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THE CONFIGURATION OF ANNOTININE AND SOME REARRANGEMENTS

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IN our full report on the structure of annotinine[1] we deduced the relative configuration portrayed in formula I. The configuration of the methyl group remained undetermined and the argument for the configuration of the oxide ring was not rigorous.

Perry, MacLean and Manske[2] described the transformation of annotinine with phenyl lithium into the diphenyl derivative II. They were able to prove the functionality of II but did not draw any configurational conclusions. The established configuration of the lactone ring[1] and the well-known geometric requirements of a concerted epoxide opening leave no doubt about the exact course of the reaction. The initially formed phenyl ketone must epimerize at the α carbon and then react with a second mole of phenyl lithium

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[1] K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and J.E. Francis, Tetrahedron 4, 87 (1958).

[2] G.S. Perry, D.B. MacLean and R.H.F. Manske, Canad. J. Chem. 36, 1146 (1958).

to give a diphenylcarbinol which is transformed to II. This reaction proves that the epoxide is cis to the four-membered ring (as in I)[3].

The reaction of oxoannotinine chlorohydrin (III) with phosphorus oxychloride followed by methanol provides a confirmation of this assignment. In addition to oxoanhydroannotinine chlorohydrin[1], formed by a simple β-elimination, we have been able to isolate compound IV, m.p. 229° (Found: C, 49.94; H, 5.85; N, 3.20; P, 4.60; Cl, 8.00; OCH_3, 13.45. $C_{18}H_{25}O_7NPCl$ requires C, 49.83; H, 5.81; N, 3.23; P, 7.14; Cl, 8.17; OCH_3, 14.31%), IR: 1775 cm^{-1} (γ-lactone), 1700 cm^{-1} (five-membered lactam). With the lactam ring in III in the more stable quasi-chair form, the hydroxyl group situated cis to the four-membered ring is antiparallel to the migrating group and the cyclic rearrangement can therefore compete with the normal elimination.

We next turned our attention to the determination of the absolute configuration of annotinine. For this purpose we have determined the rotation dispersion curve[4] of the

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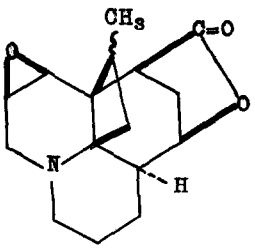
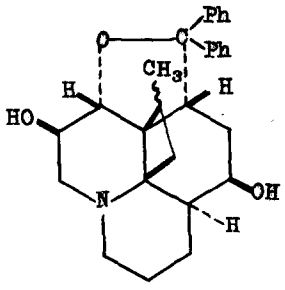
[3] Were the epoxide ring trans to the four-membered ring, a concerted intramolecular attack by the diphenyl carbinol in either configuration would be sterically impossible.

[4] For a summarizing reference, see Carl Djerassi, Optical Rotatory Dispersion. McGraw-Hill Company Inc., New York (1960).



I



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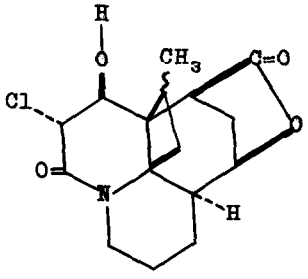
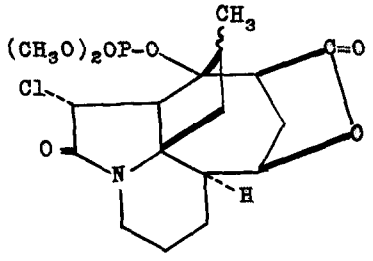


III



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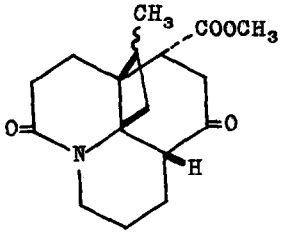
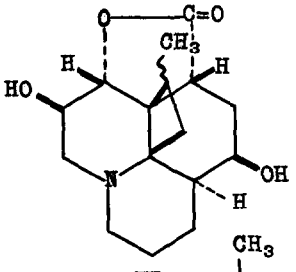
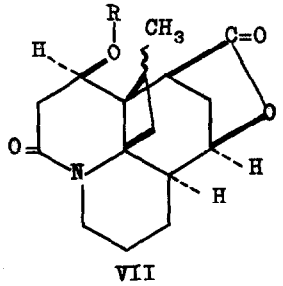


