Photoinduced Transformations. Part XXX.[1] Photorearrangement of (22S,25S)-N-Acetylveratra-5,8,13(17)-trienine-3β,11β,23β-triol 3,23-Diacetate 11-Nitrite, a Fused Cyclopentenyl Nitrite, to Two Spiroisoxazolines [2]

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Irradiation of the title nitrite (3) in protic or aprotic solvents with Pyrex-filtered light induced an extensive re-arrangement to afford two products with novel isoxazoline structures, designated photo-TVTTN and isophoto-TVTTN, in good yields. The structure and absolute configuration of photo-TVTTN (4) were determined by chemical and spectroscopic studies and by an X-ray crystallographic analysis of an iodine-containing derivative (14). The structure and absolute configuration of isophoto-TVTTN (5) were deduced by spectroscopic studies.

A photoreaction carried out with monochromatic light (362 ± 4 nm) confirmed that light was only involved in homolysis of the O—NO bond, and that photo- and isophoto-TVTTN were formed via an unstable hydroxyimino-aldehyde (19), which was isolated. The hydroxyimino-aldehyde was transformed smoothly into photo- and iso-photo-TVTTN on silica gel during t.l.c. Whereas the silica gel-induced transformation was non-stereoselective, leading to both photo- (4) and isophoto-TVTTN (5), the transformation of the hydroxyimino-aldehyde with acetic acid or [²H]acid was stereoselective, giving mainly isophoto-TVTTN (5) or [9β-²H]isophoto-TVTTN (21), respectively. Deuterium is incorporated into the TVTTNs in the course of an intramolecular Michael reaction cata-lysed by acetic [²H]acid. This unusually ready intramolecular reaction seems to be the first reported example of a Michael addition of an oxime hydroxy-group to an αβ-unsaturated carbonyl system.

WE have reported previously [3] that the photolysis of nitrites of several fused five-membered ring alcohols incorporated in a (22S,23R,25S)-jervanine or (22S,-25S)-veratr-13(17)-enine skeleton proceeds with a variety of reaction pathways. We now report studies of the photorearrangement of (22S,25S)-N-acetylveratra-5,8,-13(17)-trienine-3β,11β,23β-triol 3,23-diacetate 11-nitrite (3) into two unusual spiro-isoxazolines, designated photo-TVTTN and isophoto-TVTTN.[2]

RESULTS

Synthesis and Photolysis of the Nitrite (3).—The nitrite (3) was readily prepared (Scheme 1) by nitrosation of the corresponding 11β-ol (2), which has been prepared from isojervine.[4, †]

Irradiation of the nitrite (3) in dry toluene (8.8 × 10⁻²M) under nitrogen through Pyrex afforded a crude product with a trace of the parent 11β-ol (2) (isolated by alumina column chromatography). The recrystallized product, obtained in 42% yield, appeared to be homogeneous, even on t.l.c.,

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† The determination of the structure of veratrobasine by means of X-ray diffraction analysis (G. N. Reeke, jun., R. L. Vincent, and W. N. Lipscomb, *J. Amer. Chem. Soc.,* 1968, **90**, 1663) led to revision of the structure of jervine. On the basis of this revision, the proposed structures [4] for isojervine and all the compounds derived from it should also be revised, and isojervine should be

(A)
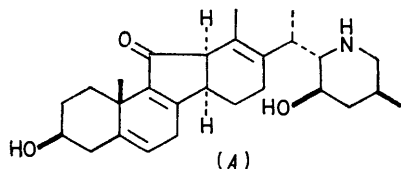
formulated as (A). The present work provides further evidence for the structure of isojervine and confirms the correctness of the revised structure for jervine.

‡ The specimen described as photo-TVTTN (4) in our pre-liminary communication [2] was thus in fact a mixture of isomers. At that time we erroneously interpreted some n.m.r. signals of this specimen on the assumption of the presence of two con-formers in CDCl₃. However, apart from this point, the present finding does not affect the structural assignments in our pre-liminary communication.

and recrystallization from various solvent mixtures did not alter its n.m.r. spectrum. However, at a later stage we became increasingly suspicious of this homogeneity, since we came across some unsatisfactory features in elucidating the n.m.r. spectrum. A further t.l.c. study with various solvent mixtures then showed that the product was ac-tually a 1 : 3 mixture of two isomers.‡ These were separ-ated by preparative t.l.c. into photo-TVTTN (4) (major) and isophoto-TVTTN (5) (minor).

The chemical ionization mass spectra of the products (4) and (5) both showed a series of fragments indicative of a molecular weight of 582. The molecular formula C₃₃H₄₆N₂O₇ agreed with this and with the analytical figures.

Chemical and Spectroscopic Properties and Structure of Photo-TVTTN (4).—The electron impact mass spectrum of photo-TVTTN (4) revealed prominent fragment ions at m/e 385 (2.6%), 198 (47.9%), 156 (base peak), and 114 (22.9%). The latter three fragments were immediately ascribable to the heterocyclic units.[3f] The fragment m/e 385 corresponded to loss of the C-17 substituent. These results showed that the 13,17-double bond with the sub-stituent at C-17 of the nitrite (3) was intact in photo-TVTTN (4).[3f] ¹H N.m.r. data for photo-TVTTN (4), confirmed by double-irradiation studies, are shown in Table 6. The position of the doublet due to the 21- and 26-protons is

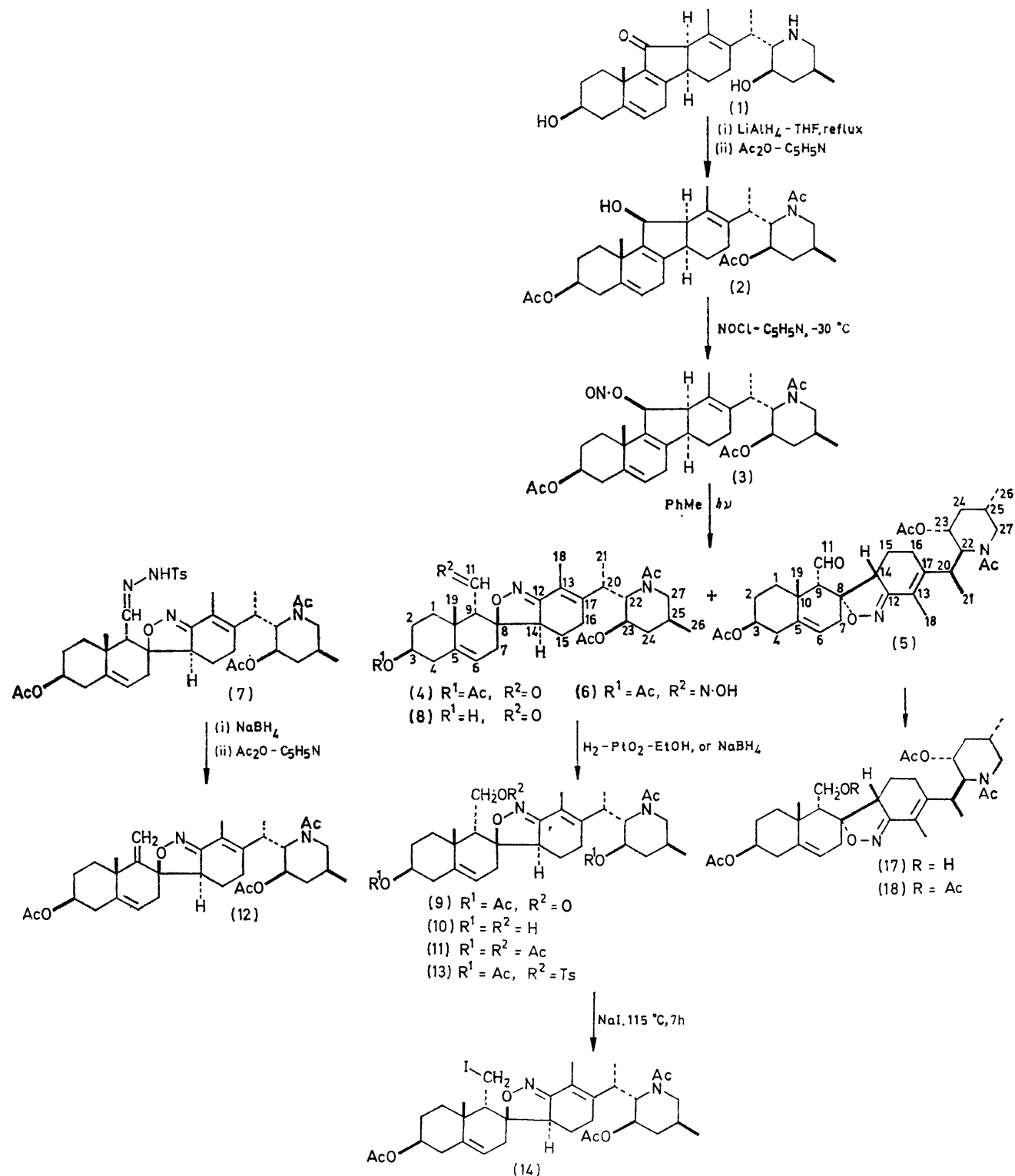[1] Part XXIX, H. Suginome, A. Furusaki, K. Kato, and T. Matsumoto, *Tetrahedron Letters,* 1975, 2757.

[2] Preliminary communication, H. Suginome, T. Tsuneno, N. Sato, T. Masamune, H. Shimanouchi, Y. Tsuchida, and Y. Sasada, *Tetrahedron Letters,* 1972, 661.

[3] (a) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Letters,* 1967, 1557; (b) H. Suginome, N. Sato, and T. Masamune, *Bull. Chem. Soc. Japan,* 1969, **42**, 215; (c) H. Suginome, I. Yamazaki, O. Ono, and T. Masamune, *Tetrahedron Letters,* 1968, 5259; (d) H. Suginome, I. Yamazaki, H. Ono, and T. Masamune, *J. Chem. Soc. Japan, Ind. Chem. Sect.,* 1969, **72**, 243; (e) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Letters,* 1969, 3353; (f) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron,* 1971, **27**, 4863; (g) H. Suginome, T. Mizuguchi, and T. Masamune, *J.C.S. Chem. Comm.,* 1972, 376; (h) H. Suginome, T. Mizuguchi, and T. Masamune, *Tetrahedron Letters,* 1971, 4723.

[4] (a) T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara, and T. Irie, *J. Org. Chem.,* 1964, **29**, 2282; (b) W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein, *ibid.,* 1963, **28**, 293; (c) O. Wintersteiner and M. Moore, *ibid.,* 1964, **29**, 262.

the same as in the parent 11β-ol (2) and in the nitrite (3). This again proved the survival of the 13,17-double bond in photo-TVTTN (4).[3f] On the basis of our knowledge of the mode of photoreaction of the nitrite of a related compound,[3f] a hydroxyimino-aldehyde (Scheme 2) was inferred as a

probable intermediate. Consideration of the probable modes of the reaction of this assumed intermediate led us to assign the isoxazoline formula (4) (except for the stereo-chemistry at C-8 and C-9) as the most probable structure which accounted for the spectral data.

(i) LiAlH₄ - THF, reflux
(ii) Ac₂O - C₅H₅N

NOCl - C₅H₅N, -30 °C

PhMe hν

(4) R¹ = Ac, R² = O
(8) R¹ = H, R² = O

(6) R¹ = Ac, R² = N·OH

(5)

(7)

(i) NaBH₄
(ii) Ac₂O - C₅H₅N

H₂ - PtO₂ - EtOH, or NaBH₄

(12)

(9) R¹ = Ac, R² = O
(10) R¹ = R² = H
(11) R¹ = R² = Ac
(13) R¹ = Ac, R² = Ts

(17) R = H
(18) R = Ac

NaI, 115 °C, 7h

(14)

SCHEME 1

In agreement with the assumed structure (4), photo-TVTTN gave an oxime (6) and a tosylhydrazone (7). Hydrolysis of photo-TVTTN (4) afforded a dideacetylated compound (8). Catalytic hydrogenation ($EtOH-PtO_2$) or reduction with sodium borohydride of photo-TVTTN (4) at room temperature readily afforded an alcohol, $C_{33}H_{48}N_2O_2$ (9) which (i) on hydrolysis with aqueous methanolic 5% potassium hydroxide gave a dideacetylated compound (10), (ii) on acetylation gave a monoacetyl derivative (11), and (iii) reverted to photo-TVTTN (4) on Jones oxidation. Reduction of the tosylhydrazone (7) with sodium borohydride afforded compound (12), $C_{33}H_{46}N_2O_6$ (M^+ 566), in poor yield, identified on the basis of u.v. and ^1H n.m.r. spectral data (Table 6). Although the major course of the reduction of tosylhydrazones with complex metal hydrides [5] is known to be the formation of corresponding saturated hydrocarbones, olefin production has been observed in some cases [6] and a mechanism for this has been advanced.[6b]

Base-catalysed deuterium exchange of the 1 : 3 mixture of the two isomeric photoproducts resulted in deuterium incorporation. A high resolution mass spectrum indicated the presence of a mixture in which deuterium atoms were incorporated in various degrees. The presence of four intense molecular ion peaks [m/e 586.3548 (20.3%), 587.3593 (32.8%), 588.3601 (31.2%), and 589.3666 (15.6%)] suggested a mixture of [$^2H_4$]- to [$^2H_7$]-compounds. Two, five, and five intense fragment ions corresponding to the heterocyclic fragments (I), (II), and (III) respectively were observed. The masses observed and their intensities (%) were as follows: 114.0891 (35), 115.0949 (43), 156.1030 (48), 157.1037 (78), 158.1130 (100), 159.1163 (86), 160.1237 (29), 198.1119 (33), 199.1173 (70), 200.1187 (100), 201.1282 (96), and 202.1309 (40). Moreover, four intense ions corresponding to fragments free of the C-17 substituent were observed, at m/e 387.2332 (58%), 388.2482 (57), 389.2522 (45), and 390.2555 (10).

