A New Rearrangement of Ketonic Nitrones; a Convenient Alternative to the Beckmann Rearrangement

By **Derek H. R. Barton,* Michael J. Day, Robert H. Hesse,** and **Maurice M. Pechet,** Research Institute for Medicine and Chemistry, Cambridge, Massachussets 02142, U.S.A.

Ketonic nitrones are smoothly transformed by treatment with toluene-*p*-sulphonyl chloride in pyridine in the presence of some water into *N*-alkyl amides. The regiospecificity, stereospecificity, and mechanism of this new reaction have been investigated. The overall procedure provides a convenient alternative to the Beckmann rearrangement.

REARRANGEMENTS [1] of nitrones under photochemical and thermal conditions, or by electrophilic or basic attack to give imides, oxaziridines, *O*-alkyl oximes, *etc.* are well established processes.

Recently [2] we have described the novel rearrangement of *N*-methyl nitrones with toluene-*p*-sulphonyl chloride in pyridine to give A-aza-A-homo-steroid analogues. We now describe this work in detail as well as its extension to other types of nitrone. The nitrones (Ia)—(Va), (VIIIa), and (Xa) were prepared as stable crystalline compounds from the corresponding ketones and hydroxy-(methyl)ammonium chloride in pyridine. On treatment with toluene-*p*-sulphonyl chloride the nitrones (Ia)—(Va) smoothly gave the lactams (Ib)—(Vb). The constitution of the lactams was apparent from their 240—241 nm (ε 10 700—12 900) u.v. absorption. In contrast, Beckmann rearrangement of oximes [3] derived from Δ^1- or Δ^4-3-ketones gives lactams of type (XIII) which absorb at 218 nm (ε 11 000).

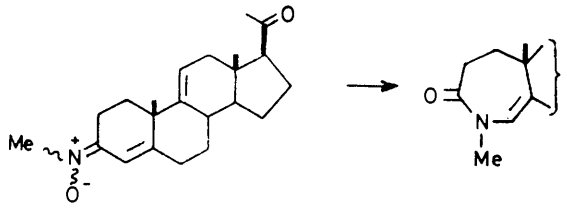
The formation of the lactam (VIIIb) from the nitrone (VIIIa) by rearrangement followed by acetylation was confirmed by comparison with the product of Beckmann rearrangement and methylation of the oxime (IXa).

In contrast to the Beckmann rearrangement,[3] the nitrone rearrangement does not depend on stereochemistry: both *syn*- and *anti*- [for definition see formulae (XIV) and (XV)] isomers give the same lactam. Nitrone stereochemistry was assigned from u.v. spectra and confirmed by lanthanide-induced [Eu(fod)$_3$] shifts in the n.m.r. The *anti*- (XIV) Δ^4-steroid 3-nitrones (IIIa)—(Va) showed $\lambda_{max.}$ 289—290 nm (ε 25 700—27 200) and τ 4.0—4.08 (4-H) and 6.30—6.33 (NMe) and the *syn*- (XV) isomers $\lambda_{max.}$ 294—295 nm (ε 17 600—19 300) and τ 3.23—3.38 (4-H) and 6.32—6.37 (NMe). The u.v. extinction coefficients of cisoid and transoid enones have been found to be proportional to the square of the chromophore length.[4] An estimate from molecular models of b^2/a^2 for *anti*- (XIV) and *syn*- (XV) nitrones of 0.78 was in good agreement with the extinction coefficient ratio of 0.72. Since the nitrone (Va) lacked other functional groups, lanthanide-induced shifts in the n.m.r. gave unequivocal proof of stereochemistry (see Experimental section). If the shift reagent co-ordinates only with the oxygen atom the C-4 proton signal will shift more in the case of the *syn*- (1.0 p.p.m.) than of the *anti*-isomer (0.17 p.p.m.) and the C-2 proton signal more in the case of the *anti*- (1.3 p.p.m.) and less in that of the *syn*- (0.1 p.p.m.) isomer. Recently Weintraub and Tiernan [5] have prepared and assigned the stereochemistry of a number of pairs of steroidal nitrones including those from Δ^4-3-ketones. In contrast to our results they report that the *anti*-isomer (XIV) absorbs at longer wavelength in the u.v. and has the 4-H signal at lower field in the n.m.r. than the *syn*-isomer (XV). We believe that our arguments, based on intensity of u.v. absorption [4] and on n.m.r. shifts, are more reliable.

