

ALKALOID STUDIES—XIX*

ALKALOIDS OF SOME HAWAIIAN *RAUWOLFIA* SPECIES: THE STRUCTURE OF SANDWICINE AND ITS INTERCONVERSION WITH AJMALINE AND AJMALIDINE

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Abstract—The alkaloid composition of the following three Hawaiian *Rauwolfia* species—*R. sandwicensis* A.DC., *R. degeneri* Sherff and *R. mauiensis* Sherff—was determined. Aside from the known alkaloids serpentinine, ajmaline, tetraphylline and tetraphyllicine there were encountered trace amounts of two new dihydroindole alkaloids, mauiensine and sandwicensine as well as larger quantities of an isomer of ajmaline, which was named sandwicine ($C_{20}H_{26}N_2O_2$). Since sandwicine and ajmaline yield different dihydro derivatives which are convertible by lead tetra-acetate oxidation to a common indole hemi-acetal, sandwicine represents the C-17 epimer of ajmaline. Dihydro-sandwicine was found to be identical with tetrahydroajmalidine, the sodium borohydride reduction product of ajmalidine, thereby proving that ajmalidine is 17-dehydroajmaline.

THE current interest in *Rauwolfia* alkaloids¹ has resulted in an examination of a large number of different *Rauwolfia* species. Our past work in this field has been limited to species indigenous to the American continent^{2,3,4,5} in a search for alkaloids of unknown structure and it appeared of interest to study some Hawaiian species⁶ of this genus. The chief reason was that the Hawaiian species are grouped in a separate section (*Ochrosioides*)⁷ and it was conceivable that the alkaloid composition might differ from that of the other species.

The three species available to us were collected by one of the authors (P. J. S.) together with Dr. Harold St. John of the Botany Department of the University of Hawaii and were immediately processed by essentially the scheme developed by Hochstein *et al.*⁸ for the separation of *Rauwolfia* alkaloids of different basicities.

* Paper XVIII in the Wayne series, W. B. Mors, O. R. Gottlieb and C. Djerassi *J. Amer. Chem. Soc.* **79**, 450 (1957).

† Post-doctorate research fellow at Wayne State University, 1956

‡ Lilly pre-doctorate research fellow at Wayne State University.

¹ A. Chatterjee, S. C. Pakrashi and G. Werner *L. Zechmeister's Progress in the Chemistry of Organic Natural Products* (Edited by Zechmeister). Vol. XIII, pp. 346-443. Springer Verlag, Vienna (1956).

² C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso *J. Amer. Chem. Soc.* **76**, 4463 (1954).

³ C. Djerassi and J. Fishman *Chem. (Rev.) Ind.*, 627 (1955).

⁴ S. C. Pakrashi, C. Djerassi, R. Wasicky and N. Neuss *J. Amer. Chem. Soc.* **77**, 6687 (1955).

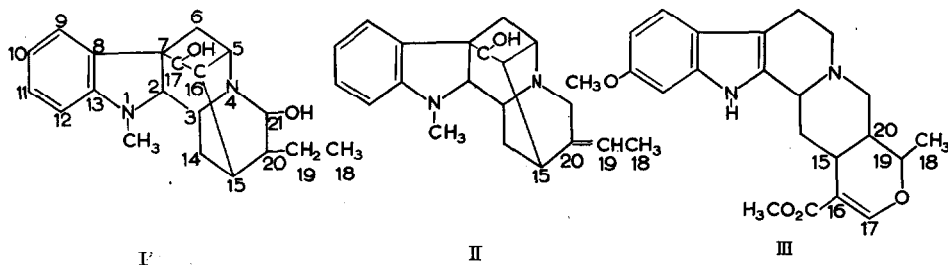
⁵ W. B. Mors, P. Zaltzman, J. J. Beereboom, S. C. Pakrashi and C. Djerassi *Chem. (Rev.) Ind.*, 173 (1956).

⁶ E. E. Sherff *A Preliminary Study of Hawaiian Species of the Genus Rauwolfia* Vol. 23, No. 7. Botanical Series, Field Museum of Natural History (1947).

⁷ R. E. Woodson, H. W. Youngken, E. Schlittler and J. A. Schneider *Rauwolfia* Chapter I. Little, Brown & Co., Boston (1957).

⁸ F. A. Hochstein, K. Murai and W. H. Boegemann *J. Amer. Chem. Soc.* **77**, 3551 (1955).