These data suggested that (a) 0—4 deuterium atoms were incorporated into the heterocyclic part and the mass 201.1282 was due to the ion (IV) (theory, 201.1318) and (b) 0—4 deuterium atoms were incorporated into the c-nor-D-homosteroid part. The deuteriated photo-TVTTN

(I) $R^1 = R^2 = Ac$
(II) $R^1 = H, \quad R^2 = Ac$
(III) $R^1 = Ac, \quad R^2 = H$
(IV) $R^1 = Ac, \quad R^2 = CO \cdot CD_3$
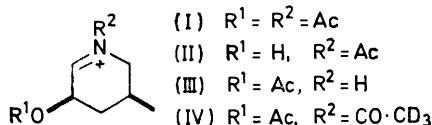
was reduced to the corresponding dihydro-derivative with sodium borohydride. Comparison of the n.m.r. spectrum of the product with that of dihydro-TVTTN showed that the signals due to the 6- and the 11-H appeared as a sharp singlet in the former, whereas the shapes of the 18-, 14α-, and the 20β-H signals were unchanged. These observations suggested that deuterium atoms were not only incorporated at position 9 as expected, but also at the 4-, 7-, and 16-positions.

The full structure of photo-TVTTN together with its absolute stereochemistry was finally clarified by X-ray crystallographic analysis of the iodine-containing derivative (14), prepared by the treatment of the tosylate (13) of dihydrophoto-TVTTN (9) with sodium iodide in boiling acetonylacetone.

[5] L. Caglioti and M. Magi, Tetrahedron Letters, 1962, 126; L. Caglioti, Tetrahedron, 1966, 22, 487.

X-Ray Structure Determination of the Iodine-containing Derivative (14).—The crystals used were obtained as plates from absolute methanol and were coated with α-cyano-acrylate polymer film in order to reduce sublimation.

Crystal data. $C_{33}H_{47}IN_2O_6$, $M = 694.65$. Monoclinic, $a = 13.79(2)$, $b = 12.66(1)$, $c = 10.13(1)$ Å, $\beta = 92.2(1)°$, $U = 1\,754.6$ Å^3, D_m (by flotation) $= 1.306$, $D_c = 1.314$ g cm^{-3}, $Z = 2$. Systematic absences: $0k0$ when k odd, space group $P2_1$. $\mu(Cu-K_\alpha) = 76.7$ cm^{-1}.

TABLE 1

Final atomic co-ordinates × 10^4 and temperature factors with their estimated standard deviations

Atom	x/a	y/b	z/c	$B(Å^2)$
I	−2 117(2)	5 000(0)	7 034(3)	*
O(1)	−69(18)	−674(21)	7 090(24)	5.2(0.6)
O(2)	483(23)	−1 066(30)	9 128(33)	8.7(0.9)
O(3)	1 112(14)	5 301(18)	7 152(19)	3.9(0.5)
O(4)	5 811(17)	2 396(21)	13 288(23)	4.9(0.6)
O(5)	6 438(36)	858(44)	13 788(49)	15.4(1.6)
O(6)	4 691(23)	2 839(29)	9 661(31)	8.4(0.9)
N(1)	1 756(21)	5 687(26)	8 329(29)	4.8(0.7)
N(2)	5 049(26)	4 061(34)	11 257(36)	7.5(1.0)
C(1)	−681(23)	2 172(31)	7 932(32)	3.7(0.7)
C(2)	−786(25)	868(33)	7 810(35)	4.5(0.8)
C(3)	123(22)	492(27)	7 147(31)	3.5(0.7)
C(4)	376(26)	811(34)	6 004(36)	4.9(0.8)
C(5)	479(20)	2 076(26)	6 170(28)	2.5(0.6)
C(6)	1 349(22)	2 452(29)	5 930(30)	3.3(0.7)
C(7)	1 512(21)	3 678(28)	6 084(30)	3.0(0.7)
C(8)	1 008(21)	4 040(29)	7 222(30)	3.2(0.7)
C(9)	−143(20)	3 923(28)	6 851(29)	2.7(0.6)
C(10)	−327(24)	2 662(31)	6 730(33)	4.1(0.8)
C(11)	−677(18)	4 473(23)	7 843(27)	2.1(0.5)
C(12)	1 981(21)	5 078(46)	9 014(29)	4.6(0.7)
C(13)	2 666(21)	4 907(46)	10 326(30)	4.8(0.7)
C(14)	1 356(26)	3 890(34)	3 668(35)	4.6(0.8)
C(15)	2 119(24)	3 000(32)	9 036(34)	4.2(0.8)
C(16)	2 506(23)	2 952(31)	10 584(33)	4.0(0.8)
C(17)	2 897(26)	4 144(34)	10 907(36)	4.9(0.8)
C(18)	2 972(30)	6 126(38)	10 677(43)	6.3(1.0)
C(19)	−1 279(28)	2 681(37)	5 579(39)	5.8(1.0)
C(20)	3 538(25)	4 108(32)	12 310(34)	4.4(0.8)
C(21)	3 007(30)	3 546(38)	13 420(41)	6.1(1.0)
C(22)	4 498(22)	3 519(29)	12 087(31)	3.5(0.7)
C(23)	5 231(33)	3 345(42)	13 512(46)	7.5(1.2)
C(24)	5 733(31)	4 355(36)	14 061(43)	6.7(1.1)
C(25)	6 228(40)	4 848(79)	13 052(54)	12.0(1.7)
C(26)	7 231(34)	4 258(41)	12 530(46)	7.5(1.2)
C(27)	5 535(34)	5 004(79)	11 739(47)	10.0(1.3)
C(28)	99(35)	−1 414(43)	8 011(48)	7.8(1.3)
C(29)	−113(29)	−2 545(37)	7 817(40)	6.0(1.0)
C(30)	5 817(46)	1 846(59)	13 851(62)	11.9(1.9)
C(31)	5 494(35)	1 746(45)	15 249(49)	8.2(1.3)
C(32)	5 044(39)	3 616(44)	9 926(54)	8.1(1.3)
C(33)	5 597(66)	4 338(75)	8 981(89)	19.2(3.6)

* Anisotropic temperature factors × 10^5 in the form

$$\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)].$$

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
I	511(11)	1 849(34)	1 533(29)	351(60)	−3(29)	−149(96)

Reflections were recorded on multiple-film equi-inclination Weissenberg photographs for $h0l$—$h9l$ and $hk0$—$hk1$, by using Cu-K_α radiation. Intensities were measured with a TV densitometer,[7] 1 453 non-zero reflections being obtained out of a possible 2 132. Corrections for Lorentz and polarization factors were made as usual and those for variation of spot-size in higher layer photographs by the

[6] (a) L. Caglioti and M. Magi, Tetrahedron Letters, 1961, 1261; (b) M. Fischer, Z. Pelah, D. H. Williams, and C. Djerassi, Chem. Ber., 1965, 98, 3236.
[7] T. Izumi, Japan J. Appl. Phys., 1971, 10, 1724.

method proposed by Takenaka and Sasada.[8] No correction was made for absorption effects. The structure was solved

TABLE 2

Bond lengths and angles

Bond lengths (Å) *

I–C(11)	2.16	C(9)–C(10)	1.62
O(2)–C(28)	1.27	C(12)–C(13)	1.55
O(4)–C(23)	1.48	C(13)–C(18)	1.63
O(6)–C(32)	1.12	C(17)–C(20)	1.58
N(2)–C(27)	1.43	C(22)–C(23)	1.67
C(1)–C(10)	1.50	C(25)–C(26)	1.71
C(4)–C(5)	1.61	C(30)–C(31)	1.54
C(6)–C(7)	1.57	O(1)–C(28)	1.32
C(8)–C(14)	1.50	O(3)–C(8)	1.61
C(10)–C(19)	1.64	O(5)–C(30)	1.52
C(13)–C(17)	1.16	N(2)–C(22)	1.38
C(16)–C(17)	1.62	C(1)–C(2)	1.66
C(20)–C(22)	1.56	C(3)–C(4)	1.31
C(24)–C(25)	1.44	C(5)–C(10)	1.51
C(28)–C(29)	1.47	C(7)–C(8)	1.49
O(1)–C(3)	1.50	C(9)–C(11)	1.49
O(3)–N(1)	1.48	C(12)–C(14)	1.75
O(4)–C(30)	0.90	C(14)–C(15)	1.56
N(1)–C(12)	1.06	C(20)–C(21)	1.59
N(2)–C(32)	1.46	C(23)–C(24)	1.53
C(2)–C(3)	1.57	C(25)–C(27)	1.55
C(5)–C(6)	1.34	C(32)–C(33)	1.59
C(8)–C(9)	1.59		

Bond angles (°) †

C(3)–O(1)–C(28)	131	N(1)–O(3)–C(8)	110
C(23)–O(4)–C(30)	120	O(3)–N(1)–C(12)	113
C(22)–N(2)–C(27)	119	C(22)–N(2)–C(32)	115
C(27)–N(2)–C(32)	126	C(2)–C(1)–C(10)	113
C(1)–C(2)–C(3)	105	O(1)–C(3)–C(2)	100
O(1)–C(3)–C(4)	110	C(2)–C(3)–C(4)	127
C(3)–C(4)–C(5)	104	C(4)–C(5)–C(6)	114
C(4)–C(5)–C(10)	118	C(6)–C(5)–C(10)	128
C(5)–C(6)–C(7)	117	O(3)–C(8)–C(9)	100
O(3)–C(8)–C(7)	103	O(3)–C(8)–C(14)	99
C(9)–C(8)–C(7)	110	C(9)–C(8)–C(14)	114
C(7)–C(8)–C(14)	127	C(8)–C(9)–C(10)	105
C(8)–C(9)–C(11)	111	C(10)–C(9)–C(11)	115
C(6)–C(7)–C(8)	108	C(1)–C(10)–C(5)	116
C(1)–C(10)–C(9)	114	C(1)–C(10)–C(19)	106
C(5)–C(10)–C(9)	114	C(5)–C(10)–C(19)	108
C(9)–C(10)–C(19)	98	N(1)–C(12)–C(13)	140
N(1)–C(12)–C(14)	114	C(13)–C(12)–C(14)	107
C(12)–C(13)–C(17)	131	C(12)–C(13)–C(18)	100
C(17)–C(13)–C(18)	129	C(8)–C(14)–C(12)	100
C(8)–C(14)–C(15)	117	C(12)–C(14)–C(15)	106
C(14)–C(15)–C(16)	113	C(15)–C(16)–C(17)	103
C(13)–C(17)–C(16)	128	C(13)–C(17)–C(20)	125
C(16)–C(17)–C(20)	107	C(17)–C(20)–C(21)	113
C(17)–C(20)–C(22)	106	C(21)–C(20)–C(22)	111
N(2)–C(22)–C(20)	113	N(2)–C(22)–C(23)	106
C(20)–C(22)–C(23)	112	O(4)–C(23)–C(22)	105
O(4)–C(23)–C(24)	121	C(22)–C(23)–C(24)	114
C(23)–C(24)–C(25)	110	C(24)–C(25)–C(26)	120
C(24)–C(25)–C(27)	112	C(26)–C(25)–C(27)	103
N(2)–C(27)–C(25)	114	O(1)–C(28)–O(2)	114
O(1)–C(28)–C(29)	126	O(2)–C(28)–C(29)	121
O(4)–C(30)–O(5)	125	O(4)–C(30)–C(31)	132
O(5)–C(30)–C(31)	102	O(6)–C(32)–N(2)	121
O(6)–C(32)–C(33)	126	N(2)–C(32)–C(33)	113
I–C(11)–C(9)	113		

* Average standard deviation estimated as 0.07 Å.
† Average standard deviation estimated as 4°.

by the heavy atom method and refined by the block-diagonal matrix least-squares method with unit weights to the final R value of 0.14.
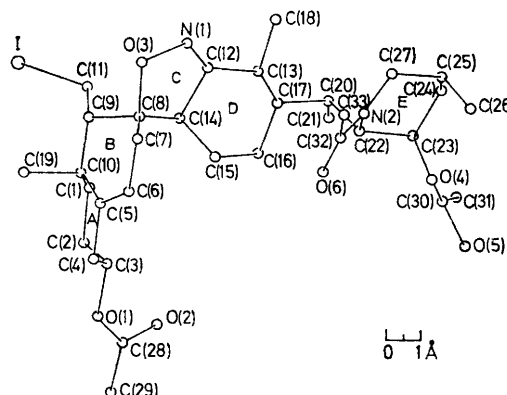
The atomic parameters thus obtained are given in Table 1, and the bond lengths and angles in Table 2. The large

‡ For details see Notice to Authors No. 7, in *J.C.S. Perkin I*, 1975, Index issue.

standard deviations are ascribed partly to crystal deterioration due to radiation damage, and partly to sublimation. The absolute configuration of the molecule was determined by using the anomalous dispersion effect of the iodine atom. Significant differences in intensity were found in each set of nine Bijvoet pairs. For such pairs, $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$ were calculated by using the values $f' = -1.20$ and $f'' = 7.00$ for iodine with Cu-K_α radiation.[9] The co-ordinate systems of real and reciprocal spaces were left-handed. As shown in Table 3, the inequalities observed in all pairs agreed with those calculated. The molecular structure with the absolute configuration is shown in the Figure. It was thus established that the chirality at C(20) is R and that the substituents at C(23) and C(25) are in axial positions.