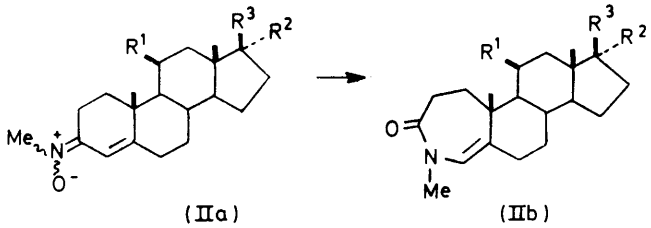
Both *syn*- and *anti*-3-methyliminoandrost-4-en-17β-ol *N*-oxides (IVa) were stable in pyridine but equilibrated slowly in the presence of toluene-*p*-sulphonyl chloride and rapidly with pyridinium chloride, the *anti*-isomer

[1] M. Lamchen, 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1968, vol. 1, p. 1.
[2] D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1971, 945.
[3] C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J. Chem. Soc.*, 1962, 1050; C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, *ibid.*, 1965, 5868; R. H. Mazur, *J. Org. Chem.*, 1963, **28**, 248.
[4] R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403.
[5] P. M. Weintraub and P. L. Tiernan, *J. Org. Chem.*, 1974, **39**, 1061.

being the more stable. Nitrones recovered from incomplete rearrangements were also partially equilibrated.



(Ia) (Ib)



(IIa) (IIb)

R^1 = H, R^2 = OAc, R^3 = Ac

(IIIa) (IIIb)

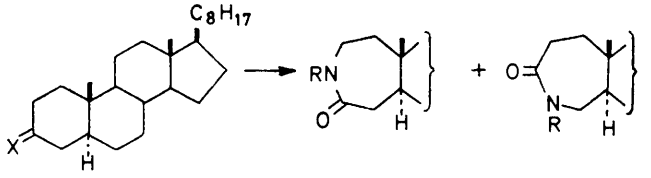
R^1 = OH R^2 = OH, R^3 = CO·CH_2·OH

(IVa) (IVb)

R^1 = R^2 = H, R^3 = OH

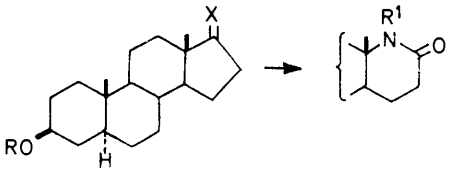
(Va) (Vb)

R^1 = R^2 = H, R^3 = C_8H_{17}



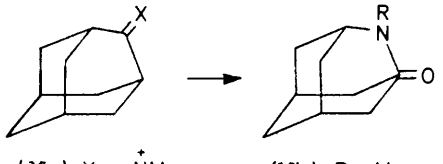
(VIa) X = $\overset{+}{N}$–Me (O$^-$) (VIb) R = Me (VIc) R=Me

(VIIa) X = NOH (VIIb) R = H (VIIc) R= H



(VIIIa) X = $\overset{+}{N}$Me (O$^-$), R = H (VIIIb) R^1=Me, R = Ac

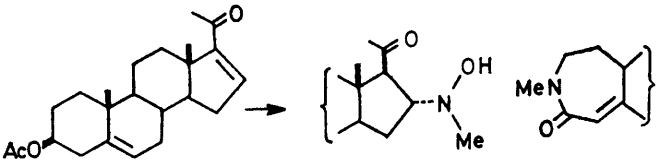
(IXa) X = NOH, R = Ac (IXb) R^1 = H, R = Ac



