Photo-induced Transformations. Part 44.[1] Formation of Lactams in the Photolysis of Some Steroidal Acetylhydrazones in the Presence of Oxygen

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Irradiation of 3α-acetoxy-5α-androstan-17-one acetylhydrazone (3) or 3β-acetoxyandrost-5-en-17-one acetylhydrazone (5) in dioxan in the presence of oxygen afforded 17-oxo-17a-aza-D-homosteroid [(6) or (11)] and its 13α-isomer [(7) or (12)], while when oxygen was excluded none of these lactams were formed under otherwise similar conditions. 5α-Cholestan-6-one acetylhydrazone (20) under similar conditions also afforded very low yields of 6-aza-D-homo-5α-cholestan-7-one (21) and 7-aza-B-homo-5α-cholestan-6-one (22) upon photolysis. In contrast with the acetylhydrazones, the corresponding hydrazone (2), upon photolysis in dioxan without the exclusion of oxygen, afforded the corresponding azine (13) without any accompanying lactams [(6) and (7)]. There is a distinct difference in behaviour between the hydrazones and the *N*-acetyl derivatives towards oxygen under irradiation. Although as yet no definite conclusion can be drawn on the mechanism of lactam formation, some plausible paths are discussed.

ALTHOUGH the photochemistry, especially the photoreduction, of imines and related compounds [2] has been studied quite extensively, relatively little attention has been paid to the photo-oxygenation of imines and related compounds.[3,4]

We report a new photo-induced lactam formation which takes place when 17-oxo-steroid acetylhydrazones are irradiated in the presence of oxygen. The properties of the corresponding hydrazones towards light are also compared with those of the *N*-acetyl derivatives.[5] Androsterone hydrazone (2), two steroidal acetylhydrazones [*i.e.* 3α-acetoxy-5α-androstan-17-one acetylhydrazone (3) and 5α-cholestan-6-one acetylhydrazone (20)], and 3β-acetoxyandrost-5-en-17-one diacetylhydrazone (4) were chosen for this study.

RESULTS

The hydrazones (2), (10),[6] and (19) were prepared by the standard method. Although the configuration of the hydrazones (2) and (10) cannot be ascertained either by ^{1}H n.m.r. spectroscopy or by chemical reaction, these groups have probably the *E*-configuration by analogy with the configuration of the corresponding oximes.[7] The *E*-configuration of the hydrazone (19) was determined by the ^{1}H n.m.r. spectrum which showed a double doublet at τ 7.24 (*J* 12.3 and 3.9 Hz). The configuration of the hydroxyimino-group of the corresponding oxime has already been assigned on the basis of the deshielding effect of the hydroxyimino-group on the hydrogen α to it, together with the result of the Beckmann rearrangement.[8] We may safely apply the same rule for alicyclic hydrazones. Thus, the doublet is assigned to the 7β-equatorial hydrogen deshielded by the eclipsing C=N–NH_2 group and the configuration of the NH_2 is as depicted (Scheme 2).

Acetylation of these hydrazones by the standard method afforded the *N*-acetyl derivatives (3), (5), or (20) together with a small amount of the *NN*-diacetyl derivative. The *NN*-diacetyl derivative (4) and its geometrical isomer were the major products when the hydrazone (2) was acetylated in heated pyridine.

The photoreaction of the hydrazone (2) was carried out in dry dioxan in an atmosphere of (a) commercial nitrogen and (b) oxygen, with a 15-W low-pressure mercury arc.

Photolysis of androsterone hydrazone (2) for 7 h in an atmosphere of commercial nitrogen afforded, in addition to recovered starting material, a mixture of at least six compounds. Two major components, androsterone (11%) and a new compound, were isolated by preparative t.l.c. The mass spectrum and the elemental analysis of the new compound were in accord with the molecular formula $C_{38}H_{60}O_2N_2$ and the compound was confirmed to be the corresponding azine (13) by its i.r., u.v., and n.m.r. spectra (Table) and by direct comparison with a sample prepared by ground-state reactions. Thus, androsterone acetate and hydrazine hydrate in ethanol in the presence of hydrochloric acid were heated at *ca.* 60 °C for 30 min to afford the acetoxyandrostanone azine (15) in 66% yield. Hydrolysis of the diacetate (15) with base afforded the azine (13) which was identical with the specimen obtained from the photoreaction. Reaction of the androsterone (1) with hydrazine hydrate under the same conditions resulted only in the formation of the hydrazone (2), which separated as crystals in the course of the reaction.

In order to exclude the possibility that the azine (13) is formed under the experimental conditions in the absence of light, a solution of androsterone hydrazone alone or androsterone hydrazone and androsterone in dioxan was stirred in the dark at room temperature and the solutions were worked up as for the photoreaction. No azine (13) was detected, proving that the azine (13) is only formed photochemically.

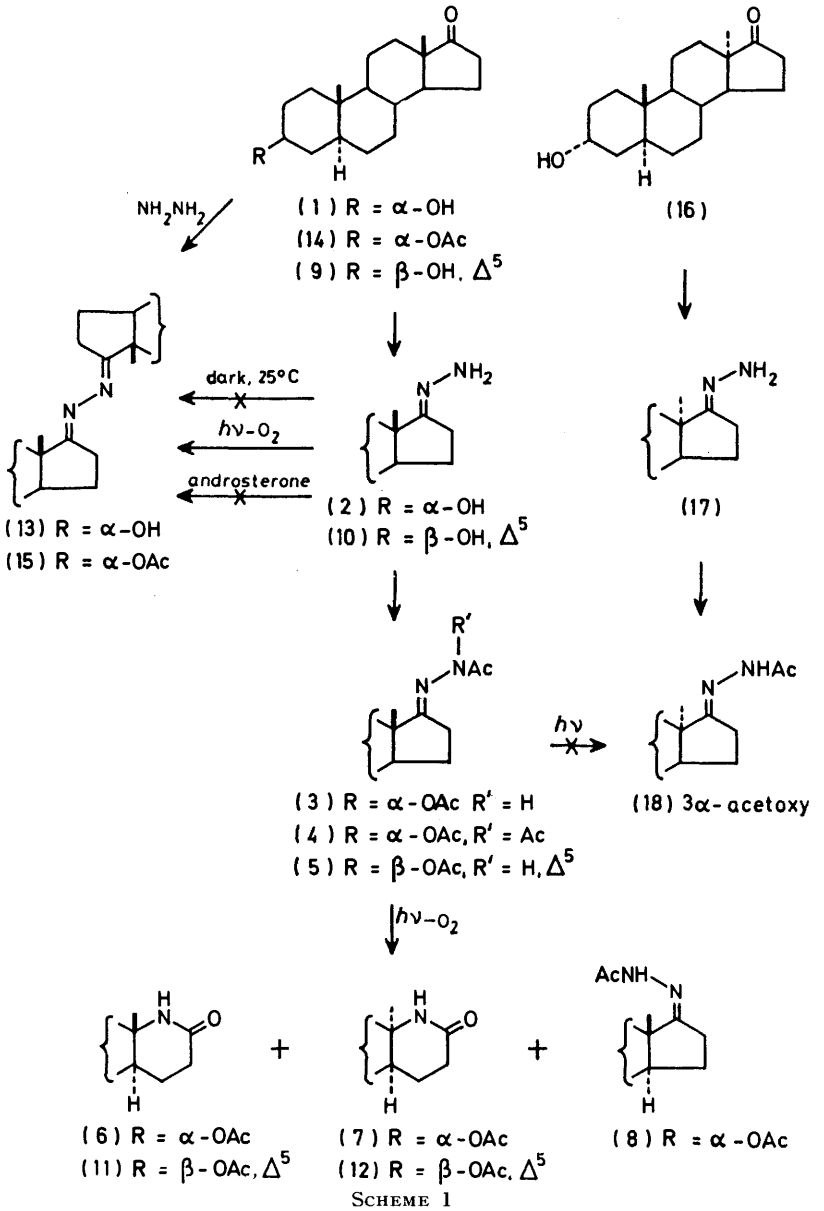
The azine (13) was found to be the exclusive product when the hydrazone (2) in carbon tetrachloride was irradiated with monochromatic light (198 ± 8 nm), generated by a CRM-FA grating spectro-irradiator, for 9 h. The photoreaction of the hydrazone (2) was then carried out in a solution saturated with oxygen. Photolysis for 4 h afforded a mixture from which only androsterone was obtained.

