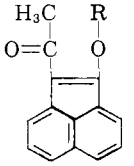
31–32° (pentane); split carbonyl at 5.80 and 5.83μ and the strong band at 9.22–9.30 μ (CCl_4); Found: C, 44.4; H, 7.5; P, 9.8; mol. wt., 297 (calcd. 296). Hydrolysis of crystalline oxyphosphorane IIIA gave crystalline diketol IVA, exclusively (over 95% yield of recrystallized IVA).

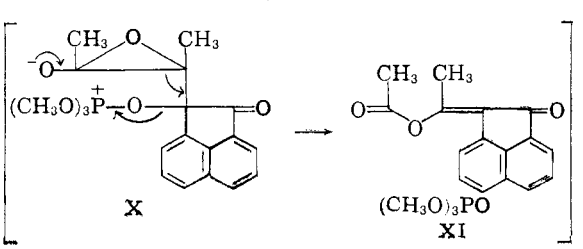
The pentaalkoxyphosphorane structure III is based mainly on a comparison with the unsaturated oxyphosphorane I. (1) The large P^{31} n.m.r. shifts to high field of the phosphoric acid reference (+ 51 for III and + 53 p.p.m. for I) suggest comparatively large shielding of the phosphorus nucleus in III and I, inconsistent with the phosphonium group of open dipolar structures. It should be noted that the dipolar structure of I should show strong carbonyl absorption in the infrared, contrary to our observations[2] with pure 1:1 adduct I. (2) The infrared absorption in the CH_3OP region is very similar in III and I (as well as in VII): there is a very strong and broad band at 9.2–9.35 μ, which is considerably lower than the normal methyl phosphate ester absorption.

The 1:1 adduct I (10.1 g.) and acenaphthenequinone VI (8.7 g.) were allowed to react for 10 hours at 20° in methylene chloride (750 ml.), under nitrogen. The solvent was removed *in vacuo*, the crystalline residue was dissolved in carbon tetrachloride (200 ml.); 0.54 g. of naphthalic anhydride was filtered-off. Evaporation *in vacuo* gave 18 g. of crystalline 2:1 adduct VII. After recrystallization from cyclohexane, VII had m.p. 95–96°; strong bands at 5.76, 5.80 (shoulder), 9.22–9.30 μ (CCl_4). Calcd. for $C_{19}H_{21}O_7P$: C, 58.2; H, 5.4; P, 7.9. Found: C, 58.1; H, 5.0; P, 7.9. VII and III were sensitive to moisture.

When a solution of the 2:1 adduct VII in methanol was heated for 30 minutes, a rearrangement occurred. Three products were isolated: trimethyl phosphate, methyl acetate and 1-acetyl-2-acenaphthenone (75% yield based on acenaphthenequinone VI) written as the probable enol VIII. VIII is yellow, m.p. 112–113° (methanol); bands at 6.05 and 6.20μ (CH_2Cl_2); calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8; found: C, 79.4; H, 4.9. VIII gives a yellow methyl ether IX (with diazomethane); m.p. 150–151° (methanol); bands at 5.92 and 6.20 μ (CH_2Cl_2); calcd. for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4; found: C, 80.1, H, 5.2. The β-diketone VIII was cleaved to acenaphthenone by dilute alkali.



VIII, R = H
IX, R = CH_3



X XI

A possible mechanism[5] for the rearrangement of the 2:1 adduct VII to an enol-acetate XI, with concomitant *ejection of phosphate ester*, is indicated in formula X. The β-diketone VIII and methyl acetate would result from the enol-acetate XI and methanol by a transesterification.

(5) H. F. von Pechmann, *Ber.*, **21**, 1421 (1888). Our experience with the Zn–H_2SO_4 reduction of biacetyl will be described elsewhere.

(6) Alfred P. Sloan Fellow, 1961–1963.

