Synthesis of 17β-Hydroxy-1′-*H*-5α-androst-2-eno[3,2-*b*]pyrrole and 17β-Hydroxy-1′-*H*-5α-androst-3-eno[3,4-*b*]pyrrole from *O*-(2-Hydroxyethyl)ketoxime Precursors

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Received December 1, 1989

Pyrrolosteroids such as 17β-hydroxy-1′-*H*-5α-androst-2-eno[3,2-*b*]pyrrole (**1**) and the novel 17β-hydroxy-1′-*H*-5α-androst-3-eno[3,4-*b*]pyrrole (**12**) can be synthesized from the corresponding *O*-(2-hydroxyethyl)ketoxime precursors. In the case of **1**, yields compare favourably with previously reported literature methods.

J. Heterocyclic Chem., **27**, 1091 (1990).

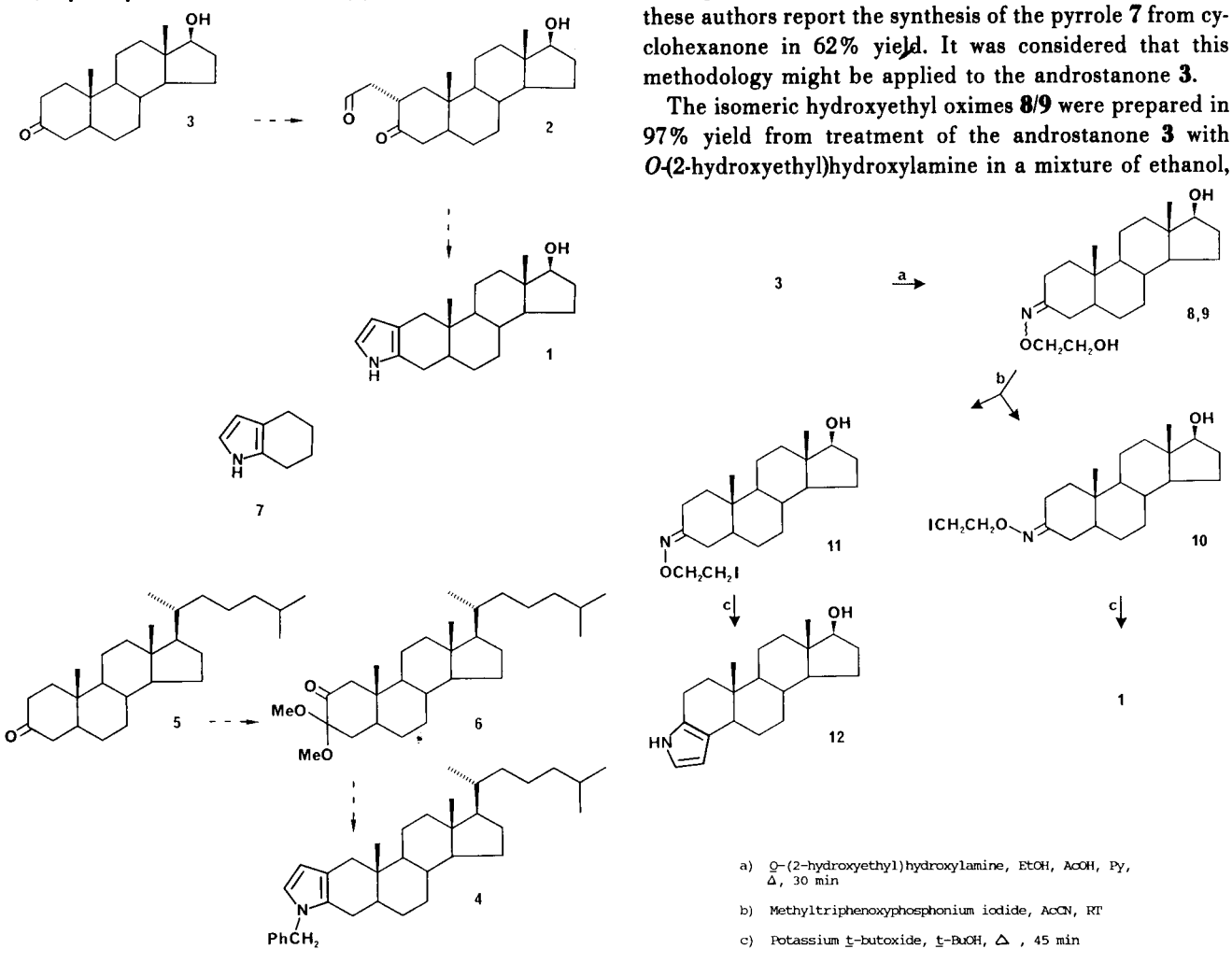
In connection with studies involving the synthesis of novel ring A modified steroids it was desirable to reinvestigate synthetic routes to pyrrolosteroids as exemplified by 17β-hydroxy-1′-*H*-5α-androst-2-eno[3,2-*b*]pyrrole (**1**). The synthesis of this compound has previously been described by Miller and Christiansen [1] *via* the intermediate 2α-(formylmethyl)-17β-hydroxy-5α-androstan-3-one (**2**) in five steps and 5.6% overall yield from the starting material 17β-hydroxy-5α-androstan-3-one (**3**).

