PHOTOCHEMICAL FORMATION OF CYCLIC NITRONE FROM NITRITE OF A FUSED 5-MEMBERED RING ALCOHOL[1]

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Abstract—Photochemical formation of α-hydroxycyclic nitrone from the nitrite of a fused 5-membered ring alcohol is described. The nitrite (VI) of N-acetyl-22,27-imino-12α-jerv-4, 13(17)-dien-11β-ol-3,23-dione was prepared from jervine and photolyzed under the conditions of the Barton reaction to afford a single rearranged product VII. The structure of VII was established as a cyclic nitrone (VII) on the basis of the Mass, IR, UV, NMR spectroscopy, chemical and photochemical evidence and the consideration of the mode of the formation. The reaction is unprecedented. The unusual formation of oxaziridine (XIa, XIb) and pyridine nucleus (XII) from hydroxynitrone (VII) under the condition of acylation has been found.

WE HAVE recently reported[2] the results of the photolysis of nitrites of several fused 5-membered ring alcohols incorporated in the 22.27-imino-17.23-oxidojervane framework. It has been found that 11-alkoxyl radicals from the respective nitrites reacted to afford a variety of products depending on the structure round the nitrito group.
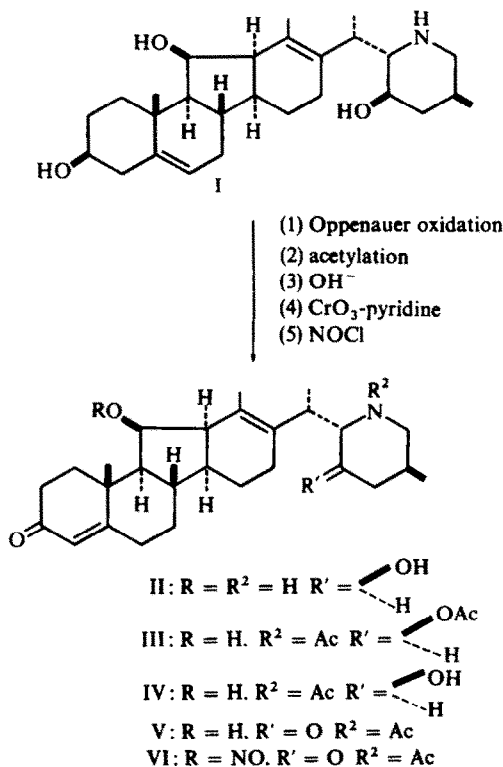
In this paper. the photochemistry of the nitrite (VI) of N-acetyl-22.27-imino-12α-jerv-4,13(17)-dien-11β-ol-3,23-dione is described. Although the photolysis of nitrite esters of fused 5-membered ring alcohols gives cyclic hydroxamic acids.[3] it has been found that the irradiation of the nitrite (VI) induced an extensive reorganization of the molecule and that a novel cyclic nitrone (VII) was formed in excellent yield.

## RESULTS

Synthesis of nitrite

As shown in Scheme 1. the nitrite (VI) was prepared from jervine. Birch reduction of jervine followed by the reduction of the resulting 22.27-imino-12α-jerv-5.13(17)-diene-3β.23β-diol-11-one with LAH afforded 22.27-imino-12α-jerv-5.13(17)-diene-3β.11β.23β-triol (I).[4]

The Oppenauer oxidation of I afforded the corresponding Δ^4-3-one (II) which was obtained as the chloroform complex. m.p. 122–125°. The Δ^4-3-one structure was evident from the NMR. UV and IR spectra. II was subsequently converted into the N-acetyl derivative (IV). m.p. 158–160°. followed by the hydrolysis of the resulting 23-O.N-diacetyl derivative (III). The over-all yield from I to IV was 63%. Selective oxidation of an OH group at C-23 of IV with CrO_3-pyridine afforded a keto-alcohol (V). m.p. 106–107°. in 82% yield. Formation of C=O at C-23 of V was evident from the 100 MHz NMR spectrum of V (Table 1). In the NMR spectrum of IV. the C-23α-H appeared as a broad singlet at τ 5·85 which partially coincided with double doublets signal at τ 5·78 due to the C-11α-H ($J = 3·0$ and $5·0$ Hz). However. in the 100 MHz NMR spectrum of V. a signal due to the C-23α-H had disappeared and the low field region of the spectrum showed only signals due to the C-11α-H (τ 5·75. dd. $J = 3·0$ and 5·0 Hz). the C-22β-H (τ 4·98. d. $J = 11·0$ Hz) and the C-4-H (τ 4·28). Presence of

(1) Oppenauer oxidation
(2) acetylation
(3) OH⁻
(4) CrO₃-pyridine
(5) NOCl

II: R = R² = H R' = <OH / H

III: R = H. R² = Ac R' = <OAc / H

IV: R = H. R² = Ac R' = <OH / H

V: R = H. R' = O R² = Ac

VI: R = NO. R' = O R² = Ac

SCHEME 1

at C=O at C-23 of V was also evident from the comparison of the mass spectra of IV and V. In the mass spectrum of IV, the parent peak appeared at m/e 469 (3%) and the spectrum is characterized by the prominent fragment ions A, B and C. at m/e 156 (base peak). m/e 114 (29%) and at m/e 314 (9%). Ion B is a heterocyclic species derived from α-fission and C corresponds to the ion formed by expulsion of the elements of ketene from species B.[5]

A: m/e 314   B: m/e 156   C: m/e 114
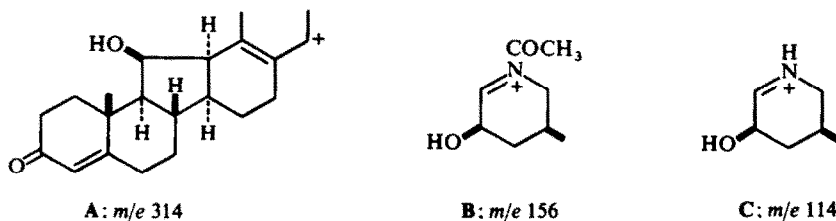
On the other hand, in the mass spectrum of V, the prominent fragment ions D, E. F. and G. beside the parent ion at m/e 467. appeared at m/e 155 (base peak). m/e 313. m/e 295. and at m/e 113. These were assigned to the following fragment ions including charged enol species arising from the migration of a hydrogen at the 18-Me in a 6-membered cyclic transition state Va[6] as depicted. Moreover, the IR spectrum of V exhibited bands at 3400 and 3500 cm⁻¹ (11β-OH group). 1715 cm⁻¹ (6-membered

Va

+

D: *m/e* 155

E: *m/e* 313   **F**: *m/e* 295   **G**: *m/e* 113
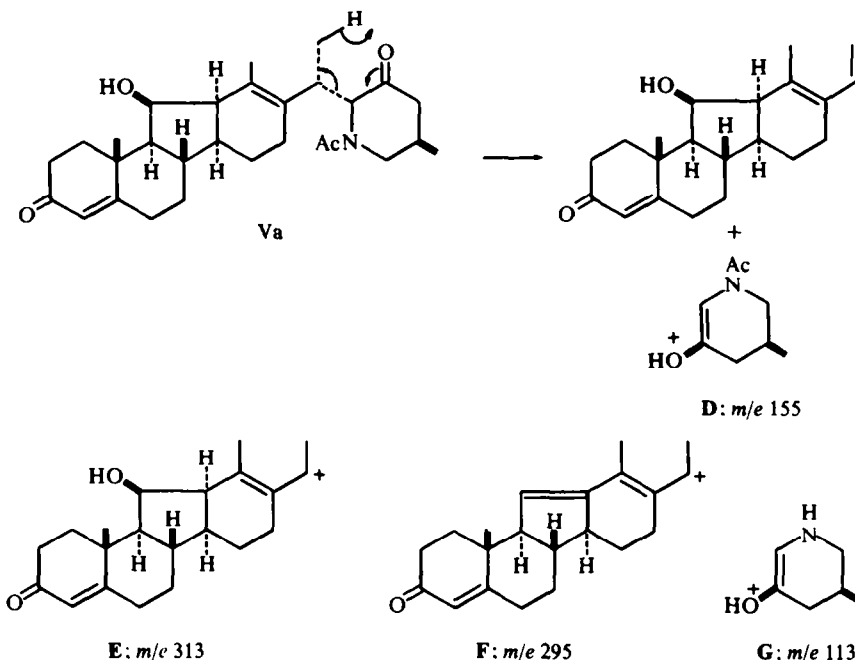
ring ketone). 1655 cm^{-1} (Δ^4-3-one) and 1622 cm^{-1} (N—Ac) in agreement with the assigned structure.