TABLE 3

Comparison between structure factor magnitudes in Bijvoet pairs (Cu-K_α radiation)

h	k	l	$|F_c(hkl)|$	$|F_c(\bar{h}\bar{k}\bar{l})|$	$I_0(hkl)$	$I_0(\bar{h}\bar{k}\bar{l})$
2	1	0	36	25	>	
1	1	0	27	20	>	
3	1	0	69	53	>	
9	1	0	18	25	<	
2	6	0	60	65	<	
4	1	1	15	32	<	
5	1	2	44	50	<	
6	5	3	34	36	<	
2	1	4	46	34	>	

Perspective drawing of the molecule of the iodo-compound (14) viewed down the [101] direction, with atomic numbering and ring designations

Rings A and E are in the chair form, and rings B and D assume a distorted half-chair conformation. Torsion angles in the rings and equations of the least-squares planes are given in Tables 4 and 5, respectively. The torsion angle H(20)–C(20)–C(22)–H(22), is estimated to be 175° in the crystal. There are no abnormally short intermolecular contacts in the crystal.

Observed and calculated structure factors are deposited as Supplementary Publication No. SUP 21721 (9 pp.).‡

On the basis of the molecular structure of (14), photo-TVTTN (4) is assigned the structure and absolute stereochemistry shown in Scheme 1.

¹H and ¹³C N.m.r. Spectra of Photo-TVTTN (4) and Derivatives.—With the aid of extensive double irradiation studies we assigned nearly all the low-field signals in the

[8] A. Takenaka and Y. Sasada, presented at the Annual Meeting, Cryst. Soc. Japan, Osaka, Japan, 1973, Abstracts, p. 27.
[9] 'International Tables for X-Ray Crystallography,' Kynoch Press, Birmingham, 1968, vol. 3.

¹H n.m.r. spectra of photo-TVTTN (4) and its derivatives. These data were essential for elucidation of the structure of isophoto-TVTTN. Details are given in Table 6.

Thus, the quartet at τ 6.83 was due to the 20β-H ($J_{20\beta,22\beta}$ 11.3, $J_{20\beta,21}$ 6.8 Hz). The coupling constants confirmed that the photo-product (4) in $CDCl_3$ exists in a conformation in which the torsion angle between the C(20)β-H and C(22)β-H bonds is *ca.* 180°.[10] Another quartet, at τ 7.08, could be assigned to the 14-H by double irradiation and by comparison with the corresponding signal in the spectrum

TABLE 4

Torsion angles around the rings (°)

Ring A

C(10)–C(1)–C(2)–C(3)	−40
C(2)–C(3)–C(4)–C(5)	−57
C(4)–C(5)–C(10)–C(1)	−45
C(1)–C(2)–C(3)–C(4)	56
C(3)–C(4)–C(5)–C(10)	47
C(5)–C(10)–C(1)–C(2)	42

Ring B

C(6)–C(5)–C(10)–C(9)	−9
C(10)–C(9)–C(8)–C(7)	−67
C(8)–C(7)–C(6)–C(5)	−37
C(5)–C(10)–C(9)–C(8)	35
C(9)–C(8)–C(7)–C(6)	68
C(7)–C(6)–C(5)–C(10)	8

Ring C

C(14)–C(8)–O(3)–N(1)	−18
O(3)–N(1)–C(12)–C(14)	10
C(12)–C(14)–C(8)–O(3)	19
C(8)–O(3)–N(1)–C(12)	4
N(1)–C(12)–C(14)–C(8)	−22

Ring D

C(13)–C(12)–C(14)–C(15)	40
C(16)–C(17)–C(13)–C(12)	5
C(14)–C(15)–C(16)–C(17)	55
H(14α)–C(14)–C(15)–H(15α)	−58 *
C(17)–C(13)–C(12)–C(14)	−13
C(15)–C(16)–C(17)–C(13)	−23
C(12)–C(14)–C(15)–C(16)	−65
H(14α)–C(14)–C(15)–H(15β)	−177 *

Ring E

C(27)–N(2)–C(22)–C(23)	52
C(22)–C(23)–C(24)–C(25)	53
C(24)–C(25)–C(27)–N(2)	53
N(2)–C(22)–C(23)–C(24)	−50
C(23)–C(24)–C(25)–C(27)	−53
C(25)–C(27)–N(2)–C(22)	−56

* These angles are based on the hydrogen positions calculated geometrically from the pertinent carbon atom co-ordinates.

of the dihydro-derivative (9). Irradiation at τ 7.3 decoupled this quartet to a doublet (J 11.8 Hz). In the reduced compound (9), the corresponding quartet appeared significantly further downfield at τ 6.22 (Δ 0.86 p.p.m.). This shift was mainly attributable to deshielding by the newly formed CH_2OH group, which exists in a 1,3-diaxial-like relationship with the 14α-H. Although the geminal C-11 protons in dihydrophoto-TVTTN (9) were equivalent in the ¹H n.m.r. spectrum, the corresponding protons in compounds (13) and (11), containing the bulkier tosyloxy- or acetoxy-group, were non-equivalent. Thus, irradiation of the signal due to 9β-proton of the acetate (11) caused collapse of the signals due to the C-11 methylene protons into the four lines of a typical AB system with a small δ/J value.

The ¹³C n.m.r. spectrum of photo-TVTTN (4) shows

resonances for 28 carbon atoms. With the aid of off-resonance decoupling we could assign only the sp^2 carbon atoms and those bearing oxygen with reasonable certainty. The formyl carbon signal and a signal for three OAc groups appeared at 205.796 and 170.364 p.p.m. (from $MeSi_4$). Among the five sp^2 carbon signals, those at 118.612 and 160.213 p.p.m. were assignable to C-6 and C-12. By analogy with the effect of a conjugated carbonyl group on β-olefinic shielding, the lowest field peak (147.188 p.p.m.) of the remainder was assigned to C-17. Moreover, by analogy with cholesteryl acetate,[11] a signal at 137.844 p.p.m. was assigned to C-5. The remaining signal at 120.614 p.p.m. should then be due to C-13. The structure (4) contains three sp^3 carbon atoms bearing oxygen, and three signals immediately downfield of the above olefinic signals were therefore assigned to these nuclei. The quaternary nature of the carbon atom giving the lowest field signal (85.788 p.p.m.) was confirmed by off-resonance decoupling; therefore this signal was assigned to C-8. The remaining two signals at 73.169 and 69.165 p.p.m., due to C-3 and C-23, were not clearly distinguished. However, again by analogy with cholesteryl acetate we tentatively assigned the former to C-3 and the latter to C-23.

Structure of Isophoto-TVTTN (5).—From the mass, i.r., n.m.r., and u.v. spectra it was immediately apparent that isophoto-TVTTN (5) was a stereoisomer of photo-TVTTN (4). The fragmentation pattern in the electron impact mass spectrum of isophoto-TVTTN (5) was qualitatively the same as that of photo-TVTTN (4) (see Experimental section). Evidence with regard to stereochemistry was obtained from ¹H n.m.r. spectra. The spectrum of isophoto-TVTTN (5) revealed a considerable similarity to that of photo-TVTTN (4) with the exception of the three one-proton signals due to the formyl proton (shifted upfield by 0.49 p.p.m.), the C-14 proton (downfield by 0.12 p.p.m.), and the C-9 proton (downfield by 0.34 p.p.m.). Spectral data assigned with the aid of double irradiation studies are shown in Table 6. As might be expected, the ¹³C n.m.r. spectrum of isophoto-TVTTN (5) was also similar to that of photo-TVTTN (4). Of the 33 carbon atoms, peaks for 30 could be seen. As for photo-TVTTN (4), the assignments were made only for the sp^2 carbon atoms and those bearing oxygen, with the aid of off-resonance decoupling. The assignments (p.p.m. from Me_4Si) are as follows: 201.913 (C-11 formyl), 170.248 (two acetyl), 169.763 (one acetyl), 160.172 (C-12), 147.188 (C-17), 137.966 (C-5), 120.305 (C-13), 118.430 (C-6), 85.303 (C-8), 72.805 (C-3), and 69.165 (C-23).

The stereochemistry of the two photoproducts (4) and (5) was expected to differ at C-8 and/or C-9. Three formulae, (5), (15), and (16), were thus possible for isophoto-TVTTN. The structures (15) and (16), in which the formyl substituents at C-9 are β-oriented, were excluded on the basis of the ¹H n.m.r. spectra of isophoto-TVTTN, the dihydro derivative (17) (obtained by reduction of isophoto-TVTTN with sodium borohydride) and the acetate (18), of the dihydro-derivative.

The critical observations were the relative chemical shifts of the 19-H of isophoto-TVTTN and the dihydro-derivative (17), and of the dihydro-derivative (17) and the acetate (18). If the formyl group of isophoto-TVTTN was

[10] N. S. Bhacca and D. H. Williams, 'Application of NMR Spectroscopy in Organic Chemistry,' Holden–Day, San Francisco, 1964.

[11] J. B. Stothers, ' Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972; G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972.

TABLE 5

Some least-squares planes, with equations expressed in the form $lx' + my' + nz' + p = 0$, where $x' = x + z\cos\beta$, $y' = y$ and $z' = z\sin\beta$; distances marked with an asterisk refer to atoms defining the plane

Plane	1	2	3	4	5
l	−0.888	0.302	−0.834	−0.792	0.771
m	0.240	−0.163	0.145	0.291	−0.543
n	0.393	0.939	0.533	0.536	0.334
p	−3.79	−5.39	−4.44	−5.49	−5.24

Deviation of atoms (Å)

O(3)	−0.087 *	C(10)	0.016 *	C(12)	−0.006 *	N(1)	0.010 *	C(22)	0.000 *
N(1)	0.014 *	C(5)	−0.035 *	C(13)	0.017 *	C(12)	−0.021 *	C(27)	0.000 *
C(12)	−0.099 *	C(6)	0.032 *	C(16)	0.006 *	C(13)	0.007 *	C(32)	0.000 *
C(14)	0.131 *	C(7)	−0.014 *	C(17)	−0.016 *	C(14)	0.004 *		
C(8)	−0.132 *							N(2)	0.016
		C(9)	−0.058	C(14)	0.273	O(3)	−0.181		
C(9)	1.052	C(8)	0.733	C(15)	−0.533	C(17)	−0.155		
C(7)	−1.437	C(4)	0.033	C(18)	0.114	C(18)	0.345		
C(13)	−0.323			C(20)	0.139				
C(15)	−0.888			N(1)	−0.075				

Interplanar angles (°)

| Plane	2	3	4	5
1	86	10	10	133
2		77	77	51
3			9	123
4				126

TABLE 6

Chemical shifts (τ values) and coupling constants (Hz) of protons in the photoproducts and their derivatives

Compd.	3α-H	6-H	9β-H	1-H	14α-H	18-H	19-H	20β-H	21-H	22β-H	23α-H	26-H	27-H	NAc, OAc
(2)	5.35br	4.50br (s) *		5.32 (d) *	a	8.20 (s)	8.66 (s)	6.86 (q) *	8.88 (d)	5.21br (d) *	4.86br (s) W½ 8.6	8.88 (d)	6.59 (d)	7.95 (s), 7.97 (s)
(3)	5.36br	4.50br (s)		3.37 (d)	b	8.38 (s)	9.04 (s)	b	8.91 (d)	5.26br (d) *	4.96br (s) W½ 8.6	8.91 (d)	b	7.97 (s), 8.01 (s), 8.03 (s)
(4)	5.37br	4.60br (s)	7.74 (d) *	0.00 (d) *	7.08 (q) *	8.02 (s)	8.54 (s)	6.83 (q) *	8.85 (d)	5.14br (d) *	4.88br (s) W½ 7.6	8.85 (d)	6.65br (s)	7.95 (s)
(5)	5.38br	4.54br (s) *	7.40 (d) *	0.49 (d) *	6.96 (q) *	8.03 (s)	8.55 (s)	6.84 (q) *	8.85 (d)	5.16br (d) *	4.54br (s) W½ 7.5	8.85 (d)	6.67br (s)	7.95 (s), 7.97 (s)
(6)	5.39br	4.06br (s)	7.68 (d) *	2.41 (d) *	a	8.00 (s)	8.67 (s)	a	8.80 (d)	5.08br (d) *	4.72br (s) W½ 8.6	8.83 (d)	a	7.92 (s), 7.95 (s)
(7)	5.50br	4.67br (s)	7.64 (d) *	2.71 (d) *	7.18 (q) *	8.11 (s)	9.02 (s)	6.88 (q)	8.88 (d)	5.17br (d) *	4.90br (s) W½ 7.8	8.88 (d)	6.65br (s)	7.95 (s)
(9)	5.39br	4.68br (s)	8.36 (d) *	6.06 (d) *	6.22 (q) *	8.02 (s)	8.80 (s)	6.77 (q) *	8.84 (d) *	5.13br (d) *	4.89br (s) W½ 7.8	8.86 (d)	6.67br (s)	7.96 (s)
(10)	a	4.68br (s)	a	a	a	8.00 (s)	8.82 (s)	6.88 (q)	a	5.23br (d) *	a	a	6.67br (s)	7.92 (s)
(11)	5.39br	4.70br (s)	8.21br (d) *	5.53 (d) 5.83 (q)	a	8.03 (s)	8.80 (s)	6.79 (q)	8.84 (d) *	5.14br (d) *	4.89br (s) W½ 7.5	8.86 (d)	6.68br (s)	7.97 (s)
(12)	5.45br	4.64br (s)	a	4.76 (s) 4.93 (s)	a	8.01 (s)	8.60 (s)	6.84 (q)	8.84 (d)	5.14br (d) *	4.92br (s) W½ 7.8	8.84 (d)	6.68br (s)	7.97 (s)
(13)	5.46br	4.73br (s)	8.11 *	5.6—5.8 (m)	a	8.06 (s)	8.88 (s)	6.84 (q)	8.81 (d) *	5.14br (d)	4.89br (s) W½ 9.1	8.86 (d)	6.67br (s)	7.95 (s)
(14)	5.48br	4.68br (s)	b	b	b	8.03 (s)	8.50 (s)	b	8.84 (d)	5.16br (d) *	4.91br (s) W½ 8.0	8.84 (d)	6.68br (s)	7.98 (s)
(17)	5.48br	4.66br (s)	7.64br (d) * 6.28 (q) *	5.99 (q) *	6.75 (q) *	8.03 (s)	8.65 (s)	a		5.15br (d) *	4.88br (s) W½ 8.6		6.62br (s)	7.95 (s)
(18)	5.42br	4.59br (s)	7.70 *	5.69 (q) * 5.83 (q) *	6.90 (q) *	8.01 (s)	8.59 (s)	6.81 (q) *	8.82 (d)	5.10br (d) *	4.83br (s) W½ 9.0	8.82 (d)	6.61br (s)	7.91 (s)

