Rearrangement of a Pregn-17(20)(*E*)-en-21-amide Epoxide to a 17-Keto-*D*-homoandrostane-17aα-carboxamide

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In the course of a study directed toward the partial synthesis of a *D*-homo-17aβ-carboxamide of an azasteroid, it became of interest to utilize the pregn-17(20)(*E*)-en-21-amide analogue 1 in which the *E* geometry of the double bond could be used to indirectly lead to a stereochemically controlled rearrangement to a D-homo system.

We sought to examine the Tiffeneau rearrangement of the 17α-hydroxy-20α-amino steroid 4 which can be selectively prepared from 1. The deaminative rearrangement of 4 could lead to two possible products, 5 and/or 8, which would result from trans antiplanar movement of the C_{13} and/or C_{16} bond from C_{17} to the C_{20} carbon as the nitrogen molecule departs (Scheme I).

The fact that only the 17aα-carboxamide was isolated from the reaction indicates that intermediate A best represents the preferred orientation of the side-chain functionalities for the rearrangement. Intramolecular hydrogen bonding of the 17α-hydroxy group to the 21-carboxamide (structure C) could predispose the molecule to rearrange this way by holding the diazonium function nearly antiparallel to the migrating C_{13} bond.

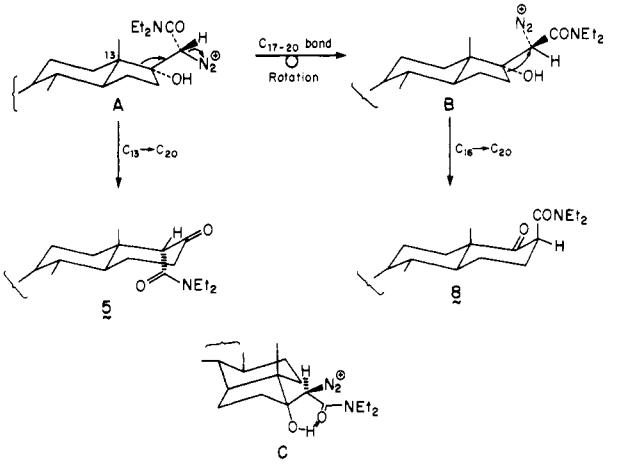
The olefin 1 was prepared via Wittig–Horner reaction of the 17-ketoandrostane derivative 7 with an excess of triethyl phosphonoacetate.[1] The orientation of the C-17(20) double bond formed in this reaction has been shown to be exclusively of the *E* geometry.[2] The initially formed ester was converted to the corresponding amide 1 by hydrolysis to the acid and reaction with oxalyl chloride, followed by treatment with diethylamine.

Treatment of the olefin 1 with *m*-chloroperbenzoic acid in chloroform at room temperature for 7 days afforded a single epoxide 3. The assignment of α stereochemistry to this epoxide is based on ample precedent for peracid oxidation of C-17(20) olefins.[3]

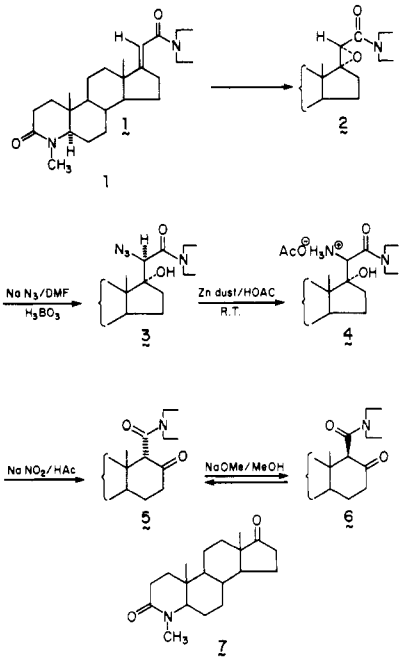
Epoxide 3 reacted with sodium azide/boric acid/DMF at 110–115 °C[4] to afford the azide derivative 3. At a somewhat higher temperature (120–130 °C), the retroaldol product 7 was readily formed, resulting in proton lower yield of azide 3. Reduction of azido derivative 3 with Zn dust/HOAc gave rise to the intermediate 20α-amino-17α-hydroxy analogue 4 which was directly diazotized with nitrous acid to afford the rearrangement product 5 in 60% yield (Scheme II).

