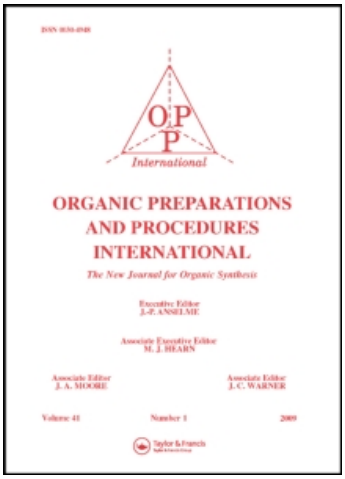

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IMPROVEMENTS IN THE SEMMLER-WOLF REARRANGEMENT OF 19-NORTESTOSTERONE OXIME

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IMPROVEMENTS IN THE SEMMLER-WOLF REARRANGEMENT OF 19-NORTESTOSTERONE OXIME

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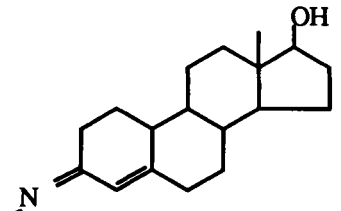
In our hands, the preparation of 3-amino-1,3,5(10)-estratrien-17-one (**3a**) from estrone and 4-chloro-2-phenylquinazoline[1] has not proven reliable for small samples of starting material. Several steps including a pyrolysis are required, and yields are small or nil under these conditions. In contrast, the conversion of the oxime (**2**) of 19-nortestosterone (**1**) to 3-acetamido-1,3,5(10)-estratrien-17β-ol acetate (**3b**) by the Semmler-Wolf aromatization readily proceeds as reported by Gold and Schwenk[2] in a reproducible 45% yield. Since in principle **3b** could be used to obtain **3e** (via **3c** and **3d**), it was of interest to ascertain if the yield of **3b** could be enhanced and if the structure of the oxime **2** (presumeably a 1:1 mixture was used) played a role on the yield of **3b**.



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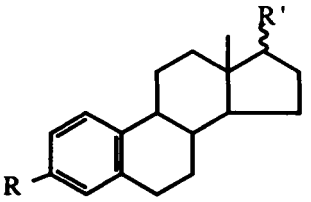

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(a) R = Ac_2N , R' = β -OAc (d) R = NH_2, R' = β -OH
(b) R = AcNH , R' = β -OAc (e) R = NH_2 , R' = keto
(c) R = AcNH , R' = β -OH

19-Nortestosterone oxime (**2**) easily prepared in 97% yield, can be separated into the *syn-* and *anti-* isomers by either preparative TLC or fast column chromatography over silica gel using benzene-acetone 4:1 as the eluting solvent. Their structures were assigned by conventional NMR techniques with the aid of

lanthanide shift reagents.

In the procedure of Gold and Schwenk,[2] the oxime mixture is refluxed in acetic anhydride and the product chromatographed over alumina. Refluxing samples of either pure oxime isomer produced reaction mixtures identical by ^{1}H and ^{13}C NMR to those from the mixed oximes. The crude product mixture consisted of one major component and two or three compounds in lesser amounts. The major component was **not** the product **3b** reported by Gold and Schwenk, which appeared only after the chromatography step. The initial product was quite dark colored, and TLC under a variety of conditions gave a complex smear with few distinct spots. Numerous attempts to isolate the initially formed major product were made using a variety of conditions for crystallization and chromatography. All chromatographic attempts resulted in the conversion of the major component to **3b**.

Subsequently, it was found that by lowering the reaction temperature to 110°C and extending the reaction time to 39 hours, it was possible to prepare the precursor to **3b** in nearly pure form in 91% yield. The quantitative conversion to **3b** by heating in ethanol-water with a few drops of acetic acid coupled with a more detailed examination of the pure material by NMR, led to the postulation that the preursor was the 3-diacetamido compound **3a**. Apparently extensive decomposition of **3a** occurs on the column during the conversion to **3b**. Material recovered from the column indicated a complex mixture not present in the intial reaction product. Refluxing **3b** in acetic anhydride gave **3b**. Basic hydrolysis of **3b** afforded the 3-acetamido-1,3,5(10)-estratrien-17β-ol (**3c**) in 91% yield. Hydrolysis in methanolic hydrochloric acid was less satisfactory giving a 45% yield of the 3-amino compound **3d** in addition to a complex mixture of neutral material.