J/Hz

Compd.	11α,12α	11,9β	14α,15α	14α,15β	20β,21	20β,22β	22β,23α	25α,26	Other signals
(2)	6.0 *		a	a	6.5 *	11.0 *	1.5 *	ca. 7	
(3)	6.0		b	b	6.6	10.5 *	1.5 *	6.6	
(4)		4.8 *	4.3 *	11.8 *	6.8 *	11.3 *	1.5 *	6.7	
(5)		5.4 *	4.5 *	13.5 *	6.8 *	10.5 *	1.5 *	6.4	
(6)		9.0 *	a	a	6.3 *	10.8 *	1.5 *	6.0 *	
(7)		8.3	4.5	12.8	6.0	10.5	1.5 *	6.0	7.58 (s, p-Me of Ts) 2.74 (d, m-H of Ts, J 7.8), 2.23 (d, o-H of Ts, J 7.8)
(9)		4.2 *	4.3 *	14.3	6.8 *	10.8 *	1.5 *	6.3 *	
(10)		a	a	a	a	10.5 *	1.5 *	a	
(11)	(5.53) 0—1 (5.83) 7.6 {11-H₂ gem * 11.8}				6.1 *	11.2 *	1.5 *	6.7 *	
(12)		6.6	a	a	7.5	10.4	1.5 *	6.6	
(13)		a	a	a	6.8 *	10.6 *	1.5 *	6.0 *	7.55 (s, p-Me of Ts), 2.68 (d, m-H of Ts, J 7.8), 2.24 (d, o-H of Ts, J 7.8)
(14)		b	b	b	6.5	12.0	1.5 *	6.5	
(17)	(5.99) 7.7 (6.28) 2.3 {11-H₂ gem * 11.8}		a	a	a	11.3 *	1.5 *	ca. 7	
(18)	(5.69) 2.3 (5.83) 6.8 {CH₂ gem * 12.0}		3.8 *	11.9 *	6.5 *	10.7 *	1.5 *	ca. 7	

* Confirmed by decoupling.

a Unassignable.   b Attempts were not made to assign these signals.

β-oriented, downfield shifts of the signal of the 19-H due to deshielding by the OH in going from isophoto-TVTTN to dihydroisophoto-TVTTN (17) or from the actate (18) to the dihydroisophoto-TVTTN (17) would be expected. However, the reverse was true, upfield shifts of 0.10 and 0.06 p.p.m., respectively, being observed. Therefore isophoto-TVTTN possesses structure (5).

(15)

(16)
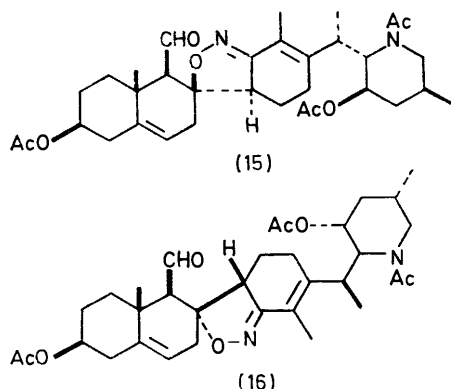
The n.m.r. data of isophoto-TVTTN and its derivatives can reasonably be interpreted on the basis of this structure. In the region τ 5.9—6.8 the reduction product (17) exhibited a series of signals corresponding to six protons, attributable to the 20β-H the C-27 methylene protons, the C-11 methylene protons, and the 14-H. Unequivocal assignments were made with the aid of double irradiation studies. In this region two quartets were observed, and spin-decoupling enabled us to obtain coupling constants for the quartet centred at τ 5.98 (J 7.7 and 11.8 Hz) and for the signal centred at τ 6.29 (J 2.3 and 11.8 Hz). The smaller couplings (7.7 and 2.3 Hz) were eliminated by irradiation at τ 7.64, and the two quartets collapsed to a pair of doublets with the typical pattern expected for an AB system with a small δ/J value [centred at τ 5.98 and 6.29 (d, J 11.8 Hz)]. The coupling constant of 11.8 Hz was compatible with geminal coupling, and these signals were assignable to a CH₂OH group. The chemical shifts of two protons were calculated to be τ 5.99 and 6.28. Double resonance also defined the chemical shift of the 9β-proton as ca. τ 7.64. The smaller J values (2.3 and 7.7 Hz) should be ascribable to coupling between the 9β-H and each of the C-11 methylene protons. The observed non-equivalence of the geminal C-11 protons clearly demonstrated steric inhibition of free rotation around the 10,11-bond in dihydroisophoto-TVTTN (17). The n.m.r. spectrum of the corresponding acetate (18) also showed this effect. However, similar steric inhibition of rotation was not observed in dihydrophoto-TVTTN (9). This difference can be explained as follows. Dreiding models of the two isomeric compounds (9) and (17) demonstrated that an intramolecular hydrogen bond between the C-11 OH and the oxygen atom of the isoxazoline nucleus was only possible in dihydroisophoto-TVTTN (17), and that no such bonding could occur between the C-11 OH and the nitrogen atom of the isoxazoline ring in the alcohol (9); thus the observed restricted rotation in the alcohol (17) is probably due to intramolecular hydrogen bond formation.

With regard to assignments of the rest of signals, a broad two-proton singlet centred at τ 6.62 and a diffuse quartet centered at τ 6.75 immediately upfield of the signals of the C-11 methylene protons of the alcohol (17) were observed. The former was attributable to the C-27 methylene protons. The signal area of the latter corresponded to two protons. One of these was safely assignable as the 20β-H by comparison with the corresponding signal of dihydro-photo-TVTTN (9). The other should be the 14-H, showing a 0.21 p.p.m. downfield shift from the corresponding signal of isophoto-TVTTN (5). As already mentioned, the 14-H signal showed a marked downfield shift in dihydrophoto-TVTTN (9) in comparison with photo-TVTTN (4). This was attributed to deshielding by the newly formed hydroxy-group. Dreiding models of isophoto-TVTTN (5) and the dihydro-derivative (17) indicated that a similar downfield shift corresponding to the transformation of isophoto-TVTTN (5) into the dihydro-derivative (17) would not be expected, since the 14-H and the CH₂OH group in dihydro-isophoto-TVTTN (17) were not in a 1,3-diaxial-like relationship. However the value of 0.21 p.p.m. was actually considerably smaller than that found in going from photo-TVTTN (4) into dihydrophoto-TVTTN (9) (0.86 p.p.m.). This small downfield shift was, therefore, consistent with our assignments of the configurations of the C-8 and C-9 substituents of isophoto-TVTTN (5).

The difference of the effects of the hydroxy-group on the chemical shifts of the 14α-H of dihydroisophoto-TVTTN (17) and dihydrophoto-TVTTN (9) was further illustrated by comparison of relevant signals of dihydroisophoto-TVTTN (17) and the O-acetyl derivative. In the O-acetyl derivative of dihydroisophoto-TVTTN (17) the 14α-H signal appeared at τ 6.90, 0.15 p.p.m. upfield from that of the parent compound (17). In contrast to this small difference the corresponding upfield shift of the 14α-H signal in going from dihydrophoto-TVTTN (9) to the O-acetyl derivative was at least 0.5 p.p.m. [the 14α-H signal of the O-acetyl derivative (11) was hidden in the C-27 methylene envelope and could not be located exactly].

Probable Photo-rearrangement Pathways.—On the basis of accumulated evidence on the photolysis of nitrites,[12] we can envisage several pathways which terminate in the formation of the twin isoxazolines (4) and (5), as shown in Scheme 2. A β-scission of the 11β-alkoxyl radical (A) may afford a discrete allyl radical (B), since the overall migration of NO generated from a nitrito-group to C-12 of (22R,-25S)-veratr-13(17)-enin-11β-yl nitrite has been proved to take place in an intermolecular manner.[3h] α-Cleavage is followed by combination of NO· and the allyl radical (B) to form a nitroso-aldehyde(s) (C) and/or (D).

For the rearrangement from the nitroso-aldehyde(s) to the isoxazolines (4) and (5), several pathways can be considered as possible under the present photolytic conditions (light of wavelength over 300 nm): (i) initial thermal isomerization[13] to a hydroxy-imino-aldehyde (19) and nucleophilic addition of the hydroxyimino-group to the 8,9-double bond from both the α- and β-sides (mechanism A), or to the excited 8,9-double bond with or without involvement of an enol (mechanism A'); (ii) formation of a 1,4-cycloadduct (E)[14] and subsequent thermal isomerization

[12] For reviews see (a) A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 1962, **17**, 35; (b) M. Akhtar, *Adv. Photochem.*, 1964, **2**, 263; (c) R. O. Kan, 'Organic Photochemistry,' McGraw-Hill, New York, 1966, p. 233; (d) R. H. Hesse, *Adv. Free-Radical Chem.*, 1969, **3**, 83.

[13] J. H. Boyer, 'The Chemistry of the Nitro and Nitroso Groups,' ed. H. Feuer, Interscience, New York, 1969, part 1, p. 215.

[14] J. Hamer and M. Ahmad, '1,4-Cycloaddition Reactions,' ed. J. Hamer, Academic Press, New York, 1967, p. 419.

(mechanism B); (iii) direct Michael addition of the nitroso-group to afford the isoxazolines (4) and (5) with or without the involvement of enols and with intra- or inter-molecular migration of the 12-H either to the carbonyl or to the

bearing an excited or a non-excited NO group (12-H) [15] by the $n \longrightarrow \pi^*$ excited $\alpha\beta$-unsaturated carbonyl group, with concomitant isoxazoline ring formation (mechanism C). Of these possibilities, although we previously favoured

SCHEME 2
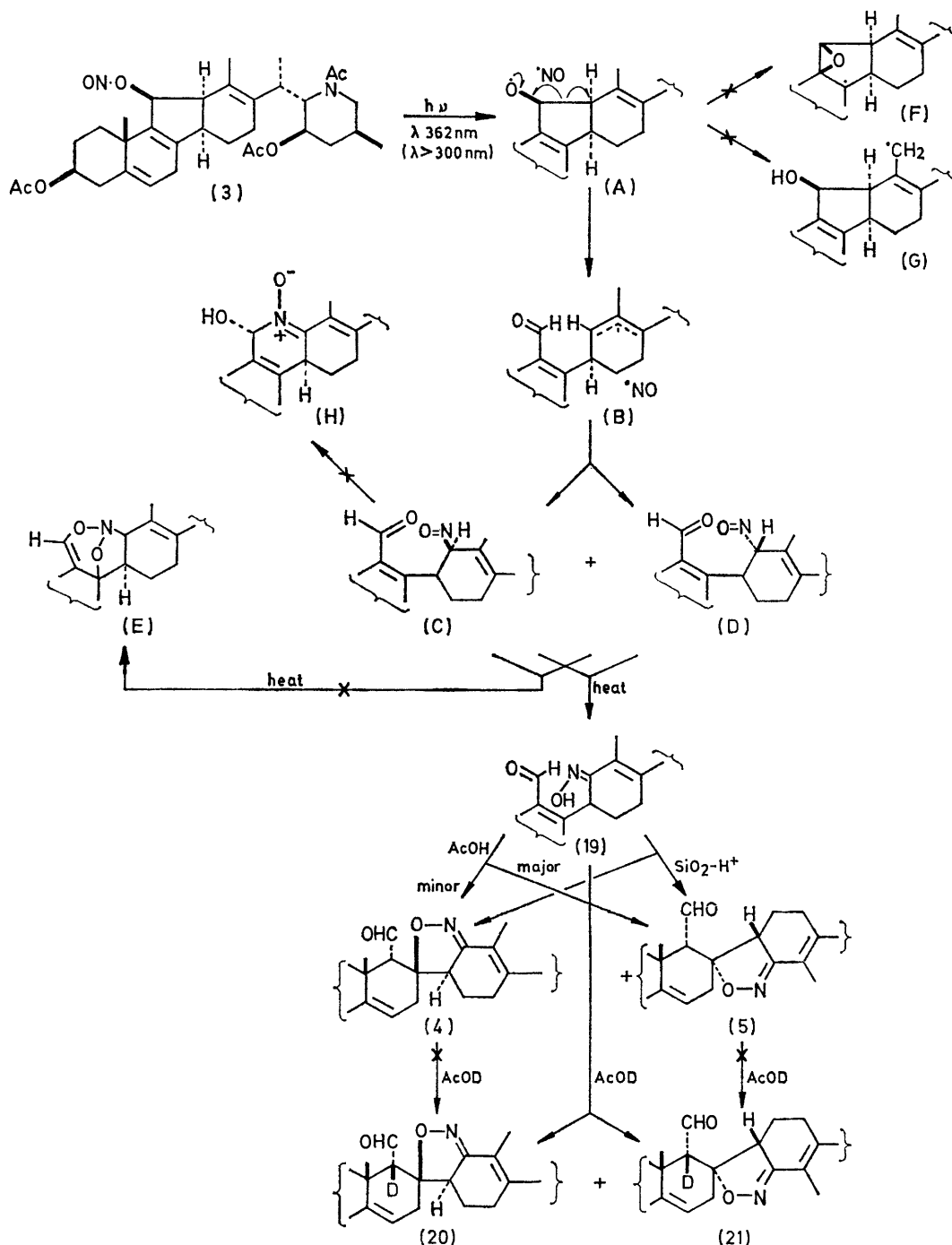
9-position of the nitroso-aldehyde(s) (mechanism C); (iv) abstraction of a hydrogen atom attached to a carbon

† The nitrite showed some end-absorption above 300 nm due to double bond $\pi \longrightarrow \pi^*$ absorption and to the intramolecular charge-transfer band of the nitrite group. It is not likely that this could have participated in giving rise to the rearrangement products.

pathway A,[3] several other mechanisms cited above could not be eliminated.†

In order to confirm pathway A, we (a) carried out the photolysis of the nitrite with a monochromatic light, which

[15] E. S. Stern and C. J. Timmons, ' Electronic Absorption Spectroscopy in Organic Chemistry,' Arnold, London, 1970, p. 78.

does not excite any chromophores of the assumed intermediate(s), and (b) investigated the photoreaction intermediates in various solvents including deuteriated systems.

