Synthesis and Photoreaction of *D*-Nor-5α-androstan-16-one Acetylhydrazone in the Presence of Oxygen[1)]

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D-Nor-5α-androstan-16-one was prepared *via* seven steps from 16-diazo-3β-hydroxyandrost-5-en-17-one. The major products of the photolysis of its acetylhydrazone in dioxane containing oxygen were the parent ketone and 17-oxa-5α-androstan-16-one, accompanied by low yields of three isomeric lactams: 17-aza-5α-androstan-16-one, 16-aza-5α-androstan-17-one, and 17-aza-5α,13α-androstan-16-one. These three are the same lactams formed in the photo-Beckmann rearrangement of the corresponding oxime, *D*-nor-5α-androstan-16-one oxime. Their formation from the acetylhydrazone may have some mechanistic significance with regard to the path of the formation of lactams in the photolysis of 5α-androstan-17-one acetylhydrazone in the presence of oxygen reported previously. The mass spectrometric fragmentations of fifteen *D*-nor-5α-androstanes with functional groups at their C-16 positions are described.

In the previous paper,[2)] it was reported that *O*-acetylandrosterone acetylhydrazone and its analogue afforded a pair of lactams, 17-oxo-17a-aza-*D*-homosteroid and its 13α-isomer, in 32% yield, upon photolysis in the presence of oxygen; the corresponding hydrazone afforded no lactams and yielded the corresponding azine as the major product. To gain more insight into the pathway of the formation of lactams, we have undertaken the photolysis of *D*-nor-5α-androstan-16-one acetylhydrazone (**20**), a steroidal four-membered ring ketone acetylhydrazone. The study is described in this paper.

Results

Synthesis of D-*Nor-5α-androstan-16-one Hydrazone (18) and Its* N-*Acetyl Derivative* ***20***. The parent ketone, *D*-nor-5α-androstan-16-one (**16**) was synthesized by the method devised by Cava *et al.*,[3)] adopted for steroids first by Mateos,[4)] then by Meinwald *et al.*[5)] and Cava and Moroz,[6)] with some modifications. Thus, a 1 : 5.5 mixture of methyl 3β-hydroxy-*D*-norandrost-5-en-16α- and 16β-carboxylates **2** and **3** were directly obtained by photolysis of 16-diazo-3β-hydroxyandrost-5-en-17-one (**1**)[5)] in THF containing methanol in 89% yield. Recrystallization of the mixture from acetone readily afforded 16β-isomer **3** in 62% yield.

16β-Isomer **3** was hydrogenated in acetic acid in the presence of Adams' platinum catalyst to afford methyl 3β-hydroxy-*D*-nor-5α-androstane-16β-carboxylate (**5**),[7)] mp 141—142 °C, in 76% yield. Jones oxidation of **5** afforded methyl 3-oxo-*D*-nor-5α-androstane-16β-carboxylate (**7**), mp 157—158 °C, in 81% yield. This was subjected to Wolff-Kishner reduction to yield *D*-nor-5α-androstane-16β-carboxylic acid (**9**), mp 226—227 °C, in 90% yield. This sequence of the reaction was repeated on the mixture of methyl 16α- and 16β-carboxylates **2** and **3** to afford a mixture of *D*-nor-5α-androstane-16α-carboxylic acid (**8**) and the 16β-isomer **9**. These isomers could be separated by recrystallization and column chromatography.

Treatment of 16β-isomer **9** with methyllithium afforded *D*-norpregnan-20-one (**11**), mp 125—127 °C, in 90% yield. A similar treatment of 16α-isomer **8**, mp 208—209 °C, gave 16α-*D*-norpregnan-20-one (**10**), mp 135—137 °C, in 68% yield.

Baeyer-Villiger oxidations of 20-ones **10** and **11** afforded *D*-nor-5α-androstan-16α-yl acetate (**12**) and the 16β-isomer (**13**) respectively. Without purification, these were hydrolyzed with methanolic potassium hydroxide to afford 16α-hydroxy-*D*-nor-5α-androstane (**14**), mp 171—173 °C, and the 16β-isomer (**15**), mp 132—135 °C, in 21 and 84% yields.

The Sarret's oxidation of 16β-isomer **15** then afforded 16-oxo-*D*-nor-5α-androstane (**16**), mp 128—129 °C. On the other hand, the Jones oxidation of **15** resulted in the formation of 17-oxa-5α-androstan-16-one (**17**). Its structure was confirmed by spectral data and through its preparation by Baeyer-Villiger oxidation of ketone **16**.

D-Nor-5α-androstan-16-one hydrazone (**18**), mp 116 °C (dec), was readily prepared by the standard method. In this procedure, evaporation of solvent from the reaction mixture caused dimerization of hydrazone **18** to give rise to the corresponding azine (**19**). Hydrazone **18** was therefore isolated by the addition of water to the solution after the formation of the hydrazone was complete. On the basis of its NMR spectrum, hydrazone **18** in solution was concluded to be a mixture of *E* and *Z* isomers although one isomer predominated; as in the case of oximes,[8,9)] it is believed that protons attached to carbon α of the $-C{=}N-NH_2$ group generally resonate at a lower field when the proton is eclipsed by the C=N bond and the NH_2 group *syn* to it. The NMR spectrum of **18** exhibited a multiplet signal at τ 7.14—7.56 assignable to the C-16 methylene protons and a doublet signal centered at τ 6.49 (J=6.9 and 14.3). The combined integral area of these signals corresponded to two protons and the ratio of the area of the signal at the lower field to that of the signal at the higher field was approximately 5 : 1. A double doublet signal at the lower field is assignable to the 15α-H deshielded by the eclipsed $C{=}N-NH_2$ group, assuming that the conformation of the ring D of **18** and the coupling constants of the 15α-H are similar to those of the parent ketone **16**. On the basis of this integral ratio of signals, the ratio of *syn* and *anti* isomers with respect to the C-13–C-16 bond was calculated

