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ASYMMETRIC SYNTHESIS OF 19-NORSTEROIDS[1]

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The work of Ananchenko and Torgov[2] opened the way to a very efficient total synthesis of d,l-estradiol-3-methyl ether[3]. The key intermediate, I (X=MeO), in this synthesis is a prochiral molecule, since reaction at one of the carbonyl groups would create an asymmetric center at C-13 (steroid numbering). For example, microbiological fermentation of I (X=MeO) with Saccharomyces Uvarum (CBS 1508) formed the optically active ketol II in 74% yield.[4] The first purely chemical asymmetric synthesis followed later utilizing L-tartaric amide hydrazide under conditions where the monohydrazone III was insoluble in the reaction mixture.[5] Both II and III were related to the natural steroids.

Parallel to the work in the 3-methoxy series, we developed a total synthesis of 3-dialkylaminoaromatic steroids. We had shown that in particular the 3-morpholino derivatives could be converted in yields of over 90% to the desired 19-nor-3-keto-$\Delta^{5,10}$steroids.[3] In our hands neither of the above asymmetric syntheses was found to be applicable to the 3-amino steroids studied.

While studying the resolution of oxime derivatives V and VI obtained by the condensation of the diketone I (X=morpholino) with optically active reagents of the type IV we discovered that one of the two possible oxime derivatives was formed in preponderance. A general procedure was developed for assay purposes: the products V and VI were cyclized with acid and the oxime derivatives VIIa and VIIIa were cleaved with either chromous acetate[6] or titanium trichloride[7] to yield IX and X respectively. Both reagents gave excellent results after 16 hours at 30-40° in an aqueous THF solution. Since neither reagent cleaved methoximes or the methyl esters VIIb and VIIIB it was apparent that the presence of the carboxyl group in close proximity to the N-O bond being

reduced was essential for this reaction. Reduction of the crude IX and X and assay of the carbinol mixture XI and XII by the method of Mosher[8] permitted an accurate analysis of the optical purity obtained.

In this manner when I (X=morpholino) was allowed to react with R-2-aminoöxy-4-methylvaleric acid* (R-IV Y=i-butyl)[9] in pyridine solution at -15° for 3 weeks, the ratio of the ultimate products XII to XI was determined to be 75:25. With the corresponding S-reagent, S-IV (Y=i-butyl), $[\alpha]_D$-87.3° (1.1% 6N HCl), prepared in the same manner from D-leucine, the ratio of XI to XII was 75:25. When run similarly in THF solution the ratio was 69:31 and in 1:1 THF-methanol the ratio dropped to 61:39. Results in the methoxy series (X=MeO) were similar in pyridine solution but in THF the reaction proceeded slowly requiring several weeks at room temperature and then producing a ratio of 62:38. Other α-aminoöxy acids IV, namely where Y is methyl, i-propyl, or t-butyl were used. The best results were found when Y=t-butyl where a 79:21 ratio was obtained in pyridine solution.

The preparation of reagent R-IV or S-IV (Y=t-butyl) was readily accomplished. The reaction of 2-bromo-3,3-dimethylbutyric acid with acetone oxime in the presence of potassium t-butoxide in t-butanol produced R,S-2-isopropylidene-aminoöxy-3,3-dimethylbutyric acid, m.p. 98-99° from n-hexane, in 31% yield. Resolution through the l-amphetamine salt (isopropanol) led to the S acid in 72% yield m.p. 96-96.5° from n-hexane, $[\alpha]_D$-5.5° (1% MeOH). Hydrolysis in 2N HCl afforded S-2-aminoöxy-3,3-dimethylbutyric acid hydrochloride, m.p. 183-184° from isopropanol $[\alpha]_D$-67.4° (1% H_2O), in 92% yield. The corresponding free aminoöxy acid crystallized from water, m.p. 185-186°, $[\alpha]_D$-95.8° (1% 6N HCl). The R enantiomer was similarly obtained using d-amphetamine in the resolution. The configurations were assigned on the basis of the preponderant enantiomer resulting from the asymmetric synthesis reaction, and on the comparison of the rotations with those of the corresponding R and S 2-aminoöxy-4-methylvaleric acids.

