The Preparation and Optical Rotary Dispersion of 7-Benzyl-7H-yohimbanes

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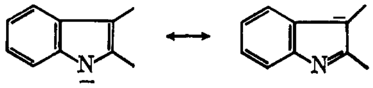
1-Benzylyohimbane and both epimeric 7-benzyl-7H-yohimbanes were prepared. The structure, configuration, and conformation were determined from ultraviolet, infrared, pmr, and mass spectra. It was shown that, in agreement with literature reports on aspidospermine- and strychnine-type alkaloids and some 7-acyloxy-7H-yohimbanes, the 7α configuration is associated with a positive Cotton effect, and the 7β configuration being associated with a negative Cotton effect. The optical rotary dispersion curves of the two 7H epimers were found to very nearly bear a mirror-image relationship to each other.

Recent literature reports[1,2] indicate that the Cotton effect of compounds containing the indolenine chromophore is controlled by the substituents at C-3, presumably because of their proximity to the chromophoric group. In the course of steric correlations in the field of aspidospermine- and strychnine-type alkaloids, Klyne, *et al.*,[1] have shown that the α configuration[3] is associated with a positive Cotton effect and the β configuration is associated with a negative Cotton effect. Similarly, using X-ray crystallographic analysis, Finch, *et al.*,[2] have found that the same correlation applies to 7α-acetoxy-7H-yohimbine and related compounds. In addition, study[2] of the 7-chloro-7H-yohimbane[4] epimers has revealed that the optical rotary dispersion curves of these compounds bear a mirror-image relation to each other, despite conformational differences and the presence of several other asymmetric centers. Although analogous antipodal relationships of ORD curves have been observed frequently in the field of keto steroids and other cyclohexanone derivatives,[5] the 7-chloro-7H-yohimbanes are the only epimers to have been studied in the yohimbane field, and their configurations at C-7 have not been established.

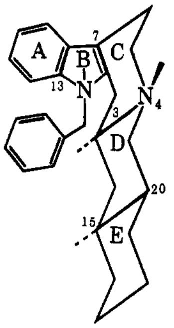
The object of the present investigation was to determine whether 7 substituents of lesser polarity, in particular those involving a C–C bond, would show analogous effects on the optical rotary dispersion, and if the above described[1] correlation of the indolenine C-3 configuration with the sign of the Cotton effect is valid for a representative of the 7-alkyl-7H-yohimbane class.

The synthetic scheme for the introduction of the desired angular substituent was based on the ambident nature of the indole anion[6] (I). Alkylations at indole C-3, though not previously described for yohimbanes, are well known in the indole[7] and carbazole[8] fields.

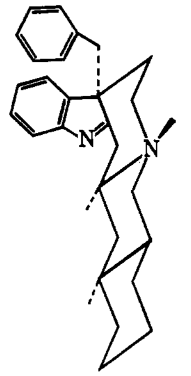


I

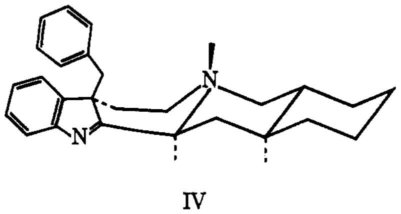
When yohimbane was allowed to react with sodium amide and benzyl bromide in liquid ammonia, three products were obtained which were separated by fractional crystallization. The major component [mp 184–186.5°, R_f (tlc) 0.7] had ultraviolet absorption bands typical of a 1-alkylyohimbane[9] [λ_{max}^{EtOH} 227 mμ (ϵ 35,000), 284 (8000), 292 sh (7000)] and was assigned the 1-benzylyohimbane structure II. The infrared and pmr spectra were in agreement with this assignment [ν_{max}^{Nujol} 690, 720 (monosubstituted benzene), 740 cm^{-1} (1,2-disubstituted benzene), no NH bands; $\delta_{110°}^{DMSO}$ singlet at 5.37 ppm (PhCH$_2$N<)].



II



III



IV

The remaining two substances (A, mp 166–168.5°, R_f (tlc) 0.55 and B, mp 142–144°, R_f (tlc) 0.82) were isomeric with II. Their ultraviolet and infrared spectra [λ_{max}^{EtOH} 257 mμ (ϵ 6100) for A and 263 (6100) for B; ν_{max}^{Nujol} 1580 cm^{-1} (PhN=C<), identical in both isomers], which pointed to the presence of the indolenine

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(1) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *Helv. Chim. Acta*, **48**, 443 (1965).

