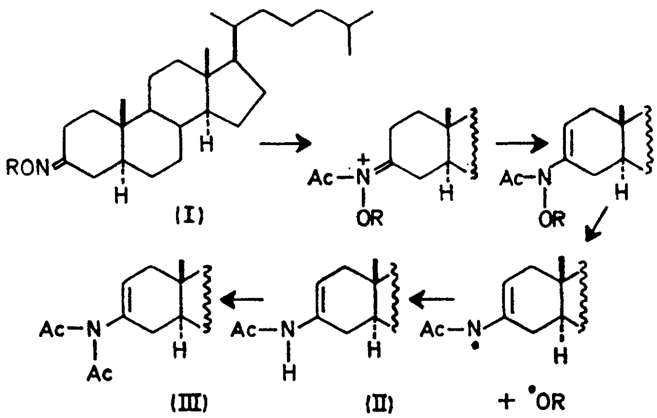
A Simple Synthesis of Enamides from Ketoximes

By **Robin B. Boar,*** **James F. McGhie,** and **Mick Robinson,** Department of Chemistry, Chelsea College, London SW3 6LX
Derek H. R. Barton,* **David C. Horwell,** and **Robert V. Stick,** Department of Chemistry, Imperial College, London SW7 2AY

Ketoximes are converted into enimides [as (III)] in excellent yield by refluxing acetic anhydride in pyridine. Use of alumina chromatography during work-up affords the corresponding enamides [as (II)]. The latter are also prepared by reducing oxime acetates in the presence of acetic anhydride with reagents such as chromium(II). The generality of these reactions is established. Enamides show limited chemical reactivity in comparison with enamines. A particular exception is their efficient α-acetoxylation by reagents such as lead tetra-acetate. Attention is directed to the preparation and use of titanium(III) acetate.

WE describe a new and apparently general reaction of ketoximes which results in their conversion in excellent yield into enamides. Enamides are a relatively little studied class of compounds,[1-5] a reflection of the fact that no convenient general method of synthesis has hitherto been available.

In an initial experiment, 5α-cholestan-3-one oxime (I; R = H) in acetic anhydride and pyridine was heated under reflux until neither starting material nor oxime acetate remained (t.l.c.) (10 h). The solution was evaporated to dryness and the black tarry residue was partitioned between ether and sodium carbonate solution. Despite initial appearances † further processing including chromatography on alumina then yielded 3-acetylamino-5α-cholest-2-ene (II) in 93% yield. The structure of the product was evident from spectral data and from its hydrolysis by acid to 5α-cholestan-3-one. The ^{1}H n.m.r. spectrum of the enamide (II) suggested that it was contaminated by *ca.* 10% of the Δ^3-isomer.[6] Under similar conditions the oxime acetate (I; R = Ac), the oxime benzoate (I; R = PhCO), and the oxime ethers (I; R = Me or $PhCH_2$) gave an identical product with similar efficiency, although in the cases of the oxime ethers longer reaction times were required. Alternatively, pyridine could be replaced by other bases, or even omitted (see Table).



SCHEME

When the crude reaction product was purified by either direct crystallisation or chromatography on silica gel, a new product, the enimide (III) was obtained. The

† Black solutions are characteristically obtained during prolonged refluxing of acetic anhydride with organic bases.

[1] H. Ruschig, W. Fritsch, J. Schmidt-Thomé, and W. Haede, *Chem. Ber.*, 1955, **88**, 883; 1963, **96**, 68.

[2] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 1956, **21**, 520; J. Furukawa, A. Onishi, and T. Tsuruta, *ibid.*, 1958, **23**, 672; S. Nakanishi, *J. Medicin. Chem.*, 1964, **7**, 108; F. Eiden and B. S. Nagar, *Arch. Pharm.*, 1964, **297**, 367 and references therein; Y. H. Suen and H. B. Kagan, *Bull. Soc. Chim. France*, 1965, 1460 and references therein.

[3] D. Ben-Ishai and R. Giger, *Tetrahedron Letters*, 1965, 4523; H. Böhme and G. Berg, *Chem. Ber.*, 1966, **99**, 2127; J. P. Chupp and E. R. Weiss, *J. Org. Chem.*, 1968, **33**, 2357; W. L. Salo and H. G. Fletcher, *ibid.*, 1969, **34**, 3189; P. Kurtz and H. Disselnkotter, *Annalen*, 1972, **764**, 69.

[4] N. S. Crossley, C. Djerassi, and M. A. Kielczewski, *J. Chem. Soc.*, 1965, 6253.

[5] S. Julia and G. Bourgery, *Compt. rend.*, 1967, **264C**, 333.

