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In an unsuccessful attempt to effect remote functionalization at C9, 4,4-dimethylxazolidine-*N*-oxyl (doxyl) derivatives at C3 of 5 β -androstan-3,17-dione and 5 β -androstan-17 β -ol-3-one were prepared and photolyzed. The former doxyl yielded its C13 stereoisomer; the latter was converted very slowly to intractable material.

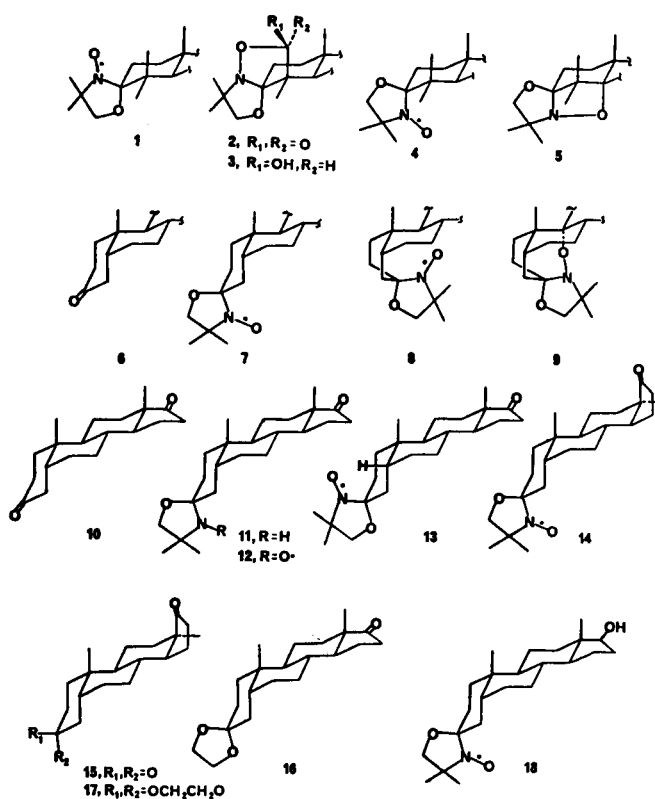
J. Heterocyclic Chem., **16**, 807 (1979).

Abstraction of hydrogen from carbon by photoexcited nitroxides, first reported by Keana (1), has been applied by us (2) to functionalization of the 4 β methyl group of a steroid through conversion of doxyl **1** (3), derived from 4,4-dimethylcholestanone, to photoproducts **2** and **3**. In this note are reported the preparation and photolysis of doxyl derivatives of 5 β -androstan-3-ones in an unsuccessful attempt to effect remote functionalization at C9. Such functionalization at C9 can lead to the synthesis of corticosteroids, as has been elegantly demonstrated by Breslow (4). We were encouraged to try to emulate his success by the fact that photolysis of **4**, the minor doxyl isomer obtained during preparation of **1**, afforded **5**, a product of oxygenation at a tertiary site, in 39% yield (2).

Our strategy was based on precedents (2,5,6) indicating that steroidal ketones afford doxyl derivatives with the C-N bond equatorial. In the case of an A/B *cis*-fused C3 ketone (**6**), formation of **7** would be expected. The nitroxide moiety of **7** cannot undergo any intramolecular reaction when photoexcited except during that presumably small fraction of time when ring A has a twist-boat conformation, as in **8**. In **8**, the nitroxide is well placed to abstract the C9 α hydrogen (**7**), which could lead to formation of **9**, the photoproduct analogous to **5**. Although conformation **8** is unfavorable, there is a report of C9 α functionalization, albeit in low yield, by reaction with lead tetraacetate of 5 β -pregnane-3 α , 20 β -diol-11-one to form 3 α , 9 α -oxido-5 β -pregnane-20 β -ol-11-one (8).

Recognizing that functionality at C17 could eventually be needed for corticosteroid synthesis, but embarrassingly oblivious of the facile C/D ring fusion photoisomerization of steroidal 17-ketones (9), we chose doxyl **12** as our initial substrate. This nitroxide was readily prepared by selective condensation of 5 β -androsta-3,17-dione (**10**) with 2-amino-2-methyl-1-propanol (3) to afford oxazolidine **11** (91%), followed by *m*-chloroperbenzoic acid oxidation (3) to give **12** (75%). Reconversion of **12** to **10** was effected in 82% yield by treatment with nitric oxide/nitrogen dioxide in ethanol (10). The stereochemistry of the doxyl ring shown in **12**, assigned on the basis of precedent (2,5,6), is consis-

tent with the photochemical behavior described below, since isomer **13** would be expected to abstract its 5 β hydrogen upon photolysis (*cf.*, 4 - 5).



