# THE TOTAL SYNTHESIS OF AKUAMMICINE AND 16-EPI-STEMMADENINE. THE ABSOLUTE CONFIGURATION OF STEMMADENINE.

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A synthetic route leading to akuammicine (VI) and 16-epi-stemmadenine (XI) is presented. The synthesis employs Wieland-Gumlich aldehyde (III), a well-known degradation product of strychnine (II), as a starting material. Introduction of functionality at $C_{16}$ in the intermediate VIII is done in a stereochemically unambiguous fashion thereby allowing direct comparison of the synthetic substances with the natural stemmadenine series. In this manner the complete absolute configuration of stemmadenine (I) is derived.

Stemmadenine (I) was first isolated in 1958[1] and its structure established in 1962.[2] Further investigations in the Strychnos alkaloid area provided correlations with various members[3,4,5] and allowed a configurational assignment at $C_{15}$ but as yet the absolute configuration at $C_{16}$ remains unsettled. The importance of this alkakoid and its close relatives in the later stages of indole alkaloid biosynthesis is now well established[6-9] and a complete stereochemical assignment as well as a synthetic entry into this series attain particular interest. It was thus desirable to develop a synthetic sequence which would hopefully provide information about the remain-

ing stereochemical problem and possess sufficient versatility to allow introduction of radioactive label at appropriate sites of the molecule for purposes of biosynthetic experiments. The results presented in this communication provide a solution to these objectives.

Degradation of strychnine (II) by well established procedures recently refined by Schmid[10] led to Wieland-Gumlich aldehyde (III) and the latter was then converted to methyl 18-hydroxy-2β,16α-cur-19-en-17-oate (IV) according to the procedures described by Edwards and Smith.[11] This intermediate became the crucial starting material for all of our investigations.

As shown in Figure 1, successive treatment of hydroxy ester IV with hydrogen bromide and zinc in acetic acid resulted in the formation of methyl 2β,16α-cur-19-en-17-oate (V, 2,16-dihydroakuammicine) in 65% yield. The spectral and analytical data provided conclusive evidence for the structural assignment.[12] The nmr spectrum revealed a quartet at δ 5.48 (olefinic $C_{19}H$) and a doublet of doublets at 1.58 (J = 2 and 7 Hz) for the vinylic $C_{18}$ methyl group while retention of the ester group was evident from a three-proton signal at 3.70. A typical mass spectral fragmentation pattern[13] (m/e 251, 194 (base peak), 144, 139 and 130) and high resolution measurement (324.177, $C_{20}H_{24}N_2O_2$ requires 324.183) left no doubt about the assigned structure V. Further supporting evidence was provided from the lead tetraacetate oxidation of V to the known alkaloid akuammicine (VI),[11] thereby completing the synthesis of this alkaloid.

One of the considered alternative routes to the stemmadenine system involved the conversion of akuammicine (VI) to the ring-opened indole ester VII by treatment of VI with sodium borohydride in acetic acid.[14] In general the yields were low and moreover, attempts to introduce the required hydroxy-

