Acknowledgments. This work was supported by grants from the National Institutes of Health (GM 09686) and from the Hoffmann-La Roche Anniversary Foundation. Professor K. Biemann and Dr. G. Albers-Schönberg kindly measured many mass spectra and Mr. R. Rosati was most helpful with the nuclear magnetic resonance spectra. We are also indebted to Dr. S. Seshadri for his participation in exploratory studies on the condensation of dihydropyridines with dienophiles.

The Structures of Two Alkaloids from Patchouli Oil

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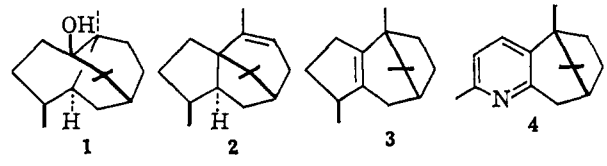
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received March 18, 1966*

Abstract: Two new alkaloids, for which the names patchoulipyridine and epiguaipyridine are suggested, have been isolated from the essential oil of *Pogostemon patchouli* Pellet. Spectral evidence was used to derive structures which were confirmed by total synthesis of patchoulipyridine and by conversion of guaiol to dihydroepiguaipyridine.

The voluminous literature on essential oil components refers to an enormous number of lower terpenes but to essentially no mono- and sesquiterpene alkaloids. By contrast alkaloids derived from diterpenes and steroids are widespread in plants. Furthermore, most recent investigations have shown the varied group of indole alkaloids to be biogenetically derived from monoterpenes.[2-4] This situation then raises the question of whether low molecular weight alkaloids derived from mono- and sesquiterpenes are indeed rare in nature or not sufficiently volatile to show up in essential oils or simply escaped detection.

In the course of structural studies on patchouli alcohol we had an opportunity to examine the oil of *Pogostemon patchouli* Pellet for alkaloidal constituents. Extraction of the essential oil with aqueous hydrochloric acid removed the basic constituents and chromatography of the regenerated bases yielded two pure substances which, for reasons to become clear in the sequel, we have named patchoulipyridine and epiguaipyridine. The former was obtained as colorless crystals and is optically active. Combustion analysis revealed a molecular composition of $C_{15}H_{21}N$ and this was reinforced by a mass spectrum. Patchoulipyridine exhibits ultraviolet light absorption typical of alkyl-substituted pyridines[5] and the substitution pattern became clear from the proton magnetic resonance spectrum. A low-field AB pattern (J = 8 cps) with chemical shifts of 7.38 and 6.88 ppm is attributed to the γ and β protons on the pyridine ring and a three-proton singlet at 2.48 ppm is assigned to a methyl group attached to the α position of this ring.[6] The two remaining locations on the pyridine nucleus are occupied by alkyl groups other than methyl. Two protons situated on carbon atoms adjacent to the aromatic ring give rise to two broad absorptions centered at 3.12 and 2.9 ppm, respectively. Singlets at 0.80, 1.03, and 1.26 ppm are assigned to three methyl groups and the remaining five protons appear as a very broad multiplet in the region of 1.7 ppm. Vinylic hydrogen atoms are clearly absent and the compound was indeed found to be resistant to catalytic reduction. The empirical formula dictates the presence of three rings and considering the coexistence of the alkaloid with patchouli alcohol (**1**),[7] α-patchoulene (**2**)[8] and β-patchoulene (**3**)[8] in the essential oil structure (**4**) for patchoulipyridine seemed most reasonable on biogenetic grounds. In agreement with this assignment ozonization yielded, *inter alia*, a



1 **2** **3** **4**

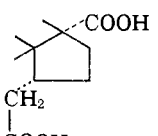
dicarboxylic acid which chromatographically was indistinguishable from homocamphoric acid (**5**) but positive identification was thwarted by lack of material.