When a benzene solution of **12** was irradiated through a Pyrex filter using a 450-watt Hanovia lamp for 72 hours, 35% of isomeric doxyl **14** was obtained. Treatment of **14** with nitric oxide/nitrogen dioxide in ethanol (10) afforded the previously unreported 5 β -13-*iso*androstan-3,17-dione (**15**). To confirm the identity of the photoproduct, ethylene ketal **16** was prepared in the standard manner, and photolyzed to afford **17** (29%), which also afforded **15** upon hydrolysis.

Since the C17 carbonyl function was incompatible with the overall synthetic strategy, doxyl **12** was reduced with

sodium borohydride in isopropyl alcohol to give 81% of **18**, possessing the photochemically inert hydroxyl group (11). Photolysis of **18** under the same conditions used for **12** proceeded very slowly; after 14 days about half of the **18** remained. The rest of the material was a complex mixture from which no discrete compound possessing promising spectral properties could be isolated. We were forced to conclude that photolysis of doxyl derivatives of 5 β -androstan-3-ones is not a promising method for efficient C9 functionalization.

EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. Ir spectra of solids were obtained as potassium bromide pellets and of liquids as neat films on a Perkin-Elmer 137 spectrophotometer. Nmr spectra were determined in deuteriochloroform on a Perkin-Elmer R-24 spectrometer with TMS as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory. Mass spectra were determined by Dr. Catherine Costello at the MIT Mass Spectrometry Facility, sponsored by USPHS Division of Research Resources Grant RR00317. Preparative tlc was performed on 20 x 20 cm plates coated with 1.45-mm thick layers of silica gel PF₂₅₄₊₃₆₆ (Brinkmann Instruments, Inc., Westbury, New York). For preparative tlc of nitroxides the silica gel was mixed with 0.002% Rhodamine 6G dye (Eastman Kodak Co., Rochester, New York). Uv light was used to visualize the plates. Brine refers to saturated aqueous sodium chloride solution.

Oxazolidine 11.

According to the procedure of Keana (3), a mixture of 1.44 g. (5.0 mmoles) of 5 β -androstan-3,17-dione (Steraloids), 0.71 g. (8.0 mmoles) of distilled 2-amino-2-methyl-1-propanol (Aldrich), and a small crystal of *p*-toluenesulfonic acid monohydrate in 10 ml. of dry benzene was stirred magnetically and refluxed for 13 hours, during which period the reflux condenser was removed several times for 3 minutes to allow azeotropic distillation of water. The mixture was allowed to cool to room temperature, diluted with 50 ml. of ether, and extracted with 3 x 40 ml. of water. The ether layer was dried (sodium sulfate) and evaporated to afford after evacuation on an oil pump, 1.62 g. (91%) of crude gummy **11**; ir: 1735 cm⁻¹; nmr: δ 0.82 (s), 0.94 (s), 1.20 (s) and 3.55 (s).

Doxyl 12.

Essentially according to the procedure of Keana (3), a solution of 1.03 g. (6.0 mmoles) of *m*-chloroperbenzoic acid (Aldrich) in 10 ml. of anhydrous ether was added dropwise over 10 minutes to an ice-cooled solution of 1.80 g. (5.0 mmoles) of **11**, freshly prepared as described, in 10 ml. of ether. The mixture was allowed to warm to room temperature and stirred for 24 hours. It was then diluted with 50 ml. of ether, and washed with 4 x 50 ml. of brine and 2 x 25 ml. of water. The ether layer was dried (sodium sulfate) and evaporated to afford 1.84 g. of orange semisolid (tlc showed two components). Column chromatography on 75 g. of silica gel using 2:1 ether-hexane yielded 1.40 g. (75%) of **12** and 0.40 g. of crude **10**. After recrystallization from hexane pure **12** was obtained, m.p. 158.5-159.5° dec; ir: 1727 cm⁻¹; uv (diethyl ether): λ max 437 nm (ϵ = 8.5); esr (benzene, degassed) a_N = 14.3 G(t); ms: M⁺ m/e 374.2670 (calcd. for C₂₅H₃₆NO₃, 374.2695).

Anal. Calcd. for C₂₅H₃₆NO₃: C, 73.80; H, 9.63; N, 3.74. Found: C, 73.74; H, 9.66; N, 3.79.

Conversion of 12 to 10.

