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# A TOTALLY SYNTHETIC ENTRY INTO THE VERATRUM ALKALOID SKELETON*

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In connection with a program directed toward the total synthesis of steroidal alkaloids and related steroidal derivatives (1,2,3), we have been interested in developing a synthesis of the veratrum alkaloids. This latter group provides an interesting challenge since its members possess the C-nor-D-homo steroid skeleton, a unique system among the various members of the steroidal alkaloid class. We would now like to present a successful synthesis of the C-nor-D-homo intermediates VIIa and VIIb which we feel show promise as useful intermediates for the synthesis of veratrum alkaloids.

In a previous report (2) we had described the total synthesis of the keto-acetate, I, and had indicated the potential use of this intermediate in the synthesis of ring C modified steroidal derivatives. The experiments described below provide support for this proposal.

The keto-acetate, I, was reduced ($NaBH_4$ in aqueous methanol) and the crude alcohol acetate was immediately dehydrated to the olefin, II, by means of phosphorus pentoxide in refluxing benzene. The crystalline olefin†**

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* Part IV in the series entitled "Total Synthesis of Steroidal Derivatives".

** Satisfactory elemental analyses were obtained for all new compounds reported.

m.p. 105-106.5°, exhibited all the expected spectral properties. The ultraviolet spectrum, $\lambda_{max}^{95\% \text{ EtOH}}$ 221 mμ (ε 27,700), 262.5 (8,800), 270 (sh) (7,520), 302 (3260), 312 (sh) (2500); $\lambda_{min}$ 247 mμ (ε 6,780), 284 (3000), was characteristic for a m-methoxystyrene chromophore while the infrared spectrum showed only one carbonyl absorption at 5.81 μ and a weaker band at 6.15 μ for the styrene double bond. Finally the NMR spectrum*** was very instructive and the most noteworthy signals are the following: 9.15τ ($C-CH_3$), 8.02 (OAc), 6.29 ($OCH_3$), 5.30 ($C_8H$), 4.08 (doublet, $C_{12}H$, $J_{11,12}$ = 10 c.p.s.), 3.66 quartet, $C_{11}H$, $J_{11,10b}$ = 2.5 c.p.s., $J_{12,11}$ = 10 c.p.s.). The olefin was then converted to the 11,12-diol, III, m.p. 225-226°, $\lambda_{max}^{95\% \text{ EtOH}}$ 276 mμ (ε 1634), 282 (1541). The NMR spectrum of the latter (in pyridine) showed no absorption in the olefinic region but now new signals at 5.24 τ (doublet, $C_{12}H$, $J_{12,11}$ = 4 c.p.s.) and 5.61 (triplet, $C_{11}H$, half-height width = 9 c.p.s.) confirmed the structural assignment for the diol. Furthermore the NMR data indicated that the stereochemical orientation of the hydroxyl functions at $C_{11}$ and $C_{12}$ must be β on the basis of several significant features. Firstly, the small coupling which occurs (4 c.p.s.) between the protons at $C_{11}$ and $C_{12}$ is consistent with the axial-equatorial coupling expected for the cis diol whereas a significant downfield shift of the angular methyl protons (9.13 τ) established that the hydroxyl group at $C_{11}$ must be in a β orientation. It is well known from detailed NMR studies in our laboratory (to be published later) that the chemical shift of the angular methyl group in this entire series is very sensitive to the effect of substituents in close proximity to it. For example, it is pertinent to point out that the trans-anti-trans acetate, VIII, which bears no functionality in ring C exhibits a methyl signal (in