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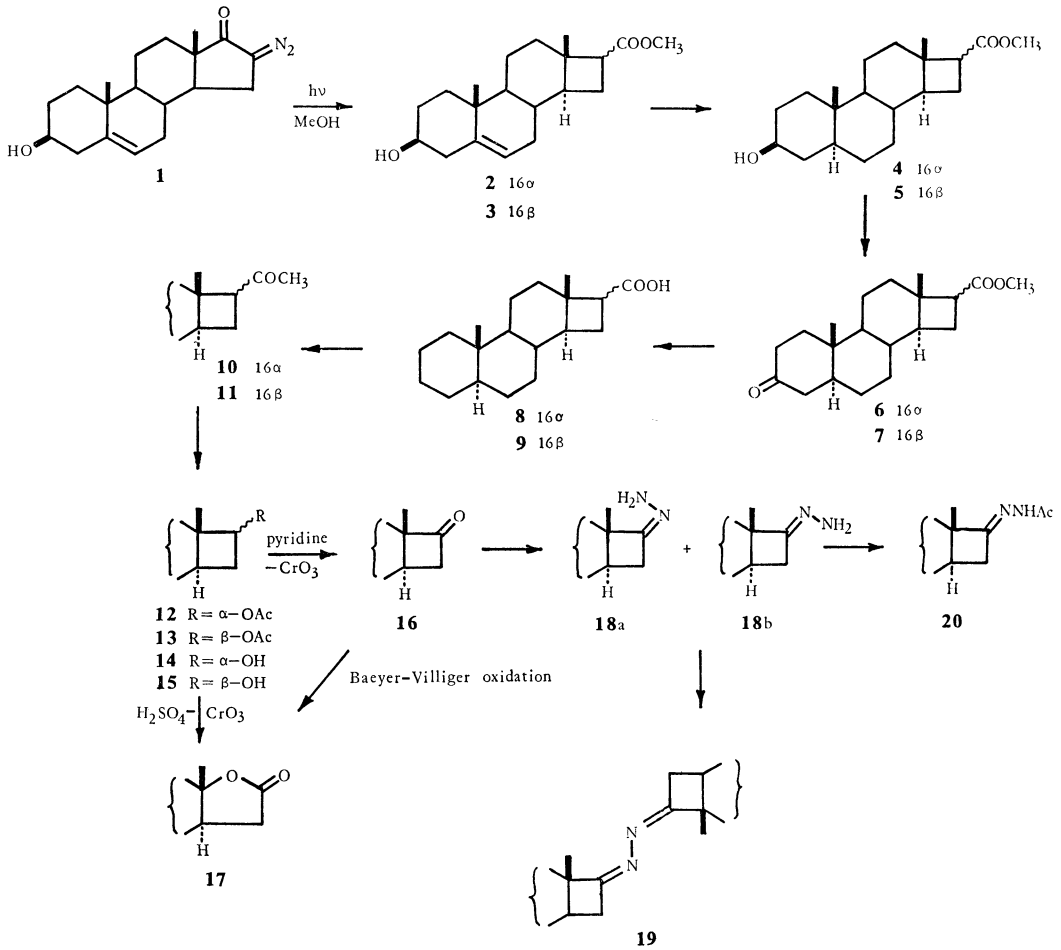


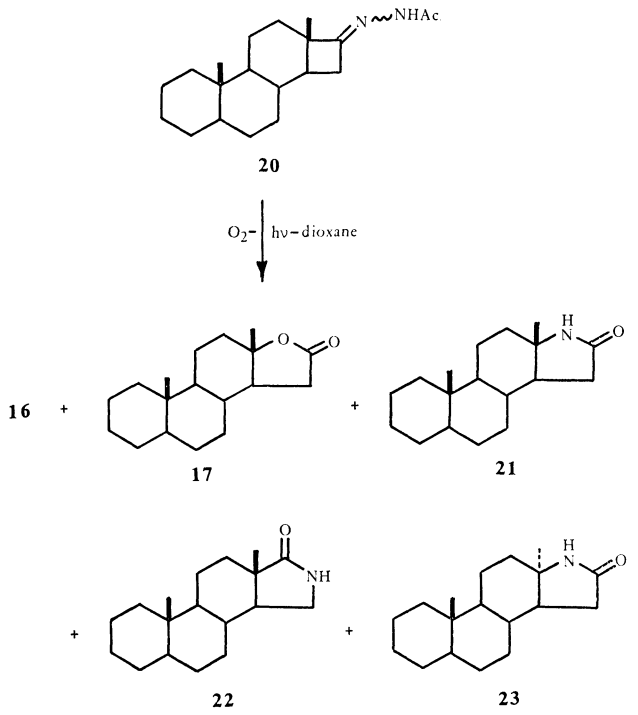
Scheme 1.

to be approximately 2 : 1.

Acetylation of the mixture of hydrazones **18a** and **18b** under controlled conditions afforded a mixture of *N*-acetyl- and *N*-diacetylhydrazones, from which *N*-acetyl derivative (**20**), mp 204—206 °C, was obtained by column chromatography in 61% yield.