More convincing evidence in favor of structure **4** was provided by synthesis. The acid-stable β-patchoulene (**3**) was selected as starting material and for nitrogen insertion we chose treatment with hydrazoic acid, a reaction which served previously in the synthesis of muscopyridine.[9] Exposure of β-patchoulene (**3**) to the action of hydrazoic acid in the presence of sulfuric acid furnished an unstable mixture of unsaturated amines which, after rapid distillation, was dehydrogenated in hot 1-methylnaphthalene over a carbon-supported palladium catalyst. Thin layer chromatographic analysis of the resulting basic products revealed the presence of two major, and at least one minor, components which were separated on a preparative scale by chromatography on silica gel. Both major constituents

(1) National Institutes of Health Postdoctoral Fellow, 1960–1962.
(2) F. McCapra, T. Money, A. I. Scott, and I. G. Wright, *Chem. Commun.*, 537 (1965).
(3) H. Goeggel and D. Arigoni, *ibid.*, 538 (1965).
(4) A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, *ibid.*, 46 (1966).
(5) H. E. Podall, *Anal. Chem.*, **29**, 1423 (1957).
(6) A detailed discussion of the nmr spectra of pyridines was presented by F. A. L. Anet, *Can. J. Chem.*, **36**, 902 (1958).
(7) M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Büchi, and J. Padilla, *Proc. Chem. Soc.*, 383 (1963).
(8) G. Büchi, R. E. Erickson, and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961).
(9) K. Biemann, G. Büchi, and B. H. Walker, *ibid.*, **79**, 5558 (1957).

were obtained in crystalline form and one of them was found to be identical in every respect, including optical rotation with patchoulipyridine (**4**). The conversion of β-patchoulene (**3**) to the alkaloid (**4**) also establishes the absolute configuration of the latter and in a formal sense represents a total synthesis because β-patchoulene (**3**) has previously been prepared from the elements.[10] The second of the major reaction products was a Schiff base of the composition $C_{15}H_{25}N$ but its detailed structure remains unknown.

The minor product from the dehydrogenation was purified further by preparative thin layer chromatography and obtained as a colorless liquid. It is isomeric with patchoulipyridine (**4**) and detailed comparison of the nuclear magnetic resonance spectrum with that of **4** provides support for structure **6**. The chemical shifts of the α- and β-pyridine protons are 8.15 and 6.78 ppm and the coupling constant of 6 cps is



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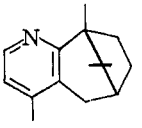

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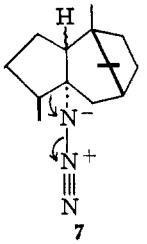
as expected.[6] In agreement with anticipation the two protons located on the carbon atom adjacent to the pyridine ring are shifted to higher field giving rise to broad signals at 2.78 and 2.53 ppm, respectively. A similar upfield shift to 2.14 ppm is observed for the methyl group now attached to the γ position of the pyridine ring while the chemical shifts and multiplicities of the remaining 14 protons are virtually identical. If attack of hydrazoic acid does lead to the two isomeric azides (**7** and **8**) the eventual production of two isomeric pyridines (**4** and **6**) can be explained (**7**, arrows; **8**, arrows).



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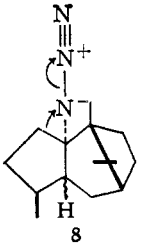

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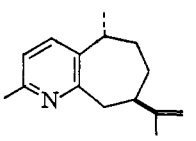
Epiguaipyridine, the second alkaloid isolated from patchouli oil, was obtained in the form of a colorless liquid. It is isomeric with patchoulipyridine (**4**), optically active, and according to its ultraviolet spectrum also a polysubstituted pyridine. It is most clearly distinguished from its companion alkaloid by the proton spectrum which agrees with structure **9**. Two pyridine protons appear as an AB pattern (J = 8 cps) at 7.28 and 6.88 ppm. The two vinylic hydrogens give rise to a broad signal at 4.7 ppm and the three protons situated on the two carbon atoms adjacent to the aromatic ring appear as a broad multiplet centered at 3.10 ppm. Methyl groups attached to the pyridine nucleus, the aliphatic double bond, and the cycloheptane ring are present as singlet, singlet with fine splitting, and doublet (J = 8 cps) at 2.47, 1.80, and 1.3 ppm, respectively. A broad area of absorption in the region of 1.90 ppm is caused by the remaining five cycloheptane hydrogens. Chemical evidence for the presence and location of the aliphatic double bond was adduced as follows. Catalytic hydrogenation gave dihydroepiguai-



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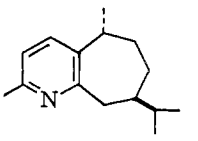

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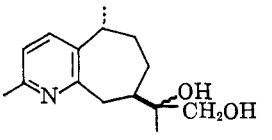

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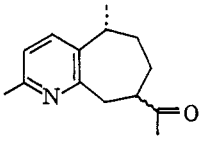

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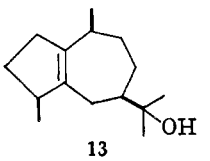
pyridine (**10**) and, in association with this change, signals due to the isopropenyl group in the nmr spectrum of the natural product **9** were now absent and a four-line pattern typical for an isopropyl group appears at 0.9 ppm. Furthermore, oxidation of the alkaloid **9** with osmium tetroxide yielded a mixture of diastereomeric diols (**11**) which was rapidly cleaved to formaldehyde and the methyl ketone (**12**) by means of periodic acid.

