Tetrahedron Letters No. 8, pp 661 - 664, 1972. Pergamon Press. Printed in Great Britain.

PHOTOINDUCED REARRANGEMENT OF "3-O,23-O,N-TRIACETYLISOJERVINE 11β-OL" NITRITE (1)

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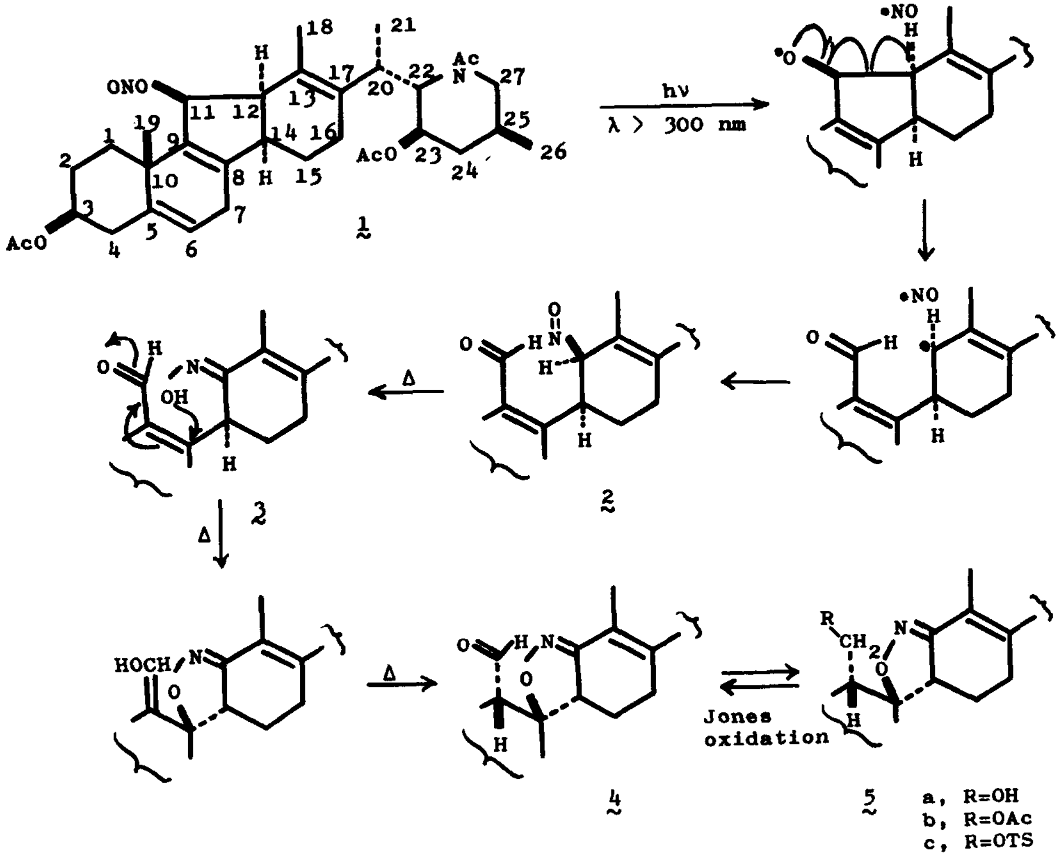
(Received in Japan 9 December 1971; received in UK for publication 18 January 1972)

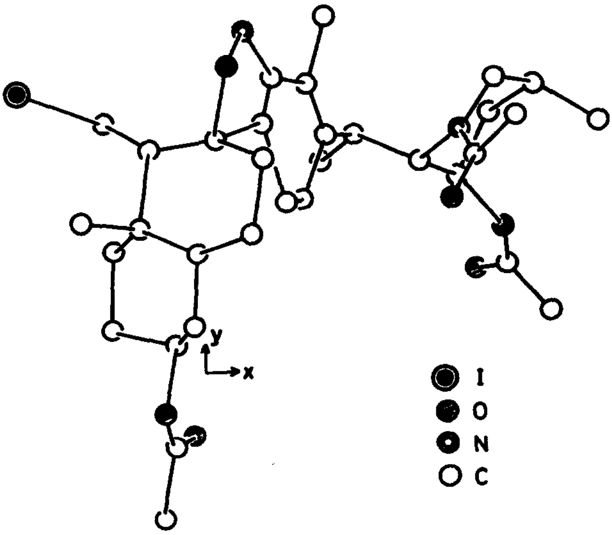
In a series of previous papers we have reported on the photoinduced formation of cyclic nitrone from nitrites of fused five-membered ring alcohols (2). In this communication, we wish to report on the photoinduced formation of a novel compound with isoxazoline structure from a nitrite 1 of a fused five-membered ring alcohol incorporated in C-nor-D-homosteroidal alkaloid.

Photolysis of "3-O,23-O,N-triacetylisojervine 11β-ol" nitrite 1, m.p. 215-217°, (3) in toluene by a 150 W high pressure Hg arc lamp through pyrex, resulted in the formation of a virtually single product 4, 217-218°, $C_{33}H_{46}O_7N_2$ (M.W., Found 582.3318, Calcd for $C_{33}H_{46}O_7N_2$, 582.3305) in ca. 50 % yield.