Photolysis of Acetylhydrazone 20. The photolysis of acetylhydrazone **20** was carried out under the same procedure as described for the photo-rearrangement of androsterone acetylhydrazone in the previous paper.[2] Thus, acetylhydrazone **20** in dioxane was bubbled with oxygen and was irradiated with a 15-W low pressure mercury arc for 7 h. Extensive preparative TLC of the product mixture afforded lactone **17** (6%), parent ketone **16** (38%), and a mixture of lactams. The separation of the lactam mixture into its components was not possible by preparative TLC. However, the mixture could be separated into its three isomeric lactam components (**21**, **22**, and **23**) by high performance liquid chromatography. The yields of **21**, **22**, and **23** were 0.7, 1.1, and 0.7%. These lactams (**21**, **22**, and **23**) were identified as 17-aza-5α,13α-androstan-16-one by mass, IR, and NMR spectra and by direct comparisons with the authentic specimens obtained by the Beckmann and the Photo-Beckmann rearrangements of *D*-nor-5α-androstan-16-one oxime.[9] Thus, the major products in the present reaction were the parent ketone and 17-oxa-5α-androstan-16-one and the lactams were formed in only low yields. These results are in contrast to those in the photolysis of *O*-acetylandrosterone acetylhydrazone,[2] a fused cyclopentanone analogue of **20** obtained under similar conditions. In the photolysis of *O*-acetylandrosterone acetylhydrazone, 17-oxo-17α-aza-*D*-homosteroid and its 13α-isomer are formed in 32% yield.

In the previous paper,[2] some plausible paths of the formation of the lactams in the photo-reaction of the steroidal 17-one acetylhydrazone in the presence of oxygen were discussed on the basis of various available experimental results, including those of the photolysis of the corresponding hydrazone in the presence of oxygen. Thus, oxygen is required for the formation of the lactams.[2] One of the most probable paths suggested was the one involving intermediate(s) common with those involved in the formation of the lactams in the photorearrangement of the corresponding oxime, since the same lactams are formed in a comparable ratio in photo-reactions of both an oxime and the corresponding acetylhydrazone. The formation of three lactams **21**, **22**, and **23**, despite their low yields, may have a mechanistic significance. Not only two isomeric 17-azalactams, **21** and **23**, resulting from the migration of the more substituted carbon center were formed, but 16-aza-lactam **22** resulting from the migration of the less substituted carbon center was also obtained in the present reaction. These three (**21**, **22**, and **23**) are the



Scheme 2.

very lactams which arise from the photo-Beckmann rearrangement of *D*-nor-5α-androstan-16-one oxime.[9] Thus, the present results reinforce the validity of the pathway suggested in the previous paper.[2] The reason why the lactams are not major products in the fused cyclobutanone acetylhydrazone **20** is not clear at the present stage.

The formation of the parent ketone from the *N*-acetylhydrazones has been discussed in the previous paper.[2] It almost certainly involves the thermal decomposition of hydroperoxides which will be generated by either a radical-induced autoxidation, as was observed for benzaldehyde phenylhydrazones[11] and for some steroidal ketone phenylhydrazones,[12] or by the other pathway proposed for the photo-oxidation of some imines.[13] If the reaction proceeds through the autoxidation pathway, the initiator of the chain reaction can be a radical species generated by irradiation, since we found that no hydroperoxide nor any ketone derived from it was formed from steroidal ketone acetylhydrazone[2] under conditions similar to the formation of hydroperoxide of steroidal ketone phenylhydrazones[12] and that irradiation is necessary for the progress of the reaction. There is another possibility: the formation of the parent ketone by photo-oxidation with singlet oxygen, as was initially observed for acetone phenylhydrazone.[14] However, generation of singlet oxygen by sensitization with the substrate itself is not likely and this path may be excluded.

It is almost certain that 17-oxa-5α-androstan-16-one (**17**) is formed by the reaction of an oxocarbene,[15,16] generated photochemically from the ketone **16**, with molecular oxygen. Careful examination of the reaction mixture showed the absence of the 13-epimer of **17** in the product. This stereospecificity favors a concerted process for the formation of the oxocarbene from the ketone **17**, at least in this instance.[17]

Notes on the Mass Spectra of D-*Nor-5α-androstane Derivatives.* The mass spectra of 16-functionalized *D*-nor-5α-androstanes are of interest since they may give some information on the competition between the decomposition directed by their monofunctionalized cyclobutane ring and the fragmentation of the hydrocarbon framework. In Table 2, the intensities of some significant fragments are summarized. Some of the characteristic features of these results are the following:

a) Isomeric carboxylic acids **8** and **9**, isomeric methyl ketones **10** and **11**, hydrazone **18**, and azine **19** give strong molecular ion peaks.