Treatment of V with nitrosyl chloride and pyridine[7] gave an almost quantitative yield of the stable 11-nitrite ester (VI). m.p. 179–182°. The signal due to the 19-Me in the NMR spectrum of VI appeared at a considerably higher field than that of V ($\Delta = +0.33$ ppm) (Table 1). This shift is due to shielding by the 11β-nitrito group as we have already reported.[8]

TABLE 1. 100 MHz NMR SPECTRAL DATA OF COMPOUNDS IV, V AND VI (τ)

	18-Me	19-Me	21- and 26-Me	N-Ac	23 α-H	22β-H	11α-H	C-4-H
IV (CDCl$_3$)	8·26	8·66	8·79 (*J* = 7·0) and 8·89 (*J* = 6·6)	7·89	5·85	5·23. d. (*J* = 11·0)	5·78. dd. (*J* = 3·0 and 5·0)	4·26
(pyridine d$_5$)	8·17	8·56	8·63 (*J* = 6·5) and 8·89 (*J* = 7·0)	7·78	5·72		5·62. dd. (*J* = 2·5) and 5·0)	4·15
V (CDCl$_3$)	8·24	8·63	8·97 (*J* = 6·7) and 9·04 (*J* = 7·0)	7·93		4·98. d. (*J* = 11·0)	5·75. dd. (*J* = 3·0 and 5·0)	4·28
(pyridine d$_5$)	8·14	8·56	8·95 (*J* = 7·0) and 9·15 (*J* = 6·5)	7·83		4·64. d. (*J* = 11·0)	5·57. dd. (*J* = 3·0 and 4·3)	4·15
VI (CDCl$_3$)	8·38	8·96	9·01 (*J* = 6·0) and 9·08 (*J* = 6·6)	7·90		4·99. d. (*J* = 11·0)	3·75. dd. (*J* = 5·4 and 3·2)	4·31

on the large shielding effect for Me protons situated 1.3-diaxial to a nitrito group. Methine hydrogen (C-11α-H) attached to the carbon bearing the nitrito group of VI resonated at τ 3·75. as double doublets (J = 5·4. 3·2 Hz). 2·00 ppm downfield from the corresponding proton of V.

Photolysis

Structure and reactions of the photoproduct. The nitrite ester (VI) was photolyzed under the conditions adopted for the Barton reaction.[9] The progress of the reaction was monitored by TLC and after 3 hr the decomposition of the nitrite was complete. The TLC showed. except for a small amount of the parent alcohol (V). the presence of virtually a single product. The pure photo-product VII. m.p. 220–222°. was obtained by direct recrystallization of the crude product in 59% yield.

Structure VII of the photo-product was deduced on the basis of the spectroscopic. chemical and photochemical evidence and the considerations of the mode of the formation.

The molecular formula of VII was determined as $C_{29}H_{40}O_5N_2$ from the elemental analyses and the mass spectrum which showed the extremely weak molecular ion of *m/e* 496. confirming an isomerization reaction. The IR spectrum of VII showed bands at 3300. 1705. 1668. 1621 and 1565 cm^{-1}. These bands are attributable to OH. 6-membered ring ketone. Δ^4-3-one. N—Ac and N═C respectively. A notable change in the lower field of the 100 MHz NMR spectrum (Figs 1 and 2) in going from V to VII was the disappearance of double doublets due to the C-11α-H observed in the NMR of V and the appearance of a clear doublet at τ 5·14 (J = 7·5 Hz) in the NMR of VII. Moreover a signal (τ 7·84) due to the 18-Me of VII was found to be considerably deshielded when compared with the corresponding signal (τ 8·24) of V. Hydroxamic acids VIIa or VIIb; (R = H). which are formed[3] in the photolysis of nitrites of steroidal 5-membered D-ring alcohols. or the tautomer VIIc (R = H) of VIIb (R = H)
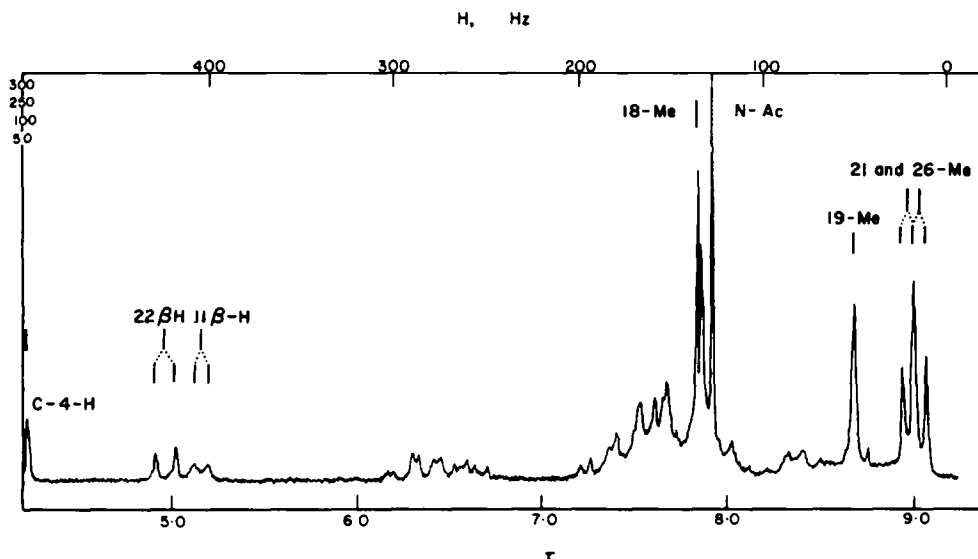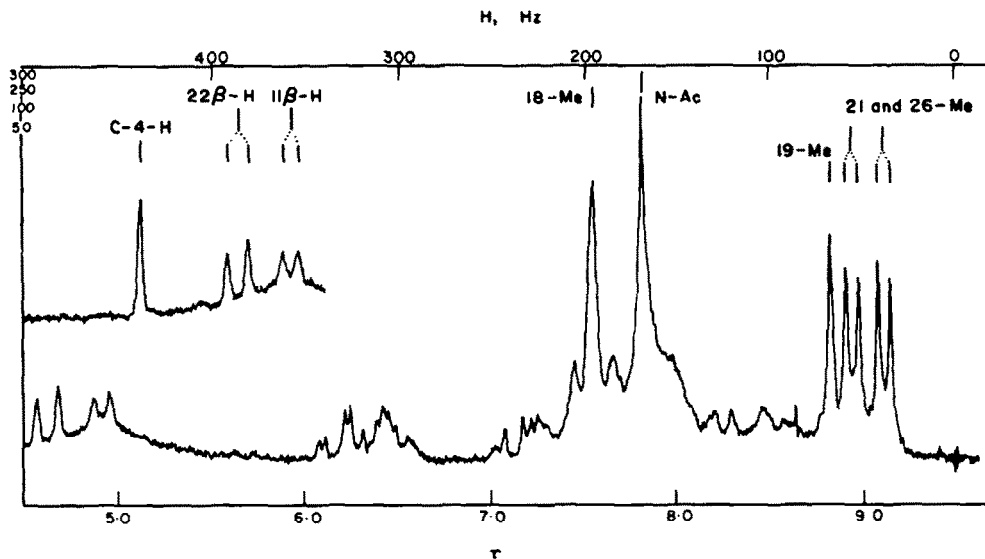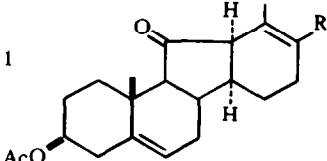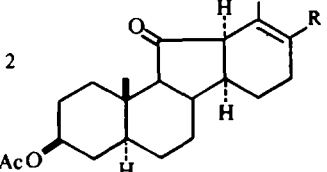
H,   Hz

