On the Mechanism of the Formation of Steroidal Cyclic Hydroxamic Acids in the Photolysis of Steroidal 17β-ol Nitrite[1)]

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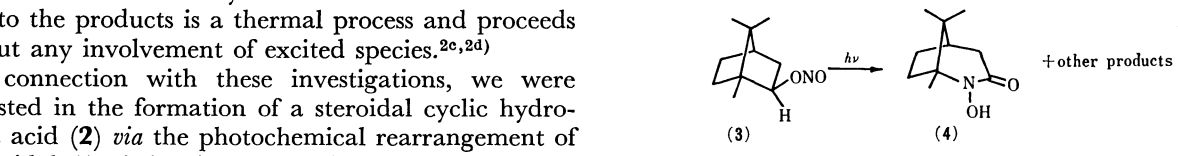
The Photolysis of 5α-androstane-3α,17β-diol 3-acetate 17-nitrite (**1**) in benzene with monochromatic light (372 ±4 nm) afforded two rearranged products, 17a-aza-D-homo-5α-androstane-3α,17a-diol-17-one 3-acetate (**2**) and the C-13 epimer (**8**). This result confirmed that the cyclization of the nitroso aldehyde intermediate (**C**) to the two products **2** and **8** proceeds without the involvement of excited species of the nitroso aldehyde intermediate **C**. This conclusion differs from that obtained for bornyl and isobornyl nitrites by Kabasakalian and Townley. The results of photolysis in carbon tetrachloride are also compared with that in benzene. The photolysis of the nitrite **1** in an EPA matrix at 77 K showed that essentially no β-cleavage of the 17β-oxyl radical takes place at the temperature of liquid nitrogen.

In previous papers, the formations of steroidal cyclic nitrones and spiroisoxazolines *via* the photochemical rearrangement of steroidal cyclopentyl and cyclopentenyl nitrites were reported.[2a-2e)] The reaction pathways of these photoinduced rearrangements were confirmed to involve nitroso aldehyde intermediates formed *via* the β-cleavage of the oxyl radical to afford the allyl radical, followed by the combination of NO and the allyl radical.[2b,2c)] The cyclization of the nitroso aldehyde to the products is a thermal process and proceeds without any involvement of excited species.[2c,2d)]

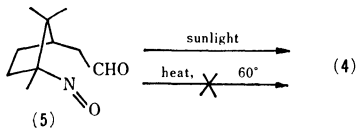
In connection with these investigations, we were interested in the formation of a steroidal cyclic hydroxamic acid (**2**) *via* the photochemical rearrangement of a steroidal 17-nitrite (**1**) reported by Barton and his collaborators,[3)] since the proposed pathway for this photoinduced rearrangement, which is illustrated in Scheme 1, involved also the formation of a nitroso aldehyde intermediate (**C**) and its cyclization to the product **2**.[3)] Although the proposed pathway is quite reasonable, no experimental evidence for the intermediacy of the nitroso aldehyde **C** has been available and the problem of whether the cyclization of the nitroso aldehyde **C** is a thermal process or a photochemical one seemed also to remain to be clarified.

Subsequent to this work,[3)] Kabasakalian and Townley[4)] and Nakazaki and Naemura[5)] reported an analogous photorearrangement of bornyl and isobornyl nitrites. These two groups of investigators found that the photolysis of bornyl and isobornyl nitrites (*e.g.*, **3**) in benzene or in trichlorotrifluoroethane with black light or ultraviolet light led to the formation of 1,8,8-trimethyl-2-hydroxy-2-azabicyclo[3.2.1]octan-3-one (**4**) in a 27—30% yield, together with several products derived from a β-cleavage of the corresponding oxyl radical, as is depicted in Scheme 2. Moreover,



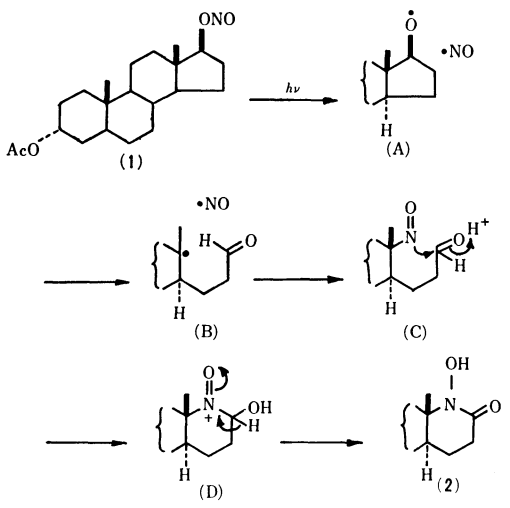
Scheme 2.