(2) N. Finch, C. W. Gemenden, I. Hsiu-Chu Hsu, A. Kerr, G. A. Sim, and W. I. Taylor, *J. Am. Chem. Soc.*, **87**, 2229 (1965).

(3) The absolute configurations of yohimbine and strychnine being known, the prefixes α and β have the meaning ascribed to them in steroids; see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 1.

(4) J. Shavel and H. Zinnes, *J. Am. Chem. Soc.*, **84**, 1318 (1962).

(5) C. Djerassi, "Optical Rotary Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 84.

(6) See for example: M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, **No. 18**, 1183 (1963).

(7) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 83.

(8) (a) Y. Kanaoka, Y. Ban, O. Ynemitsu, K. Irie, and K. Miyashita, *Chem. Ind.* (London), 473 (1965); (b) M. Nakazaki and S. Isoe, *Nippon Kagaku Zasshi*, **76**, 1159 (1955); *Chem. Abstr.*, **51**, 17877*f* (1957); (c) M. Nakazaki, *Bull. Chem. Soc. Japan*, **34**, 334 (1961); *Chem. Abstr.*, **55**, 16511*f* (1961).

(9) The ultraviolet spectrum of 1-methylyohimbane, prepared according to B. Witkop [*J. Am. Chem. Soc.*, **75**, 3361 (1953)] showed λ_{max} 229 mμ (ϵ 38,000), 285 (7500), 292 sh (7000); yohimbane itself has 225.5 mμ (ϵ 34,500), 282 (7250), 289 sh (6000).

nucleus,[10] led to the assignment of the 7-benzyl-7H-yohimbane structure to both compounds. The presence of strong Bohlmann bands in the 2700–2800-cm^{-1} region[11] in the infrared (chloroform solution, CaF_2 prism) indicated that both A and B were in the *trans*-quinolizidine conformation.[12] An attempt at assignments of configuration from rates of quaternization[13] failed when it was found that the rates of methiodide formation for A and B are within 10% of each other.[14] However, examination of pmr spectra of A and B revealed significant differences which were sufficiently characteristic to serve as the basis of configurational assignments. The spectrum of A, (Figure 1) similar to that of yohimbane, shows no signals below 3.2 ppm (other than the aromatic bands) whereas two bands at 3.88 and 3.65 ppm are displayed by the spectrum of B (Figure 2) in addition to bands at 3.20 and 2.97 ppm superimposed on other signals. These four bands constitute an AB quartet centered approximately at 3.42 ppm. While the benzylic protons in both possible configurations, III and IV, are chemically nonequivalent,[15] their magnetic nonequivalence[16] might be expected to be much more important in IV than in III because of the greater proximity (2.3 *vs.* 3.3 A as measured in Dreiding models) of the nitrogen, in the boat-shaped C ring of IV, to one of the benzylic hydrogens. For the same reason, this particular hydrogen should resonate at lower field in IV as compared to III; it is known in other instances[17] that spatial proximity of a proton to nitrogen causes a downfield shift.[18] Therefore, configuration and conformation III should be assigned to compound A, configuration and conformation IV to compound B. Evidence in support of these assignments was obtained from examination of the mass spectra. Since IV, in either of it's conformations,[12] is less stable than III, the ion of IV should decompose faster causing a smaller peak at *m/e* 370.[19] Accordingly, the intensity of the molecular ion peak of III is 7.9% Σ_{80} whereas for IV this intensity is 4.8% Σ_{80}. The same consideration applies to fragments resulting from loss of the benzyl group. The intensities of the M − 91 peaks are 34% Σ_{80} for III and 17.3% Σ_{80} for IV.

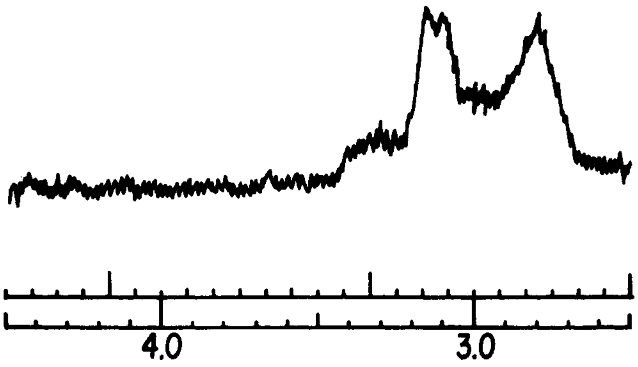

Figure 1.—Pmr spectrum of 7α-benzyl-7H-yohimbane (2.5–4.5-ppm section).