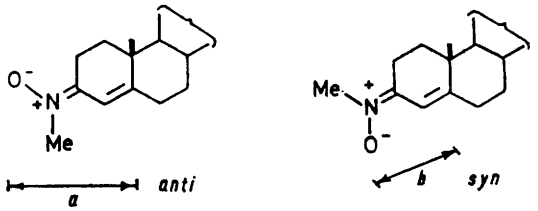
(Xa) X = $\overset{+}{N}$Me (O$^-$) (Xb) R = Me

(XIa) X = NOH (XIb) R = H

Nitrone rearrangement according to Scheme 1 is consistent with lack of steric control, preference for vinyl migration, *syn–anti* equilibration, and increased

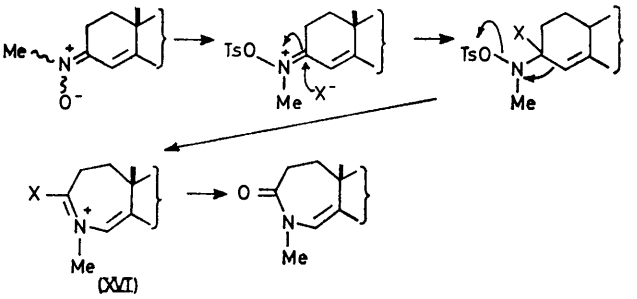


(XIIa) (XIIb) (XIII)



(XIV) (XV)

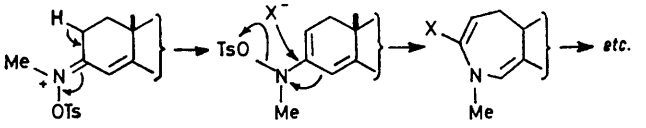
yields on addition of water. The yield of the lactam (IVb) from the nitrone (IVa) rearrangement increased



(X = nucleophile, possibly H_2O)

SCHEME 1

from 32% in anhydrous pyridine to 92% in the presence of 15 mol. equiv. of water. This was attributed to formation of the lactam (IVb) in the presence of water prior to work-up. In the absence of water the intermediate (XVI) would remain and perhaps decompose before work-up. An alternative reaction scheme (Scheme 2) was inconsistent with the rearrangement of 2-



SCHEME 2

methyliminoadamantane *N*-oxide (Xa) giving the lactam (Xb) and with the lack of deuterium incorporation at C-2 when the rearrangement was carried out in the presence of D_2O. That 3-methyliminocholestane *N*-oxide (VIa) gave a 1 : 1 mixture of lactams (VIb and c) argued against a vinylhydroxylamine toluene-*p*-sulphonate intermediate. Such an intermediate would give the

lactam (VIc) as the major product since both thermodynamic and kinetic factors favour the Δ^2-3-hydroxylamine toluene-*p*-sulphonate over the Δ^3-isomer.

The structures of the lactam (Xb) and the lactam mixture (VIb and c) were confirmed by comparison with the products of Beckmann rearrangement of the oximes (XIa) and (VIIa), followed by *N*-methylation. The optical rotation (+18°) of the lactams (VIIb and c) derived from 3-hydroxyiminocholestane (VIIa) indicated a 1 : 1 mixture,[3] thus confirming the ratio for the lactams (VIb and c).

An attempt to prepare 3β-acetoxy-20-methyliminopregna-5,16-diene *N*-oxide from (XIIa) and compare its rearrangement with the Beckmann rearrangement of the corresponding oximes [6] was unsuccessful. Only the hydroxylamine (XIIb) was isolated.

Our ready rearrangement of nitrones provides a direct route to *N*-methyl or *N*-substituted lactams which are less readily available from the Beckmann rearrangement. It has already received an elegant application.[7] Furthermore, the yields obtained, at least in the presence of water, may be superior to those obtained in the Beckmann rearrangement.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. Unless otherwise stated, i.r. spectra were recorded for KBr discs, u.v. spectra for solutions in methanol, n.m.r. spectra for solutions in deuteriochloroform, and optical rotations for solutions in chloroform. Pyridine was of reagent grade unless specified to the contrary.