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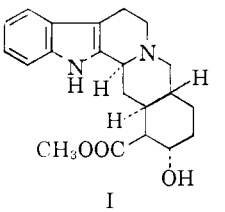
RECEIVED DECEMBER 29, 1961

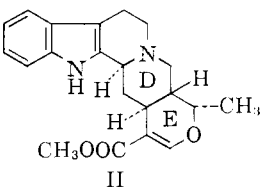
THE CONVERSION OF TETRAHYDRO-β-CARBOLINE ALKALOIDS INTO OXINDOLES. THE STRUCTURES AND PARTIAL SYNTHESES OF MITRAPHYLLINE AND RHYNCOPHYLLINE[1]

Sir:

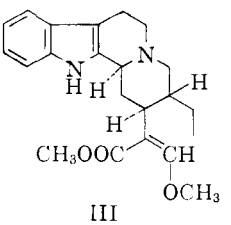
The relationship between indole and oxindole alkaloids often has been discussed.[2]



I



II



III

Conversion of certain oxindole alkaloids into known indole alkaloids or *vice versa* would enable the detailed stereochemistry of the former to be elucidated. We now wish to report the conversion of yohimbine (I) into its oxindole and the preparation of mitraphylline and rhyncophylline from ajmalicine[3] (II) and dihydrocorynantheine (III), respectively.

Yohimbine (I) was transformed into a 50:50 mixture of epimeric C_7 chloroindolenines (γ_{max} 1710 $cm.^{-1}$, 1595 $cm.^{-1}$, no NH; λ_{max} 282 mμ) by the action of tertiary butyl hypochlorite.[4] Meth-

(1) Presented at the New York, North Jersey Meeting-in-Miniature, New York, January 22, 1962.

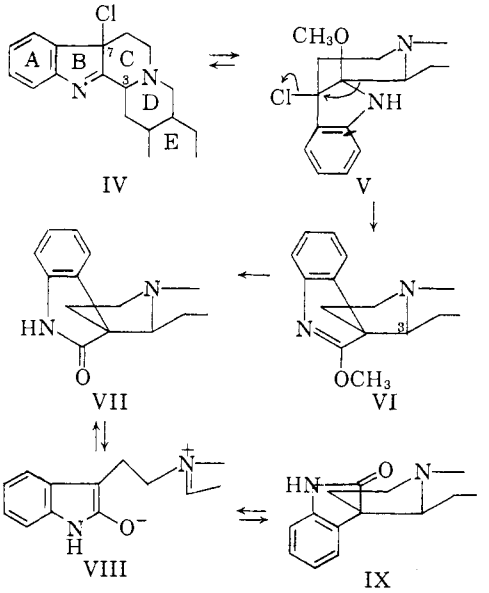
(2) (a) B. Witkop, *Bull. Soc. Chim. France*, 423 (1954); (b) E. E. van Tamelen, K. V. Siebrasse and J. B. Hester, *Chem. and Ind.*, 1145, (1956); (c) T. Nozoye, *Chem. Pharm. Bull.*, **6**, 300, (1958); (d) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharya, *J. Am. Chem. Soc.*, **81**, 3863 (1959).

(3) The conversion of ajmalicine into mitraphylline has also been accomplished by J. Shavel and H. Zinnes, *ibid.*, **84**, 1320 (1962).

(4) W. O. Godtfredson and S. Vangedal, *Acta. Chem. Scand.*, **10**, 1414 (1956), employed this reagent to prepare Δ^3 compounds of the yohimbine class. Only deserpidine yielded a crystalline isolatable chloro compound, which was assigned an incorrect structure. Our observations provide proof of the 7-chloroindolenine structure proposed by J. E. Saxton (R. H. Manske, "The Alkaloids," Vol. VII,

anolysis of the chloroyohimbines (IV) gave in 40% yield the imido ester (VI)[5] (m.p. 198–199°, $[\alpha]^{26}D$ + 109°; ν_{max} 1708, 1582 cm.$^{-1}$) which on hydrolysis in refluxing aqueous acetic acid gave two oxindoles (VII and IX). Yohimbine oxindole B[6] (IX) (m.p. 222–224°, $[\alpha]^{26}D$ −9°; γ_{max} 1705, 1620 cm.$^{-1}$ λ_{max} 251–254 mμ (log ε 3.86); pK_a 6.4) was obtained crystalline directly but yohimbine oxindole A (m.p. 168–170°, $[\alpha]^{24}D$ + 59°; γ_{max} 1714, 1623 cm.$^{-1}$; λ_{max} 251–254 mμ (log ε 3.83); pK_a 5.3) was obtained crystalline only after preparative thin layer chromatography.[7]

