Photoinduced Transformations. Part XXXI.[1] Photoinduced Rearrangement of (22S,25S)-N-Acetyl-5α-veratra-8,13(17)-dienine-3β,11β,23β-triol 3,23-Diacetate 11-Nitrite to Two Spiro-isoxazolines

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Photolysis of the title nitrite (9) in toluene with Pyrex-filtered light or monochromatic light (362 ± 4 nm) afforded two isomeric spiro-isoxazolines, (10) and (11), designated photo-TVDTN and isophoto-TVDTN. Only the former was obtained pure and its structure was deduced from spectral evidence. The structure of the latter, obtained only as a mixture with photo-TVDTN, was inferred from spectra. The present results, in conjunction with those in the preceding paper, indicate that the presence or absence of a 5,6-double bond has little effect on the formation of these isoxazolines.

In the preceding paper [1] we reported the photoinduced formation of the isomeric isoxazolines (2) and (3) from (22S,25S)-N-acetylveratra-5,8,13(17)-trienine-3β,11β,-23β-triol 3,23-diacetate 11-nitrite (1). A pathway involving acid-catalysed intramolecular Michael addition of an intermediate hydroxyimino-aldehyde was confirmed for this reaction.[1] We noted that whereas the nitrite (1) rearranged exclusively to the isomeric isoxazolines, photo-TVTTN and isophoto-TVTTN, on irradiation, the nitrite (4), of similar structure but without the 8,9-double bond, yielded exclusively a nitrone (5), without any isoxazolines [2,3] (Scheme 1). Although we attributed this difference to the reduced reactivity of a formyl carbon atom of an αβ-unsaturated carbonyl toward the nitroso-group of the nitroso-intermediate(s) in the former reaction, the pathway from the nitroso-

aldehyde intermediate probably depends on a variety of factors.

In particular, the mode of the intramolecular interaction of the ambient nitroso-group with the αβ-unsaturated formyl group of the intermediate from the nitrite (1) might depend on an appropriate geometry of both interacting groups. We therefore examined the products of photolysis of the 5,6-dihydro-derivative (9) of the nitrite (1), since the saturation of the 5,6-double bond, introducing a slight change in geometry of the interacting groups of the intermediates, might have been expected to change the course of the reaction.

RESULTS AND DISCUSSION

Synthesis and Photolysis of the Nitrite (9).—The nitrite (9) was synthesized *via* three steps from 5α,6-dihydroiso-
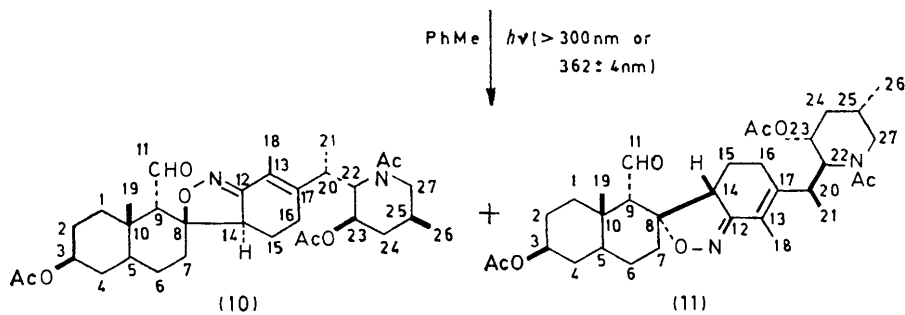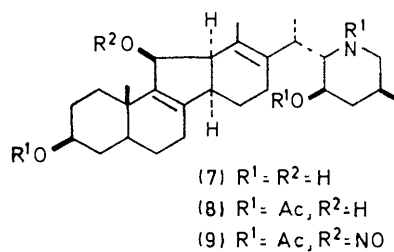
[1] Part XXX, H. Suginome, T. Tsuneno, N. Sato, N. Maeda, T. Masamune, H. Shimanouchi, Y. Tsuchida, and Y. Sasada, preceding paper.
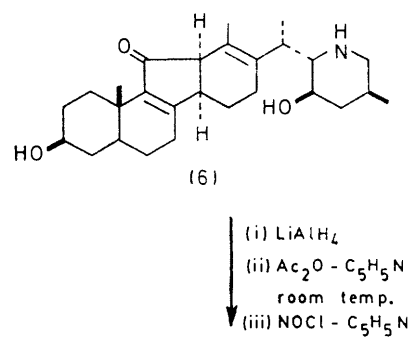
[2] H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Letters*, 1969, 3353; *Tetrahedron*, 1971, **27**, 4863.