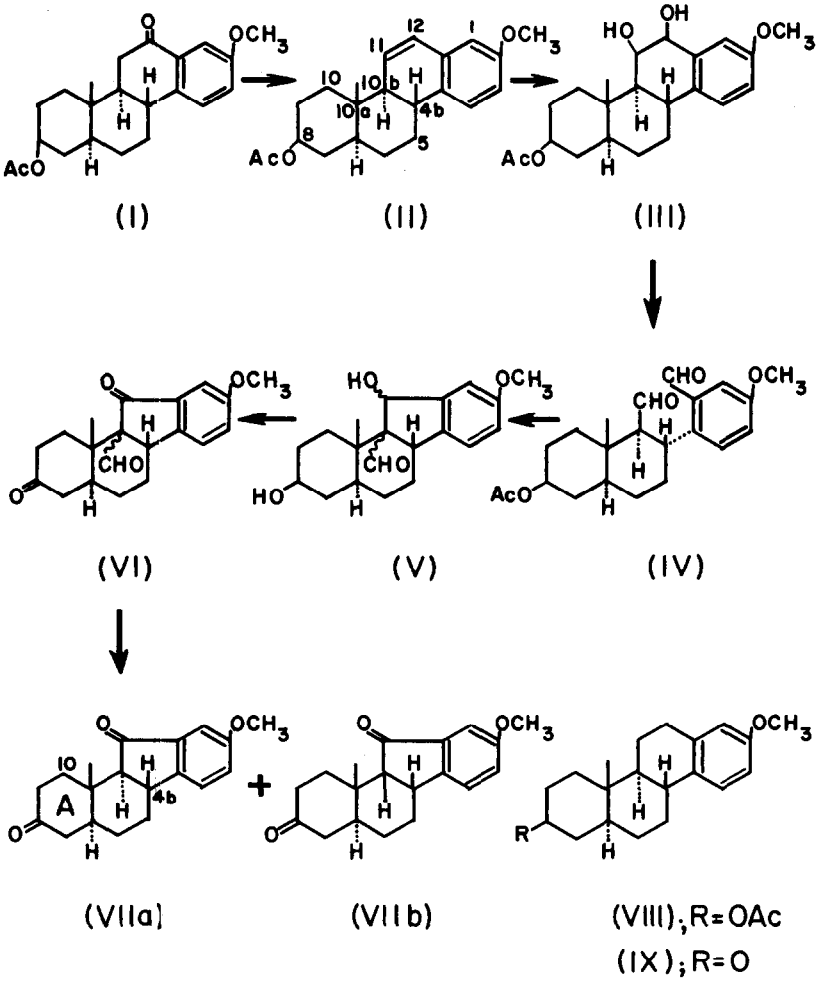
*** All NMR spectra were taken on a Varian A60 spectrometer and the values given are in the Tiers τ scale. Tetramethylsilane was used as the internal standard and deuterochloroform was the solvent unless otherwise stated.

pyridine) at 9.26 τ. On this basis the effect of the 11-β (axial) hydroxyl group on the methyl group resonance is shown by a downfield shift of 0.13 τ. It is also well established that in the steroid series the C-19 methyl group signal is shifted by a β hydroxyl substituent at $C_{11}$ (4).

The next step in the sequence involved the cleavage of the diol with periodic acid to provide the ring C opened dialdehyde, IV, m.p. 130-133°, $\nu_{max}$ 3.63 μ, 5.79, 5.87, 5.97; $\lambda_{max}^{95\%\ EtOH}$ 225 mμ (ε 21,200), 255.5 (7190), 321 (3140); $\lambda_{min}$ 242.5 mμ (ε 5610), 281 (502 ). Of particular note was the NMR spectrum which confirmed the presence of two aldehydic protons - a doublet at 0.46 τ (CH-CHO, J = 4 c.p.s.) and a singlet at -0.3 τ (Ar-CHO) - one acetate methyl at 7.90 and the angular methyl group at 8.85 τ. Furthermore the stereochemistry at positions 4b and 10b was the expected <u>trans</u> as indicated in structure, IV, since $J_{10b,4b}$ = 12 c.p.s. and, therefore, consistent with diaxial coupling (5).

The synthesis of the desired C-nor-D-homo skeleton present in the veratrum series was accomplished by an internal aldol condensation (NaOH in aqueous methanol) of the dialdehyde. The reaction product isolated as a crystalline compound, m.p. 175-182°, could be assigned the aldol structure, V, on the basis of the following spectral data. The ultraviolet spectrum ($\lambda_{max}^{95\%\ EtOH}$ 284 mμ (ε 2280), 289 (sh, 2065); $\lambda_{min}$ 257 mμ (ε 550) of the latter was now quite characteristic of the anisole-type chromophore already well known from our previous studies and the infrared spectrum with absorptions at 2.96, 3.65, and 5.90 μ was in accord with the presence of only hydroxyl and saturated aldehyde functions. Finally the NMR spectrum indicated the presence of only <u>one</u> aliphatic aldehydic proton (0.30 τ, doublet, J= 3.c.p.s.) and an angular methyl signal (8.90 τ) thereby confirming the aldol structure, V. We wish to emphasize at this time that this product may still represent

a mixture of isomers epimeric at either $C_{10b}$ or $C_{11}$ but this is unlikely since we have made various attempts to try and detect more than one component. The compound is certainly homogeneous to a rather extensive thin-layer chromatography investigation.



