reflux temperature, a solution of 20.0 g. (0.12 mole) of diphenylacetylene in 100 ml. of xylene was added over a period of 1 hr. with vigorous stirring. The mixture was refluxed for 2 hr. after addition was complete, then filtered and concentrated. Hexane was added to dissolve by-products, and the crude product was filtered. Purification by recrystallization from toluene and vacuum sublimation yielded 1.2 g. of I (5% based on diphenylacetylene), m.p. 329–330° (lit.[1] 324–328°). *Anal.* Calcd. for $C_{32}H_{32}Si_2$: C, 81.4; H, 6.78. Found: C, 81.3; H, 6.71. The infrared spectral features and chemical properties agree with those reported by the earlier workers.[1,2] The analytical data eliminate from consideration the five-membered ring "silole" structure also suggested as a possibility for I.[5]

Determination of the molecular weight by the Rast method in camphor gives, as Vol'pin and his co-workers state,[2] a value of about 240. (The calculated mol. wt. for I is 236.) However, the Rast method is known to be unreliable for silicon compounds, and in this instance its use led directly to the incorrect structural assignment. The low solubility of I in many organic solvents makes determination of its molecular weight by usual methods difficult. Therefore, the technique of vapor phase osmometry, which has been found to give excellent results for other high molecular weight organosilicon compounds,[8] was employed. By this method we find the molecular weight of I to be 475 (average of six determinations ranging from 453 to 506, benzene solution). A dimeric structure is therefore indicated.

Structure III is favored over less-symmetrical alternatives because the tetra-*p*-tolyl analog of I, prepared in an analogous manner from di-*p*-tolylacetylene, shows only one sharp n.m.r. resonance peak for the tolylmethyl protons, at τ 7.70. An equivalent magnetic environment for the four methyl groups is indicated, consistent with a structure of type III. *Anal.* Calcd. for $C_{36}H_{40}Si_2$: C, 81.8; H, 7.62; mol. wt., 529. Found: C, 82.6; H, 7.71; mol. wt., 510 (average of three determinations in benzene).

Compound I and its tetra-*p*-tolyl analog are rather unreactive toward many of the usual reagents which add to carbon-to-carbon double bonds (Br_2 in CCl_4, $KMnO_4$ in acetone, H_2/Pt). The low reactivity can be attributed in part to steric hindrance to the attacking reagent and perhaps in part to delocalization of the olefinic π-electrons by participation of 3d-orbitals of silicon in the π-bonding.[9]

Acknowledgments.—This research was supported by a grant from the Air Force Office of Scientific Research of the Air Research and Development Command. The authors are grateful to Dr. F. Johnson for an extensive discussion of this problem.

(8) H. Gilman and G. L. Schwebke, *J. Am. Chem. Soc.*, **85**, 1016 (1963); "Advances in Organometallic Chemistry," Vol. I, in press.

(9) L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. J. Evans, and F. C. Whitmore, *J. Am. Chem. Soc.*, **76**, 1613 (1954); E. Larsson, *Chalmers Tek. Hogskol. Handl.*, **25**, 115 (1951).

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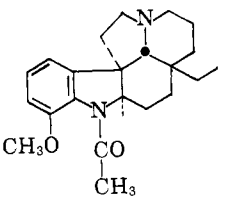
RECEIVED JUNE 3, 1963

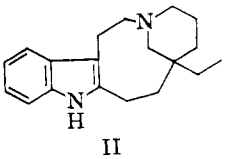
The Total Synthesis of *dl*-Aspidospermine and of *dl*-Quebrachamine

Sir:

The alkaloid aspidospermine, isolated from *Aspidosperma quebracho blanco*, has been shown to have structure I by a combination of degradative[1] and X-ray[2] evidence. In the short time since the determination of its structure, it has become apparent that aspidospermine is a member of a large class of indole alkaloids based on the same general skeleton, while others [*e.g.*, quebrachamine (II)] are simply related to the group.[3]



I



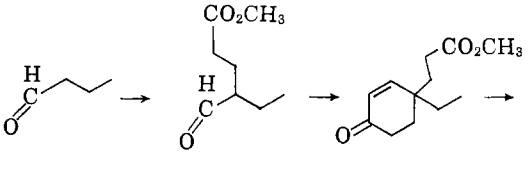
II

We have now succeeded in achieving the total synthesis of *dl*-aspidospermine, as well as that of *dl*-quebrachamine.

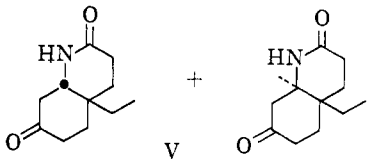
Reaction of the pyrolidine enamine of butyraldehyde with methyl acrylate, followed by aqueous acetic acid hydrolysis at room temperature, gave a 67% yield of methyl 4-formylhexanoate (III), b.p. 95–98° (10 mm.).[4] This was once more submitted to the enamine alkylation reaction, using the pyrolidine enamine of III and methyl vinyl ketone. Treatment of the reaction mixture, following initial condensation, with hot acetic acid resulted in cyclization to the desired 4-ethyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (IV), b.p. 105° (0.05 mm.) λ_{max}^{EtOH} 226 mμ (ϵ 12,300), in 48% yield.