We then turned our attention to the photochemistry of the *N*-acetyl derivative of the hydrazones. The *N*-acetyl derivatives [(3) or (5)] in dioxan were photolysed in an atmosphere of (a) commercial nitrogen, (b) oxygen, and (c) argon with the exclusion of oxygen.

Irradiation of the acetylhydrazone (3) in dioxan in an atmosphere of commercial nitrogen for 28 h using a 15-W low-pressure mercury arc afforded a mixture of products. Preparative t.l.c. afforded a mixture of 3α-acetoxy-5α-androstan-17-one (14) and its 13α-isomer and three other products, two of which were identified as 3α-acetoxy-17a-

aza-D-androstan-17-one (6) and its 13α-isomer (7) by comparison with authentic samples obtained from the photo-Beckmann rearrangement of 3α-acetoxy-5α-androstan-17-one oxime.[7] The third compound exhibited almost the same mass-spectral fragmentation pattern as the starting material. It differed from the isomeric 3α-acetoxy-5α,13α-ketone and its isomer were obtained. However, it was confirmed that no lactams or azines were present in the reaction products.

A similar photolysis was also undertaken with 3α-acetoxy-androst-5-en-17-one acetylhydrazone (5) with almost parallel results. Thus, when the acetylhydrazone (5) was irradiated

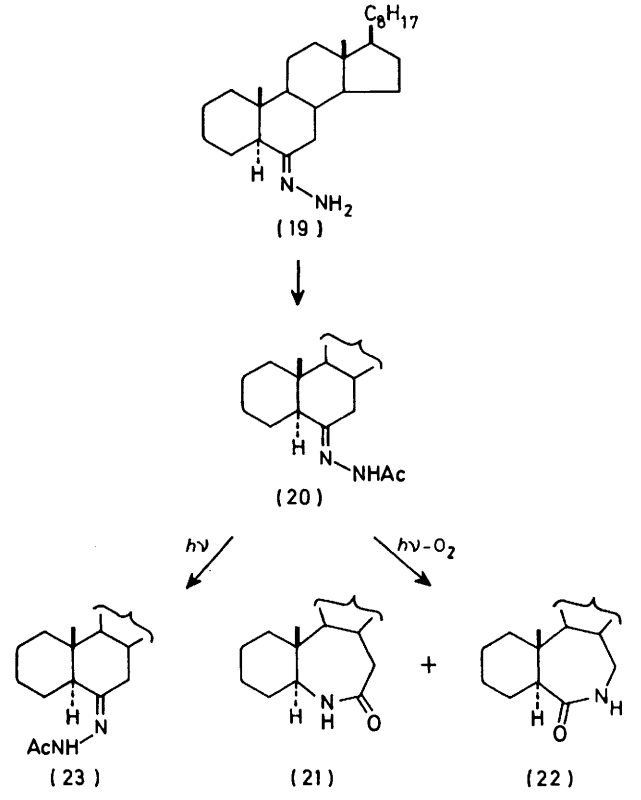


SCHEME 1

androstan-17-one acetylhydrazone (18), prepared from 13α-androsterone (16) *via* the corresponding hydrazone (17). Its n.m.r. and u.v. spectra were virtually identical with those of the starting acetylhydrazone whereas the i.r. spectrum differed. On the basis of these spectral data, the new compound is assigned structure (8), *i.e.* a geometrical isomer of the starting acetylhydrazones with the NHAc group *syn* with respect to the C-13–C-17 bond. When the acetylhydrazone (3) was irradiated in an atmosphere of argon (excluding oxygen), a complex mixture was obtained from which, apart from starting material, only the parent in dioxan saturated with oxygen, two isomeric crystalline compounds containing nitrogen were obtained in 12 and 6% yields. Mass, i.r., and n.m.r. spectra (Table) of these two compounds were in agreement with the D-homo-structures (11) and (12). Compound (11) was identified as the 13β-isomer, prepared previously by Kaufman [9] and by Anliker *et al.*[10] by the Beckmann rearrangement of 3β-acetoxy-androst-5-en-17-one oxime. Compound (12) must therefore be the 13α-isomer. As was observed for the acetylhydrazone (3), virtually no lactams (11) and (12) were obtained when the photolysis was carried out in an atmosphere of commer-

cial argon. The foregoing experiments confirm that oxygen is required for the formation of the lactams.

In order to clarify further the structural requirements for the formation of the lactams, the *NN*-diacetylhydrazone (4) was irradiated in the presence of oxygen when a complex mixture of products was obtained from which only the parent ketone, its 13α-isomer, and diastereoisomeric



SCHEME 2

dioxan dimers [11] were identified. Neither lactam nor azine was present in the products.*

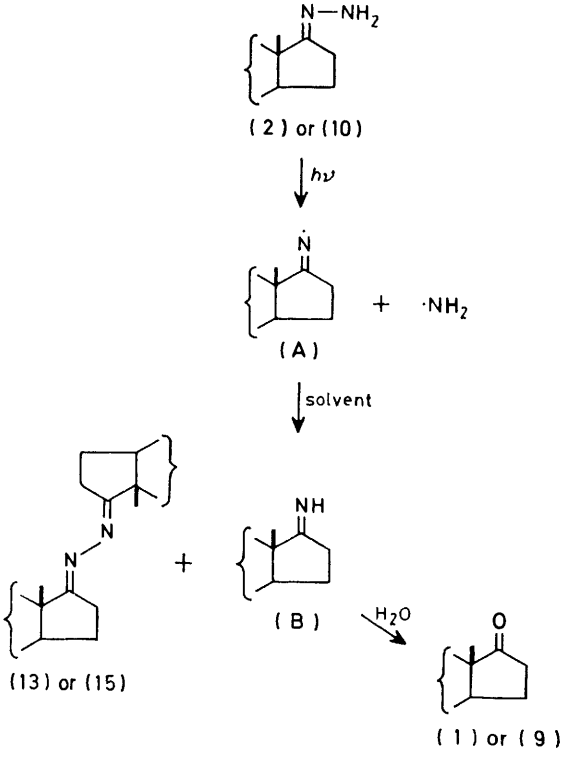
The formation of dioxan dimers contrasts with the results from the photolysis of monoacetyl hydrazones where no dioxan dimers are formed. It seems that a major photoreaction in this case is abstraction of hydrogen from the solvent by excited diacetylhydrazone or by species generated during the photolysis.

