Steroids. Part 43.[1] Thermal Decomposition of Steroidal Azidoformates

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Thermolysis of the four possible isomeric 3-methoxy-16-methylestra-1,3,5(10)-trien-17-yl azidoformates **1b**, **6b**, **10b** and **14b**, of 3-methoxyestra-1,3,5(10)-trien-17β-yl azidoformate **17b**, and of 16β-azidoformyloxymethyl-3-methoxyestra-1,3,5(10)-triene **21b** was realized at 100 °C. Thermolysis results in insertion of the nitrene intermediate into C–H bonds, the site of which depends on the steric position of the substituents in the D ring of the sterane skeleton.

The singlet nitrene of high energy originating from thermal or photochemical decomposition of acyl azides becomes inserted in the appropriate C–H bond(s) with retention of configuration.[2–4] In the case of intramolecular transformation, oxazolidinone and tetrahydrooxazinone derivatives can be formed.[5–8] This unique method for the development of condensed heterocycles still did not gain widespread application, since the structure of the products and their composition are strongly affected by both the reaction temperature and stereochemical factors.

Studies on these reactions revealed that the reactivity of the alkoxycarbonyl nitrene nitrogen decreases in the order tertiary > secondary > primary C–H bonds[9] and that the formation for the five-membered oxazolidinone ring is more favoured than that of the six-membered tetrahydrooxazinone.[10]

During investigations of this reaction of *cis*- and *trans*-2-methylcyclohexyl azidoformate the former compound was found to yield the homogeneous *cis*-annellated cyclic product while the reaction of the *trans*-isomer may result in the development of both the *cis*- and *trans*-annellated ring systems. The composition of the product depends on the temperature of the reaction and this can be explained by the influencing action of temperature on the conformational equilibrium.[11,12]

The 3α- and 3β-azidoformates, as well as 7α- and 7β-azidoformates, of lanostane with a relatively rigid skeleton, can be converted into heterocycles with different numbers of ring members and with different types of annellation.[13,14] The thermal reaction of 3-methoxyestra-1,3,5(10)-trien-17-yl azidoformate epimers yielded oxazolidinone and tetrahydrooxazinone ring systems, and their hydrolysis resulted in steroidal amino alcohols.[11]

Starting from the four isomeric 3-methoxy-16-methylestra-1,3,5(10)-trien-17-yl azidoformates **1b**, **6b**, **10b** and **14b** stereochemical studies on the cyclization reaction could be carried out, including the preparation of heterocycles condensed onto the estrane skeleton.

Recently we reported[15,16] the preparation and the confirmation of the structure of the four possible isomers of 16-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-ol. These compounds were converted into the corresponding 16-(*p*-tolylsulphonyloxymethyl) derivatives.[17] The next step was $LiAlH_4$ reduction in tetrahydrofuran (THF), which furnished the desired 17-hydroxy-16-methyl isomers **1a**, **6a**, **10a** and **14a**.[1]

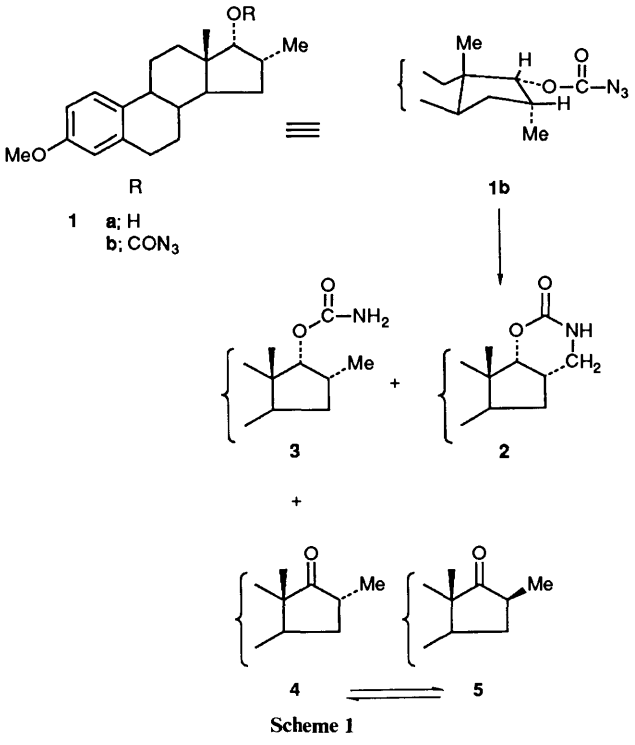
These were allowed to react with phosgene to obtain the C-17 chloroformates, which were converted with NaN_3 in acetone, without isolation, into the corresponding azidoformates. These compounds were subjected to thermolysis in CCl_4 solution at 100 °C for 6 h in a sealed tube. The usually employed temperature (135–150 °C)[11] was altered, since at 135 °C a significant extent of resin formation and precipitation of an insoluble product were observed.