A more recent synthesis of this ring system was reported by Trost and Kienan [2] who prepared the benzylated pyrrolocholestane **4** in 12% overall yield from 5α-cholestan-3-one (**5**) *via* the intermediate monoketal **6** [3].

A shorter and higher yielding route into the parent ring system is clearly desirable.

Reese *et al* [4,5] have recently described the facile synthesis of pyrroles derived from cycloalkanones *via* their corresponding *O*-(2-hydroxyethyl)ketoximes. In particular these authors report the synthesis of the pyrrole **7** from cyclohexanone in 62% yield. It was considered that this methodology might be applied to the androstanone **3**.

The isomeric hydroxyethyl oximes **8/9** were prepared in 97% yield from treatment of the androstanone **3** with *O*-(2-hydroxyethyl)hydroxylamine in a mixture of ethanol,



glacial acetic acid and pyridine, under reflux for 30 minutes. This pair of hydroxyethyloximes was treated with methyltriphenoxyphosphonium iodide in acetonitrile at room temperature to afford the corresponding pair of iodoethyloximes (**10**/**11**) in 94% yield. Careful chromatography at this stage enabled separation of the isomers affording the (*E*)isomer **10** in 43% and the (*Z*)-isomer **11** in 36% yield with additional unresolved material. No products due to additional iodination at C-17 were observed despite use of excess methyltriphenoxyphosphonium iodide.

The assignment of stereochemistry to the isomers **10** and **11** was based on interpretation of their ^{13}C-nmr spectra. These are presented in Table 1. The ^{13}C nmr spectrum of the androstanone **3** has previously been described by Rizvi and Williams [6]. These authors assign C-2 to a signal at 38.1 ppm and C-4 to a signal at 44.6 ppm. On the basis of shifts observed between signals from cyclohexanone and cyclohexanone oxime [7], the greater shielding is to be expected from the carbon *cis* to the oxime sidechain. If the same relationship holds true for the steroidal system, the signals for C-2 and C-4 should be further separated when the oxime is orientated toward C-2 (the *cis* isomer **10**) and brought closer when the oxime has the opposite configuration (*trans*, *i.e.* isomer **11**). Thus for the isomer assigned as (**10**) we find signals for C-2 and C-4 at 21.5 and 34.4 ppm respectively. For the isomer assigned as (**11**) we find these signals at 27.8 and 28.2 ppm. Comparison of the ^{13}C nmr spectra of **10** and **11** reveal no other significant differences.