Preparation and Rearrangement of Steroidal Nitrones.—The ketone (2 mmol) and hydroxy(methyl)ammonium chloride (2.4 mmol) in pyridine (15 ml) were stirred at 20 °C under nitrogen until t.l.c. indicated complete reaction (*ca.* 8 h). Dilution with water, extraction with ethyl acetate, and evaporation gave the crude nitrone, which was purified by p.l.c. and/or recrystallisation.

Toluene-*p*-sulphonyl chloride (1.2 mmol) was added to the nitrone (1 mmol) in pyridine (10 ml) giving immediately a red colouration. After 10 min stirring at 20 °C the *N*-methyl lactam was isolated by dilution with water, extraction with ethyl acetate, evaporation, and p.l.c.

3-*Methyliminopregna*-4,9(11)-*dien*-20-*one* N-*oxide* (Ia) (64%) had m.p. 150—153° (decomp.) (from ethyl acetate–hexane), $[\alpha]_D^{22}$ +182° (*c* 1.0), $\nu_{max.}$ 1 705s, 1 560m, and 1 200s cm^{-1}, $\lambda_{max.}$ 292 nm (ε 26 500), *m/e* 341 (M^+) (Found: C, 77.45; H, 8.85; N, 4.0. $C_{23}H_{31}NO_2$ requires C, 77.35; H, 9.15; N, 4.1%).

N-*Methyl*-3a-*aza*-A-*homopregna*-4,9(11)-*diene*-3,20-*dione* (Ib) (45%) had m.p. 144—145° (from ethyl acetate–hexane), $[\alpha]_D^{21}$ −33° (*c* 0.35), $\nu_{max.}$ 1 705s and 1 645s cm^{-1}, $\lambda_{max.}$ 241 nm (ε 12 900), *m/e* 341 (M^+) (Found: C, 77.25; H, 8.9; N, 4.0. $C_{22}H_{31}NO_2$ requires C, 77.35; H, 9.15; N, 4.1%). 17α-*Acetoxy*-3-*methyliminopregn*-4-*en*-20-*one* N-*oxide* (IIa) (79%) had m.p. 174—179° (decomp.) (from ethyl acetate), $[\alpha]_D^{20}$ +193° (*c* 0.8), $\nu_{max.}$ 1 725s, 1 270s, 1 255s, and 1 200m cm^{-1}, $\lambda_{max.}$ 293—294 nm (ε 21 400), *m/e* 401 (M^+) (Found: C, 70.35; H, 8.65; N, 3.3. $C_{24}H_{35}NO_4$,0.5H_2O requires C, 70.2; H, 8.85; N, 3.4%).

17α-*Acetoxy*-N-*methyl*-3a-*aza*-A-*homopregn*-4-*ene*-3,20-*dione* (IIb) (43%) had m.p. 208—209° (from dichloromethane), $[\alpha]_D^{21}$ −37° (*c* 0.65), $\nu_{max.}$ 1 725s, 1 660s, 1 265s, 1 250s, and 1 210m cm^{-1}, $\lambda_{max.}$ 240 nm (ε 11 300), *m/e* 401 (M^+) (Found: C, 71.95; H, 8.6; N, 3.4. $C_{24}H_{35}NO_4$ requires C, 71.8; H, 8.8; N, 3.5%).