Rauwolfia degeneri Sherff⁶ roots, collected on the Island of Oahu, yielded four known alkaloids—ajmaline (I),^{*,9,10} tetraphyllicine (II),¹¹ tetraphylline (III)¹¹ and serpentinine^{11,12}—and it is striking to note that the same alkaloids were also encountered in the West Indian *Rauwolfia tetraphylla* L.¹¹ The co-occurrence of these four alkaloids is of definite biogenetic significance since it has already been pointed out¹³ that a precursor of tetraphyllicine (II) is probably responsible for the origin of the



heterocyclic *E* ring of alkaloids of the tetraphylline (III) type as is already implied by the numbering system employed in the structural formulae.

A similar examination of *Rauwolfia sandwicensis* A.DC.⁶ furnished tetraphylline (III), serpentinine, sandwicine (see below), a trace quantity of an impure dihydroindole alkaloid, which may have been tetraphyllicine (II) since the infrared spectra were virtually identical, and a small amount of a new dihydroindole alkaloid ("sandwicensine"), m.p. 260–262°, $[\alpha]_D + 56^\circ$ (methanol), whose analysis was most compatible with $C_{19}H_{22}N_2O \cdot CH_3OH$.

From *R. mauiensis* Sherff⁶ there were isolated tetraphyllicine (II), serpentinine, sandwicine (see below) and a trace of a crystalline alkaloid ("mauiensine"), m.p. 240–242°, $[\alpha]_D + 184^\circ$ (methanol), which appeared to correspond by analysis to $C_{20}H_{26}N_2O$. Unfortunately, sufficient amounts of sandwicensine and mauiensine could not be secured for further work but the ultraviolet and infrared data as well as the positive rotations clearly indicate that these substances should be assigned to the ajmaline group of alkaloids.

The principal alkaloid of *R. sandwicensis* and *R. mauiensis* was gelatinous and could not be induced to crystallize even after repeated purification by chromatography and countercurrent distribution. Its empirical formula corresponded to that of ajmaline ($C_{20}H_{26}N_2O_2$) and this was confirmed by analytical determinations on the crystalline dihydrochloride and dihydroiodide salts. The ultraviolet absorption spectrum was typical of a dihydroindole alkaloid and the infrared spectrum (Fig. 1) showed considerable similarities to that of ajmaline (I) which is also reproduced in Fig. 1 for comparison. Functional group analysis indicated the presence of one

* We are using a numbering system in the ajmaline series which is based on the hypothetical biogenetic precursor (see ref. 11) and the yohimbine numbering.

⁹ R. B. Woodward *Angew. Chem.* **68**, 13 (1956); R. Robinson *Festschrift Arthur Stoll* pp. 457–467. Birkhauser, Basel (1957).

¹⁰ R. B. Woodward, R. Robinson *et al.* *Tetrahedron*. To be published.

¹¹ C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi *J. Amer. Chem. Soc.* **79**, 1217 (1957).

¹² E. Schlittler, H. U. Huber, F. E. Bader and H. Zahnd *Helv. Chim. Acta* **37**, 1912 (1954).

¹³ C. Djerassi, M. Gorman, S. C. Pakrashi and R. B. Woodward *J. Amer. Chem. Soc.* **78**, 1259 (1956).