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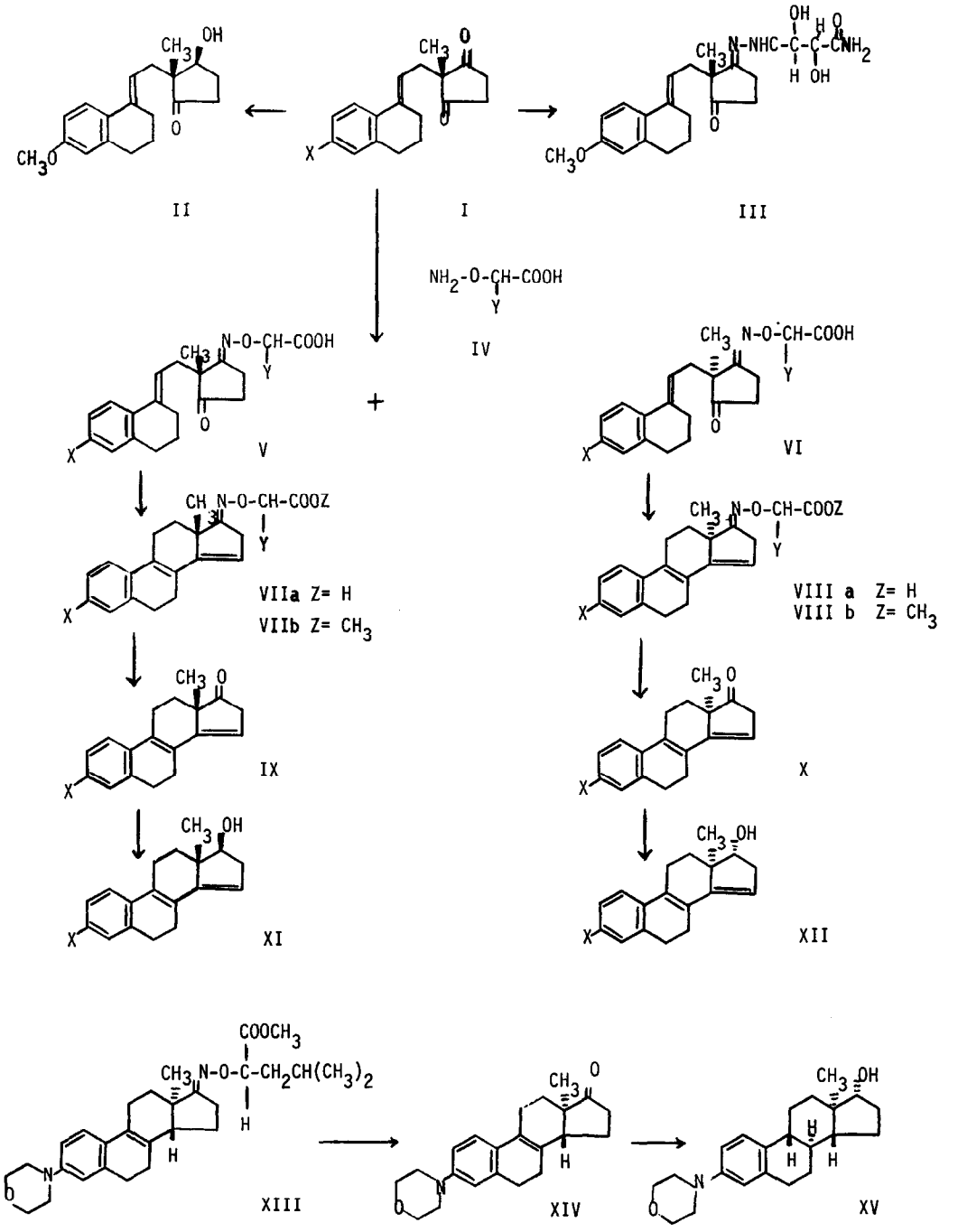
* The absolute configuration of this reagent derived from L-leucine is known to be R since it has been hydrogenolyzed to D(+)-leucic acid. Testa et al.[9] wrongly assigned an L configuration for (+)-leucic acid. The correct configuration for (-)-leucic acid is L or S[10] and that for (+)-leucic acid produced in this case is D or R.


II
I
III
IV
V
VI
VIIa Z= H
VIIb Z= CH3
VIII a Z= H
VIII b Z= CH3
IX
X
XI
XII
XIII
XIV
XV

For preparative purposes in the methoxy series, intermediate IX (X=MeO) prepared via an S-reagent IV (Y=i-butyl or t-butyl) could be crystallized in high optical purity from ether, m.p. 141-142°, $[\alpha]_D$-102° (1% $CHCl_3$) (lit.[5] m.p. 143°, $[\alpha]_D$-103°). When Y=t-butyl the overall yield of IX was 36%. Reduction with lithium aluminum hydride produced XI, m.p. 110-111° from aqueous methanol, $[\alpha]_D$-141.5° (lit.[11] m.p. 55°, $[\alpha]_D$-126°). This was converted in normal fashion[11] to natural estradiol-3-methyl ether.

In the morpholino series the ester VIIIb (X=morpholino) prepared from R-IV (Y=i-butyl) m.p. 155-160°, $[\alpha]_D$-82.4° (1% $CHCl_3$) could be separated from its isomer VIIb by crystallization from ether in about 55% overall yield. The oxime cleavage could not be carried out on the ester, vide supra, and because of the lability of the estrapentaene system the material was hydrogenated to the 14,15-dihydro compound XIII which was hydrolyzed with dilute base and cleaved with titanium trichloride to produce XIV. Reduction with lithium aluminum hydride followed by reaction with sodium and aniline in ammonia produced ent-3-morpholino-17β-hydroxyestra-1,3,5-triene (XV), m.p. 228-229° from ethyl acetate, $[\alpha]_D$-67.8° (1% $CHCl_3$). The corresponding material derived from natural sources by reactions similar to those of Alvarez and Ruiz[1,2] had m.p. 228-229° and $[\alpha]_D$+72.1°.

These results, allow for facile total synthesis of optically active 19-norsteroids belonging to either the d or the l series.

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