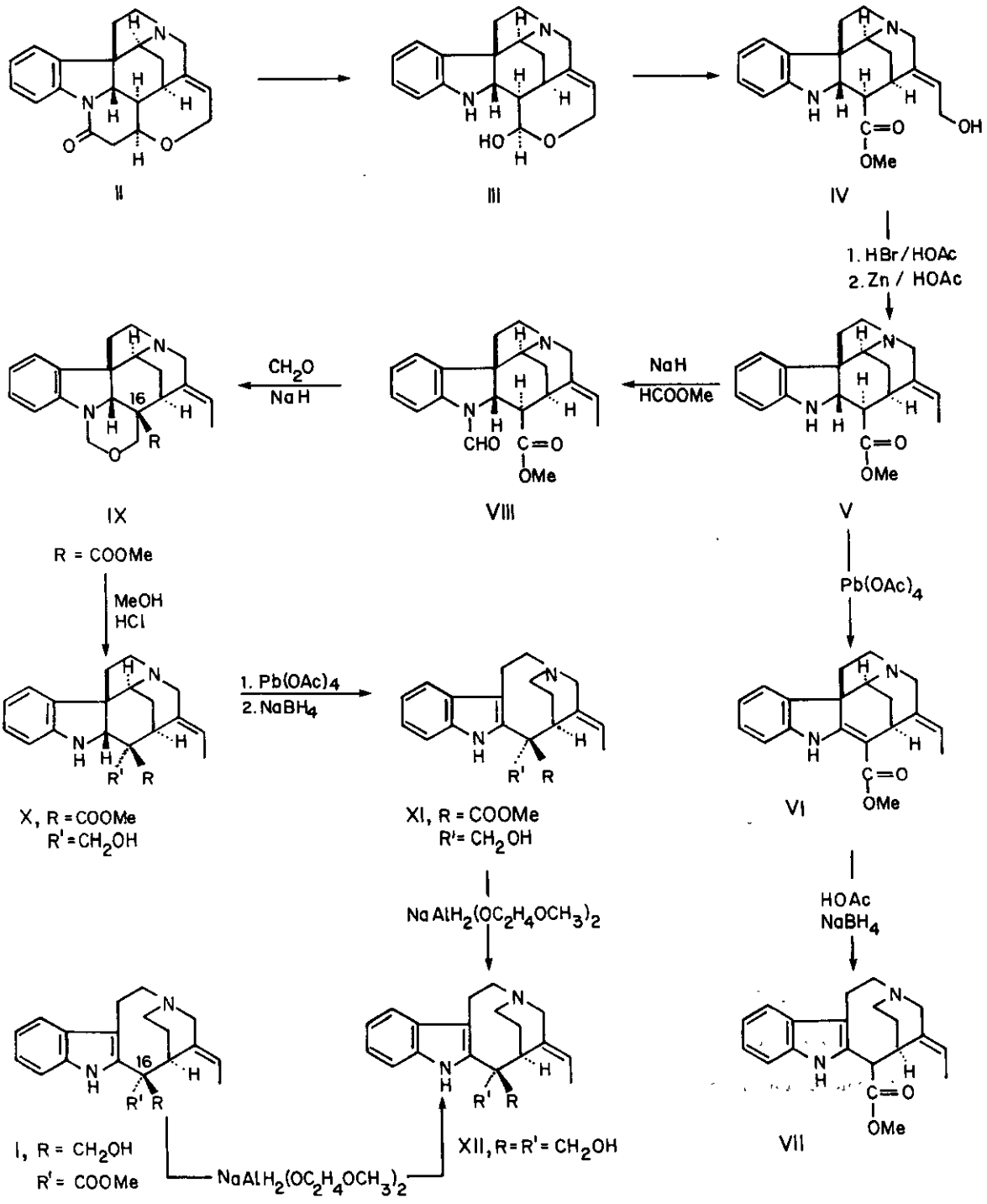
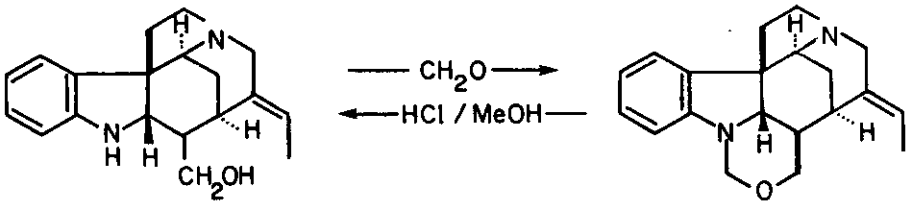



Figure 1. The Total Synthesis of Akuammicine (VI) and 16-Epi-Stemmadenine (XI).

methylene group at $C_{16}$ in VII were not successful so this approach was abandoned.

Introduction of the $C_{16}$ substituent prior to oxidation of the indoline system provided however a successful route to the desired system. Treatment of V with methyl formate and sodium hydride resulted in an 80% yield of the corresponding N-formyl derivative VIII, m.p. 168-170° (ir: 1730, 1668 and 1600 $cm^{-1}$; uv: $\lambda_{max}$ 287, 278 and 250 nm). Treatment of VIII with formaldehyde and sodium hydride in dimethyl sulfoxide led to a 78% yield of the carbomethoxy tetrahydrooxazine IX. This unexpected but synthetically useful product was fully characterized. The ir spectrum of IX showed no N-H bonds and only one carbonyl absorption (1730 $cm^{-1}$) while the uv spectrum ($\lambda_{max}$ 299, 246 nm) indicated an indoline chromophore. The nmr spectrum revealed the presence of the carbomethoxy group ($\delta$ 3.70, 3H, s) and the tetrahydrooxazine system (N-$CH_2O$, AB pattern at 5.18 and 4.71, J = 10 Hz) while the high resolution mass spectrum (366.191, $C_{22}H_{26}O_3N_2$ requires 366.194, m/e 336, loss of $CH_2O$) established the molecular formula.

In order to provide further evidence for the proposed structure IX, it was decided to synthesize the analogous descarbomethoxy compound XIV via an independent route. Thus 2β,16α-cur-19-en-17-ol (XIII) prepared by hydrogenolysis of Wieland-Gumlich aldehyde (III), was allowed to react with paraformaldehyde in a procedure analogous to that previously described for the related alcohol, geissoschizoline.[15-17] The desired product XIV was obtained in good yield and its spectroscopic properties were in excellent agreement with those noted above (uv: $\lambda_{max}$ 297 and 249 nm; nmr: typical AB pattern




XIII XIV

at δ 5.23 and 4.67, J = 11 Hz, N-$CH_2O$; mass spectrum: 308.193, $C_{20}H_{24}ON_2$ requires 308.189, m/e 278, loss of $CH_2O$). When XIV was treated with 10% HCl in methanol at room temperature, the product, obtained in quantitative yield, was the starting material XIII.