For final structure proof it was decided to synthesize dihydroepiguaipyridine (**10**). Guaiol (**13**), of established relative and absolute configuration,[11-13] was converted to dihydro-α-guaiene (**14**) by a known procedure.[14] Treatment with hydrazoic acid followed by dehydrogenation over palladium yielded a mixture of products and an nmr spectrum indicated the presence of two isomeric 2,3,6-trisubstituted pyridines in an approximate ratio of 5:1. These isomers were separable by preparative thin layer chromatography and the major component, dihydroguaipyridine (**15**), after



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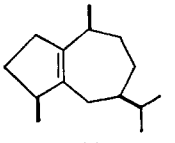
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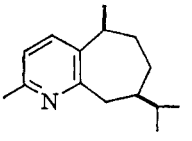

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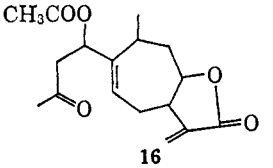

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further purification was obtained pure and characterized by preparation of a crystalline hydroperchlorate, $[\alpha]_D$ +6°. Nuclear magnetic resonance and infrared spectra were clearly different from those of the product prepared by catalytic hydrogenation of the original alkaloid (**9**) and it was assumed that the two sets of products differ in the configuration of the methyl group.

(10) G. Büchi and W. D. MacLeod, Jr., *J. Am. Chem. Soc.*, **84**, 3203 (1962); G. Büchi, W. D. MacLeod, Jr., and J. Padilla, *ibid.*, **86**, 4438 (1964).

(11) H. Minato, *Tetrahedron Letters*, 280 (1961); *Tetrahedron*, **18**, 365 (1962); K. Takeda and H. Minato, *Tetrahedron Letters*, **22**, 33 (1960).

(12) L. Doejš, A. Mironov, and F. Šorm, *ibid.*, **11**, 18 (1960).

(13) E. J. Eisenbraun, T. G., George, B. Riniker, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 3648 (1960).

(14) K. Takeda, H. Minato, and S. Nosaka, *Tetrahedron*, **13**, 308 (1961).

The minor product from the dehydrogenation was suspected to be the epimer **10** resulting from configurational inversion presumably triggered by the palladium catalyst. Indeed, further exposure of the original reaction mixture to this catalyst at elevated temperature caused further epimerization yielding an approximately equal mixture of isomers. Separation was achieved by preparative thin layer chromatography and the faster moving isomer was identified as dihydroepiguaipyridine (**10**) by comparison of infrared and mass spectra. The corresponding hydroperchlorates exhibited identical infrared spectra and identity was confirmed further by determination of melting points and mixture melting point. The synthetic salt had a specific rotation of $-1°$ while a value of $-8°$ was determined for the salt of "natural" dihydroepiguaipyridine. This observation shows that configurational equilibration is accompanied by extensive racemization and in view of the small optical rotation of the synthetic salt we only tentatively conclude that natural epiguaipyridine has the absolute configuration indicated in **9**. When a sample of dihydroepiguaipyridine (**10**) of natural provenance was equilibrated over a palladium-on-charcoal catalyst an approximately equal mixture of starting material (**10**) and its epimer (**15**) was produced. Chromatographic separation yielded pure dihydroguaipyridine (**15**), identical with material prepared from guaiol (**13**), but the optical rotation of the corresponding hydroperchlorate, $[\alpha]D$ $+0.5°$, not unexpectedly indicated essentially complete racemization.

Patchoulipyridine (**4**) and epiguaipyridine (**9**) are structurally related to the patchoulenes (**2** and **3**) and to guaiol (**13**), respectively. A biosynthetic derivation from these sesquiterpenes or their close relatives seems most likely, particularly if one considers that substances, *e.g.*, xanthinin (**16**),[15] containing the carbon skeleton present in epiguaipyridine (**9**) are already known to occur in nature.