[3] H. Suginome, T. Mizuguchi, and T. Masamune, *J.C.S. Chem. Comm.*, 1972, 376.
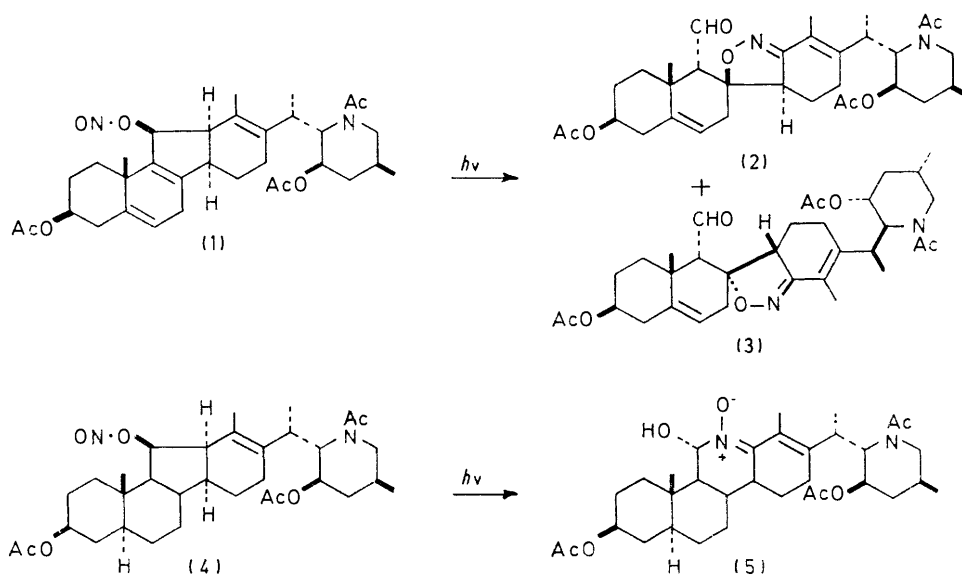
SCHEME 1

SCHEME 2

jervine (6).[4] Reduction of 5α,6-dihydroisojervine (6) with lithium aluminium hydride in tetrahydrofuran afforded a mixture of the corresponding 11α- and 11β-ols. Since it was not easy to separate these compounds by conventional means, the mixture was acetylated directly. Recrystallization of the acetylated mixture afforded the 3β,11β,23β-triol 3,23-diacetate (8), nitrosation of which gave the nitrite (9) (Scheme 2).

The photolysis was carried out in toluene with Pyrex-filtered light by the same procedure as in the previous case.[1] After completion of the reaction, t.l.c. revealed a distribution of spots similar to that observed with the nitrite (1). Preparative t.l.c. afforded crystals, m.p. 226—229°, the n.m.r. spectrum of which showed considerable similarity to that of the mixture of photo-TVTTN (2) and isophoto-TVTTN (3).[1]

It was apparent that the crystals were a mixture of two isoxazolines, (10) and (11), which were stereoisomeric

side chain appeared at m/e 156 (base peak), 198 (31.9%), and 114 (22.0%). The c-nor-D-homosteroidal fragment, free from the C-17 substituent appeared at m/e 387 (1.2%). The u.v. spectrum (solvent methanol) revealed a single maximum at 258 nm (ε 13 600), assignable to an isoxazoline chromophore. The i.r. spectrum showed a series of bands at 1 732, 1 715sh, and 1 641 cm^{-1} ascribable to the O-acetyl, formyl, and N-acetyl groups. The n.m.r. spectrum, in conjunction with double irradiation studies, enabled us to confirm the formula (10) (Table). The C-19 proton signal of photo-TVDTN (10) appeared further downfield (Δ 0.05 p.p.m.) than that of isophoto-TVDTN (11), which we were unable to isolate. In the isoxazolines either C-14 or the oxygen atom is in a quasi-1,3-diaxial relationship with the C-19 protons; it is therefore reasonable to assign the configuration of the C-8 oxygen atom of (10) as β. The downfield shift (Δ 0.08 p.p.m.) of the aldehydic proton of