Reaction of the unsaturated keto ester IV with aqueous ammonia at room temperature led to the bicyclic keto lactam V as a mixture of *cis* and *trans* epimers.

There was good reason to believe that with either the *cis* or the *trans* bicyclic ketolactam V, the Fischer indole synthesis[5] would involve the enamine tautomer of the phenylhydrazone with the double bond parallel to the ring junction[6] and would thus lead, even in the *cis* case, to the undesirable linear system of VI.



III IV



V

In fact, cyclization of the *o*-methoxyphenylhydrazones derived from V in the presence of hot acetic acid gave two crystalline tetracyclic lactams, m.p. 269–271° and m.p. 237°, in about 15% yield each. These lactams represent the two possible stereoisomers of the linear

(1) H. Conroy, P. R. Brooks, and V. Amiel, *Tetrahedron Letters*, **No. 11**, 4 (1959); G. F. Smith and J. T. Wróbel, *J. Chem. Soc.*, 1463 (1960).

(2) J. F. D. Mills and S. C. Nyburg, *ibid.*, 1458 (1960).

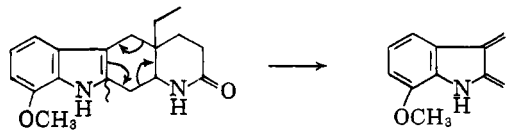
(3) *Cf.* K. Biemann, M. Friedmann-Spiteller, and G. Spiteller, *Tetrahedron Letters*, **No. 14**, 485 (1961); K Biemann and G. Spiteller, *ibid.*, **No. 9**, 299 (1961); C. Djerassi, H. Budzikiewicz, and J. M. Wilson, *ibid.*, **No. 6**, 235 (1962); M. Plat, J. Le Men, M.-M. Janot, J. M. Wilson, H. Budzikiewicz, L. Durham, Y. Nakagawa, and C. Djerassi, *ibid.*, **No. 7**, 271 (1962); C. Djerassi, L. D. Antonaccio, H. Budzikiewicz, J. M. Wilson, and B. Gilbert, *ibid.*, **No. 22**, 1001 (1962); H. K. Schnoes, A. L. Burlingame, and K. Biemann, *ibid.*, **No. 22**, 993 (1962); C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, and L. D. Antonaccio, *Tetrahedron*, **16**, 212 (1961); S. McLean, K. Palmer, and L. Marion, *Can. J. Chem.*, **38**, 1547 (1960); C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi, and R. A. Corral, *Experientia*, **18**, 113 (1962).

(4) Satisfactory analyses have been obtained for all key intermediates.

(5) The mechanism of the Fischer indole synthesis has been discussed by R. B. Carlin and E. E. Fisher, *J. Am. Chem. Soc.*, **70**, 3421 (1948).

(6) *Cf.* bromination and oxidation of 10-methyl-*cis*-2-decalone, M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

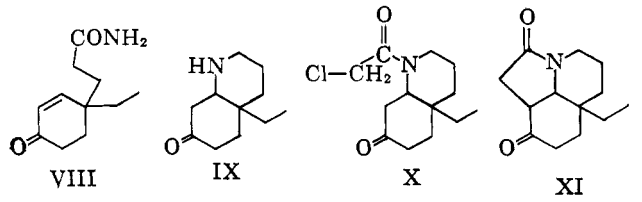
system VI, as was easily determined by the mass spectral fragmentation,[7] which in both cases showed a major peak at *m/e* 173, corresponding to the expected formation of the dimethylene indole VII. The rest of the fragmentation patterns was almost identical for the two substances.



VI VII

Steps were now taken to favor cyclization in the non-linear sense.

Ketalization of the cyclohexenone IV, followed by reaction with aqueous ammonia, gave the crystalline ketal amide VIII, m.p. 64–66°, which upon reduction with lithium aluminum hydride, followed by successive treatment with aqueous acid and base, gave the desired 10-ethyl-7-ketodecahydroquinoline (IX), m.p. 47–50°. Advantage was then taken of the relative position of the amino group in order to introduce the third ring on the proper side of the carbonyl group. Acylation with chloroacetyl chloride led to the chloroacetamide X, m.p. 75–77°, which was smoothly cyclized to the tricyclic ketolactam XI, m.p. 116–118°, by means of potassium *t*-butoxide in benzene.

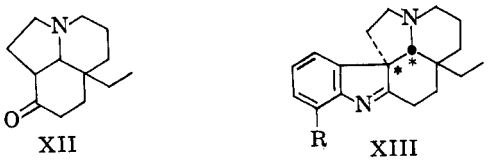


VIII IX X XI

The Fischer indole cyclization with the *o*-methoxyphenylhydrazone of XI[8] gave only neutral (indole) substances after heating with acetic acid, showing that the additional substitution next to the carbonyl group was not sufficient to lead to angular cyclization. The situation was expected to be considerably more favorable in the related tricyclic ketoamine XII: two of the three trigonal atoms present in the five-membered ring in the transition state for the desirable cyclization become tetrahedral with the reduction of the amide link.