[6] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 161 *et seq.*; S. K. Malhotra, D. F. Moakley, and F. Johnson, *Chem. Comm.*, 1967, 448.

enimide (III) and the enamide (II) could be quantitatively interconverted by use on the one hand of acetic anhydride and pyridine, and on the other of sodium methoxide or chromatography on alumina. With succinic anhydride and pyridine 5α-cholestan-3-one oxime was converted

A tentative radical mechanism of N–O bond cleavage consistent with the above facts is shown in the Scheme. When the reaction with the oxime acetate (I; R = Ac) was conducted at 100°, the enamide (II) was detected as an intermediate.

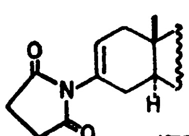
Reductive acylation of oximes

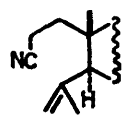
Starting material	Reagent	Temp.	Time (h)	Chromatography on alumina?	Product(s)	Yield (%)
5α-Cholestan-3-one oxime (I; R = H)	Ac_2O–pyridine	Reflux	10	√	Enamide (II)	93
	Ac_2O–Me_2N·CHO–$Cr(OAc)_2$	50°	20	—		74
	Ac_2O	Reflux	30	√		71
5α-Cholestan-3-one *O*-acetyloxime (I; R = Ac)*	Ac_2O–pyridine	Reflux	10	√		92
	Ac_2O–collidine	Reflux	8	√		92
	Ac_2O–Et_3N	Reflux	25	√		90
5α-Cholestan-3-one *O*-benzoyloxime (I; R = Bz) †	Ac_2O–pyridine	Reflux	17	√		89
5α-Cholestan-3-one *O*-benzyloxime (I; R = $PhCH_2$)	Ac_2O–pyridine	Reflux	96	√		92
5α-Cholestan-3-one *O*-methyloxime (I; R = Me) [a]	Ac_2O–pyridine	Reflux	48	√	Enamide (II) + starting material	56 38
5α-Cholestan-3-one oxime (I; R = H)	$(CH_2·CO)_2O$–pyridine	Reflux	48	√	Enimide (IV)	68
Cyclohexanone oxime	Ac_2O–pyridine	Reflux	48	√	Enamide (X; R = H)	65
Cyclohexanone oxime or *O*-acetyloxime	Ac_2O–Me_2N·CHO–$Cr(OAc)_2$	Room temp.	20	—		82
	Ac_2O–Me_2N·CHO–$Ti(OAc)_3$	Room temp.	5	—		80
5α-Lanost-8-en-3-one oxime	Ac_2O–pyridine	Reflux	40	√	3-Acetylamino-5α-lanosta-2,8-diene	76
	Ac_2O–Me_2N·CHO–$Cr(OAc)_2$	50°	70	—		64
3β-Acetoxypregn-5-en-20-one oxime	Ac_2O–pyridine	Reflux	40	√	3β-Acetoxy-20-acetylamino-pregna-5,17(20)-diene [b]	89
	Ac_2O–$Cr(OAc)_2$ or $Ti(OAc)_3$	60°	30	—	3β-Acetoxy-20-acetylaminopregna-5,17-(20)-diene and oxime acetate	20 65
	$(CH_2·CO)_2O$–pyridine	Reflux	50	—	3β-Acetoxy-20-succinimido-pregna-5,17(20)-diene	52
Cholest-4-en-3-one oxime [c]	Ac_2O–pyridine	Reflux	24	√	3-Acetylamino-cholesta-3,5-diene	87
Cholestane-3,6-dione dioxime [d]	Ac_2O–pyridine	Reflux	48	√	3,6-Bis(acetylamino)-cholesta-3,5-diene	28 ‡
Butan-2-one oxime	Ac_2O–Me_2N·CHO–$Cr(OAc)_2$	Room temp.	25	—	(*E*)- and (*Z*)-2-Acetylaminobut-2-ene (8·5 : 1·5)	66
Isophorone(3,5,5-trimethylcyclohex-2-en-one) oxime [e]			17	√	Dienamides (VI)—(VIII) (1 : 3·5 : 5·5)	70
2-Methylcyclohexanone oxime			18	—	Enamide (XIII) Enamide (XIV)	38 26
2,2-Dimethylcyclohexanone oxime [f]		80°	50	—	Enamide (XIII; R = Me)	57
3β-Acetoxy-25,26,27-trinor-5α-lanost-8-en-24-al oxime	Ac_2O–pyridine	Reflux	10	—	3β-Acetoxy-25,26,27-trinor-5α-lanost-8-en-24-onitrile	92

* M.p. 115—117°, $[\alpha]_D$ + 27°. † M.p. 141—143°, $[\alpha]_D$ + 30°. ‡ Insolubility and high chromatographic polarity precluded efficient isolation of the product.