Fig 1. 100 MHz NMR spectrum of VII in CDCl$_3$
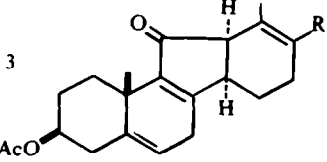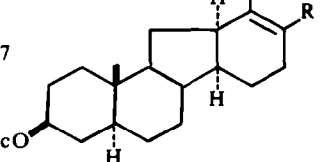
FIG 2. 100 MHz NMR spectrum of VII in pyridine d₅

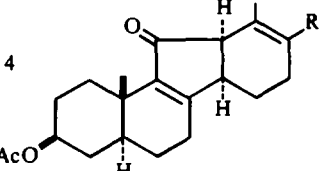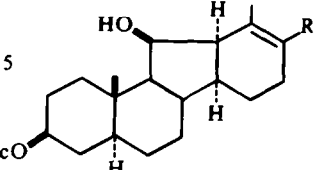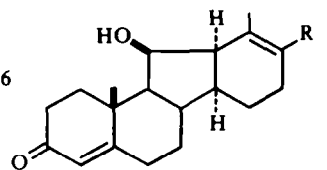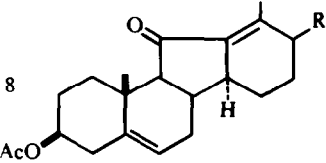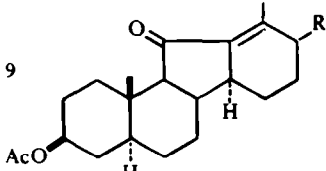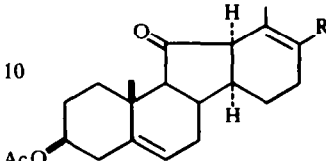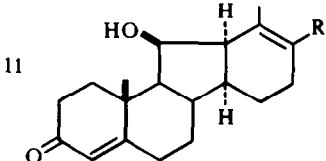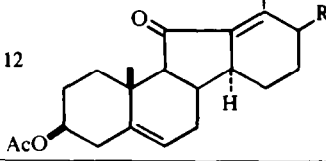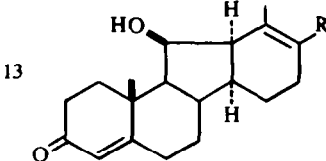could accommodate these spectral properties. VII in EtOH developed a red colour on addition of FeCl₃ and this property has been taken as evidence for the presence of an hydroxamic acid function.[10] However, the UV spectrum excluded the structures VIIa or VIIb (R = H) due to strong absorptions in two regions, one at 238 nm (ε, 16.500) and another at 289 nm (ε. 10.700). The former is attributed to a Δ^4-3-one chromophore and the intensity and the position of the latter roughly correspond to those of a conjugated azomethine chromophore.*

VIIa

VIIb

VIIc
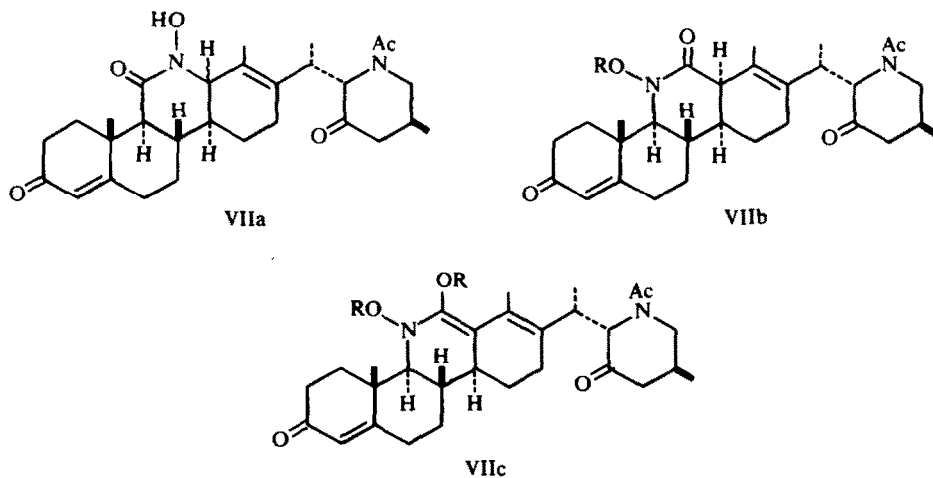
* $\diagup C{=}C{-}C{=}N\diagdown$ possesses UV absorption at 274–278 nm (ε, 20,000).[11]

Table 2

compounds	R	Chemical shifts (*J* in brackets)			Reference
		21-Me	26-Me	Pattern	
1	A	8·88 or 8·90 (6·6)	8·88 or 8·90 (6·6)	coincident doublets	12
2	A	8·91 (6·6)	8·91 (6·6)	coincident doublets	12
3	A	8·88 (6·6)	8·88 (6·6)	coincident doublets	12
4	A	8·92 (6·7)	8·92 (6·7)	coincident doublets	12
5	A	8·97 (6·6)	8·97 (6·6)	clear coincident doublets	13
6	A	8·86 (6·6)	8·86 (6·6)	clear coincident doublets	13
7	A	8·89 (6·6)	8·89 (6·6)	broad coincident doublets	14

| Compounds | R | Chemical shifts (J in brackets) | | | Reference |
		21-Me	26-Me	Pattern	
8	A	9·20 (6·6)	8·81 (6·0)	two separated doublets	15
9	A	9·18 (6·6)	8·79 (6·0)	two separated doublets	16
10	B	8·96 or (6·0)	8·81 (6·6)	two separated doublets	17
11	B	8·79 or (7·0)	8·89 (6·6)	two separated doublets	13
12	B	9·25 or (6·6)	8·73 (6·0)	two separated doublets	17
13	C	9·04 or (7·0)	8·97 (6·7)	coincident triplets	13
14 Photo-product	C	9·03 (6·9)	8·96 (5·9)	coincident triplets	

R = A   B   C
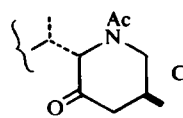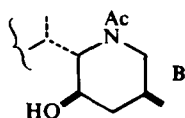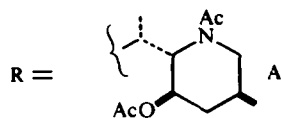
Spectral data of 11. 13 and 14 were those taken by a 100 MHz spectrometer

The enol acetate (VIIc: R = H) of a hydroxamic acid (VIIb; R = H). another possibility since it could account for the UV spectrum as well as the NMR spectrum of VII. was ruled out by the following acetylation.