Photolysis of the Nitrite by Monochromatic Light.—In the u.v. spectrum of the triacetyl derivative (2) in methanol, a strong olefin absorption due to a $\pi \longrightarrow \pi^*$ transition occurs at 213 nm (ε 8 660).[16] After nitrosation, a characteristic structured absorption due to $n_N \longrightarrow \pi^*$ of the ONO group appeared at *ca.* 375 nm (ε 91) together with olefin $\pi \longrightarrow \pi^*$ absorption [$\lambda_{max.}$ 219 nm (ε 4 520)].

For prediction of the positions of the maxima due to $n \longrightarrow \pi^*$ transitions of the $\alpha\beta$-unsaturated aldehyde groups of the hypothetical nitroso-aldehyde intermediates (C) and (D) or the hypothetical hydroxyimino-aldehyde intermediate (19), model compounds were employed, since these intermediates possess cyclohexa-1,4-diene as a part structure and intramolecular charge transfer has been observed for cyclohexa-1,4-diene.[17] For this purpose isojervine [18] and 5,6-dihydroisojervine were studied. *NOO*-Triacetylisojervine [4] and *NOO*-triacetyl-5,6-dihydroisojervine [4] in tetrahydrofuran showed $n \longrightarrow \pi^*$ absorptions at 330 and 334 nm, with molar absorptivities 150 and 140.† This confirmed that the double bond at C-5 caused only a slight blue shift of the $n \longrightarrow \pi^*$ band of these compounds. Therefore, it would be reasonable to assume that the nitroso-aldehydes have one absorption at *ca.* 330 nm due to an $n \longrightarrow \pi^*$ transition of the $\alpha\beta$-unsaturated aldehyde group,[15] and another at 670 nm due to the $n \longrightarrow \pi^*$ transition of the C-nitroso-group.[20] Another hypothetical intermediate, the hydroxyimino-aldehyde (19), would have the absorption at around 330 nm due to the $n \longrightarrow \pi^*$ transition of the $\alpha\beta$-unsaturated aldehyde group.[15,†] The nitrite (3) was therefore irradiated with light of wavelength 362 ± 4 nm, generated by CRM-FA grating spectroirradiator, in order to excite only the ONO chromophore ($n \longrightarrow \pi^*$ transition). We initially used tetrahydrofuran as a solvent transparent at wavelengths greater than 230 nm, and a dilute solution (5.4×10^{-4}M). The progress of the reaction was monitored by u.v. spectrometry. After 105 min a banded absorption due to the $n \longrightarrow \pi^*$ transition of the nitrito-group had disappeared. However, no absorption due to isoxazolines had appeared (*ca.* 260 nm) and only a slight bathochromic shift of an absorption at 226 nm due to the $\pi \longrightarrow \pi^*$ absorption was observed. After removal of the solvent, t.l.c. revealed the absence of photo-TVTTN and isophoto-TVTTN and instead the formation of a product with high R_F value.‡

In a second series of experiments a more concentrated solution was used, on a preparative scale, with or without penta-1,3-diene as triplet quencher. It was confirmed that compounds (4) and (5) were obtained by irradiation with monochromatic light followed by preparative t.l.c., irrespective of the presence or absence of quencher. Table 7 shows the isolated yields and ratio of (4) and (5), estimated from n.m.r. spectra.

The Hydroxyimino-aldehyde (19) *as an Intermediate.*—The foregoing experiments showed that the nitroso-aldehyde–

† In general, a hydroxyimino-group conjugated with a carbon–carbon double bond reveals a high intensity band near 240 nm, probably related to the $n \longrightarrow \pi^*$ transition and no absorption over 300 nm.[19]

‡ The products formed by irradiation of the dilute solution will be described in a later paper.

isoxazoline transformation did not involve any excitations of the functional groups of the initial aldehyde and the probable intermediate. We next attempted to identify the

TABLE 7

Irradiations of the nitrite (3) with monochromatic light

Solvent	Concentration (M $\times 10^2$)	Yields (%) of isolated photo- and isophoto-TVTTN [a]	Ratio (4) : (5) [b]
Tetrahydrofuran	4.75	24	1 : 2.2
Tetrahydrofuran–penta-1,3-diene	5.65	30	1 : 3.4

[a] Obtained by preparative t.l.c. followed by one recrystallization. [b] Estimated by integration of peaks due to the aldehydic protons of a mixture of photo-TVTTN and isophoto-TVTTN. [c] Ratio 2 : 1 (v/v).

intermediates involved. Thus, after completion of the photoreaction of the nitrite in dry tetrahydrofuran with Pyrex-filtered light, the u.v. spectrum of the solution exhibited no absorption due to the chromophore of photo-TVTTN and isophoto-TVTTN (259 nm) but instead an intense maximum at 239 nm with a shoulder at 246 nm. This indicated the absence of photo-TVTTN and isophoto-TVTTN in detectable concentration immediately after the photolysis. Removal of the solvent and preparative t.l.c., however, gave photo-TVTTN and isophoto-TVTTN. This showed that the compound responsible for the above absorption maximum was intermediate in the formation of photo- and isophoto-TVTTN, probably either the nitroso-aldehyde or the hydroxyimino-aldehyde, since these both have an $\alpha\beta$-unsaturated aldehyde group and this chromophore should have an absorption maximum at 244 nm (on the basis of the Woodward–Fieser empirical rule [21] of enone absorption). The $\alpha\beta$-unsaturated hydroxyimino-group of the latter would show absorption at *ca.* 240 nm,[19] close to the value observed. Further, the u.v. spectrum of the above photolysate lacked any absorption at wavelengths greater than 400 nm, indicating that the observed absorption was due to the hydroxyimino-aldehyde (19), since the C-nitroso-compounds (C) and (D) should show an absorption maximum at *ca.* 690 nm. The formation of the hydroxyimino-aldehyde was also demonstrated by the 100 MHz n.m.r. spectrum. When the solvent was removed from the photolysate at 20 °C, the 100 MHz n.m.r. spectrum of the residue exhibited no signals due to photo- and isophoto-TVTTN, and instead showed a series of new signals at τ 0.02 (1 H, s, CHO), 7.95 (9 H, s, NAc and OAc), 8.06 (3 H, s, 18-H), 8.65 (3 H, s, 19-H), and 8.84 (6 H, d, J 6.0 Hz, 21- and 26-H). A singlet at τ 0.02 was attributable to an aldehydic proton; moreover its singlet character proved that the series of new signals was due to the hydroxyimino-aldehyde. Judged from the shapes of the signals, the hydroxyimino-aldehyde (19) was probably a single compound, although *syn*- and *anti*-geometrical isomers might be expected. However, whether the configuration of the hydroxyimino-group was *syn* or *anti* with respect to the 12,13-bond could not be

[17] E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 1956, 4073.

[18] W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, 1947, **170**, 635.

[19] P. J. Orenski and W. B. Clossen, *Tetrahedron Letters*, 1967, 3629.

[20] Ref 15, p. 60.

[21] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 18.

[16] D. W. Turner, *J. Chem. Soc.*, 1959, 30; K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, 1959, **42**, 1480; P. S. Ellington and G. D. Meakins, *J. Chem. Soc.*, 1960, 697.

distinguished from the n.m.r. spectrum. On the basis of relative stabilities, the *syn*-configuration seems more favourable. The hydroxyimino-aldehyde was unstable: transfer of the CDCl₃ solution into a flask from the n.m.r. tube, addition of reagent grade CHCl₃ washings to this solution, evaporation of the combined solution, and re-determination of the n.m.r. spectrum gave new signals at τ 0.00 (d), 0.49 (d), and 8.54 (s) at the expense of the intensities of the signals of the hydroxyimino-aldehyde. These were apparently due to newly formed photo- and isophoto-TVTTN. The ratios of the hydroxyimino-aldehyde and photo- and isophoto-TVTTN were estimated to be 0.9 : 1.0 : 1.9. The intermediacy of the hydroxyimino-aldehyde was also confirmed in a photoreactions with Pyrex-filtered light in toluene as the solvent, and with monochromatic light in penta-1,3-diene–tetrahydrofuran. In the toluene case the n.m.r. spectrum of the residue from the photolysate demonstrated the presence of three aldehydes, *i.e.* the hydroxyimino-aldehyde, photo-TVTTN, and isophoto-TVTTN, in the ratios 1.9 : 1.0 : 1.6.

Some Observations on the Cyclization of the Nitroso-aldehyde(s) to Photo-TVTTN and Isophoto-TVTTN. Photolysis in Various Solvents.—Although the observations described above could be taken as conclusive evidence that the cyclization of the nitroso-aldehyde takes place largely *via* prior isomerization to the hydroxyimino-aldehyde, we carried out some further experiments to define the conditions under which this unusually smooth Michael addition took place, and to obtain further information on the mode of cyclization. For these purposes, photolysis was performed in dry tetrahydrofuran containing D₂O. After photolysis was complete the solvent was partly removed below 30 °C, with particular care to exclude moisture. The solution was then extracted with dry chloroform, and the extract was treated with anhydrous sodium sulphate and evaporated. The aldehydic region of the n.m.r. spectrum of the residue revealed, besides two doublets due to the formyl protons of photo-TVTTN and isophoto-TVTTN and a singlet due to the hydroxyimino-aldehyde (19), a new singlet at τ 0.49 ascribable to an aldehydic proton of [9β-²H]isophoto-TVTTN (21). The ratios of compounds (19), (4), (5), and (21) estimated from the n.m.r. spectrum were *ca.* 2.4 : 1.0 : 0.9 : 0.2.

This crude product was subjected to preparative t.l.c. to isolate the aldehydes. However the hydroxyimino-aldehyde was completely transformed into photo- and isophoto-TVTTN on the t.l.c. plate, and after recrystallization, photo-TVTTN (4), isophoto-TVTTN (5), and [9β-²H]isophoto-TVTTN (21) were obtained in the ratios 1.0 : 1.2 : 0.1 (see Table 8). {A small amount of [9β-²H]photo-TVTTN (20) was probably formed in this experiment, but its signal was hidden under that due to the hydroxyimino-aldehyde.}

In further experiments, the tetrahydrofuran–D₂O photolysate was heated at 46—50 °C for 80 min, and the solvent was removed.* The aldehydic region of the n.m.r. spectrum of the residue exhibited the presence of the hydroxyimino-aldehyde (19), photo-TVTTN (4), isophoto-TVTTN (5), and [9β-²H]isophoto-TVTTN (21) in the ratios of *ca.* 1.7 : 1.0 : 1.1 : 0.4. Interestingly, a signal due to [9β-²H]-photo-TVTTN (21), which should appear at the centre of the doublet of the formyl proton of photo-TVTTN, was not distinct. The mixture was again dissolved in dry tetra-

* In this procedure, the tetrahydrofuran was partly removed below 30 °C and the two-layer solution was extracted with chloroform. The extract was worked up as usual.

hydrofuran containing D₂O and the solution was refluxed for 10 h. After work-up as above, surprisingly, the n.m.r. spectrum of the residue disclosed that a part of the hydroxy-imino-aldehyde (19) still survived (7%), and a slight increase of [9β-²H]isophoto-TVTTN (21) over isophoto-TVTTN (5) was observed. When this mixture was submitted to preparative t.l.c., transformation of the hydroxy-imino-aldehyde into photo- and isophoto-TVTTN again occurred. The n.m.r. spectrum of the mixture obtained by preparative t.l.c. indicated the formation of four products, photo-TVTTN (4), isophoto-TVTTN (5), [9β-²H]photo-TVTTN (20), and [9β-²H]isophoto-TVTTN (21), in the ratios 1.0 : 1.8 : 0.2 : 0.6.

Photolysis of the nitrite was also carried out in CH₃OD as solvent. The n.m.r. spectrum of the crude product indicated the formation of the hydroxyimino-aldehyde (19), photo-TVTTN (4), and isophoto-TVTTN (5), in the ratios 0.9 : 1.0 : 1.5. Unexpectedly, no deuteriated photo- and isophoto-TVTTN were detected. After purification of the product by preparative t.l.c. followed by one recrystallization, photo- and isophoto-TVTTN were obtained in the ratio 1.0 : 1.3. Roughly the same result (1.0 : 0.7) was obtained when methanol was used as solvent. Photo-TVTTNs were similarly obtained when CCl₄ was used as solvent. Results of photolysis by Pyrex-filtered light in various solvents, in which preparative t.l.c. was employed for the isolation, are summarized in Table 8.