[a] H. M. Fales and T. Luukkainen, *Analyt. Chem.*, 1965, **37**, 955; H. Hjeds, *Acta Chem. Scand.*, 1965, **19**, 1764. [b] D. H. R. Barton, R. B. Boar, J. F. McGhie, and M. Robinson, following paper. [c] C. W. Shoppee, G. Kruger, and R. N. Mirrington, *J. Chem. Soc.*, 1962, 1050. [d] L. Ruzicka, W. Bosshard, W. H. Fischer, and H. Wirz, *Helv. Chim. Acta*, 1936, **19**, 1147. [e] R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, 1952, **17**, 823. [f] F. G. Fischer and K. Wunderlich, *Ber.*, 1941, **74**, 1544.

into the enimide (IV), which was stable to chromatography on alumina.


(IV)


(V)

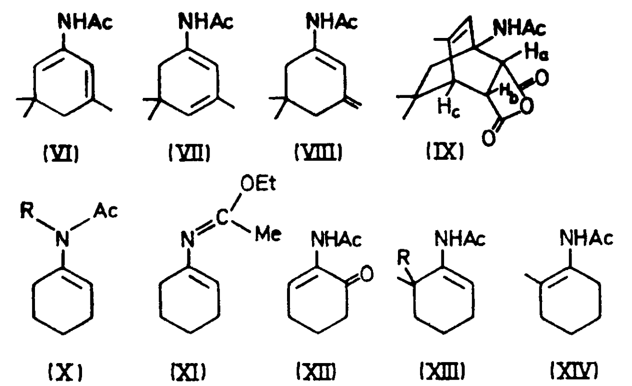
Reduction of ketoximes or their acetates by reagents such as chromium(II), vanadium(II), or titanium(III) yields imines, and this fact has been developed into a mild and efficient method for the regeneration of ketones from their oximes.[7] We now report that similar reduc-

[7] E. J. Corey and J. E. Richman, *J. Amer. Chem. Soc.*, 1970, **92**, 5276; G. H. Timms and E. Wildsmith, *Tetrahedron Letters*, 1971, 195.

tions carried out in the presence of acetic anhydride provide an alternative method for the conversion of oximes into enamides (see Table). Under the reaction conditions the enamides are not further acetylated to enimides. Enamides have been previously prepared by the reaction of *pre-formed* imines with acetic anhydride.[1] Aesthetic considerations apart, we consider acetic anhydride in pyridine to be the reagent of choice for the reductive acetylation of ketoximes.

The experiments outlined in the Table establish the generality of this new reaction. Even with sterically hindered substrates the reaction proceeds well, although more drastic conditions are needed. With acetic anhydride in pyridine as the reagent there was evidence in some cases for the formation of small amounts of seco-nitrile [*e.g.* (V) from 5α-lanost-8-en-3-one oxime] *via* 'abnormal' Beckmann rearrangement.[8] In no case were products attributable to normal Beckmann re-arrangement or Wolff–Semmler aromatisation [9] detected. As expected, similar treatment of an aldoxime simply afforded the corresponding nitrile.

In cases where the formation of isomeric enamides was possible, there was substantial correlation with the product distribution observed for the corresponding enamines (see Table and ref. 10). Thus isophorone oxime afforded the dienamides (VI)—(VIII) in the ratios 1 : 3·5 : 5·5, strikingly similar to those observed for the corresponding dienamines.[11] Despite these ratios, treatment of the dienamide mixture with maleic anhydride gave the *endo*-adduct (IX) in 63% yield,[12] showing that the dienamides too [13] can readily equilibrate.



We next investigated the behaviour of enamides with some of the reagents which make the enamine such an important functional group.[10] In many cases the enamide did not react, and from the few positive reactions it was evident that the nitrogen lone pair was largely delocalised within the amide portion of the molecule. Thus, 1-acetylaminocyclohexene reacted with alkyl halides only after prior anion formation with sodium hydride, and then the product was exclusively the *N*-alkyl enamide (X). The same substrate with triethyl-oxonium tetrafluoroborate afforded the imino-ether (XI), a reaction typical of amides.[14,15]

Oxidation of 1-acetylaminocyclohexene with selenium dioxide in refluxing dioxan gave the enone (XII) in 39% yield. The structure of the product was confirmed by hydrolysis to cyclohexane-1,2-dione, identified as the bis-(2,4-dinitrophenylhydrazone). Similar oxidation of the enamide (XIII; R = H) afforded the allylic alcohol (XIII; R = OH) (19%).

As would be expected, the enimides proved even less reactive than their enamide counterparts. Thus, 3-diacetylamino-5α-cholest-2-ene (III) was unaffected by peroxy-acids, ozone, and lead tetra-acetate, whereas in each case the corresponding enamide (II) gave 2α-acetoxy-5α-cholestan-3-one in good yield.