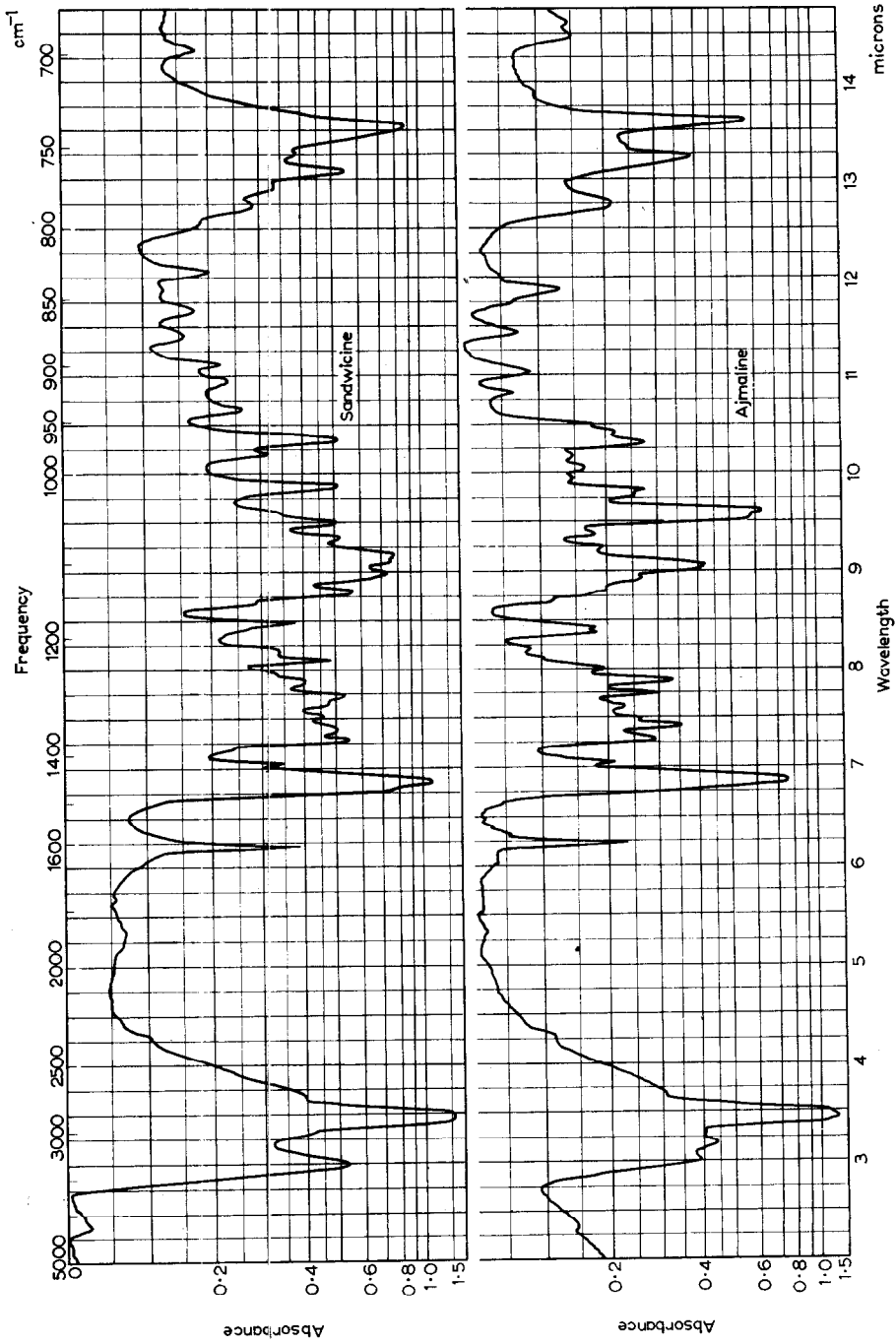


FIG. 1. Infrared absorption spectra (nujol mull) of sandwicine and ajmaline.

C-methyl and one N-methyl group and the absence of methoxyl functions. The basicity of sandwicine (pK_a' 8.5) is the same as that of ajmaline and its rotation is strongly positive (Table 1) as is that of ajmaline and related alkaloids, in contrast to that of most other *Rauwolfia* alkaloid types.

TABLE 1. MOLECULAR ROTATIONS IN THE SANDWICINE AND AJMALINE SERIES

Substance	$[\alpha]_D$	Solvent	$[M]_D$	$\Delta[M]_D^a$
Ajmaline	+144°	CHCl ₃	470	
<i>iso</i> Ajmaline	+72°	CHCl ₃	242	-238
Dihydroajmaline	+54°	CHCl ₃	179	-291
Ajmaline dihydroiodide	+72°	CH ₃ OH	417	
<i>iso</i> Ajmaline dihydroiodide	+64°	CH ₃ OH	373	-44
Sandwicine	+171°	CH ₃ OH		
	+180°	CHCl ₃	592	
<i>iso</i> Sandwicine	+99°	CHCl ₃	322	-270
Dihydrosandwicine	+102°	CHCl ₃	336	-256
	+103°	CH ₃ OH		
Sandwicine dihydroiodide	+84°	CH ₃ OH	490	
<i>iso</i> Sandwicine dihydroiodide	+74°	CH ₃ OH	431	-59

$$^a\Delta[M]_D = [M]_D (\text{alkaloid}) - [M]_D (\text{corresponding derivative}).$$

The presence of at least one hydroxyl group in sandwicine was demonstrated by acetylation to an amorphous acetate, which exhibited infrared bands at 5.78 and 8.1 μ typical of alcoholic acetates. Quantitative microhydrogenation with a platinum oxide catalyst resulted—just as with ajmaline—in the uptake of 3 moles of hydrogen, thus excluding the presence of an ethylidene function as is found in tetraphyllicine (II).^{11,13}