The D-homo product 5 was isolated by preparative HPLC and characterized by the NMR shift of the 17a methine proton at δ 3.25. On close inspection, a small (1.7 Hz) four-bond w coupling between the 17a and the 16 proton was noted, thus establishing a 1,3-equatorial relationship between the two protons. This necessitates that the amide side chain be in an axial configuration. Confirmation of this assignment was determined by X-ray analysis and is depicted in the ORTEP drawing in Figure 1.

Scheme I



Scheme II



Treatment of the α-isomer 5 with sodium methoxide at room temperature gave rise to the β-isomer 6 as a major product and a trace of a crystalline byproduct. Comparison of the ^{1}H NMR spectra of the isomeric amides shows a difference between the chemical shifts of the methine protons at the 17a position and a downfield shift of the C-18 methyl group for the β-isomer.

Treatment of the α-isomer with lithium diisopropyl amide (LDA) in dry tetrahydrofuran at −78 °C followed by quenching with glacial acetic acid regenerated exclusively α-isomer as shown by HPLC. This result can be explained on the basis that kinetic proton removal is more facile from the 2 and/or 16 positions than from the 17a position where the equatorially disposed hydrogen would not lead directly to an enolate with proper overlap with both of the adjacent carbonyl groups. Alternatively, the 17a hydrogen may be sterically inaccessible to the bulky amide base.

This observation was reconfirmed through rapid deuteration of the LDA enolate with CD_3COOD. The deuterium uptake as shown by the mass spectrum is $M^{+\cdot}$ +

(1) Rasmusson, G. H.; Johnston, D. B. R.; Arth, G. E. U.S. Patent 4 377 584, March 22, 1983.
(2) Wicha, J.; Bal, K.; Pickut, S. *Synth. Commun.* **1977**, *7(3)*, 215.
(3) Oliveto, E. P. In "Organic Reactions in Steroid Chemistry"; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. 2, 127.
(4) Kirk, D. N.; Wilson, M. A. *J. Chem. Soc. C* **1971**, 414.

0022-3263/84/1949-4731$01.50/0

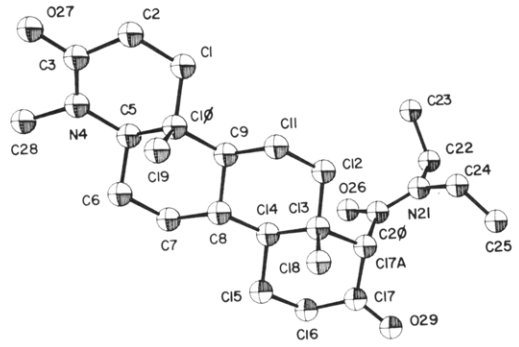


Figure 1. Perspective drawing of 17a-α-(diethylcarbamoyl)-*D*-homo-4-aza-4-methyl-5α-androstane-3,17-dione (**5**). For clarity, hydrogens have not been included.

D; $M^{+\cdot}$ + 2D; $M^{+\cdot}$ + 3D, in a ratio of 46:30:8, and the NMR data indicate that the exchange occurred primarily at C-16 and C-2.

Equilibration experiments with pure α- and β isomers **5** and **6**, respectively, using potassium acetate in methanol under reflux conditions for 20 h, resulted in the same ratio of **5**:**6** (2:1). The product mixture was analyzed by HPLC and by measurement of the C-18 methyl peak heights in the NMR spectrum. These results indicate surprisingly that the thermodynamically more stable product is the axial α-isomer **5**.

