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ON THE STRUCTURE OF ASPIDOSPERMINE[1]

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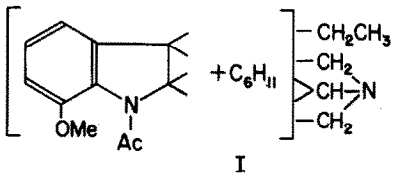
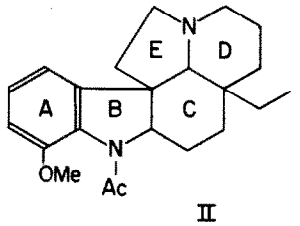
IN Part II[2] we outlined the development of the partial structural formula (I) for the alkaloid aspidospermine. The additional chemical evidence



I



II

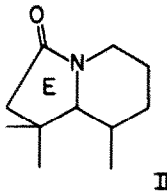
described in this Letter confirms those conclusions and has a considerable further bearing on the structure. While mainly limited to elucidation of the nature of rings D and E enclosing the basic nitrogen (N_b), our results

[1] Part III of a series. Contribution numbered 1570 from the Sterling Chemistry Laboratory at Yale University.

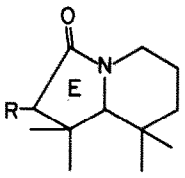
[2] H. Conroy, P. R. Brook, M. K. Rout and N. Silverman, J. Amer. Chem. Soc. 80, 5178 (1958).

to that extent are fully in support of the complete formulation (II) which is deduced by Mills and Nyburg on the basis of their recent elegant X-ray crystallographic studies and discussed in an accompanying communication.

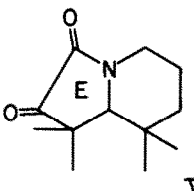
Chromium trioxide-pyridine oxidation of the alkaloid gave a neutral fraction, separable into three components by chromatography on Florisil. The first eluted was aspidospermine lactam-B (III), m.p. 115° from benzene (Found: C, 75.18; H. 7.70; N, 6.19. $C_{22}H_{28}O_3N_2 \cdot C_6H_6$ requires: C, 75.30; H, 7.67; N, 6.27.)[3] with $\nu\nu_{max}$ 1652 (N_a-acetyl) and 1680 cm^{-1} (five-membered lactam). Aspidospermine lactam-C (IVa) moved more slowly in the



III



IV, R=OH
VI, R=Cl
VII, R=OAc



V

chromatogram; it was crystallized from benzene and gave the m.p. 228-230° (transition at 147°) (Found: C, 72.59; H, 7.22; N, 6.04. $C_{22}H_{28}O_4N_2 \cdot C_6H_6$ requires: C, 72.70; H, 7.41.; N, 6.06.)[3] and $\nu\nu_{max}$ 1692 (lactam carbonyl) and 3305, 3520 cm^{-1} (hydroxyl). Lactam-D (V), with intermediate mobility

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[3] The inclusion of benzene in these stable crystalline solvants was shown independently of the analysis in each case by the intense singlet benzene absorption in the NMR spectrum of the analytical sample.

in the chromatogram, has the m.p. 249° from benzene (Found: C, 72.84; H, 7.05; N, 6.04. $C_{22}H_{26}O_4N_2 \cdot C_6H_6$ requires: C, 73.02; H, 7.00; N, 6.08.)[3] and gives the very characteristic infrared doublet $\nu\nu_{max}$ 1721 and 1770 cm^{-1} of the five-membered α-keto-lactam[4] as well as ν_{max} 1660 cm^{-1} (N_a-acetyl). Lactam-D oxime, m.p. 261° from benzene (Found: C, 68.06; H, 6.97; N, 9.92. $C_{22}H_{27}O_4N_3 \cdot \frac{1}{3}C_6H_6$ requires: C, 68.06; H, 6.90; N, 9.92.)[3] formed rather slowly. Potassium borohydride reduction of the ketonic carbonyl of V gave the α-hydroxylactam (IVb), m.p. 247° from ethyl acetate (Found: C, 69.08; H, 7.58; N, 7.91. $C_{22}H_{28}O_4N_2$ requires: C, 68.72; H, 7.34; N, 7.29.) with $\nu\nu_{max}$ 1654 (N_a-acetyl) 1697 (lactam carbonyl) 3310 and 3510 cm^{-1} (hydroxyl). Lactam-C and the borohydride reduction product are epimeric at the hydroxylated carbon. Lactams -B and -C were interrelated by conversion of -C to the α-chlorolactam (VI), m.p. 294-296°, (ν_{max} 1718 cm^{-1}; Found: C, 65.46; H, 6.77; Cl, 8.55. $C_{22}H_{27}O_3N_2Cl$ required: C, 65.68; H, 6.75; Cl, 8.80) with phosphorus oxychloride followed by zinc dust reduction of VI to III. Absence of any skeletal change in the oxidation was shown by reduction of lactam-B to N_a-ethyldeacetylaspidospermine[5] with lithium aluminum hydride.