Table 1

^{13}C NMR Data for Isomeric Iodoethyloximes (10) and (11)

C	3	10	11
1	38.6	37.6	38.5
2	38.1	21.5	27.8 [a]
3	211.5	161.3	161.2
4	44.6	34.4	28.2 [a]
5	46.8	46.8	45.6
6	28.9	28.6	28.7
7	31.3	31.4	31.4
8	35.5	35.5	35.5
9	54.0	54.2	54.2
10	35.8	36.3	36.3
11	21.1	20.8	20.8
12	36.7	36.8	36.8
13	43.0	43.0	43.0
14	50.9	51.0	51.0
15	23.4	23.4	23.4
16	30.5	30.6	30.6
17	81.7	81.9	81.8
18	11.2	11.1	11.1
19	11.5	11.4	11.6
OCH_2CH_2I	-	73.2	73.2
OCH_2CH_2I	-	3.5	3.5

[a] May be interchaeable.

Treatment of the iodoethyloxime **10** with potassium *t*-butoxide in *t*-butyl alcohol under reflux afforded, after chromatography and subsequent sublimation, the known pyrrolosteroid **1** in 35% yield. Treatment of the isomeric iodoethyloxime **11** under the same reaction conditions gave a more complex mixture of products from which, after careful chromatography and subsequent sublimation, was isolated the novel pyrrolosteroid **12** in 12% yield. Other products appeared by tlc to include the isomeric pyrrolosteroid (**1**).

The overall yield of the desired pyrrolosteroid **1** by this three step route was 15%.

EXPERIMENTAL

Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr's were recorded on a Bruker AC 80 or WM 300 and are reported relative to internal tetramethylsilane.

17β-Hydroxy-5α-androstan-3-one *O*-(2-Hydroxyethyl)oxime **8**/**9**.

A solution of 17β-hydroxy-5α-androstan-3-one (**3**) (47.6 g, 0.164 mole) in ethanol (630 ml), pyridine (14.5 ml) and glacial acetic acid (10.2 ml) was treated with *O*-(2-hydroxyethyl)hydroxylamine (14 g, 0.180 mole) and heated under reflux with stirring for 30 minutes. The reaction mixture was allowed to cool and the solution volume reduced to *ca* 400 ml *in vacuo* before being poured into iced water. The mixture was stirred for 4.5 hours and then the solid product removed by filtration and washed with water. The product was dried under vacuum at 60° to afford, as a mixture of isomers, the desired oximes (**8**/**9**), (55.5 g, 97%), mp 111-118°; ν max 3,370 (OH) and 1,635 cm^{-1} (oxime); ^{1}H nmr (deuteriochloroform): δ 0.74 (2 × 3H, s), 0.90 (2 × 3H, s), methylene envelope, 3.00 (1H, br d), 3.20 (1H, d d), 3.60 (2 × 1H, br t), 3.9 (2 × 2H, br m) and 4.2 (2 × 2H, m); ^{13}C nmr (deuteriochloroform); 11.1 (C-18), 11.3 (C-19(*E*)), 11.5 (C-19(*Z*)), 20.8 (C-11), 21.2 (C-2(*E*)), 23.4 (C-15), 27.9 (C-2(*Z*)), 28.5 (C-4(*Z*)), 28.7 (C-6), 30.5 (C-16), 31.4 (C-7), 34.5 (C-4(*E*)), 35.5 (C-8), 36.2 (C-10), 36.8 (C-12), 37.4 (C-1(*E*)), 38.4 (C-1(*Z*)), 43.0 (C-13), 45.5 (C-5(*Z*)), 46.7 (C-5(*E*)), 51.0 (C-14), 52.2 (C-9), 62.9 (CH_2OH), 62.9 (CH_2OH), 74.0 (CH_2-CH_2OH), 81.8 (C-17) and 160.7 (C-3) ppm.

Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72.16; H, 10.09; N, 4.01. Found: C, 71.91; H, 10.43; N, 4.05.

17β-Hydroxy-5α-androstan-3-one *O*-(2-Iodomethyl)oximes **10**/**11**.

