Hawaiian Plant Studies. X.[1] The Structure of Mauiensine

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The structure of mauiensine was shown to be 17-epitetraphyllicine by epimerization of tetraphyllicine at C-17 and by converting ajmaline to 17-epidexoyisoajmaline which was identical with dihydromauiensine. Small amounts of ajmalidine were isolated from *Rauvolfia mauiensis* in addition to the previously encountered alkaloids.

In 1957[3] we isolated from a sample of root bark of *Rauwolfia mauiensis* Sherff tetraphyllicine, serpentinine, sandwicine and a trace of a crystalline alkaloid which we named mauiensine, m.p. 240–242°. Spectral data and positive rotation indicated that the base was a member of the ajmaline group of alkaloids. A single combustion analysis was compatible with the composition $C_{20}H_{26}N_2O$, including one N-methyl group.

Between 1959 and 1962 we collected further quantities of plant material on the island of Maui and resumed our structural studies. In the course of the earlier column chromatography of the pH 7 bases we had eluted mauiensine, followed by tetraphyllicine and the serpentinine-sandwicine mixture. During the present work, however, we encountered ajmalidine in the fraction preceding the serpentinine–sandwicine mixture. Ajmalidine after recrystallization from methanol has m.p. 236–238° (lit.[4] m.p. 241–242°) and an infrared spectrum identical with the published one.[5]

The physical data of mauiensine were in accord with those previously found (m.p. was now 237–238° instead of 240–242°), but duplicate combustion analyses agreed with $C_{20}H_{24}N_2O$ rather than with the earlier $C_{20}H_{26}N_2O$ formulation. A yellow color with tetranitromethane supported the indicated presence of an olefinic linkage. Analysis of crystalline mauiensine hydrochloride, m.p. 295° dec., further supported the new empirical formula.

In order to determine whether the single oxygen atom of mauiensine was present at C-17 or C-21 we attempted to prepare the oxime of the possible carbinol amine at C-21 or to reduce this function with sodium borohydride. Both reactions resulted in recovery of starting material. These negative results suggested that mauiensine was 17-epitetraphyllicine. Positive support of this hypothesis was found by a comparison of the molecular rotation data shown in Table I.

TABLE I

MOLECULAR ROTATION CHANGES ARISING FROM EPIMERIZATION AT C-17

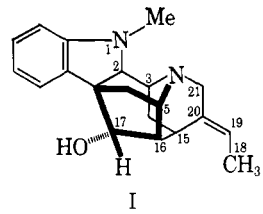
Transformation	MD, °
Ajmaline → sandwicine	+122
Dihydroajmaline → dihydrosandwicine	+157
Ajmaline $(HI)_2$ → sandwicine $(HI)_2$	+ 73
Isoajmaline $(HI)_2$ → isosandwicine $(HI)_2$	+ 58
Deoxyajmaline → 17-epideoxyajmaline	+693
Tetraphyllicine → mauiensine	+501
Deoxyisoajmaline → dihydromauiensine	+220

Of several possible avenues by which one might prove that mauiensine was indeed identical with 17-epitetraphyllicine the simplest approach seemed to lie in catalytic hydrogenation of mauiensine to the known 17-epideoxyajmaline,[6] m.p. 262–264°, $[\alpha]D$ +347° ($CHCl_3$). Mauiensine hydrochloride was hydrogenated analogously with Djerassi's[7] hydrogenation of tetraphyllicine. The product after recrystallization from acetone was obtained in two distinct but mutually interconvertible forms, m.p. 198–201° and 215–217°, $[\alpha]D$ +229° (MeOH). It did not yield satisfactory analytical data. It was clearly not identical with 17-epideoxyajmaline. Apparently hydrogen had added from the side of the C-15 → C-16 carbon bridge and led to formation of 17-epideoxyisoajmaline.

