615. *The Rotatory Dispersion of Yohimbine and Some Derivatives.*

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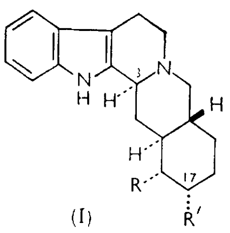
The rotatory dispersion for visible light of yohimbine, yohimbone, yohimbane, ψ-yohimbine, and ψ-yohimbane in water (as salts), in methanol, and in chloroform are analysed in terms of the equation $[M] = A/(\lambda^2 - 0{\cdot}08) + B/\lambda^2$ (λ in mμ × 10^{-3}), and the results discussed.

THE rotatory dispersions of yohimbone and of yohimbane in dioxan have been described;[1] for the former the dispersion is dominated by a large component due to the carbonyl group, while in the case of yohimbane the indole band with $\lambda_{max.}$ at about 280 mμ is only weakly active. As the stereochemistry of yohimbine and its derivatives is known, and because changes in the numerators of the Drude terms describing the dispersions might be more informative than molecular-rotation differences measured at a single wavelength, the optical rotations for visible light of yohimbine (I; $R = CO_2Me$, $R' = OH$), yohimbone (I; R = H, C:O at position 17), yohimbane (I; R = R′ = H), and their epimers at position 3 were chosen for examination. However, after attempts to prepare ψ-yohimbane by two routes had failed to give useful yields, preparation of this compound was abandoned.



(I)

EXPERIMENTAL

Materials.—The starting material was yohimbine hydrochloride; before use, the free base was recrystallised from ethyl acetate, then from ether. The sample used for the dispersion measurements had m. p. 234—236° (decomp.) (lit.,[2] 234°), and the specific rotation as the sulphate in water had values (given below) that could be expressed by the equation $[\alpha]_D^{16} = 114{\cdot}5c^{0{\cdot}085}$ (c = concentration of base in g. per 100 ml. of solution):

Concentration	1·617	1·043	0·8086	0·6469	0·4043
α found, 2 dm. tube	3·86°	2·39° [a]	1·82°	1·44°	0·86°
α calculated	3·86°	2·40°	1·82°	1·43°	0·86°

[a] At 22°; value taken from Table 1.

This equation predicts a value for the specific rotation of yohimbine hydrochloride which is higher than that found by Janot and Goutarel[3] (found, $[\alpha]_D$ +96·9°, c 1; calc., +103·8°), but ones that agree with the figures quoted by Hahn and Brandenberg[4] ($[\alpha]_D^{20}$ +103—104°, c 1; calc., +103·8°) and by Warnat[5] (found, $[\alpha]_D^{25}$ +101·9°, c 0·800; calc., +101·0°).

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[1] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.
[2] Witkop, *Annalen*, 1943, **554**, 83.
[3] Janot and Goutarel, *Bull. Soc. chim. France*, 1949, **16**, 509.
[4] Deutsches Artzneibuch, quoted by Hahn and Brandenberg, *Ber.*, 1927, **60**, 707.
[5] Warnat, *Ber.*, 1930, **63**, 2959.

Yohimbone was prepared by Oppenauer oxidation of yohimbic acid.[2] The rigorous drying of the reagents specified was unnecessary, as water was evolved during the reaction. The product had m. p. 288° (decomp.), $[\alpha]_D^{19}$ $-109°$ (c 0·759 in pyridine) {lit., m. p. 307° (decomp.), $[\alpha]_D$ $-106°$ (c 0·65 in pyridine)}.

Yohimbane was prepared by Wolff–Kischner reduction of yohimbone by the method used for the conversion of ψ-yohimbone into yohimbane.[6] The product, which showed no carbonyl absorption in the infrared spectrum, had m. p. 204° (decomp.), $[\alpha]_D^{21}$ $-115°$ (c 0·496 in pyridine) {lit., m. p. 205—206°, $[\alpha]_D$ $-115°$ (c 1 in pyridine)}.

ψ-Yohimbine was prepared in 10—20% yield by dehydrogenation of yohimbine, then reduction,[7] and was easily separated from the other products of the reaction by recrystallisation from methanol, in which it is sparingly soluble; recycling the crude recovered yohimbine raised the overall yield to about 30%. The product had m. p. 264° (decomp., effervescence), $[\alpha]_D^{23}$ $+29°$ (c 0·9095 in pyridine) {lit., m. p. 268°; [6] 277—278°; [7] $[\alpha]_D^{19}$ $+28°$ (c 1 in pyridine) [7]}.