To a solution of the isomeric oximes **8**/**9** (1.75 g, 5 mmoles) in acetonitrile (125 ml) under an atmosphere of nitrogen was added methyltriphenoxyphosphonium iodide (2.5 g, 5.5 mmoles) with stirring and the mixture maintained at room temperature for 18 hours. After this time tlc (ethyl acetate:cyclohexane (3:7)) revealed that in addition to products there remained considerable starting material. Further methyltriphenoxyphosphonium iodide (3.75 g, 8.25 mmoles) was added over the next hour until tlc in the above system revealed reaction to be complete. The reaction mixture was poured into water and the acetonitrile removed *in vacuo* to afford an oily suspension which was dissolved by addition of 5*M* aqueous sodium hydroxide. The aqueous solution was extracted with diethyl ether and the organic phase dried over anhydrous magnesium sulphate before being removed *in vacuo* to afford a gum. Chromatography on silica gel in increasing proportions of

ethyl acetate in cyclohexane yielded, as a mixture of isomers, the desired iodides **10/11** (2.17 g, 94%), mp 135-136°.

Anal. Calcd. for $C_{21}H_{34}INO_2$: C, 54.90; H, 7.46; N, 3.05. Found: C, 54.78; H, 7.33; N, 3.09.

The above reaction was repeated on a further quantity (69 g) of **8/9** and the crude product carefully chromatographed on silica gel, in increasing proportions of ethyl acetate in toluene, to afford, as a gum, the (*E*)-isomer **10** (39.5 g, 43%); ^{1}H-nmr (deuteriochloroform): δ 0.74 (3H, s), 0.90 (3H, s), methylene envelope, 3.2 (1H, d d), 3.3 (2H, t), 3.6 (1H, br t), and 4.2 (2H, t); ^{13}C nmr: see Table 1.

Later fractions afforded the (*Z*)-isomer **11** (33 g, 36%), mp 147-148°; ^{1}H-nmr (deuteriochloroform): δ 0.74 (3H, s), 0.90 (3H, s), methylene envelope, 3.0 (1H, br d), 3.3 (2H, t), 3.6 (1H, br t) and 4.2 (2H, t); ^{13}C nmr: see Table 1.

17β-Hydroxy-1′-*H*-5α-androst-2-eno[3,2-*b*]pyrrole (**1**).

The iodide **10** (36.7 g, 80 mmoles) in *t*-butyl alcohol (1.16 *l*) was heated under reflux and treated with potassium *t*-butoxide (44.8 g, 400 mmoles). The reaction mixture was stirred under an atmosphere of nitrogen for 45 minutes. The mixture was cooled, reduced in volume *in vacuo*, poured into water and acidified with 5*M* hydrochloric acid. This was then extracted with dichloromethane and the organic phase dried over anhydrous magnesium sulphate before being removed *in vacuo* to afford a gum. This material was chromatographed on alumina in increasing proportions of ethyl acetate in dichloromethane to afford slightly impure product which, after sublimation (180°, 0.04 mm Hg) yielded the desired product **1**, (8.79 g, 35%), mp 235-245° dec (lit [1] 244-245°); ir (potassium bromide): ν max 3530 (NH), 3370 cm^{-1} (OH); ^{1}H nmr (perdeuteriopyridine): 0.86 (3H, s), 1.00 (3H, s), methylene envelope, 3.9 (1H, t), 6.0 (1H, br s), 6.25 (1H, t), 6.98 (1H, t) and 11.1 (1H, br s); ^{13}C nmr (perdeuteriopyridine): 11.8 (C-18), 12.0 (C-19), 21.3 (C-11), 23.9 (C-15), 28.2 (C-6), 29.6 (C-4), 31.0 (C-16) 31.8 (C-7), 36.2 (C-8), 37.1 (C-10), 37.6 (C-12), 38.5 (C-1), 43.3 (C-5), 43.5 (C-13), 51.4 (C-14), 54.6 (C-9), 81.4 (C-17), 107.8 (C-4^1), 115.9 (C-2), 116.4 (C-5^1) and 125.4 (C-3) ppm.

Anal. Calcd. for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.58; H, 9.91; N, 4.47.

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