11β,17α,21-*Trihydroxy*-3-*methyliminopregn*-4-*en*-20-*one* N-*oxide* (IIIa) (72%; *syn–anti* mixture separated by p.l.c.) syn-*isomer* had m.p. >300°, $\nu_{max.}$ 3 450s, 3 200s, 1 705s, 1 190s, and 1 170s cm^{-1}, $\lambda_{max.}$ 295 nm (ε 19 300), τ [$CDCl_3$–$(CD_3)_2SO$] 3.30br (1 H, s, 4-H) and 6.37 (3 H, s, NMe), *m/e* 391 (M^+) (Found: C, 67.4; H, 8.5; N, 3.55. $C_{22}H_{33}NO_6$ requires C, 67.5; H, 8.4; N, 3.6%); the anti-*isomer* had m.p. >300°, $\nu_{max.}$ 3 300s, 1 705s, 1 205s, and 1 190s cm^{-1}, $\lambda_{max.}$ 290 nm (ε 27 200), τ [$CDCl_3$–$(CD_3)_2SO$] 4.08br (1 H, s, 4-H) and 6.33 (3 H, s, NMe), *m/e* 391 (M^+) (Found: C, 67.35; H, 8.5; N, 3.5%).

11β,17α,21-*Trihydroxy*-N-*methyl*-3a-*aza*-A-*homopregn*-4-*ene*-3,20-*dione* (IIIb) (70% from *syn* or *anti*) had m.p. 145—148° (from dichloromethane–methanol), $[\alpha]_D^{22}$ +78° (*c* 0.4), $\nu_{max.}$ 3 500m, 3 350m, 1 700m, and 1 640m cm^{-1}, $\lambda_{max.}$ 240 nm (ε 10 700), *m/e* 391 (M^+) (Found: C, 67.4; H, 8.3; N, 3.4. $C_{22}H_{33}NO_6$ requires C, 67.5; H, 8.4; N, 3.6%).

3-*Methyliminoandrost*-4-*en*-17β-*ol* N-*oxide* (IVa) syn-*isomer* (30%) had m.p. 169—170° (decomp.) (from ethyl acetate), $[\alpha]_D^{24}$ +226° (*c* 1.0), $\nu_{max.}$ 3 350m, 3 150m, 1 505w, 1 190m, and 1 170m cm^{-1}, $\lambda_{max.}$ 294 nm (ε 17 600), τ 3.23br (1 H, s, 4-H), 6.33 (3 H, s, NMe), 6.50 (1 H, m, 17α-H), 8.95 (3 H, s, 19-H_3), and 9.22 (3 H, s, 18-H_3), *m/e* 317 (M^+) (Found: C, 75.5; H, 9.85; N, 4.3. $C_{20}H_{31}NO_2$ requires C, 75.65; H, 9.85; N, 4.4%); the anti-*isomer* (49%) had m.p. 211—214.5° (decomp.) (from ethyl acetate), $[\alpha]_D^{24}$ +157° (*c* 1.0), $\nu_{max.}$ 3 250m, 1 605w, 1 215m, and 1 200m cm^{-1}, $\lambda_{max.}$ 289 nm (ε 25 700), τ 4.0br (1 H, s, 4-H), 6.30 (3 H, s, NMe), 6.60 (1 H, m, 17α-H), 8.93 (3 H, s, 19-H_3), and 9.20 (3 H, s, 18-H_3), *m/e* 317 (M^+) (Found: C, 75.5; H, 9.75; N, 4.3%).

The equilibration of *syn*- and *anti*-isomers is summarised in the Table.

Equilibration of 3-methyliminoandrost-4-en-17β-ol *N*-oxides (IVa and b) (estimated by t.l.c. and n.m.r.)

Conditions	Isomer	Extent of isomerisation
Pyridine	*syn*	10% (8 days)
	anti	<5% (8 days)
Pyridine–toluene-*p*-sulphonyl chloride	*syn* [a]	10—15% (20 h), 65% (8 days)
	anti [a]	<5% (20 h), 25—30% (8 days)
	syn [b]	30% (recovered nitrone)
	anti [b]	5% (recovered nitrone)
Pyridine–pyridinium chloride (1% w/w w.r.t. nitrone)		25% (1 h), 60—65% (3 h), 65—70% (20 h)
		10% (1 h), 20% (3 h), 25—30% (20 h)

[a] 1% w/w of toluene-*p*-sulphonyl chloride w.r.t. nitrone. [b] 0.4 equiv. of toluene-*p*-sulphonyl chloride (see general conditions).