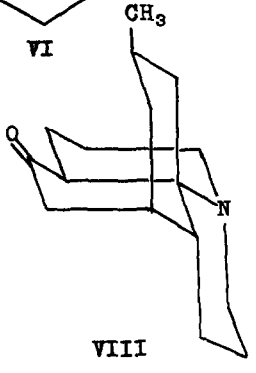
V



VI



VII



VIII

ketoester V[1]. It showed a negative rotation maximum at 322 mμ ($[\alpha] = -3{,}450^{\circ}$) and the application of the octant rule[4,5] to this result led to the absolute configuration given in formula V for this compound. We have checked this result by applying Hudson's lactone rule[6] to annotinine hydrate[1] (VI). The rotation of VI in methanol was $[\alpha]_D = -28.4^{\circ}$. After addition of one mole of KOH and hydrolysis of the lactone, the rotation changed to $[\alpha]_D = -21.6^{\circ}$. Thus, $\Delta[\alpha]_D = -6.8^{\circ}$. Both the lactone and the salt showed monotonous rotation dispersion curves with $\Delta[\alpha]$ negative in the entire region studied ($\Delta[\alpha]_{400\ m\mu} = -40^{\circ}$). This result is to be expected[6] if the absolute configuration is as shown in formula VI.

A third verification of the absolute configuration was accomplished by the application of the Prelog method[7] to the alcohol VII[1] (R=H). The phenylglyoxylic ester of this alcohol (VII, R= $-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-C_6H_5$) gave by treatment with methylmagnesium iodide an excess of negatively rotating atrolactic acid. This result is indicative of the absolute configuration portrayed in the formula VII. If it should appear that

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[5]We wish to thank Dr. Carl Djerassi for a discussion of the dispersion curves.

[6]B. Witkop, Experientia 12, 372 (1956).

[7]V. Prelog, Helv. Chim. Acta, 36, 308 (1953), and following papers.

the use of three independent methods for the deduction of the absolute configuration is excessive, we would point out that if we base the absolute configuration exclusively on the Hudson rule, then the Prelog method may be regarded as a new and convincing proof of the relative configuration of the hydroxyl in VII (R=H) and consequently of the oxide ring in annotinine. The application of the octant rule to the ketoester V may in turn be regarded as a confirmation of our previous deduction[1] that the asymmetric centre adjacent to the keto group in V has a configuration epimeric to the configuration of this centre in annotinine. Thus, we see that the agreement of various methods of absolute configuration determination is interdependent with the correct assignment of relative configurations to the derivatives used.

Recently, the structure[8] and stereochemistry[9] of lycopodine have been deduced and are represented in formula VIII. Since lycopodine occurs in the same plant as annotinine and the skeleta of the two alkaloids differ only by one carbon-carbon bond, it is very probable that both compounds have the same absolute configuration. We have

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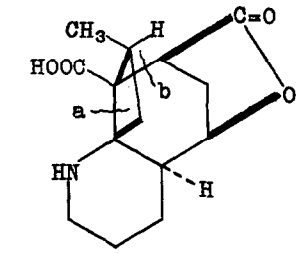
[8] W. A. Harrison and D. B. MacLean, Chem. and Ind. p. 261 (1960).

[9] F.A.L. Anet, Tetrahedron Letters 20, 13 (1960).

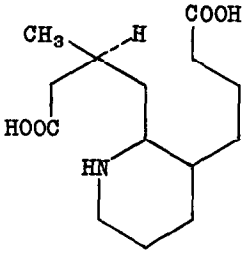
determined the rotation dispersion curve of lycopodine and found a rotation maximum at 307 mμ ($[\alpha] = +2,300$). The application of the octant rule[4,5] to this result leads to the absolute configuration of lycopodine shown in formula VIII, which is in agreement with the absolute configuration I for annotinine.

All these results show that annotinine must be represented by the absolute and relative stereostructure I in which the relative configuration of the methyl group is the only unknown feature. In order to determine this last detail we have decided to use the dehydrogenating rearrangement of the amino acid IX to the lactam carboxylic acid XI[1]. This rearrangement had been assumed[1] to proceed by the cleavages (a) and (b) via an intermediate with the gross skeletal structure X.