TABLE 8

Irradiation of the nitrite (3) with Pyrex-filtered light in various solvents

Solvent	Concentration (M × 10²)	Yields (%) of photo- and isophoto-TVTTN [a]	Ratio (4) : (5) [b]
PhMe	8.8	50	1 : 0.8
CCl₄	4.1	33	1 : 3.5
THF [c]	5.7	35	1 : 1.8
MeOH	0.98	30	1 : 0.7
CH₃OD	1.1	42	1 : 1.3
THF [c]–D₂O	3.3	41	1 : 1.3 [d]

[a] Purified by preparative t.l.c. followed by one recrystallization. [b] Estimated by integrations of peak areas due to each aldehydic proton. [c] Tetrahydrofuran. [d] This value includes [9β-²H]isophoto-TVTTN.

The foregoing experiments confirmed that the intramolecular Michael reaction occurred on the silica gel used in t.l.c. In order to obtain more information on the catalytic action of acids, we attempted to cyclize the hydroxyimino-aldehyde (19) with acetic acid instead of silica gel. Thus, when the photolysis of the nitrite in D₂O–tetrahydrofuran was complete, a small amount of acetic acid was added and the solution was set aside for 90 min. After the usual work-up, the n.m.r. spectrum of the residue indicated that a large amount of the hydroxyimino-aldehyde remained unchanged (see Experimental section). However, in another run, when the nitrite in tetrahydrofuran was photolysed and the residue (42 mg) from the photolysate was dissolved in acetic acid (4 ml) and set aside for 18.5 h at room temperature, the n.m.r. spectrum of the product indicated the formations of photo- and isophoto-TVTTN in the ratio 1.0 : 3.2. This showed the predominant transformation of the hydroxyimino-aldehyde (19) into isophoto-TVTTN (5) rather than photo-TVTTN (4) in the presence of an organic acid as catalyst. The role of acetic acid was more rigorously demonstrated when we used acetic [²H]acid as the solvent.

The product in this case contained the four aldehydes photo-TVTTN (4), [9β-²H]photo-TVTTN (20), isophoto-TVTTN (5), and [9β-²H]isophoto-TVTTN (21), together with 12% of the hydroxyimino-aldehyde (19). After preparative t.l.c. the amounts of each aldehyde were: (4) 16%, (20) 7%, (5) 43%, and (21) 34%, *i.e.* the ratio of former two to the latter two was 1 : 3.4. The ratio of photo- to isophoto-TVTTN was even greater (1 : 4.3) when the photolysis was carried out in tetrahydrofuran–D₂O, and the residue freed from the solvent was then treated with acetic [²H]acid. In these experiments it was apparent that deuterium was incorporated into the TVTTNs in the course of the intramolecular Michael reaction, since none was incorporated when the TVTTN was simply dissolved in acetic [²H]acid and set aside for 18 h at room temperature. Results of the formation of photo- and isophoto-TVTTN by acetic [²H]acid-catalysed cyclization are shown in Table 9.

TABLE 9

Formation of photo- and isophoto-TVTTN by acetic [²H]acid-catalysed cyclization

Solvent	Concentration (M × 10²)	Yields (%) of isolated photo- and isophoto-TVTTN [a]	Ratio (4) : (5) [b]
THF [c]	6.2	15	1 : 3.4
THF [c]–D₂O	4.2	38	1 : 4.3

[a] Before purification by preparative t.l.c., the crude product was treated with acetic [²H]acid. [b] Estimated from the n.m.r. spectrum. [c] Tetrahydrofuran.

DISCUSSION

The formation of an isoxazoline ring from the photolysis of the nitrite ester of a fused five-membered ring alcohol is unprecedented. The 11β-alkoxyl radical (A) might be expected to react by any of three major pathways: (*a*) intramolecular hydrogen abstraction from either C-19 or C-18, [22] (*b*) intramolecular addition to C-9 leading to an α-nitroso-epoxide, [23] or (*c*) β-cleavage.

It is now well established that the most favoured transition state for intramolecular hydrogen abstraction is six-membered. The distance requirement for such an intramolecular hydrogen transfer has also been investigated extensively in rigid polycyclic sytsems, and estimates from Dreiding models indicate that an alkoxyl radical is favourably positioned for abstracting hydrogen from the methyl groups of steroids when the C to alkoxyl O internuclear distance is *ca.* 2.5—2.7 Å.[24] In the present case a Dreiding model revealed that the C-10 methyl to 11β-alkoxyl oxygen distance is *ca.* 3.2 Å and that the C-13 methyl, and the 11β-alkoxyl oxygen are *ca.* 2.6 Å apart.* Thus hydrogen transfer from C-18 to the 11β-alkoxyl radical is by no means unexpected. On the other hand, the 11β-alkoxyl radical is attached to a strained cyclopentene ring, and cleavage between C-11 and C-12 generates a stabilized allyl radical. However, the photolysis products were exclusively those

from the β-cleavage, neither of the alternative products (F) and (G) being formed, although addition of an alkoxyl radical to cyclopentene double bond is an exclusive process in certain steroidal allyl alcohol nitrites.[23]

In the present case, β-cleavage seems a more rapid process than any of the others. The observed β-fission would be assisted considerably by relief of strain in the cyclopentene nucleus, and the cleaved species (B) is stabilized both by the formation of an allyl radical and by concomitant generation of an αβ-unsaturated carbonyl group.

In the previous cases,[3e-g] the intermediate(s) (C) and/or (D), in which an 8,9-double bond is lacking, isomerized to afford a nitrone (H). However, no nitrone was formed in the present case; the two isoxazolines (4) and (5) were formed exclusively. There are two problems with regard to this isomerization: (*a*) what factors decide which pathway from the nitroso-aldehyde will be followed, and (*b*) what is the mechanism of the isomerization? The results of the experiments with monochromatic light ruled out mechanisms involving excitation of the *C*-nitroso-groups or the αβ-unsaturated aldehyde systems of the nitroso-intermediate(s) (C) and/or (D) or the hydroxyimino-aldehyde intermediate (19).

Of at least three ground-state modes of formations of photo-TVTTN and isophoto-TVTTN from the nitroso-aldehyde intermediate(s), the ratio of photo-TVTTN and isophoto-TVTTN formed would be merely a reflection of the ratio between the α- (D) and the β-nitroso-aldehyde (C) formed by the combination of NO and the allyl radical in the mechanism *C*. However, our experiments confirmed that at least a portion of photo- and isophoto-TVTTN from the nitroso-aldehyde(s) are formed through prior isomerization to the hydroxyimino-aldehyde in the photolysate. This isomerization is followed by an intramolecular Michael addition of the hydroxyimino-group to the 8,9-double bond which takes place during work-up. The major part of the Michael addition was confirmed to proceed during preparative t.l.c. on silica gel. Although this solid acid was confirmed as a very effective catalyst in this Michael addition, organic acid such as acetic acid were sufficiently effective to cause cyclization at room temperature. The acidic catalysts may have multiple roles. Acid-catalysed intramolecular Michael addition is possible only in the *anti*-isomer, and one important role of acid might be associated with an acceleration of *syn* —► *anti*-isomerization.[25] The stereochemical outcome of the transformations of the hydroxyimino-aldehyde into photo- and isophoto-TVTTN by silica gel-catalysed Michael addition and by acid catalysis in solution were significantly different. Whereas the hydroxyimino-aldehyde was transformed largely into

* Dreiding model of the nitrite (3) demonstrated that there are probably conformers, one with ring D quasi-boat in which C-12 and the C-16 methylene group are in a quasi-bow–stern relationship, and the other with ring D quasi-chair. The distance of 2.6 Å is based on the latter conformation. In the former the corresponding distance is *ca.* 3.4 Å.

[22] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1961, **83**, 4076, and subsequent papers.

[23] A. L. Nussbaum, R. Wayne, E. R. Yuan, O. Zagneetko, and E. P. Oliveto, *J. Amer. Chem. Soc.*, 1965, **87**, 2451.

[24] K. Heusler and J. Kalvoda, *Angew. Chem.*, 1964, **76**, 518.

[25] C. G. McCarty, ' The Chemistry of the Carbon–Nitrogen Double Bond,' ed. S. Patai, Interscience, New York, 1970, p. 363.

isophoto-TVTTN in the latter case, Michael addition induced by silica gel afforded both photo- and isophoto-TVTTN. The greater stereoselectivity of the Michael addition in acetic acid is readily understandable since attack by the oxine oxygen at C-8 in solution should occur more readily from the α- than from the β-side. Attack from the β-side is prevented by the presence of the 10β-methyl group, which is located in a 1,3-diaxial relationship with the incoming hydroxyimino-group. The pathways clarified in the present experiments are summarized in Scheme 2.

Although the present studies have shown that the transformation of the hydroxyimino-aldehyde into photo- and isophoto-TVTTN is difficult without an acid catalyst, the favourable geometry of the relevant

tant isoxazoline ring formation as shown in Scheme 3. We believe that this possibility is not great, although it is not definitely ruled out, and the formation of TVTTN without deuterium in deuteriated solvents would be still governed by the mechanism *via* the hydroxyimino-aldehyde. In this case the proton to be attached at C-9 of TVTTN could be that removed from C-12 of the nitroso-aldehyde, and attachment to C-9 would occur inter- or intra-molecularly, probably in a condensed solution at the final stage of work-up.

In the transformation of the hydroxyimino-aldehyde into photo- and isophoto-TVTTN, the generated configurations of the C-9 formyl substituents of both compounds are α. The acid-catalysed intramolecular Michael addition of the hydroxyimino-group to the
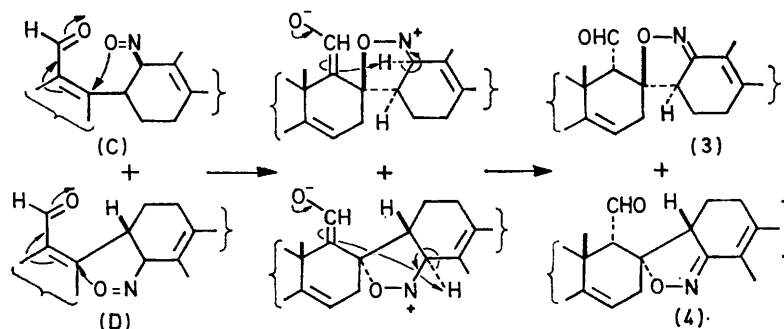
SCHEME 3
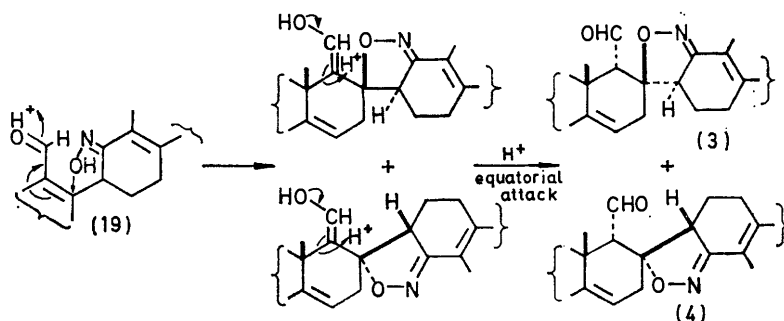
SCHEME 4

functional groups in the hydroxyimino-aldehyde (19) makes this intramolecular Michael addition occur unusually readily.

The formation of significant amounts of photo- and isophoto-TVTTN was always observed in the crude products immediately after photolysis and before treatment with acid. Also, photo- and isophoto-TVTTN without deuterium incorporated at C-9 were found in crude products from photolysis in CH_3OD and in tetrahydrofuran–D_2O. Whether or not these facts are an indication of another pathway for the formation of photo- and isophoto-TVTTN cannot be definitely answered at present. One possibility would be the direct formation of TVTTN from the nitroso-aldehyde(s) in which a hydrogen atom at C-12 of the nitroso-aldehyde(s) migrates intramolecularly C-9 with concomi-

αβ-unsaturated formyl group should involve enols as intermediates (Scheme 4). According to Zimmerman the stereochemistry of the ketonization reaction of enols derived from a ketone function located exocyclically to a cyclohexane ring is determined by preferential attack of a proton at the less hindered π-electron lobe of the α-carbon atom.[26] In the present example, the observed stereochemistry of the formation of photo- and isophoto-TVTTN, with regard to the configuration of the C-9 substituent, would be the outcome of such a preferential equatorial attack of a proton donor. The presence of the 10β-methyl group in the hydroxyimino-aldehyde does not affect this equatorial attack. As might be expected, solvents did not affect the total yields of photo- and

[26] H. E. Zimmerman and T. W. Cutshall, *J. Amer. Chem. Soc.*, 1959, **81**, 4305, and earlier papers.

isophoto-TVTTN. However, the ratios of photo- to isophoto-TVTTN were not quite the same in all solvents used (Table 8). Photolysis in carbon tetrachloride gave a particularly high yield of (5) and those in methanol or toluene gave low yields of (5). When the carbon tetrachloride solvent was removed from the photolysate, the n.m.r. spectrum of the residue indicated overwhelmingly predominant formation of photo-TVTTN. Thus in this case predominant formation of photo-TVTTN occurs before silica gel treatment. The reason for this is not obvious.

