Conversion of compound **4** into compound **1** was accomplished by oxidation with *m*-chloroperbenzoic acid in methylene chloride and *tert*-butyl alcohol at 0 °C. This oxidation reaction, even at 0 °C, leads directly to the unsaturated lactone **1**. Presumably the transformation of **4** into **1** involves the intermediacy of the sulfoxide **5**, which undergoes elimination of the elements of PhSOH at unusually low temperatures.[3] The low temperature for this elimination-type reaction is clearly reminiscent of the behavior exhibited by organoselenium compounds[4] and the thermal lability of **5** is most probably due to the β-dicarbonyl residue present in the molecule.

Experimental Section

Infrared spectra were taken on a 467 Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were obtained on a Joel MH-100 spectrometer in the solvent indicated with tetramethylsilane as the internal reference and are expressed as δ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were taken on a Dupont 21-490B instrument.

Preparation of 2. To a 2-L Morton flask equipped with mechanical stirrer, addition funnel, and condenser was added sodium hydride (28 g, 50% dispersion in mineral oil). The sodium hydride was washed five times with hexane, dried under a stream of nitrogen, and then covered with DME (300 mL). Dimethyl carbonate (73.5 mL) was added followed by butyrolactone (25 g, 0.29 mol, 21 mL) and the resulting mixture was then stirred and warmed to 45 °C. After 15 min, a vigorous evolution of gas occurred and the reaction solidified. Heating was discontinued and the reaction was allowed to stand for 2 h at room temperature. Sufficient ice water was added to permit stirring, whereupon 6 N HCl (150 mL) was added. The resulting mixture was extracted with $CHCl_3$ (3 × 75 mL), dried by vacuum filtration through $MgSO_4$, and then evaporated to give an orange oil. Distillation of this oil gave 29 g of **2** (72% yield): bp 110 °C (0.5 mm); IR ($CHCl_3$) 1778 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (m, 2 H), 3.5 (m, 1 H), 3.7 (s, 3 H), 4.28 (m, 2 H); MS parent *m/e* 144.

Preparation of 3. To a solution of diphenyl disulfide (50 g, 0.229 mol, 1 M in ether) contained in a 1-L three-necked flask equipped with magnetic stirrer, addition funnel, and condenser was added 40% peracetic acid (100 mL) dropwise (1 drop/s) at 0–5 °C. The reaction mixture was allowed to slowly warm to room temperature, stirred for 12 h, treated with more 40% peracetic acid (10 mL), and stirred an additional 4 h at room temperature. The reaction was poured into a 2-L Erlenmeyer flask and celite then added followed by the slow addition of K_2CO_3 (120 g). The resulting mixture was stirred for 20 min at room temperature and filtered under vacuum, and the filtrate was evaporated to dryness to yield 45 g of **3** as a white crystalline solid, mp 35–37 °C (lit.[5] mp 37.5–38.5 °C).

Preparation of 4. Sodium hydride (2.06 g, 50% dispersion in mineral oil) was placed in a three-neck flask equipped with reflux condenser. After washing five times with hexane and drying over nitrogen, the sodium hydride was covered with 70 mL of benzene, whereupon the lactone ester **2** (5 g, 35.7 mm) was added. Compound **3** (10.7 g) was then added (as a solid) and the resulting mixture was heated at 100 °C for 2.5 h. After cooling to room temperature, ice followed by water was added to the reaction mixture and the resulting two-phase system was then extracted with $CHCl_3$ (3 × 50 mL) and dried by filtration through $MgSO_4$, and the filtrate was evaporated to dryness to yield 8.8 g of crude material which, by NMR analysis, contained 74% of the desired product **4**. Of this crude mixture 5.1 g was filtered (under vacuum) through 30 g of silica gel G (10–40 μm), eluted first with 520 mL of hexane:ether (4:1), followed by 350 mL of hexane:ether (1:1). Evaporation of the latter eluent gave 2.8 g (55% yield) of compound **4** suitable for conversion into the lactone **1**. Spectral properties of compound **4** obtained in this manner are as follows: IR ($CHCl_3$) 1775 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.85 (m, 2 H), 3.8 (s, 3 H), 4.22 (m, 2 H), 7.5 (m, 5 H); MS parent *m/e* 252.