This hypothesis was proven by the preparation of 17-epideoxyisoajmaline from ajmaline. Ajmaline[8] was converted to isoajmaline as described by Robinson,[9] thence to deoxyisoajmaline as described by the Ciba group.[6] Deoxyisoajmaline was in turn oxidized with potassium *t*-butoxide and 9-fluorenone in benzene to the oily oxo compound (carbonyl band at 5.74 μ), which was reduced by sodium borohydride to 17-epideoxyisoajmaline, $C_{20}H_{26}N_2O$, m.p. 243–244°, $[\alpha]D$ +228° (MeOH). Dihydromauiensine and 17-epideoxyisoajmaline had identical rotations, infrared spectra, and thin layer chromatograms; the discrepancy in melting points remained unexplained.

In a more direct manner the structure of mauiensine was related to tetraphyllicine. The 17-hydroxy group of tetraphyllicine was epimerized by oxidation to the oily 17-oxo compound (carbonyl band at 5.75 μ), followed by sodium borohydride reduction. The resulting product, m.p. 240–241°, was identical with mauiensine (I) in all respects.

It is interesting to note that *R. mauiensis* has yielded tetraphyllicine and its 17-epimer (mauiensine), the 17-epimer of ajmaline (sandwicine) and the 17-oxo com-



I

(1) Part IX of this series, F. Werny and P. J. Scheuer, *Tetrahedron*, in press.

(2) NIH Post-doctoral Fellow, 1961–1962.

(3) M. Gorman, N. Neuss, C. Djerassi, J. P. Kutney, and P. J. Scheuer, *Tetrahedron*, **1**, 328 (1957).

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

(5) "Physical Data of Indole and Dihydroindole Alkaloids," 4th Rev. Ed., N. Neuss, Ed., Eli Lilly and Co., Indianapolis, Ind., 1960.

(6) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962).

(7) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *ibid.*, **79**, 1217 (1957).

(8) Generously supplied by Dr. W. I. Taylor and by L. Light and Co., Ltd.

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

pound (ajmalidine), although ajmaline itself was not found.

Experimental[10]

Isolation.—The bark was collected on the island of Maui[11] from trees growing in barren a'a lava, 4.8 miles from Ulupalakua School on the road to Hana and prepared in the usual way. Extraction with refluxing methanol was carried out until the extracts no longer gave a positive Mayer's test. The methanol extracts were concentrated on the stripper, and as much as possible of the remaining solvent was removed under vacuum on the rotary evaporator. The tarry residue was weighed and redissolved in about 2.5 times its weights of methanol. To this solution was added 5% acetic acid, twice the volume of the methanol used. This mixture was extracted with hexane until the hexane washes were no longer colored. (The extracted material gave a negative Mayer's test.)

The acidic solution was cooled to about 5°, brought to pH 10 with concentrated ammonia, and the precipitated bases were filtered off. The filtrate was extracted with chloroform and the extract was combined with the precipitated solids.

The basic material was then dissolved in five times its weight of chloroform and extracted four times with an equal volume of 5% acetic acid, removing the strong and medium bases. The chloroform layer was washed once with 5% ammonia, dried over sodium sulfate, and the solvent was removed under vacuum. This residue was labeled "weak bases."

After cooling to about 5°, the acetic acid extracts were adjusted to pH 7–7.5 with 20% ammonia; the precipitated alkaloids were filtered off; and the filtrate was extracted with chloroform until the extracts gave only a slightly positive Mayer's test. The material thus collected was labeled "pH 7 bases."

The aqueous solution was again cooled, brought to pH 10, and chloroform extraction removed the "strong bases." Both the weakly and strongly basic fractions were set aside, and attention was directed toward repeating the reported isolation of mauiensine from the "pH 7 bases."

For chromatography, the pH 7 bases were dissolved in chloroform and dried over sodium sulfate. To the filtered solution an equal volume of benzene was slowly added. A column of acetic acid-deactivated alumina,[3] 30 to 60 times the weight of the crude bases, was packed in 1:1 benzene–chloroform solution. With this solvent mixture mauiensine was eluted, followed immediately by tetraphyllicine. The alkaloid elution pattern was similar to the one reported by Gorman, *et al.*,[3] with the exception that ajmalidine replaced an unknown base encountered in the earlier work.[3] This alkaloid was eluted from the column after tetraphyllicine and before the serpentinine–sandwicine mixture. Roughly, from about 1.5 kg. of dried bark we extracted 100 g. of tarry material, half of which precipitated at pH 10. About 20% of the total crude alkaloids was removed from the aqueous phase at pH 7.

