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THE TOTAL SYNTHESIS OF SAMANINE

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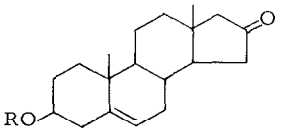
Samanine is a novel type azasteroid isolated from toxic secretion of Salamandra maculosa taeniata and its structure has been elucidated by Habermehl as (X) in plane form from infrared and mass spectral evidence (1). From the biogenetic standpoint and structural relationship of samanine to the other salamander alkaloids, we have presumed that it would have 5β-A/B-cis ring fusion and 16β-hydroxyl configuration. In present paper we will report the specific synthesis of 16β-hydroxy-3-aza-A-homoandrostane (X), predicted structure of samanine.

We have reported in the previous paper (2) the stereoselective synthesis of 17β-hydroxy-3-aza-A-homoandrostan-4-one via specific Beckmann rearrangement of the pure syn oxime of the corresponding 3-oxosteroid (3). The method was thought to be applicable to the synthesis of samanine.

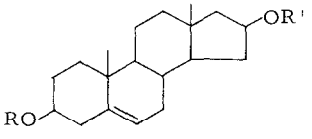
3β-Hydroxyandrost-5-en-16-one (Ia) (4), prepared from epiandrosterone by our own method (5) in over 50% yield, was selected as a starting material. Reduction of the acetate (Ib) with sodium borohydride bellow 0° afforded almost 16β-hydroxy compound (IIa), mp 53-54° (6). However, presence of a very small amount of an epimeric alcohol in the mother liquor of recrystallization was confirmed at the later stage in our synthetic route (vide infra). Benzoylation of (IIa) with benzoyl chloride in pyridine gave a benzoate (IIb), mp 141-142°, which was hydrolyzed partially with an equimolar amount of potassium hydroxide to give a hydroxy benzoate (IIc), mp 153-155°. Oppenauer oxidation of (IIc) gave an enone benzoate (IIIa), $\nu_{max}^{CHCl_3}$: 1713, 1664, 1615 cm^{-1}, which was hydrolyzed to give a hydroxy enone (IIIb), mp 170-171°; ν_{max}^{KBr}: 3420, 1645, 1610 cm^{-1}, in 90% over-all yield based on (IIa).

On the other hand, the mother liquor of (IIa) was subjected to the consequtive reactions as above to give a mixture showing two spots on tlc. Silica gel column chromatography of the mixture resulted in separation of (IIIa) as a first eluate and then its epimeric 16α-hydroxy enone (IV), mp 185-187°; ν_{max}^{KBr}: 3509, 1661, 1610 cm^{-1}; the latter was isolated in 3% yield based on total (IIIb). The 13β-methyl protons resonated at δ 1.00 ppm for the compound (IIIb) and δ 0.76 ppm for (IV) were consistent with the assigned structures. Catalytic hydrogenation of the enone (IIIb) on palladized charcoal was accomplished stereoselectively leading to a 4,5β-dihydro ketone (V), $\nu_{max}^{CHCl_3}$: 3400, 1710 cm^{-1}; retention time: 6.1 min. (0.75% SE-30 on Chromosorb-W, carrier gas N_2 30cc/min., column temperature at 210°), as expected from the usual hydrogenation of 4-en-3-one steroids.

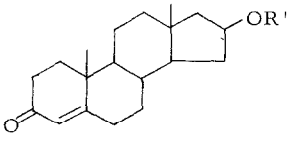
The oxime prepared from (V) showed two spots at Rf 0.55 and 0.48 on silica gel tlc



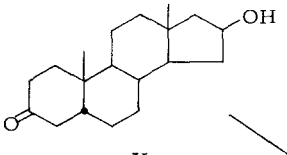
Ia, R=H
b, R=Ac



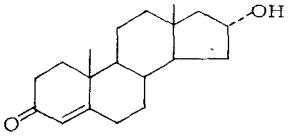
IIa, R=Ac; R'=H
b, R=Ac; R'=Bz
c, R=H; R'=Bz



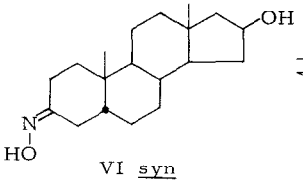
IIIa, R=Bz
b, R=H



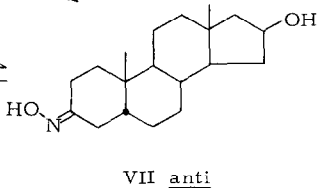
V



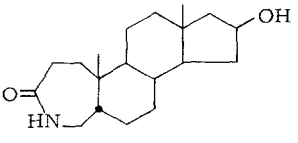
IV



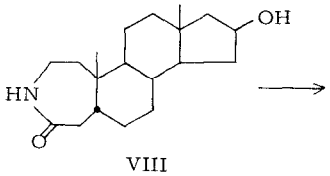
VI syn



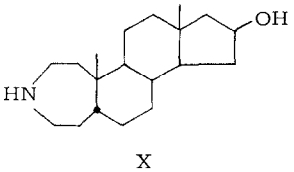
VII anti



IX



VIII



X

developed with a 2 : 1 mixture of benzene and ethyl acetate. Resolution of the oximes by column chromatography using 1000 times of silica gel (Wako gel-C (200 mesh), Wako Pure Chem. Co. (Tokyo)) in weight afforded the syn compound (VI), mp 112-115°*; δ 3.12 ppm, 1H double doublet, J=16 and 5 Hz, $C_{4\beta}$-H**, as the first eluate and then the anti compound (VII), mp 112-114°*; δ 3.27 ppm, 1H double triplet, J=15 and 4 Hz, $C_{2\beta}$-H**, with a ratio of 3 : 2, respectively.