Kabasakalian and Townley were able to isolate a nitroso aldehyde intermediate (**5**), although none of its physical constants were given in the paper.[4)] They also reported that they succeeded in converting the nitroso aldehyde **5** into the hydroxamic acid **4** on exposure to sunlight or a neon lamp (585—660 nm), but failed to transform the aldehyde **5** into the hydroxamic acid **4** by heat at 60 °C (Scheme 3). On the basis of these results, they concluded that the cyclization of the nitroso aldehyde **5** to the hydroxamic acid **4** took place from an excited species of the nitroso aldehyde **5**.



Scheme 3.

It would not be unreasonable to extrapolate these results to the pathway of the analogous rearrangement of the steroidal 17-nitrite. In order to obtain independent evidence for the intermediacy of the nitroso aldehyde **C** and the mode of cyclization in the steroidal rearrangement, however, we carried out the photolysis of the nitrite **1** with a monochromatic light and the photolysis of the nitrite **1** in an EPA matrix at 77 K. Thus, if the hydroxamic acid **2** is formed from the assumed nitroso aldehyde **C**, we can readily ascertain whether this process is thermal or photochemical by the photolysis of the nitrite **1** with monochromatic light, which will be able to excite only the O–NO group of

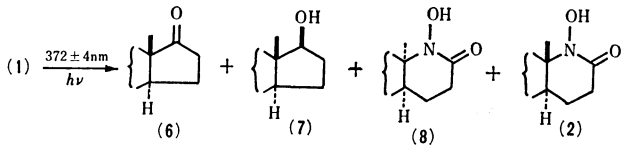


Scheme 1.

the nitrite **1**, not the C–NO group or the CHO group of the assumed nitroso aldehyde intermediate(s) **C** in Scheme 1.

Results and Discussion

The O–NO group generally has a characteristic structured band centred at *ca.* 370 nm due to the n→π* transition.[6] The stronger absorption at the shorter wave length was ascribed to the intramolecular charge-transfer band.[7] The UV spectrum of 5α-androstane-3α-17β-diol 3-acetate 17-nitrite (**1**) in benzene or in THF exhibited a characteristic structured absorption due to the n→π* of the ONO group centred at *ca.* 372 nm (ε; 112 in benzene). On the other hand, the nitroso aldehyde (**1**) would have one weak absorption at *ca.* 290 nm[8] due to an n→π* transition of the aldehyde group, and another at 670 nm due to the n→π* transition of the C-nitroso group.[9] Therefore, the nitrite **1** in dry benzene was photolyzed with 372±4 nm monochromatic light generated by a CRM-FA grating spectroirradiator in order to excite only the ONO chromophore. A careful separation of the products by preparative TLC afforded 5α-androstan-3α-ol-17-one 3-acetate (**6**) (8%), 5α- androstane-3α, 17β-diol 3-acetate (**7**) (12%), a new compound (**8**) (mp 118—120 °C), (21%), and 17a-aza-D-homo-5α-androstane-3α,17a-diol-17-one 3-acetate (**2**)[3] (20%), in the order of decreasing mobilities in TLC (Scheme 4). The electron-



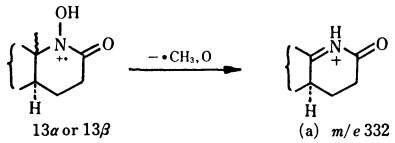
Scheme 4.

impact mass spectrum of the new compound **8** revealed a fragmentation pattern very similar to that of the hydroxamic acid **2**. They both show a molecular ion at *m/e* 363 and the principal fragment ions at *m/e* 348, 332, 272 and 150. The relative intensities of the principal ions in the mass spectra of the two compounds **2** and **8** are shown in Table 1. This mass spectrum, together with the IR and NMR spectra, suggest that the structure of the new compound is 17a-aza-D-homo-5α, 13α-androstane-3α, 17a-diol-17-one 3-acetate.