The absolute configuration at $C_{16}$ in IX and, in turn, in the subsequent compounds in the series follows directly from several lines of evidence. It has been shown by Edwards and Smith[11] that the hydroxy ester IV is not epimerizable. This result is clear since if ring C in IV is in a chair conformation, the $C_{16}\beta$ carbomethoxy group is in the favourable equatorial orientation. A similar argument obviously applies to VIII. Furthermore molecular models of VIII clearly indicate that approach of an electrophile from the α face would be much more favourable than from the hindered β face. Strong support for these arguments comes forth from a careful comparison of the nmr data for IV, V, VIII and IX. The chemical shifts of the ester methyl signals and those of the olefinic side chain are essentially identical, a situation consistent only with the β configuration for the ester group in these molecules (see below).

Hydrolysis of IX in a manner already described above for XIV provided a good yield (92%) of the hydroxyester X (ir: 1725 $cm^{-1}$; uv: $\lambda_{max}$ 296 and 244 nm; nmr: 3.73, 3H, s, $COOCH_3$). The latter was converted to the indole derivative XI by an oxidative-reductive process involving initial oxidation with lead tetraacetate followed by treatment of the intermediate with sodium borohydride in acetic acid. The isolated product clearly contained the desired indole chromophore ($\lambda_{max}$ 291, 284 and 225 nm) and exhibited a mass spectrum possessing a molecular ion at m/e 354 and fragments at $M^+$-17, $M^+$-18 and $M^+$-30 corresponding to loss of OH, $H_2O$ and $CH_2O$ in accord with that already described for stemmadenine.[2,18] A comparison of the nmr data of the synthetic product with that of natural stemmadenine[3,18] in shown in Table I. It is of particular interest to note the marked influence of the configuration at $C_{16}$ on the chemical shifts of the various proton signals.

Table I. Comparison of NMR Data on Natural (I) and Synthetic (16-Epi-Stemmadenine, XI) Systems.

| Compound | Indole N-H | $C\underline{H}CH_3$ | $\underline{CH_2}OH$ | $COO\underline{CH_3}$ | $CH\underline{CH_3}$ |
|---|---|---|---|---|---|
| Natural | 9.4 | 5.4 | 4.38 | 3.79 | 1.7 |
| Synthetic | 10.14 | 5.4 | 4.36 | 3.88 | 1.5 |

In order to prove that the synthetic material was indeed 16-epi-stemmadenine (XI) both the natural (I) and synthetic materials were reduced to the diol XII by means of sodium bis (methoxyethylenoxy) aluminum hydride. Both products obtained were found to be identical (superimposable ir and nmr spectra).

In conclusion the above investigations provide a synthesis of 16-epi-stemmadenine (XI) and thereby establish the stereochemistry about $C_{16}$ in stemmadenine to be as shown in I.

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References

1. F. Walls, O. Collera, and A. Sandoval, Tetrahedron, 1958, 2, 173.
2. A. Sandoval, F. Walls, J. N. Shoolery, J. M. Wilson, H. Budzikiewicz and C. Djerassi, Tetrahedron Letters, 1962, 409.
3. K. Biemann, A. L. Burlingame and D. Stauffacher, ibid., 1962, 527.
4. D. Schumann and H. Schmid, Helv. Chim. Acta, 1963, 46, 1996.
5. M. M. Janot, Pure Appl. Chem., 1963, 6, 635.
6. A. I. Scott, Acc. Chem. Res., 1970, 3, 151, and references cited therein.
7. J. P. Kutney , J. F. Beck, E. Ehret, G. A. Poulton, R. S. Sood and N. D. Westcott, Bioorg. Chem., 1971, 1, 194, and references cited therein.
8. J. P. Kutney, J. Het. Chem., 1972, 9, Suppl. Issue, S-1, and references cited therein.
9. G. A. Cordell, Lloydia, 1974, 37, 219, and references cited therein.

10. J. R. Hyman, H. Schmid, P. Karrer, A. Boller, H. Els, P. Fahrni and A. Furst, Helv. Chim. Acta, 1969, 52, 1564. We are very grateful to Professor H. Schmid for a generous gift of Wieland-Gumlich aldehyde for our studies.

11. P. N. Edwards and G. F. Smith, J. Chem. Soc., 1961, 152.

12. Complete characterization data were obtained for all new compounds reported. Nuclear magnetic resonance spectra were recorded at 100 MHz on Varian HA100 and XL100 spectrometers. Values are reported in the δ scale. High resolution mass spectral measurements were obtained on an AEI MS 902 mass spectrometer.

13. H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Levy, J. Le Men and M. M. Janot, Tetrahedron, 1963, 19, 1265.

14. J. P. Kutney and V. R. Nelson, unpublished results. This procedure was employed successfully in a related alkaloid series.

15. F. Puisieux, A. LeHir and M. Delepine, Compt. Rend., 1961, 252, 902.

16. F. Puisieux, A. LeHir, R. Goutarel, M. M. Janot and J. Le Men, Ann. Pharm. Franc., 1959, 17, 626.

17. F. Puisieux, R. Goutarel, M. M. Janot, J. Le Men and A. LeHir, Compt. Rend., 1960, 250, 1285.

18. A sample of natural stemmadenine employed in our studies was kindly provided by Dr. U. Renner, Ciba-Geigy Research Laboratories, Basle, Switzerland.

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