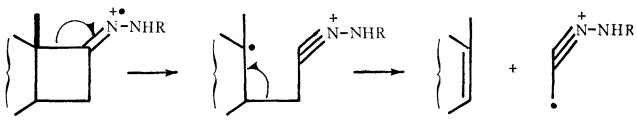
b) In the mass spectra of isomeric carboxylic acids **8** and **9**, isomeric 16-ols **12** and **13**, isomeric acetates **14** and **15**, and ketone **16**, the M^+—ring D peak (*m/e* 218)[18] is either their base peak or the second most intense fragment; a peak at *m/e* 203, which probably arises from ejections of their 10β-CH_3 and ring D from the molecular ion, is prominent. Moreover, in the mass spectra of isomeric carboxylic acids **8** and **9**, isomeric methyl ketones **10** and **11**, and a lactone **17**, a peak at *m/e* 217, arising from cleavage of ring D involving hydrogen rearrangements,[18] is also prominent.

c) The mass spectra of a pair of methyl ketones **10** and **11** exhibit the base peak at *m/e* 230, which is attributable to M^+—Ac—CH_3.

d) No significant difference in their fragmentation and intensity between isomers was found in a pair of isomeric 16-carboxylic acids **8** and **9**, a pair of isomeric methyl ketones **10** and **11**, a pair of 16-ols **12** and **13** and a pair of 16-ol acetates.

e) Analogous to the 3β-methoxy derivative,[19] the base peak in the mass spectrum of lactone **17** was the one attributable to the ejection of 13β-CH_3 from the molecular ion.

f) The mass spectra of hydrazone **18** and acetylhydrazone **20** exhibited the base peaks at *m/e* 56 and 98, respectively, and M^+—ring D as well as M^+—ring D—CH_3 were appreciable only in the hydrazone. Apart from the base peak, no fragment ions which exceed 3% in their intensity were found in the spectrum of acetylhydrazone **20**. The ions at *m/e* 56 and 98 may be generated *via* the pathway depicted in Scheme 3.



Scheme 3.

g) In all the *D*-nor-5α-androstanes **8**—**19** other than **20**, the mass spectra exhibited two very intense peaks at *m/e* 108 and 109 [the base peak in **14**] regardless of their 16-functional group.

Experimental

Instruments and general procedures are described in the preceding paper.[2] All the low resolution mass spectra were taken with a Hitachi RMU-6E spectrometer (ion-source temperature 200° and ionizing voltage 80 eV) in the Faculty of

Table 1. NMR parameters (100 MHz) for the *D*-nor-5α-androstane derivatives
Chemical shifts (τ) and splittings (Hz; in parentheses).

Compound	18-H	19-H	16-H	$COOCH_3$ or $COCH_3$	Others
5	9.04(s)	9.17(s)	7.15 (dd) (7.2; 8.4)	6.35(s)	6.44 br (3-H)
7	8.99(s)	8.95(s)	7.24 (dd) (6.8; 8.6)	6.34(s)	
8	8.79(s)	9.20(s)	7.20 (dd) (1.4; 4.9)	—	
9	8.98(s)	9.20(s)	7.23 (dd) (7.2; 9.0)	—	
10	8.74(s)	9.20(s)	7.03 (dd) (0.7; 5.4)	7.92(s)	
11	9.11(s)	9.20(s)	7.18 (dd) (6.0; 9.6)	7.98(s)	
12	8.93(s)	9.20(s)	5.34 (d) (4.1)	7.90(s)	
13	9.05(s)	9.19(s)	5.51 (dd) (6.0; 8.0)	7.96(s)	
14	9.01(s)	9.18(s)	5.95 (d) (3.9)	—	
15	8.99(s)	9.17(s)	6.23 (dd) (5.5; 7.9)	—	
16	8.85(s)	9.18(s)	—	—	7.44 (15α-H) (dd) (7.8; 13.8) 6.89 (15β-H)(dd) (12.8; 13.8)
17	8.77(s)	9.20(s)	—	—	7.66 (dd) (10.0; 1.1)
18	8.86(s)	9.17(s)	—	—	5.82 (br) (NH_2), 7.14—7.56(m) 1.7H, 6.49 (dd), 0.3H(6.9; 14.3)
19	8.81(s)	9.17(s)	—	—	
20	8.83(s)	9.17(s)	—	7.82(s)	7.21—7.42(m) (15-H), 1.96(s)(NH)

Table 2. Intensity of some important fragements in the mass spectra of *D*-nor-5α-androstane derivatives

Compound	Intensity of fragments (%)								Others
	M^+	M^+-CH_3	M^+—ring-D—CH_3(*m/e* 203)	M^+—ring-D—H (*m/e* 217)	M^+—ring-D (*m/e* 218)	$M^+-Ac-CH_3$ (*m/e* 230)	*m/e* 108	*m/e* 109	
8	13	37	70	37	90	7	65	85	
9	15	38	71	32	100	7	59	13	
10	13	5	29	47	31	96	26	56	
11	12	9	36	59	39	100	47	78	
12	0.2	1	45	7	100	—	51	65	
13	1	5	46	8	100	—	53	65	
14	1	2	34	0	96	—	59	100	
15	4	5	54	5	100	—	60	85	
16	1	1	52	8	100	—	61	76	
17	7	100	9	48	12	—	33	39	
18	10	7	37	5	45	—	66	96	100 (*m/e* 56)
19	9	2	27	9	39	—	21	95	
20	0.2	0.4	0.6	0.3	0.5	—	1	2	100 (*m/e* 98)

Pharmaceutical Sciences, with the exceptions of compounds **18** and **20**, the spectra of which were taken with a Hitachi JMS-D 300 spectrometer. The high resolution mass spectrum of **19** was measured in the Faculty of Agriculture (ion-source temperature 220 °C and ionizing voltage 70 eV).

*Methyl 3β-Hydroxy-*D*-norandrost-3-ene-16α- and 16β-carboxylates, (2 and 3).* 16-Diazo-3β-hydroxyandrost-5-en-17-one (**1**)[7] (18 g) in dry tetrahydrofuran (720 ml) and absolute methanol (180 ml) was irradiated through a Pyrex filter with a 200-W high pressure mercury arc (Ushio UMB-200 H3) for 34 h, while nitrogen gas was bubbled slowly through the mixture. After removal of the solvent, the residue was recrystallized from acetone to yield methyl 3β-hydroxy-*D*-norandrost-5-ene-16β-carboxylate (11.29 g).[7] The residue from the filtrate (6.803 g) was subjected to column chromatography (Wakogel C-200, 90 g). Elutions with benzene afforded a 1 : 1 mixture of 16α- and 16β- carboxylates, (4.972 g).