A convenient preparation of titanium(III) acetate is described in the Experimental section. This reagent is a more powerful reductant than chromium(II) acetate and should find more extensive use.

EXPERIMENTAL

Unless otherwise stated, n.m.r. data are for deuterio-chloroform solutions with tetramethylsilane as internal reference. I.r. spectra are of Nujol mulls, and u.v. spectra of solutions in ethanol. Rotations are of solutions in chloroform with *c* 0·5.

Typical Procedure for Acetic Anhydride–Pyridine and Related Reactions.—Cholestanone oxime (200 mg) in dry pyridine (15 ml) and reagent grade acetic anhydride (10 ml) was refluxed under nitrogen until no oxime acetate could be detected by t.l.c. (10 h). The solvent was removed under reduced pressure, the residual black tar was taken up in ether (100 ml), and N-sodium carbonate solution (50 ml) was added. The mixture was shaken, then filtered through a Celite pad, which was washed thoroughly with ether. The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The product in benzene (5 ml) was chromatographed on silica gel. Elution with benzene afforded *3-diacetylamino-5α-cholest-2-ene* (III), which crystallised as needles from methanol (220 mg, 94%), m.p. 145—146°, $[\alpha]_D$ +55°, $\nu_{max.}$ 1715, 1695, 1280, 1240, and 1215 cm^{-1}, τ 4·45 and 4·70 (total 1H, each br s, 2-H and 4-H of 2-ene and 3-ene, respectively), 7·66 (6H, s, NAc_2), 9·15 (3H, s, 19-H_3), and 9·32 (3H, s, 18-H_3), M^+ 469 (Found: C, 79·4; H, 10·7; N, 2·8. $C_{31}H_{51}NO_2$ requires C, 79·3; H, 10·9; N, 3·0%). Alternatively, the reaction product in benzene (5 ml) was adsorbed on a column of alumina and left for 1 h. Elution with benzene–ether (85 : 15 v/v) then afforded 3-acetylamino-5α-cholest-2-ene (II) (202 mg, 93%), m.p. (from methanol) 200—202° (lit.,[4,5] 215 or 188°), $[\alpha]_D$ +66° (lit.,[4,5] +68 or +92°), $\nu_{max.}$ 3285, 3200, 3070, 1670, and 1570 cm^{-1}, $\lambda_{max.}$ 232 nm (ε 8300), τ 3·7br (1H, s, NH), 4·12 and 4·32 (total 1H, each br s, 2-H and 4-H of 2-ene and 3-ene, respectively), 8·01 (3H, s, Ac), 9·22 (3H, s plus shoulder,

[8] G. P. Moss and S. A. Nicolaides, *Chem. Comm.*, 1969, 1077.
[9] R. T. Conley and S. Ghosh, 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley, Chichester, 1971, vol. 4, p. 197 *et seq.*
[10] 'Enamines: Synthesis, Structure and Reactions,' ed. A. G. Cook, Dekker, London, 1969.
[11] N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (*B*), 1969, 293.
[12] Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, 1970, **92**, 6548.
[13] A. J. Birch and E. G. Hutchinson, *J.C.S. Perkin I*, 1973, 1757.
[14] M. Meerwein, P. Borrer, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, 1956, **89**, 2060.
[15] R. F. Borch, *Tetrahedron Letters*, 1968, 61.

19-H_3 of 2 isomers), and 9·33 (3H, s, 18-H_3), M^+ 427 (Found: C, 81·5; H, 11·4; N, 3·15. Calc. for $C_{29}H_{49}NO$: C, 81·4; H, 11·5; N, 3·3%). Identical material was also obtained from the various other experiments outlined in the Table.