Chemical shifts (τ values) and coupling constants (Hz)

Compd.	3α-H	11-H	9β-H	18-H	19-H	12α-H	14α-H	20β-H	21-H	22β-H	23α-H	26-H	27-H	OAc, NAc
(8)	ca. 5.3br	5.42 (d)		8.25 (s)	8.95 (s)		a	a	8.90 (d)	5.26br (d)	4.91br (s)	8.90 (d)	6.64br (s)	8.01 (s)
(9)	ca. 5.3br	3.42 (d)		8.42 (s)	9.27 (s)	a	a	a	8.94 (d)	5.27br (s)	4.97br (s)	8.94 (d)	a	7.99 (s, 3 H), 8.05 (s, 6 H)
(10)	5.31br	0.10 (d) *	8.14 *	8.07 (s)	8.68 (s)	a	7.17 (q) *	6.86 (q) *	8.87 (d)	5.17br (d)*	4.93br (s),* $W_{\frac{1}{2}}$ 9.0)	8.87 (d)	6.71br (s)	9.01 (s, 6 H), 9.04 (s, 3 H)
(11)	b	0.18 (d) *	7.52 (d) *	b	8.73 (s)	a	b	b	b	b	b	b	b	b

Coupling constants

Compd.	9β,11	11α,12α	14α,15α	14α,15β	20β,21	20β,22β	22β,23α	25α,26
(8)		6.0	a	a	ca. 7	10.5	1.5	ca. 7
(9)		6.9	a	a	6.9	10.5	1.5	6.9
(10)	4.8 *		4.5 *	13.5 *	6.8 *	10.5 *	1.5 *	6.7
(11)	4.8 *		b	b	b	b	b	b

a Unassignable. *b* These signals were probably superimposed on the corresponding signals of compound (10); the coupling constants should be nearly the same as those of compound (10).

* Confirmed by spin decoupling.

[two clear doublets due to the formyl protons appeared at τ 0.10 (J 4.8 Hz) and 0.18 (J 4.8 Hz)]. When the solvent was removed carefully from the photolysate below 30 °C, the n.m.r. spectrum of the residue revealed, besides two doublets due to the formyl protons of (10) and (11), a sharp singlet at τ 0.23, which coincided with a doublet due to (11). This was assignable to a formyl proton of an intermediate hydroxyimino-aldehyde. The ratio of the two isoxazolines [(10) and (11)] was 1 : 0.25 (estimated by integration of the formyl proton signals). We designate these two isoxazolines as photo-TVDTN and isophoto-TVDTN.

The formation of photo-TVDTN and isophoto-TVDTN is presumably governed by the same mechanism as the formation of photo-TVTTN and isophoto-TVTTN.[1] Since in both cases two isoxazolines are formed it appears reasonable to assume that the stereochemical relationship is the same in each case, i.e. that photo-TVDTN and isophoto-TVDTN are epimeric only at C-8.

Preparative t.l.c. enabled us to isolate only major isoxazoline, photo-TVDTN (10), in a pure state.

Structures of Photo-TVDTN and Isophoto-TVDTN.— The electron impact mass spectrum of photo-TVDTN (10) showed M^+ 584 (1.7%) in agreement with the molecular formula $C_{33}H_{48}N_2O_7$, and, as in the case of isoxazolines from the nitrite (1), the fragments due to the C-17

photo-TVDTN (10) in comparison with that of isophoto-TVDTN (11) is also parallel with the relation between the two aldehydic proton signals of photo-TVTTN and isophoto-TVTTN (2) and (3).