The structures of all compounds in this study were determined by proton and carbon NMR using standard pulse 1-D and 2-D techniques, based on the assigned

chemical shifts for a number of estratrienes of Wittstruck and Williams[3] as summarized and modified by Blunt and Stothers.[4] Literature assignments for estrone and the two 17-estradiols list carbons 11,7 and 6 in order of decreased shielding. Based on the data collected here, the chemical shifts given in the Table reflect our reversal of the assignments for carbons 7 and 11. Reasonably this reversal should be applied also to estrone.

TABLE. The ^{13}C NMR Parameters for the Steroids in This Study

Carbon	1	2(syn)	2(anti)	3a	3b	3c	3d	3e[a]
1	26.6	27.1	25.9	126.7	125.9	125.6	126.1	126.2
2	36.4	27.3	21.0	125.6	117.5	117.8	113.1	113.1
3	200.1	155.0	157.0	140.8	136.4	136.4	143.8	144.1
4	124.5	111.5	118.0	128.7	120.4	120.6	115.5	115.3
5	166.9	154.0	150.9	136.8	137.4	137.2	137.6	137.3
6	35.5	35.7	35.1	29.3	29.6	29.6	29.6	29.5
7	30.7	31.1	30.9	26.3	27.1	26.2	26.3	25.9
8	40.5	40.7	40.6	38.0	38.4	38.6	38.9	38.5
9	49.7	49.8	49.9	44.1	44.0	44.1	43.9	43.9
10	42.6	43.2	42.0	138.4	135.4	135.6	130.8	130.0
11	26.1	26.1	26.3	27.5	27.6	27.2	27.3	26.6
12	36.5	36.5	36.6	36.9	36.9	36.7	36.7	35.9
13	43.0	43.0	43.0	42.9	42.9	43.2	43.2	43.9
14	49.6	49.9	49.7	49.9	49.8	50.1	49.9	50.4
15	23.2	23.2	23.2	23.2	23.2	23.1	23.1	21.6
16	30.4	30.3	30.3	25.9	26.0	30.3	30.4	35.9
17	81.6	81.7	81.6	82.5	82.7	81.9	81.8	-
18	11.9	11.1	11.1	12.1	12.1	11.2	11.1	13.9
Acetate				21.1	21.2			
				170.9	171.3			
CH_3CONH				25.9	24.6	24.3		
				173.1	168.3	169.1		

a. An authentic sample was prepared by the method of ref. 1b.

EXPERIMENTAL SECTION

NMR spectra were acquired on a Varian XL-300 NMR spectrometer operating at 300 MHz for protons and 75 MHz for carbon; version 6.4 software was used

throughout. The 2-D NMR conditions have been described previously.[5] Mps were taken on a Koelfler Heisbank apparatus.

19-Nortestosterone Oxime.- A mixture of 1 g (3.64 mmol) of 19-nortestosterone, 1.0 g of hydroxylamine hydrochloride, 5.0 mL of pyridine and 5.0 mL of absolute ethanol was refluxed under nitrogen for 2 hrs. The solvents were removed under vacuum by rotary evaporation. Trituration with 5.0 mL of ice water produced a solid mixture of the two oximes (1.02 g, 97%) which were recovered by filtration and dried.