Either oxindole equilibrated to the same mixture in refluxing aqueous acetic acid, a behavior characteristic of the naturally occurring oxindoles.[8] Equilibration also could be achieved by refluxing pyridine, but the position of equilibrium differed. In acetic acid oxindole B predominated, in pyridine oxindole A, and this relationship was shown to exist between the natural oxindoles and their isomers. The mechanism of this equilibration has been discussed previously.[2d,8] Chlorination and methanolysis of ψ-yohimbine gave only a 4% yield of the imido ester (VI) obtained from yohimbine; therefore, as expected, the migrating group (C_3) moves with predominant retention of configuration. Thus the hydrogen atom at C_3 in VI is α. Hydrolysis of the methiodide of the imido ester gave the methiodide of oxindole A, hence the C_3 hydrogen in oxindole A itself is α.



The p.m.r. spectra of both oxindoles show that the carbomethoxy group is strongly shielded by the aromatic ring and approximately to the same extent in both[9] (14 c.p.s. in oxindole A, 13 c.p.s. in oxindole B, relative to yohimbine).

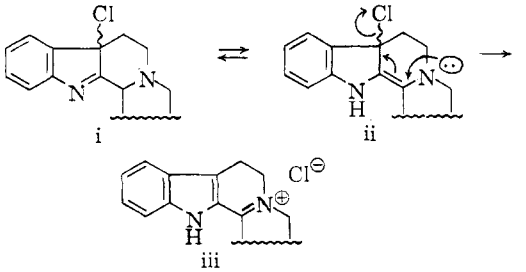
Shielding effects are strongly dependent on both the distance from and the inclination of the aromatic ring to the shielded group.[10] Therefore, the transformation of oxindole A into oxindole B cannot involve a change in the stereochemistry between rings C and D, and in oxindole B the hydrogen at C_3 must be α. Oxindole B must be represented by IX as this isomer would be expected to be the stronger base, due to stabilization of the conjugate acid by hydrogen bonding to the lactam carbonyl.

Methyl isodeserpidate (D E rings *cis*) on chlorination and methanolysis gave a poor yield (5%) of an imido ester (VI). The chlorination mixture consisted predominantly of one compound and the desired epimer (IV) probably was the minor constituent. It was therefore surprising that ajmalicine, which had been thought to be *cis* at rings D/E[11] paralleled the behavior of yohimbine, giving an imido ester VI (m.p. 196–197°; γ_{max} 1700, 1618, 1590 cm.$^{-1}$; λ_{max} 239–240 mμ (log ε 4.19)) in 40% yield. Hydrolysis of this imido ester gave a product identical with natural mitraphylline.[12]

The properties (pK_a differences, rotations chromatographic behavior, and position of equilibrium in acetic acid and pyridine) of mitraphylline and iso-mitraphylline were completely analogous to those of yohimbine oxindoles B (IX), and A (VII), respectively, and therefore we may assign structures analogous to IX and VII with the rings D/E probably *trans*. This tentative conclusion was in complete agreement with the recent demonstration by a physical method[13] that rings D and E of ajmalicine (II) were *trans* as well as the complete stereochemistry of II deduced from its p.m.r. spectrum.[14] In a similar manner dihydrocorynantheine[15] was chlorinated to a mixture of chloroindolenines, methanolyzed to the glassy imido ester (γ_{max} 1700, 1648, 1592 cm.$^{-1}$) which on hydrolysis gave rhyncophylline (IX).[16]

Rhyncophylline and isorhyncophylline were com-

p. 90) for chlorodeserpidine. Conversion to Δ^3 compounds under acid catalysis may be represented as i ⇄ ii → iii.



(5) Satisfactory analytical data have been obtained for all the compounds described in this note, all rotations were measured in $CHCl_3$; pK_a's were determined in 80% methylcellosolve water, infrared spectra in chloroform, and ultraviolet spectra in ethanol.