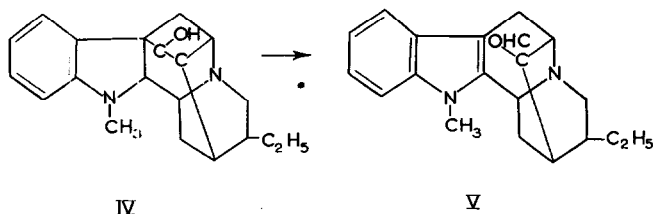
The above data strongly suggest a close structural similarity to ajmaline and this could be supported further by the following reactions. The presence of a carbinol amine moiety (as in ajmaline (I)) was shown by the fact that sandwicine could be reduced with sodium borohydride¹⁴ to crystalline dihydrosandwicine (C₂₀H₂₈N₂O₂), the shift in molecular rotation (Table 1) being of the same order as observed in the ajmaline \rightarrow dihydroajmaline transformation.¹⁵ Furthermore, when sandwicine was boiled with methanolic potassium hydroxide, it was transformed into an isomer—*isosandwicine*—with identical ultraviolet, but slightly different infrared spectrum. The very considerable change in the rotation, however, was again comparable (Table 1) to that observed in the ajmaline \rightarrow *iso*ajmaline reaction¹⁶ which is known to involve simply epimerization at C-20.

The spectroscopic and chemical data cited so far present unequivocal evidence for the presence of an N-methyldihydroindole nucleus as well as a structural unit encompassed by C-18, 19, 20, 21 and N-4 of ajmaline (I). The most cogent experiment for the attachment of the hydroxyl bearing C-17 carbon atom of ajmaline (I) to the β -position (C-7) of the dihydroindole nucleus is the lead tetra-acetate oxidation^{9,10} of desoxyajmaline (IV) to the aldehyde (V) which now contains an indole ring.

¹⁴ S. Bose *J. Indian Chem. Soc.* **32**, 450 (1955).

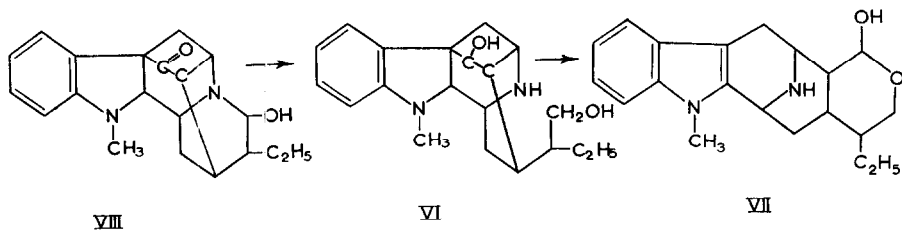
¹⁵ R. Robinson *Chem. (Rev.) Ind.*, 285 (1955).

¹⁶ F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler *J. Chem. Soc.* 1242 (1954).



It was not possible to prepare the requisite desoxyajmaline since the conditions of the Robinson desoxyajmaline synthesis¹⁵—pyrolysis of dihydroajmaline hydrobromide—proved too strenuous when applied to dihydrosandwicine hydrobromide, the substance decomposing before reaching the desired temperature. Lead tetraacetate oxidation of ajmaline itself leads to a mixture, probably due to concurrent attack of the carbinol amine system, but it has been shown^{10,*} that dihydroajmaline (VI) readily undergoes this reaction to yield an indolic hydroxy aldehyde (similar to V) which spontaneously cyclizes to the hemi-acetal (VII). When this oxidation was carried out with dihydrosandwicine, the identical hemiacetal (VII) (Fig. 2) was obtained as evidenced by mixture melting point determination as well as comparison of the infrared and ultraviolet absorption spectra, X-ray diffraction patterns and rotations. It is pertinent to note that the rotation shifts on oxidation from a positive value typical of the *Rauwolfia* dihydroindole alkaloids to a negative value characteristic of the *Rauwolfia* indole alkaloids. Since the only asymmetric center involved in the above oxidation is C-17, dihydroajmaline and dihydrosandwicine differ only at C-17. Sandwicine can, therefore, be named 17-epiajmaline although it is appreciated that isomerism at C-21 has not been excluded rigorously.

Dihydrosandwicine (VI) proved to be identical with tetrahydroajmalidine which was obtained† by sodium borohydride reduction of ajmalidine (VIII).⁴ This



establishes the skeletal structure of ajmalidine as 17-dehydroajmaline (VIII) as had been proposed earlier^{11,13} on circumstantial evidence.