Experimental Section

Melting points were observed in evacuated capillaries and are uncorrected. Ultraviolet spectra were obtained with a Cary, Model 11MS, automatic recording spectrophotometer. Infrared spectra were recorded with a Baird-Atomic Model AB-2 spectrophotometer using a beam condensing unit utilizing silver chloride lenses, and Perkin-Elmer Models 21, 137, and 237 double-beam spectrophotometers, as noted. Band centers are accurate to 5 cm^{-1} at wavenumbers below 1500 cm^{-1} and are followed parenthetically by the observed per cent transmission. All proton magnetic resonance spectra were obtained on a Varian Associates, Model A-60, high-resolution spectrometer using carbon tetrachloride solutions (unless otherwise noted) containing tetramethylsilane as an internal standard. Chemical shifts are presented in ppm downfield from the standard. The abbreviations s, d, t, and m refer to singlet, doublet, triplet, and multiplet, respectively. Low-resolution mass spectra were determined with a CEC Model 21-103C mass spectrometer. Thin layer chromatography was carried out on 250-μ thick layers of silica gel G employing solvent systems of 4.5% methanol in benzene ($R_f^{4.5\%}$) and 20% ethyl acetate in cyclohexane ($R_f^{20\%}$), unless otherwise noted. Preparative layers were 2 mm thick and prewashed with the solvent system used in the particular separation. The standard developing agent employed was Draggendorff's reagent unless otherwise noted. Vapor phase chromatography was carried out on a standard MIT unit employing a 5-ft column of 0.25-in. diameter containing 20% silicone grease on firebrick. The elemental analyses were carried out by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

(15) T. A. Geissman, *J. Org. Chem.*, 27, 2692 (1962).

Isolation of Epiguaipyridine (9) and Patchoulipyridine (4). Crude patchouli oil (1.4 kg) obtained from R. D. Webb and Co., New York, N. Y., was diluted with an equal volume of ether and extracted exhaustively (nine 75-ml portions) with dilute aqueous hydrochloric acid (0.02 *N*). All acidic aqueous portions were combined, made basic with 28% ammonia, and extracted repeatedly with ether. The organic portions were combined, washed, and dried (anhydrous magnesium sulfate), and the solvent was removed *in vacuo* to yield a dark yellow residue (923 mg). The combined material (1.82 g) from two successive 1.4-kg extractions was chromatographed on alumina (Woelm, almost neutral), activity grade I. Elution with 1% ether in pentane yielded a yellow oil (548 mg). Distillation (~60°, 0.1 mm) produced a colorless liquid base, epiguaipyridine (**9**): mol wt, 215 (mass spectrum), R_f 0.52 (5% methanol in benzene); vpc (210°) retention time 495 sec; $[\alpha]^{25.5}D$ $-34.5°$ (*c* 2.69, EtOH); λ_{max}^{EtOH} 278 mμ (sh) (ϵ 7959), 273 (sh) (5168), 270 (4962), 215 (sh) (3824); $\nu_{max}^{15\%\ CCl_4}$ 3077(68), 2962(14), 2922(7), 1779(91), 1644(46), 1591(23), 1574(31), 1462(6), 1439(27), 1402(58), 1377(35), 1349(81), 1335(80), 1284(80), 1262(84), 1254(85), 1242(79), 1224(83), 1193(85), 1162(80), 1128(59), 1089(86), 1070(75), 1040(73), 1027(71), 1001(69), 887(9), 817(51) (P and E 21); nmr ($CDCl_3$) 1.30 (d, 3 H) (*J* = 8 cps), 1.80 (s, 3 H), 1.90 (m, 5 H), 2.47 (s, 3 H), 3.10 (m, 3 H), 4.70 (m, 2 H), 6.88 (d, 1 H) (*J* = 8 cps), and 7.28 ppm (d, 1 H) (*J* = 8 cps).

Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.78; H, 9.89; N, 6.52.

Anal. Calcd for CH_3 (Kuhn–Roth): on C-1, 6.98; on C-2, 73.95. Found: 8.47.

Epiguaipyridine Hydroperchlorate. In ether solution **9** yielded a crystalline salt when titrated (congo red) with 10% methanolic perchloric acid. Recrystallization from methanol–ether afforded waxy plates: mp 105–105.5°; $[\alpha]^{29}D$ $-17°$ (*c* 8.00, EtOH); ν_{max}^{KBr} 3420(25), 2880(7), 2700(11), 1930(69B), 1635(6), 1605(27), 1545(43), 1448(28), 1383(49), 1369(43), 1325(71), 1304(64), 1280(70), 1265(73), 1220(69), 1200(51), 1109(0), 936(3), 889(37), 847(53), 823(62), 750(89), 713(85), 685(80), 620(34) (Baird Atomic, AB-2).