*Catalytic Hydrogenations of Methyl 3β-Hydroxy-*D*-nor-5α-androstane-16β-carboxylate (3) and a Mixture of 16α- and 16β-Carboxylates (2 and 3).* (*a*): 16β-Carboxylate **3** (11 g), obtained as given above, in acetic acid (100 ml) in the presence

of Adams' platinum catalyst (300 mg) was hydrogenated under an atmosphere of hydrogen until absorption of hydrogen ceased (24 h). After removal of the catalyst and the solvent, the residue was dissolved in dichloromethane. The solution was washed with 5% sodium hydrogencarbonate, saturated sodium chloride solution, and water successively, and dried (Na_2SO_4). Removal of the solvent left a residue which was recrystallized from acetone to yield the hydrogenated product **5** (8.345 g), mp 141—142 °C. Found: C, 75.00; H, 10.19%. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06%. IR (Nujol): 3527 and 3438 (OH), 1736 and 1714 ($COOCH_3$), 1258, 1198, and 1049 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity): 320 (M^+, 10%), 305 (M^+-CH_3, 14), 287 (9), 271 (8), 234 (M^+—ring-D, 39), 219 (28), 216 (M^+—ring-D—H_2O, 49), 201 (M^+—ring-D—H_2O—CH_3, 31), 190 (28), 173 (16), 147 (26), 108 (100), 107 (67), 95 (27), 93 (37), 91 (29), 81 (36), 67 (27), 55 (42), 41 (33), and 28 (87).

(*b*): A mixture of carboxylates **2** and **3** was similarly hydrogenated to afford a mixture of the dihydro derivatives of carboxylates **4** and **5** in 95% yield.

*Oxidations of Methyl 3β-Hydroxy-*D*-nor-5α-androstane-16β-carboxylate (5) and of a Mixture of 16α- and 16β-Carboxylates (4 and 5).* (*a*): To the 3β-ol **5** (8.345 g) in acetone (180 ml), there was added dropwise Jones reagent (20 ml) at 0 °C. After stirring for 1.5 h, a saturated sodium hydrogen sulfite solution was added until the color of the solution became blue. The solution was filtered and the filtrate was partly evaporated. The crystals of ketone **7** (4.622 g) was collected by filtration and the filtrate was extracted with diethyl ether. The diethyl ether solution was worked up in the usual way. The crude product was recrystallized from acetone to yield ketone **7** (1.243 g). The residue from the filtrates of this recrystallization was purified by column chromatography (Wakogel C-200) with benzene to afford a further amount of ketone **7** (0.750 g). The total yield of **7**, mp 157—158 °C, was 81%. Found: C, 75.27; H, 9.76%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%. IR (Nujol): 1731 (6-membered ring ketone), 1710 ($COOCH_3$), 1350, 1224, 1192, 1172, 1047 and 1028 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity) 318 (M^+, 11%), 303 (5), 287 (6), 271 (9), 244 (11), 232 (M^+—ring-D, 50), 218 (75), 203 (6), 175 (11), 149 (17), 109 (27), 95 (18), 93 (18), 91 (15), 81 (25), 67 (17), 55 (36), 41 (25), and 28 (100).

(*b*): A mixture of carboxylates **4** and **5** was similarly oxidized to afford a mixture of ketones **6** and **7** in 70% yield.

Wolff-Kishner Reduction of Methyl D*-Nor-3-oxo-5α-androstane-16β-carboxylate (7) and of a Mixture of 16α- and 16β-Carboxylates (6 and 7).* (*a*): Ketone **7** (5.92 g), hydrazine (16 ml), and potassium hydroxide (16 g) were refluxed in triethylene glycol (160 ml) for 1 h. After removal of the excess of hydrazine and water, the solution was refluxed for 1.5 h. The cooled solution was poured into water–ice (200 ml). The pH of the solution was adjusted by the addition of 6 mol dm^{-3} hydrochloric acid and the solution was stirred for 0.5 h and set aside for 0.5 h. The crystals were collected by filtration and dissolved in dichloromethane. The solution was washed with water and dried (Na_2SO_4). The product was recrystallized from methanol to afford *D*-nor-5α-androstane-16β-carboxylic acid (3.16 g), mp 226—227 °C. (lit,[13] mp 207—209 °C). The residue from the filtrate afforded a further amount of the product (1.668 g) on column chromatography (Wakogel C-200, benzene). The total yield was 90%. Found: C, 78.53; H, 10.50%. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%. IR (Nujol): 3200—2400 (COOH), 1692 (COOH), 1268 and 958 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity): 290 (M^+, 15%), 275 (38), 230 (7), 218 (100), 217 (32), 203 (71), 189 (15), 175 (62), 161 (23), 148 (55), 109 (13), 108 (59), 95 (40), 93 (29), 91 (18), 81 (46), 79 (27), 67 (39), 55 (38), 41 (33), and 28 (72).