EXPERIMENTAL‡

Isolation of alkaloids from Rauwolfia sandwicensis A.DC. The oven dried (44°) roots§ (1098 g) were ground in a Wiley mill to pass a 1 mm screen and extracted by

* We are greatly indebted to Prof. R. B. Woodward of Harvard University for providing us with excellent experimental details prior to publication.

† This experiment was performed by Dr. S. C. Pakrashi at Wayne State University.

‡ Melting points were determined on the Kofler block. The infrared and ultraviolet absorption spectra were determined in part by Mrs. Dolores Phillips (Wayne State University) and in part by the Physical Chemical Dept. of Eli Lilly & Co. We are indebted to the Lilly microanalytical group (B. Brown, G. M. Maciak, C. Hunter and G. Beckmann) for all microanalyses and to the Lilly Analytical Department for the optical rotations.

§ The root material (2200 g) was collected at 1600 ft altitude in the Kalanoo-North Halawa area, Koolau Mountains, Island of Oahu, and the botanical identification was carried out by Dr. Harold St. John.

heating under reflux three times for 18 hr each, with methanol. The combined methanolic extracts were evaporated *in vacuo* to yield 95 g of brown solid. This residue was dissolved in 700 cm³ of methanol, and 200 cm³ of glacial acetic acid, followed by 1100 cm³ of water, were added. Filtration through Celite and thorough extraction with hexane removed non-alkaloidal contaminants. The aqueous acid

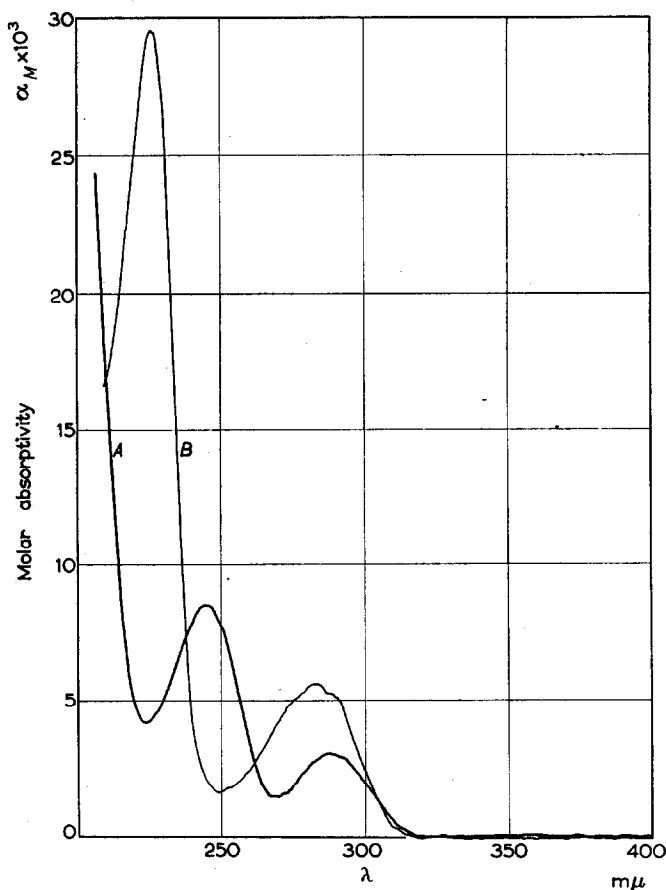


Fig. 2. Ultraviolet absorption spectra of dihydrosandwicine (VI) and (VII).
A—dihydrosandwicine
B—Pb(OAc)₄ oxidation product

solution was extracted with twelve 300 cm³ portions of benzene followed by chloroform and these extracts—containing the weakly basic alkaloids—were washed separately with 5 per cent ammonium hydroxide, dried and evaporated to yield respectively 6.0 g (benzene) and 8.0 g (chloroform) of solids.

The acidic solution was cooled in ice, ammonium hydroxide was added until pH 7 was reached and the medium strength bases (11.9 g) were extracted with chloroform. Finally the aqueous layer was made strongly alkaline (pH 11) with sodium hydroxide and extracted with chloroform to afford 6.0 g of strong bases.

Chromatography of the benzene-soluble acetate fraction on alumina did not provide any crystalline material. The chloroform-soluble acetates upon crystallization gave colorless crystals (0.04 per cent based on dry root) with a double m.p. 125° and

220–222°. These were identified as *tetraphylline* (III)¹¹ by mixture melting point determination as well as comparison of the X-ray diffraction patterns and infrared and ultraviolet spectra with those of an authentic specimen. Chromatography of the mother liquors on alumina led only to oils.