Preparation of 1. Compound **4** (2 g, 8.06 mm), 1 M in CH_2Cl_2, was treated dropwise at 0 °C with *m*-chloroperbenzoic acid (1.8 g) dissolved in a mixture of CH_2Cl_2 (6 mL) and *t*-BuOH (2 mL). After addition of the peracid was complete, the reaction was stirred for 2 h at 0 °C. Saturated sodium bicarbonate was added and the mixture was extracted with $CHCl_3$ (3 × 20 mL), dried over anhydrous sodium sulfate for 2 h, filtered under vacuum, and evaporated to dryness to yield a white solid which on crystallization from Et_2O:$CHCl_3$ gave 0.87 g (79% yield) of white crystals: mp 103–105 °C; IR ($CHCl_3$) 1820 (shoulder), 1785, and 1733 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 3 H), 5.05 (d, 2 H), 6.42 (m, 1 H); MS parent *m/e* 142. Anal. Calcd for $C_6H_6O_4$: C, 50.70; H, 4.23; O, 45.07. Found: C, 50.61; H, 4.32.

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Registry No.—**1**, 63731-11-3; **2**, 19406-00-9; **3**, 1212-08-4; **4**, 63731-12-4; dimethyl carbonate, 616-38-6; butyrolactone, 96-48-0; diphenyl disulfide, 882-33-7.

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Chiroptical Properties of Pelletierine and Anaferine

J. Cymerman Craig,* S.-Y. Catherine Lee, and S. K. Roy

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143

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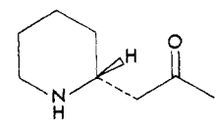
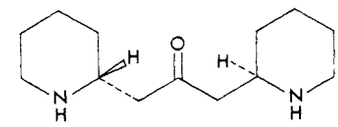
The alkaloid (−)-pelletierine **1** [1-(2-piperidyl)propan-2-one] has been shown to have the D configuration (= *R*) by the isolation of L-(−)-pipecolic acid on chromic acid oxidation of (+)-pelletierine,[1] while the closely related natural anaferine[2] [1,3-bis(2-piperidyl)propan-2-one] appears to be the meso isomer.[3] However, since it has been reported[4] that the resolved enantiomers of anaferine racemize readily, and that under the same conditions the racemate is converted into the meso form[5] in aqueous solution, it remains possible that natural anaferine



1



2

is one of the optically active forms and undergoes isomerization during the isolation procedure. Since resolved (−)-1,3-bis(2-piperidyl)propan-2-one yielded D-(+)-pipecolic acid on chromic acid oxidation,[6] resolved (−)-anaferine possesses the D,D configuration (= *R*,*R*) **2**.

From recent work on the ORD and CD spectra of 2-alkylpiperidines[7] it is clear that the negative plain curve below 225 nm found (in addition to a negative Cotton effect at 280 nm for the n → π* transition of the ketone) in an earlier ORD spectrum of (−)-pelletierine sulfate[8] is due to the π → π* absorption of the ketone and cannot be used for configurational assignments by comparison with 2-alkylpiperidines. However, such a comparison can be made if the rotational contribution of the ketone chromophore is removed by chemical means which do not interfere with the asymmetric center.