Anal. Calcd for $C_{15}H_{22}ClO_4N$: C, 57.05; H, 7.02; Cl, 11.23; N, 4.44. Found: C, 57.14; H, 7.07; Cl, 11.14; N, 4.42.

Further elution of the chromatogram with 5% ether in pentane yielded an additional oily base (155 mg). Distillation of the residue (~80°, 0.1 mm) afforded patchoulipyridine (**4**) as white waxy needles: mp 24–26.5°; mol wt, 215 (mass spectrum); $[\alpha]^{28}D$ $-31.3°$ (*c* 5.06, EtOH); $R_f^{4.5\%}$ 0.60; vpc (205°) retention time 386 sec; λ_{max}^{EtOH} 283 mμ (ϵ 4658), 277 (sh) (5913), 273 (6270), 270 (sh) (5465), 217 (6450); ν_{max}^{neat} 3060(72), 2975(5), 2950(3), 2920(6), 2875(16), 2845(63), 1590(21), 1575(43), 1480(16), 1468(7), 1447(22), 1434(23), 1410(60), 1395(18), 1380(33), 1375(45), 1340(62), 1318(61), 1283(81), 1267(76), 1260(61), 1240(85), 1212(88), 1168(51), 1139-(81), 1127(76), 1098(45), 1086(71), 1056(73), 1032(67), 1009(93), 983(94), 961(80), 945(83), 935(92), 922(93), 880(85), 864(83), 824(38), 803(89), 782(85), 766(41), 725(93), 709(80), 667(81), 639(65) (P and E 237); nmr ($CDCl_3$) 0.80 (s, 3 H), 1.03 (s, 3 H), 1.26 (s, 3 H), 1.7 (m, 5 H), 2.48 (s, 3 H), 2.90 (m, 1 H), 3.12 (m, 1 H), 6.88 (d, 1 H) (*J* = 8 cps), and 7.38 ppm (d, 1 H) (*J* = 8 cps).

Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.61; H, 10.02; N, 6.37.

Patchoulipyridine Hydroperchlorate. An ether solution of **4** yielded a crystalline salt when titrated (congo red) with 10% methanolic perchloric acid. Recrystallization from methanol–ether afforded white needles: mp 276–279°; ν_{max}^{KBr} 3170(8), 2920(5), 2840(12), 1638(6), 1605(23), 1576(61), 1545(30), 1475(35), 1444(20), 1388(36), 1374(31), 1328(55), 1297(52), 1268(34), 1231(72), 1210(62), 1179(33), 1157(25), 1137(20), 1092(0), 1048(13), 951(69), 936(77), 924(75), 915(78), 870(58), 850(41), 817(27), 776(61), 737(77), 720(86), 696(77), 662(80), 620(36) (Baird Atomic AB-2).

Anal. Calcd for $C_{15}H_{22}ClO_4N$: C, 57.05; H, 7.02; Cl, 11.23; N, 4.44. Found: C, 56.75; H, 7.03; Cl, 11.43; N, 4.38.

Anal. Calcd for CH_3 (Kuhn–Roth): on C-1, 4.75; on C-2, 9.42. Found: 7.02.

Oxidation of Patchoulipyridine (4). A solution of patchoulipyridine (**4**, 34 mg, 0.16 mmole) in 2 ml of glacial acetic acid was allowed to react with ozone (output of Welsbach ozonizer, Model T19, with oxygen input) at room temperature for 4 hr. The mixture was poured into ice-cold 5% aqueous hydrogen peroxide and allowed to stand overnight at room temperature. The aqueous solution was then allowed to reflux for 2 hr and was then extracted with ether. The ether extracts were washed with 1% sodium hydroxide solution and water, and dried over anhydrous sodium sulfate. Removal of the ether *in vacuo* gave 24 mg of starting

material. The basic extracts were acidified with 10% hydrochloric acid and extracted continuously for 72 hr with 50 ml of ether. The ether extracts were washed with water and dried over anhydrous sodium sulfate. Removal of the ether gave a yellow residue (8 mg). A portion of this material was compared using tlc on silica gel G against a reference sample of homocamphoric acid (**5**) using a solvent system of chloroform saturated with formic acid. Color development of migration areas was accomplished with bromothymol blue as the detection agent. Although the residue was shown to contain several components, the major migration area possessed both an R_f value and a coloration (yellow) identical with that of the reference compound (**5**).

