

STEREOSELECTIVE SYNTHESIS OF SAMANDARINE NUCLEUS

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We have already reported the synthesis of the aza-oxa-bicyclooctane ring system appeared in the salamander alkaloids, which led us to success in the total synthesis of the major alkaloid, samandarone (1). The construction of the ring system has been accomplished in the final step of the synthesis by mild hydrolysis with 75% acetic acid of one to one mixture of the epimers, 2-benzylamino-3,3-ethylenedioxy-2,3-seco-5 β -androstan-1 ξ ,17 β -diol (I). One of the hydrolysates was 3-benzyl-3-aza-1 α ,4 α -epoxy-A-homo-5 β -androstan-17 β -ol (IIIa) and another (IV) was preliminarily assigned as a hemiacetal by its ir spectrum (1).

In this paper we will report the correct structure of IV and a Walden type inversion permitting the conversion of IV to the natural skeleton (IIIa). Very recently, we knew that Eggart et al. (2-5) had been trying to synthesize samandarine through different pathways from ours and, in spite of succeeding in construction of all the atomic rearrangement needed for the bicyclic system, had to give up their further effort only from one view-point that their last intermediate (Vb) (5), connecting directly to the samandarine ring system, had a reverse configuration of the aminomethyl group at C-1 position. It should be, however, noticed that our questioned intermediate (Va) is merely a benzyl derivative of theirs and that the inversion to the natural structure was readily achieved by the treatment with hydrochloric acid.

The material (IV) showed a single spot on tlc, and its ir spectrum suggested the presence of an ether linkage in its molecule (1). However, the nmr spectrum exhibited two signals due to 10 β -methyl protons at δ 0.82 and 0.89 ppm, being almost equal intensity. Since a possibility of a seco-aldehyde structure (II, 1 α -OH) was excluded by the absence of any signal in the formyl proton region, these signals might indicate that IV was a mixture consisting of

both a carbinol amine (IVa) and a hemiacetal (IVb).

Careful repetition of silica gel column chromatography of the product (IV) resulted in partial separation of the components; one of them was obtained in a pure state as the first eluate but the other as the mixture. From the nmr spectrum of the purely isolated material, it was assigned to be a carbinol amine (IVa). As illustrated in the Fig. 1 the spectrum showed one proton quartet at δ 2.83 ppm, assignable to one of the N-methylene hydrogens at C-2 position.