Acetylation of the photo-product yielded only two major products. XIa and XII. If the structure of the photo-product is formulated as VIIc (R = H). the product of acetylation should have the structure (VIIb: R = Ac) and/or (VIIc: R = Ac). XIa obtained in an amorphous form showed bands in the IR spectrum at 1654 cm^{-1} (N—Ac). 1668 cm^{-1} (Δ^4-3-one) and 1730 cm^{-1} (OAc) but no absorption due to OH. N=C and enol acetate. However. XIa showed only UV absorption at 238 nm (ε. 23.600). which was attributed to a Δ^4-3-one chromophore, and the absorption at the longer wave length observed in VII had disappeared. This disproved the structure VIIc. (R = Ac) as correct for XIa. The NMR spectrum of XIa showed an extra acetyl group incorporated into the molecule and this is also against structure VIIc (R = H). The formation of type VIIb (R = Ac) from type VIIc (R = H) stabilized by a H-bonding was also excluded since the acetylated product XIa was not hydrolyzed under basic conditions. It was subsequently found that the second acetylation product XII had a pyridine nucleus (*vide infra*) and therefore the structure of the photo-product could not be any of the cyclic hydroxamic acids (VIIa. VIIb: R = H. VIIc: R = H).

As mentioned previously. the UV spectrum of VII showed two maxima. one attributable to the Δ^4-3-one chromophore and another at the longer wave length which did not exist in the starting nitrite and was apparently newly formed in the product. It was inferred that the 13(17) double bond was retained in its original position in the new molecule and most probably constituted part of the new con-jugated system responsible for the new UV absorption of VII. We proved this by NMR spectroscopy.

A comparison of the NMR spectra of a series of compounds possessing a N-acetyl-22,27-iminojervane framework revealed that the pattern of the signals of their 21-Me and 26-Me depends significantly on the position of the double bond in the D-ring of the C-nor-D-homosteroidal part of the molecule.

In Table 2 the chemical shifts of 21-Me and 26-Me of a series of compounds having the N-acetyl-22,27-iminojervane framework are shown. It is apparent from the examination of Table 2, that in a series of compounds with the double bond at the 13(17) position and with the same substituent A at C-17, chemical shifts of their 21-Me and 26-Me are nearly the same and these signals coincide and appear as a sharp or a broad single doublet, while in the corresponding compounds with the double bond at 12(13) position the signals of 21-Me and 26-Me do not coincide and appear as a double doublet.

A reason for this difference could be that, no matter whether the double bond of N-acetyl-22,27-iminojervanes with the same substituent at the C-17 occupies the 12(13) position or the 13(17) position, chemical shifts of the remote 26-Me are kept nearly constant whereas the 21-Me protons of these compounds are not and when the double bond occupies the 12(13) position 21-Me protons are significantly more shielded and resonate more upfield than the corresponding compound with the double bond at the 13(17) position. It can further be seen that the positions of the double bonds and the presence or absence of the double bonds in the A. B and C rings of these compounds do not have any significant influence on the chemical

shifts of their 21-Me and 26-Me when the substituent at C-17 is the same and the substituents at the C-23 effect the chemical shifts of the 21-Me and the 26-Me of these compounds.

In the compound V the doublets due to the 21-Me and the 26-Me were close to one another and appeared as a triplet. In the photoproduct VII signals due to these methyls also appear as a triplet and no significant difference of chemical shifts of the 21-Me and the 26-Me of VII with those of V was observed. Therefore. it would be reasonable to conclude that a double bond at the 12(13) position of V is retained in its original position in the photoproduct and, in turn. it would be certain that this doubl bond constitutes a part of the chromophore responsible for an UV absorption of VII at a longer wave length. The unusual behaviour observed in the acetylation of VII suggested that a nitrone[18] or a N-oxide grouping[19] may exist in the molecule since the formation of the rearranged acetates in the acetylation of N-oxides[20] or nitrones[18] is well-known in the chemistry of these compounds. These facts further suggested that the nitrone group and 13(17) double bond in VII are conjugated and the chromophore responsible for 289 nm absorption of VII is an α.β-unsaturated

$$\vec{O} \qquad\qquad \overset{-}{O}$$
$$| \qquad\qquad\qquad |$$
nitrone. i.e.. either $\underset{+}{—N}\!=\!C—C\!=\!C—$ or $—C\!=\!\underset{+}{N}—C\!=\!C—$. The possibility of the

latter being a chromophore is excluded on the basis of mechanistic considerations for the formation of VII. which will be described later.

The irradiation of a nitrone in protic or aprotic media readily affords oxaziridines[21] which are thermally unstable and readily revert back to the starting nitrone.[22] When VII in EtOH was irradiated, a rapid conversion of VII into a less polar substance was observed on TLC. By the end of 2 hr. nearly all the starting nitrone was converted into a less polar substance XIV and the UV of the solution revealed only a single absorption maximum at 237 nm due to the Δ^4-3-one chromophore and the absorption at 284 nm in the starting substance vanished. The compound was extremely unstable thermally and the removal of the solvent under reduced pressure at 40° caused a partial reversion of XIV into the original photo-product VII yielding a mixture of VII and XIV. When this mixture in acetone was heated at about 60° for a short period, VII was recovered unchanged. These thermal and photochemical changes are in accord with those of oxaziridine and nitrone respectively.

A N atom in the α.β-unsaturated nitrone grouping must then be in a 6-membered ring since a compound XII with pyridine nucleus is obtained by the acetylation of VII (Scheme 2). This partial structure of VII was extended to XV in the following way. In the NMR spectrum of XII, we observed only a single proton having the chemical shift corresponding to α-position of a pyridine nucleus. Based on this together with the mechanistic considerations on the formation of VII and on the results of acetylation (*vide infra*), an OH group, the presence of which was confirmed by IR. must be positioned at a carbon attached to N-oxide nitrogen.

All these results can only reasonably be accommodated in terms of the structure VII. The assignments of the signals of the NMR spectrum (Fig 1) of VII are shown

XV
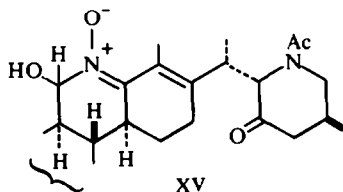
as figures in the formula VII. Here, configuration of an OH group* is assigned as α based on the following evidence. In the NMR spectrum of VII. XIa and XIb. the respective hydrogen attached to carbon bearing the OH group or attached to an oxaziridine ring appears as a clear doublet with $J = 7.5 \sim 9.7$ Hz. These coupling constants fit in with a *trans-* rather than a *cis-* arrangement of 9α-hydrogen and C-11-hydrogen. Secondly. the α-assignment for the OH group is consistent with a result of a pyridine-induced solvent shift of the NMR spectrum of VII. An OH function occupying positions 1,3-diaxial to Me groups was found to exert deshielding effects of the order of 0.20–0.40 ppm in pyridine relative to $CDCl_3$.[23] A comparison of the NMR spectra of VII in $CDCl_3$ (Fig 1) and pyridine-d_5 (Fig 2) revealed that the 19-Me is shielded by 0.17 ppm in pyridine-d_5 relative to that in $CDCl_3$. If the OH group of VII is β oriented the OH should cause a large deshielding effect on the 19-Me group. whereas the reverse is true here.† Therefore, α-configuration of OH of VII is preferred.‡

This large shielding effect ($+0.17$ ppm) for the 19-Me and deshielding effect ($\Delta = -0.26$ ppm) for the 18-Me observed are unusual. Although the exact nature of the solute-solvent complex in the present case is not clear. the polar N-oxide group must play a considerable role in these effects.

Based on the structure VII for the photoproduct the structures and the mode of the formation of XIa and XII obtained by acetylation of VII, will now be discussed (Scheme 2). The UV of XIa revealed only a single absorption due to Δ^4-3-one chromophore. This means that the nitrone chromophore, $\bar{O}-\overset{+}{N}=C-C=C$ of the photoproduct was lost during acetylation. In the NMR spectrum of XIa. a clear doublet observed at τ 5.14 in VII moved considerably downfield and appeared at τ 3.64 with $J = 9.7$ Hz. In the higher field of the spectrum a new three proton singlet at τ 7.82 appeared and was ascribed to a newly introduced acetoxyl group.