Spectral properties of 4 are as follows: ir (Nujol); no OH or NH, 1636 cm^{-1} (NAc), 1733 cm^{-1} with shoulders at 1723 and 1743 cm^{-1} (OAc, CHO); uv; λ_{max}^{EtOH} 258 nm (ε; 21,200); nmr (100 MHz) τ8.86, 6H (d, J=6.6 Hz)(21- and 26-CH_3), τ8.55, 3H (19-CH_3), τ8.02, 3H (18-CH_3), τ7.96, 3H (N-Ac), τ5.41, 1H, broad, (C-3H), τ5.19, 1H (d, J=12.0 Hz)(C-22β-H), τ4.92, 1H (C-23 α-H), τ4.62, 1H (C-6H) τ0.53, 0.25H, τ0.04, 0.75H (CHO). This showed that the D-ring of 1 with the double bond at the 13,17-position and with the substituent having heterocyclic ring was intact in the photo-rearrangement since the position of a doublet due to 21- and 26-CH_3 groups of the nmr spectrum of 4 was exactly the same as in the original 11β-ol (2b). The heterocyclic part of 4 was also shown by the presence of the



Scheme 1



Figure

intense fragment peaks at m/e 114, at m/e 156 (base peak) and at m/e 198 in the mass spectrum of 4 as is usual in this class of compounds (2b).

On the basis of our knowledge on the mode of the photolysis of nitrite of C-nor-D-homosteroid 11β-ol (2), an oximino-aldehyde 3, formed as in Scheme 1, would come as a most probable intermediate in the present photoinduced transformation. Indeed, uv absorption of 4 described above, gave evidence of the presence of R-O-N=C-C=C- chromophore. The photoproduct 4 afforded readily dideacetylated product 4a, m.p. 251-253°, which showed a band at 1710 cm^{-1} in the ir attributable to either a formyl or an unstrained ketone function. In agreement with this, 4 gave an oxime, m.p. 221-222° and a tosylhydrazone, m.p. 261-262°. Oppenauer oxidation of 4a afforded a product with Δ^4-3-one chromophore (uv) which showed that A-ring with the double bond at the 5-position of 1 survived in 4. Catalytic hydrogenation (EtOH-PtO_2) or $NaBH_4$ reduction of 4 at room temperature readily afforded an alcohol, $C_{33}H_{48}O_2N_2$, 5a, m.p. 224-226° (ir, 1709 and 1730 cm^{-1}, OAC, 1634 cm^{-1}, N-Ac, 3458 cm^{-1}, OH, monoacetate 5b, m.p. 189-191.5°) which, on hydrolysis with 5 % aq. methanolic KOH, gave dideacetylated compound, m.p. 173-176°, (no C=O except amide type) and reverted back to the photoproduct 4 on Jones oxidation.

Then, consideration of the probable mode of the reaction of an assumed intermediate 3 together with the partial structures clarified leads to isoxazoline formula 4 as a probable structure which accommodates the above chromophores. However, the presence of two doublets assignable to the aldehydic proton at τ0.04 and at τ0.53 with the same J (5.4 Hz, the relative area, one proton in total, of these two varies with the concentration) in the nmr was unusual. Even more unusual was the fact that, notwithstanding the presence of aldehydic group, 4 is remarkably stable to base and deuterium exchange of 4 for three times with NaOD and dioxane at 100° for 10 minutes followed by the acetylation, gave a deuterated product in which incorporation of seven deuterium was confirmed by high resolution mass spectrometry.

These ambiguities of the structure of 4 together with its absolute stereochemistry was now clarified by X-ray crystallographic analysis of iodine-containing derivative 5d, m.p. 221-222°, of 4 which was prepared by the treatment of the tosylate 5c with NaI in acetonylacetone.

Crystals of 5d were grown from absolute methanol solution as colourless plates. Crystals are monoclinic, a=13.79, b=12.66, c=10.13 Å, β=97.2°, space group $P2_1$, D(obs.)=1.327, D(calc.)=1.315 g. cm^{-3}, Z=2.

The intensity data were collected from equi-inclination Weissenberg photographs taken with Cu-Kα radiation and measured visually. As the crystals are fairly sublimable, they were coated with the α-cyanoacrylate polymer film. The structure was solved by the heavy atom method. The interpretation of the Fourier map phased by the iodine atom was not easy because of a pseudo-symmetry of the map. However, all the non-hydrogen atoms were located step by step by using the criterion of the peak arrangement with suitable distance and angle. No chemical and other information was used. The atomic parameters thus obtained were refined by the least-squares method. The R factor was reduced to 0.15. The absolute configuration was also determined using anomalous dispersion effect of the iodine atom. The perspective drawing of the structure is shown in the Figure.

On the basis of this molecular structure of 5d, the structure of the photoproduct together with its absolute stereochemistry should be as 4 in Scheme 1. In this Scheme nitroso-aldehyde 2 would thermally isomerize to an oximino-aldehyde 3 and ground state nucleophilic addition of the oximino-group to the double bond from the β-side of 3 may afford solely more stable isomer 4. The isomer due to addition from the α-side should be less stable, owing to the interaction between the formyl and the 19-methyl group. The presence of two doublets in the aldehydic region of the nmr of 4 is explained as being due to the presence of two conformers of an aldehyde in $CDCl_3$ (2.58×10^{-1} M) with the ratio of approximately 3:1.

References and notes

1) Photoinduced Transformation. XX, paper XIX, H. Suginome, T. Mizuguchi, and T. Masamune, Tetrahedron Letters, in press.
2) a) H. Suginome, N. Sato, and T. Masamune, Tetrahedron Letters, 3353 (1969); b) Tetrahedron, 27, 4863 (1971); c) H. Suginome, T. Mizuguchi, and T. Masamune, 3rd International Congress of Heterocyclic Chemistry, August, (1971), Sendai, Japan.
3) This was prepared from jervine via four steps. Details of this preparation will be published in our full paper.

Acknowledgement: We are grateful to Professor K. Biemann and Dr. C. E. Hignite of Massachusetts Institute of Technology for the determination of the high resolution mass spectra of the photoproduct and the deuterated sample.