(*b*): A mixture of the 16α- and 16β-carboxylates (6.256 g) was similarly subjected to reduction to afford a mixture of 16α- and 16β-carboxylic acids **8** and **9**. This was recrystallized from methanol to afford 16β-carboxylic acid **9** (2.690 g). The residue (2.330 g) from the filtrate was subjected to column chromatography (Wakogel C-200) with benzene to afford three fractions: A, B, and C. The first fraction (0.988 g) was 16α-carboxylic acid **8**. An analytical specimen was obtained by recrystallizing it from methanol, mp 208—209 °C. Found: C, 78.48; H, 10.47%. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%. IR (Nujol): 3600—2400 (COOH), 1695 (COOH), 1418, 1332, 1238, and 943 cm^{-1}; for NMR see Table 1. MS *m/e* (rel intensity); 290 (M^+, 13%), 275 (37), 230 (7), 218 (90), 217 (37), 203 (70), 189 (13), 175 (52), 161 (24), 148 (54), 109 (85), 108 (65), 95 (40), 93 (31), 91 (20), 81 (45), 79 (28), 67 (40), 55 (38), 41 (34), and 28 (100). The second fraction (0.3 g) was a mixture of carboxylic acids **8** and **9**. The third fraction (0.808 g) was a pure 16β-carboxylic acid **9**.

Preparation of D*-Norpregnan-20-one (11).* To 16β-carboxylic acid **9** (3.651 g) in benzene (300 ml) was added, dropwise with stirring, 1 M methyllithium (40 ml) in diethyl ether. The solution was stirred for 1 h at room temperature and was then poured into water–ice. The solution was extracted with diethyl ether and the solution was worked up as usual. After removal of the solvent, the residue was recrystallized from methanol to yield *D*-norpregnan-20-one (**11**) (3.254 g, 90%), mp 125—127 °C. (lit,[18] oil). Found: C, 83.22; H, 11.30%. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18%. IR (Nujol): 1715 (Ac), 1354, 1186, and 1161 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity) 288 (M^+, 12%), 270 (12), 230 (100), 218 (39), 217 (59), 215 (35), 203 (36), 189 (11), 175 (32), 161 (26), 148 (32), 135 (28), 121 (37), 109 (78), 108 (47), 95 (40), 93 (30), 91 (19), 81 (50), 79 (29), 67 (37), 55 (40), 43 (50), and 28 (42).

Preparation of D*-Nor-16α-pregnan-20-one (10).* 16α-Carboxylic acid **8** was similarly transformed into *D*-nor-16α-pregnan-20-one (**10**), mp 135—137 °C, in 68% yield. Found: C, 83.08; H, 11.32%. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18%. IR (Nujol) 1697 (Ac), 1356, 1180, and 1108 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity); 288 (M^+, 13%), 270 (11), 255 (14), 230 (96), 218 (31), 217 (47), 215 (29), 203 (29), 189 (9), 175 (25), 161 (21), 148 (28), 135 (18), 121 (26), 109 (56), 108 (26), 95 (22), 93 (19), 91 (14), 81 (28), 79 (15), 67 (22), 55 (23), 43 (21), 41 (17), and 28 (100).

The Baeyer-Villiger Oxidation of D*-Norpregnan-20-one (11).* *D*-Norpregnan-20-one (**11**) (3.408 g), *m*-chloroperbenzoic acid (3.5 g) and *p*-toluenesulfonic acid (60 mg) in dichloromethane (100 ml) in a vessel covered by an aluminium foil were stirred for 72 h at room temperature. Further amounts of the reagents [*m*-chloroperbenzoic acid (500 mg) and *p*-toluenesulfonic acid (100 mg)] were added after 26 h and 41 h. The excess peracid was decomposed by adding 5% sodium thiosulfite to the solution. The solution was washed first with 10% sodium hydrogencarbonate, then with water, and dried (Na_2SO_4). The crude acetate **13** in methanol (100 ml) was hydrolyzed by adding potassium hydroxide (3.0 g) and by stirring the solution for 2 h at room temperature. The solution was neutralized with 2 mol dm^{-3} hydrochloric acid and extracted with diethyl ether. The solution was worked up as usual. The crude product was recrystallized from acetone to yield *D*-nor-5α-androstan-16β-ol (**15**) (1.619 g), mp 132—135 °C (dec). (lit,[13] mp 103—105 °C). The residue from the filtrate was subjected to column chromatography (Wakogel C-200, benzene) to yield a further amount

of the product (0.993 g). The combined yield was 84%. Found: C, 82.38; H, 11.79%. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52%. IR (Nujol) 3600—3200 (OH), 1191, 1131, and 1062 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity): 262 (M^+, 4%), 247 (5), 233 (8), 299 (5), 218 (100), 203 (54), 175 (51), 161 (27), 148 (52), 135 (17), 122 (17), 109 (85), 108 (60), 95 (30), 93 (25), 91 (13), 81 (30), 67 (30), 55 (32), and 41 (28). The acetate **13** was prepared by the standard method, mp 50—53 °C. Found: C, 78.87; H, 10.95%. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59%. IR (Nujol): 1745 (Ac), 1235 (C–O), and 1042 cm^{-1}. For NMR see Table 1. MS *m/e* (rel intensity) 304 (M^+, 1%), 289 (5), 262 (4), 244 (8), 299 (8), 218 (100), 203 (46), 175 (44), 161 (19), 148 (49), 135 (15), 121 (14), 109 (65), 108 (53), 95 (24), 93 (21), 91 (12), 81 (26), 67 (26), 55 (26), 43 (42), 41 (25), and 28 (55).