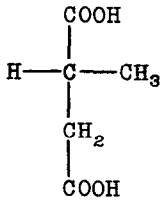
If the relative configuration of the methyl group is as pictured in formula IXa, then the absolute configuration of XI formed by this mechanism must be as given in formula XI. Conversely, the relative configuration of the methyl group as in IXb must, by this mechanism, result in the mirror image of XI. The absolute configuration of compound XI was easily determined by ozonolysis which gave D(+)



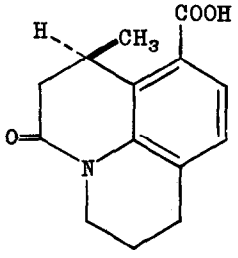
IXa



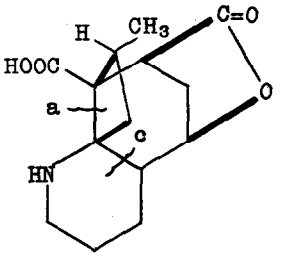
X



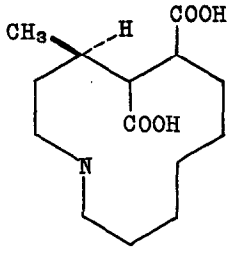
XII D(+)



XI



IXb



XIII

methylsuccinic acid (XII)[10] (m.p. 112°; IR identical with authentic sample $[\alpha]_D$ = +13.1° (ethanol)).

This result seemed to show that the absolute and relative stereostructure of the amino acid IX must be IXa.

In a brilliant X-ray analysis, Przybylska[11] confirmed our structure proposal[12] for annotinine and at the same time derived the relative stereochemistry for this compound. While there is complete agreement in all other respects, the X-ray work postulated that the methyl group of annotinine is cis to the lactone ring. Consequently, if we retain our absolute configuration assignment, the amino acid IX should be portrayed by the formula IXb.

This discrepancy cannot be reconciled and it means that one piece of information (or one assumption) is incorrect. One can, of course, argue that our chemical data are all unexceptional and that, consequently, the relative configuration of the methyl (as in IXb) determined

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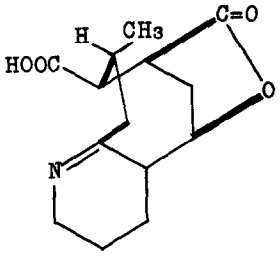
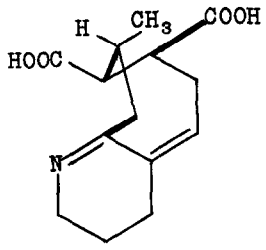
[10] c.f. J. A. Mills and W. Klyne in Progress in Stereochemistry, Edited by W. Klyne, Vol. I. Academic Press Inc., New York, pp. 177-204.

[11] M. Przybylska and L. Marion, Canad. J. Chem. 35, 1075 (1957); M. Przybylska and F. R. Ahmed, Acta Cryst. 11, 718 (1958).

[12] K. Wiesner, Z. Valenta, W.A. Ayer and C. Bankiewicz, Chem. and Ind. 1019 (1956); K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta, Chem. and Ind. 564 (1957).



XIV



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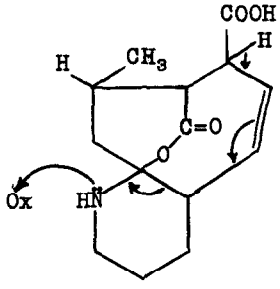
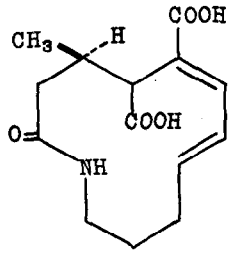
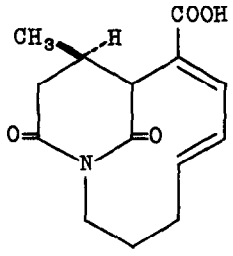


XVI



XVII



XVIII

by the X-ray study is incorrect. A careful analysis shows, however, that the mechanism IX→XI may be the source of the discrepancy. If the configuration of the amino acid is IXb (in agreement with X-ray) and the rearrangement proceeds by the breaks (a) and (c) via an intermediate with the gross structure XIII, the correct enantiomer XI yielding D(+) methylsuccinic acid XII on ozonolysis is obtained. This alternative gross mechanism is consequently compatible with all known chemical and crystallographic data. One of the possible detailed elaborations of this transformation is represented by the structures IXb→XIV→XV→XVI→XVII→XVIII→XI.