Finally, 5α-cholestan-6-one acetylhydrazone (20) was irradiated in an atmosphere of oxygen in order to investigate six-membered-ring ketone derivatives. However, only very low yields of 6-aza-B-homo-5α-cholestan-7-one [12] (21) and 7-aza-B-homo-5α-cholestan-6-one [8] (22) were formed. The photolysis of (20) with exclusion of oxygen was also carried out, but the products were the parent ketone and a new compound. No lactams were formed, as for the androstane series. The new compound was confirmed to be an isomeric 5α-cholestan-6-one acetylhydrazone (23) by its u.v., n.m.r., i.r., and mass spectra.

DISCUSSION

The above experiments confirm that while the photolysis of alicyclic ketone hydrazones in dioxan without the exclusion of oxygen affords the corresponding azine or the parent ketone as the major products, acetylhydrazones under similar conditions undergo a new photo-induced rearrangement to lactams accompanied by the parent ketone. The difference in the products between alicyclic ketone hydrazones and their *N*-acetyl derivatives is significant.

The azine (13) in the photolysis of hydrazone (2) should be formed by homolysis of the N–N bond of the excited hydrazones to form an imino-radical (A) followed by coupling. A competing reaction of the imino-radical (A) could be abstraction of hydrogen from the solvent to form an imine (B) which may ultimately afford the parent ketone through hydrolysis during work-up (Scheme 3). The ketone could well be formed by another pathway when oxygen is present, where the reaction of the hydrazone with oxygen may effectively compete with the N–N bond cleavage. In fact, the hydrazone (2) in an atmosphere of oxygen afforded a high yield of the ketone. However, it is certain that excited hydrazones react rather sluggishly with oxygen,



SCHEME 3

as indicated by the formation of the azine (13) in substantial yield even in the presence of oxygen. It is of interest that the photolysis of benzophenone hydrazone in methanol using a high-pressure mercury arc with a Vycor filter affords only benzophenone and diphenylmethane without any accompanying benzophenone azine.[13]

Although there are insufficient data available to define the mechanism of the lactam formation at the

* The product also contained a considerable amount of ill-defined substances probably resulting from radical chain oligomerization of solvent.

present stage and we need much more experimentation, it is interesting to speculate on some of the plausible mechanisms. A rationalization of the formation of the lactams would be one which involves a three-membered cyclic intermediate [5] analogous to that in the photo-

proceeds as depicted in Scheme 4 although the possibility of the involvement of singlet oxygen cannot entirely be excluded.* In this case, the initiator of the chain reaction can be a radical species generated by irradiation.†

N.m.r. parameters (100 MHz) for the hydrazones, azines, and *N*-acetylhydrazones in $CDCl_3$ solution [τ values; *J* values (Hz) in parentheses]

Compound	18-H	19-H	3-H	6-H	7-H	16-H	N-Ac	O-Ac	NH
(2)	9.17 (s)	9.20 (s)	5.98br (s) ($W_{\frac{1}{2}}$ 8.1)	*a*	*a*	7.83br (t) (7.5)(2H)			5.32br
(3)	9.13 (s)	9.17 (s)	4.99br (s) ($W_{\frac{1}{2}}$ 7.5)	*a*	*a*	*a*	7.77 (s)	7.95 (s)	1.95 (s)
(4)	8.97 (s)	9.17 (s)	4.98br (s) ($W_{\frac{1}{2}}$ 9.0)	*a*	*a*	*a*	7.66 (s)	7.95 (s)	
(5)	9.10 (s)	8.93 (s)	5.39br	4.58br (s)	*a*	*a*	7.75 (s)	7.95 (s)	2.00 (s)
(8)	9.13 (s)	9.17 (s)	5.02br (s) ($W_{\frac{1}{2}}$ 6.9)	*a*	*a*	*a*	7.78 (s)	7.95 (s)	1.94 (s)
(10)	9.10 (s)	8.94 (s)	4.62 (d) (5.4)	5.23br	*a*	*a*			6.47br
(11)	8.82 (s)	8.98 (s)	5.39br	4.61br (s)	*a*	*a*		7.95 (s)	3.17 (s)
(12)	8.72 (s)	9.05 (s)	5.38br	4.62br (s)	*a*	*a*		7.96 (s)	4.24 (s)
(13)	9.15 (s)	9.22 (s)	6.02br (s) ($W_{\frac{1}{2}}$ 7.5)	*a*	*a*	*a*			
(15)	9.14 (s)	9.20 (s)	5.10br (s) ($W_{\frac{1}{2}}$ 7.5)	*a*	*a*	*a*		8.01 (s)	
(17)	9.04 (s)	9.39 (s)	6.00br (s) ($W_{\frac{1}{2}}$ 8.4)	*a*	*a*	*a*			6.60br
(18)	8.98 (s)	9.35 (s)	4.96br (s)	*a*	*a*	*a*	7.73 (s)	7.94 (s)	1.87 (s)
(19)	9.14 (s)	9.20 (s)	5.10br (s) ($W_{\frac{1}{2}}$ 7.5)		7.24 (dd) (12.3; 3.9) (7β-H)	*a*			*a*
(20)	9.35 (s)	9.31 (s)	*a*		7.38 (dd) (12.0; 2.4) (7β-H)	*a*	7.75 (s)		1.30 (s)
(23)	9.35 (s)	9.21 (s)	*a*		*a*	*a*	7.74 (s)		1.39(s)

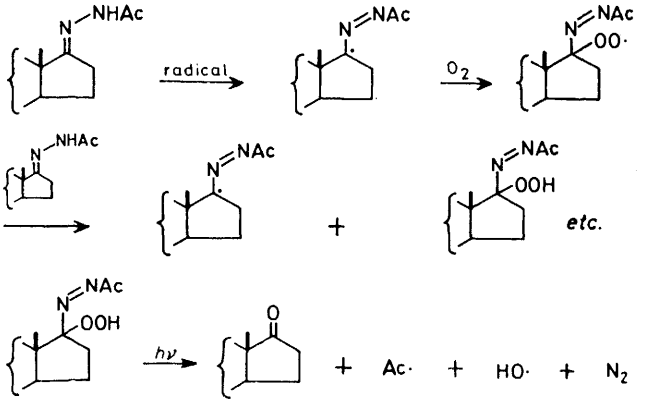
[a] Unassignable.