(6) Nomenclature used describes the stronger base as B and the weaker base as A, in a pair of isomeric oxindoles, in accord with the literature.[2c]

(7) This technique has been described by B. P. Korzun and L. Dorfman in a paper presented before The Pharmaceutical Manufacturers Association Meeting in Colorado Springs, October, 1961.

(8) J. C. Seaton, M. D. Nair, O. E. Edwards and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960).

(9) J. N. Shoolery, Mellon NMR Bulletin, in press.

(10) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(11) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(12) We are indebted to Drs. L. Marion and N. Neuss for authentic samples of this alkaloid and to the latter for X-ray powder diagrams of the natural and synthetic bases.

(13) M. Shamma and J. B. Moss, *J. Am. Chem. Soc.*, **83**, 5038 (1961).

(14) E. Wenkert, B. Wickberg and C. L. Leicht, *J. Am. Chem. Soc.* **83**, 5037 (1961).

(15) We are indebted to Prof. M.-M. Janot for a sample of corynantheine which made this transformation possible.

(16) Compared with an authentic sample from Dr. D. F. Dickel,

pletely analogous in behavior to yohimbine oxindoles B and A, and may be assigned structures of the type IX and VII, respectively.

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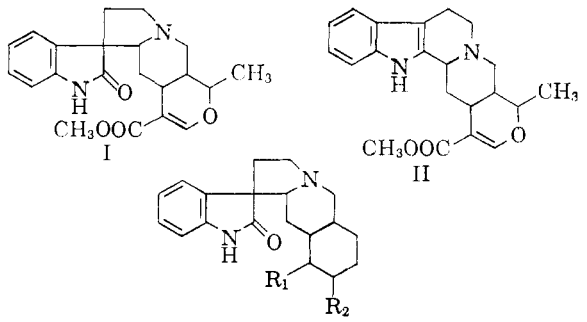
OXINDOLE ALKALOIDS. I. OXIDATIVE-REARRANGEMENT OF INDOLE ALKALOIDS TO THEIR OXINDOLE ANALOGS

Sir:

Mitraphylline, an alkaloid occurring in *Mitragyna* species, has been assigned the structure I[1] without stereochemical assignments. It is an oxindole ana-



I

II

III, R_1 = COOMe, R_2 = OH
IV, R_1 = R_2 = H

log of ajmalicine[2] (II) whose stereochemistry[3,4] has been well established except for the configuration of the C-19 methyl group. Recently the total synthesis of *dl*-ajmalicine[5] has been reported by a method which the authors claim will permit the establishment of the complete stereochemistry of ajmalicine and other hetero-ring E indole alkaloids.

We wish to report the facile preparative conversion of ajmalicine to mitraphylline and isomitraphylline[6] (I) by an oxidative-rearrangement procedure of general utility for the conversion of indole alkaloids to their oxindole analogs.[7] Thus our results confirm the structural assignment of mitraphylline and, in addition, show that mitraphylline and ajmalicine have the same stereochemistry in rings D and E. This represents the first experimental proof that the universality of the C-15 α-hydrogen configuration[8] extends to the oxindole alkaloids since this configuration has been shown to be present in ajmalicine.[8]

Ajmalicine, when oxidized by *tert*-butyl hypochlorite,[9] gave a residue which when refluxed in aqueous methanolic solution adjusted to pH 6 gave a mixture of mitraphylline and isomitraphylline. Recrystallization from methanol gave mitraphylline (I), m.p. 265–266°, $[\alpha]_D$ −38° (0.1 *N* HCl). Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.60. Found: C, 68.20; H, 6.72; N, 7.63. Comparison of our material with authentic mitraphylline[10] revealed that the two compounds gave no mixed melting point depression, behaved identically on paper chromatography, and had superimposable ultraviolet and infrared spectra. The methanol filtrate afforded isomitraphylline (I) which was isolated as the picrate, m.p. 207–209°.[11] Calcd. for $C_{27}H_{27}N_5O_{11}$: C, 54.27; H, 4.56; N, 11.72. Found: C, 54.54; H, 4.58; N, 11.48. Examination by mixture melting point, paper chromatography, and infrared spectra with authentic isomitraphylline picrate[11] showed them to be identical. We have also obtained isomitraphylline picrate from our "synthetic" mitraphylline by equilibration in refluxing pyridine.[6]