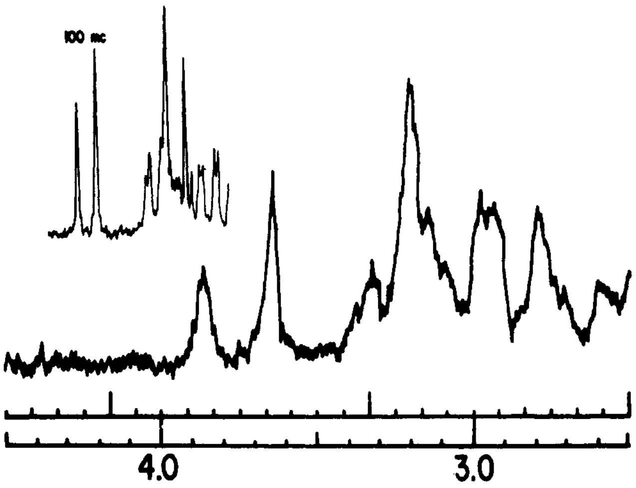

Figure 2.—Pmr spectrum of 7β-benzyl-7H-yohimbane (2.5–4.5-ppm section).

On determination of the optical rotary dispersion spectra of III and IV, it was found that, in agreement with the above discussed correlation,[1] the α epimer (III) gives rise to a positive Cotton effect and the β epimer (IV) to a negative one. The wavelengths and molecular rotations (Φ) of the peaks and troughs are as follows: for III, peak 288 mμ (+5187°), trough 256 mμ

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[10] Absorption bands in these regions are characteristic of the anilino group in general [R. B. Barnes, R. C. Gore, R. W. Stafford, and V. Z. Williams, *Anal. Chem.*, **20**, 402 (1948); H. W. Thompson, *J. Chem. Soc.*, 328 (1948)] and of indolenines in particular [B. Witkop, *J. Am. Chem. Soc.*, **72**, 614 (1950); J. B. Patrick and B. Witkop, *ibid.*, **72**, 633 (1950); **73**, 713 (1951); **73**, 1558 (1951)]. For example, in the last references λ_{max} 257 mμ (ϵ 6150) and γ_{max} *ca.* 1595 cm^{-1} is reported for 11-methyltetrahydrocarbazolenine.

[11] F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *Chem. Ber.*, **91**, 2157 (1958); E. Wenkert and D. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956); W. E. Rosen, *Tetrahedron*, 481 (1961).

[12] The *trans*-quinolizidine conformation could not be assumed *a priori* for the compound subsequently assigned configuration IV since the possibility existed that an inversion would take place at N-4 to give the *cis*-quinolizidine all-chair conformation, in order to avoid the half-boat ring C form required by the *trans*-quinolizidine conformation. However, the preference for the boat conformation is not really surprising since the alternate chair would contain a *syn*-axial–axial methylene–methylene interaction in addition to the instability of the *cis*-quinolizidine ring fusion, and achievement of the boat conformation is less costly, energywise, in a piperidine than in a cyclohexane: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 38, 244.

[13] The rates of quaternization have been determined by a gas chromatographic measurement of consumption of CH_3I. The details of this study will be described in a publication by F. S. Hom.

[14] The rate of quaternization generally reflects the steric environment of the nitrogen [M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963)], therefore the more stericly hindered quinolizidine nitrogen of IV was expected to quaternize at a slower rate. On the theoretical side, the quaternization measurements are beclouded by the following issue. Compound IV could quaternize on the quinolizidine nitrogen in the alternate chair conformation[12] (in which there is a CH_2–CH_2 *syn*-axial interaction but in which the quinolizidine nitrogen is much more accessible). Since the rate of quaternization in this conformation may be quite fast (possibly faster than for III!) and the population of the conformation could be easily as high as 20–30% without conflict with the data at hand (the Bohlmann bands[11] only give evidence as to the *major* conformational isomer), a large difference in quaternization rate at the quinolizidine nitrogen between III and IV might not be confidently predicted. Conformational changes upon quaternization have been observed in the field of heteroyohimbanes by M. Schamma and J. B. Moss [*J. Am. Chem. Soc.*, **89**, 1739 (1962)], who arrived at the conclusion that "it is the conformer with the less hindered nitrogen atom that undergoes methylation."