Synthesis of Patchoulipyridine (4). In a 100-ml, three-neck flask, fitted with thermometer, dropping funnel, and reflux condenser, which was connected to a gas-measuring buret, a mixture of 65 ml of chloroform (Mallinckrodt, analytical reagent), 2 ml of absolute ethanol, and 3 ml of concentrated sulfuric acid was heated at 50°. While the contents of the flask were stirred magnetically a solution of 2.1 g (0.01 mole) of β-patchoulene (**3**) in 12 ml (0.02 mole) of 1.7 *N* hydrazoic acid in chloroform[16] was added during 1 hr (125 ml of nitrogen evolved). A total of 2.4 ml of concentrated sulfuric acid was added in three portions during the following 2 hr, and an additional 200 ml of nitrogen was evolved during that time. The mixture was cooled to 0°, poured into 40 ml of ice-cold sodium chloride solution and 10 g of ice, and made slightly alkaline (pH 8) with cold, concentrated sodium hydroxide. The mixture was stirred and kept between 0 and 10° while adding the base. The chloroform phase was separated, the aqueous layer was extracted twice (two 30-ml portions) with chloroform, and the combined chloroform portions were washed with sodium chloride solution, dried (anhydrous sodium sulfate), and concentrated *in vacuo* at *ca.* 30°. The remaining brown oil was distilled (Späth bulb) quickly at 1 mm and a bath temperature of 145–185°. The residue formed a dark resin. The distillate (730 mg), a slightly yellow oil, was dissolved in 3 ml of 1-methylnaphthalene (predistilled from 10% palladium on carbon) and the mixture was heated under reflux in a metal bath with 150 mg of 10% palladium on carbon. A stream of carbon dioxide was passed through the apparatus[17] and the rate of evolution of hydrogen was followed by absorbing the carrier gas in potassium hydroxide solution. After 3.5 hr hydrogen evolution was complete and the cooled reaction mixture was diluted with petroleum ether (3 ml, bp 39–53°), filtered (deactivated alumina), and extracted three times (three 5-ml portions) with 2% sulfuric acid. The aqueous phase was washed with petroleum ether, alkalized, and extracted again with petroleum ether. The petroleum ether was washed twice with water (two 2-ml portions) and dried over anhydrous sodium sulfate; the solvent was evaporated *in vacuo* to give 300 mg of a brownish oil. The combined crude dehydrogenation products from two additional reactions (total β-patchoulene (**3**) employed, 20.4 g) amounted to 6.68 g. Thin layer chromatographic analysis of the crude reaction products gave identical results in each case, and indicated the presence of at least two major components ($R_f^{4.5\%}$ 0.60 and 0.15, vpc (205°) retention time 386 and 486 sec) in addition to several minor basic products, one of which possessed an $R_f^{4.5\%}$ value (0.65) similar to that of one of the major components. The combined crude products were chromatographed on silica gel (180 g) employing benzene and chloroform as eluates (see Table I).

Table I

Fractions	Solvent	Wt, g	Thin layer R_f values
4,5	$CHCl_3$	0.225	0.65, 0.60 (~1:2)
6–15	$CHCl_3$	1.932	0.60
17–21	$CHCl_3$	2.965	0.10

Distillation of the combined fractions 6–15 at ~80° (0.1 mm) gave 1.28 g of a colorless liquid which was dissolved in ether and titrated (congo red) with 10% methanolic perchloric acid. Three recrystallizations from methanol–ether afforded 1.08 g of patchoulipyridine hydroperchlorate as fine white needles, mp 276–279°. This material was identical in infrared spectrum, melting point, and mixture melting point with a sample prepared from the natural base. The hydroperchlorate (962 mg) on treatment with dilute sodium hydroxide yielded the free base which on extraction, drying, and distillation gave patchoulipyridine (**4**, 643 mg), mp 23–25°. This material was identical in optical rotation, infrared spectrum, nuclear magnetic resonance spectrum, mass spectrum and thin-layer R_f values with the natural alkaloid.