17β-*Hydroxy*-N-*methyl*-3a-*aza*-A-*homoandrost*-4-*en*-3-*one* (IVb) [50% from either isomer; when water was present during isomerisation the yield varied: 32% (anhydrous; dried over KOH), 71% (2), 82% (5), 92% (15) (the figures in parentheses indicate mol. equiv. of water)] had m.p. 217—218° (from ethyl acetate), $[\alpha]_D^{16}$ −5° (*c* 0.91), $\nu_{max.}$ 3 450m and 1 635s cm^{-1}, $\lambda_{max.}$ 240 nm (ε 11 600), *m/e* 317 (M^+) (Found: C, 75.6; H, 9.8; N, 4.35. $C_{20}H_{31}NO_2$ requires C, 75.65; H, 9.85; N, 4.4%).

[6] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 1956, **21**, 520.
[7] P. W. Jeffs and G. Molina, *J.C.S. Chem. Comm.*, 1973, 3.

3-*Methyliminocholest*-4-*ene* N-*oxide* (Va) (91%) syn-*isomer* had m.p. 146—149° (decomp.) (from ethyl acetate), $[\alpha]_D^{21}$ +188° (*c* 1.02), $\nu_{max.}$ 1 550m, 1 215s, and 1 090m cm^{-1}, $\lambda_{max.}$ 294 nm (ε 18 800), τ 3.38br (1 H, s, 4-H; *S* * 1.0 p.p.m.) and 6.32 (3 H, s, NMe; *S* 0.75 p.p.m.) (Found: C, 81.05; H, 11.25; N, 3.65. $C_{28}H_{47}NO$ requires C, 81.3; H, 11.45; N, 3.4%); the anti-*isomer* had m.p. 127—131° (decomp.) (from ethyl acetate), $[\alpha]_D^{21}$ +123° (*c* 0.96), $\nu_{max.}$ 1 550m, 1 215s, and 1 200s cm^{-1}, $\lambda_{max.}$ 289 nm (ε 27 000), τ 4.07br (1 H, s, 4-H; *S* 0.17 p.p.m.), 6.31 (3 H, s, NMe, *S* 0.68 p.p.m.) (Found: C, 81.0; H, 11.15; N, 3.4%).

N-*Methyl*-3a-*aza*-A-*homocholest*-4-*en*-3-*one* (Vb) (53% from either isomer) had m.p. 98—98.5° (from ethyl acetate–hexane), $[\alpha]_D^{21}$ −5° (*c* 0.82), $\nu_{max.}$ 1 655s cm^{-1}, $\lambda_{max.}$ 240 nm (ε 11 800) (Found: C, 81.1; H, 11.3; N, 3.4. $C_{28}H_{47}NO$ requires C, 81.3; H, 11.45; N, 3.4%).

3-Methyliminocholestane *N*-oxide (VIa) was too unstable to be characterised and was immediately converted into the lactams (VIb and c). This mixture had m.p. 155—161° (from hexane), $[\alpha]_D^{20}$ +18° (*c* 1.17), $\nu_{max.}$ 1 640s cm^{-1} (Found: C, 81.05; H, 11.65; N, 3.25. Calc. for $C_{28}H_{49}NO$: C, 80.9; H, 11.9; N, 3.35%).

Treatment of 3-hydroxyiminocholestane (VIIa) with thionyl chloride [3] gave a 1 : 1 mixture of 3-aza-A-homocholestan-3a-one (VIIb) and 3a-aza-A-homocholestan-3-one (VIIc) ($[\alpha]_D^{20}$ 18°).[3] Alkylation (n-butyl-lithium–iodomethane) gave the lactams (VIb and c), identical (mixed m.p., $[\alpha]_D$, i.r., and n.m.r.) with the product from the nitrone (VIa).