Baeyer-Villiger Oxidation of D-*Nor-16α-pregnan-20-one (**10**).* *D*-Nor-16α-pregnen-20-one (800 mg) was similarly oxidized and was hydrolyzed to yield *D*-nor-5α-androstan 16α-ol (**14**) (154 mg). This was recrystallized from acetone to yield a pure 16α-ol **14**, mp 171—173 °C (dec). Found: C, 82.43; H, 11.70%. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52%. IR (Nujol) 3237 (OH), 1174, 1030, 1037, 999 and 976 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity): 262 (M^+, 4%), 247 (5), 233 (6), 299 (5), 218 (48), 203 (66), 175 (62), 161 (30), 148 (66), 135 (18), 122 (20), 109 (100), 108 (70), 95 (35), 93 (29), 91 (16), 81 (36), 67 (36), 55 (37), and 41 (31). The acetate **12** was prepared by the standard method, mp 56—57 °C. Found: C, 77.90; H, 10.51%. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59%. IR (Nujol): 1751 (OAc), 1239 (C–O), 1030, and 1019 cm^{-1}. For NMR see Table; MS *m/e* (rel intensity) 304 (M^+, 0.2%), 289 (1.4), 262 (3), 244 (7), 229 (7), 218 (100), 203 (45), 175 (41), 161 (17), 148 (48), 135 (14), 121 (17), 109 (65), 108 (51), 95 (21), 93 (18), 91 (10) 81 (24), 67 (25), 55 (25), 43 (42), 41 (20), and 28 (34).

Sarret's Oxidation of D-*Nor-5α-androstan-16β-ol (**15**).* *D*-Nor-5α-androstan-16β-ol (**15**) (320 mg) in pyridine (2 ml) was added dropwise to a solution of chromium trioxide (320 mg) in pyridine (2 ml) at room temperature and stirred for 48 h. The solution was then dissolved in dichloromethane and washed first with water, then with 2 mol dm^{-3} -hydrochloric acid, and again with water, and dried (Na_2SO_4). The crude product was purified by column chromatography (Wakogel C-200) with a 1: 1 mixture of hexane and benzene. The first fraction (178 mg) was a crude *D*-nor-5α-androstan-16-one (**16**) which was recrystallized from methanol to afford the pure ketone, mp 128—219 °C. Found: C, 83.15; H, 10.94%. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84%. IR (Nujol): 1775 (4-membered ring ketone), 1143, 1019, 987 and 973 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity) 260 (M^+, 1%), 245 (1), 232 (3), 218 (100), 203 (52), 175 (50), 161 (21), 148 (26), 135 (13), 122 (17), 121 (15), 109 (76), 108 (61), 95 (21), 93 (23), 91 (11), 81 (26), 67 (26), 55 (20), and 41 (22).

The Baeyer-Villiger Oxidation of D-*Nor-5α-androstan-16-one (**16**).* The ketone **16** (50 mg), *m*-chloroperbenzoic acid (100 mg), and *p*-toluenesulfonic acid monohydrate (50 mg) in dichloromethane (5 ml) were stirred for 3.5 h at room temperature. The solution was washed with 5% sodium thiosulfite solution, sodium hydrogencarbonate solution and water successively, and dried (Na_2SO_4). After removal of the solvent, the residue (60 mg) was recrystallized from aq acetone (13 mg) to give lactone **17**, mp 185—187 °C. Found: C, 78.22; H, 10.33%. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21%. IR (Nujol): 1775 (lactonic C=O), 1210, 1161, 1050, 1003, 954, and 910 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity) 276 (M^+, 7%), 261 (100), 232 (34), 217 (48), 149 (60), 109 (33), 108 (39), 95 (35), 81 (36), 67 (34), 55 (36), and 43 (38).

Jones Oxidation of D-*Nor-5α-androstan-16β-ol (**15**).* To *D*-nor-5α-androstan-16β-ol (**15**) (2.612 g) in acetone (50 ml), there was added Jones reagent (5 ml) dropwise at room temperature in the course of 1 h. After the addition of a saturated sodium hydrogensulfite solution until the color of the solution became blue, the solution was extracted with diethyl ether. The residue (2.72 g) was recrystallized from acetone to yield 17-oxa-5α-androstan-16-one (**17**), mp 185—187 °C, (400 mg). Column chromatography of the residue from the filtrate afforded a further amount (769 mg) of the lactone **17.**

Preparation of D-*Nor-5α-androstan-16-one Hydrazone (**18a** and **18b**).* Ketone **16** (500 mg) and hydrazine hydrate (5 ml) in ethanol (15 ml) were refluxed for 1.5 h. After a part of the solvent was removed, water was added to the solution. Crystals of hydrazones **18a** and **18b** were collected by filtration (302 mg). The filtrate afforded a further amount of crystals (214 mg), mp 116 °C (dec). The combined yield was 98%. Found: C, 78.93; H, 11.03; N, 9.93%. Calcd for $C_{18}H_{30}O_2$: C, 78.77; H, 11.02; N, 10.21%. IR (Nujol): 3345 (NH_2), 1162, 1112, 926, 910, and 896 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity): 274 (M^+, 10%), 259 (M^+-CH_3, 7), 258 (M^+-NH_2, 5), 218 (45), 203 (35), 175 (37), 161 (8), 148 (49), 123 (9), 109 (96), 108 (66), 95 (24), 93 (22), 84 (23), 81 (26), 67 (41), 56 (100), 55 (39), and 41 (30). In this procedure, extraction of the hydrazone in aq ethanol with diethyl ether and evaporation of the solvent resulted in the formation of azine **19,** as described in the next procedure.