The following compounds were also prepared by the above method (see Table for general directions): *3-diacetylamino-5α-lanosta-2,8-diene*, m.p. (from methanol) 133—135°, $[\alpha]_D$ +129°, $\nu_{max.}$ 1705, 1270, 1230, and 1215 cm^{-1}, τ 4·4 (1H, m, 2-H) and 7·61 and 7·65 [each 3H, s, NAc_2, restricted rotation of C(3)–N bond] (Found: C, 80·2; H, 10·8; N, 2·65. $C_{34}H_{55}NO_2$ requires C, 80·1; H, 10·9; N, 2·75%); *3-acetylamino-5α-lanosta-2,8-diene*, m.p. (from methanol) 154—156°, $[\alpha]_D$ +153°, $\nu_{max.}$ 3330, 3180, 1665, and 1510 cm^{-1}, τ 3·56br (1H, s, NH), 3·96 and 4·53 [0·6H and 0·4H, respectively, each br s, 2-H, restricted rotation of C(3)–N bond], and 7·93 (3H, s, NHAc) (Found: C, 82·05; H, 11·3; N, 2·9. $C_{32}H_{53}NO$ requires C, 82·2; H, 11·4; N, 3·0%); *3-diacetylaminocholesta-3,5-diene*, m.p. (from methanol) 143—145°, $[\alpha]_D$ −103°, $\nu_{max.}$ 1720, 1695, 1280, 1240, and 1225 cm^{-1}, $\lambda_{max.}$ 240 nm (ε 19,400), τ 4·15br (1H, s), 4·50br (1H, s), 7·65 (6H, s, NAc_2), 8·99 (3H, s, 19-H_3), and 9·29 (3H, s, 18-H_3) (Found: C, 79·6; H, 10·7; N, 2·9. $C_{31}H_{49}NO_2$ requires C, 79·6; H, 10·6; N, 3·0%); *3-acetylaminocholesta-3,5-diene*, m.p. (from methanol) 226—229°, $[\alpha]_D$ −120°, $\nu_{max.}$ 3270, 1670, 1630, and 1560 cm^{-1}, $\lambda_{max.}$ 271 nm (ε 20,000), τ 3·6br (2H, s, NH and 4-H), 4·64br (1H, s, 6-H), 7·98 (3H, s, Ac), 9·03 (3H, s, 19-H_3), and 9·30 (3H, s, 18-H_3) (Found: C, 81·7; H, 10·9; N, 3·25. $C_{29}H_{47}NO$ requires C, 81·8; H, 11·1; N, 3·3%); *3,6-bis(acetylamino)cholesta-3,5-diene*, m.p. (from methanol) 247—249°, $[\alpha]_D$ −71°, $\nu_{max.}$ 3250, 3180, and 1670 cm^{-1}, $\lambda_{max.}$ 281 nm (ε 10,400) (Found: C, 76·5; H, 10·4; N, 5·4. $C_{31}H_{50}N_2O_2$ requires C, 77·1; H, 10·4; N, 5·8%); 3β-acetoxy-25,26,27-trinor-5α-lanost-8-en-24-onitrile, m.p. (from methanol) 189—191°, $[\alpha]_D$ +67°, $\nu_{max.}$ 2240, 1730, and 1240 cm^{-1}, τ 5·5 (1H, t, 3α-H) and 8·0 (3H, s, OAc).

3-Succinimido-5α-cholest-2-ene (IV).—Cholestanone oxime (400 mg) and succinic anhydride (1·5 g) in dry pyridine (50 ml) were refluxed for 48 h. Work-up as above, with chromatography on silica gel, gave the *succinimido-derivative* (IV) (320 mg, 68%), m.p. (from chloroform–methanol) 217—218°, $[\alpha]_D$ +57°, $\nu_{max.}$ 1710 and 1205 cm^{-1}, τ 4·4br (1H, s, 2-H), 7·3 (4H, s, CO·CH_2·CH_2·CO), 9·13 (3H, s, 19-H_3), and 9·32 (3H, s, 18-H_3) (Found: C, 79·6; H, 10·45; N, 2·95. $C_{31}H_{49}NO_2$ requires C, 79·6; H, 10·6; N, 3·0%).

Similarly prepared, *3β-acetoxy-20-succinimidopregna-5,17(20)-diene* had m.p. (from methanol) >300°, $[\alpha]_D$ −61°, $\nu_{max.}$ 1725, 1710, 1260, and 1195 cm^{-1}, τ 4·6br (1H, s, 6-H), 5·4 (1H, m, 3α-H), 7·31 (4H, s, CO·CH_2·CH_2·CO), and 8·02 (3H, s, 21-H_3) (Found: C, 73·8; H, 8·8; N, 3·1. $C_{27}H_{37}NO_4$ requires C, 73·8; H, 8·5; N, 3·2%).

Typical Procedure for Chromium(II) *Acetate Reactions*.—Cyclohexanone oxime (2·27 g) in dry *NN*-dimethylformamide (10 ml) was stirred under nitrogen and acetic anhydride (10 ml) was added. After 1 h anhydrous chromium(II) acetate [16] (10·2 g) was added. Stirring was continued for 20 h. The solvent was removed under reduced pressure, N-sodium carbonate solution (100 ml) was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated to afford 1-acetylaminocyclohexene (X; R = H) (2·28 g, 82%), m.p. (from light petroleum) 69—69·5° (lit.,[5] 65—66°), $\nu_{max.}$ 3280, 1655, and 1560 cm^{-1}, $\lambda_{max.}$ 228 nm (ε 8300), τ 2·22br (1H, s, NH), 3·95br (1H, s, 2-H), and 7·98 (3H, s, Ac) (Found: C, 69·0; H, 9·3; N, 10·0. Calc. for $C_8H_{13}NO$: C, 69·0; H, 9·4; N, 10·0%). The product was unaffected by prolonged treatment with acetic anhydride in *NN*-dimethylformamide.