The enolate formed by methoxide treatment is likely obtained via removal of the 17a hydrogen. Acid quenching of this enolate thus results in kinetic quenching (axial protonation) and favored formation of the less stable 17aβ-carboxamide compound **6**.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 1420 spectrometer. ^{1}H NMR spectra were obtained on a Varian SC 300 spectrometer. Mass spectra were obtained with an LKB Model 9000 spectrometer equipped with GC and direct inlet system. Analytical high-pressure LC separations were made on a Waters Associates ALC 200 series chromatograph equipped with a Model 6000A pump, a 3.9 mm × 30 cm μPorasil column, and a Series 400 refractometer. Preparative high-pressure LC separations were made on a Whatman Magnum 20, Partisil 10 silica column. X-ray data were collected on a fully automated CAD4 diffractometer.

***N*,*N*-Diethyl-4-methyl-3-oxo-4-aza-17α,20(*E*)-epoxy-5α-pregnan-21-amide (2).** *N*,*N*-Diethyl-4-aza-4-methyl-3-oxopregn-17(20)(*E*)-en-21-amide (**1**) (1.0 g) was treated with *m*-chloroperbenzoic acid (1.0 g) in $CHCl_3$ (20 mL) solution. The reaction was stirred under nitrogen at room temperature for 7 days, then diluted with $CHCl_3$ (20 mL) and washed with 5% $NaHCO_3$, water, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to a pale yeilow oil. The oil crystallized from ethyl acetate to give white crystals (789.5 mg): mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 0.875 (18 CH_3), 0.90 (19 CH_3), 1.12 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), and 1.2 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 2.45 (q, J = 6.0 Hz, 2 H), 2.94 (s, NCH_3), 3.06 (q, J = 4.0 Hz, 1 H), 3.46 (m, J = 6.0 Hz, 4 H, CH_3CH_2N), 3.40 (s); MS, m/e found M^+ 416, calcd M^+ 416 for $C_{25}H_{40}O_3N_2$.

Anal. Calcd for $C_{25}H_{40}O_3N_2$: C, 72.07; H, 9.68; N, 6.73. Found: C, 72.01; H, 9.76; N, 6.36.

***N*,*N*-Diethyl-4-methyl-3-oxo-17α-hydroxy-20α-azido-4-aza-5α-pregnane-21-carboxamide (3).** The epoxide derivative **2** (2.33 g) in dimethylformamide (20 mL) with sodium azide (2.33 g) and boric acid (2.33 g) was heated at 110–115 °C (oil bath temperature) under N_2 for 17 h. The reaction mixture was brought to room temperature, the solvent was removed, and crude product was obtained as a yellow oil. The residue was dissolved in chloroform, washed with water and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to a yellow oil in vacuo to afford 2.36 g of crude product. Crystallization from ethyl acetate afforded white material (1.09 g); mp 224–225 °C dec. The mother liquor of the first crop was evaporated to dryness and the residue was then chromatographed on silica gel with 70:30 acetone/hexane to afford **3** as rhombic crystals (477.5 mg): mp 224–225 °C dec: IR ($CHCl_3$) λ_{max} 4.78, 6.18 μm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.74 (18 CH_3), 0.90 (19 CH_3), 1.18 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 1.31 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 2.42 (q, J = 6.0 Hz, 2 H), 2.92 (s, NCH_3), 3.04 (q, J = 4.0 Hz, 1 H), 3.39 (m, J = 6.0 Hz, 4 H, CH_3CH_2N), 3.53 (s, 1 H); MS, m/e found M^+ 459, calcd M^+ 459 for $C_{25}H_{41}O_3N_5$.

Anal. Calcd for $C_{25}H_{41}O_3N_5 \cdot {}^1/_4H_2O$: C, 64.67; H, 9.01; N, 15.08. Found: C, 64.97; H, 8.74; N, 14.84.