The keto-amine XII was easily prepared by ketalization, lithium aluminum hydride reduction, and regeneration of the ketonic function. It was obtained as an oil, b.p. 110 ± 5° (0.1 mm.), and was characterized as its picrate, m.p. 157–160°.

We were now ready to perform the crucial last stages of the total synthesis.[9] Cyclization of the *o*-methoxyphenylhydrazone of XII with hot acetic acid, followed by lithium aluminum hydride (to convert the indolenine, XIII, R = OCH_3, into the indoline), and acetylation with acetic anhydride gave a crude material from which



XII XIII

crystalline *dl*-aspidospermine, m.p. 195–195.5°, was readily obtained.

The identity of the synthetic material as *dl*-aspidospermine was rigorously established by the superposability of the infrared and mass spectra[10] with those of the natural alkaloid.

Cyclization of the phenylhydrazone of XII to a mixture containing XIII, R = H, followed by reductive cleavage with potassium borohydride[11] gave *dl*-quebrachamine, m.p. 113–116° (reported[12] m.p. 112–115°), identical by infrared analysis, thin layer chromatography, and mass spectroscopy[10] with authentic material.[13]

(7) We wish to thank Prof. C. Djerassi for determining and interpreting these mass spectra.

(8) The Fischer indole synthesis toward the junction between two rings was first reported by V. Georgian, *Chem. Ind.* (London), 1124 (1957).

(9) The stereochemistry of the various bicyclic and tricyclic intermediates which are described in this communication is left open at this point. This stereochemical ambiguity is not operationally significant here: the indolenine XIII is formed under conditions which would lead to equilibration at the two centers marked by asterisks *via* reverse Mannich reaction (*cf.* G. F. Smith and J. T. Wróbel, *J. Chem. Soc.*, 792 (1960)). The most stable relative arrangement of the three asymmetric centers of XIII woud thus be expected to result whatever the stereochemistry of the intermediates or the detailed course of the indolenine cyclization process. There are good *conformational* arguments that this most stable arrangement should coincide with that of dehydroaspidospermine (XIII, R = OCH_3) and there is some *experimental* evidence in support of this conclusion (private communication from Dr. G. F. Smith).

(10) We are very grateful to Professor K. Biemann for this comparison.

(11) *Cf.* K. Biemann and G. Spiteller, ref. 3.

(12) F. Walls, O. Collera, and A. Sandoval, *Tetrahedron*, **2**, 173 (1958).

(13) This work was supported by grants from the National Institutes of Health and the National Science Foundation.

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RECEIVED AUGUST 9, 1963

Synthesis of Peptide Polymers with Repeating Sequences

Sir:

We have now succeeded in developing a general route to an important new class of peptide polymers having known repeating sequences in chains of random length. These polymers should prove of great value in working out relationships between structure and physical, chemical, and biological properties. There is also the not entirely remote prospect that appropriately constituted polyfunctional polymers may exhibit catalytic activity.

Polymers with repeating sequences have, of course, been investigated before.[1] The pronounced ease of ring closure to cyclic di- and hexapeptides as well as to other ring sizes[2] has, however, raised questions about practical routes to such polymers. Furthermore, the efficient incorporation of amino acids having functional side chains has received little attention.

We have found that the active ester method[3] is suitable for preparing (L-Asp-(OCH_3)-Gly-Gly)$_n$[4] with average degrees of polymerization which we estimate to be 25 (75 amino acid residues, wt. av. mol. wt. 12,000) or more. A concentrated solution of HBr·H-Asp-(OCH_3)Gly-Gly-ONP of high analytical purity (C, H, N, Br, $-OCH_3$, –ONP all agree closely with theory[6]) in dimethyl sulfoxide, dimethylformamide, or N-methylpyrrolidone was treated with the exact

(1) Previous work has been summarized in the admirable review by E. Katchalski and M. Sela, *Advan. Protein Chem.*, **13**, 449 456, (1958). *Cf.* also C. H. Bamford, H. Elliott, and W. E. Hanby, "Synthetic Polypeptides," Academic Press, New York, N. Y., 1956, p. 26.

(2) These syntheses have been elegantly pursued by R. Schwyzer and others: R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **41**, 2186, 2190 (1958), and references therein.

(3) M. Bodanszky, *Nature*, **175**, 685 (1955); B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 373 (1957).

(4) The following abbreviations are used; Asp, Gly, Phe are the standard amino acid abbreviations[6]; Z = benzyloxycarbonyl, NP = *p*-nitrophenyl; Asp(OCH_3) is the β-methyl ester of aspartic acid; Asp(imide) is the α-aminosuccinimide group; DP = degree of polymerization, *i.e.*, the number of tripeptide units.

(5) *Cf.*, *e.g.*, M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 465 (1957).

(6) Microanalyses by Dr. F. Pascher, Bonn, and by Mrs. L. Ross, FSU. Techanical assistance by Mr. E. Heimer.