Rearrangement of 19-Nortestosterone Oximes.- One gram of the oxime mixture (3.45 mmol) was heated in 20 mL of acetic anhydride at 110° for 39 hrs. Excess acetic anhydride was removed under vacuum by rotary evaporation and then by pumping at 0.3 mm at RT to yield 1.25 g.(91%) of a tan or brown glass. This material displayed the C^{13} NMR absorptions reported in the Table for the 3-diacetamido-1,3,5(10)-estratrien-17b-ol acetate(**3a**). ^1H NMR: δ 0.84 (s, 18-methyl), broad methylene envelope between 1.1-2.5 ppm, , 2.06 (s, acetate methyl), 2.86 (m, 6-a, b), 4.70(t, H-17), 6.85(bs, H-4), 6.89 and 7.36 (2H, AB quartet, J = 8.3Hz). Repeated attempts to purify this material by crystallization or chromatography failed. The crude reaction product could be converted to **3b** by chromatography over alumina with significant loss. A better procedure is as follows: 1.28 g of the crude reaction product (*ca.* 3.2 mmoles) was refluxed overnight in 10 mL of ethanol, 5 mL of water and 0.5 mL of acetic acid. The mixture was reduced to dryness under vacuum on the rotary evaporator to give 1.04 g (92%) of essentially pure **3b.** Depending on the color the material was either crystallized directly from a minimum of methanol or first passed through a plug of Florisil using a 10% ether in methylene chloride eluant then crystallized to give pure 3-acetamido-1,3,5(10)-estratrien-17b-ol acetate(**3b**), mp. 210°, lit.[2] mp. 207.5-209.8°.

The procedure of Gold and Schwenk[2] revealed a complex mixture composed mainly (roughly estimated from the ^{13}C spectrum as 75-85%) of the diacetamide **3a.** Chromatography of this material through alumina as described gave 3-acetamido-1,3,5(10)-estratrien-17b-ol acetate (**3b**) in 45% yield, mp. 208° (methanol). Examination by ^{13}C NMR of the material left on the column from either method of preparation above indicated a complex mixture.

Basic Hydrolysis of **3b.** - A solution of sodium methoxide in methanol (4 g of metal to 100 mL of methanol) was stirred with **3b** generated from 1 g of oxime. After 4 hrs, the excess solvent was removed by rotary evaporation under reduced pressure. The residue was stirred with 100 mL of water for 30 min. and then extracted with three 30 mL portions of methylene chloride. After drying (sodium sulfate), filteration and evaporation *in vacuo* (rotary evaporator), the residue (0.98 g., 91%) was shown (^{13}C NMR) to be a single product, 3-acetamido-1,3,5(10)-estratrien-17β-ol (**3c**), mp. 250°, lit.[6] mp. 262-264°.

Acidic Hydrolysis of **3a** -Oxime (0.5 g) was converted to **3b** by the method above, and this material in 3 mL of conc. hydrochloric acid, and 10 mL of methanol was refuxed for 4 hrs. The mixture was cooled, and 10 mL of water added. The methanol was removed under vacuum, and the aqueous solution was extracted with three 20 mL portions of methylene chloride and discarded. The aqueous portion was made basic with solid sodium hydroxide and extracted with three 20 mL portions of methylene chloride. After drying over sodium sulfate, the solvent was removed on a rotary evaporator. The product was a dark glass (0.19 g, 45%) with the ^{13}C spectrum (Table) expected of 3-amino-1,3,5(10)-estradien-17b-ol. This material is difficult to purify by crystallization,[2] and no further attempt was made to purify the product. The neutral fraction consisted of 0.145 g of dark material which gave a complex ^{13}C spectrum indicating a number of by-products.

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RERENCES

1. (a) D. F. Morrow and R. M. Hofer, *J. Med. Chem.*, 9, 149(1966); (b) R. B. Conrow and S. Bernstein, *Steroids, 11*, 151(1968).

2. A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **81**, 2198(1959).

3. T. A. Wittstruck, and K. I. H. William,*J. Org. Chem.*, **38**, 1542(1973).

4. J. W. Blunt and J. B. Stothers, *Organ. Magn. Reson.*, **9**, 439(1977).

5. W. B. Smith, *Magn. Reson. Chem.*, **25**, 981(1987).

6. J. Jiu and A. H. Goldkamp, **U.S.** 3,282,915; *C.A.* ,**66**, 29001(1967).

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