Chromatography of the pH 7 fraction was complicated by the fact that solution of the solids in chloroform caused a large amount of gelatinous substance to be formed which could be removed only by tedious filtration. Chromatography of the filtrate yielded about 1% of slightly impure mauiensine, based on total dry weight of the pH 7 fraction. More of this alkaloid could be isolated after chromatography of the gelatinous material. Mauiensine and tetraphyllicine always occurred together in the eluted fractions, but a fairly good separation could be effected by trituration of the solid with cold acetone in which mauiensine is more highly soluble.

Mauiensine.—This alkaloid was crystallized from acetone and melted at 237–238° (previously,[3] 240–242°). Its infrared spectrum in potassium bromide and optical rotation in methanol at 589 mμ checked with the previously reported data.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C 77.88; H, 7.84. Found: C, 78.15, 78.02; H, 7.62, 7.53.

Mauiensine and tetranitromethane gave a yellow solution.

Attempted Reaction with Hydroxylamine.—Impure mauiensine (110 mg.) was treated with hydroxylamine hydrochloride (114 mg.) according to the procedure described for the preparation of ajmaline oxime.[9] A crude crystalline material was obtained (91 mg.) which had an infrared spectrum identical with that of mauiensine hydrochloride. On treatment with base mauiensine was recovered, and this was confirmed by a comparison of the infrared spectra.

Attempted Reaction with Sodium Borohydride.—Mauiensine (12 mg., m.p. 232–233°) was treated with sodium borohydride (30 mg.) according to the procedure described for sandwicine.[3] The identity of the product isolated with that of the starting material was verified by its melting point and infrared spectrum.

Mauiensine Hydrochloride.—To mauiensine dissolved in a minimal amount of chloroform was added chloroform saturated with gaseous hydrogen chloride. The precipitate, after removal of the solvent, was crystallized from methanol, giving colorless needles melting at 295° dec.

Anal. Calcd. for $C_{20}H_{24}N_2O \cdot HCl$: C, 69.64; H, 7.31; N, 8.12. Found: C, 69.32; 69.45; H, 7.12, 7.33; N, 8.81.

Tetraphyllicine.—After elution from the column this compound was crystallized from acetone, m.p. 274–275°. Its infrared spectrum was identical with that of an authentic sample.[12]

Ajmalidine.—Ajmalidine was isolated from the pH 7 fraction by elution from the column following the tetraphyllicine fractions. It was also found in the "weak base" fraction. On washing the chloroform solution of the weakly basic alkaloids with 5% ammonia a precipitate (16.3 g.) was obtained which was first triturated with petroleum ether, then with ether. The residue on evaporation of the ether solubles (2 g.) contained a crystalline material which could be separated by treatment with benzene and filtering. Recrystallization of the solid (108 mg.) from methanol gave colorless needles, m.p. 236–238°. An infrared spectrum in chloroform was identical with that published for ajmalidine.[5]

Dihydromauiensine.—The reduction of mauiensine was carried out in the manner described by Djerassi for tetraphyllicine.[7] A theoretical uptake of roughly 1 mole of hydrogen per mole alkaloid could be observed within an hour after addition of the salt to the suspension of prereduced platinum oxide in ethanol and no further uptake occurred when one run was left on overnight. The product, obtained as the free base, was crystallized from acetone. It was isolated in two distinct forms, melting at 198–201° and 215–217°, which were mutually interconvertable. Repeated recrystallization of the originally isolated high-melting form from acetone led to the low-melting form, which on sublimation was converted back to the high-melting form. Both forms exhibited some degree of crystal rearrangement at about 180°. The infrared showed an absence of peaks at 10.05, 10.9 and 12.2 μ assigned to the trisubstituted double bond in mauiensine; $[\alpha]^{23}D$ +229° (*c* 0.119 g./2 ml. of methanol).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44. Found: C, 76.09, 76.64; H, 8.27, 8.16.

