane/hexane (R_f 0.3) and crystallization from methanol – ethyl acetate, **25** formed fine needles, mp 236–242°C. It had ν_{max} 1627 cm^{-1}.

*Urea **26***: The 5β urea **26** crystallized from dichloromethane – methanol or ethyl acetate, mp 250–252°C. It had ν_{max} 1626 cm^{-1}.

N-*Acetyl-3-aza-5α-A-norcholestane **27***: This was hard to free from a trace of UV – visible contaminant. Recrystallization from methanol gave **27** as fine needles, mp 122–123°C. It had ν_{max} 1642 cm^{-1}.

N-*Acetyl-3-aza-5β-A-norcholestane **28***: Preparative TLC (2% ethanol in chloroform (R_f 0.2), then 80% ethyl acetate – 20% hexane) failed to remove a trace of UV-active impurity. Recrystallization from hexane, then aqueous methanol, gave **28** as flat needles, mp 94°C. It gave ν_{max} 1641 cm^{-1}.

*A-Nor-β-homo-4-azacholestan-3-one **32***
A suspension of 26 mg of 10% Pd on charcoal in 4 mL of 95% ethanol was saturated with hydrogen, then 36 mg of enamide **15** was added. Uptake of 2.5 mL (1.1 mol) of hydrogen was rapid. The filtrate from removal of the catalyst was evaporated. The residue was suspended in hexane, then filtered from a trace of insoluble product. A concentrated hexane solution gave twisted hair-like crystals of **32**, mp 117–118°C. This had ν_{max} 1665 cm^{-1}.

*Action of methanesulfonic acid on **17** in TMU*
A solution of 125 mg of **17** and 98 mg of methanesulfonic acid in 5 mL of tetramethylurea was heated in a bath at 180°C under argon for 3 h. The solvent was removed under 1 Torr pressure in a bath at 60°C, the residue was dissolved in dichloromethane, and this was washed with aqueous sodium carbonate. The dried dichloromethane solution yielded 129 mg of gum after evaporation and heating at 100°C under 0.1 Torr pressure. This crystallized from a hexane–dichloromethane mixture, giving 53 mg of recovered enamide **17**. The mother liquor was evaporated and the residue separated on a 1 Torr silica gel plate using 80% ethyl acetate – 20% hexane mixture. The products in order of decreasing R_f were enamide **17**

(12 mg; total recovered 62 mg), unknown (14 mg), and enamide **16** (30 mg). The yield of **16** was 50% based on unrecovered **17**.

4-Aza-6-ethoxymethylcholest-5-en-3-one 31

A solution of paraformaldehyde (59 mg), *p*-toluenesulfonic acid hydrate (8 mg), and *p*-toluenesulfonic anhydride (14 mg) in 3 mL of dry chloroform and 0.3 mL of absolute ethanol was prepared. After addition of 48 mg of enamide **17** the mixture was heated in a bath at 60°C for 24 h. A crop of crystals was removed by filtration, then the filtrate was evaporated to small volume. The residue was dissolved in chloroform, and the solution was shaken with aqueous sodium carbonate, dried, and distilled, leaving 63 mg of product. This was separated on a 1 mm plate using 5% ethanol in chloroform. The main ultraviolet–visible zone yielded 34 mg of crude **31**, which crystallized from ethyl acetate – hexane to give 26 mg, mp 143°C (47%). Recrystallization of this from hexane gave **31** with mp 146–148°C after sintering at 143°C (heating started at 135°C). It had ν_{max}: 3310 and 1659 cm^{-1}. For λ_{max} see Table 1.

Coupling of 6-ethoxymethyl enamide 31 and enamide 17

A mixture of 16 mg of 4-aza-6-ethoxymethylcholest-5-en-3-one **31**, 4.7 mg of *p*-toluenesulfonic acid hydrate, 7.7 mg of *p*-toluenesulfonic anhydride, and 14 mg of enamide **17** in 3 mL of dry ethanol-free chloroform was left in a bath at 65°C under argon for 4 h. The cooled solution was extracted with aqueous sodium bicarbonate, dried, and distilled. The residue was separated on a 1 mm SiO_2 plate using 5% methanol in ethyl acetate. The main UV – visible zone yielded 26 mg (91%) of product, identified as the dimeric enamide **16** by ^1H and ^{13}C NMR.

Enamide 15 and acetic acid

A solution of **15** (21 mg) in 1 mL of acetic acid and 17 mg of acetic anhydride containing 9 mg of toluenesulfonic acid hydrate was left at room temperature for 2 days. After addition of 21 mg of sodium bicarbonate and 0.05 mL of water the mixture was stirred for 1 h. It was then evaporated to small volume on a rotating evaporator (bath at 55°C), finally under 0.5 Torr pressure. The residue was extracted with dichloromethane, filtered, then the filtrate evaporated, finally under 0.5 Torr. The residue gave an ^1H NMR spectrum identical to that of **15**.

Action of acids on enamide 17

(*a*) Dry hydrogen chloride was bubbled into a solution of 65 mg of **17** in 4 mL of dry ethanol-free chloroform at 0°C for 5 h. The residue from evaporation of the solvent crystallized from ethyl acetate giving 55 mg (84%) of unchanged **17**. The mother liquor contained a mixture of products (TLC) giving ^{13}C NMR signals at 132.5, 130.9, and 128.8 ppm.

(*b*) A solution of 138 mg of **17** and 89 mg of *p*-toluenesulfonic acid hydrate in 10 mL of dry methanol (heat) was left overnight, then refluxed for 6 h. The residue after evaporation of the solvent (rotating evaporator) was dissolved in dichloromethane. After washing with aqueous sodium carbonate and drying (Na_2SO_4), this was evaporated, yielding 140 mg of semi-crystalline solid. This was suspended in methanol and filtered, giving 46 mg of unchanged **17**. The contents of the filtrate were separated on a 1 mm SiO_2 plate using 5% methanol in chloroform. The highest R_f component (53 mg) proved, by IR and ^1H NMR to be **5** (R = CH_3). Other than another 13 mg of **17**, the other minor products were not identified.

Acknowledgements

The authors would like to thank Professor J.W. ApSimon for the opportunity to finish this work at Carleton University, John Nikiforuk for the NMR spectra, Ottawa University mass spectrometry centre and Guy Dupont for the mass spectra, and Professor C. Bensimon for the X-ray structure of **19**. B. Blackwell would like to dedicate this paper to her mother, Joan Blackwell, who succumbed to Parkinson's Syndrome during the final stages of preparing this manuscript. This publication constitutes No. 971130 for the Eastern Cereal and Oilseed Research Centre.

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