Yohimbine, similarly rearranged, gave its epimeric oxindole analogs. The slower moving epimer (III) (R_f = 0.16) had m.p. 214–216° dec., $[\alpha]_D$ + 17 (95% EtOH), $\lambda_{max}^{95\%\ EtOH}$ 251 mμ (ε 7220). Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.08; H, 7.08; N, 7.56. Found: C, 68.02; H, 7.21; N, 7.43. The hydrochloride had m.p. 231–235° dec., $[\alpha]_D$ + 25 (H_2O). Calcd. for $C_{21}H_{27}N_2O_4Cl$: C, 61.98; H, 6.69; N, 6.89; Cl, 8.71. Found: C, 61.92; H, 6.86; N, 7.05; Cl, 8.91. The faster moving epimer (III) (R_f = 0.41) was isolated as the hydrochloride, m.p. 231–235° dec., $[\alpha]_D$ +101 (H_2O), $\lambda_{max}^{95\%\ EtOH}$ 251 mμ (ε 6800). Found: C, 61.80; H, 6.88; N, 6.64; Cl, 8.86.

Yohimbane on treatment with *tert*-butyl hypochlorite gave two epimeric chloro derivatives. The negatively rotating epimer had m.p. 256–268° dec., $[\alpha]_D$ −72 (CH_2Cl_2), λ_{max}^{EtOH} 226 mμ (ε 21,400), 266 mμ (ε 2200 sh), 292–296 mμ (ε 2800). Calcd. for $C_{19}H_{23}N_2Cl$: C, 72.48; H, 7.36; N, 8.90; Cl, 11.26. Found: C, 72.69; H, 7.42; N, 8.96; Cl, 11.37. The positively rotating epimer had m.p. 256–268° dec., $[\alpha]_D$ + 84 (CH_2Cl_2), λ_{max}^{EtOH} 224 mμ (ε 21,800), 266 mμ (ε 2400), 285–293 mμ (ε 2600). Found: C, 72.52; H, 7.14; N, 9.00; Cl, 11.53.

Subjecting the crystalline unfractionated mixture of chloroyohimbanes to the hydrolytic procedure gave the mixture of epimeric oxindole analogs.

(1) For references see J. C. Seaton, R. Tondeur, and L. Marion, *Can. J. Chem.*, **36**, 1031 (1958).

(2) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown, and Co., Boston, Mass., 1957, Chapter 3, and references contained therein.

(3) N. Neuss and H. E. Boaz, *J. Org. Chem.*, **22**, 1001 (1957).

(4) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.* 1613 (1958).

(5) E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.*, **82**, 2594 (1961).

(6) J. C. Seaton, M. D. Nair, O. E. Edwards and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960), prepared this C_4 epimer of mitraphylline by refluxing the latter in pyridine. According to the numbering system of these authors the C_4 position of the oxindole alkaloids would correspond to the C_3 position of the indole alkaloids.

(7) Other related rearrangements of indoles to give oxindoles have been reported: W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, **123**, 676 (1923); S. G. P. Plant and R. Robinson, *Nature*, **165**, 36; (1950); E. E. van Tamelen, K. V. Siebrasse, and J. B. Hester, *Chem. Ind.*, 1145 (1956); A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4748 (1958); W. B. Lawson, A. Patchornik, and B. Witkop, *ibid.*, **82**, 5918 (1960); W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).

(8) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959).

(9) This differs from the method of W. O. Godftredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1959), in that the hydrogen chloride treatment of the residue is omitted.

(10) Ref. 1 reports constants for naturally occurring mitraphylline: m.p. 275–276°, $[\alpha]^{24}D$ −39° (0.1 *N* HCl). A sample of this mitraphylline, graciously supplied to us by Dr. Leo Marion, was found to melt at 265–266° in our apparatus. All our melting points are uncorrected.

(11) Ref. 6 reports m.p. 223° dec. for isomitraphylline picrate. The sample of this substance supplied to us by Dr. Marion had m.p. 209–211° in our apparatus.