17-Epideoxyisoajmaline.—Deoxyisoajmaline (340 mg.), prepared from ajmaline by published procedures,[9,6] was oxidized with potassium *t*-butoxide (~4 g.) and 9-fluorenone (~3 g.) in benzene (400 ml.) and the resulting oily oxo compound (302 mg.) was reduced with sodium borohydride (150 mg.) in ethanol (20 ml.) to crude 17-epideoxyisoajmaline (184 mg.) which was recrystallized from aqueous methanol to give colorless fine prisms, m.p. 243–244° (subliming around 220°); $[\alpha]^{20}D$ +228° (methanol, *c* 0.595).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.32; H, 8.56; N, 9.00.

Mauiensine from Tetraphyllicine.—A hot solution of tetraphyllicine (100 mg.) and 9-fluorenone (500 mg.) in benzene (150 ml.) was added to the suspesion of potassium *t*-butoxide (~2 g.) in benzene (50 ml.) and refluxed for 8 hr. with stirring in an atmosphere of nitrogen. The resulting mixture was extracted with three 50-ml. portions of dilute hydrochloric acid. The acidic solution was made basic with 20% sodium hydroxide and extracted with chloroform. Evaporation of the dried chloroform extracts gave a yellow sticky oil which was purified by eluting with chloroform on alumina. The purified oil (80 mg.) was dissolved in ethanol (2 ml.) and reduced with sodium borohydride (100 mg.) by keeping it standing overnight at room temperature. After decomposing an excess of sodium borohydride with a few drops of acetone, the solution was diluted with water. Colorless crystals gradually separated; they were re-

(10) Combustion analyses was by Dr. A. Bernhardt, Mülheim/Ruhr, Germany. Melting points were determined on a micro hot stage and are uncorrected. Ultraviolet spectra were measured on a Beckman DK-2, infrared spectra on a Beckman IR-5 instrument.

(11) We should like to thank Mr. Henry C. Inciong for his invaluable assistance during our collection trips.

(12) Kindly furnished by Professor C. Djerassi.

crystallized from aqueous methanol to give colorless prisms (62 mg.), m.p. 240–241°, identical in all respects with mauiensine.

Thin Layer Chromatography.—The R_f values were found to be dependent on concentration, the thickness of the alumina on the plates, and other variables in the system which reduced their reproducibility. These values are relative, and the difference between any two may vary as greatly as 0.1 units in a given chromatogram. The system of 2% ethanol in benzene afforded a better separation of the components of a mixture than did 4% ethanol in benzene. The chromatograms were developed by spraying with the modified Dragendorff's reagent.[13]

(13) N. A. Robles, *Pharm. Weekblad*, **94**, 178 (1959).

	Ethanol in benzene	
	2%	4%
Ajmaline		0.9
Mauiensine	0.56	
Dihydromauiensine	0.40	
Tetraphyllicine		0.66

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A Study of 1,2-Benzyl and 1,3-Phenyl Radical Migrations

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The 2,2-dibenzylethyl radical, generated in solution either by the decarbonylation of 3,3-dibenzylpropanal or by the "Kharasch reaction" of 1,1-dibenzyl-2-chloroethane, does not rearrange *via* a 1,2-benzyl shift. Evidence suggests that for free radicals the migratory aptitude is in the order phenyl > benzyl. These results are compared with those reported for carbanions. The 3-phenylpropyl-1-C^{14} radical similarly generated does not rearrange to the 1-phenylpropyl-1-C^{14} radical *via* a 1,3-phenyl shift.

Very few examples have been reported of authentic radical 1,2-alkyl migrations. In fact, several workers have established firmly that such rearrangements do not occur within certain selected radicals. These have been generated either in solution, *via* radical additions to olefins, decarbonylation of aldehydes and decomposition of azo compounds,[1] or in the gas phase by the reaction of iodine and other free radical sources with hydrocarbons at elevated temperatures[2] (400–600°).

Reports of certain reactions thought to give products of radical rearrangement have been shown to be incorrect[3,4] or to involve cleavage–recyclization[5] rather than a true 1,2-alkyl shift.