The keto group in (−)-pelletierine sulfate was converted to the dimethyl ketal by reaction with methanolic hydrogen chloride[9] at room temperature. The resulting solution then

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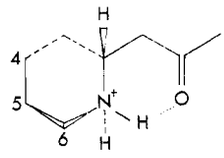
Table I. ORD and CD Spectra

Compd	Registry no.	Solvent	Molecular ellipticity $[\theta]_{max}$ (nm)	Molecular rotation [Φ] (nm) Peak	Trough
D-(−)-Pelletierine sulfate	2133-57-5	95% EtOH	−365 (281)	+180 (264)	−314 (298)
		H_2O	−290 (272)	−760 (258)	−930 (282)
D-(−)-Pelletierine base	2858-66-4	95% EtOH	−127 (285)	−25 (260)	−238 (295)
		H_2O	+140 (292)	−9.5 (305)	−162 (280)
D-(−)-Pelletierine dimethyl ketal·HCl	63731-39-5	MeOH	0 (208–300)		
D-(−)-Pelletierine dimethyl ketal base	63731-40-8	MeOH	−158 (208!)	+284 (210!)	
D-(−)-Anaferine·2HCl	19519-54-1	95% EtOH	+276 (287)[a]		
Reduced anaferine·2HCl	63783-46-0	MeOH	0 (203–300)		
Reduced anaferine base	63783-47-1	MeOH	−4700 (203!)[a]	+9800 (198!)	−690 (217)
D-(+)-Coniine[b]	458-88-8	95% EtOH	−630 (205)	+1900 (200!)	
D-(+)-Allo-Sedridine	26171-47-1	95% EtOH	−915 (205)		
D-(−)-Sedridine	5320-51-4	95% EtOH	−518 (205)		

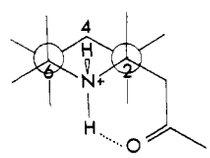
[a] Corrected for optical purity. [b] $[\alpha]_D$ +5.0° (*c* 2.95% EtOH).

showed a negative plain ORD curve below 230 nm (Table I) and no CD between 200 and 300 nm because the n → σ* transition of nitrogen does not exist in acidic solution. After the solution was made alkaline, it had a positive plain ORD curve, and a negative CD maximum below 208 nm,[10] in agreement with the chiroptical properties of D-(+)-coniine (Table I) and with the chemically established D configuration[1] for natural (−)-pelletierine.

The sensitivity of pelletierine to conformational changes is shown by its chiroptical properties (Table I). Assuming the piperidine ring to be in the more stable chair form[11] and equatorially substituted at C-2,[12] pelletierine sulfate can form two six-membered pseudoring structures through H bonding with the carbonyl oxygen: a trans-fused conformation **3a** (C-5 and C-6 in the front upper left octant) associated by the octant rule[13] with a negative Cotton effect, and a cis-fused structure **3b** (C-4, -5 and, -6 in the front lower left octant) corresponding



3a



3b

to a positive Cotton effect. The observed negative CE in both 95% ethanol and in water (Table I) suggests that the former structure (**3a**) predominates at room temperature.[14] The CD and ORD of (−)-pelletierine base in 95% ethanol, measured immediately after basification of the salt, showed essentially the same features as the salt (Table I).[17]

However in water the sign of the n → π* Cotton effect for (−)-pelletierine base was reversed[18] (Table I) suggesting a conformational change such as might occur by solvation of the equatorial electron pair of nitrogen, causing the carbonyl oxygen to form a cis-fused pseudoring structure resembling **3b**, with a positive Cotton effect.[13]

Unlike (−)-pelletierine, (−)-anaferine (**2**) resisted attempts to form the dimethyl ketal, probably due to steric factors. However, reduction proceeded rapidly by catalytic hydrogenation and gave a product which (as the dihydrochloride salt) showed no CD in the range 200–300 nm, indicating complete disappearance of the carbonyl chromophore (Table I). On making the solution alkaline, the base displayed a strong negative CE in its ORD spectrum (Table I). These observations resemble the CD and ORD findings for D-(+)-coniine and D-(+)-allosedridine (Table I), and agree with the chemically established configuration[6] of (−)-anaferine (**2**) as D,D (= *R*,*R*). The greater intensity of the ellipticity (as compared to coniine) may be due to the reduced conformational freedom of this diamino alcohol through intramolecular H bonding.[19]

The CD spectrum of (−)-anaferine dihydrochloride (**2**·2HCl) shows a positive ellipticity for the n → π* carbonyl transition (Table I) of about the same magnitude as for (−)-pelletierine sulfate but of opposite sign, indicating major conformational changes of an unknown nature.