Commercial nitric oxide (containing nitrogen dioxide) was bubbled through a solution of 0.093 g. (0.25 mmoles) of **12** in 2.5 ml. of absolute ethanol for 6 minutes, at which time the original orange color had disappeared and tlc analysis showed no **12** remained. Evaporation left a dark oil which was purified by preparative tlc (2:1 ether:hexane) to afford

0.059 g. (82%) of **10**, which had m.p. 133-134° after recrystallization from ether, and whose identity was confirmed by ir, nmr, tlc and mixture melting point.

Photoisomerization of 12 to 14.

Initial trial photolyses of **12** in benzene solution using a Pyrex filter with a 450-watt Hanovia medium pressure mercury lamp were run under the following conditions: a) 4 x 10⁻²M; b) 4 x 10⁻³M with the solution vacuum degassed by the repeated freeze-thaw method; and c) 5 x 10⁻⁴M. In each case the analysis showed that all **12** had been consumed after 72 hours, that the same mixture of products had been formed, and that a principal product (**14**) was being formed at a shorter time and undergoing further conversion upon prolonged irradiation. Preparation of **14** was maximized by the following procedure. A solution of 1.870 g. (5 mmoles) of **12** in 200 ml. of benzene was photolyzed (not degassed) for 18 hours. The solvent was evaporated and the residue was separated by preparative tlc (2:1 ether-hexane) into two fractions: 1.283 g. (69%) of unconsumed **12** and 0.245 g. (13%) of **14**. The recovered **12** was redissolved in a proportional amount of benzene, and the photolysis and separation cycle was repeated three times, at the end of which there remained 0.428 g. (23%) of **12** and a total of 0.647 g. (35%) of **14** had been obtained from the 77% conversion of **12**. Recrystallization from hexane afforded pure orange **14**, m.p. 151-152° dec; ir: 1725 cm⁻¹; uv (diethyl ether): λ max 439 nm (ϵ = 8.5); esr: a_N = 14.3 G(t); ms: M⁺ m/e 374.2685 (calcd. for C₂₅H₃₆NO₃, 374.2695).

Anal. Calcd. for C₂₅H₃₆NO₃: C, 73.80; H, 9.63; N, 3.74. Found: C, 73.76; H, 9.57; N, 3.78.

Conversion of 14 to 15.

Essentially as in the conversion of **12** to **10**, treatment of 0.084 g. (0.2 mmoles) of **14** with nitric oxide/nitrogen dioxide in absolute ethanol afforded, after preparative tlc, 0.045 g. (70%) of **15**, which after recrystallization from hexane had m.p. 101-102°; ir: 1727 and 1709 cm⁻¹; nmr: δ 0.91 (s) and 1.03 (s); ms: M⁺ m/e 288.2081 (calcd. for C₁₉H₂₈O₂, 288.2089).

Anal. Calcd. for C₁₉H₂₈O₂: C, 79.17; H, 9.72. Found: C, 79.21; H, 9.82.

Ketal 16.

A mixture of 1.00 g. (3.47 mmoles) of **10**, 0.22 g. (3.47 mmoles) of ethylene glycol, and a small crystal of *p*-toluenesulfonic acid monohydrate in 75 ml. of dry benzene was heated at reflux connected to a Dean-Stark trap for 1 hour. The mixture was allowed to cool to room temperature and was washed with 4 x 50 ml. of saturated aqueous sodium bicarbonate and 2 x 40 ml. of water. The benzene layer was dried (sodium sulfate) and evaporated and the white solid residue was recrystallized from hexane-ether to afford 0.879 g. (76%) of **16**, m.p. 128-129°; ir: 1733 cm⁻¹; nmr 0.90 (s), 1.03 (s), and 3.93 (s); ms: M⁺ m/e 332.2346 (calcd. for C₂₁H₃₂O₃, 332.2351).

Anal. Calcd. for C₂₁H₃₂O₃: C, 75.90; H, 9.64. Found: C, 76.07; H, 9.58.

Photoisomerization of 16 to 17.

A solution of 0.854 g. (2.57 mmoles) of **16** in 155 ml. of benzene was irradiated through a Pyrex filter with a 450-watt Hanovia medium pressure mercury lamp for 5 hours. The solvent was evaporated and the product was separated by preparative tlc (2:1 ether-hexane) to afford 0.400 g. of **16** and 0.122 g. of **17**. Re-photolysis of the recovered **16** yielded an additional 0.103 g. of **17** for a total yield of 0.225 g. (29%) from an 82% conversion of **16**. Ketal **17**; ir: 1733 cm⁻¹; nmr: 0.72 (s), 0.91 (s), and 3.89 (s), was homogeneous by tlc but could not be induced to crystallize, so it was carried on as described next without further characterization.