The 60 mc/sec NMR spectrum[6] of lactam-B shows a well resolved two proton nonequivalence quartet centered at τ = 7.63 with J = 16.2 cps,

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[4] Thus 1,5-diphenyl-2,3-diketopyrrolidine absorbs at 1712 and 1770 wavenumbers [H. H. Wasserman and R. C. Koch, Chem. & Ind. 428 (1957); Cf, P. L. Southwick, E. P. Previc, J. Casanova, Jr. and E. H. Carlson, J. Org. Chem. 21, 1087 (1956).].

[5] B. Witkop and J. B. Patrick, J. Amer. Chem. Soc. 76, 5603 (1954).

[6] NMR spectra were measured on a Varian Associates instrument with 99.5% deuteriochloroform as solvent and tetramethylsilane as internal reference.

absent in the corresponding regions of the curves for aspidospermine, for lactam-C or for lactam-D, which must be ascribed to the methylene immediately adjacent to the lactam-B carbonyl. The NMR spectrum of lactam-C O-acetate (VII), m.p. 211° [$\nu\nu_{max}$ 1706 (lactam carbonyl) and 1754 cm^{-1} (O-acetyl); Found: C, 67.41; H, 7.04; N, 6.68. $C_{24}H_{30}O_5N_2$ requires: C, 67.58; H, 7.09; N, 6.57.)], is marked by a sharp one proton singlet peak at τ = 4.90; the corresponding O-methine absorption of lactam-C is higher, at τ = 6.17. Since neither pair in the methylene quartet is further split by a vicinal third proton, while the peak associated with the acetoxylated methine ($C-CH<^{OAc}_{CO-N}$) is isolated from any spin coupling, the groupings in question must be joined to a quaternary center and the five-membered ring E of aspidospermine contains the system $C-\overset{C}{\underset{C}{C}}-CH_2-CH_2-N<$.

Mercuric acetate oxidation[7] of the alkaloid gave a mixture of enamines from which one, dehydroaspidospermine-A (VIII), was isolated as the iminium perchlorate, m.p. 256-287°, dec., (Found: C, 58.60; H, 6.74; N, 5.95. $C_{22}H_{29}O_6N_2Cl$ requires: C, 58.31; H, 6.45; N, 6.19.) with ν_{max} 1698 ($[>C=N<]^+$) and no band near 2400 cm^{-1} ($[R_3N-H]^+$). Further oxidation of the regenerated enamine with silver oxide in aqueous dioxane gave the neutral aspidospermine lactam-A (IX), m.p. 174-176°, (Found: C, 71.47; H, 7.45; N, 7.47. $C_{22}H_{28}O_3N_2$ requires C, 71.71; H, 7.66; N, 7.60.) with very strong absorption at 1625 cm^{-1}, the result of superposition of the bands due to a six-membered lactam carbonyl and the N_a-acetyl function. Deacetylaspidospermine lactam-A, prepared by acid hydrolysis and purified via the hygroscopic perchlorate,

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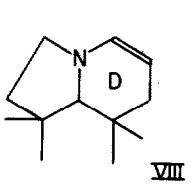
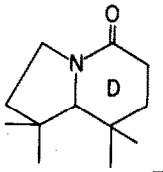
[7] Cf. N. J. Leonard and F. P. Hauck, Jr., J. Amer. Chem. Soc. 79, 5279 (1957).

m.p. 210-217°, (Found: C, 56.20; H, 6.47; N, 6.62. $C_{20}H_{27}O_6N_2Cl$ requires: C, 56.27; H, 6.38; N, 6.56.) still has ν_{max} 1621 cm^{-1}. Absence of skeletal change in the oxidations was shown by reduction of dehydroaspidospermine-A perchlorate to aspidospermine with sodium borohydride and reduction of lactam-A to N_a-ethyl-deacetylaspidospermine with lithium aluminum hydride.



VIII



IX

Dehydroaspidospermine-A bears one olefinic hydrogen at the β position (with respect to N_b) as shown by the infrared shoulder at 1651 cm^{-1} given by the free base and by the sharp peak at 1650 cm^{-1} in the spectrum of the deacetylated enamine.[8] The enamine (VIII) coupled readily with p-nitrobenzenediazonium chloride to give an intensely red dyestuff, yellow in acidic solution, as shown:

$$>N-CH=CH- \longrightarrow >\overset{+}{N}=CH-CH< \underset{N=N-Ar}{} \quad \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \quad >N-CH=C< \underset{N=N-Ar}{},$$

which should not have been possible if the enamine had been more highly substituted at the β carbon.

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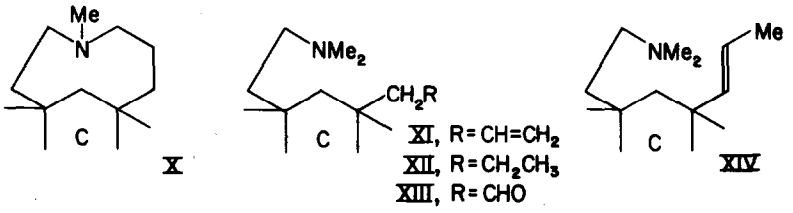
[8] If fully substituted at the β carbon, an αβ-unsaturated amine absorbs in the infrared range 1666-1673 wavenumbers; otherwise the characteristic peak is at lower frequencies (1640-1652 wavenumbers) (Ref. 7).