These spectroscopic properties together with the reaction are consistent with the oxaziridine formula (XIa). Thus. in accord with the oxaziridine structure. XIa in acetic acid-2-propanol rapidly oxidized the iodide ion to yield iodine.[22]

As described previously. XIa is stable under alkaline conditions. Unusual stability under alkaline treatment is characteristic of oxaziridines with a trisubstituted carbon attached to the nitrogen.[22] Inertness for basic hydrolysis of the acetoxyl group is also

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* The configuration of the hydroxyl group of VII was previously assigned as β.[1]

† Δ value observed for 19-Me protons situated 1,3-diaxial to a 11β-hydroxyl function of a normal steroid is -0.33.[23] In the present study, Δ values of -0.10 and -0.07 were observed for the chemical shifts of 19-Me protons of IV and V respectively. These rather small Δ values should be general in 11β-hydroxy-C-nor-D-homosteroids.

‡ Although no precise IR spectral study has been made, it seems certain that the α-hydroxy nitrone group in the photoproduct VII is stabilized by an intramolecular five-membered hydrogen bond as formulated.
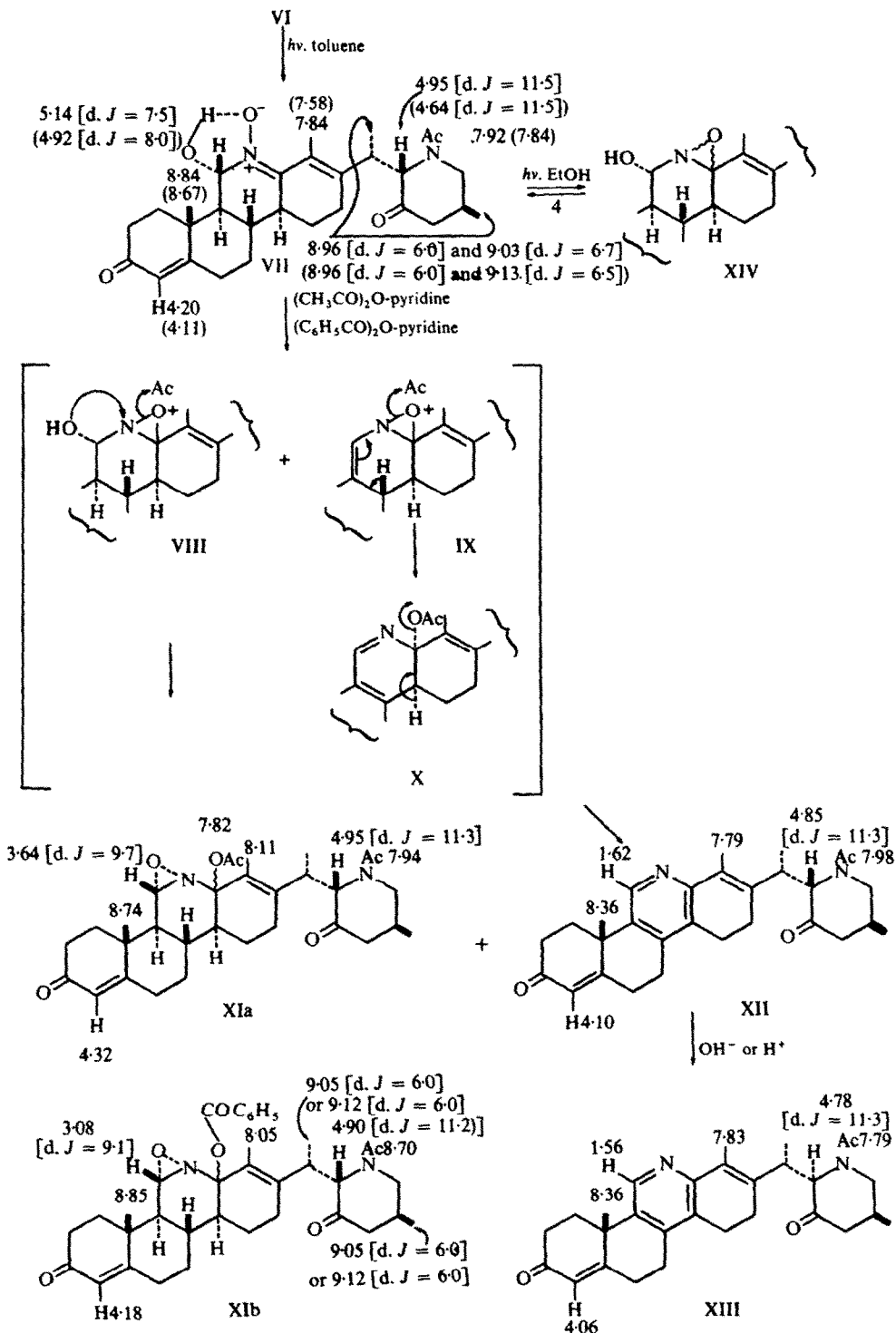
SCHEME 2
Numerals in brackets denote data in pyridine-d_5.

explained by the assigned formula in which the $CH_3COO—$ is attached to tertiary carbon. In contrast to the character for base treatment, XIa was unstable toward acids, although no well-defined product was obtained from the acidic treatment. The formation of XIa can be explained as follows: in the treatment of VII with acetic anhydride and pyridine, the intermediate VIII should be formed.[18] The cleavage of the oxaziridine ring and attack at the nitrogen by an oxygen of the hydroxyl group would probably occur in a concerted manner to afford the oxaziridine XIa. The ionic migration of the acyloxy group during N-oxide acylation has been established.[20] Although this tentative rationalization of the formation of XIa is plausible an alternative mode of the acylation which involves an intermolecular ionic process should not be excluded.[24]

The second product XII from acetylation was obtained in crystalline form and melted at 225–229°. The molecular formula of XII was established as $C_{30}H_{36}O_3N_2$ by elemental analysis and the mass spectrum (M^+ 460). In the UV of XII an absorption at 289 nm in VII was replaced by strong aromatic absorptions at 225 nm ($\varepsilon.$ 25.000) and 298 nm ($\varepsilon.$ 20.800). The presence of a pyridine nucleus in the molecule was demonstrated by the NMR spectrum which showed a characteristic one proton singlet at τ 1·62 due to the α-hydrogen of the pyridine nucleus. Another distinct feature here was the disappearance of a doublet at τ 5·14 observed in VII. Its IR showed no absorption in the OH region. 1708 cm^{-1} (6-membered ring ketone). 1679 cm^{-1} (Δ^4-3-one). 1629 cm^{-1} (N—Ac) and 1570 cm^{-1} (N=C). These spectroscopic results together with consideration of the mode of the formation are only explicable by the structure XII. The probable sequence of the formation of XII can be rationalized as follows: (1) the initial loss of the elements of water followed by the formation of an oxaziridine intermediate IX, (2) the cleavage of the N—O bond of oxaziridine, the migration of the double bond and the loss of a proton in a concerted manner to afford dihydropyridine of type X, (3) the elimination of the elements of acetic acid and aromatization of the heterocyclic ring to afford XII. This sequence is only tentative as in the case of the formation of XIa. In this sequence, the driving force to give an intermediate X from IX could be strain of the oxaziridine ring.

The chemical shifts of the signals in the NMR of XII are given out in the formula XII. It was found that XII was readily transformed into XIII, m.p. 269·5–271°. which showed bands at 1707 cm^{-1} (6-membered ring ketone). 1661 cm^{-1} (Δ^4-3-one). 1643 cm^{-1} (N—Ac) and 1578 cm^{-1} (N=C) in IR, either during separation on TLC of silicagel or with 2·5% methanolic KOH. The UV of XIII is nearly identical with that of XII the only significant difference being a downfield shift of the signal due to N-acetyl protons. On the basis of this spectroscopic evidence, XIII was formulated as an epimer of XII, in which the C-22-hydrogen has α-configuration.