During conversion of the 16α,17α-isomer **1b** one single insertion product, the tetrahydrooxazinone **2** condensed to the D-ring of the sterane skeleton in the α,α-position was formed in 23% yield; that is, the insertion of the 17α-oxycarbonylnitrene nitrogen occurred into the C–H bond of the methyl group in the α-position. In theory, insertion would have been possible at the C-16–H bond, too; however, only the sterically unfavoured *trans*-annellated oxazolidinone could be formed. During the conversion the 16-methyl 17-carbamate **3** was formed *via* intermolecular stabilization of the nitrene and it was isolated in 37% yield. Its formation can also be explained by the singlet→triplet conversion of the nitrene and intermolecular hydrogen abstraction.[18] In addition to this, 3-methoxy-16-methylestra-1,3,5(10)-trien-17-one epimers **4** and **5** were also isolated from the reaction mixture in 29% yield. Isomerization of steroidal 16α-methyl-17-ketones taking place in both acid and alkaline media to yield the thermodynamically more stable 16β-analogue has been known in the androstane series.[19] This isomerization was observed in the case of all the four diastereoisomers **1b**, **6b**, **10b** and **14b** of 16-methyl-17-azidoformates. The ratio of 16α- and 16β-methyl ketones is *ca.* 1:2, considering compounds **1b** and **6b**, while this value is 1:5 in the case of isomers **10b** and **14b** (Scheme 1).

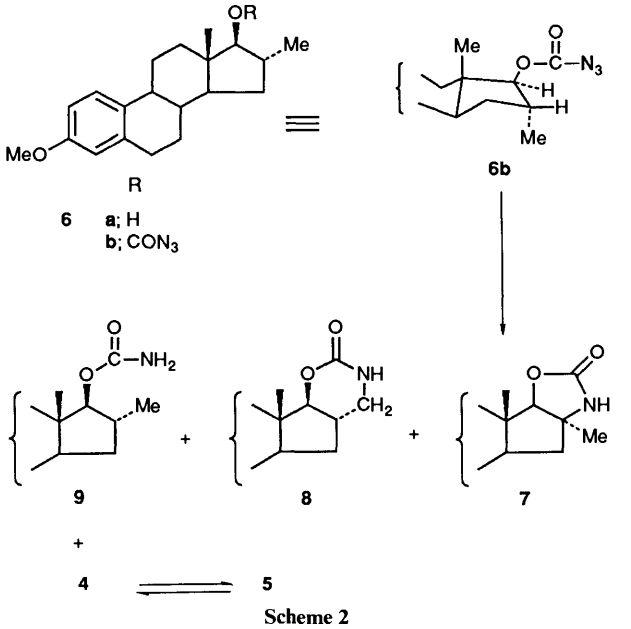
In the reaction of the 16α,17β-isomer **6b** the insertion products **7** and **8** were obtained. The formation of the *cis*-annellated (β,β-condensed) oxazolidinone **7** is, of course, favoured (38% yield) and the *trans*-annellated tetrahydrooxazinone with 16α,17β-configuration **8** appeared as the by-product (15% yield). Further products of the conversion were the urethane **9** (17%) and the ketone epimers **4** and **5** (overall yield 21%) (Scheme 2).

During the conversion of the 16β,17α-isomer **10b** two heterocycles were again formed and the main product was the *cis*-annellated 16α,17α-oxazolidinone **11** (44%). The *trans*-annellated dihydrooxazinone **12** was obtained in 16% yield. Further products of the conversion were the urethane **13** (15%) and the mixture of the 16-methyl 17-ketone isomers **4** and **5** (overall yield 18%) (Scheme 3).

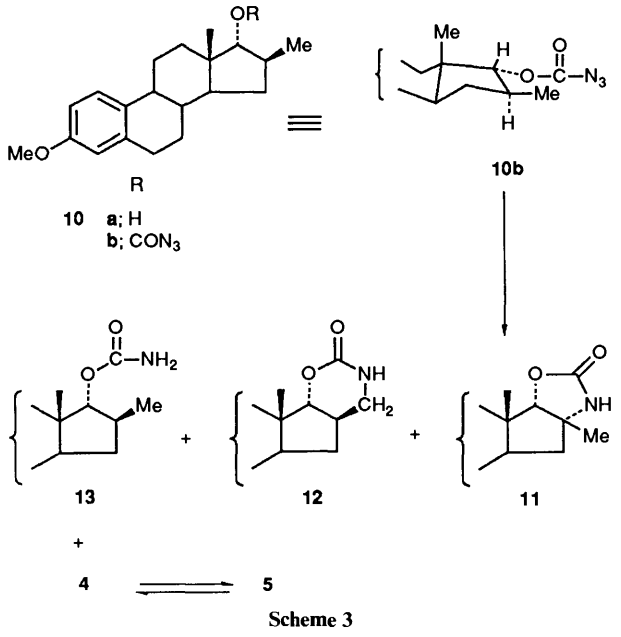
The reaction of the 16β,17β-isomer **14b** yielded one single insertion product, the tetrahydrooxazinone **15** (19%). Similarly to the case of the other starting compound with *cis*-configuration **1b**, no *trans*-annellated oxazolidinone derivative was formed. Further products were the urethane **16** (23%) and ketones **4** and **5** (overall yield 32%) (Scheme 4).