17aα-(Diethylcarbamoyl)-4-methyl-*D*-homo-4-aza-5α-androstane-3,17-dione (5). To the hydroxy azide **3** (1.37 g) in acetic acid (35.0 mL) was added zinc powder (1.37 g) in small portions over a period of 45 min at 20 °C. The reaction mixture was stirred for 2 h at room temperature after which gas evolution had ceased. The reaction mixture was filtered through Supercel and the excess of zinc was thoroughly washed with 27.8 mL of water containing 12.0 mL of acetic acid. The combined filtrates were diluted with water (100 mL) and extracted with ethyl acetate. The extract was washed twice with water, and these washings were added to the acid layer. The latter was cooled in ice and the pH adjusted to 3–4, and sodium nitrite (1.3 g) was added in portions. The diazotization was allowed to proceed overnight at 0–5 °C with constant stirring. The reaction mixture was extracted with ethyl acetate (4×), and the organic layer was washed with water and saturated aqueous NaCl, dried ($MgSO_4$), then filtered, and concentrated to a pale yellow oil (1.07 g). This was then chromatographed on 60.0 g of EM silica gel with 60:40 acetone/hexane to give the impure α-isomer **5** as an amorphous material (683.0 mg) and a polar material as foam (153.0 mg). Further purification of the α-isomer on HPLC using an M-20 10/50 Partisil Whatman column and 60:40 acetone/hexane as eluant gave the α-isomer **5** (548.0 mg): ^{1}H NMR ($CDCl_3$) δ 0.86 (18 CH_3), 0.89 (19 CH_3), 1.11 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 1.21 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 2.42 (m, 2 H), 2.94 (s, NCH_3), 3.03 (d, d, J = 4.0 Hz, 12 Hz, C_5-H), 3.25 (d, J = 1.73 Hz, 1 H), 3.2–3.5 (m, CH_3CH_2N, 4 H); MS, m/e found M^+ 416, calcd M^+ 416 for $C_{25}H_{40}N_2O_3$. Recrystallization from ethyl acetate afforded **5**, mp 159–160 °C.

Anal. Calcd for $C_{25}H_{40}N_2O_3 \cdot {}^1/_2H_2O$: C, 70.56; H, 9.71; N, 6.58. Found: C, 70.69; H, 9.46; N, 6.53.

X-ray Crystallographic Study of 17aα-(Diethylcarbamoyl)-4-methyl-*D*-homo-4-aza-5α-androstane-3,17-dione (5). A single-crystal X-ray diffraction experiment on a specimen of structure **5** grown from ethyl acetate (containing water of solvation) was carried out at room temperature to determine the stereochemistry of the side chain at C17A relative to C18 and C19 whose absolute stereochemistries were known. The unit cell parameters found are a = 8.242 (3) Å, b = 12.772 (11) Å, c = 23.112 (10) Å, $\alpha = \beta = \gamma = 90°$, and V = 2433 (4) Å^3 in the noncentrosymmetric space group $P2_12_12_1$ (Z = 4). Of a total of 1926 reflections, 1646 (85.5%) were considered observeds at the level $I \gtrsim 3\sigma(I)$. A trial structure consisting of 25 atoms was obtained by the multiple tangent formula procedure of MULTAN[5] and expanded to a complete structure through a series of difference electron density syntheses. Full matrix refinement of non-hydrogen atoms was carried out with anisotropic temperature factors. Hydrogen atoms were calculated at idealized positions, assigned equivalent isotropic temperature factors of the atoms to which they were bound, and refined for positional parameter variation only. The final residual index R [= $\Sigma(|F_o| - |F_c|)/|F_o|$] was 0.0480. The function minimized by least squares was $w(|F_o| - |F_c|)^2$ where w is $1/\sigma(F_o)^2$.