17-*Methyliminoandrost*-5-*en*-3β-*ol* N-*oxide* (VIIIa) (60%) had m.p. 217—220° (decomp.) (from methanol), $[\alpha]_D^{18}$ −7° (*c* 0.54 in dioxan), $\nu_{max.}$ 3 300m, 1 535w, 1 170m, and 1 075s cm^{-1}, $\lambda_{max.}$ 239 nm (ε 10 500), *m/e* 317 (M^+) (Found: C, 75.35; H, 9.8; N, 4.15. $C_{20}H_{31}NO_2$ requires C, 75.65; H, 9.85; N, 4.4%).

3β-*Acetoxy*-N-*methyl*-17a-*aza*-D-*homoandrost*-5-*en*-17-*one* (VIIIb) (from the foregoing nitrone followed by acetylation; 52%) had m.p. 147.5—149° (from ethyl acetate), $[\alpha]_D^{20}$ −62° (*c* 0.74), $\nu_{max.}$ 1 735s, 1 645s, and 1 250s cm^{-1} (Found: C, 73.4; H, 9.1; N, 3.7. $C_{22}H_{33}NO_3$ requires C, 73.5; H, 9.25; N, 3.9%).

Rearrangement of 17-hydroxyiminodehydroepiandrosterone 3β-acetate (IXa) with thionyl chloride and methylation (Bu^nLi–MeI) gave the lactam (VIIIb), identical (mixed m.p., $[\alpha]_D$, i.r., and n.m.r.) with the product from the nitrone (VIIIa) rearrangement.

2-*Methyliminoadamantane* N-*oxide* (Xa) (45%) had m.p. (sublimed at 100 °C and 0.2 mmHg) 84—88°, $\nu_{max.}$ 1 460m and 1 080m cm^{-1}, *m/e* 179 (M^+) (Found: C, 73.65; H, 9.4; N, 7.5. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.55; N, 7.8%).

N-*Methyl*-4-*azatricyclo*[4.3.1.1^{3,8}]*undecan*-5-*one* (Xb) (70%) had m.p. (sublimed at 120 °C and 2.0 mmHg) 66—68°, $\nu_{max.}$ 1 620s cm^{-1}, *m/e* 179 (M^+) (Found: C, 73.95; H, 9.55; N, 7.75. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.55; N, 7.8%).

Isomerisation with sulphuric acid [8] and methylation (NaH–MeI) of 2-hydroxyiminoadamantane (XIa) gave the lactam (Xb) (25%), identical (mixed m.p., i.r., and n.m.r.) with that from the nitrone (Xa).

3β-*Acetoxy*-16-(N-*methylhydroxyamino*)*pregn*-5-*en*-20-*one* (XIIb).—Treatment of 3β-acetoxypregna-5,16-dien-20-one (XIIa) with hydroxy(methyl)ammonium chloride and pyridine gave *compound* (XIIb) (77%), m.p. 182.5—184° (from methanol–chloroform), $[\alpha]_D^{23}$ −18° (*c* 0.78), $\nu_{max.}$ 3 400m, 1 730s, 1 700s, and 1 240s cm^{-1}, τ 4.60 (1 H, m, 6-H), 5.40 (1 H, m, 3α-H), 6.30 (1 H, m, 16-H), 7.15 (1 H, m, OH), 7.57 (3 H, s, NMe), 7.80 (3 H, s, 21-H_3), 8.97 (3 H, s, 19-H_3), and 9.33 (3 H, s, 18-H_3) (Found: C, 71.8; H, 9.15; N, 3.8. $C_{24}H_{37}NO_4$ requires C, 71.45; H, 9.25; N, 3.45%).

[5/402 *Received*, 26*th February*, 1975]

* *S* = shift downfield on addition of $Eu(fod)_3$ (0.4 equiv.); tentative shifts for 2-H: 1.3 p.p.m. (*anti*), 0.1 p.p.m. (*syn*).

[8] J. G. Korsloot and V. G. Keizer, *Tetrahedron Letters*, 1969, 3517.