Experimental Section

ORD and CD curves were measured at 25 °C on a JASCO ORD-CD 5 spectropolarimeter and on a JOUAN 185 Mark II dichrograph.

Pelletierine Dimethyl Acetal. A solution of 5.6 mg of natural (−)-pelletierine sulfate, $[\alpha]_D$ −29.5° (*c* 1, H_2O), in 3 mL of methanol was treated with 1 drop of 10 N HCl. After standing at 25 °C for 20 h, the CD signal at 280 nm had essentially disappeared. The solution was then cooled to 0 °C (ice) and made alkaline with sodium methoxide to liberate the free base. After removal of precipitated sodium chloride, the solution was immediately used for CD measurement.

Reduction of Anaferine. A solution of 23.4 mg of (−)-anaferine dihydrochloride, $[\alpha]_D$ −22.1° (*c* 0.8 EtOH), in 3 mL of 95% ethanol was reduced with Adams' catalyst (PtO_2) and hydrogen. The solution was filtered and cooled to 0 °C (ice), and the filtrate was made alkaline with 10% aqueous KOH and used immediately for CD measurement.

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(17) On reacidification, the (−)-pelletierine had essentially the original rotation.
(18) The assumption[4] that the contribution of the C=O chromophore in acid does not differ significantly from that in alkaline medium does therefore not appear to be valid.
(19) The alternate suggestion that the greater intensity of the CD of reduced anaferine could be due to the effect of the newly generated asymmetric center does not seem valid since (a) the prochiral ketone **2** (C_2 symmetry) represents a trigonal system Yk_1k_2i in which the two faces of the carbonyl carbon are indistinguishable[20] as k_1 and k_2 are chemically and configurationally identical, (b) k_1 and k_2 are also identical in the reduced compound.
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Total Synthesis of Steroids. 12.[1] Final Evidence of the Configuration of the C-14 Hydroxyl Group in 3-Methoxy-14β-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione

Andrzej Robert Daniewski, Maria Guzewska, and Marian Kocór*

Institute of Organic Chemistry, Polish Academy of Sciences, 00-961 Warszawa, Poland

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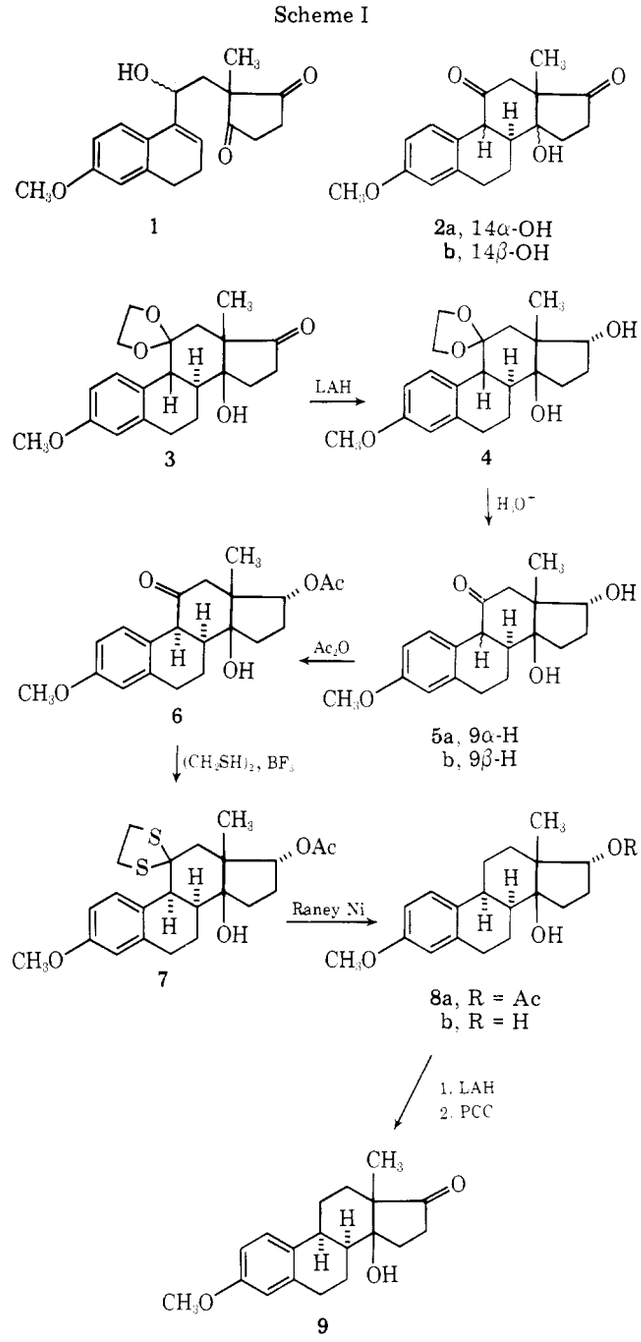
In one of the previous papers[2] of this series we described the synthesis of *rac*-3-methoxy-14α-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione (**2a**) from the allylic alcohol **1** by cyclization with Meerwein reagents. The stereochemistry of compound **2a** at chiral carbon atoms 8, 9 and 13 was proved beyond any doubt. The configuration at C-14 was assumed to be α, on the basis of Sondheimer's observation[3] that either epoxidation or hydrogenation of the C-14 (15) double bond in nonaromatic steroids takes place from the β side of the molecule.