Isomerization of α-Isomer 5 to β-Isomer 6. A flask containing α-isomer **5** (306 mg) in 6.0 mL of methanol was evacuated

(5) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data, Universities of York, England and Louvain, Belgium.

with a vacuum pump and purged with nitrogen, and the procedure was repeated several times. Sodium methoxide (4.4 M, 650 μL) was injected dropwise via syringe. The reaction was stirred for 5 h at room temperature under nitrogen. The reaction mixture was concentrated to dryness and treated with water. The product was extracted with ethyl acetate, washed with 2.5 N HCl, and dried ($MgSO_4$), and the solution was evaporated to dryness in vacuo to give 220 mg of crude product. This was chromatographed on HPLC (M-10 10/50 Partisil 10 silica column) and eluted with 60:40 acetone/hexane. The minor first eluted material, after crystalline from ethyl acetate, afforded 26.0 mg; mp 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (18 CH_3), 0.90 (19 CH_3), 1.14 (t, 3 H, CH_3CH_2N), 1.15 (t, 3 H, CH_3CH_2N), 1.77 (d, J = 7.0 Hz, 3 H, (CH_3CH=), 2.45 (m, H_2), 2.82 (d, d, J = 5 and 16 Hz, 1 H), 2.95 (s, NCH_3), 3.04 (d, d, J = 13.0 and 3 Hz, 1 H, H_5), 3.20–3.45 (m, CH_3CH_2N), 6.91 (q, t, J = 7.3 Hz, 1 H, CH_3CH=); MS, m/e found M^+ 442.31818 corresponding to empirical formula $C_{27}H_{42}N_2O_3$, calcd M^+ 442.3193. This material appears to be the 16-ethylidene derivative of the ketone **6**.

The major product **6** was isolated (85.0 mg): mp 156–158 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (19 CH_3), 1.14 (t, J = 6.0 Hz, 3, CH_3CH_2N), 1.15 (t, J = 6.0 Hz, 3 H, CH_3CH_2N), 1.20 (18 CH_3), 2.53 (m, 2 CH_2), 3.02 (s, NCH_3), 3.12 (d, d, J = 13.5 and 3.5 Hz, 5-CH), 3.21 (m, NCH_2CH_3), 3.49 (m, NCH_2CH_3), 3.40 (s, 1, 17a-CH); MS, m/e found M^+ 416, calcd H^+ 416 for $C_{25}H_{40}N_2O_3$.

Anal. Calcd for $C_{25}H_{40}N_2O_3 \cdot {}^1/_5H_2O$: C, 71.45; H, 9.69; N, 6.67. Found: C, 71.21; H, 9.59; N, 7.05.

Equilibrium Studies of β-Isomer 6 and α-Isomer 5. A solution of 12.6 mg of β-isomer **6** and 12.0 mg of potassium acetate in 10.0 mL of methanol was refluxed under nitrogen for 20 h. The reaction mixture was concentrated to dryness. The product was extracted into ethyl acetate, washed with water, dried ($MgSO_4$), and isolated as a solid. The product mixture was analyzed by HPLC on a Porosil column and by measurement of the C-18 methyl peak heights in the NMR. In this way **5** separated from **6** in a ratio of 2:1 favoring the α-isomer.

Similarly, the α-isomer (12.6 mg) was treated as above, and again **6** separated from **5** in a ratio of 2:1 favoring the α-isomer.

Deuterium Incorporation in α-Isomer 5. Isopropylamine (10.5 μL) was dissolved in 0.3 mL of dry tetrahydrofuran, the mixture was purged with nitrogen, and the solution was treated dropwise at −78 °C with BuLi (34.1 μL, 22 mM). After 45 min at −78 °C, α-isomer **5** (10.0 mg) in 0.3 mL of tetrahydrofuran was added via syringe. The reaction was stirred at this temperature for 1 h under nitrogen, followed by quenching with 0.5 mL of CD_3COOD. The reaction mixture was concentrated to dryness; the product was extracted in ethyl acetate, washed with water and with saturated aqueous NaCl, dried ($MgSO_4$), and isolated as a white solid. The product isolated had a retention time on HPLC identical with the α-isomer **5**. The proton NMR of the isolated product indicates that the deuterium incorporation has been localized primarily at C_{16} δ 3.00 and C_2 2.43. Surprisingly, no appreciable exchange has occurred at C_{17a} δ 3.26 based on inspection and area measurement.