Preparation of D-*Nor-5α-androstan-16-one Azine (**19**).* Ketone **16** (50 mg) and hydrazine hydrate (0.5 ml) in ethanol (1.5 ml) were refluxed for 2 h. After a part of the solvent was removed by a rotary evaporator, the solution was extracted with diethyl ether. The diethyl ether solution was washed with water and dried (Na_2SO_4). Removal of the solvent left a residue which was recrystallized from methanol to yield azine **19** (5 mg), mp 220 °C (dec). Found: *m/e* 516.4460. Calcd for $C_{36}H_{56}N_2$ M^+ 516.4443. IR (Nujol): 1699 cm^{-1} (C=N–N=C). For NMR see Table. MS *m/e* (rel intensity): 516 (M^+. 8.5%), 501 (17), 314 (78), 258 (29), 218 (39), 203 (27), 175 (30), 148 (37), 109 (95), 95 (56), 93 (53), 91 (42), 81 (71), 79 (61), 67 (88), 55 (69), and 41 (100).

Preparation of D-*Nor-5α-androstan-16-one Acetylhydrazone (**20**)* Hydrazone **18** (516 mg) and acetic anhydride (2.5 ml) in pyridine (10 ml) were stirred for 16 h at room temperature. After the addition of methanol, a part of the solvent was removed. The solution was extracted with diethyl ether. The diethyl ether solution was washed with water, 5% acetic acid, and water again, and dried (Na_2SO_4). Removal of the solvent afforded a residue which was recrystallized from methanol (300 mg). The residue from the filtrate was subjected to column chromatography (Wakogel C-200) with benzene to afford two fractions. The first fraction (35 mg) was found to be *D*-nor-5α-androstan-16-one acetylhydrazone (**20**) by its NMR spectrum. The total yield was 61%. Recrystallization from methanol afforded an analytical specimen, mp 204—206 °C, Found: C, 75.79; H, 10.15; N, 8.73%. Calcd for $C_{20}H_{32}N_2O$: C, 75.90; H, 10.19; N, 8.85%. IR (Nujol): 3207 (NH), 1664 (NHCO), 1558, 1290, and 1079 cm^{-1}. For NMR see Table. MS *m/e* (rel intensity): 317 (M+1, 0.3%) 316 (M^+, 0.2), 301 (0.4), 290 (0.7), 275 (0.5), 258 (0.5), 218 (0.5), 203 (0.6), 175 (0.6), 161 (0.5), 125 (2.4), 112 (1.2), 109 (1.9), 98 (100), 67 (1.9), 55 (1.9), 43 (1.5), and 41 (1.7).

Photo-reaction of D-*Nor-5α-androstan-16-one Acetylhydrazone (**20**) in the Presence of Oxygen.* Acetylhydrazone **20** (350 mg) in dioxane (150 ml) was bubbled with oxygen. The solution

was irradiated with a 15-W low pressure mercury arc for 7 h under an atmosphere of oxygen. After removal of the solvent, the residue was dissolved in dichloromethane. The solution was washed with water and dried (Na_2SO_4). The product was subjected to preparative TLC with a 99: 1 mixture of diethyl ether and methanol to afford ten fractions (A to J) in the order of decreasing polarity. Fractions A (93 mg) and B(36 mg) were a mixture of the parent ketone and 17-oxa-5α-androstan-16-one (**17**). Fraction A was recrystallized from methanol to afford the parent ketone (47 mg). The residue from the filtrate and fraction B were combined and subjected to preparative TLC with benzene (Wako gel B-5F) to afford the parent ketone (61 mg) as the most mobile fraction (B_1). The second mobile fraction B_2 (54 mg) was subjected to preparative TLC with a 50: 1 mixture of benzene and diethyl ether to afford three fractions: B_{2a} (18 mg), B_{2b} (9 mg) and B_{2c} (1 mg). Fractions B_{2a} (5%) was 17-oxa-5α-androstan-16-one **17** and was recrystallized from acetone-water to afford 4 mg of lactone **17**, identical with the specimen prepared by the Baeyer-Villiger oxidation of ketone **16**. The third mobile fraction (171 mg) was subjected to preparative TLC with a 50 : 1 mixture of benzene and diethyl ether to afford five fractions: B_{3a} (7 mg), B_{3b} (6 mg), B_{3c} (6 mg), B_{3d} (21 mg), and B_{3e} (12 mg). The fractions B_{3d} was subjected to HPLC (column, μ-Bondapak CN; diethyl ether as the solvent; detector, JASCO UVIDEC-100; pump, Varian series 4100) to give two fractions. The fraction with a shorter retention time was evaporated to yield crystals of 16-aza-5α-androstan-17-one (**22**) (3.3 mg), mp 259—261 °C, identical with a specimen obtained by the Beckmann rearrangement of *D*-nor 5α-androstan-16-one oxime.[9] (lit,[10] mp 259—260 °C). The fraction (5.1 mg) with a longer retention time was still a mixture and this mixture was again subjected to preparative HPLC (column; μ-Bondapak NH_2, diethyl ether as the solvent). The fraction (2 mg) with the shorter retention time was 17-aza-5α-androstan-16-one (**21**),[10] identical with an authentic specimen obtained by the Beckmann rearrangement.[9] The fraction (2 mg) of a longer retention time was 17-aza-5α,13α-androstan-16-one (**23**), mp 154—157 °C(diethyl ether), identical with a specimen obtained by the photo-Beckmann rearrangement.[9]

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