The medium strength bases, isolated at pH 7, were dissolved in benzene–chloroform (1 : 1) and chromatographed on 700 g of alumina which had been deactivated by the addition of 21 cm³ of 10 per cent aqueous acetic acid. Elution with the same solvent mixture yielded 12 mg of colorless crystals, m.p. 269–272°, raised to 274–275° upon further recrystallization. The ultraviolet absorption spectrum ($\lambda_{\max}^{\text{EtOH}}$ 248 and 292 m μ , log ϵ 4.01 and 3.58) was typical of a dihydroindole and the infrared spectrum (KBr pellet) was virtually identical with that of *tetraphyllicine* (II). Further purification was precluded by lack of material but it is likely that this substance was impure tetraphyllicine. *Anal.* Calcd. for C₂₀H₂₄N₂O: C, 77.88; H, 7.84. Found: C, 77.19; H, 8.11.

Further elution with benzene–chloroform (1 : 3) yielded 40 mg of *sandwicencine*, m.p. 253–257°. The analytical sample was obtained from methanol whereupon it exhibited m.p. 260–262°, $[\alpha]_{\text{D}} + 56^\circ$ (CH₃OH), $\lambda_{\max}^{\text{EtOH}}$ 246 and 290 m μ , log ϵ 3.82 and 3.35. The infrared spectrum (nujol mull) was similar but not identical with that of *isoajmaline*¹⁸ (m.p. 264–265°) and the mixture melting point was depressed by over 6°. No material was available for further work or duplicate analyses. *Anal.* Calcd. for C₁₉H₂₂N₂O·CH₃OH: C, 73.59; H, 8.03; N, 8.58; O, 9.80; methoxyl, 9.50. Found: C, 73.35; H, 8.27; N, 8.94; O, 9.76; methoxyl, 9.25; after redrying at 90° *in vacuo*, 0.73.

Further elution of this chromatogram with chloroform–methanol (99 : 1) afforded 1.0 g of *sandwicine*, the purification of which is discussed below.

The strongly basic alkaloid fraction was chromatographed on 400 g of deactivated alumina and elution with chloroform–methanol (99 : 1) yielded 50 mg of yellow solid, melting partially at 152–155° and the remainder near 260°. Recrystallization from methanol afforded *serpentinine*, m.p. 265–270° (dec.) identified by infrared, ultraviolet and X-ray comparisons with an authentic sample. The mother liquor material could not be crystallized but the infrared spectrum strongly indicated that it consisted chiefly of serpentine.

Isolation of alkaloids from Rauwolfia mauiensis Sherff. From 422 g of root material* there was obtained 249 g of dried powder and 25 g of methanol extract. When processed in the manner outlined above there was encountered (a) 0.15 g of benzene-soluble acetates, (b) 0.60 g of chloroform-soluble acetates, (c) 6.03 g of medium bases (pH 7 extractable) and (d) 0.10 g of strong bases. Chromatography of fractions (a), (b) and (d) did not yield any crystalline material.

The pH 7 bases were chromatographed on 400 g of acetic acid-deactivated alumina. Elution with benzene–chloroform (1 : 1) gave 30 mg of *mauiensine*, m.p. 235–240°, raised to 240–242° after recrystallization from acetone, $[\alpha]_{589} + 184^\circ$, $[\alpha]_{325} + 1038^\circ$ (CH₃OH), † $\lambda_{\max}^{\text{EtOH}}$ 249 and 291 m μ , log ϵ 3.92 and 3.35. The infrared spectrum was typical of the ajmaline group of alkaloids and exhibited a characteristic band at 6.13 μ in a potassium pellet. Sufficient material for only one analysis was

* Collected by Dr. Harold St. John in the Hana district of East Maui near Kanao at 1900 ft elevation in barren lava.

† Measured on a Rudolph spectropolarimeter with a xenon lamp.

available. *Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03; N—CH₃, 4.84. Found: C, 77.16; H, 8.04; N, 8.59; N—CH₃, 6.58.

Additional elution with the same solvent pair furnished 11 mg of *tetraphyllicine*, m.p. 305–306° after recrystallization from acetone, and identified by direct comparison with an authentic specimen.¹¹

Further development of the chromatogram with chloroform and chloroform-methanol (99 : 1) yielded 0.78 g of sandwicine containing a bright yellow impurity. This crude product was subjected to a seven stage countercurrent distribution with each funnel containing 50 cm³ each of chloroform (stationary phase) and citrate-phosphate buffer of pH 6.75. Combination of the contents of the first two funnels and crystallization from methanol gave 25 mg of *serpentinine*, m.p. 265–270° (dec.), identified with an authentic specimen. From the center funnels, 0.43 g of colorless *sandwicine* (see below) was obtained.