[15] K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p. 72.

[16] Regarding magnetic nonequivalence of benzylic protons, see R. K. Hilland and T. H. Chan [*Tetrahedron*, **21**, 2015 (1965)] who reported in close analogy to this case, an AB quartet with a coupling constant of 14 cps and a chemical shift difference of 0.6 ppm in N-benzyl-*trans*-2,6-dimethylpiperidine.

[17] (a) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964); (b) S. Yamaguchi, S. Okuda, and N. Nakagawa, *ibid.*, **11**, 1465 (1963).

[18] The shift difference observed with 7β-Benzyl-7H-yohimbane is larger than that described by Yamaguchi for certain morphine alkaloids.[17] This is explained by the fact that the magnitude of such shift differences must be critically dependent on the conformation of the methylene group in question and on the remainder of it's chemical environment as well as the N–CH_2 distance.

[19] K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 144.

(−34,267°); for IV, trough 288 mμ (−4651°), peak 256 mμ (+28,952°). It is apparent that, similarly to the 7-chloro-7H-yohimbanes, the curves very nearly bear a mirror-image relationship to each other. This phenomenon is therefore not dependent on the presence of the highly polarizable halogen atom. As pointed out earlier,[1] the octant rule,[20] or rather an extended form thereof (taking C═N in lieu of C═O) does not seem to apply[21] in the cases of indolenines such as III and IV (unless one assumes that the benzyl group makes its principal contribution in that conformation in which it is in a front octant[22]).

Experimental Section

Melting points were determined using the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated the nmr spectra were determined in deuterated chloroform with tetramethylsilane as an internal standard using a Varian A-60 spectrometer. Thin layer chromatography was carried out on silica gel G according to Stahl (Merck, Darmstadt) in an ammonia atmosphere using benzene as the eluent. The chromatograms were developed by spraying with aqueous potassium iodoplatinate. The pK_a values were determined by dissolving 0.03 mmole of compound in 5 ml of ethanolic 0.05 *N* HCl and 1 ml of H_2O and titrating with 0.1 *N* NaOH. Rotations were taken in a 1-dm tube, using a Rudolph (800) photoelectric polarimeter. The optical rotary dispersions were obtained with a Cary spectropolarimeter (60) using 5.6% methanol solutions and cells of 0.1-dm path length. The mass spectra were determined with a Consolidated Electronics Corp. mass spectrometer, No. 21-103C. The ionizing current was kept at 10 μa while the ionizing energy was maintained at 70 ev. Samples were heated in an all-glass inlet system at 200°.