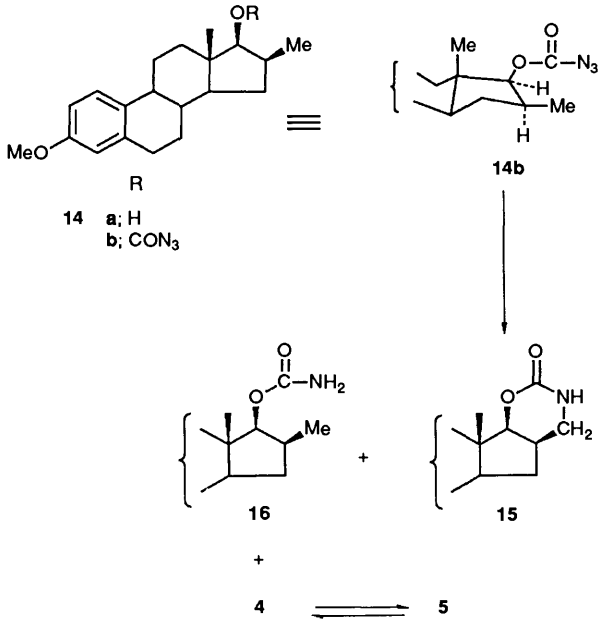
Scheme 1



Scheme 2



Scheme 3



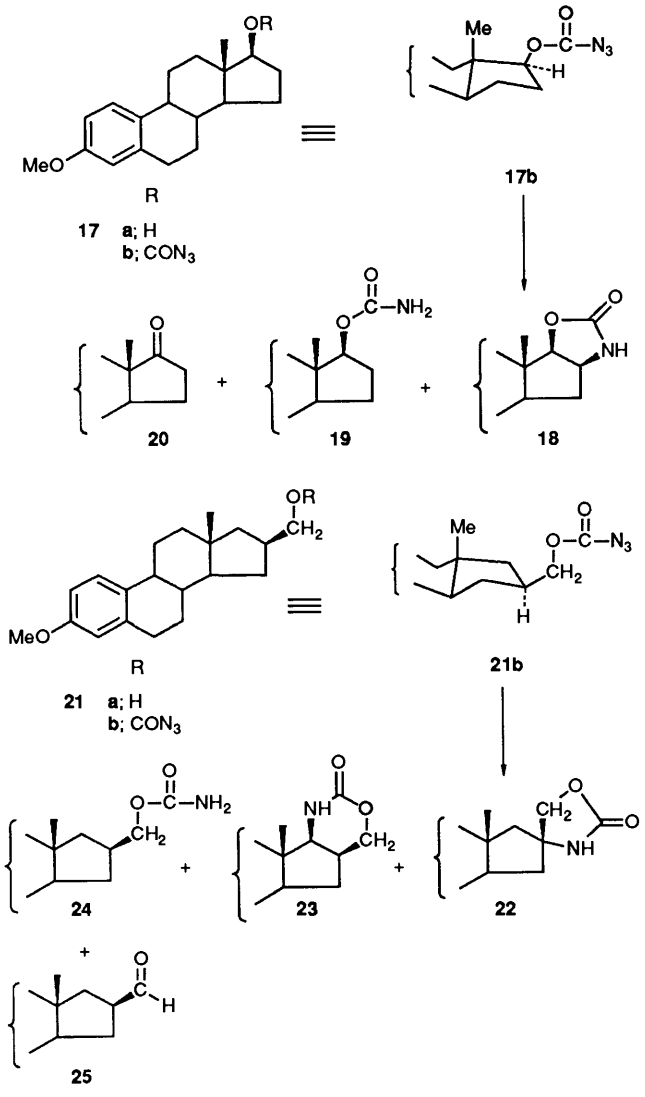
Scheme 4

For comparison purposes, the thermal reactions of 3-methoxyestra-1,3,5(10)-trien-17-yl azidoformate **17b** and 16-azidoformyloxymethyl-3-methoxyestra-1,3,5(10)-triene **21b** were also accomplished. When the conversion of compound **17b** was effected at temperatures lower than that given in the literature,[11] a different result was obtained: 16β,17β-oxazolidinone **18** was formed in 24% yield; in addition, a significant amount of carbamate **19** (31%) and 17-ketone **20** (35%) could be isolated.

The main product of the thermal reaction of compound **21b** was the 16-spirooxazolidinone **22** (42%). The ready formation of this compound could be explained by the participation on the tertiary C-16–H bond. In the reaction of the C-17–H bond, 16β, 17β-tetrahydrooxazinone **23** (11%) was also formed. The product was not stereochemically homogenous and the 16β,17β ring-annellated compound contained some 16β,17α-isomer. Two further products of the reaction were 16β-carbamoyloxymethyl compound **24** (21%) and 3-methoxyestra-1,3,5(10)-triene-16β-carbaldehyde **25** (16%) (Scheme 5).

The structure of the products of thermal reaction discussed in this paper was elucidated by the synthesis of further comparative substances and by IR and ^{1}H- and ^{13}C NMR investigations. Spectral data are summarized in Tables 1 and 2.