Beckmann rearrangement.[14] Since it is now found that oxygen participates in the reaction, this mechanism should be excluded. We can envisage a number of other modes for the participation of oxygen in the formation of the lactam. Of these modes, any pathways which involve the imino-radical (A) may be excluded since no lactams are formed from the hydrazone and no azines are formed from the acetylhydrazones. The formation of the parent ketone from the *N*-acetylhydrazones *via* the imino-radical depicted in Scheme 3 may also be excluded for the same reason. The formation of the parent ketone, which seems closely associated with the formation of the lactams, is discussed first. The parent ketones are almost certainly formed by the photo-chemical and/or thermal decomposition of hydroperoxides generated by either a radical-induced autoxidation, as was observed for benzaldehyde phenylhydrazones [15,16] and for some steroidal ketone phenylhydrazones,[17] or by sensitized photo-oxidation as was observed for acetone phenylhydrazone.[3] The latter involves singlet oxygen.[18]

With regard to the possibility of autoxidation, it was found that neither a hydroperoxide nor the ketone (14) was formed from the acetylhydrazones (3) under conditions similar to those in the formation of the hydroperoxide of steroidal ketone phenylhydrazones [17] by autoxidation, and irradiation is needed for the reaction to proceed. Nevertheless, it is probable that the reaction

* The excited substrate or the parent ketone may possibly act as a sensitizer.

It is of interest that whereas aromatic imines, anilides,[4] and substituted hydrazones [3] on photo-oxygenation afford only ketones and amides, the cyclic ketone

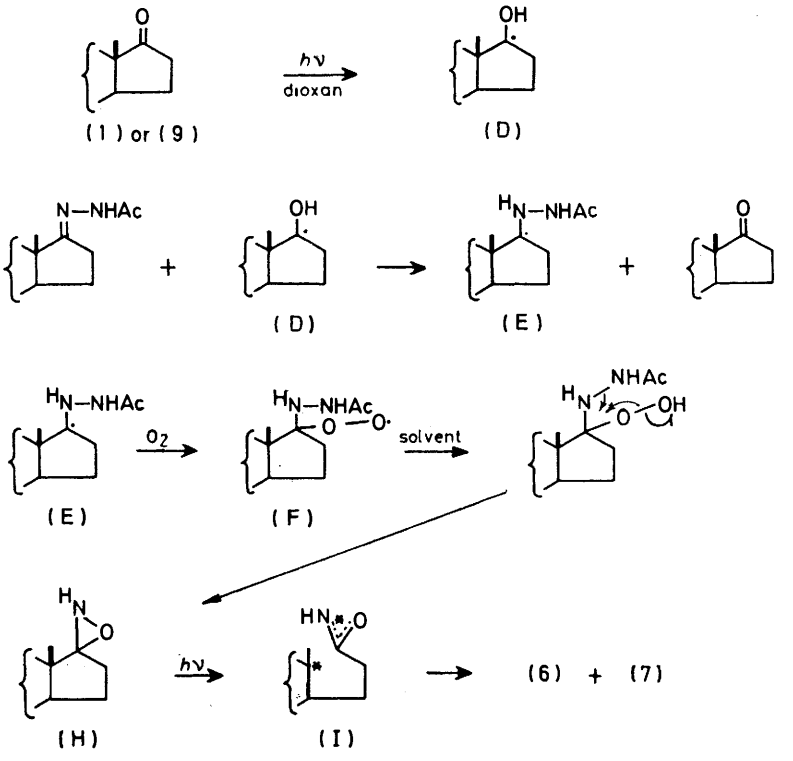


SCHEME 4

acetylhydrazones afford lactams together with the parent ketones. As already noted, a significant feature of the present reaction is that pairs of lactams (16)/(17) and (21)/(22) are formed in the photolyses of the androsterone acetylhydrazone (3) and the cholestanone acetylhydrazone (20), respectively, and identical pairs

† It has been found that hydroperoxides are formed by irradiation of benzophenone acetylhydrazones in carbon tetrachloride containing oxygen, the reaction being induced by chlorine atoms (H. Suginome and T. Uchida, to be published). This chlorine-atom-induced autoxidation may be considered as an aromatic counterpart of the present reaction.

are also formed in the photo-Beckmann rearrangement of the corresponding oximes.[7,8,*] To be more precise, no lactams arising from the migration of the less substituted carbon centre were formed either in the photo-rearrangement of the acetylhydrazone (3) or in the photo-Beckmann rearrangement, whereas lactams arising from migration of both the less and the more substituted carbon centres were formed both in the photo-rearrangement of the cholestanone acetylhydrazone (20) and in the photo-Beckmann rearrangement of the corresponding oxime.



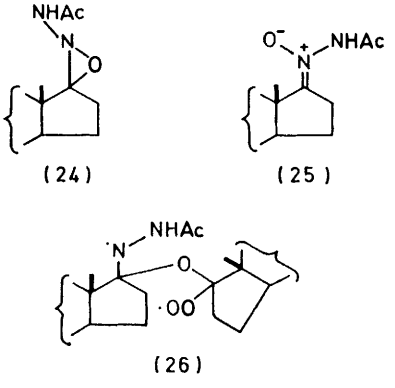
SCHEME 5

This suggests the involvement of a common intermediate in both reactions. A probable reaction pathway is depicted in Scheme 5 in which an excited parent ketone abstracts a hydrogen atom from the solvent to yield a ketyl radical (D). This ketyl radical transfers a hydrogen to the nitrogen centre of the acetylhydrazone to form a radical intermediate (E). In other words, the parent ketone may possibly act as a chemical sensitizer [19] in the present rearrangement. Combination of molecular oxygen with the radical (E) affords a peroxy-radical (F). Further intramolecular rearrangement [20] then affords an oxaziridine intermediate (H) which finally rearranges photochemically to form the two observed lactams *via* another ring-opened species (I).[7] It should be noted that involvement of a species cleaved at the C-13–C-17 bond [*e.g.* (I)] is required in the rearrangement to yield lactam (7). The intermediate (I) could also be formed without the intervention of the oxaziridine (H). The formation of lactam (7) *via* photochemical isomerization to the 13α-acetylhydrazones (8) and (18) through an α-cleavage–recombination sequence is excluded, since no 13α-acetylhydrazone (18) was detected after partial photolysis of the acetylhydrazone (3).†

No azine is formed upon photolysis of the *N*-acetyl-

* In addition to these results, it has recently been found that the three lactams are formed in the photoreaction of D-nor-5α-androstan-17-one acetylhydrazone and the same three lactams in the photo-Beckmann rearrangement of the corresponding oxime (H. Suginome and T. Uchida, *Bull. Chem. Soc. Japan*, in the press).