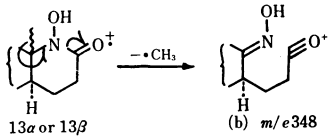
Table 1. Relative intensities (%) of the principal ions in the mass spectra of compounds **2** and **8**

Compd	$M^{+\cdot}$	*m/e*			
		348	332	272	150
2	1	12	100	10	24
8	4	48	100	16	10

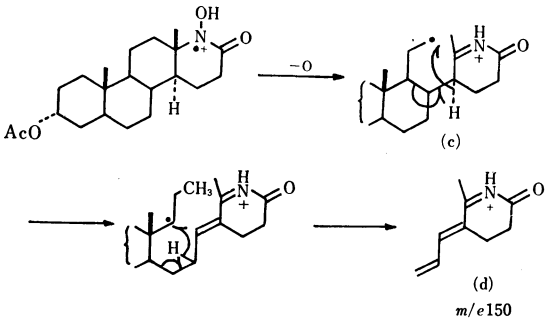
The base peak of the two compounds **2** and **8** is the fragment ion 332 corresponding to $[M-CH_3, O]^+$. The (a) in Scheme 5 is a possible representation of this fragment. The intense fragment ion at *m/e* 348 involves the elimination of CH_3, and this ion may possess the structure (b) in Scheme 6. The intense peak at *m/e* 150 is most probably formed *via* an ion (c)[10] identical



Scheme 5.



Scheme 6.



Scheme 7.

with the ion postulated for the mass spectral fragmentation[11] of 17a-aza-5α-androstan-17-one and is represented as having a structure (d). The pathway for the formation of the ion (d) from the ion (c) suggested by Budzikiewicz and his collaborators[11] is illustrated in Scheme 7.

This structure for the hydroxamic acid **8** was confirmed by its conversion into 17a-aza-D-homo-5α,13α-androstan-3α-ol-17-one 3-acetate: the reduction of the product **8** with zinc and acetic acid under reflux[3] afforded the corresponding known lactam identical with an authentic sample[12] prepared by the Beckmann rearrangement of an oxime of 5α,13α-androstan-3α-ol-17-one acetate. Very similar results were obtained in the photolysis of the nitrite **1** with Pyrex-filtered light, as is shown in Table 2.

Since the monochromatic light of 372±4 nm is unable to excite the formyl group or the nitroso group of the hypothetical intermediate **C**, it may be concluded that the cyclization of the nitroso aldehyde **C** to the observed hydroxamic acids **2** and **8** is a thermal process. This conclusion differs from the one obtained for bornyl and isobornyl nitrites by Kabasakalian and Townley.[4]

Table 2. Yields (%) of the products in the photolysis of the nitrite **1** with monochromatic light in various solvents

	6	**7**	**8**	**2**
Benzene[a]	10	9	20	20
Benzene	8	12	21	20
THF	trace[b]	52	13	12
CCl_4	21	52	8	8

a) Results with Pyrex-filtered light.
b) Detected by TLC.

The mode of the transfer of the 17-hydrogen of the nitrite **1** remains to be clarified.

In order to examine the effects of solvents, the photolysis of the nitrite **1** in two aprotic solvents, THF and carbon tetrachloride, was studied. Thus, it was found that the four products, **6**, **7**, **8**, and **2**, are also formed in two solvents under conditions comparable to the case in benzene and with light of a 372±4 nm wave length. However, the ratios of the four products are different, as is shown in Table 2.

Thus, it is apparent that the hydroxamic acids are generally produced in aprotic solvents.[13] However, the main product in THF and in carbon tetrachloride is the parent alcohol **7**. Needless to say, THF is a better hydrogen-donating solvent than benzene, and hydrogen abstraction by the 17β-oxyl radical from a hydrogen attached to the oxygen-bearing carbon of THF may take place readily to produce the parent alcohol. In the photolysis in carbon tetrachloride, the ketone **6** is formed in a considerable amount, together with the parent alcohol. Some of these compounds, **6** and **7**, may perhaps be formed *via* the disproportionation of the 17β-oxyl radical (**A**).

We also carried out the photolysis of bornyl nitrite **3** in benzene. Let us discuss the results briefly. The photolysis of the nitrite **3** in benzene with monochromatic light (358±8 nm) gave the hydroxamic acid **4**,[4,5] although the yield was only 3% and the major product was the parent borneol, as was confirmed by TLC. A repetition of the photolysis with Pyrex-filtered light also afforded the hydroxamic acid **4** in an equally poor yield (*ca.* 2%) and borneol as the major product (TLC).[14] These results indicate that the hydroxamic acid **4** may also be formed by a thermal cyclization of the nitroso aldehyde **5**.