The C-16, -17 configurations are confirmed unambiguously by the $^3J_{16,17}$ coupling constants. The rigid *trans*-annellated D-ring – when there is no significant steric interaction between the C-16, -17 substituents – exists in an envelope form in which C-13 is out of the plane of the other carbon atoms. In this conformation the dihedral angle of the 16-H$^\alpha$ and 17-H$^\beta$ bonds is *ca.* 90°, thus[20] in the 16β,17α-substituted compounds **10**, **12** and **13** the coupling constant $^3J_{16\alpha H,17\beta H}$ is > 1.2 Hz. 16α,17β-Isomers **6**, **8** and **9** can be characterized by a coupling constant of 7.5 ± 0.2 Hz (dihedral angle ~150°). Owing to the steric hindrance occurring between the 17β-substituent and the C-18



Scheme 5

methyl group being in a *cis* relationship the ^{13}C NMR line of the latter compound is shielded by *ca.* 5.5 ppm compared with that observed in the analogous 16β,17α compounds (steric effect, steric compression shift).[21] This upfield shift also appears in the 16β,17β-isomers **14–16** and **18**. The coupling constant $^3J_{16\alpha H,17\alpha H}$ is 10.0 ± 0.2 Hz. This is explained by the fact that the 16β-substituent and the C-18 methyl group produce steric hindrance and the D-ring thus takes a conformation in which the two groups get further apart and thus the 16α,17α dihedral angle approaches zero and the coupling constant $^3J_{16\alpha H,17\alpha H}$ increases continuously. (In the envelope form of ring D the C-14 atom is not in the plane defined by the other carbon atoms.) The chemical shift in compound **18** (12.1 ppm) and the magnitude of the $^3J_{16\alpha H,17\alpha H}$ coupling constant (9.6 Hz) are thus unambiguous evidence for β,β (*cis*) annellation of the oxazolidinone ring.

In the 16α,17α series **1–3**, however, the $^3J_{16\beta H,17\beta H}$ coupling is lower (5.6 ± 0.1 Hz), thus here the steric hindrance between the substituents causes a distortion of ring D in which the corresponding dihedral angle deviates from zero: C-17 stands out from the plane of the envelope form. Meanwhile the two substituents move away from each other and 16-H$^\beta$ approaches the C-18 methyl group. This causes a moderate upfield shift in the carbon line of the methyl group: the average shift characteristic of the 16β,17α-compounds is 18.2 ppm, whereas the shift is 17.2 ppm in the 16α,17α series.

The structure of the 17-oxo derivatives **4** and **5** is confirmed by the carbon resonance line of the carbonyl group (222.3 and 222.8 ppm), whose shift again indicates that a five-membered cyclic ketone group is present (the shift of saturated ketone carbonyl atoms in rings A–C of steranes is <215 ppm).[22a] The spectra of the isomers hardly differ from each other. The upfield shifts of the C-13 and C-16 signals (1.4 and 4.5 ppm) in the ^{13}C NMR spectrum of the ketone obtained from the 16α-methyl-substituted starting compound indicate an unchanged C-16 configuration: the steric effect is explained by the more crowded steric structure of the 16α-methyl isomer.

In the oxazolidinone compounds **7**, **11**, **18**, and **22**, the carbonyl frequency is higher than that in the open-chain or six-membered cyclic analogues observed for the corresponding urethane band, being >1750 cm^{-1}, in accord with literature data.[23]

The chemical shift of the quaternary C-16 atom is characteristically high in compounds **7**, **11**, and **22** (62–64 ppm), owing to the increase in substitution and the vicinity of the nitrogen atom.[22b] The latter produces similar consequences in compound **18**, too [δ(C-16) 54.5 ppm], when compared with the analogues carrying one methyl substituent at the C-16 atom (here the shift of the C-16 line falls in the interval 33–41 ppm). In compounds **7** and **11**, the presence of the quaternary C-16 atom causes an increase in the shift of the neighbouring C-15 atom and the C-16 methyl group. (An increase in the shift of the C-15 line also appears for the spectrum of compound **22**).

The C-16 methylene group in compounds **21a**, **21b**, **22** and **24** produces a strongly shifted signal, owing to the vicinity of the oxygen, in both the ^1H and ^{13}C NMR spectra. A similar, but less extensive, shift is observed for the effect of nitrogen substitution in compounds **2**, **8**, **12** and **15**. The C-17 methylene signals, however, produced a lower shift than that of the corresponding CH groups, also for compound **25**.

In compound **25**, the 16-formyl group can be identified unambiguously in both the ^1H (δ_H 9.77 s, 1 H) and the ^{13}C NMR (δ_C 204) spectra. In conclusion, azidoformates are capable of useful and predictable functionalization of steroids. Furthermore, five-membered steroid-oxazolidinone ring formation is preferred over six-membered tetrahydrooxazinone in intramolecular insertion.

Experimental

M.p.s were determined on a Kofler block and are uncorrected.

Specific rotations were measured with POLAMAT-A polarimeter for solutions in chloroform (*c* 1). The IR spectra were recorded in KBr pellets with a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ solution in 5 or 10 mm (^{13}C) tubes, at room temperature on a Bruker WM-250 and/or WP-80-SY FT-spectrometer controlled by an Aspect 2000 computer at 250.13 MHz (^1H) and 62.89 or 20.14 MHz (^{13}C), respectively, and using the deuterium signal of the solvent as the lock and $SiMe_4$ as internal standard. The most important measurement parameters were: sweep width 5 and 15 or 5 kHz; pulse width 1 (^1H) and 7 or 3.5 (^{13}C) μs (~20° and ~30° flip angle); acquisition time 1.64, 1.02, or 1.64 s; number of scans 32 (^1H) and 1–32 K (^{13}C); computer memory 16 K. Complete proton noise decoupling (~3 or ~1.5 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used, with line width 0.7 (1H) and 1.0 or 2.0 Hz (^{13}C).