† The formation of the *N*-substituted oxaziridine (24) followed by its photochemical rearrangement to the lactams may be another possibility. The oxaziridine (24) might be formed either *via* oxidation with $^1O_2$ [21] generated from the parent ketone triplet and oxygen,[22] or by an oxygen-atom transfer from a Bartlett biradical [23] generated from the triplet parent ketone and oxygen. This possibility may be excluded because (a) instead of oxaziridine the nitrone (25) is formed along with *m*-chloroperbenzoic acid and its photolysis does not afford the lactams (6) and (7);[24] and (b) the formation of any species such as (26) would lead to the formation of an azo-species which will readily decompose upon irradiation.



hydrazones and diacetylhydrazones. Fission of the N–N bond in the excited acetylhydrazones is probably overshadowed by a carbon–nitrogen α-fission of N–$COCH_3$, a common photochemical reaction of amides.[25]

EXPERIMENTAL

For instruments used and general procedures see ref. 26 unless stated otherwise. Dioxan was purified by the procedure of Fieser.[27] Mass spectra were taken with a Hitachi RMU-6E spectrometer. An ionizing voltage of 80 eV and ion-source temperature of 200 °C were used for compounds (3), (5), (8), (18), (19), (20), and (23). For compounds (2) and (13) an ionizing voltage of 80 eV and ion-source temperature of 250 °C were used, while for compounds (11) and (12) an ionizing voltage of 70 eV and ion-source temperature of 175 °C were employed. The mass spectra of compound (4) and its isomer were taken with a Hitachi JMS-D 300 spectrometer (ion-source temperature 175 °C, ionizing voltage 70 eV).

Preparation of Androsterone Hydrazone (2).—Androsterone (200 mg) and hydrazine hydrate (3 ml) in ethyl alcohol (5 ml) were refluxed for 1 h. The colourless crystals (183 mg) which separated were filtered off, washed with ethyl alcohol and water, and dried to afford the *hydrazone* (183 mg, 87%), m.p. 230—231 °C (decomp.) (Found: C, 74.6; H, 10.55; N, 9.05. $C_{19}H_{32}N_2O$ requires C, 74.95; H, 10.95; N, 9.2%), $\nu_{max.}$ 3 372 (OH and NH_2), 1 629 (C=N), 1 271, 1 007, and 761 cm^{-1}; $\lambda_{max.}$ (MeOH), 198 nm (ε 3 900); for n.m.r. see Table; *m/e* 304 (M^+, 3%), 79 (16), 72 (19), 67 (19), and 41 (100).

Photoreaction of Androsterone Hydrazone (2).—(a) *In commercial nitrogen.* Androsterone hydrazone (1 g) in dry dioxan (250 ml) was irradiated in a nitrogen atmosphere with a 15-W low-pressure mercury arc for 7 h. After removal of the solvent, the oily residue was subjected to preparative t.l.c. to afford six fractions: A (50 mg), B (109 mg), C (75 mg), D (183 mg), E (117 mg), and F (149 mg), in order of decreasing mobilities. Fraction B was recrystallized from acetone to yield the parent ketone. Fraction D was the recovered hydrazone. Fraction E was recrystallized from acetone to yield the *androsterone azine* (13) (81 mg), m.p. 247—248 °C (Found: C, 79.05; H, 10.2; N, 4.5. $C_{38}H_{60}N_2O_2$ requires C, 79.1; H, 10.5; N, 4.85%); $\lambda_{max.}$ (MeOH) 210 nm (ε 15 000) and 228 nm (ε 3 700); $\nu_{max.}$ 3 343 (OH), 1 656 (C=N–N=C), 1 247, 1 074, and 1 007 cm^{-1}; for n.m.r. see Table; *m/e* 576 (M^+, 36%), 561 (25), 540 (21), 341 (23), 323 (21), 290 (59), 288 (23), 272 (50), 161 (30), 148 (34), 147 (38), 145 (27), 119 (44), 109 (51), 107 (69), 105 (60), 96 (100), 87 (71), 67 (59), 55 (71), and 45 (88).

(b) *In oxygen.* Oxygen was bubbled through a solution of androsterone hydrazone (480 mg) in dry dioxan (200 ml) for 0.5 h and the solution was irradiated for 7 h. Work-up as described in (a) and preparative t.l.c. afforded four fractions (A—D). The most mobile fraction, A (56 mg), was again subjected to preparative t.l.c. with 5 : 1 v/v benzene–diethyl ether as eluant to afford four fractions: A_1 (8 mg), A_2 (6 mg), A_3 (5 mg), and A_4 (5 mg). Fraction A_1 was recrystallized from methanol to afford unidentified crystals (2 mg), m.p. 176—179°, M^+, 328 (100%). Fraction A_4 (5 mg) was the parent ketone. Fraction B (195 mg) was the parent ketone which was recrystallized from methanol–diethyl ether (63 mg). Fraction C (267 mg) was subjected to preparative t.l.c. with 5 : 1 dichloromethane–acetone to afford several fractions of which the most mobile fraction (10 mg) was the parent ketone. Fraction D (220 mg) was also an intractable mixture but the absence of the azine was confirmed.

(c) *In carbon tetrachloride with monochromatic light* (198 ± 8 nm). Argon was bubbled through a solution of androsterone hydrazone (2) (30 mg) in purified carbon tetrachloride (4 ml) in a quartz vessel which was then placed in a chamber of a CRM-FA grating spectro-irradiator equipped with a 2-kW xenon arc and was irradiated. The progress of the reaction was monitored by n.m.r. spectroscopy and by t.l.c. After 9 h, the n.m.r. spectrum showed that the signals of the starting material had been replaced by those of the azine (13). After removal of the solvent, the residue was recrystallized from methanol to yield the azine (13) (6 mg). No other product was formed (t.l.c.).

Androsterone Azine (13).—To androsterone acetate (272 mg) in ethanol (4 ml) was added hydrazine hydrate (0.6 ml) and concentrated hydrochloric acid (0.3 ml) at room temperature. The solution was heated in a water-bath for 0.5 h and was then set aside for 1 h to cool to room temperature. The crystals (572 mg) which separated were filtered off and recrystallized from methanol to afford *3α-acetoxy-5α-androstan-17-one azine* (15) (501 mg), m.p. 238—240 °C (Found: C, 76.2; H, 9.55; N, 4.15. $C_{42}H_{64}N_2O_4$ requires C, 76.35; H, 9.75; N, 4.25%); $\nu_{max.}$ 1 727 (OAc), 1 641 (C=N), 1 259, 1 243, 1 231, 1 023, and 978 cm^{-1}; for n.m.r. see Table; *m/e* 660 (M^+, 15%), 169 (17), 131 (21), 119 (21), and 69 (100). This diacetate (100 mg) and potassium hydroxide (100 mg) were stirred in methanol (5 ml) for 10 h. The solution was extracted with chloroform and the organic layer worked up as usual. The androsterone azine (13) was recrystallized from methanol (70 mg).