Finally, treatment of VII with benzoic anhydride and pyridine afforded XIb. m.p. 253–254°, which was found to be a benzoyl analogue of XIa by the IR. NMR. UV and Mass spectra. The IR of XIb revealed bands at the expected positions ($\alpha.\beta$ unsaturated C=O. 1680 cm^{-1}, benzoyl and 6-membered ring ketone. 1709 cm^{-1}. N—Ac. 1650 cm^{-1}). In the 100 MHz NMR of XIb, the signals due to C-4-H (τ 4·18). C-11-H (τ 3·08, d, $J = 9·1$ Hz). C-22β-H (τ 4·90, d, $J = 11·2$ Hz). 21-Me and 26-Me (τ 9·05, d, $J = 6·0$ Hz and τ 9·12, d, $J = 6·0$ Hz) and benzoyl protons (τ 1·74–τ 2·46. m) appeared at the expected positions and were assigned in a manner analogous to the acetyl analogue (XIa). A broad singlet at τ 8·05 was assigned to the 18-Me. Moreover.

a couple of singlets at τ 8·70 and τ 8·85 were ascribed to the N—Ac and the 19-Me. However, definite assignments with regard to which signal is due to the N—Ac or the 19-Me have not been obtainable.* In either case, acetyl protons attached to the nitrogen of the piperidine ring are considerably shielded. This must be due to the strong anisotropy of the benzene ring of the angular benzoyloxy group. Whether the benzoyloxy group is α or β or in other words, whether the C/D ring juncture is *cis* or *trans* has not been determined. The UV spectrum of XIb showed an expected single maximum at 238 nm (ε, 22.000) due to the Δ^4-3-one chromophore. Examination of the mother liquor by TLC revealed the presence of two major compounds which were isolated by preparative TLC. One was proved to be identical with XII obtained by acetylation. Identification of the second product has not been successful.

DISCUSSION

The formation of α-hydroxynitrone in the photolysis of the nitrite ester of a fused 5-membered ring alcohol is unprecedented and the probable sequence leading to the photoproduct and the implication of the present results for the nitrite photochemistry are discussed.

The steric requirements for intramolecular hydrogen transfer in the Barton reaction have been extensively investigated and the most favourable transition state for hydrogen abstraction has been found to be a 6-membered cyclic one.[25] In the present case, the examination of the Dreiding model reveals that the distance requirement[26] for hydrogen abstraction from the 19-Me by the 11β-alkoxyl radical is satisfied (distance between O and C-19: 2·5 Å).

Therefore, we can expect the products, one from intramolecular hydrogen abstraction and another from C—C bond cleavage. However, the experiments revealed that at least in the present system, C—C bond cleavage was a more favoured process than hydrogen abstraction and the product exclusively resulted from the cleavage.

It has been reported by Barton *et al.*[3] that products from the photolysis of nitrite esters of steroidal 5-membered ring alcohols are cyclic hydroxamic acids. Later, further examples of similar observations were reported.[3] In this process, cleavage of the α,β-single bond of the cyclopentoxyl radical afforded a carbon radical with which nitric oxide combined with ring formation. A probable sequence of nitrone formation in the present case is viewed as indicated in Scheme 3. In the sequence, the irradiation of the nitrite ester (VI) generates the corresponding alkoxyl radical. The first occurrence should be the cleavage of either the C-9–C-10 bond or the C-10–C-11 bond of the nitrite (VI) and the cleavage of the latter occurs exclusively in the present case, as expected, since this bond is more susceptible to fission owing to the presence of the 13(17) double bond.

The carbon radical thus formed combines with nitric oxide and gives a nitroso-aldehyde. Whether the process from this nitroso-aldehyde to a nitrone is photo-induced or thermal or whether it is radical or ionic is not certain†. One of the probable rationalizations is the following. Since a hydrogen at C-12 of the intermediary nitroso-compound in the present case is activated by the 13(17) double bond, this would readily isomerize[27] to give an oximino-aldehyde. The nitrogen of the oximino-group and the formyl carbon of this intermediate would be in the appropriate

* This point is further being clarified.
† See "Added in proof".
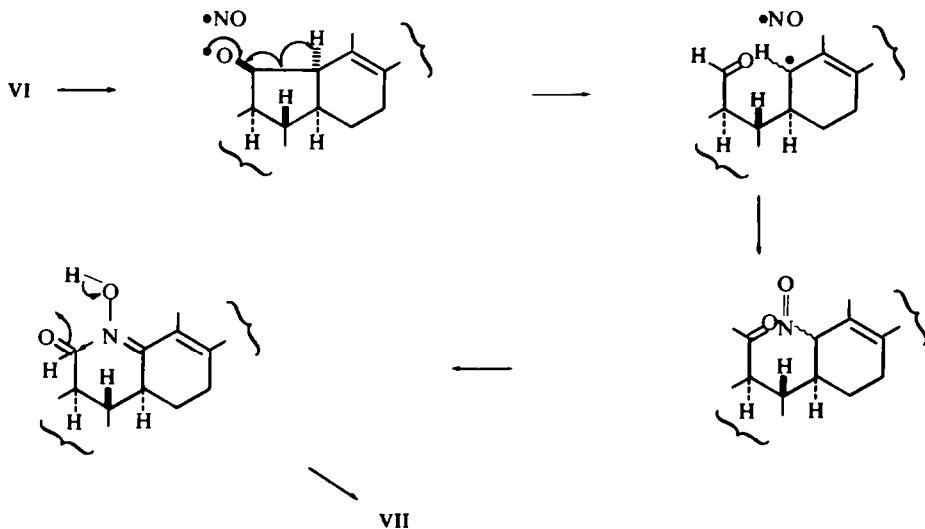
SCHEME 3

proximity for interaction and therefore the attack of the nitrogen of the oximino-
function upon the formyl carbon, the uptake of a proton by the carbonyl oxygen and
the eventual loss of a proton from the OH or the oximino function succeed to give a
nitrone. Whether these processes are radical or ionic or whether these processes are
light-catalyzed or not is unknown at the present stage.

The oximino-group has an ambident character[28] and the nucleophilic attack by
the nitrogen of the oximino-group upon the carbonyl carbon to form nitrones is a
known ground state process, although it is known to require rather forced condi-
tions.[29] In the present case, the smooth cyclization occurs under very mild conditions.
i.e., at room temperature and under neutral conditions. Therefore, although it is not
denied that the facile cyclization at the ground state intermediate would be assisted
by the proper geometry between the attacking nitrogen and the formyl carbon, it is
very probable that light does play a role in the facile cyclization.

An investigation to gain more insight into the mechanistic aspect of this cyclization
is in progress.

It is of interest that while the photochemical transformation from a nitrone to an
oxaziridine in protic or aprotic media is a well-known process, only the nitrone is
isolated at the stage of complete disappearance of the starting nitrite in the present
case. This is attributable to the relative slowness of the process (VII → XIV) in
comparison with the process (VI → VII) using toluene as the solvent. Smooth
transformation of the nitrone into the corresponding oxaziridine occurs in a protic
medium as already described.

Finally, the mass spectra of the photo-product VII and products XIa. XIb. XII.
from acetylation and benzoylation, will be described.