Finally, an experiment aimed at proving the intermediacy of the nitroso aldehyde **C** will be described. In a previous publication[2c] we described the photolysis of a nitrite carried out in an EPA matrix at 77 K. This technique successfully proved the intervention of a nitroso aldehyde in the photorearrangement of the nitrite to nitrone. In the present case, the nitrite **1** in an EPA matrix (8.3×10^{-3} M) was photolyzed at 77 K through a Pyrex glass filter in the hope that we might be able to trap the nitroso aldehyde intermediate **C**. The reaction was monitored by UV spectroscopy in the 250—800 nm region, as in the previous case.[2c] However, in contrast to the case of the nitrite-nitrone transformation,[2c] the increase in the absorption maximum at *ca.* 670 nm in the matrix due to the C-nitroso compound **C** was not signifcant, even after a prolonged irradiation. This is due to the fact that the β-cleavage of the 17β- oxyl radical (**A**) at 77 K took place to only a small extent, as was proved by the presence of the hydroxamic acids on the thin-layer chromatogram of the EPA solution after irradiation.

Experimental

For the instruments and general procedures, see Part 30[2d] in this series.

5α-Androstane-3α,17β-diol 3-Acetate 17-Nitrite (1). This nitrite was prepared by the procedure of Barton and his colleagues.[3] Mp 183—184 °C (lit,[3] 177—180 °C) NMR: τ 9.26 (18-H), 9.20 (19-H), 7.94 (OAc), 5.00 (bs. $W_{1/2}$=7.5 Hz) (3β-H), 4.78 (t, J=8.4 Hz) (17α-H). UV: $\lambda_{max}^{benzene}$ (nm) 372 (112), 360 (116), 348 (96), 336 (72). λ_{max}^{THF} (nm) 372 (93), 360 (96), 348 (81), 336 (64).

Photolysis of the 17-Nitrite 1 with Pyrex-filtered Light. A solution of the nitrite **1** (300 mg) in dry benzene (30 ml) was irradiated for 1.5 h under an argon atmosphere with a 100-W high pressure Hg arc at room temperature. After the removal of the solvent by means of rotatory evaporator at 30 °C, the residue was subjected to preparative TLC. Four fractions, A, B, C, and D, were obtained in order of decreasing mobilities. The most mobile fraction, A (26 mg, 10%), was 5α-androstan-3α-ol-17-one acetate (**6**). The second most mobile fraction, B (26 mg, 9%), was 5α-androstane-3α,17β-diol 3-acetate **7**. The fraction C was recrystallized from aq ethanol to afford a new compound (**8**) (60 mg, 20 %); mp 118—120 °C. Found: C, 69.11; H, 9.19; N, 3.70 %. Calcd for $C_{21}H_{33}O_4N$: C, 69.39; H, 9.15; N, 3.85%. IR: 1742 (OAc), 1628 (amide C=O), 3127 cm^{-1} (hydrogen bonded hydroxyl). NMR: τ 9.28 (19-H), 8.64 (18-H), 7.06 (OAc), 4.99 (bs. $W_{1/2}$=7.5 Hz) (3β-H) 7.44—7.62 (m, 2H, 16α- and 16β-H).

The fraction D was recrystallized from ether to afford 17α-aza-D-homo-5α-androstane-3α,17a-diol-17-one 3-acetate (**2**) (59 mg, 20%). Mp 230—234 °C. (Lit,[3] mp 229—233 °C). NMR: τ 9.21 (19-H), 8.74 (18-H), 7.95 (OAc), 4.99 (b.s. $W_{1/2}$=7.5 Hz) (3β-H), 7.46—7.62 (m, 2H, 16α- and 16β-H).