Attempted Formation of Androsterone Azine (13) *from Androsterone Hydrazone* (2).—Androsterone hydrazone (180 mg) in methanol (90 ml) was stirred under argon for 6 h at room temperature. After removal of the solvent, t.l.c. indicated the absence of azine (13).

Reaction of Androsterone Hydrazone (2) *and Androsterone in the Dark.*—The hydrazone (105 mg) and androsterone (100 mg) in dioxan (50 ml) were stirred for 5 h at room temperature in the dark. T.l.c. indicated the absence of androsterone azine (13).

3α-Acetoxy-5α-androstan-17-one Acetylhydrazone (3).—Androsterone hydrazone (2) (343 mg) and acetic anhydride (4 ml) in pyridine (6 ml) were stirred for 3 h at 60 °C. After cooling, methanol was added and the solvent partially evaporated off. After the addition of chloroform, the solution was washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue was recrystallized from acetone to yield the *acetylhydrazone* (3), (349 mg), m.p. 218—220 °C (Found: C, 71.0; H, 9.45; N, 7.15. $C_{23}H_{36}N_2O_3$ requires C, 71.1; H, 9.35; N, 7.2%); $\lambda_{max.}$ (MeOH) 231 nm (ε 6 200); $\nu_{max.}$ 3 027 (NH), 1 739 (OAc), 1 674 (NAc), 1 256, 1 246, and 1 016 cm^{-1}; for n.m.r. see Table; *m/e* 338 (M^+, 14%), 153 (81), 111 (71), 43 (67), and 28 (100). The residue from evaporation of the filtrate was subjected to preparative t.l.c. with chloroform–acetone 4 : 1 v/v as eluant to afford two fractions. The more mobile fraction (24 mg) was recrystallized from methanol to afford *3α-acetoxy-5α-androstan-17-one diacetylhydrazone* (4) (12 mg), m.p. 151—153 °C (Found: C, 69.55; H, 8.85; N, 6.3. $C_{25}H_{38}N_2O_4$ requires C, 69.75; H, 8.9; N, 6.5%); $\nu_{max.}$ 1 738, 1 721, 1 698, and 1 660 (NAc and OAc) and 1 249 cm^{-1}; for n.m.r. see Table; *m/e* 430 (M^+, 11%), 388 (51.9), 153 (29.0), 111 (100), 102 (20.2), and 43 (50.9).

Alternative Synthesis of the Diacetylhydrazone (4).—Androsterone hydrazone (2) (89 mg) and acetic anhydride (1.5 ml) in pyridine (2 ml) were refluxed for 7 h. After cooling, methanol was added and the solvent was evaporated off with added benzene. The residue was dissolved in dichloromethane and the solution was washed with 2N-hydrochloric acid and water and dried (Na_2SO_4). Evaporation left a residue (140 mg) which was recrystallized from methanol to yield the *NNO*-triacetyl derivative (4) (30 mg). The residue from evaporation of the filtrate was subjected to preparative t.l.c. (dichloromethane–acetone 5 : 1 v/v as eluant) to afford two fractions. The more mobile fraction (104 mg) was again subjected to preparative t.l.c. (dichloromethane–ethyl acetate 99 : 1 v/v as eluant) to afford two fractions, the more mobile of which (23 mg) was recrystallized from methanol to afford crystals (5 mg), m.p. 160—161 °C, most probably a geometrical isomer of (4) (Found: M^+, 430.286 6. $C_{25}H_{38}N_2O_4$ requires M, 430.283 0); $\nu_{max.}$ 1 734 (OAc), 1 667 (NAc), 1 309, and 1 259 cm^{-1}; τ 9.20 (3 H, s, 19-H), 9.14 (3 H, s, 18-H), 7.99 and 7.95 (each 3 H, s, OAc and NAc), 7.75 (3 H, s, NAc), and 4.97 (1 H, br s, 3β-H); *m/e* 430 (M^+, 6.0%), 388 (48.9), and 111 (100%). The less mobile fraction (42 mg) was the *NNO*-triacetyl derivative (4). The combined yield was 57%.

Photoreaction of the Acetylhydrazone (3).—(a) *In the presence of oxygen.* The acetylhydrazone (3) (432 mg) in dioxan (216 ml) was irradiated with a 15-W low-pressure mercury arc for 28 h whilst commercial nitrogen containing oxygen was slowly bubbled through the solution. After removal of the solvent at room temperature, the residue was subjected to preparative t.l.c. (chloroform–acetone 4 : 1 v/v to afford four fractions (A to D). The most mobile fraction (A) (137 mg) was a mixture of 3α-acetoxy-5α-androstan-17-one (14) and 3α-acetoxy-5α,13α-androstan-17-one (n.m.r.). The second fraction (B) (110 mg) was a mixture of the recovered acetylhydrazone (3) and its isomer (8). The mixture was treated with acetone–diethyl ether to afford the crystalline (Z)-*acetylhydrazone* (8) (12 mg), m.p. 232—234 °C (Found: C, 71.3; H, 9.2; N, 7.2. $C_{23}H_{36}N_2O_3$ requires C, 71.1; H, 9.35; N, 7.2%); $\nu_{max.}$ 3 200 (NH), 1 736 (OAc), 1 678, 1 662 (shoulder) and 1 646 (NHAc), 1 544, 1 230—1 256, 1 128, and 884 cm^{-1}; *m/e* 388 (M^+, 27%), 373 (38), 153 (100), 112 (43), 111 (77), 105 (25), 93 (22), 91 (25), 81 (24), 79 (32), 67 (27), 55 (32), 43 (72), 41 (33), and 28 (33). Fraction C (82 mg) was crude 3α-acetoxy-17a-aza-D-homo-5α,13α-androstan-17-one (7) which was recrystallized from diethyl ether (76 mg), m.p. 193—194°, identical with an authentic specimen.[7] Fraction D (46 mg) was pure 3α-acetoxy-17a-aza-D-homo-5α-androstan-17-one (6).

(b) *In the absence of oxygen.* The acetylhydrazone (3) (500 mg) was dissolved in dioxan (250 ml) through which was bubbled argon, previously passed through Fieser's solution.[24] The solution was irradiated for 24 h under the same conditions as for procedure (a). During irradiation, argon, previously passed through Fieser's solution, was slowly bubbled through the solution. The photolysate was worked up in the usual way. The product was subjected to preparative t.l.c. (chloroform–acetone 5 : 1 v/v) to yield a mixture of 3α-acetoxy-5α-androstan-17-one and its 13α-isomer (252 mg) as the most mobile fraction. The next fraction (86 mg) was recovered starting material. The fractions less mobile than these two products were intractable mixtures and could not be identified. The absence of lactams was confirmed by t.l.c. and by the n.m.r. spectrum of the mixture.