The mass spectrum of the photo-product VII showed the extremely weak parent
peak at m/e 496 and the base peak at m/e 306. Prominent ions were observed at m/e
460, m/e 155 and at m/e 113. Based on the structure VII, ions of m/e 155 and m/e 113
are apparently the fragments D and G due to McLafferty rearrangement which we

have already described. In the spectrum, M^+-18 ion (m/e 478) was more significant than M^+ peak. This ion must result from the loss of water in the molecular ion and is assigned to the fragment H. Intervention of an oxaziridine ion as intermediate in the fragmentation of nitrones has recently been suggest d.[30] The ion. m/e 306. which is base peak, is then assigned to fragment I derived from α-fission and aromatization of the cyclic nitrone ring probably through the type H. The ion m/e 460 would

H : m/e 478   I : m/e 306
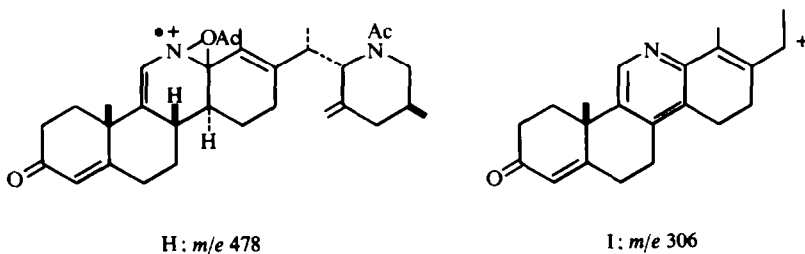
probably be a fragment J and must result from aromatization of the molecular ion. In the mass spectrum of XIa, XIb and XII, the base peaks were ion m/e 306 and the prominent ions m/e 155, m/e 113 and m/e 460 were observed. These are assigned to

J : m/e 460
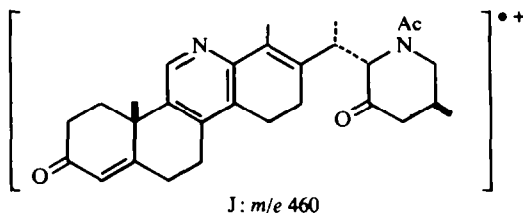
the fragments I, D, G and J, respectively. The intensity of each ion in those molecules so far discussed is tabulated below.

TABLE 3

| m/e | VII | Relative intensity of | | |
		XIa	XIb	XII
538		0·2 (M^+)		
496	0·02 (M^+)			
478	0·3			
460	5	13	8	2 (M^+)
306	100	100	100	100
155	8	41	3	1
113	17	35	4	7

Note added in proof. It has now been unambiguously proved that the nitrone VII formed by the *thermal* cyclization of the short-lived nitroso-aldehyde shown in Scheme 3. This conclusion has been deduced from the spectrophotometric observation of the formation of nitroso-aldehyde in EPA matrix at 77°K, the photolysis of the nitrite by 365 nm monochromatic light, as well as the isolation and the reaction of the oxime-aldehyde shown in Scheme 3.

These results will be published shortly.

EXPERIMENTAL

All m.ps were determined with a Yanagimoto type hot-stage and uncorrected. Unless stated otherwise. IR were determined in Nujol using a Jasco model IR-E spectrophotometer. 60 MHz NMR spectra were determined on a Japan electron optics 3H 60 high resolution NMR spectrometer in $CDCl_3$ soln using TMS as an internal reference. Unless stated otherwise NMR values are those taken by a 60 MHz spectrometer. The course of the reactions and the progress in column chromatography were followed by TLC on Wakogel B-5.

Preparation of 22,27-imino-12α-jerv-4,13(17)-diene-11β,23β-diol-3-one (II)

Compound I (5·7 g) was dissolved in dry toluene (500 ml). A small volume (100 ml) of the solvent was distilled off. To this soln was added cyclohexanone (70 ml) and a further 100 ml of the solvent was removed by distillation. Then aluminiumisopropoxide (10·0 g) in 50 ml dry toluene was added and a small volume of the solvent was further removed by distillation. The soln was refluxed for 9 hr. After cooling 30 ml water was added and the soln was steam-distilled. The soln was extracted with CH_2Cl_2 and the organic layers were combined and washed with water. The residue (6·6 g) after evaporation was treated with $CHCl_3$ to yield a crystalline $CHCl_3$ complex. yield 6·15 g. m.p. 122–125°; IR: (C=C—C=O) 1645 cm^{-1}. 1606 cm^{-1}; NMR: 19-Me (τ 8·60). 18-Me (τ 8·27). 26-Me (τ 9·14, d, J = 6·0 Hz), 21-Me (τ 8·78. d. J = 6·6 Hz). C-4-H (τ 4·26). C-11-H (t. τ 5·71); UV: λ_{max}^{EtOH} 238 nm (ε, 23,000).

The desired amorphous II which was free of $CHCl_3$ was obtained by dissolving in EtOH and removing the solvent under reduced pressure 4·92 g.

Preparation of N-acetyl-derivative (IV)

Compound II (4·77 g) obtained above was treated with Ac_2O (25 ml) and pyridine (30 ml) for 1 hr. The mixture was poured into water (700 ml) and the ppt was collected by filtration to yield the crude acetylated substance which was hydrolyzed with methanolic 5% KOH (50 ml) at room temp. This was poured into a large amount of water. The resultant ppt was collected. washed with water repeatedly and recrystallized from aqueous EtOH to yield 3·63 g of IV. The analytical sample had m.p. 158–160°; IR: (C=C—C=O) 1611 cm^{-1}. 1643 cm^{-1}. (NAc) 1661 cm^{-1}; NMR: see Table 1; $[\alpha]_D$ +76·2° (c. 4·0. MeOH). (Found: C. 74·16: H, 9·24: N. 2·85. $C_{29}H_{43}NO_4$ requires: C, 74·16: H. 9·23: N, 2·98%): Mass M$^+$ 469: UV: 238 nm (ε. 24,000).

Synthesis of 22,27-imino-12α-jerv-4,13(17)-dien-11β-ol-3,23-dione (V)

To a soln of IV (1·0 g) in pyridine (50 ml) CrO_3 (1·0 g) was added with cooling. After stirring for 4·5 hr at room temp. THF (150 ml) was added. A solid separated and was removed and washed with THF 3 times. The combined filtrates were treated with sat $NaHSO_3$ aq to decompose the excess CrO_3. The ppt was removed by filtration and repeatedly washed with hot THF. The combined filtrates were concentrated to about 50 ml. The soln was extracted with $CHCl_3$. The organic layer was washed with water. dried. and evaporated. A resinous residue dissolved in aqueous EtOH yielded crystals of V (860 mg). The analytical sample melted at 106–107°: IR: (11β-OH. broad) 3400 cm^{-1}. 3500 cm^{-1}. (6-membered ring ketone) 1717 cm^{-1}. (Δ⁴-3-one) 1657 cm^{-1}. (NAc) 1622 cm^{-1}: NMR: see Table 1: $[\alpha]_D$ — 92·7 . (c. 1·8, MeOH). (Found: C. 74·44: H. 8·92: N. 2·84. $C_{29}H_{41}O_4N$ requires: C. 74·48: H. 8·84: N. 3·00%): Mass: M$^-$ 467: UV: λ_{max}^{EtOH} 234 nm (ε. 23.000).

The nitrite (VI)

Compound V (1·5 g) in pyridine (1 ml) was nitrosated with NOCl-pyridine at −20° to −30°. Usual work-up of the mixture yielded the desired O-nitrosoderivative (1·8 g) which. after purification from n-hexane–acetone. melted at 179–182°: IR: (6-membered ring ketone) 1711 cm^{-1}. (N=O) 1672 cm^{-1}. (Δ⁴-3-one) 1655 cm^{-1}. (N—Ac) 1631 cm^{-1}. (N—O) 766 cm^{-1}; NMR: see Table 1: $[\alpha]_D$ +115° (c. 2·0. $CHCl_3$).