Noteworthy is the work of Cvetanović who has presented some evidence that alkyl migrations occur within diradicals formed by the addition of oxygen atoms (obtained by the mercury sensitized photolysis of nitrous oxide) to olefins.[6] However, these migrations may be only partly internal. Other reports of saturated alkyl shifts have been made, but further work is needed to establish the mechanisms.[7]

A recent molecular orbital treatment of the chemistry of 1,2-shifts has indicated that carbanions should be even less prone to rearrangement, *via* 1,2-alkyl group migrations, than are free radicals.[8] For this reason, the observation of Grovenstein and Williams that the benzyl group does undergo a 1,2-shift within carbanions even more readily than the phenyl group[9] is very interesting. One might therefore expect that the migratory aptitude of the benzyl group would be greater than that of an alkyl group or even an aryl group in a radical system. In an attempt to establish this point, we have sought to bring about a 1,2-benzyl migration. Incidental to this study, a test was also made for a 1,3-phenyl migration within the 3-phenylpropyl-1-C^{14} radical.

Results and Discussion

As a test for a 1,2-benzyl shift, the peroxide-induced decarbonylation of 3,3-dibenzylpropanal (equation 1) was studied. The intermediate radical A propagates

$$(C_6H_5CH_2)_2CHCH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[\Delta]{\text{peroxide}} (C_6H_5CH_2)_2CHCH_2\overset{O}{\overset{\|}{C}}\cdot \longrightarrow (C_6H_5CH_2)_2\underset{A}{CHCH_2}\cdot + CO \quad (1)$$

the chain reaction by abstracting a hydrogen from the reactant aldehyde to give 1,1-dibenzylethane. Should radical A rearrange *via* a 1,2-benzyl shift prior to abstracting a hydrogen, 1,4-diphenylbutane would be the product (equation 2). Very dilute *o*-dichlorobenzene

$$(C_6H_5CH_2)_2CHCH_2\cdot \xrightarrow{o} C_6H_5CH_2\dot{C}HCH_2CH_2C_6H_5 \longrightarrow C_6H_5CH_2CH_2CH_2CH_2C_6H_5 \quad (2)$$

(R = $\overset{O}{\overset{\|}{C}}H$)

solutions of the aldehyde (0.075–1.0 molar) and rather high decarbonylation temperatures (~160°) were used to encourage possible rearrangements. Both conditions have been shown to be beneficial to radical rearrangements.[10,11] Approximately 78% decarbonylation was obtained when a one molar solution of the aldehyde was

(1) (a) W. von E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952); (b) S. J. Cristol and G. D. Brindell, *ibid.*, **76**, 5699 (1954); (c) J. A. Berson and W. M. Jones, *ibid.*, **78**, 6045 (1956); (d) F. G. Bordwell and J. A. Reeder, *ibid.*, **79**, 3493 (1957); (e) F. H. Seubold, Jr., *ibid.*, **75**, 2532 (1953); (f) F. H. Seubold, Jr., *ibid.*, **76**, 3732 (1954); (g) C. G. Overberger and M. B. Berenbaum, *ibid.*, **74**, 3293 (1952); (h) J. A. Berson and C. J. Olsen, *ibid.*, **84**, 3178 (1962).

(2) (a) L. H. Slaugh and J. H. Raley, *ibid.*, **82**, 1259 (1959); **84**, 2640 (1962); (b) L. H. Slaugh, R. D. Mullineaux, and J. H. Raley, *ibid.*, in press.

(3) M. S. Kharasch, Y. C. Liu, and W. Nudenberg, *J. Org. Chem.*, **19**, 1150 (1954); **20**, 680 (1955).

(4) J. D. Backhurst, *J. Chem. Soc.*, 3497 (1959).

(5) J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Am. Chem. Soc.*, **82**, 5000 (1960); **84**, 3337 (1962).

(6) R. J. Cvetanović, *Can. J. Chem.*, **36**, 623 (1958).

(7) (a) F. F. Rust, and D. O. Collamer, *J. Am. Chem. Soc.*, **76**, 1055 (1954); (b) J. A. G. Dominguez and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 940 (1962).

(8) H. E. Zimmerman and A. Zweig, *J. Am. Chem. Soc.*, **83**, 1196 (1961).

(9) E. Grovenstein, Jr., and L. P. Williams, Jr., *ibid.*, **83**, 2537 (1961).

(10) Ref. 1e.

(11) L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959).