13α-Androsterone Hydrazone (17).—13α-Androsterone (16) (34 mg) and hydrazine hydrate (1.2 ml) in ethanol (2 ml) were refluxed for 6 h. After removal of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with water and dried (Na_2SO_4). Removal of the solvent and recrystallization from ethanol–aqueous ammonia yielded *13α-androsterone hydrazone* (17) (9 mg), m.p. 259—261°, $\nu_{max.}$ 3 367 (OH and NH_2), 1 633 (C=N), 1 280, and 1 005 cm^{-1}; for n.m.r. spectrum see Table; *m/e* 304 (M^+, 6.1%), 289 (13), and 111 (100).

3α-Acetoxy-5α,13α-androstan-17-one Acetylhydrazone (18).—13α-Androsterone hydrazone (130 mg) and acetic anhydride (1 ml) in pyridine (2 ml) were stirred for 48 h at room temperature. After removal of the solvent, the residue was subjected to preparative t.l.c. (chloroform–diethyl ether 4 : 1 v/v) to afford three fractions A, B, and C. Fraction B (26 mg) was crude 3α-acetoxy-5α,13α-androstan-17-one diacetylhydrazone. Fraction C (70 mg) was the *acetylhydrazone* (18) which was recrystallized from methanol (16 mg), m.p. 222—224 °C (Found: C, 71.3; H, 9.3; N, 6.95. $C_{23}H_{36}N_2O_3$ requires C, 71.1; H, 9.35; N, 7.2%); $\nu_{max.}$ 3 190 (NH), 1 739 (OAc), 1 679infl., 1 634 (NHCO), 1 577, and 1 239 cm^{-1}; for n.m.r. see Table; *m/e* 388 (M^+, 15%), 373 (20), 166 (23), 153 (100), 112 (36), 111 (59), 105 (20), 93 (26), 81 (24), 79 (34), 67 (25), 55 (27), 43 (63), 41 (32), and 28 (20).

3β-Hydroxyandrost-5-en-17-one Hydrazone (10).—Androsterone (1 g) and hydrazine hydrate (10 ml) in ethanol (30 ml) were refluxed for 3 h. Work-up as usual and crystallization from aqueous ethanol afforded the hydrazone (10) (1.044 g) as needles, m.p. 240° (decomp.) (lit.,[5] 287 °C after sintering at 210 °C), $\nu_{max.}$ 3 374—3 194 (NH_2) and 1 054 cm^{-1}; for n.m.r. see Table; *m/e* 302 (M^+, 100%), 287 (43), 286 (96), 268 (42), 211 (13), 105 (20), 91 (24), 84 (43), 79 (23), and 41 (21).

3β-Acetoxyandrost-5-en-17-one Acetylhydrazone (5).—The enone hydrazone (10) (1 g) and acetic anhydride (10 ml) in pyridine (20 ml) were stirred for 17 h at room temperature. The *NO*-diacetate was collected by filtration and washed with methanol. After the addition of methanol to the ice-cooled filtrate, the solvent was removed with added benzene. The residue was dissolved in chloroform and the organic layer washed with 2N-hydrochloric acid and then with water and dried (Na_2SO_4). Filtration and evaporation gave the almost pure diacetate. All the diacetate obtained was combined and recrystallized from methanol to afford the *diacetate* (5) (1.09 g), m.p. 227—228 °C (Found: C, 71.25; H, 8.95; N, 7.25. $C_{23}H_{34}N_2O_3$ requires C, 71.45; H, 8.85; N, 7.25%); $\lambda_{max.}$ (MeOH) 231 nm (ε 7 400), $\lambda_{max.}$ (dioxan) 235 nm (ε 12 400); $\nu_{max.}$ 3 200 (NH), 1 735 (OAc), 1 681, 1 663 and 1 650 (NHCO), 1 565, and 1 247 cm^{-1}; for n.m.r. spectrum see Table; *m/e* 386 (M^+, 1%), 326 (86), 311 (25), 252 (36), 153 (96), 112 (42), 111 (38), 105 (32), 91 (38), 79 (26), 66 (23), 55 (30), 43 (100), and 28 (65).

Photoreaction of 3β-Acetoxyandrost-5-en-17-one Acetylhydrazone (5).—(a) *In the presence of oxygen.* Oxygen was bubbled through a solution of the diacetate (5) (500 mg) in dioxan (250 ml) which was then irradiated with a 15-W low-pressure mercury arc for 18 h under oxygen. After removal of the solvent, the crude product was subjected to preparative t.l.c. with 5 : 1 v/v chloroform–acetone as eluant. Seven fractions, A (181 mg), B (54 mg), C (39 mg), D (71 mg), E (53 mg), F (29 mg), and G (50 mg), were obtained in order of decreasing mobility. The most mobile fraction A was recrystallized from methanol to afford the parent ketone (80 mg). The residue from the filtrate and fraction B were

combined and subjected to preparative t.l.c. to afford the parent ketone (106 mg) and 3β-hydroxy-13α-androst-5-en-17-one acetate (11 mg). Fraction D was again purified by preparative t.l.c. to afford 3β-*acetoxy*-17a-*aza*-D-*homo*-13α-*androst*-5-*en*-17-*one* (12) (25 mg) which was recrystallized from methanol–diethyl ether (9 mg), m.p. 220—222 °C (Found: C, 72.8; H, 8.8; N, 3.8. $C_{21}H_{31}NO_3$ requires C, 73.1; H, 9.05; N, 4.05%); $\nu_{max.}$ 3 387 and 3 227 (NH), 1 732 (OAc), 1 638 (NHCO), 1 251, and 1 034 cm^{-1}; for n.m.r. see Table; *m/e* 345 (M^+, 0.1%), 330 ($M^+ - CH_3$, 8), 285 (90), 270 (100), and 105 (16). Fraction E was the 13β-isomer (11). After recrystallization from acetone it had m.p. 306—307 °C (lit.,[9,10] 295—298 °C); $\nu_{max.}$ 3 190 and 3 053 (NH), 1 735 (OAc), 1 691 (NHCO), 1 621, 1 254, and 1 042 cm^{-1}; for n.m.r. see Table; *m/e* 345 (M^+, 0.1%), 330 ($M^+ - CH_3$, 5), 285 (93), 270 (100), and 165 (15).

(b) *In the absence of oxygen.* Argon was bubbled through a solution of the diacetate (5) (500 mg) in dioxan (200 ml) and the solution was irradiated under argon for 18 h. After removal of the solvent, the residue was subjected to preparative t.l.c. (4 : 1 v/v chloroform–acetone) to afford five fractions, A (378 mg), B (63 mg), C (15 mg), D (10 mg), and E (61 mg). The most mobile fraction A was a mixture of the crude parent ketone and the 13α-epimer. The mixture was recrystallized from methanol to yield the parent ketone (232 mg). The residue from the filtrate was subjected to preparative t.l.c. with benzene to afford two fractions. The more mobile fraction (13 mg) was the 13α-epimer and the less mobile (75 mg) was the parent ketone. No lactams were found in fractions B, C, D, and E.