However, this assumption does not hold true for ring A aromatic steroids, and in fact the configuration of the 14-OH group in the cyclization product should be β, as in **2b.** This was demonstrated by the sequence of reactions shown in Scheme I.

The cyclization product **2b** was transformed into **3** as reported previously.[2] Reduction of the C-17 carbonyl group with lithium aluminum hydride led solely to the 17α-OH compound **4.** The configuration of the 17-OH group was proved to be α, because the hydrolysis products **5a** and **5b** and the acetyl derivative **6** obtained from **5a** were different in all respects from their epimers prepared previously[1] from optically active Torgov's secolone (with 17β-OH). Subsequently, compound **6** was converted by standard methods into *rac*-3-methoxy-14β-hydroxy-8α-estra-1,3,5(10)-trien-17-one (**9**). The latter compound had a MS spectrum identical with that reported by Wulfson et al.[4] Direct comparison of our sample **9** with the compound prepared by Zakharychev et al.[5] confirmed their identity.

Thus, the position of the C-14 hydroxyl group in compound **2** obtained by cyclization of **1** was proved to be β (as in **2b**) but not α (compound **2a**), contrary to the previous report.[2] This means that epoxidation of the C-14 (15) double bond in ring A aromatic 8-isosteroids takes place in a manner opposite, i.e., from the α side, to that observed during hydrogenation of the same double bond.

Scheme I



Consequently, the configuration at C-14 of all compounds with the 14-OH group described in our previous papers,[1,2,6] as well as in compounds **15, 16, 22,** and **24–28** reported in Part 7 of this series,[7] should be reversed.

If we assume that the π orbitals must overlap in the transition state for the cyclization **1** → **2**, reexamination of Dreiding models indicates that the preferred geometry of the product at C-8 and C-14 should be trans with a cis C/D ring junction.

Experimental Section[8]

3-Methoxy-11,11-ethylenedioxy-8α,9β-estra-1,3,5(10)-triene-14β,17α-diol (4). To a solution of **3** (1.0 g, 2.79 mmol) in THF (100 mL) was added 0.2 g of LAH, and the mixture was stirred at room temperature for ca. 10 min. The reaction was quenched with aqueous $(NH_4)_2SO_4$ and after standard workup a quantitative yield of **4** was obtained: mp 185–186.5 °C (from C_6H_6); IR no CO band, 3450 cm^{-1}; ^1H NMR δ 1.28 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 4.18 (t, 1, H-17), 6.58–6.73 (m, 2, H-2 and H-4), 7.32 ppm (d, 1, H-1).

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