ψ-Yohimbone was prepared from ψ-yohimbine by the method described by Witkop.[2] The product had m. p. 268—270° (decomp.) (lit., m. p. 268°), and $[\alpha]_D^{22}$ $-17°$ (c 0·94 in pyridine). A previous determination, on different samples of ψ-yohimbone and pyridine, gave $[\alpha]_D^{18}$ $-17°$ (c 0·621). These figures do not agree with the value in the literature [6] of $[\alpha]_D^{20}$ $-24°$ (c 1 in pyridine).

With the exception of yohimbane, the final recrystallisation of each base was from ether; the use of a higher-boiling solvent was accompanied by some oxidation of the base. Yohimbane was precipitated by methanol from a concentrated solution in ether, and the product dried at 100°/16 mm. for not less than 2 hr.

Attempted Preparation of ψ-Yohimbane.—(*a*) (cf. ref. 8). Hydrogen chloride was passed through a solution of ψ-yohimbone (100 mg.) in glacial acetic acid (10 ml.) and ethanedithiol (1 ml.) for 30 min.; after being kept overnight at room temperature, the solution was evaporated to dryness on a steam-bath under reduced pressure. Recrystallisation of the residue from benzene–light petroleum (b. p. 100—120°) gave the *ethylene dithioacetal* of ψ-yohimbone as aggregates, m. p. 218—222° (decomp.) (Found: C, 68·0; H, 6·95. $C_{21}H_{26}N_2S_2$ requires C, 68·1; H, 7·0%). Treatment of this with Raney nickel in boiling ethanol caused extensive decomposition, but a trace of an unidentified crystalline substance, m. p. 262°, was isolated.

(*b*) (cf. ref. 9) Yohimbane was dehydrogenated by mercuric acetate, and the product reduced with zinc and glacial acetic acid. The chief crystalline product was yohimbane, but repeated recrystallisation from methanol gave a small yield of ψ-yohimbane, m. p. 99° (lit., 96—97°). Its hydrochloride and sulphate were both insoluble in cold water.

Solvents.—(*a*) The base was suspended in distilled water, a small excess (0·00—0·02 ml.) over the calculated volume of N-acid added, and the solution made up to 20 ml.

(*b*) " AnalaR " methanol was used without further purification; it had $n_D^{17\cdot2}$ 1·3297; pure methanol has $n_D^{17\cdot2}$ 1·3297 (by interpolation).[10a]

(*c*) " AnalaR " chloroform was washed once with an equal volume of 2N-sodium carbonate, five times with an equal volume of distilled water, dried (Na_2SO_4), and distilled through an 18″ column packed with nickel wire. The sample used had b. p. 61·5°/760 mm., n_D^{18} 1·4471. Pure chloroform has b. p. 61·3°/760 mm., n_D^{18} 1·4468.[10b] Carbon tetrachloride is the most probable impurity, and the refractive index suggests the presence of *ca.* 2%; the impurity was not ethanol, as this lowers both the b. p.[11a] and the refractive index [11b] of chloroform. The point is important, as the optical activity of yohimbine in solution in chloroform is markedly affected by traces of ethanol:

Ethanol (%) in chloroform	0	*ca.* 1 [a]	2
$[\alpha]_D$/Temperature	+3°/21°	+9°/17°	+10°/21°

[a] Commercial chloroform.

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[6] Janot, Goutarel, Le Hir, Amin, and Prelog, *Bull. Soc. chim. France*, 1952, **19**, 1085.

[7] Weisenborn and Diassi, *J. Amer. Chem. Soc.*, 1956, **78**, 2022.

[8] Huebner, St. Andre, Schlittler, and Uffer, *ibid.*, 1955, **77**, 5725.

[9] Wenkert and Roychaudhuri, *ibid.*, 1956, **78**, 6417.

[10] Timmermans, " Physico-Chemical Constants of Pure Organic Compounds," Elsevier Publ. Co., New York, 1950, (*a*) p. 305, (*b*) p. 220.

[11] International Critical Tables, MacGraw-Hill Book Co. Inc., New York, 1933, (*a*) Vol. III, p. 312, (*b*) Vol. VII, p. 78.

Because of the low solubilities of some of the compounds, all the solutions were dilute, to avoid an excessive scatter in the range of concentrations; necessarily, the angles of rotation were small.

Apparatus.—A Hilger Microptic polarimeter was used with the same 2 dm. tube and end-plates throughout; the tube was sealed against leakage by coating the ground faces with high-vacuum grease for aqueous and methanolic solutions, and with glycerol for solutions in chloroform. With chloroform this sealing was important; if the seal was defective the solution darkened, and after an induction period the values of α drifted, even though there was no apparent leakage of the solution. Runs in which this occurred were discarded.