Isolation of pure compounds from the combined fractions 4 and 5 (225 mg) was possible only by preparative thin layer chromatography (700 μg/cm, 4% ethanol in cyclohexane) and furnished 65 mg of pseudopatchoulipyridine (**6**) as a colorless liquid: $R_f^{4.5\%}$ 0.65; ν_{max}^{neat} 3090(72), 2970(22), 1595(48), 1575(68), 1465(54), 1440(46), 1395(56), 1380(60), 1360(64), 1300(79), 1257(89), 1240(89), 1224(88), 1209(81), 1149(77), 1127(86), 1100(78), 1080(88), 1064(78), 1020(86), 992(43), 966(93), 947(90), 934(92), 922(93), 912(92), 883(93), 847(82), 821(62), 804(90), 795(90), 750(91), (P and E 137); nmr 0.80 (s, 3 H), 1.04 (s, 3 H), 1.33 (s, 3 H), 1.70 (m, 5 H), 2.14 (s, 3 H), 2.53 (m, 1 H), 2.78 (m, 1 H), 6.78 (d, 1 H) (J = 6 cps), and 8.15 ppm (d, 1 H) (J = 6 cps).

Pseudopatchoulipyridine Hydroperchlorate. An ether solution of **6** when titrated (congo red) with 10% methanolic perchloric acid yielded a crystalline derivative. Four recrystallizations from methanol–ether gave 44 mg of pseudopatchoulipyridine hydroperchlorate as fine, white needles: mp 143–145°; $[\alpha]^{30}D$ −57° (*c* 6.30, EtOH); ν_{max}^{KBr} 3430(30), 3205(40), 3020(25), 2950(6), 1625(6), 1600(18), 1514(21), 1478(27), 1469(20), 1447(28), 1420(49), 1391(47), 1375(47), 1369(51), 1348(71), 1337(58), 1295(37), 1283(54), 1261(44), 1253(32), 1230(67), 1206(47), 1176(44), 1109(0), 1055(17), 1035(39), 1009(66), 970(76), 949(73), 940(66), 925(67), 848(70), 815(43), 792(47), 757(76), 677(82), 620(36) (Baird Atomic AB-2).

Anal. Calcd for $C_{15}H_{22}ClO_4N$: C, 57.05; H, 7.02; Cl, 11.23; N, 4.44. Found: C, 57.04; H, 7.10; Cl, 11.34; N, 4.30.

Fractions 17–21 contained the second major component ($R_f^{4.5\%}$ 0.1) in the form of a dark oil. A portion (1.01 g) of this material was purified *via* the hydroperchlorate salt. After distillation the free base (94 mg) was obtained in large, lustrous, white needles, mp 64–65°; $[\alpha]^{29}D$ −157° (*c* 13.20, EtOH); vpc (205°) retention time 486 sec; $R_f^{4.5\%}$ 0.15; $\lambda_{max}^{isooctane}$ 253 mμ (ε 174); λ_{max}^{EtOH} 242 mμ (ε 198); ν_{max}^{neat} 3420(70), 3190(79), 2880(3), 1700(85), 1648(10), 1438(20), 1425(18), 1372(30), 1355(26), 1324(72), 1310(63), 1300(79), 1250(78), 1227(61), 1194(65), 1166(79), 1149(70), 1126(48), 1108(46), 1083(60), 1072(84), 1067(84), 1035(64), 1010(92), 997(83), 983(70), 972(67), 951(58), 940(45), 925(77), 905(78), 893(91), 870(91), 848(91), 830(87), 808(82), 748(83), 739(77), 700(87), 687(75) (P and E 137); nmr 0.72, 0.83, 0.90, 0.94, 1.03, 1.07, 1.35, 1.74, 2.27, 3.65, and 3.80 ppm.

Anal. Calcd for $C_{15}H_{25}N$: C, 82.12; H, 11.49; N, 6.39. Found: C, 82.38; H, 11.50; N, 6.34.

Methyl Ketone 12. Epiguaipyridine (**9**, 164 mg, 0.77 mmole), dissolved in pyridine (2 ml), was mixed with a solution of osmium tetroxide (390 mg, 1.54 mmoles) in pyridine (4 ml) and the solution was stored at room temperature. After approximately 24 months the dark brown supernatant liquid was decanted into a solution of 10% mannitol and 1% potassium hydroxide (20 ml) and the mixture was stored overnight. The combined ether portions from several extractions of the basic solution were washed with water and dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to yield 117 mg of a viscous yellow oil. Chromatography on alumina (20 g), activity I, gave a mixture of diols (**10**) (ν_{max}^{neat} 3450(22), ref 2920(20), 1043(26)) on elution with methanol.