Photolysis of the 17-Nitrite 1 with Monochromatic Light (372± 4 nm). a) Photolysis in Benzene: A solution of the nitrite (200 mg) in dry benzene (3 ml) in a quartz cell (10×10×45 mm) was flushed with argon and then placed in the chamber of a JASCO CRM-FA grating spectroirradiator. Irradiation was carried out with light of 372±4 nm. The progress of the reaction was monitored by means of TLC. After the completion of the photolysis (33.3 h), the solution was evaporated *in vacuo*. The TLC of the residue exhibited 4 spots (benzene/ether=1/5); the residue was subjected to preparative TLC (benzene/ether=1/1) as has been described above. The yields of the four products were as follows: ketone **6** (15 mg, 8%); 17β-ol **7** (22 mg, 12%); hydroxamic acid **8** (41 mg, 21%); isomeric hydroxamic acid **2** (40 mg, 20%). *b) Photolysis in THF*: A solution of the nitrite **1** (200 mg) in dry THF (3 ml) in a quartz cell was flushed with nitrogen and then photolyzed as in the photolysis in benzene. Eleven hours was required for the completion of the photolysis. The yields of the four products were as follows; ketone **6** (trace); 17β-ol **7** (96 mg, 52%); hydroxamic acid **8** (26 mg, 13%); isomeric hydroxamic acid (**2**) (23 mg, 12%). *c) Photolysis in Carbon Tetrachloride*: A solution of the nitrite (200 mg) in dry carbon tetrachloride (luminazol, dotite, Wako) (3 ml) in a quartz cell was flushed with argon and then photolyzed as has been described above. Forty hours were required for the completion of the photolysis. The yields of the four products were as follows: ketone **6** (37 mg, 21%); 17β-ol **7** (95 mg, 52%); hydroxamic acid **8** (16 mg, 8%); isomeric hydroxamic acid (**2**) (15 mg, 8%).

17a-Aza-D-homo-5α,13α-androstan-3α-ol-17-one 3-Acetate by Reduction of the Hydroxamic Acid 8. Into a solution of the hydroxamic acid **8** (14 mg) in glacial acetic acid (2.8 ml), we stirred Zn dust (70 mg). After solution has then been heated under reflux for 3 h, the reaction mixture was filtered and the filtrate poured into ice water. The solution was neutralized with saturated sodium hydrogencarbonate solution and extracted with methylene chloride. The dichloromethane solution was worked up in the usual way. The residue

(12 mg) was purified by preparative TLC to afford the lactam, **8**, R=H, (4 mg) (mp 192.5—193.5 °C), identical with an authentic specimen.[12]

Photolysis of dl-*Bornyl Nitrite* ***3*** *with Monochromatic Light 385 ±8 nm.* A solution of the nitrite (1.5 g) in dry benzene (2 ml) in a quartz cell was flushed with argon and then photolyzed as in the photolysis of steroidal nitrites. Eighty-five hours were required for the completion of the photolysis. The yellowish green solution was evaporated *in vacuo*, and the residue was subjected to preparative TLC (benzene/ether; 4/1). The polar fraction containing the hydroxamic acid was then again subjected to preparative TLC (ether). The least mobile fraction (46 mg, 3%) was the hydroxamic acid **4**. The analytical results of a specimen obtained by chromatographic purification were in agreement with the $C_{10}H_{17}NO_2$ formula. (Found: C, 65.80, H, 9.21, N, 7.48%) MS, *m/e* 183 (M^+); NMR: τ 8.65 (1-methyl), 8.95, 8.99 (8.8-gem dimethyl) IR: 1637 (amide C=O), 3131 and 3411 cm^{-1} (hydrogen-bonded hydroxyl).

Photolysis of d-*Bornyl Nitrite* ***3*** *in Benzene with Pyrex-filtered Light.* Bornyl nitrite **3** (2 g) in dry benzene (200 ml) was photolyzed for 12 h. A brownish solution was evaporated, and the residue was recrystallized from hexane to yield the crude hydroxamic acid. The compound was again recrystallized from benzene–hexane to yield 37 mg (2%) of the hydroxamic acid **4**.

Irradiation of the Nitrite ***1*** *in an EPA Matrix at 77 K.* The matrix was prepared by dissolving the nitrite **1** (30 mg) in EPA (diethyl ether–isopentane–ethanol 1 : 1 : 2 in volume) 10 ml (8.3×10^{-3} M) and by then freezing the solution with liquid nitrogen. The matrix was degassed by freeze-thaw cycles. This matrix was irradiated through a Pyrex-filter with a 250-W super high-pressure Hg arc (USHIO UI 501C). The change in the spectrum was monitored at appropriate time intervals by means of a Carry ultraviolet spectrometer. After a 30-min irradiation, a very weak broad absorption at 695 nm due to the C-nitroso compound appeared, although the banded absorption due to the O–NO (385, 372, 358, 348, and 336 nm) nearly vanished. After the matrix had been brought to room temperature, a TLC examination of the solution revealed that the major product was the 11β-ol **7**, though traces of the hydroxamic acids **2** and **8** were also present.

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13) Because of the solubility problem, the photolysis of the nitrite **1** in protic solvents such as alcohol has not been studied.

14) We could not achieve the yield described in the literature in spite of repeated experiments under various concentrations. The reason for the low yield is obscure.