It is worth mentioning that relationship between their geometrical structures and Rf values was inversed by the transformation of the hydroxyl group from C-17 to C-16 position. Furthermore, acylation of hydroxyl group at C-17 or 16, respectively, resulted in failure in resolution of the isomers of the oxime even by tlc in spite of their actual existance by nmr spectra. These facts, we suppose, might be based on the result of synchronous adsorptivity of both the lone-pair electrons of nitrogen atom and hydroxyl group of D-ring on the surface of the adsorbent, that will be reported in detail in our full paper.

In acetone, the anti oxime (VII) turned into an equilibrium mixture of syn and anti forms and the syn oxime was recovered almost quantitatively from the anti isomer by repetition of this procedure followed by silica gel column chromatography. The Beckmann rearrangement of the syn oxime (VI) was carried out with a three molar equivalent of p-toluenesulfonyl chloride in about a 200 molar equivalent of pyridine at room temperature. Under this reaction condition, the 16β-hydroxyl group was intact. Thus the pure 3-aza-lactam (VIII), mp 247-248°; ν_{max}^{KBr}: 3448, 3367, 1667, 1634 cm^{-1}; δ 3.05-3.40 ppm, 2H multiplet, NCH_2, was prepared in 50% over-all yield based on (V).

On the other hand, we also prepared the lactam mixture, mp 232-235°; ν_{max}^{KBr}: 3509, 3440, 3363, 3289 cm^{-1}, from the oxime mixture as a single product on tlc. The nmr spectrum of this material exhibited two kinds of signals due to NCH_2 protons. One of them was identical with that of (VIII) and another, multiplet at δ 3.60-3.95 ppm which was changed into a quartet (J=10 and 15 Hz) by addition of deuteroxide, was assigned to that of a 4-aza-lactam (IX). Consequently, the lactam (VIII) prepared from the pure syn oxime could not be contaminated with any slight amount of the 4-aza-isomer as far as confirmed by ir and nmr.

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* These samples converted into syn and anti mixture after heating to their melting points.
** These signals were identical with those of 17β-hydroxy analogues (3).

Reduction of the 3-aza-lactam (VIII) with lithium aluminum hydride lead to 16β-hydroxy-3-aza-5β-A-homoandrostane (X), mp 196-197°; reported 197° (1). Identity of our material with samanine was confirmed by Dr. Habermehl[***], but, surprisingly, he pointed out that it is contaminated with the 4-aza-isomer. However, further careful examination of our lactam and final product by ir and nmr spectrometry did not indicate presence of the 4-aza-isomer at all.

In spite of his communication that he succeeded to obtain the pure 3-aza-lactam from a mixture with the 4-aza-lactam, this procedure has already been confirmed by us before this investigation (2) to be so difficult that it was not applicable to the specific synthesis of samanine. Similar evidence has been reported by many workers for Beckmann rearrangement of 3-oxosteroid oximes leading to either inseparable or barely separable mixtures of the two lactams (7).

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*** To our request to ask him identification of our synthetic material with his natural samanine from our ir spectrum, he replied to us that he has also succeeded in the synthesis by different way from ours and will publish it in Ann. Chem..

REFERENCES

1. G. Habermehl, The Alkaloids, Vol. IX, p.427. Academic Press, New York (1967).
   G. Habermehl, Progress in Organic Chemistry, Vol. 7, p. 35. Butterworth & Co., London (1968).
2. K. Oka and S. Hara, Chem.Ind., in press.
3. K. Oka and S. Hara, ibid., 911 (1968).
4. J. Fajkoš and F. Sǒrm, Coll. Czech. Chem. Comm., 19, 349 (1954).
   M.N. Huffman, M.H. Lott, and A. Tillotson, J. Biol. Chem., 218, 565 (1956).
   S. Hara and Y. Ike, Yakugaku Zasshi, 87, 1573 (1967).
   A. Hassner, J.M. Larkin, and J.E. Dowd, J. Org. Chem., 33, 1733 (1968).
   G. Just and Y.C. Lin, Chem. Comm., 1350 (1968).
5. S. Hara, S. Yagishita, and K. Oka, in preparation.
6. M.N. Huffman, M.H. Lott, and A. Tillotson, J. Biol. Chem., 222, 447 (1956).
7. For a review of the Beckmann rearrangement and Schmidt reaction of steroid ketones, see H. Singh, V.V. Parashar, and S. Padmanabhan, J. Sci. & Ind. Res., 25, 200 (1966).