With regard to the formyl group of photo-TVDTN and isophoto-TVDTN, the same mechanistic consideration as in the case of the photolysis of the nitrite (1) led us to assign the configuration as 9α. Comparison of the n.m.r. spectra of photo-TVDTN (10) and the 5,6-didehydro-analogue, photo-TVTTN (2), demonstrated that differences were not significant, but the 19-H and the 14α-H were more shielded by 0.14 and by 0.09 p.p.m., respectively, in the former. The most significant difference was the upfield shift of a doublet due to the 9β-H of photo-TVDTN. In photo-TVTTN (2), the 9β-H gave as doublet at τ 7.74, whereas the corresponding signal of photo-TVDTN (10) was hidden in the methylene envelope. Double irradiation experiments, however, showed that the 9β-H of photo-TVDTN (10) was shielded by about 0.4 p.p.m. in comparison with the corresponding proton of photo-TVTTN (2) and located at τ 8.14.

The observed upfield shifts of several signals caused by the 5,6-double bond in photo-TVDTN (10) were consistent with the assigned structure.

[4] T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara, and T. Irie, *J. Org. Chem.*, 1964, **29**, 2282.

Isophoto-TVDTN (11), which was obtained only as a mixture with photo-TVDTN (10), was formulated as the 8-epimer of photo-TVDTN (10). Its formation was confirmed by the presence of a doublet at τ 0.18 (J 4.8 Hz) (CHO) and a singlet at τ 8.73 (19-H) in the n.m.r. spectrum of the initial mixture. In a double irradiation experiment on the mixture of two isoxazolines (10) and (11), irradiation at τ 7.52 caused a collapse of the doublet at τ 0.18 to a singlet. This defined the chemical shift of the 9β-proton of (11) as τ 7.52.

Photolysis by Monochromatic Light.—The nitrite was irradiated with monochromatic light (362 $\pm$ 4 nm) in toluene as solvent. The solvent was then removed below 30 °C and the n.m.r. spectrum of the product was taken immediately. As in the case of photolysis with Pyrex-filtered light, the aldehydic proton region revealed, besides two doublets due to (10) and (11), in the ratio of 1 : 0.22, a sharp singlet at τ 0.23, coincident with a doublet due to (11), and assignable to the formyl proton of an intermediate hydroxyimino-aldehyde. As in the case of the photolysis of the nitrite (1) attempts to isolate this intermediate by preparative t.l.c. were not successful.[1] We obtained only a mixture of photo-TVDTN (10) and isophoto-TVDTN (11), in 33% yield and in a ratio roughly the same as in the case of photolysis of the nitrite (1).

The foregoing results demonstrate that isoxazoline formation is little affected by the presence or otherwise of a 5,6-double bond. The presence of the double bond αβ to the formyl group in the nitroso-intermediate therefore appears crucial for switching of the reaction pathway from nitrone to isoxazoline formation.

EXPERIMENTAL

Instruments and general procedures are described in the preceding paper.[1]

Reduction of 5α,6-Dihydroisojervine (6).—5α,6-Dihydroisojervine (3 g) and lithium aluminium hydride (260 mg) in dry tetrahydrofuran (150 ml) were stirred at 0 °C. After 4, 4.5, 17, and 19.5 h, more hydride (680, 500, 410, and 150 mg) in tetrahydrofuran (100 ml) was added. The solution was stirred at 0 °C for 5 h, at room temperature for 28.5 h, and at 30—40 °C for 2 h, then cooled to 0 °C, and the excess of hydride was decomposed by adding ice–water in portions. The solution was extracted with ether (700 ml) and tetrahydrofuran (500 ml). The extract was washed with water, dried (Na₂SO₄), and evaporated to leave an amorphous residue (3.36 g). A part of this (260 mg) was twice recrystallized from acetone to yield 19 mg of (22S,25S)-5α-veratra-8,13(17)-dienine-3β,11β,23β-triol (7) (19 mg), m.p. 172—174° (Found: C, 75.2; H, 9.9; N, 3.1. $C_{27}H_{43}NO_3$ requires C, 75.5; H, 10.1; N, 3.25%); m/e 429 ($M^{+\cdot}$, 0.2%), 298 (4.0), 396 (4.0), 383 (35), and 114 (100); $\lambda_{max.}$ (MeOH) 205 nm (ε 10 100).