In addition to some compounds already described the following compounds were prepared by this method (see Table): *2-acetylaminobut-2-ene*, oil, $\nu_{max.}$ (film) 3300, 1660, and 1550 cm^{-1}, $\lambda_{max.}$ 225 nm (ε 6300), τ 1·97br (1H, s, NH), 4·30 (0·85H, q, *J* 3·5 Hz, 3-H of *E*-isomer), 4·90 (0·15H, q, *J* 3·5 Hz, 3-H of *Z*-isomer), 7·95 and 8·00 (total 3H, each s, Ac of two isomers), and 8·16 and 8·39 (each 3H, m and d, respectively) (Found: C, 63·7; H, 9·5; N, 12·5. $C_6H_{11}NO$ requires C, 63·7; H, 9·8; N, 12·4%); *2-acetylamino-3,3-dimethylcyclohexene* (XIII; R = Me), m.p. (from light petroleum) 74—75°, $\nu_{max.}$ 3250, 1650, and 1520 cm^{-1}, $\lambda_{max.}$ 214 nm (ε 2400), τ 2·91br (1H, s, NH), 3·97br (1H, s, 2-H), 7·94 (3H, s, Ac), and 8·91 (6H, s, 3-Me_2) (Found: C, 72·0; H, 10·1; N, 8·4. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·25; N, 8·4%); *2-acetylamino-3-methylcyclohexene* (XIII; R = H), oil, $\nu_{max.}$ (film) 3280, 1660, and 1555 cm^{-1}, $\lambda_{max.}$ 228 nm (ε 4800), τ 2·36br (1H, s, NH), 3·99 (1H, t, *J* 4 Hz, 2-H), 7·94 (3H, s, Ac), and 8·93 (3H, d, *J* 7 Hz, 3-Me) (Found: C, 70·45; H, 9·75; N, 9·0. $C_9H_{15}NO$ requires C, 70·55; H, 9·9; N, 9·1%); *1-acetylamino-2-methylcyclohexene* (XIV), m.p. (from ethyl acetate–light petroleum) 90—91°, $\nu_{max.}$ 3230, 3180, 1660, and 1555 cm^{-1}, $\lambda_{max.}$ 215 nm (ε 4400), τ 2·71br (1H, s, NH), 7·95 (3H, s, Ac), and 8·38 (3H, s, 2-Me) (Found: C, 70·5; H, 9·8; N, 9·0%); the dienamide mixture (VI)—(VIII), m.p. (from ether–light petroleum after chromatography on alumina) 116—120°, $\nu_{max.}$ 3280, 3190, 3080, 1660, and 1555 cm^{-1}, $\lambda_{max.}$ 272 nm (ε 13,000), τ[11] 2·23br (1H, s, NH), 3·27br (0·55H, s), 3·63br (0·35H, s), 4·13 (0·1H, m), 4·32 (0·1H, s), 4·97 (0·35H, m), 5·22br (0·55H, s), 7·70—8·0 (m), 7·92 (3H, s, Ac), 8·27 (m, vinylic Me), and 9·00 and 9·04 (6H) (Found: C, 73·65; H, 9·5; N, 7·8. Calc. for $C_{11}H_{17}NO$: C, 73·7; H, 9·6; N, 7·8%). This dienamide mixture (359 mg) in benzene (5 ml) was treated with maleic anhydride (216 mg) overnight at room temperature. Chromatography on silica gel then gave *1-acetylamino-5,8,8-trimethylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride* (IX) (258 mg, 63%), m.p. (from ethyl acetate–light petroleum) 240·5—241°, $\nu_{max.}$ 3400, 1830, 1775, 1680, 1540, and 1240 cm^{-1}, τ (C_5D_5N) 1·1br (1H, s, NH), 4·0br (1H, s, vinylic H), 5·32 (1H, d, *J* 9 Hz, H_a), 6·08 and 6·23 (1H, d, of d, $J_{b,c}$ 4 Hz, H_b), 7·37 and 8·69 (2H, AB_q, *J* 13 Hz, CH_2), 7·47 (1H, d, H_c), 7·89 (3H, s, Ac), 8·26 (3H, d, *J* 1·5 Hz, vinylic Me), and 8·96 and 9·18 (6H, d, CMe_2) (Found: C, 64·85; H, 6·7; N, 4·9. $C_{15}H_{19}NO_4$ requires C, 65·0; H, 6·9; N, 5·05%).