A Leitz sodium lamp, an Osram cadmium lamp, and a K.B.B. mercury-in-quartz arc were used. Readings for lines other than the D-line were made by using a set of Perkin eyepieces (slitless direct-vision spectroscopes); to read the rotation for Hg 4047 Å. a filter was used as well. The rotations quoted in Table 1 are the means of at least 10 readings; those for Hg 4047 Å. are less precise than for other lines.

TABLE 1. *Observed and calculated optical rotations.*

	Water[a]		Methanol		Chloroform	
Yohimbine	*c* 1·0430; 22°.		*c* 1·3125; 22°.		*c* 1·3045; 21°.	
	α		α		α	
Wavelength (Å)	Found	Calc.	Found	Calc.	Found	Calc.
6438	+1·95°	+1·95°	+1·41°	+1·36°	+0·05°	+0·05°
5893	2·39	2·39	1·66	1·66	0·08	0·08
5780[b]	2·50	2·50	1·74	1·75	0·10	0·09
5461	2·87	2·86	1·99	1·99	0·12	0·12
5086	3·41	3·41	2·39	2·38	0·17	0·17
4800	3·96	3·95	2·73	2·76	0·22	0·24
4358	5·13	5·13	3·62	3·62	0·43	0·42
Yohimbone	*c* 0·3830; 21°.		*c* 0·1558; 21°.		*c* 0·7380; 19°.	
6438	−0·22	−0·22	−0·20	−0·19	−1·16	−1·12
5893	0·25	0·26	0·23	0·23	1·40	1·40
5780[b]	0·27	0·27	0·24	0·24	—[c]	—
5461	0·31	0·31	0·28	0·28	1·69	1·70
5086	0·37	0·36	0·33	0·33	2·07	2·07
4800	0·40	0·41	0·38	0·38	2·45	2·45
4358	0·52	0·52	0·48	0·48	3·30	3·31
Yohimbane[d]			*c* 0·2465; 20°.		*c*, 0·2385; 20°.	
6438	—	—	−0·32	−0·32	−0·34	−0·32
5893	—	—	0·38	0·38	0·38	0·38
5780[b]	—	—	0·40	0·39	0·40	0·40
5461	—	—	0·44	0·44	0·45	0·45
5086	—	—	0·51	0·50	0·52	0·52
4800	—	—	0·56	0·56	0·59	0·59
4358	—	—	0·66	0·67	0·70	0·72
4047	—	—	0·80	0·76	0·89	0·85
ψ-Yohimbine[e]	*c* 0·8350; 20°.		*c* 0·5115; 22°.		*c* 0·7420; 23°.	
6438	−0·15	−0·11	−0·12	−0·11	−0·56	−0·52
5893	0·18	0·18	0·15	0·16	0·68	0·70
5780[b]	0·21	0·21	0·18	0·18	0·74	0·74
5461	0·29	0·29	0·24	0·24	0·90	0·90
5086	0·45	0·43	0·36	0·34	1·17	1·16
4800	0·61	0·61	0·44	0·44	1·42	1·43
4358	1·05	1·07	0·78	0·78	2·13	2·13
4047	1·72	1·70	1·21	1·21	2·99	2·99
ψ-Yohimbone	*c* 0·9565; 20°.		*c* 0·9275; 21°		*c* 0·8108; 22°	
6438	−0·72	−0·72	−0·51	−0·48	−0·69	−0·65
5893	0·93	0·93	0·65	0·65	0·87	0·88
5780[b]	1·00	0·99	0·70	0·70	0·94	0·94
5461	1·18	1·19	0·85	0·86	1·12	1·14
5086	1·53	1·51	1·14	1·14	1·47	1·47
4800	1·85	1·85	1·45	1·45	1·82	1·83
4358	2·71	2·71	2·23	2·23	2·74	2·74
4047	3·72	3·76	3·22	3·23	3·88	3·87

[a] As the sulphate. [b] Optical mean of doublet. [c] No readings taken. [d] Neither yohimbane sulphate nor yohimbane hydrochloride is soluble in water. [e] As hydrochloride in water; the sulphate is only sparingly soluble in water.