Isolation of alkaloids from Rauwolfia degeneri Sherff. Methanol extraction of 6350 g of fresh roots* (2550 g after drying) gave 319 g of methanol extract which was divided into 50 g of weak bases, 60 g of medium strength bases and 8 g of strong bases. Chromatography of the medium bases in the above described manner afforded in order of increasing polarity 45 mg of *tetraphyllicine* (II), m.p. 308–310°, 255 mg of *tetraphylline* (III)† m.p. 223–225°, 0.96 g of *serpentinine*, m.p. 260° (dec.) and 0.60 g of *ajmaline* (I), m.p. 158°. Identity was established in each instance by mixture melting point determination and infrared comparison with authentic samples.

Sandwicine. The alkaloid was obtained in a gelatinous form from both *R. sandwicensis* and *R. mauianensis* and could not be crystallized. It was best purified by dissolving in acetone and precipitating from a hot solution by the gradual addition of hexane. Countercurrent distribution (24 tubes) between chloroform and citrate-phosphate buffer (pH 6.73) on a sample of sandwicine from *R. sandwicensis* yielded—just as described above for *R. mauianensis*—a small amount of *serpentinine* from tubes 1 and 2. The contents of tubes 12–20 were pooled and redistributed into 24 fractions using the same system but no additional separation was encountered and the alkaloid behaved like a single entity with the following solvent systems in paper chromatograms: (a) *n*-butanol–water–acetic acid (4 : 5 : 1); (b) ethyl acetate–pyridine–water (7 : 2 : 1); (c) ethyl methyl ketone—1 per cent methanol saturated with water; (d) benzene–formamide. Sandwicine was identified by spraying with *p*-dimethylamino-benzaldehyde (blue color developing slowly on heating) or Dragendorff's reagent. The amorphous alkaloid exhibited $[\alpha] + 171^\circ$ (CH₃OH), $+ 180^\circ$ (CHCl₃) and its ultraviolet ($\lambda_{\max}^{\text{EtOH}}$ 246 and 292 m μ , log ϵ 3.91 and 3.46) absorption spectrum was typical of a dihydroindole. The infrared spectra (nujol mull) of sandwicine and ajmaline (I) are reproduced in Fig. 1. *Anal.* Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58; O, 9.80; C—CH₃, 4.60; mol. wt. 326. Found: C, 72.87; H, 8.22; N, 9.08; O, 10.54; C—CH₃, 3.48; mol. wt. (potentiometric titration), 322; *pK'a* (66 per cent DMF), 8.5.

Acetylation of sandwicine with acetic anhydride–pyridine (24 hr at 25°) yielded an amorphous acetate with strong infrared alcoholic acetate absorption ($\lambda_{\max}^{\text{CHCl}_3}$ 5.78 and 8.1 μ).

* Collected on the ridge east of the central Makaleha valley, Mokuleia, Waianae Mountains, Island of Oahu, 1400 ft elevation. The two trees from which the roots were taken were identified by Dr. Harold St. John.

† An additional 1.0 g of tetraphylline was secured from the weakly basic fraction.

Sandwicine dihydroiodide was prepared by dissolving 50 mg of sandwicine in 10 cm³ of boiling acetone and adding 1 cm³ of 48 per cent hydroiodic acid. Crystallization commenced immediately and after concentrating to one-half the original volume, the solution was chilled and the crystals collected. The analytical sample was obtained by recrystallization from acetone or from methanol-hydroiodic acid, m.p. 238–240°, $[\alpha]_D + 84^\circ$ (CH₃OH), pK_a' 8.5 (66 per cent dimethyl formamide, initial pH 2.65). The infrared and ultraviolet spectra were typical of dihydroindole salts. Sandwicine dihydroiodide could be prepared directly from the medium base fraction by treatment with acetone-hydroiodic acid.

Anal. Calcd. for C₂₀H₂₈O₂I₂N₂: C, 41.25; H, 4.85; N, 4.81; I, 43.58; mol. wt., 582. Found: C, 41.30; H, 5.00; N, 4.44; I, 43.36; mol. wt., 610 (potentiometric titration).