Photolysis of the nitrite (VI)

The nitrite (1·8 g) in dry toluene (110 ml) was irradiated for 3 hr by a 150 W high pressure Hg arc lamp. Disappearance of the nitrite was confirmed by TLC. The solvent was removed by distillation. By following the same procedure. a further 2·1 g of the nitrite was photolyzed. The residue from both photolyses was extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water. dried and evaporated. TLC of the residue showed three spots. Except for the most polar one. the other two spots were very faint. The crude product

was crystallized from acetone to yield VII (2·3 g, 58%). A small amount of the parent alcohol (V) was recovered from the mother liquor. An analytical sample was obtained by recrystallization from acetone. m.p. 220–222°: IR: (broad, OH) 3300 cm^{-1}, (6-membered ring ketone) 1705 cm^{-1}, (Δ^4-3-one) 1668 cm^{-1}. (N—Ac) 1621 cm^{-1} and (N=C) 1566 cm^{-1}: NMR: see numerals on the formula VII: $[\alpha]_D$ + 100°, (c. 2·4, CHCl$_3$). (Found: C. 70·04: H. 7·89: N. 5·58. C$_{29}$H$_{40}$O$_5$N$_2$ requires: C. 70·13: H. 8·12: N. 5·64%): Mass. M$^+$ 496. An alcoholic soln of the photo-product developed an intense red color on addition of one drop of alcoholic FeCl$_3$ solution: UV: λ_{max}^{EtOH} 238 nm (ϵ. 16.500), 289 nm (ϵ. 10.700).

Acetylation of the photoproduct (VII)

The photo-product (300 mg) was treated with Ac$_2$O (3 ml) and pyridine (3 ml) for 1 hr at room temp. After addition of a small volume of MeOH, the solvent was evaporated with benzene. The residue was extracted with CHCl$_3$. After work-up, the residue was examined by TLC which showed two spots. Recrystallization from acetone–n-hexane afforded crystals of XII (22 mg). The analytical specimen from aqueous MeOH melted at 227–229·5°: IR: (6-membered ring ketone) 1708 cm^{-1}, (Δ^4-3-one) 1679 cm^{-1}. (N—Ac) 1629 cm^{-1} and (N=C) 1570 cm^{-1}: NMR: see numerals on the formula XII: $[\alpha]_D$ −97° (c. 2·0. CHCl$_3$). (Found: C. 75·62: H. 7·95: N. 5·94. C$_{29}$H$_{36}$O$_3$N$_2$ requires: C. 75·62: H. 7·88: N. 6·08%): Mass. M$^+$ 460: UV: λ_{max}^{EtOH} 225 nm (ϵ. 25.000), 298 nm (ϵ. 8700). 239 nm (Shoulder. ϵ. 20.800).

Evaporation of the mother liquor from the above crystallization yielded a residue 278 mg which was submitted to preparative TLC (silica gel). The TLC plates were developed twice with a mixture of MeOH and Et$_2$O (1:5 in volume). Of the two bands developed, the upper band was eluted to yield 77 mg of amorphous XIa: IR: $\lambda_{max}^{CHCl_3}$ (N—Ac) 1654 cm^{-1}, (Δ^4-3-one) 1668 cm^{-1} and (O—Ac) 1730 cm^{-1}: NMR: see numerals on the formula XIa. (Found: C. 66·24: H. 7·79: N. 4·72. C$_{31}$H$_{42}$O$_6$N$_2$ requires: C. 69·12: H. 7·86: N. 5·20%): UV: λ_{max}^{EtOH} (ϵ. 23.600) 238 nm.

Addition of KI to a soln of this compound in AcOH and 2-PrOH caused rapid production of I$_2$. The colour reaction with FeCl$_3$ was negative. The lower band in the thin layer was eluted to yield crude XII (42 mg), which was slightly contaminated by the isomerized product XIII as revealed by TLC. XIa (50 mg) in 5% methanolic KOH (5 ml) was set aside for 4 days. TLC of the soln disclosed that no hydrolyzed material was produced.

Irradiation of nitrone (VII) in EtOH

Nitrone VII (0·3 g) in abs EtOH (40 ml) was irradiated in a pyrex vessel for 2 hr by a 150 W high pressure Hg arc lamp under N$_2$ atmosphere. Progress of the reaction was followed by TLC. At the end of 2 hr. nearly all the starting nitrone was converted into a less polar substance and the UV spectrum of the soln revealed only absorption maximum at 237 nm. No absorption at 284 nm which was observed in the starting material, was observed. Removal of the solvent under reduced pressure at 40° yielded crystals m.p. 164–171°. TLC of this showed two spots due to the starting VII and a new substance (XIV). This mixture (40 mg) in acetone was heated around 60° for 3 min and the recovery of the crystals afforded compounds which were identical with the starting VII. NMR spectrum of the oxaziridine could not be obtained owing to the rapid reversion of the oxaziridine to the nitrone in CDCl$_3$. The product (50 mg) in i-PrOH or dioxan (30 ml) was refluxed for 18 hr. VII was recovered unchanged.

Isomerization of XII to XIII

(a) With silicagel. By the procedure described previously, 300 mg of VII in pyridine was acetylated. The crude product was separated by preparative TLC (Wakogel B5, MeOH–Et$_2$O 7:41 in volume). The lower band afforded 146 mg of a residue. TLC of this proved it to be a mixture of two compounds. This was again submitted to preparative TLC to yield two substances, i.e., a slightly less polar new compound XIII (17 mg) and the compound XII (108 mg). It was found that the latter again gave two bands when it was developed on a thin layer of silicagel which showed part of XII was isomerized to XIII during preparative TLC. The compound XIII was recrystallized from acetone to yield an analytical specimen. m.p. 269–271°: IR: (6-membered ring ketone) 1707 cm^{-1}, (Δ^4-3-one) 1661 cm^{-1}. (N—Ac) 1643 cm^{-1} and (N=C) 1578 cm^{-1}: NMR: see numerals on the formula XIII: $[\alpha]_D$ −9° (c. 1·0. CHCl$_3$). (Found: C. 74·79: H. 9·62: N. 5·97. C$_{29}$H$_{36}$O$_3$N$_2$ requires: C. 75·62: H. 7·88: N. 6·08%); Mass, M$^+$ 460. UV: λ_{max}^{EtOH} 226 nm (ϵ. 24.000). 238 nm (shoulder. ϵ. 20.400) and 296 nm (ϵ. 8700).

(b) With 1·5% methanolic KOH. The compound XII (1 mg) was dissolved in 1·0 ml 1·5% methanolic KOH and set aside overnight at room temp. TLC of the mixture showed two spots. R_fs of these were the same as those of XII and XIII.

Benzoylation of the photo-product VII

The photo-product (94 mg) and benzoic anhydride (100 mg) in the pyridine (4 ml) were left for 6 hr at room temp. The mixture was poured into water (100 ml). The soln was extracted with $CHCl_3$ (100 mL and then 3 times with each 50 ml). The $CHCl_3$ layer was washed with K_2CO_3 aq (50 ml × 2) and then water (50 ml × 2), dried and evaporated. Addition of acetone to the residue yielded colourless crystals (27 mg) which recrystallized from acetone to yield 16 mg of XIb, m.p. 253–254°: IR: $(OCOC_6H_5)$ and (6-membered ring ketone) 1707 cm^{-1}, (CO—C≡C) 1677 cm^{-1}, (N—Ao) 1647 cm^{-1}; NMR: see numerals on the formula (XIb); $[\alpha]_D$ − 480° (c, 4·0, $CHCl_3$). (Found: C, 70·64; H, 6·94; N, 4·89. $C_{36}H_{44}O_6N_2$ requires: C, 71·97; H, 7·38; N, 4·66%); UV; λ_{max}^{EtOH} nm (ε): 238 (22,000).

The residue (80 mg) from the filtrate showed two major spots and the preparative TLC (acetone: $CHCl_3$ 1:2 in volume) afforded two major fractions. The more polar fraction (36 mg) was recrystallized from acetone to yield 6 mg of crystals identical with XIa. Elution of the less polar fraction afforded a yellow oily residue (30 mg). UV and NMR of this crude residue showed that this is not identical with XII. However, an unsuccessful attempt was made to purify this and clarify the structure.

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