Photoreaction of the Diacetylhydrazone (4) *in the Presence of Oxygen.*—O-Acetylandrosterone diacetylhydrazone (480 mg) in dioxan (240 ml), through which oxygen had been bubbled, was irradiated for 42 h. After removal of the solvent at room temperature, the oily residue (4.8 g) was subjected to column chromatography (Wako gel C-200). Elution with benzene afforded four fractions (A, B, C, and D) and further elution with a 3 : 1 v/v of dichloromethane–diethyl ether afforded two fractions (E and F). Fractions A (41 mg), B (76 mg), and C (112 mg) were a mixture of several ill-defined products containing the parent ketone and its 13α-isomer. Fractions A and B were subjected to preparative t.l.c. with 10 : 1 v/v benzene–diethyl ether as eluant to afford a mixture of the parent ketone and its 13α-isomer (5 mg and 50 mg, respectively). Fraction C (112 mg) was also subjected to preparative t.l.c. (4 : 1 v/v benzene–diethyl ether to afford 8 fractions. The third to the fifth most mobile fractions (17 mg) were a mixture of the ketones. The least mobile fraction (14 mg) was (±)-dioxan dimer [11] identified by its n.m.r. spectrum. Fraction D (234 mg) afforded 8 fractions upon preparative t.l.c. (4 : 1 v/v benzene–diethyl ether). The second most mobile fraction (4 mg) was the parent ketone. The sixth fraction (17 mg) was (±)-dioxan dimer [11] and the seventh fraction (12 mg) was a mixture of *meso*- and (±)-dioxan dimers. The eighth fraction (10 mg) was *meso*-dioxan dimer.[11]

Fractions E (913 mg) and F (546 mg) were oily non-steroidal material, probably oligomers of dioxan [n.m.r. (an intense multiplet signal at τ 5.6—6.8). These fractions were subjected to preparative t.l.c. (4 : 1 v/v diethyl ether–acetone) which proved the absence of lactam (6) or (7).

Combined yields of the parent ketone and its 13α-isomer and diastereoisomeric dioxan dimers were 76 (21%) and 53 mg respectively.

5α-*Cholestan*-6-*one Hydrazone* (19).—5α-Cholestan-6-one (18) (520 mg) and hydrazine hydrate (5 ml) in ethanol (15 ml) were refluxed for 0.5 h. Partial removal of the solvent afforded colourless crystals which were collected by filtration and washed with 1 : 1 v/v water–ethanol to afford the *hydrazone* (19) (464 mg), m.p. 90—92 °C (Found: C, 80.9; H, 12.1; N, 6.9. $C_{27}H_{48}N_2$ requires C, 80.95; H, 12.05; N, 7.0%); $\nu_{max.}$ 3 350—3 220 cm^{-1} (NH_2); for n.m.r. spectrum see Table; *m/e* 400 (M^+, 43%), 385 (42), 370 (19), 95 (77), 81 (73), 67 (53), 55 (100), 43 (82), and 41 (80).

5α-*Cholestan*-6-*one Acetylhydrazone* (20). —5α-Cholestan-6-one hydrazone (19) (464 mg) and acetic anhydride (5 ml) in pyridine (10 ml) were stirred for 1 h 50 min. After cooling (ice-bath), methanol was added to decompose the excess of acetic anhydride. Pyridine was removed with benzene, the crystalline residue was dissolved in chloroform, and the chloroform solution was neutralized with 2N-hydrochloric acid. The solution was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from methanol to afford the *acetylhydrazone* (20), m.p. 215—217 °C (Found: C, 78.65; H, 11.4; N, 6.35. $C_{29}H_{50}N_2O$ requires C, 78.95; H, 11.5; N, 6.1); $\lambda_{max.}$ (MeOH), 216 nm (ε 6 000) and 234 (6 000), $\lambda_{max.}$ (dioxan) 236 nm (ε 12 900); $\nu_{max.}$ 3 292 (NH) and 1 669 (NHCO); *m/e* 442 (M^+, 16), 427 (54), 109 (37), 95 (57), 81 (50), 67 (55), 55 (100), 43 (100), 41 (88), and 28 (93); for n.m.r. spectrum see Table.

Photoreaction of 5α-*Cholestan*-6-*one Acetylhydrazone* (20). —(a) *In the presence of oxygen.* The *N*-acetate (20) (400 mg) in dioxan (200 ml) was irradiated for 14 h while oxygen was slowly bubbled through the solution. After removal of the solvent the residue was dissolved in chloroform. The chloroform solution was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was subjected to preparative t.l.c. (3 : 1 v/v chloroform–benzene). Six fractions A (144 mg), B (34 mg), C (18 mg), D (94 mg), E (51 mg), and F (70 mg), were obtained in order of decreasing mobility. Fraction A was recrystallized from methanol to afford 5α-cholestan-6-one (112 mg). Fraction D (94 mg) was again subjected to preparative t.l.c. (3 : 1 v/v chloroform–benzene as eluant). The t.l.c. plates were developed twice. Five fractions D_1 (4 mg), D_2 (8 mg), D_3 (12 mg), D_4 (12 mg), and D_5 (54 mg) were obtained in order of decreasing mobility. Fractions D_2 (8 mg, 2%) and D_3 (12 mg, 3%) were crude 7-aza-B-homo-5α-cholestan-6-one (22) and 6-aza-B-homo-5α-cholestan-7-one (21) (n.m.r.).

(b) *In the absence of oxygen.* Argon was bubbled through a solution of the *N*-acetate (20) (400 mg) in dioxan (200 ml) and the solution then irradiated for 33 h under argon. After removal of the solvent, the residue was subjected to preparative t.l.c. (4 : 1 v/v chloroform–diethyl ether as eluant) to afford five fractions A (137 mg), B (91 mg), C (37 mg), D (66 mg), and E (141 mg). The most mobile fraction A was the nearly pure 6-one. The second most mobile fraction B and the third fraction C were subjected to preparative t.l.c. (4 : 1 v/v chloroform–diethyl ether). Fractions B and C each afforded two further fractions. The more mobile fractions from both fractions B and C were combined to afford the crude recovered *N*-acetate (20) (45 mg) which was recrystallized from methanol to afford pure *N*-acetate (17 mg). The less mobile fractions from fractions B and C were also combined (35 mg) and recrystallized from methanol to afford the isomeric (*Z*)-*N*-acetate (23) (5 mg), m.p. 148—150 °C; $\lambda_{max.}$ (MeOH) 219 nm (ε 11 300) and 232 (11 500); $\lambda_{max.}$ (dioxan 235 nm (13 200), *m/e* 442 (M^+

26), 427 (46), 387 (60), **368** (21), 109 (23), 95 (56), 81 (52), 67 (43), 55 (88), 43 (100), 41 (88), and 28 (34); for n.m.r. spectrum see Table. The R_F value of fraction D (66 mg) was similar to those of the lactams. However, the absence of the lactams was confirmed by the n.m.r. spectrum.

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