(22S,25S)-N-*Acetyl*-5α-*veratra*-8,13(17)-*dienine*-3β,11β,23β-*triol 3,23-Diacetate* (8).—The crude amorphous triol (7) (2 g), obtained as described above and contaminated with the corresponding 11α-ol, was dissolved in pyridine (19 ml).

Acetic anhydride (2.5 ml) was added and the solution was stirred for 19.5 h at room temperature. After addition of methanol (24 ml), pyridine was removed by rotary evaporator. The residue was dissolved in chloroform and this solution was washed with 2N-hydrochloric acid (50 ml × 2) and water. Work-up as usual afforded a residue (2.6 g) which was recrystallized from acetone to yield the crude diacetate (560 mg). This was recrystallized twice from acetone to yield the *diacetate* (8) (502 mg) in two crops, m.p. 194—197° (Found: C, 71.2; H, 8.8; N, 2.55. $C_{33}H_{51}NO_6$ requires C, 71.05; H, 9.2; N, 2.5%); $\lambda_{max.}$ (MeOH) 217 nm (ε 13 800); $\nu_{max.}$ 1 741 (OAc), 1 617 (NAc), and 3 428 cm⁻¹ (OH); for n.m.r. see Table; m/e 114 (20.3%), 156 (100), 198 (60.8), 339 (20.3), and 555 ($M^{+\cdot}$, 0.3).

The 11β-*Nitrite* (9).—The diacetate (8) (120 mg) in pyridine (2 ml) was cooled (acetone–solid CO₂) and nitrosyl chloride in pyridine was added dropwise until the colour of the solution became brown. The solution was stirred for 30 min and poured into water. The precipitate (a single spot on t.l.c.) had m.p. 199—201.5°; $\nu_{max.}$ 1 732 (OAc), 1 625 (NAc), and 768 cm⁻¹ (N–O); $\lambda_{max.}$ (MeOH) 215 (ε 8 900), 391 (94), 362 (92), and 346 nm (90); for n.m.r. see Table 1.

Photolysis of the Nitrite (9).—(*a*) The nitrite (9) (1.05 g) in toluene (23 ml) in a Pyrex vessel was irradiated with a 100 W high-pressure mercury arc under argon at room temperature. After 34 h, the decomposition of the nitrite was complete and the solvent was removed at 30 °C under diminished pressure. The residue was dissolved in chloroform (80 ml). The solution was washed with water (50 ml × 3), dried (Na₂SO₄), and evaporated. The amorphous residue (1.29 g) revealed a single spot on t.l.c. Preparative t.l.c. (ether–benzene, 4 : 1) of a part (610 mg) of this afforded a mixture (230 mg) of isoxazolines, m.p. 212—223°. Two recrystallizations of this from ether afforded crystals, m.p. 226—229°. This recrystallization procedure did not alter the ratio of the two aldehydic proton signals due to photo-TVDTN and isophoto-TVDTN. A part of the product (97 mg) was purified by preparative t.l.c. (benzene–chloroform–ether, 1 : 2 : 4; three developments). Elution of the less polar band afforded pure *photo-TVDTN* (10), which was recrystallized from ether; yield 26 mg, m.p. 255—258° (Found: C, 67.55; H, 8.4; N, 4.75. $C_{33}H_{48}N_2O_7$ requires C, 67.8; H, 8.25; N, 7.5%).

The more polar band from the t.l.c. plates afforded a mixture of isoxazolines (10) and (11). Pure isoxazoline (11) was not obtained.

(*b*) A solution of the nitrite (9) (100 mg) in toluene (2.6 ml) in a silica cell (10 × 10 × 45 mm) was flushed with argon for 10 min, placed in the chamber of a JASCO CRM-FA grating spectro-irradiator, and irradiated with monochromatic light (λ 362 ± 4 nm). The reaction was monitored by t.l.c. After completion, the solvent was evaporated off below 30 °C. Photo-TVDTN and isophoto-TVDTN formed were purified by preparative t.l.c. (ether–hexane–benzene, 30 : 4 : 1) to afford a mixture (43 mg) of the isoxazolines (10) and (11). This was once recrystallized from ether (yield 33 mg); for n.m.r. data see text and Table; for (10) $\lambda_{max.}$ (MeOH) 206 (ε 10 100) and 258 nm (13 600).