Reductive Acetylation of Cyclohexanone Oxime with Titanium(III) *Acetate*.—All operations with titanium(III) acetate should be carried out in an inert atmosphere. Cyclohexanone oxime (1·14 g) in *NN*-dimethylformamide (10 ml) was treated with acetic anhydride (5 ml) at 0° for 1 h. Titanium(III) acetate [prepared by washing and drying the precipitate obtained from adding sodium acetate solution to commercial 30% titanium(III) chloride solution] (7·5 g) was added, and the mixture stirred at room temperature for 5 h. Work up then afforded 1-acetylaminocyclohexene (1·11 g, 80%), m.p. and mixed m.p. 68·5—69·5°.

Hydrolysis of 3-Acetylamino-5α-cholest-2-ene (II).—(*a*) The enamide (II) (200 mg) in methanol (70 ml) containing 2N-hydrochloric acid (10 ml) was refluxed for 1 h. The solution was poured into water and extracted with ether to yield 5α-cholestan-3-one, identical with an authentic sample.

(*b*) The enamide (II) (100 mg) in methanol (50 ml) was

[16] J. R. Hanson, *Synthesis*, 1974, 1.

added to 2,4-dinitrophenylhydrazine (250 mg) and concentrated sulphuric acid (0·5 ml) in methanol (5 ml). An immediate precipitate of 5α-cholestan-3-one 2,4-dinitrophenylhydrazone formed, and was crystallised from chloroform–methanol; m.p. and mixed m.p. with an authentic sample 225—227°.

Acetylation of 3-*Acetylamino*-5α-*cholest*-2-*ene*.—The enamide (II) (50 mg) in pyridine (2·5 ml) and acetic anhydride (1·5 ml) was heated at 100° for 1 h to give the enimide (III), m.p. and mixed m.p. 143—146°.

Partial Hydrolysis of 3-*Diacetylamino*-5α-*cholest*-2-*ene*.—The enimide (III) (200 mg) in methanol (100 ml) was treated with sodium methoxide [sodium (30 mg) in methanol (20 ml)]. After 1 h at room temperature the solution was poured into water to yield the enamide (II) (180 mg), m.p. and mixed m.p. 199—202°. The same reaction was also achieved by chromatography of the enimide on Laporte type 0 alumina.

3-*Benzyloxyimino*-5α-*cholestane* (I; R = $PhCH_2$).—5α-Cholestan-3-one (2 g) and *O*-benzylhydroxylamine hydrochloride (3 g) in pyridine (30 ml) were left at room temperature overnight. The solution was poured into water and extracted with ether to give the *oxime ether* (1·8 g), m.p. (from methanol) 115—117°, $[\alpha]_D$ +31°, τ 2·68 (5H, s, Ph) and 4·93 (2H, s, OCH_2) (Found: C, 82·8; H, 10·7; N, 2·9. $C_{34}H_{53}NO$ requires C, 83·0; H, 10·9; N, 2·85%).

3β-*Acetoxy*-25,26,27-*trinor*-5α-*lanost*-8-*en*-24-*al Oxime*.—3β-Acetoxy-25,26,27-trinor-5α-lanost-8-en-24-al [17] (1 g) and hydroxylamine hydrochloride (500 mg) in pyridine (40 ml) were left at room temperature for 24 h. The solution was poured into water and extracted with ether to afford the *oxime*, which was recrystallised from methanol (yield 600 mg); m.p. 206—208°, $[\alpha]_D$ +57°, $\nu_{max.}$ 3420, 3330, 1710, and 1280 cm^{-1}, τ 2·26 and 3·42 (each 0·5H, t, *J* 6 Hz, CH=N of *E*- and *Z*-isomers), 5·48 (1H, t, 3α-H), and 7·97 (3H, s, OAc) (Found: C, 76·1; H, 10·2; N, 3·1. $C_{29}H_{47}NO_3$ requires C, 76·1; H, 10·35; N, 3·1%).

1-(N-*Methylacetamido*)*cyclohexene* (X; R = Me).—The enamide (X; R = H) (279 mg) in dry ether (5 ml) and methyl iodide (1 ml) was treated at 0° with sodium hydride (53 mg). After 19 h water was added and the mixture extracted with ether to give, after vacuum distillation, the N-*methyl enamide* (250 mg, 83%), an oil, $\nu_{max.}$ (film) 1655 cm^{-1}, $\lambda_{max.}$ 213 nm (ε 5600), τ 4·37br (1H, s, 2-H), 7·02 (3H, s, NMe), and 7·98 (3H, s, Ac) (Found: C, 70·5; H, 9·8; N, 9·3. $C_9H_{15}NO$ requires C, 70·55; H, 9·9; N, 9·1%).