Hydrolysis of 17 to 15.

A solution of 0.126 g. (0.38 mmoles) of **17** and 40 drops of 5% aqueous hydrochloric acid in 4 ml. of THF was refluxed for 20 minutes. The mixture was poured into 50 ml. of water and extracted with 20 ml. of ether. The ether layer was dried (sodium sulfate) and evaporated and the residue was recrystallized from hexane to afford 0.101 g. (92%) of **15**, m.p. 101-102°, identical by ir, nmr, tlc, ms and mixture melting point

with **15** obtained from **12**.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.17; H, 9.72. Found: C, 79.25; H, 9.80.

Reduction of **12** to **18**.

To a solution of 0.620 g. (1.66 mmoles) of **12** in 40 ml. of dry isopropyl alcohol was added 0.100 g. (2.64 mmoles) of sodium borohydride and the resulting mixture was stirred at room temperature for 3 hours. The mixture was treated with 20 ml. of acetone and filtered and 20 ml. of water was added to the filtrate. The solvents were partially evaporated and the remainder was extracted with 25 ml. of ether. The ether layer was dried (sodium sulfate) and evaporated to afford 0.492 g. (81%) of **18**, which was recrystallized from ether to give pure yellow crystals of **18**, m.p. 176-177° dec; ir: 3470 cm^{-1} ; uv (diethyl ether): λ max 430 nm ($\epsilon = 9.3$); esr: $a_N = 14.4$ G(t); ms: M^+ m/e 376.2858 (calcd. for $C_{23}H_{38}NO_3$, 376.2844).

Anal. Calcd. for $C_{23}H_{38}NO_3$: C, 73.40; H, 10.11; N, 3.72. Found: C, 73.43; H, 10.15; N, 3.61.

Photolysis of **18**.

A solution of 0.800 g. (2.13 mmoles) of doxyl **18** in 200 ml. of benzene was photolyzed in the same manner as **12**. The reaction was monitored by tlc every 24 hours. After 14 days 40 ml. of the solution was evaporated and separated by extensive preparative tlc (3:1 ether-hexane, then ether) to afford 0.072 g. of **18** and two major product fractions (0.018 g. and 0.036 g.) which appeared to be mixtures. After 30 days of irradiation the rest of the reaction mixture was evaporated and subjected to extensive preparative tlc, affording 0.060 g. of **18**, 0.015 g. and 0.081 g. of the two product fractions just mentioned and ca. 0.4 g. of polar, intractable material.

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REFERENCES AND NOTES

- (1) J. F. W. Keana, R. J. Dinerstein and F. Batis, *J. Org. Chem.*, **36**, 209 (1971).
- (2) J. A. Nelson, S. Chou and T. A. Spencer, *J. Am. Chem. Soc.*, **97**, 648 (1975).
- (3) "Doxyl" is a convenient designation for 4,4-dimethyloxazolidine-*N*-oxyl derivatives of ketones, originally prepared by J. F. W. Keana, S. B. Keana and D. Beetham, *ibid.*, **89**, 3055 (1967).
- (4) R. Breslow, B. B. Snider and R. J. Corcoran, *ibid.*, **96**, 6792 (1974).
- (5) P. Michon and A. Rassat, *J. Org. Chem.*, **39**, 2121 (1974).
- (6) T. B. Marriott, G. B. Birrell, and O. H. Griffith, *J. Am. Chem. Soc.*, **97**, 627 (1975).
- (7) Abstraction of the secondary C7 hydrogen would also be geometrically feasible, but presumably energetically less favorable.
- (8) A. Bowers and E. Denot, *ibid.*, **82**, 4956 (1960).
- (9) A. Butenandt, A. Wolff and P. Karlson, *Chem. Ber.*, **74**, 1308 (1941); A. Butenandt, W. Friedrich and L. Poschmann, *ibid.*, **75**, 1931 (1942); A. Butenandt and L. Poschmann, *ibid.*, **77**, 392, 394 (1944).
- (10) S. Chou, J. A. Nelson and T. A. Spencer, *J. Org. Chem.*, **39**, 2356 (1974); J. A. Nelson, S. Chou and T. A. Spencer, *Chem. Commun.*, 1580 (1971).
- (11) The β -configuration is assigned to the OH group in **18** on the basis of a number of precedents for hydride reduction of steroidal C17 ketones: for a review, see D. M. S. Wheeler and M. M. Wheeler, in "Organic Reactions in Steroid Chemistry", Vol. 1, J. Fried and J. A. Edwards Eds., van Nostrand Reinhold Co., New York, N. Y., 1972, p. 61.