We have shown previously the formation of a nitrone as the sole product of photolysis of a nitrite without an 8,9-double bond.[3e,f] The pathway in this case was clarified as proceeding *via* a thermal cyclization of a nitroso-aldehyde, corresponding to the intermediate (C)/(D) in the present case.[3g] An explanation why in this case a nitrone (H) is not formed at all could be as follows. The intramolecular reaction of the nitroso-group with either an isolated formyl group or an αβ-unsaturated carbonyl group may be considered to be a reaction between a weak ambident nucleophile (*C*-nitroso-group) and an electrophile. Of the steric and electronic factors responsible for the formation of different products in the two cases, polar factors may be particularly important. In the present case, the formyl carbon atom of the αβ-unsaturated carbonyl system in the nitroso-aldehyde (C)/(D) may not be sufficiently reactive to form a nitrone, and isomerization to the corresponding oxime may proceed more rapidly.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus. I.r. spectra were determined for Nujol mulls with a JASCO IR-E spectrophotometer. U.v. spectra were determined with a Hitachi 124 double-beam spectro-photometer. 100 MHz ^{1}H N.m.r. spectra were determined with a JEOL PS 100 high-resolution spectrometer (solvent CDCl$_3$; Me$_4$Si as internal reference). T.l.c. was carried out on Wakogel B-5. Rotations were measured with a JASCO DIP-SL automatic polarimeter. Mass spectra were taken by the staff of the Faculty of Pharmaceutical Sciences of this University with a Hitachi RMU-6E spectrometer; ele-mental analyses were also performed by the staff of the Faculty of Pharmaceutical Sciences.

Nitrosation of (22S,25S)-N-Acetylveratra-5,8,13(17)-trienine-3β,11β,23β-triol 3,23-Diacetate (2).—To the 11β-ol (2)[4] (3.6 g) in dry pyridine (15 ml) nitrosyl chloride in pyridine was added dropwise at −30 °C with stirring until the colour of the solution had turned to deep blue. The solution was kept at −25 to −30 °C for 8 min, then poured into ice-water. The 11β-*nitrite* (3) was filtered off and dried (P$_2$O$_5$); yield 3.6 g; m.p. 215—217° (from acetone-n-hexane) (Found: N, 4.75. C$_{33}$H$_{46}$N$_2$O$_7$ requires N, 4.8%), [α]$_D^{22}$ +60.3° (*c* 0.9 in CHCl$_3$); ν$_{max.}$ 1 721 (OAc), 1 626 (NAc), and 771 cm^{-1} (ONO); for n.m.r. see Table 6.

Photolysis of the Nitrite (3).—The nitrite (3) (3.6 g) in dry toluene (70 ml) was irradiated in nitrogen for 9 h with stirring in a Pyrex vessel by an external 100 W high-pressure mercury arc. T.l.c. then revealed a small amount of unchanged nitrite. This (least polar) nitrite and the second least polar compound (the parent 11β-ol) were present only

in trace amounts. The most polar compound was over-whelmingly the major product The toluene was evaporated off and the residue was extracted with chloroform. The extract was washed with water, dried (Na$_2$SO$_4$), and evaporated to leave a gummy residue (4 g). This was chromatographed over neutral alumina. Elution with benzene and benzene–chloroform (1 : 1) successively gave a product which was recrystallized from acetone to afford needles (1.5 g, 42%), m.p. 198°. Repeated recrystallization from acetone raised the m.p. to 215—218°. These crystals were a mixture of photo-TVTTN (4) and isophoto-TVTTN (5). A part (640 mg) was submitted to preparative t.l.c. with n-hexane–ether (1 : 3). Development eight times en-abled us to separate the mixture into a less polar fraction (285 mg) and a slightly more polar fraction (277 mg). Re-crystallization of the less polar fraction from ethanol afforded 227 mg of pure photo-TVTTN (4) in three crops. The more polar fraction was still contaminated by photo-TVTTN (4) as judged by the aldehydic proton n.m.r. signal. Therefore this was subjected twice more to preparative t.l.c. (eight developments each time) with the same solvent mixture. The first chromatography afforded 57 mg of photo-TVTTN (4), which gave, after recrystallization, 25 mg of pure photo-TVTTN (4) in two crops; the more polar fraction (190 mg) was still contaminated with photo-TVTTN (4). The second chromatography of the more polar fraction afforded 20 mg of photo-TVTTN (4) [which afforded 5 mg of pure photo-TVTTN (4)] and 133 mg of the isophoto-TVTTN (5). Recrystallization of the latter afforded 86 mg of pure iso-photo-TVTTN (4). Thus, the total amount of photo-TVTTN (4) obtained was 257 mg (m.p. 233—235°) and that of isophoto-TVTTN (5) was 86 mg (m.p. 213.5—215.5°). *Photo-TVTTN* (4) (Found: C, 67.65; H, 8.0; N, 5.0. C$_{33}$H$_{46}$N$_2$O$_7$ requires C, 68.0; H, 7.95; N, 4.8%) showed λ$_{max.}$ (EtOH) 203 (ε 12 600) and 259 nm (14 700); [α]$_D^{25}$ +20.8 (*c* 1.0 in CHCl$_3$); ν$_{max.}$ 1 630 (NAc), 1 720 (CHO), and 1 737 and 1 747 cm^{-1} (OAc and O–N=C); for n.m.r. see Table 6; for mass spectrum see text. *Isophoto-TVTTN* (5) (Found: C, 67.6; H, 8.05; N, 4.7%) showed λ$_{max.}$ (EtOH) 203 (ε 13 300) and 257 nm (15 790); [α]$_D^{22}$ +16.1° (*c* 1.1 in CHCl$_3$); ν$_{max.}$ 1 630 (NAc), 1 720sh, (CHO), and 1 725 and 1 741 cm^{-1} (OAc and O–N=C); for n.m.r. see Table 6; *m/e* 385 (3.8%), 198 (52.4), 156 (100), and 114 (21.9).

Hydrolysis of Photo-TVTTN (4).—Photo-TVTTN (4) (54 mg) in a mixture of potassium hydroxide (0.79 g), water (1.6 ml), and methanol (13.4 mg) was stirred for 2 h at room temperature under nitrogen. After neutralization with N-hydrochloric acid the solvent was removed under reduced pressure. The residue was extracted with chloro-form. The extract was worked up as usual to afford an oily residue (44 mg). This crystallized from acetone to yield *dideacetylphoto-TVTTN* (6), m.p. 251—253° (Found: C, 70.15; H, 8.6; N, 5.5. C$_{29}$H$_{42}$N$_2$O$_5$ requires C, 69.85; H, 8.95; N, 5.6%); λ$_{max.}$ (EtOH) 259 nm (ε 19 900); ν$_{max.}$ 1 625 (NAc), 1 711 (CHO), and 3 312 and 3 388 cm^{-1} (OH). Owing to insufficient solubility in CDCl$_3$ the n.m.r. spectrum was not taken.

The Oxime (6) of Photo-TVTTN (4).—The photoproduct (4) (73 mg), hydroxylamine hydrochloride (75 mg) in water (0.2 ml), and sodium acetate (50 mg) in water (0.2 ml) were dissolved in 95% ethanol (3.3 ml). The solution was warmed for 2.5 h at *ca.* 45 °C. On cooling, crystals appeared. Ethanol was removed *in vacuo* and addition of water afforded crystals (72 mg) which were filtered off. Recrystallization from ethanol afforded *needles* (60 mg)

m.p. 243—244.5° (recorded previously [2] as 221—222°) (Found: N, 6.95. $C_{33}H_{47}N_3O_7$ requires N, 7.05%); $[\alpha]_D^{22}$ −0.6 (c 2.2 in CHCl₃); $\lambda_{max.}$ (EtOH) 205 (ε 15 000) and 257 nm (13 100); $\nu_{max.}$ 1 621 cm⁻¹ (NAc), 1 726 and 1 740 (OAc), 3 400br (OH), 1 245, 1 029, and 960 cm⁻¹ (N–O); for n.m.r. see Table 6; m/e 114 (22.0%), 156 (100), 198 (50.4), 382 (1.5), 400 (0.5), 579 (0.3), and 597 (M⁺˙, 0.1%).

Reduction of Photo-TVTTN (4) with Borohydride.— Photo-TVTTN (4) (196 mg) in dry tetrahydrofuran (15 ml) containing ethyl acetate (3 ml) was cooled in ice–water. Sodium borohydride (88 mg) was added and the solution was stirred. After 90 min more borohydride (22 mg) was added and the solution was further stirred for 40 min. The excess of borohydride was decomposed by adding ice and water, and the mixture was extracted with ether (70 ml). The extract was worked up as usual. The residue (142 mg) was recrystallized from acetone to yield the alcohol (9) (87 mg). Recrystallization of the residue from evaporation of the filtrate (from ethanol) afforded a further 28 mg of the alcohol (9). Recrystallization from ethanol gave a *sample* of m.p. 240—241.5° (recorded previously [2] as 224—226°) (Found: C, 67.6; H, 8.35; N, 4.7. $C_{33}H_{48}N_2O_7$ requires C, 67.8; H, 8.25; N, 4.8%), $[\alpha]_D^{23}$ +75.1° (c 1.2 in CHCl₃); $\lambda_{max.}$ (EtOH) 205 (ε 13 500) and 259 nm (14 300); $\nu_{max.}$ 3 477 (OH), 1 732 and 1 710 (OAc), 1 630 (NAc), 1 030, 1 244, and 1 263 cm⁻¹; for n.m.r. see Table 6 and text; m/e 144 (28.9%), 156 (100), 198 (31.6), 338 (3.4), 387 (1.9), and 584 (M⁺˙, 0.9%).

Catalytic Hydrogenation of Photo-TVTTN (4).—Platinum oxide (210 mg) in ethanol (10 ml) was hydrogenated. To this solution was added the photoproduct (4) (100 mg) and the solution was shaken in hydrogen for 18 h. Catalyst and solvent were removed and the oily residue (119 mg) was purified by preparative t.l.c. and then recrystallization to yield dihydrophoto-TVTTN (9) (52 mg), m.p. 240—241.5°. This was identical with that obtained by reduction with borohydride.

Deuterium Labelling of Photo-TVTTN.—Sodium (120 mg) was dissolved in D₂O (5 ml) under dry nitrogen. To this solution were added a 3 : 1 mixture of the photoproducts (4) and (5) (300 mg) and dry dioxan (5 ml). The solution was heated at 100—103 °C for 10 min. The solvent was removed under reduced pressure and to the residue were added D₂O (2.5 ml) and dry dioxan (2.5 ml). The solution was again heated at 100—103 °C for 10 min. This procedure was once more repeated. The solvent was removed and the residue was extracted twice with chloroform; the extract was washed twice with water, dried (Na₂SO₄), and evaporated. The residue (277 mg) was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and set aside at room temperature overnight. The solution was poured into water and the precipitate was filtered off, washed with water, dried (yield 273 mg), and recrystallized from acetone–ether to yield a deuteriated photoproduct (142 mg) as a first crop.

Reduction of the Deuteriated Photoproduct with Sodium Borohydride.—The foregoing deuteriated photoproduct (100 mg) and sodium borohydride (50 mg) in tetrahydrofuran (8 ml) were stirred for 70 min. The solution was worked up as usual to afford a crude reduced product (96 mg), which was recrystallized to yield the deuteriated dihydrophotoproduct (63 mg).

Jones Oxidation of Dihydrophoto-TVTTN (9).—Dihydrophoto-TVTTN (9) (40 mg) in pure acetone (20 ml) was cooled in ice–water and a few drops of Jones reagent were added (until the colour turned to yellowish brown). The

solution was stirred for 1 h at 0 °C. The excess of reagent was decomposed with aqueous sodium hydrogen sulphite, and the acetone was removed *in vacuo*. The solution was worked up in the usual way and the oily residue (45 mg) was purified first by t.l.c. and then by recrystallization to afford the crystals identical with photo-TVTTN (4).

Hydrolysis of Dihydrophoto-TVTTN (9).—Dihydrophoto-TVTTN (9) (90 mg), potassium hydroxide (1 g), and water (2 ml), and methanol (18 ml) were stirred for 17 h at room temperature under nitrogen. After neutralization with 2N-hydrochloric acid, the solvent was removed and the residue was extracted with chloroform. The organic layer was washed with water, dried, and evaporated. The amorphous residue (67 mg) was recrystallized from ether to yield *dideacetyldihydrophoto-TVTTN* (51 mg), m.p. 165—172°. Recrystallized from ether this had m.p. 176—179° (recorded previously [2] as 173—176°) (Found: C, 69.65; H, 8.9; N, 5.8. $C_{29}H_{44}N_2O_5$ requires C, 69.55; H, 8.85; N, 5.6%); $\lambda_{max.}$ (EtOH) 259 (ε 13 100) and 205 nm (12 700); $\nu_{max.}$ 1 611 (NAc) and 3 400br cm⁻¹ (OH); for n.m.r. see Table 6; m/e 144 (81.4%), 156 (100), 345 (9.3), and 500 (M⁺˙, 0.8%).

Acetylation of Dihydrophoto-TVTTN (9).—Dihydrophoto-TVTTN (9) (58 mg) and acetic anhydride (0.2 ml) in pyridine (0.7 ml) were stirred for 3 h at room temperature. The excess of acetic anhydride was decomposed by addition of methanol and the solution was worked up in the usual way. The oily residue (71 mg) was recrystallized from ether to yield the *acetyl derivative* (11) (37 mg), m.p. 185—188°. Further recrystallization gave a sample of m.p. 189—192° (Found: C, 66.9; H, 8.8; N, 4.6. $C_{35}H_{50}N_2O_8$ requires C, 67.05; H, 8.05; N, 4.45%); $\lambda_{max.}$ (EtOH) 206 nm (ε 13 200), 258 (15 100), and 206 nm (13 200); $[\alpha]_D^{22}$ +48.0° (c 1.1 in CHCl₃); $\nu_{max.}$ 1 629 (NAc), 1 723 (OAc), 1 240, and 1 020 cm⁻¹; for n.m.r. see Table 6; m/e 114 (20.4%), 156 (100), 198 (60.2), 429 (5.8), and 626 (M⁺˙, 0.8%).