Reaction of 1-*Acetylaminocyclohexene with Triethyloxonium Tetrafluoroborate*.—The enamide (278 mg) and triethyloxonium tetrafluoroborate (1·62 g) in dry dichloromethane (10 ml) were stirred at room temperature for 17 h. The mixture was washed with sodium hydrogen carbonate solution and water, dried, and evaporated to afford, after vacuum distillation, the *imino-ether* (XI) (207 mg, 62%) as an oil, $\nu_{max.}$ (film) 1675 and 1260 cm^{-1}, $\lambda_{max.}$ 213 nm (ε 4300), τ 5·21br (1H, s, 2-H), 5·92 (2H, q, *J* 3·5 Hz, OCH_2), 8·11 (3H, s, N=CMe), and 8·77 (3H, t, $OCH_2{\cdot}CH_3$) (Found: C, 71·6; H, 10·0; N, 8·15. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·25; N, 8·4%).

Oxidation of Enamides with Selenium Dioxide.—(i) 1-Acetylaminocyclohexene (X; R = H) (836 mg) and selenium dioxide (732 mg) in dioxan (30 ml) were refluxed for 22 h. The mixture was filtered, the filtrate evaporated to dryness, and the residue chromatographed on alumina to afford the cyclohexenone (XII) (358 mg, 39%), m.p. (from light petroleum) 60—61° (lit.,[18] 64°), $\nu_{max.}$ 3320, 1660, 1635, and 1525 cm^{-1}, $\lambda_{max.}$ 223 and 269 nm (ε 7000 and 6100), τ 2·03br (1H, s, NH), 2·22 (1H, t, *J* 4 Hz, 3-H), and 7·88 (3H, s, Ac) (Found: C, 62·55; H, 7·2; N, 9·05. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·2; N, 9·1%). Hydrolysis of this product with ethanolic hydrochloric acid gave cyclohexane-1,2-dione, isolated as the bis-2,4-dinitrophenylhydrazone, m.p. 231—233° (lit.,[19] 233—234°) (Found: C, 46·0; H, 3·4; N, 23·8. Calc. for $C_{18}H_{16}N_8O_8$: C, 45·8; H, 3·4; N, 23·7%).

(ii) The enamide (XIII; R = H) (1·23 g) and selenium dioxide (980 mg) in dioxan (40 ml) similarly gave 2-*acetylamino*-1-*methylcyclohex*-2-*enol* (XIII; R = OH) (248 mg, 19%), m.p. (from ethyl acetate–light petroleum) 119—120°, $\nu_{max.}$ 3310, 1655, 1520, and 1115 cm^{-1}, $\lambda_{max.}$ 227 nm (ε 4600), τ 2·21br (1H, s, NH), 4·07 (1H, t, *J* 4 Hz, 3-H), 5·23 (1H, s, OH), 7·91 (3H, s, Ac), and 8·70 (3H, s, Me) (Found: C, 64·2; H, 8·9; N, 8·3. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9; N, 8·3%).

Oxidation of 3-*Acetylamino*-5α-*cholest*-2-*ene* (II).—(i) The enamide (II) (200 mg) in dichloromethane (50 ml) and pyridine (0·5 ml) was treated with a stream of oxygen–ozone for 30 min. The solution was evaporated and the residue in acetic acid treated with zinc dust (1 g). The mixture was refluxed for 30 min, cooled, and filtered to yield 2α-acetoxy-5α-cholestan-3-one (195 mg, 94%), m.p. and mixed m.p.[20] 122—123°.

(ii) The enamide (II) (200 mg) in ether (100 ml) and chloroform (10 ml) was treated with monoperphthalic acid in ether (2 equiv.). After 1 h at 0° the solution was washed with sodium carbonate solution and water, dried, and evaporated. The residue was a mixture of two products (t.l.c.) but either p.l.c. or direct crystallisation gave only 2α-acetoxy-5α-cholestan-3-one (150 mg, 71%), m.p. and mixed m.p. 123—124°.

(iii) The enamide (II) (200 mg) in dry benzene (50 ml) was stirred at room temperature with lead tetra-acetate (200 mg) for 45 min. The mixture was poured into water and then filtered through a pad of Celite. Further processing of the benzene layer including chromatography on silica gel afforded 2α-acetoxy-5α-cholestan-3-one (145 mg, 69%), m.p. and mixed m.p. 122—123°.

The enimide (III) was recovered unchanged after attempted oxidation by the above three methods.

We thank the Schering-Plough Corporation for generous gifts of chemicals.

[4/2529 *Received, 5th Decmeber, 1974*]

[17] D. H. R. Barton, G. Mellows, D. A. Widdowson, and J. J. Wright, *J. Chem. Soc.* (*C*), 1971, 1142.
[18] M. M. Shemyakin, V. I. Maimind, K. M. Ermolaev, and E. M. Bamdas, *Tetrahedron*, 1965, **21**, 2771.
[19] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, 4th edn., p. 784.
[20] H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 1961, 4472.