Benzylation of Yohimbane.—Sodium (3 g) was added portionwise to liquid ammonia (1.2 l.) and the reaction mixture was stirred for *ca.* 25 min when all the metal had dissolved. Yohimbane (33.6 g) was added in portions and the stirring was continued for 1 hr. A solution of benzyl bromide (22 g) in ether (120 ml) was added dropwise over a period of 2.5 hr. The acetone–Dry Ice cooling bath was removed and ammonia was allowed to evaporate. Water (500 ml) was added and the mixture was extracted with two 500-ml portions of chloroform. The extracts were dried over sodium sulfate, filtered, and evaporated. The oily residue, on crystallization and fractionation from acetonitrile, gave the following fractions. **1-Benzylyohimbane** (**II**) was obtained: 14.6 g (33%), mp 184–186.5°, $[\alpha]^{25}\text{D}$ −115° (*c* 0.4%, pyridine). *Anal.* Calcd for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.30; H, 8.27; N, 7.59. **7β-Benzyl-7H-yohimbane** (**IV**) was obtained: 6.45 g (14.5%); mp 142–144°; $[\alpha]^{25}\text{D}$ −111° (*c* 0.7%, pyridine), −74° (*c* 0.4%, methanol); pK_a = 5.0 ± 0.1; ORD $[\Phi]_{350}$ −673.4, $[\Phi]_{300}$ −3755.5, $[\Phi]_{288}$ −4651 (trough), $[\Phi]_{267}$ +14126, $[\Phi]_{256}$ +28952 (peak), $[\Phi]_{246}$ +14126°; mass spectrum[23] *m/e* (% Σ_{80}) 91 (3.25), 150 (2.85), 182 (5.5), 183 (1.2), 206 (0.73), 218 (0.73), 219 (1.03), 220 (0.88), 221 (3.2), 222 (0.85), 232 (0.75), 233 (1.2), 234 (0.75), 235 (2.9), 236 (0.95), 249 (0.87), 263 (0.76), 273 (0.81), 274 (0.62), 275 (1.08), 276 (3.1), 277 (14.3), 278 (12.7), 279 (17.3), 280 (4.85), 281 (0.76), 303 (1.57), 269 (0.9), 370 (4.8), 371 (1.27). *Anal.* Calcd for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 83.98; H, 8.25; N, 7.59. **Methiodide** had mp 246–249°. *Anal.* Calcd for $C_{27}H_{33}IN_2$: C, 63.28; H, 6.49; I, 24.76; N, 5.47. Found: C, 63.20, H, 6.61; I, 24.81; N, 5.44. **7α-Benzyl-7H-yohimbane** (**III**) was obtained: 4.6 g (10.4%); mp 166–168.5°; $[\alpha]^{25}\text{D}$ +72° (*c* 0.4%, methanol); pK_a = 5.60 ± 0.04; ORD $[\Phi]_{350}$ +647.5 $[\Phi]_{300}$ +3282, $[\Phi]_{288}$ +5187 (peak), $[\Phi]_{267}$ −16206, $[\Phi]_{256}$ −34267 (trough), $[\Phi]_{246}$ −16206°; mass spectrum[23] *m/e* (% Σ_{80}) 91 (3.19), 150 (1.82), 168 (0.78), 169 (0.82), 182 (0.84), 183 (0.82), 218 (0.53), 220 (0.63), 221 (1.37), 232 (0.55), 233 (0.68), 234 (0.63), 235 (1.18), 276 (0.81), 277 (6.32), 278 (15.5), 279 (34), 280 (7.6), 281 (0.8), 291 (1.22), 369 (1.5), 370 (7.9), 371 (2.2). *Anal.* Calcd for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.09; H, 8.30; N, 7.81. **Methiodide** had mp 258–260°. *Anal.* Calcd for $C_{27}H_{33}IN_2$: C, 63.28; H, 6.49; I, 24.76; N, 5.47. Found: C, 63.25; H, 6.55; I, 24.66; N, 5.69. The mother liquor yielded a mixture containing II, III, IV, and some yohimbane (15.2 g).

Acknowledgment.—We wish to thank Professor E. L. Eliel for helpful discussions, Professor G. I. Fujimoto for recording of the ORD curves, and Dr. D. T. Funke for determination of mass spectra. We are indebted to Mr. A. Lewis and his associates, Mrs. U. Zeek and Mr. R. Puchalski, for analytical and spectral data.

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[20] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

[21] Some caution is advisable, since the ORD curves obtained here as well as those reported earlier[2] may not (and in some instances[2] do not) correspond to a *single* Cotton effect.

[22] This explanation could not apply to chlorine. It suggests that configurational identity of the 7-chloro-7H-yohimbanes with the 7-benzyl-7H-yohimbanes of corresponding Cotton effect cannot necessarily be assumed.

[23] Only peaks ≧0.5% Σ_{80} are recorded. However, for calculation of Σ_{80} all measurable peaks above mass 80 were taken into account.

Synthesis of Nitropolyalkylbiphenyls by Nitrative Coupling of Di- and Trialkylbenzenes

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Nitration of alkyl homologs of benzene is often accompanied by coupling to nitrobiphenyls if the nitric acid is added to the hydrocarbon. This unusual reaction, with one exception, has been overlooked in the chemical literature. *o*-Xylene, *o*-ethyltoluene, *o*-diethylbenzene, and hemimellitene gave an appreciable amount of coupling. The highest yield of isomeric coupled products (47%) has been obtained from *o*-xylene at −25°; of this 82% is 2-nitro-3′,4,4′,5-tetramethylbiphenyl. Both nitration and nitrative coupling appear to proceed through the common intermediate, the nitroaronium ion.

The addition of 90% nitric acid to *o*-xylene has been reported[1] to give not only nitroxylenes, but also small amounts of a by-product identified as 2-nitro-3′,4,4′,5-tetramethylbiphenyl. However, despite its potential value as a synthetic route to nitrobiphenyls, this side reaction, which we call nitrative coupling, has received no attention to date. Therefore, we decided to study it further to determine whether the reaction conditions could be adjusted to favor the formation of larger amounts of coupled products, and whether other aromatics undergo similar reactions.

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[1] A. W. Crossley and C. H. Hampshire, *J. Chem. Soc.*, 721 (1911).