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A NEW SYNTHETIC APPROACH TO SAMANDARINE-TYPE ALKALOIDS

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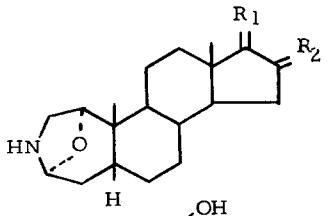
A group of alkaloids represented by samandarine (1) from salamanders: Salamandra masculosa taeniata and S. maculosa, have a modified 5β-androstane skeleton with a peculiar oxazolidine system and a 16-oxygen substitution.[1] The first synthesis of samandarine was reported by Hara and Oka in 1967.[2] The major problem inherent in the synthesis of samandarine was deemed to be the construction of its 8-aza-6-oxabicyclo [3, 2, 1] octane nucleus with correct stereochemistry, since various ways to introduce an oxygen function at C-16 were known. In fact, Hara and Oka's synthesis involved a laborious multi-step preparation of the compound (2), the 17-hydroxyl isomer of samandarine, from testosterone. Eggart, Pascual and Wehrli also reported the synthesis of the 5α-isomer of 2 in another attempt to make the similar ring system.[3]

Here, the author wishes to report a practical and stereoselective synthesis of 2, the key compound to samandarine-type alkaloids.

Ring cleavage to construct the 2,3-seco-5β-androstane carbon skeleton of samandarine was accomplished by utilizing the procedure which Autrey and Scullard had used for the synthesis of corynantheine.[4] The hydroxymethylene derivative of 17β-hydroxy-5β-androstan-3-one (3)[5] was treated with an equimolar amount of methyl p-toluenethiosulphate in the presence of potassium acetate in boiling ethanol.[4] The product, isolated after acetylation, (mp 190-192°, yield 80%), was 17β-acetoxy-2β-methylmercapto-androstan-3-one (4).[7] The introduction of the 2β-methylmercapto group was evident from the nmr data: τ (in $CDCl_3$) 7.90 (s, SCH_3) and 6.54 (q, 2H, J=6, 13HZ). The reaction of 4 with hydroxylamine hydro-

chloride in pyridine afforded the oxime (5) (mp 180-183°, a quantitative yield), probably a mixture of the syn and anti-isomers, which was submitted to the Beckmann fragmentation.[4,7] Reaction of 5 with p-toluenesufonyl chloride in refluxing pyridine for 30 min.[8] gave exclusively a seco-nitrile product, 6 (mp 105-107°, 65% yield) which displayed absorptions at 2250 cm^{-1} for a nitrile group and at 1595 cm^{-1} for an enol thioether. Removal of the methylmercapto group of 6 using Levene's deactivated Raney Ni[9] afforded the methylene derivative (7) (mp 147-148°, ν_{max}^{Nujol} cm^{-1} 2260 (C≡N), 1638 and 935 (CH_2 = CH). The yield of 7 varied from 40% to 65% and the by-product was the corresponding saturated nitrile compound. The epoxidation of 7 with m-chloroperbenzoic acid yielded a single epoxide, 8 (mp 134-135°, 80%). The desired IR-isomer was expected to be the major product by prior model examination, considering the interaction of the 19-methyl and 11-methylene groups. The non-Markownikoff opening of the epoxide with NaN_3 in refluxing methylcellosolve gave the azide (9) (mp 191°, sinters at 178°, quantitative yield, ν_{max}^{Nujol} cm^{-1}: 3480 (OH), 2260 (C ≡ N), 2120 (N_3), 1736, 1240 (acetate)). The conversion of 9 to the final product (2), namely, reduction of the azide group to an amine, reduction of the nitrile to the aldehyde level, and reductive removal of the 17-acetate group, was achieved in one step. Treatment of 9 with an excess $NaBH_4$ in refluxing isopropanol for 15 hrs., and subsequent extraction of the reaction mixture with chloroform furnished almost pure crystals of 2 in about 60% yield. Recrystallization from acetone gave a specimen, (needles, mp 191-193° (sublime at ca 170°), ν_{max}^{KBr} cm^{-1} 3400 (OH) 3320 (NH), 852 and 834 (oxazolidine)), which was identified with the authentic sample[2] by mixed melting point, ir and tlc. Since a nitrile group is not a normal target of $NaBH_4$ reduction, it was speculated that this reaction proceeded via formation of the cyclic amidine (a) or iminoester (b) which subject to $NaBH_4$ reduction with concomittant cyclization to the rigid oxazolidine ring.[10]

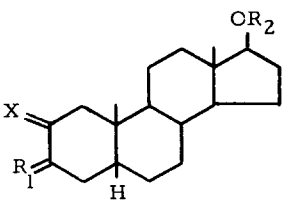
Since the compound 2 had already been converted to samandarine,[2] which was further modified to samandarone (10) and samandaridine[1], this work formally represents a new stereoselective synthesis of these alkaloids.



1 $R_1=H_2$, $R_2=$ 

2 $R_1=$  , $R_2=H_2$

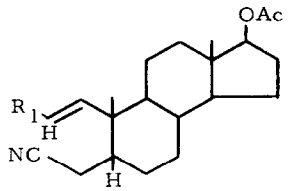
10 $R_1=H_2$, $R_2=O$



3 $R_1=O$, $R_2=H$, $X=CHOH$

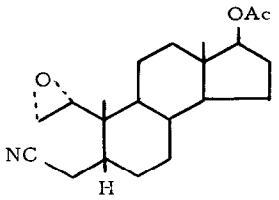
4 $R_1=O$, $R_2=Ac$, $X=$

5 $R_1=NCH$, $R_2=Ac$, $X=$

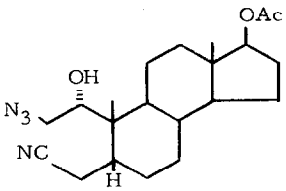


6 $R_1=SCH_3$

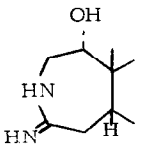
7 $R_1=H$



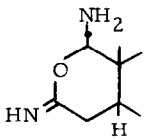
8



9



a



b

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6. Satisfactory analyses for C, H, N, S were obtained with all the new compounds described in this communication.

7. a. R. L. Autrey and P. W. Scullard, J. Amer. Chem. Soc., 90, 4924 (1968).

   b. M. Kobayashi, Y. Shimizu and H. Mitsuhashi, Chem. Pharm. Bull. (Japan), 17, 1255 (1969), and references cited therein.

8. This traditional use of tosyl chloride and pyridine was found by Autrey and Scullard not so satisfactory.[7a] However, in this case, it gave the best results.

9. Initially, the reduction was tried by $LiAlH_4$ and its various alcohol derivatives with little success. Failure seems due to the poor solubility of the substrate or its complex with the reagent.

10. An analogy is found in the reduction of anhydroajmaline oxime to ajmaline with $LiAlH_4$, where concomittant carbinol amine formation and Bredt's rule restriction of its dehydration to quatenary Schiff base prevented further reduction. F. A. L. Anet, D. Chakravarti, Sir Robert Robinson, and E. Schlittler, J. Chem. Soc., 1954, 1242.

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