DEPT spectra[24] were recorded in the usual way,[25] using only the θ 135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively.

TLC was performed on Kieselgel-G (Merck) layers of 0.5 mm thickness. The following solvents were used as developing

Table 1 Characteristic IR frequencies (in KBr, cm^{-1})[a] and ^1H NMR data (chemical shifts in δ-units, coupling constants in Hz) of compounds **1b**, **2–5**, **6b**, **7–9**, **10b**, **11–13**, **14b**, **15**, **16**, **17**, **18**, **19**, **21a** and **b**, **22**, **24** and **25** in $CDCl_3$ solution,[b] at 250 MHz[c]

Compound	ν_{NH}	$\nu_{C=O}$	18-H_3 (3 H, s)	17-H (1 H, s/d/t)[d]	16-Me or CH_2 (3 or 2 H, d)[e]	NH (1 H, s)[f]
1b		1718	0.85	4.86	0.99	
2	*ca.* 3300	1700, 1665	0.82	4.32	3.14, 3.51	6.85
3	3466, 3340	1728	0.83	4.78	0.98	4.68
4		1732	0.94		1.14	
5		1733	0.87		1.24	
6b		1725	0.83	4.45	1.13	
7	3288	1763, 1717	0.92	3.96	1.39	6.35
8	3427	1717, 1691	0.93	3.74[g]	3.20, 3.50	6.15
9	3479, 3333	1728, 1697	0.82	4.40	1.12	4.60
10b		1726	0.87	4.48	1.25	
11	3285	1751, 1722	0.86	4.12	1.53	6.68
12	3425, 3345, 3250	1650	0.76	3.62	3.25	5.50
13	3460, 3420	1722	0.84	4.40	1.23	~4.75
14b		1750, 1725	0.86	4.68	0.98	
15	3324	1728, 1680	0.90	4.29	3.08, 4.38	5.97
16	3460, 3320	1695	0.83	4.45	0.93	6.35
17b		1720	0.63	4.70		
18	3402	1761	0.92	4.45		6.55
19	3460, 3300, 3180	1730, 1695	0.81	4.63		4.68
21a	*ca.* 3400[h], *ca.* 3250[h]		0.79		3.60	
21b		1755, 1725	0.81		4.20	
22	3350	1750	0.74	0.82, 0.88	4.26, 4.36	6.95
	3450, 3420					5.00
24	3320, 3270	1700	0.79		4.02	
25		1720	0.66		9.77	

[a] Stretching vibration bands of azides: 2203, 2162 and 2140 **1b**; 2200, 2175 and 2140 **6b**; 2139 **10b**; 2180 and 2135 **14b**; 2170 and 2130 **17b**; 2180 and 2135 **21b**. [b] In $(CD_3)_2SO$ solution for compound **16**. [c] Further ^1H NMR signals: 1-H 7.15–7.20 (d, *J* 8.6 ± 0.1 Hz), 2-H 6.66–6.72 (dd), 4-H 6.60–6.64, (d, *J* 2.6 ± 0.2 Hz), CH_2 **6**: 2.8–2.9 (2 H, m), 16-H 1.6 (m) **1b**, 2.7 (m) **2**, 2.6 (m) **4**, 2.5 (m) **14b**, 4.15 (m) **18**, OMe **3** 3.71–3.78 (3 H s). [d] s for **7**, **11** and **12**, t for **17b** and **19** (*J* 7.7 Hz), 2 d (AB-type spectrum) for **22** (*J* 6 Hz), d, *J* 5.6 ± 0.1 Hz **1b**, **2** and **3**, 7.4 **6b**, 7.7 **9**, 1.2 **10b** and **13**, 10.0 **14b** and **15**, 9.7 Hz **16** and **18**. [e] *J* 7.3 ± 0.4 Hz for **1b**, **3–5**, **6b**, **9**, **10b**, **13**, **14b** and **16**; dt (*J* 11.8, 3.5 and 3.5) and dd (*J* 12.2 and 4.4) for **2** (2 × 1 H), s for **7**, **11** and **25** (1 H, aldehyde group) 1 H, dd, *J* ≈ 10, ≈9 Hz) and m (1 H) for **8** m (2 H) for **12**; t (1 H, *J* 11.5 Hz) and m (1 H) for **15**; d (2 H, *J* 7.6) for **21a** and **b** and **24**; 2 d (2 × 1 H, AB-type spectrum, *J* 8.4 Hz) for **22**. [f] Broad, intensity 2 H for **3**, **9**, **13**, **16**, **19** and **24**; d (1 H, *J* 3.5 Hz) for **2**. [g] Hidden by the OMe signal for **3**. [h] ν_{OH} Band.

agents: (*a*) benzene; (*b*) methanol–benzene (5:95). The spots were detected by spraying with 50% aq. phosphoric acid and subsequent heating at 100–120 °C for 15 min. The R_f-values were determined for the spots observed on illumination with UV light at 356 nm.