Hydrolysis of the Monoacetyl Derivative (11) of Dihydrophoto-TVTTN (9).—The monoacetate (11) (20 mg) in aqueous methanolic 5% potassium hydroxide (5 ml) was stirred for 5 h under nitrogen. After neutralization with N-hydrochloric acid, the solvent was removed and the residue was extracted with chloroform. The extract was worked up in the usual way to give an oil (14 mg). This was recrystallized from acetone–ether to yield crystals, m.p. 176—179°, identical with dideacetyldihydrophoto-TVTTN (10).

Tosylation of Dihydrophoto-TVTTN (9).—Dihydrophoto-TVTTN (9) (50 mg) and tosyl chloride (50 mg) in pyridine (0.1 ml) were set aside overnight at room temperature. The mixture was extracted with water and ether. The ethereal layer was washed with water, dried (Na₂SO₄), and evaporated and the residue was recrystallized from acetone–ether to yield pure *tosylate* (13) (45 mg), m.p. 188—191° (Found: C, 65.05; H, 7.3; N, 3.4. $C_{40}H_{54}N_2O_9S$ requires C, 65.0; H, 7.35; N, 3.8%); $\lambda_{max.}$ (EtOH) 257 (ε 14 800), 226 (18 100), and 205 nm (17 100); $\nu_{max.}$ 1 726 (OAc), 1 631 (NAc), 1 242, and 1 027 cm⁻¹; for n.m.r. see Table 6; m/e 114 (23.5%), 156 (100), 198 (51.5), and 541 (1.3).

Substitution of Tosyloxy-group in the Tosylate (9) with Iodine.—The tosylate (30 mg) and sodium iodide (10 mg) in acetonylacetone (0.7 ml) were heated on an oil-bath (bath temp. 115 °C) for 7 h. After removal of the precipitate the filtrate was evaporated. The residue showed three spots on t.l.c. (ether as solvent). Preparative t.l.c. (ether) gave a least polar fraction (4 mg) which was not the desired compound. The second least polar (major) fraction (16 mg) was

recrystallized from ether to yield needles (12 mg) of the iodide (14). The pure *iodide* had m.p. 221—222° (from absolute methanol) (Found: C, 57.0; H, 6.85; N, 3.75. $C_{33}H_{47}N_2O_6I$ requires C, 57.05; H, 6.8; N, 4.05%); $\lambda_{max.}$ (EtOH) 259 nm (ε 18 200); $\nu_{max.}$ 1 714, 1 729 (OAc), and 1 622 cm^{-1} (NAc); for n.m.r. see Table 6.

Tosylhydrazone (7) *of Photo-TVTTN* (4).—Photo-TVTTN (4) (600 mg) and tosylhydrazine (250 mg) in ethanol (15 ml) were cooled to 0 °C in ice–water, concentrated hydrochloric acid (0.25 ml) was added, and the solution was stirred for 2 h, then neutralized with aqueous 10% potassium hydroxide. Removal of the solvent afforded a residue which was extracted with chloroform. After usual work-up, the product was recrystallized from ethanol–water. The first crop of pure *crystals* (225 mg) had m.p. 257—258° (Found: C, 63.95; H, 7.3; N, 7.45. $C_{40}H_{54}N_4O_8S$ requires C, 64.0; H, 7.25; N, 7.45%); $[\alpha]_D^{22}$ −45.3° (*c* 1.3 in CHCl$_3$); $\lambda_{max.}$ (EtOH) 256 (ε 14 800), 233 (18 900), and 206 nm (23 100); $\nu_{max.}$ 1 610 (NAc), 1 727 (OAc), and 3 519 cm^{-1} (NH); for n.m.r. see Table 6; *m/e* 114 (23.5%), 156 (100), 198 (54.4), 369 (7.4), and 566 (1.0).

Reduction of the Tosylhydrazone (7) *with Borohydride.*—The tosylhydrazone (625 mg) and sodium borohydride (1.25 g) in dioxan (50 ml) were refluxed for 7 h. The excess of borohydride was decomposed with acetic acid and the solvent was removed. The residue was extracted with chloroform and the extract was worked up as usual. The residue (391 mg) was acetylated with pyridine (1 ml) and acetic anhydride (1 ml) at room temperature. The mixture was poured into water and extracted with chloroform. The extract was washed twice with 2N-hydrochloric acid and twice with water, dried, and evaporated. T.l.c. of the amorphous residue (467 mg) revealed several spots and the product was subjected to preparative t.l.c. (ether–methanol, 19 : 1). Four fractions (96, 52, 97, and 86 mg, in order of increasing polarity) were obtained and the least polar fraction was recrystallized from methanol and water to yield *crystals* (42 mg). Recrystallization from ether–n-hexane gave a specimen of m.p. 240—242° (Found: C, 69.65; H, 8.3; N, 5.15. $C_{33}H_{46}N_2O_6$ requires C, 69.95; H, 8.2; N, 4.95%); $\lambda_{max.}$ (EtOH) 258 (ε 13 000) and 205 nm (14 600); $\nu_{max.}$ 1 724 (OAc), 1 645 (NAc), and 1 248 cm^{-1}; for n.m.r. data see Table 6; *m/e* 114 (25.9%), 156 (100), 198 (42.1), 322 (3.7), 369 (6.3), and 566 ($M^{+\cdot}$, 0.8%).

Reduction of Isophoto-TVTTN (5) *with Borohydride.*—Compound (5) (110 mg) and sodium borohydride (49 mg) in tetrahydrofuran (4.5 ml) containing ethyl acetate (1 ml) were stirred for 3 h at 0 °C. The excess of borohydride was decomposed with acetone (1.2 ml) and, the mixture was extracted with ether (50 ml). The extract was worked up as usual. The residue (137 mg) was recrystallized from ether to yield *dihydroisophoto-TVTTN* (17) (61 mg), m.p. 246—249°. A specimen recrystallized from ether had m.p. 249—251° (Found: C, 67.8; H, 8.3; N, 4.8. $C_{33}H_{48}N_2O_7$ requires C, 67.8; H, 8.25; N, 4.8%); $[\alpha]_D^{25}$ −17.0 (*c* 1.1 in CHCl$_3$); $\lambda_{max.}$ (EtOH) 208 (ε 14 200) and 257 nm (14 200); $\nu_{max.}$ 3 535, 3 439 (OH), 1 732 (OAc), 1 629 (NAc), 1 240, and 1 025 cm^{-1}; for n.m.r. see Table 6; *m/e* 114 (27.3%), 156 (100), 198 (40.3), 332 (3.5), 387 (3.8), and 584 ($M^{+\cdot}$, 0.4%).

Acetylation of Dihydroisophoto-TVTTN (17).—Dihydroisophoto-TVTTN (58 mg) in pyridine (1.5 ml) was acetylated with acetic anhydride (0.3 ml) in the usual way. Recrystallization from ether yielded *crystals* (57 mg), m.p. 202—206° (Found: C, 66.8; H, 8.05; N, 4.35. $C_{35}H_{50}N_2O_8$ requires C, 67.05; H, 8.05; N, 4.4%), $[\alpha]_D^{18}$ −12.6° (*c* 1.2 in CHCl$_3$);

$\lambda_{max.}$ (EtOH) 206 (ε 13 000) and 257 (16 200); $\nu_{max.}$ 1 746sh, 1 734 (OAc), 1 631 (NAc), 1 244, and 1 027 cm^{-1}; for n.m.r. see Table 6; *m/e* 114 (21.4%), 156 (100), 198 (67.8), 429 (7.5), and 626 ($M^{+\cdot}$, 1.1%).

Solvents for Monochromatic Light Experiments.—Tetrahydrofuran (reagent grade; Wako, Japan) was refluxed over sodium and distilled over lithium aluminium hydride. Carbon tetrachloride (reagent grade; Nihonrika, Japan) was treated with N-potassium hydroxide and ethanol at 60 °C for 30 min. The organic layer was washed with concentrated sulphuric acid and water successively, refluxed with calcium carbonate, and distilled. Toluene (reagent grade) was refluxed over sodium and distilled over lithium aluminium hydride. A mixture of *cis*- and *trans*-penta-1,3-diene (Wako, Japan; reagent grade) was used. For deuteriated reagents (CH$_3$CO$_2$D, CH$_3$OD, and D$_2$O), Merck products (minimum isotopic purity 99 atom % D) were used. Spectroscopic grade methanol (Wako) was employed.

Monochromatic Light Experiments.—(*a*) Irradiation was carried out with a JASCO CRM-FA grating spectro-irradiator equipped with a 2 kW xenon arc lamp. A 5.45 × 10^{-4}M-solution of the nitrite in tetrahydrofuran in a quartz cell (10 × 10 × 45 mm) was placed in the chamber of the irradiator. Irradiation was carried out with light of wavelength 362 ± 4 nm. The progress of the reaction was monitored by u.v. spectroscopy (the cell was transferred to a Hitachi 124 double-beam spectrophotometer). (*b*) On a preparative scale the nitrite (80 mg) in tetrahydrofuran (3 ml) or the nitrite (95 mg) in tetrahydrofuran (2 ml) and penta-1,3-diene (1 ml) in a quartz cell was irradiated with light of wavelength 362 ± 4 nm. The reaction was monitored by t.l.c. and after completion the solvent was removed under vacuum. The residue was subjected to preparative t.l.c.

Detection of the Hydroxyimino-aldehyde Intermediate (19).—Argon was bubbled through a solution of the nitrite (39 mg) in tetrahydrofuran (1.2 ml) for 3 min. This solution in a Pyrex test tube was irradiated for 1.5 h with a 100 W mercury arc. A portion of the solution was diluted with a large volume of ethanol. The u.v. spectrum exhibited $\lambda_{max.}$ 239 and 246sh nm and no absorption over 400 nm. The solvent was removed at 20 °C the n.m.r. spectrum of the residue revealed a series of signals assigned to the hydroxyimino-aldehyde (19).

Photolyses with Pyrex-filtered Light.—(*a*) The procedure under which the results in Table 8 were obtained was as follows. Through a solution of the nitrite (30—50 mg) in each solvent argon gas was bubbled for 3 min. The solution was then irradiated with a 100 W mercury arc. After completion of the photolysis, the solvent was removed below 30 °C. The residue was examined by n.m.r. spectroscopy and was subjected to purification by t.l.c.

(*b*) *Formation of photo- and isophoto-TVTTN from the hydroxyimino-aldehyde* (19) *with acetic acid or* [^{2}H]*acid.* (i) The nitrite (50 mg) in tetrahydrofuran (1.8 ml) and D$_2$O (1.0 ml) was photolysed as above. After completion of the photolysis (2 h 2 min) glacial acetic acid (0.2 ml) was added to the photolysate and the solution was set aside for 90 min. The solution was extracted with chloroform and the extract was washed with aqueous 5% sodium hydrogen carbonate and water, dried (Na$_2$SO$_4$), and evaporated. The n.m.r. spectrum of the residue (4.2 mg) showed the presence of the hydroxyimino-aldehyde and photo-TVTTN. The CDCl$_3$ was removed from the n.m.r. sample and the residue was

dissolved in glacial acetic acid (2.2 ml). The solution was set aside for 17 h with constant stirring, neutralized, and worked up as usual. The n.m.r. spectrum of the residue indicated the formation of photo-TVTTN and isophoto-TVTTN in the ratio 1 : 3.1. The recovered product was then submitted to preparative t.l.c. A mixture of aldehydes (12 mg) was obtained. Recrystallization of this from ether gave the aldehydes (4.5 mg).

(ii) The results in Table 9 were obtained as follows. (A) The nitrite (65 mg) in tetrahydrofuran (1.8 ml) was treated as above. After completion of the photolysis (2 h) the solvent was removed at 19 °C and acetic [^{2}H]acid (1 ml) was added to the residue. The solution was set aside for 20 h with stirring, diluted with D_2O (5 ml), neutralized with anhydrous sodium carbonate, and extracted with dry chloroform. The extract was dried and evaporated. The residue was examined by n.m.r. spectroscopy. The ratios of the hydroxyimino-aldehyde (19), photo-TVTTN (4), [9β-^{2}H]photo-TVTTN (20), isophoto-TVTTN (5), and [9β-^{2}H]isophoto-TVTTN (21) were 0.75 : 1 : 0.25 : 2.26 : 2.0. The product was subjected to preparative t.l.c. and a mixture of aldehydes (29 mg) was obtained. This was recrystallized from ether to afford crystals (10 mg) of a mixture of four aldehydes. (B) The nitrite (105 mg) in tetrahydrofuran (3 ml) and D_2O (1.3 ml) was photolysed for 1 h. The tetrahydrofuran was removed under reduced pressure, acetic [^{2}H]acid (1 ml) was added, and the solution was set aside for 19 h 40 min, then worked up as above. The residue (136 mg) was examined by n.m.r. spectroscopy and was purified by preparative t.l.c. to afford a mixture (75 mg) of photo-TVTTN (11%), [9β-^{2}H]photo-TVTTN (8%), isophoto-TVTTN (14%), and [9β-^{2}H]isophoto-TVTTN (67%). Recrystallization from ether afforded 402 mg of crystals. The mass spectrum exhibited M^+ 583 (0.4%), the c-nor-D-homosteroidal fragment at m/e 386 (2%), and heterocyclic fragments at m/e 114 (24%), 156 (100), and 198 (61).

Attempted Deuterium Incorporation into Photo- and Isophoto-TVTTN with Acetic [^{2}H]*Acid.*—A mixture (46 mg) of photo- and isophoto-TVTTN (1 : 1.3) dissolved in acetic [^{2}H]acid (1 ml) was set aside for 18 h at room temperature. After the usual work-up, the recovered mixture was examined by n.m.r. spectroscopy, which indicated the presence of photo- and isophoto-TVTTN in the ratio 1 : 1.3.