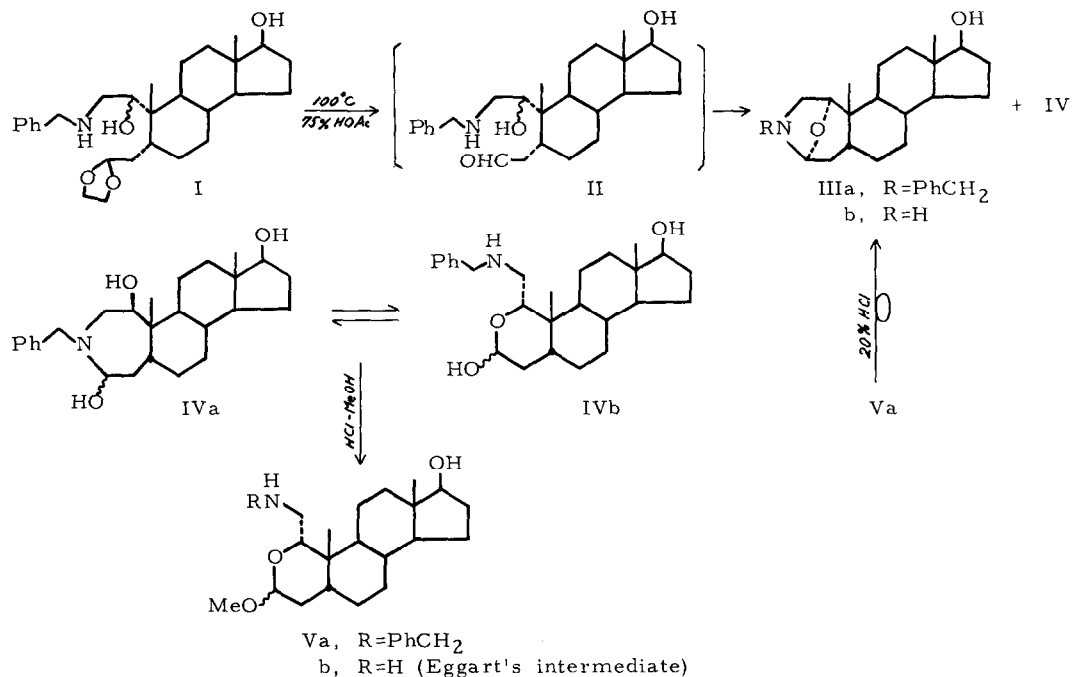
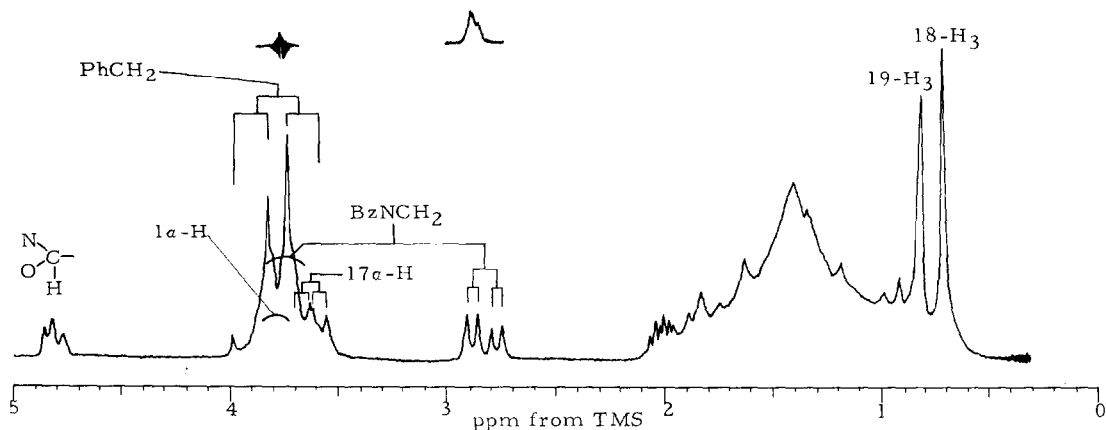