The diol aldehyde, V, was then submitted to a mild oxidation with Jones reagent (6) at room temperature and the spectral data of the crude product were consistent with the expected diketo aldehyde structure, VI. The NMR spectrum revealed the presence of the aldehydic proton as a singlet at 0.32 τ while the ultraviolet absorption ($\lambda_{max}^{95\%\ EtOH}$ 220, 255 and 326 mμ; $\lambda_{min}$ 244 and 282 mμ) was immediately reminiscent of the corresponding spectrum exhibited by the starting keto-acetate, I, which possesses the analogous chromophore. Further purification of this product was complicated by its facile loss of the aldehyde function to provide a new product possessing the diketo structure VII. For example chromatography on Woelm alumina converted VI to a mixture of ketones which proved identical with the diketones VIIa and VIIb mentioned below. This type of reaction is already known and a recent example in the sesquiterpene series may be cited (7).

The final conversion in the present sequence involved deformylation of VI to provide the isomeric diketones VIIa and VIIb. Although the alumina method was applicable a more convenient approach involved deformylation under alkaline conditions (potassium hydroxide in aqueous dioxane) (8) to give a mixture separable only by fractional crystallization into two compounds, VIIa, m.p. 192-196°; $\lambda_{max}^{95\%\ EtOH}$ 219 mμ (ε 27,700), 249 (8330), 319 (3920); $\lambda_{min}$ 237 mμ (ε 6820), 273 (950) and VIIb, m.p. 140-142°; $\lambda_{max}^{95\%\ EtOH}$ 218 mμ (ε 29,500), 249 (9500), 318 (3820); $\lambda_{min}$ 236 mμ (ε 7570), 272 (1240). Although as expected the ultraviolet spectra were essentially superimposable, the NMR spectra showed some interesting differences. Of particular note was the angular methyl group region which indicated singlets at 8.85 τ (69 c.p.s.) and 8.74 τ (75.5 c.p.s.) for VIIa and VIIb respectively. This difference in chemical shift allows assignment of the trans-anti-trans

stereochemistry to the diketone, VIIa, and the trans-syn-cis stereochemistry to the diketone, VIIb.

It is well known (9) that protons lying in conical regions extending above and below the plane of the trigonal carbon atom of a carbonyl group will be shielded by this function, while those lying elsewhere and particularly those in the plane of the trigonal atom will be deshielded. Molecular models of VIIa and VIIb reveal that in the former the angular methyl group lies in a plane perpendicular to that of the carbonyl group and is, therefore, shielded whereas in the latter, this group lies essentially in the plane of the trigonal carbon atom. The obtained results are, therefore, in complete accord with expectation. It is also pertinent to note at this point that our NMR results are in excellent agreement with those of Johnson and co-workers (10) who studied a closely analogous system. A more detailed discussion of our extensive NMR studies in this entire series, which will include long range deshielding in ring A as recently observed in the androstane series (11) and also interesting effects of solvents (12, 13), will be presented in a future publication.

Mass spectral data**** provided further confirmation for the structural assignments to VIIa and VIIb. The isomeric nature of these compounds was established beyond any doubt by the presence of an identical molecular ion peak (m/e 298) and the complete identity of their mass spectra in the range m/e 80 - m/e 225. Furthermore, only minor intensity differences occur in the range m/e 225-280. In fact, only one significant difference is noted in the two spectra and this occurs in the region m/e 280-298. Both compounds exhibit relatively intense molecular ion peaks and also appreciable

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**** Mass spectra were recorded on an AEI, type MS9, mass spectrometer.

peaks at m/e 280 (M-18) but only the trans-anti-trans diketone VIIa possesses a significant M-15 peak which indicates loss of the angular methyl group. It is interesting to note that the trans-anti-trans 8-ketone, IX, known from our previous studies also possesses significant M-15 and M-18 peaks in its mass spectrum. It, therefore, appears that the loss of the angular methyl group, at least in the 8-keto series, is a more significant process when the normal steroid stereochemistry prevails but further work is necessary before any more definitive evidence can be provided. It is also pertinent to mention that the fragmentation process observed in the above diketones, particularly in the case of VIIa, is in good agreement with the detailed investigations of Djerassi and co-workers (14) on steroidal ketones in which significant M-15 and M-18 peaks are noted.

We feel that the completion of this synthetic sequence provides versatile intermediates for the total synthesis of veratrum alkaloids and related analogues. We hope to present evidence in this direction in future publications.

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