As far as can be determined from relative areas, 0.3–0.5 D was introduced at C_{16} and has involved exclusively the lower field proton of the genuinely nonequivalent pair. The area of the 2-CH_2 appears to be about 20% below stoichiometry which corresponds to roughly the introduction of 0.4 D. The estimated total deuterium incorporation thus is reasonably compatible with the net mass spectral finding of one deuterium.

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Registry No. **1**, 92472-87-2; **2**, 92763-04-7; **3**, 92786-69-1; **5**, 92763-05-8; **6**, 92763-06-9; **6** (16-ethylidene deriv), 92763-07-0.

Supplementary Material Available: Table 1, fractional coordinates and temperature factors for structure **5**; Table 2, bond distances; Table 3, bond angles (3 pages). Ordering information is given on any current masthead page.

1,6-Bis(trimethylsilyl)hexa-1,5-diyn-3-ene: Models To Determine the Structure of Polydiacetylenes

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The title compound (**1**, as both cis and trans isomers) is the protected form of a synthon (hexa-1,3-diyn-2-ene, **2**) which has been of some interest and importance in physical organic and organometallic chemistry.[1-3] We also believe the title compound to be of value in the preparation of organic compounds of interest in solid state organic chemistry; for example, deprotection of **1** would lead to an immediate precursor to the elusive parent "polydiacetylene". Polydiacetylenes (PDA's) are polymers whose backbone consists of alternating double and triple bonds. To date only PDA's with large substituents on the ene portion of the backbone have been prepared by a solid state polymerization reaction of 1,4-disubstituted butadiynes.[4] Diacetylene itself polymerizes but does not afford the regular polymer described above for the substituted diacetylenes.[5] Attempts have been made to convert substituted PDA's to organic conductors via redox reactions ("doping"), but only very moderate increments in conductivity have been reported,[6] probably due to interference (steric, chemical, or electronic) of the substituents. It would therefore be highly desirable to be able to prepare the parent PDA (prepared by alternate procedure) to test whether indeed it could be doped to levels of metallic conductivity.

Compound **2** could also be a precursor to a large number of organic molecules containing a hexatriene of known stereochemistry and ultimately a polyene via hydroboration followed by functional group interconversion. These transformations have been carried out in our group and will be the subject of future publications.[7]

In this paper we report a very simple procedure for the preparation of **1** and **2** and full characterization of each individual isomer of **1**. The latter turned out to be of considerable importance in the structure determination of certain solvatochromic PDA's.[8]

Results and Discussion

The most recent synthesis of **2** is still multistep and affords a difficult-to-separate mixture of isomers. The isomer separation and purification are hampered by extreme instability of this highly unsaturated molecule.[1,2] We

(1) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.
(2) Van der Kerk, S. M.; Boersma, J.; Van der Kerk, G. J. M. *J. Organometl. Chem.* **1981**, *215*, 303.
(3) Okamura, W. H.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, *89*, 5991.
(4) Wegner, G. In "Molecular Metals"; Hatfield W. E., Ed.; Plenum Press: New York, 1979; pp 209–242.
(5) Russo, P. J.; Labes, M. M. *J. Chem. Soc., Chem. Commun.* **1982**, 53.
(6) Bloor, D.; Hubble, C. L.; Ando, D. J. in ref 4, pp 243–247.
(7) Walker, J. A.; Bitler, S. P., unpublished results.
(8) Patel, G. N *Polym. Prepr. Am. Chem. Soc., Polym. Chem. Div.* **1978**, *19*, 154. Plachetta, C.; Rau, N. O.; Schulz, R. C. *Mol. Cryst. Liq. Cryst.* **1983**, *96*, 141. Wegner, G.; Wenz, G. *Makromol. Chem. Rapid Commun.* **1982**, *3*, 231.

0022-3263/84/1949-4733$01.50/0