Fig. 1 Nmr spectrum of the compound IVa in $\text{CDCl}_3/\text{D}_2\text{O}$

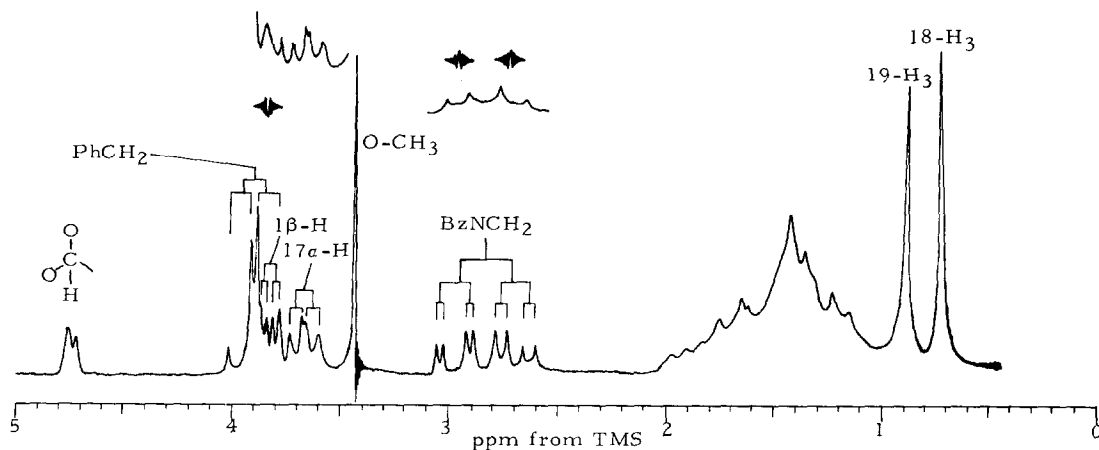


Since this signal was not affected by addition of D_2O but turned into a broad singlet by irradiation at about δ 3.75 ppm, the molecule would lack in any amino hydrogen and have an amino methylene moiety whose one of geminal protons resonated at δ 3.75 ppm where complicated signals assignable to benzyl methylene, 1α -, and 17α -hydrogens were overlapped. The large difference in chemical shifts between the geminal protons, 90 Hz, which would result from their magnetic unequivalence, could indicate that it had the aza-cyclic structure. Heating in 75% acetic acid at 100° for 5 minutes, the carbinol amine (IVa) was converted into the original mixture, IVa and IVb.

The latter chromatographic fraction obtained as a mixture of two components, one of which was the carbinol amine (IVa), was not characterized well from its equivocal nmr spectrum. However, the another component might be assigned to a hemiacetal (IVb) from the equilibrium phenomenon observed in IVa (*vide supra*). This assumption was supported by the experiment shown below.

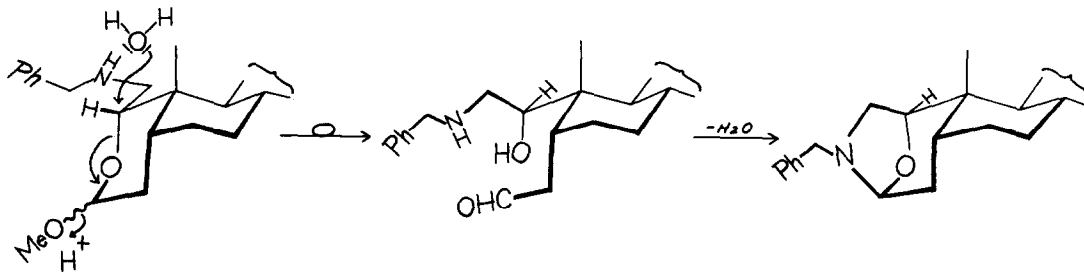
It was worth mentioning that the methylation of the mixture by dry hydrogen chloride in absolute methanol at room temperature led to a single methoxy derivative (Va). The nmr spectrum (Fig. 2) showed an ABX pattern corresponding to $>N-CH_2(AB)-\overset{|}{C}H(X)-O-$ grouping. The AB part of the spectrum was affected by addition of D_2O , and the small difference in chemical shifts between A (δ 2.72 ppm) and B (δ 2.93 ppm) was reasonable for the methylene group of which free rotation was slightly hindered by the steric circumstance of steroidal C-1 position. On the other hand, the ir spectrum of the hydrochloride of the methoxy deriva-

Fig. 2 Nmr spectrum of the compound Va in $CDCl_3/D_2O$



tive exhibited $>N^+H_2$ bending absorption at 1650 cm^{-1} showing the medium intensity. Consequently, the structure of the methoxy compound was depicted as a methoxy acetal (Va).

Hydrolysis of the methoxy acetal (Va) with 20% hydrochloric acid in aqueous acetone afforded the bicyclized compound (IIIa) whose ir spectrum was superimposable with the authentic sample (1). Further identification was made by leading it to the crystalline secondary amine (IIIb, mp 191-193°) (1). The reaction mechanism was readily recognized to be the concerted reaction involving elimination of the methoxyl group and the top side attack of a water molecule at the electron deficient C-1 carbon atom, giving rise to the Walden inversion at C-1 position of Va, followed by bicyclization of the resultant seco-oxy-aldehyde (VI) to form the thermodynamically stable system as described in the previous paper (1).



Thus the stereoselective bicyclization for the construction of samandarine nucleus was accomplished. This successive reactions, we believe, could be applicable to the total synthesis of samandarine planned by Eggart et al. (2-5), unless there were any special reason attributed to difference in chemical characters between aminomethyl and benzylamino-methyl groups at C-1a position.

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