RESULTS AND DISCUSSION

Yohimbine and its derivatives have ultraviolet absorption maxima at about 282 mμ, 256 mμ, and shorter wavelengths,[6] [12] so that the squares of the constant wavelengths in the Drude terms describing the dispersion would be expected to be (in $m\mu^2 \times 10^{-6}$) about 0·08, 0·05, or 0·00. Graphs of $1/\alpha$ against λ^2 showed that, with one exception discussed below, the dispersions required either more than one Drude term, or in a few cases, a single term with an unsuitable value for the constant wavelength. In every case the dispersion could be described by an equation of the type

$$[M] = A/(\lambda^2 - 0{\cdot}08) + B/\lambda^2$$

Thus A represents an approximate measure of the contribution from the bands with $\lambda_{max.}$ *ca.* 280 mμ (*i.e.*, the long-wavelength indole band, or in the cases of the ketones, the sum of the contributions of this band and the carbonyl band), and B is the sum of the contributions from bands with absorption maxima at shorter wavelengths. A and B were determined so that the calculated values of the optical rotation, rounded off to the nearest hundredth of a degree, should agree with the experimental ones at two wavelengths—one each from the two groups 5893 or 5780 Å, and 4358, 4800, or 5086 Å (the wavelengths in each group are listed in order of decreasing preference)—and the sum of the squares of the errors at the other wavelengths should be a minimum. Table 1 shows the observed and calculated rotations, and Table 2 the values of A and B used; these are quoted to 4 or 5 figures because these numbers of digits were used in the calculations. However, the values of A and B are sensitive to changes in the constant wavelength used (particularly if A and B have opposite signs), and digits beyond the second have no stereochemical significance. In calculating A and B it was assumed that the constant wavelength would be the same for all compounds, and independent of the solvent; this is not strictly true,[13] but the errors introduced by this simplification are less than the experimental uncertainties.

The exception mentioned above was yohimbine in solution as its sulphate in water; here the dispersion could be accurately described by the equation $[M] = 119{\cdot}3/(\lambda^2 - 0{\cdot}053)$, implying that the only active band in the near ultraviolet region was that with $\lambda_{max.}$ 226 mμ. When the two-term equation above is used, for each compound A becomes more negative as the polarity of the solvent decreases; this regularity would be destroyed by using the single-term equation for yohimbine in water, as would the near-constancy of the change in A due to inversion at position 3 in yohimbine. Consequently the apparent simplicity of the dispersion of the yohimbinium cation is considered spurious.

TABLE 2. *Values of A and B in the equation* $[M] = A/(\lambda^2 - 0{\cdot}08) + B/\lambda^2$.

Base	Solvent	*A*	*B*	Base	Solvent	*A*	*B*
Yohimbine	Water	+57·31	+66·45	ψ-Yohimbine	Water	−69·520	+76·889
	Methanol	+34·69	+32·77		Methanol	−74·063	+76·473
	Chloroform	+16·82	−18·24		Chloroform	−90·097	+59·180
Yohimbone	Water	−6·67	−26·25	ψ-Yohimbone	Water	−68·286	+38·985
	Methanol	−25·57	−42·80		Methanol	−73·312	+59·449
	Chloroform	−67·38	−8·999		Chloroform	−89·316	+61·470
Yohimbane	Methanol	+5·635	−82·04				
	Chloroform	−4·462	−72·59				

The results show that the inversion of position 3 in yohimbine ($3\alpha\text{-H} \longrightarrow 3\beta\text{-H}$) changes A by -117 ± 10, while B changes in the opposite sense. The change in A is responsible for the change in sign of the optical rotation for visible light on conversion of yohimbine into ψ-yohimbine, though the molecular rotation differences for the D-line, *viz.*, —440° in water, —280° in methanol, and —173° in chloroform are more variable than the changes in A. The low values for the specific rotation of ψ-yohimbine are due to the near cancellation of two large terms of opposite sign. This point is particularly clear in the case

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[12] Jost, *Helv. Chim. Acta,* 1949, **32**, 1297.

[13] Djerassi and Closson, *J. Amer. Chem. Soc.*, 1956, **78**, 3761.

of ψ-yohimbine in pyridine; the results are not sufficiently accurate for detailed presentation, but the specific rotation has a maximum value of about +31 at *ca.* 540 mμ, then decreasing to zero and changing sign at about 415 mμ.

In the cases of yohimbone and ψ-yohimbone the values of A are the sums of the contributions from the indole and carbonyl bands. An approximate value for the contribution of the carbonyl band in yohimbone can be obtained by assuming that $A = A$ (for yohimbane) $+ A$ (carbonyl), whence A (carbonyl) is of the order of -50. If the sign of the latter is assumed to be solvent-independent, the low value of A for yohimbone in water could then arise from a lævorotatory carbonyl band and an indole band that is dextrorotatory as in yohimbine, and by extrapolation, in yohimbane. However, the values of A for ψ-yohimbine and ψ-yohimbone are nearly the same, and the differences between the specific rotations of the two compounds are due to the different values of B.

On conversion of yohimbone into yohimbane the numerical value of A decreases, and the dispersion in the visible region of the spectrum is determined chiefly by the contributions from the absorption bands with maxima at short wavelengths. The figures in Table 2 suggest that the specific rotation of yohimbane in methanol changes sign at about 293 mμ.

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