Further information as to the constitution of ring D was obtained from aspidospermine dihydromethine[2] (X), the product of Emde reduction of aspidospermine methiodide. Hofmann degradation of the dihydromethine



X

XI, R = CH=CH$_2$
XII, R = CH$_2$CH$_3$
XIII, R = CHO

XIV

methiodide[2] with potassium t-butoxide gave the olefinic base (XI), characterized as its perchlorate, m.p. 245–246° (Found: C, 59.43; H, 7.67; N, 5.72. $C_{24}H_{35}O_6N_2Cl$ requires: C, 59.44; H, 7.69; N, 5.78.). No product corresponding to an alternative course of elimination was obtained. The base (XI) shows typical vinyl infrared absorption at 910 and 995 cm^{-1}, peaks vanishing in the spectrum of the corresponding dihydrogenated derivative (XII) [perchlorate, m.p. 261°; Found: C, 59.13; H, 7.81; N, 5.74. $C_{24}H_{37}O_6N_2Cl$ requires: C, 59.19; H, 8.07; N, 5.78.]. The 60 mc/sec NMR spectrum[6] of XI shows two overlapping symmetrically spaced quartets centered at τ = 4.95 and 4.99 associated with the A and B protons of the system $CH_AH_B{=}CH_C{-}$. If the Hofmann elimination had proceeded in the other direction, giving a vinyl function substituted upon the quaternary center, the C proton should also have appeared as a quartet, with splittings which could have been deduced from those of the A and B quartets. Instead we

observed a multiplet centered near τ = 4.24 sufficiently complex to require that the C proton be coupled to four other, as in CH_AH_B=CH_C-CH_XH_Y.[9] The evidence for an adjacent methylene further includes the spectrum of XII [derived from the olefin (XI) by osmium tetroxide-periodate fission], with a symmetrical 1:2:1 triplet at τ = 0.17 (J = 2.9 cps) associated with the aldehydic proton resonance.[10]

The olefin (XI) was transformed by hot mineral acid into an isomer [perchlorate, m.p. 199-201° (Found: , 59.60; H, 7.78; N, 5.50. $C_{24}H_{37}O_6N_2Cl$ requires C, 59.19; H, 8.07; N, 5.78.)], which loses its vinyl absorption in the infrared and NMR but gives instead a band at 970 cm^{-1} (trans -CH=CH-), a two proton olefinic resonance multiplet at τ = 4.53 and a three proton doublet at τ = 8.32 with J = 2.6 cps (allylic C-methyl). Catalytic reduction led to a dihydro base whose identity with XII was established by infrared comparison of the bases and the two salts, and by mixed m.p. of the salts. This olefin is the double bond isomer (XIV) containing a trans-propenyl group in place of the allyl residue.

These results establish the presence of the system >N-CH_2-CH_2-CH_2-C within the six-membered ring D. They exclude attachment of the C-ethyl

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[9] First order theory predicts no more than eight lines for the C resonance in CH_AH_B=CH_C-CH_XC_2 and only four in CH_AH_B=CH_C-CC_3; at least ten could be seen clearly in our spectrum and it is probable that better resolution would have disclosed twelve.

[10] The acetaldehyde -CHO resonance appears at τ = 0.28 (J = 2.85 cps).

group of I at the β carbon, as in the Witkop–Openshaw structure.[5,11,12]

The DE bicyclic system cannot be bridged so as to violate the requirements of coplanarity about N_b in the lactams and the (iminium) salt of VIII. We have no unequivocal evidence for the second quaternary center (to which is bonded the C–ethyl, in II), but its inclusion provides explanation for the isomerization (XI ⟶ XIV) proceeding no further than it does, to a disubstituted olefin, and is consistent with the behavior of the unit >CH–N_b in the NMR spectra.

In conclusion we mention that a number of our other observations, although of somewhat less direct consequence in the structural argument, are in complete agreement with the structure (II) for aspidospermine; it is with particular satisfaction that we welcome the dramatic and impressively definitive solution reached by Mills and Nyburg using the X-ray technique.

Acknowledgements – This research was supported by a grant (RG–6190) from the National Institutes of Health. Microanalyses were performed by W. Manser, E. T. H., Zurich and by Dr. S. M. Nagy, M. I. T.

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[11] The Witkop–Openshaw structure was based primarily upon Witkop's reported isolation of 3,5–diethylpyridine from zinc dust degradation of deacetylaspidospermine but it will be recalled that the product in question could not be positively identified with the synthetic sample [B. Witkop, J. Amer. Chem. Soc. 70, 3712 (1948)].

[12] H. T. Openshaw, G. F. Smith and J. R. Chalmers, XIIIth International Congress of Pure and Applied Chemistry, 1953, Abstracts, p. 223; H. T. Openshaw, and G. F. Smith, Experientia 4, 428 (1948); A. J. Everett, H. T. Openshaw and G. F. Smith, J. Chem. Soc. 1120 (1957).