In column chromatographic separation work, Al_2O_3 standardized according to Brockmann and having an activity of III–IV was used. Physical constants of the compounds are given in Table 3. Light petroleum refers to the fraction boiling in the range 40–65 °C.

Preparation of Steroidal Azidoformates **1b**, **6b**, **10b**, **14b**, **17b**, *and* **21b**: *General Procedure*.—The steroidal alcohol[1] **1a**, **6a**, **10a**, **14a**, **17a**, or **21a** was dissolved in benzene (15 cm^3), then triethylamine (1.5 cm^3, 15 mmol) was added. A 20% phosgene solution in benzene (1.5 cm^3; 1.5 mol equiv.) was added dropwise to the reaction mixture at 0 °C under continuous stirring and the conversion was monitored by TLC. The mixture was kept for 12 h to attain room temperature, and it was then evaporated to dryness under reduced pressure (aspirator pump). The crystalline, oily residue was rubbed with diethyl ether, then the ether was decanted and evaporated to dryness. The oily residue was dissolved in acetone (30 cm^3), and NaN_3 (650 mg, 20 mmol) and a few drops of water were added. The mixture was refluxed for 1 h then poured into saturated aq. NaCl (500 cm^3) and extracted with benzene (3 × 100 cm^3). The benzene fraction was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The raw product was subjected to chromatographic separation on an Al_2O_3 column with a mixture of benzene and light petroleum (1:1). The homogeneous substance obtained was crystallized from methanol.

[3-*Methoxyestra*-1,3,5(10)-*trien*-16β-*yl*]*methanol* **21a**. [3-Methoxyestra-1,3,5(10),16-tetraen-16β-yl]methanol[16] (2.98 g, 0.01 mol) was dissolved in ethyl acetate (25 cm^3), Pd/C catalyst (0.5 g) was added, and the mixture was hydrogenated at room temperature under atmospheric pressure for 6 h. The catalyst was filtered off, the solution was evaporated to dryness, and the crystalline residue obtained was recrystallized from a mixture of acetone and water.

Preparation of Steroidal Carbamates **3**, **9**, **13**, **16**, **19** *and* **24**: *General Procedure*.—The steroid alcohol **1a**, **6a**, **10a**, **14a**, **17a** or **21a** (10 mmol) was dissolved in benzene (15 cm^3), and triethylamine (1.5 cm^3, 15 mmol) was added. A 20% solution of phosgene in benzene (1.5 cm^3; 1.5 mol equiv.) was added dropwise to the stirred reaction mixture at 0 °C and conversion was monitored by TLC. The mixture was kept for 12 h to attain room temperature and was then evaporated to dryness under reduced pressure (aspirator pump). The crystalline, oily residue was rubbed with diethyl ether, and the ether was decanted and evaporated to dryness. The oily residue was dissolved in benzene (25 cm^3) and the solution was shaken thoroughly with conc. NH_4OH (25 cm^3). The white precipitate which separated from the emulsion was filtered off, dried in a vacuum desiccator over P_2O_5, and crystallized from a mixture of acetone and light petroleum.

Thermolysis of Steroidal Azidoformates: General Procedure.—The steroidal azidoformate **1b**, **6b**, **10b**, **14b**, **17b** or **21b** (10 mmol) was dissolved in anhydrous carbon tetrachloride (200 cm^3) and the solution was divided in 10 cm^3 portions into thick-walled tubes. The sealed tubes were kept at 100 °C for 6 h, then strongly cooled. The tubes were opened, and the combined reaction mixture was washed successively with water and with

Table 2 ^{13}C NMR chemical shifts [$\delta(SiMe_4)$] of compounds **1b**, **2–5**, **6b**, **7–9**, **10b**, **11–13**, **14b**, **15**, **16**, **17b**, **18**, **19**, **21a** and **b**, **22**, **24** and **25** in $CDCl_3$ solution[a] at 20.15 or 62.89[b] MHz