Sandwicine dihydrochloride was prepared in exactly the same fashion in acetone-concentrated hydrochloric acid, m.p. 210–213°, $[\alpha]_D + 129^\circ$ (CH₃OH). *Anal.* Calcd. for C₂₀H₂₈Cl₂N₂O₂: C, 60.15; H, 7.07; Cl, 17.75; N, 7.01; O, 8.01; N—CH₃, 3.75. Found: C, 59.66; H, 7.16; Cl, 17.45; N, 6.92; O, 7.81; N—CH₃, 4.22.

Dihydrosandwicine. A solution of 0.3 g of sandwicine in 20 cm³ of ethanol was mixed with 0.5 g of sodium borohydride in 10 cm³ of 60 per cent ethanol and the solution was allowed to stand overnight before evaporating to dryness. Saturated sodium sulfate solution (25 cm³) containing 1 cm³ of concentrated ammonia was added and the resulting precipitate was extracted with chloroform. Evaporation of the chloroform solution yielded 0.24 g of crystalline dihydrosandwicine which was recrystallized from acetone giving long, coarse hexagonal rods, m.p. 210–212°, $[\alpha]_D + 102^\circ$ (CHCl₃), $\lambda_{\max}^{\text{EtOH}}$ 246 and 288 m μ , log ϵ 3.90 and 3.45 (Fig. 2), $\lambda_{\max}^{\text{nujol}}$ 6.20 μ . *Anal.* Calcd. for C₂₀H₂₈N₂O₂: C, 73.13; H, 8.59; N, 8.53; mol. wt., 328.4. Found: C, 72.91; H, 8.85; N, 8.55; mol. wt. (X-ray), 327 (determined by Miss Ann Van Camp, Eli Lilly & Co.).

The hydrobromide salt (m.p. 250–255°) was prepared in the usual manner but it decomposed during attempted pyrolysis¹⁷ to desoxysandwicine.

isoSandwicine. When 0.15 g of sandwicine was heated under reflux for 8 hr with 0.3 g of potassium hydroxide and 25 cm³ of methanol, there was obtained 0.12 g of an amorphous powder, $[\alpha]_D + 99^\circ$ (CHCl₃). The ultraviolet absorption spectrum was superimposable upon that of sandwicine, but the infrared spectra measured in chloroform (1 mm path), mineral oil mull or pyridine showed minor differences in the finger print region. The *dihydroiodide*, m.p. 242–245°, $[\alpha]_D + 74^\circ$ (CH₃OH) was prepared as described above for sandwicine, and its infrared spectrum (nujol mull) proved to be different from that of sandwicine dihydroiodide. *Anal.* Calcd. for C₂₀H₂₈I₂N₂O₂: C, 41.25; H, 4.85. Found: C, 40.53; H, 4.89.

Lead tetra-acetate oxidation of dihydrosandwicine. A solution of 25 mg of dihydrosandwicine in 1 cm³ of acetic acid was treated for 15 sec with 40 mg of lead tetra-acetate dissolved in 5 cm³ of acetic acid. Hydrogen sulfide was passed into the solution, the lead sulfide was removed by filtration through Celite and the filtrate was evaporated to dryness *in vacuo*. Addition of water followed by decolorization with Norit, basification with ammonium hydroxide, extraction with chloroform, evaporation and recrystallization from benzene-methylene chloride furnished 20 mg of the hemi-acetal (VII). Its physical constants, m.p. 215–217°, $[\alpha]_D - 32^\circ$ (chloroform), $\lambda_{\max}^{\text{MeOH}}$ 226 and 283 m μ , log ϵ 4.46 and 3.80 (Fig. 2), $\lambda_{\max}^{\text{CHCl}_3}$ 2.75 (NH), 2.95 (OH),

6.13 and 9.3 μ (acetal), were identical with those of an authentic sample (m.p. 216–218°, $[\alpha]_D - 31^\circ$) of the hemi-acetal (VII) prepared^{22,19} from ajmaline (I) under identical conditions and identity was confirmed by comparison of the X-ray diffraction patterns.

*Sodium borohydride reduction of ajmalidine (VIII) to dihydrosandwicine (VI).** Ajmalidine 10 mg⁴ in 3 cm³ of ethanol was treated with 30 mg of sodium borohydride at room temperature overnight. Addition of water and chloroform extraction gave after evaporation a crystalline residue which melted at 205–207° after two recrystallizations from methanol. The X-ray diffraction pattern and infrared absorption spectrum of this material were identical with those of dihydrosandwicine (VI).

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* This experiment was performed by Dr. S. C. Pakrashi at Wayne State University.