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1b	126.1	111.6	157.7	114.0	137.8	29.8	27.9	39.1	43.5	132.5	26.0
2	126.1	111.4	157.4	113.7	137.6	29.6	27.9	39.0	43.1	132.4	25.8
3[e]	126.3	111.7	157.8	114.1	138.0	30.0	28.2	39.3	43.8	132.9	26.2
4	126.3	111.6	157.7	114.0	137.7	29.7	26.5	38.4	44.1	132.2	25.9
5	126.2	111.6	157.7	114.0	137.7	29.7	26.8	38.1	44.2	132.2	25.9
6b	126.2	111.8	157.6	114.2	137.8	29.7	27.3	38.7	44.9	132.5	26.2
7[e]	126.1	111.7	157.7	113.9	137.5	29.5	27.6	37.7[f]	43.7	132.0	26.2
8[e]	127.6	113.1	156.1	115.2	139.0	30.7	28.2	36.2	45.4	133.6	27.2
9[e]	127.6	113.1	158.6[c]	115.2	139.0	30.8	28.2	39.8	44.9	133.8	27.4
10b	126.2	111.7	157.8	114.1	137.8	29.8	28.0	38.9	43.4	132.6	25.9
11[e]	126.1	111.7	157.7	113.9	137.6	29.6	27.9	38.2	43.2	132.2	25.7
12	127.9	113.2	158.9	115.3	139.2	31.2	29.6	40.3	45.0[c]	134.2	27.7
13	126.3	111.7	157.8	114.1	138.0	29.9	28.2	38.9	43.7	132.9	26.1
14b[e]	126.2	111.5	157.6[c]	113.9	137.7	29.7	27.4	38.1	43.9	132.3	26.1
15	126.3	111.7	157.7[c]	114.0	137.7	29.7	27.6	38.1	43.9	132.3	26.2
16[e]	126.3	111.5	157.6[c]	113.9	137.9	29.8	27.5	38.2	43.9	132.7	26.2
17b	126.8	112.3	157.7	114.8	138.4	30.3	27.9	39.4	44.5	133.0	26.8
18[e]	126.2	111.7	157.8	114.0	137.5	29.5	27.7	38.0	43.8	132.0	26.2
19	126.4	111.8	157.1	114.3	138.0	29.9	27.9	39.0	44.1	132.9	26.4
21a	126.2	111.5	157.5	113.9	137.9	29.7	28.1	38.7	43.9	133.0	26.8
21b	126.2	111.8	158.0[f]	114.2	138.0	29.9	28.3	38.9	44.1	133.0	26.9
22	126.2	111.9	159.5[f]	114.2	137.8	29.8	28.1	38.7	42.2[c]	132.6	26.4
24	126.2	111.8	157.7[c]	114.2	138.0	29.9	28.3	38.9	44.1	133.2	26.9
25	126.3	111.6	157.7	114.0	137.8	29.8	26.7[c]	38.6[g]	43.9	132.6	26.6[c]

Compound	C-12	C-13	C-14	C-15	C-16	C-17	C-18	3-OMe	16-Me or -CH_2	C=O
1b	34.3	46.6	48.2	31.8	33.2	88.8	17.1	55.1	15.3	157.4
2	30.9[c]	47.3	48.7	30.5[c]	33.5	89.2	17.0	55.0	42.3[d]	156.2
3[e]	33.5	46.5	48.5	32.0	34.3	84.4	17.3	55.3	15.6	157.2
4	32.0	47.8	48.6	30.0	39.3	222.3	16.6	55.2	14.5	
5	32.1	49.2	48.3	30.7	43.8	222.8	16.9	55.2	14.2	
6b	37.3	43.9	48.4	32.3	35.6	94.2	12.6	55.2	20.2	158.0
7[e]	37.7[f]	45.8	49.1	40.1	62.0	94.6	11.5	55.1	28.8	159.3
8[e]	39.4	43.0	50.9	25.0	36.8	89.0	13.2	56.5	46.7[d]	158.8
9[e]	38.2	45.4	49.2	33.2	36.5	89.7	14.1	56.5	21.7	158.8[c]
10b	34.4	45.3	50.6	32.2	40.9	93.5	17.3	55.2	20.6	157.3
11[e]	31.9	45.3	48.1	41.3	63.8	94.0	16.8	55.1	27.7	159.2
12	33.9	46.2[c,f]	51.4[g]	31.8	50.3[g]	83.5	19.5	56.7	46.2[c,d,f]	160.1
13	34.5	45.2	50.9	32.4	41.0	89.5	17.5	55.3	20.8	157.1
14b[e]	37.7	43.8	48.8	34.0	33.2	87.9	13.1	56.1	16.5	157.2[c]
15	37.5	44.8	49.4	29.2	34.6	88.7	13.3	55.3	44.4[d]	156.4[c]
16[e]	37.9	43.6	48.9	34.1	33.5	84.1	13.3	55.2	16.8	157.0[c]
17b	37.6	44.0	50.6	23.8	28.1	87.8	12.5	55.8		158.5
18[e]	37.7	44.5	49.6	33.6	54.5	88.1	12.1	55.2		160.2
19	37.3	43.2	50.2	23.4	27.4	83.6	12.1	55.4		158.9
21a	39.4[f]	43.2	53.8	30.1	40.8	39.4[f]	19.8	55.2	68.5[d]	
21b	39.5	43.4[c]	54.2	30.3	35.9	41.1[c]	19.9	55.3	73.6[d]	158.0[f]
22	38.5	41.8	53.3	43.8[c]	63.4	57.0	18.3	55.6	79.4[d]	159.5[f]
24	36.2	41.0	54.2	30.3	39.5	43.5	19.9	55.3	70.2[d]	157.3[c]
25	38.8[g]	41.1	53.7	28.1	49.1	41.2	18.2	55.2	204.0[d]	

[a] Solvent $(CD_3)_2SO$ for compounds **8**, **9** and **12**. [b] For compounds **4**, **5**, **6b**, **14b**, **16**, **17b**, **19**, **21a** and **b**, **22**, **24** and **25**. [c] Reversed assignments may also be possible. [d] CH_2 group for compounds **2**, **8**, **12**, **15**, **21a** and **b**, **22** and **24**, aldehyde CH in the case of compound **25**. [e] Assignments were proved by DEPT measurements. [f] Two overlapping lines. [g] Reversed assignments also possible.

dil. aq. $NaHCO_3$ to neutrality (pH 7), dried over Na_2SO_4, and evaporated to dryness. The crystalline, oily residue was subjected to chromatographic separation on an Al_2O_3 column (activity III–IV).

Light petroleum, then benzene–light petroleum (1:1), eluted first the carbonyl derivatives. Benzene eluted the acid amide component, and finally benzene–chloroform (3:1), benzene–chloroform (1:1), and chloroform employed in that order eluted the insertion products.

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Table 3 Characterization data for compounds **1b**, **2–5**, **6b**, **7–9**, **10b**, **11–13**, **14b**, **15–16**, **17b**, **18–19**, **21a** and **b**, and **22–25**

Compound	M.p. (°C)	$[\alpha]_D$ (°)	R_f	Mol. formula	Found (Required) C	H	N	Yield (%)
1b	108–110	+69	0.90[a]	$C_{21}H_{27}N_3O_3$	68.15 (68.26)	7.42 (7.36)	11.35 (11.37)	
2	265–268 (265–270)[c]	+35	0.45[b]	$C_{21}H_{27}NO_3$	73.75 (73.86)	7.86 (7.97)	4.32 (4.10)	23[e]
3	250–253	+33	0.60[b]	$C_{21}H_{29}NO_3$	73.54 (73.43)	8.35 (8.51)	4.35 (4.07)	85[d], 37[e]
4	110–113	+134	0.35[a]	$C_{20}H_{26}O_2$	80.35 (80.49)	8.86 (8.78)		
5	95	+154	0.35[a]	$C_{20}H_{26}O_2$	80.35 (80.49)	8.55 (8.78)		
6b	123–125	−28	0.80[a]	$C_{21}H_{27}N_3O_3$	68.41 (68.26)	7.45 (7.36)	11.45 (11.37)	
7	221–223	+129	0.45[b]	$C_{21}H_{27}NO_3$	73.75 (73.86)	7.85 (7.97)	4.26 (4.10)	38[e]
8	295–300	+142	0.40[b]	$C_{21}H_{27}NO_3$	73.89 (73.86)	7.88 (7.97)	4.27 (4.10)	15[e]
9	259–261	+16	0.55[b]	$C_{21}H_{29}NO_3$	73.55 (73.43)	8.65 (8.51)	4.25 (4.07)	85[d], 17[e]
10b	127–129	+67	0.80[a]	$C_{21}H_{27}N_3O_3$	68.35 (68.26)	7.45 (7.36)	11.45 (11.37)	
11	277–280	+26	0.35[b]	$C_{21}H_{27}NO_3$	73.74 (73.86)	7.85 (7.97)	4.38 (4.10)	44[e]
12	225–226	+64	0.30[b]	$C_{21}H_{27}NO_3$	73.80 (73.86)	7.77 (7.97)	4.35 (4.10)	16[e]
13	209–212	+50	0.50[b]	$C_{21}H_{29}NO_3$	73.28 (73.43)	8.48 (8.51)	4.21 (4.07)	78[d], 15[e]
14b	98–99	+61	0.85[a]	$C_{21}H_{27}N_3O_3$	68.44 (68.26)	7.08 (7.36)	11.45 (11.37)	
15	310–315	+116	0.40[b]	$C_{21}H_{27}NO_3$	73.75 (73.86)	7.83 (7.97)	4.32 (4.10)	19[e]
16	264–267	+74	0.55[a]	$C_{21}H_{29}NO_3$	73.57 (73.43)	8.25 (8.51)	3.95 (4.07)	80[d], 33[e]
17b	95–97 (94–96)[f]	+35	0.85[a]	$C_{20}H_{25}N_3O_3$	67.71 (67.58)	6.95 (7.08)	11.67 (11.82)	
18	245–248 (247–249)[f]	+116	0.30[b]	$C_{20}H_{25}NO_3$	73.45 (73.36)	7.82 (7.69)	4.40 (4.27)	24[e]
19	242–245	+59	0.40[b]	$C_{20}H_{27}NO_3$	73.05 (72.91)	8.20 (8.26)	4.38 (4.24)	87[d], 31[e]
21a	146–148	+61	0.50[b]	$C_{20}H_{28}O_2$	80.08 (79.95)	9.14 (9.39)		
21b	92–96	+63	0.90[a]	$C_{21}H_{27}N_3O_3$	68.42 (68.26)	7.24 (7.36)	11.43 (11.37)	
22	196–198	+48	0.45[b]	$C_{21}H_{27}NO_3$	73.95 (73.86)	8.06 (7.97)	4.35 (4.10)	42[e]
23	208–210	+38	0.40[b]	$C_{21}H_{27}NO_3$	73.75 (73.86)	8.11 (7.97)	4.25 (4.10)	11[e]
24	148–152	+63	0.50[b]	$C_{21}H_{29}NO_3$	73.50 (73.43)	8.65 (8.51)	4.10 (4.07)	82[d], 21[e]
25	101–103	+64	0.60[b]	$C_{20}H_{26}O_2$	80.64 (80.49)	8.95 (8.78)		25[e]

[a] Benzene. [b] Methanol–benzene (5:95). [c] Ref. 26. [d] Prepared. [e] Isolated. [f] Ref. 11.

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