To a solution of the diols (**10**, 74 mg, 0.30 mmole) in 5 ml of water at room temperature was added periodic acid dihydrate (90 mg, 0.35 mmole). After 24 hr the reaction mixture was alkalized with saturated sodium bicarbonate solution and extracted repeatedly with ether. On treatment with a saturated solution of dimedone reagent the basic, aqueous phase formed a crystalline precipitate. The dimedone derivative (25 mg, 0.1 mmole) was collected by filtration, washed, and dried (mp 187–189°), and exhibited no depression when admixed with an authentic sample of the formaldehyde dimedone condensation product. The ether extracts were washed with water and dried (anhydrous sodium sulfate), and the solvent was removed *in vacuo* to give 50 mg of an oily residue. Column chromatography on alumina (10 g), activity grade II, employing 5% ether in benzene afforded 29 mg (fractions 3–5) of the crystalline methyl ketone (**12**): mp 48–49°; R_f 0.13 (5% methanol in benzene); $\nu_{max}^{CCl_4}$ 3105(70), 2960(6), 1720(0), 1598(22), 1585(35), 1460(1), 1442(16), 1440(55), 1375(27), 1355(14), 1321(63), 1310(51), 1283(43),

(16) H. Wolff, *Org. Reactions*, **3**, 307 (1946).
(17) L. F. Fieser in "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 461.

1248(49), 1216(54), 1157(10), 1123(66), 1089(50), 1068(75), 1038-(50), 1009(70), 996(67), 970(78), 944(61), 897(87) (P and E 137).

Hydroperchlorate of the Methyl Ketone 12. On titration (congo red) with 10% methanolic perchloric acid an ether solution of **12** yielded a crystalline salt. Three recrystallizations from methanol–ether gave 32 mg of the hydroperchlorate, mp 206–207°; $[\alpha]^{30}D$ +18° (*c* 4.20, EtOH); ν_{max}^{KBr} 3420(37), 3290(40), 3190(42), 3090(26), 2970(27), 2910(26), 2700(59), 1712(13), 1652(13), 1610(38), 1557-(53), 1503(78), 1465(62), 1450(44), 1419(55), 1377(59), 1357(31), 1348(45), 1324(81), 1303(53), 1294(53), 1285(68), 1260(37), 1234-(80), 1210(71), 1182(36), 1162(31), 1129(13), 1109(0), 1058(4), 995(13), 983(76), 950(55), 927(59), 892(79), 868(87), 849(45), 817-(59), 752(96), 731(91) (Baird Atomic AB-2).

Anal. Calcd for $C_{14}H_{20}ClO_5N$: C, 52.91; H, 6.34; Cl, 11.16; N, 4.41. Found: C, 53.57; H, 6.40; Cl, 11.08; N, 4.24.

Catalytic Reduction of Epiguaipyridine (9). Epiguaipyridine (411 mg) was dissolved in 20 ml of ethyl acetate and hydrogenated at room temperature and at atmospheric pressure (uptake 45 ml, theoretical 43 ml) over 10% palladium on carbon (100 mg). The catalyst was removed by filtration and evaporation of the solvent *in vacuo* followed by distillation (~80° at 0.1 mm) gave 376 mg of a colorless liquid, dihydroepiguaipyridine (**10**): mol wt, 217 (mass spectrum); $R_f^{20\%}$ 0.60; vpc (210°) retention time 259 sec; ν_{max}^{neat} 3070(68), 2930(3), 2870(7), 1590(18), 1565(29), 1453(3), 1392-(50), 1377(34), 1360(35), 1338(59), 1313(78), 1288(81), 1269(79), 1250(70), 1235(73), 1207(88), 1192(84), 1160(60), 1139(83), 1122-(70), 1100(74), 1087(77), 1058(78), 1025(59), 1010(80), 1000(64), 953(88), 930(82), 919(89), 900(88), 885(91), 820(40), 798(60), 769-(83), 763(82), 724(91), 714(91), 688(85) (P and E 137); nmr 0.90 (2 d, 6 H) (J = 6 cps), 1.26 (d, 3 H) (J = 7 cps), 1.65 (m, 6 H), 2.39 (s, 3 H), 2.94 (m, 3 H), 6.73 (d, 1 H) (J = 8 cps) and 7.15 ppm (d, 1 H) (J = 8 cps).

Dihydroepiguaipyridine Hydroperchlorate. On titration with 10% methanolic perchloric acid an ether solution of **10** afforded the salt. Several recrystallizations from methanol–ether gave the hydroperchlorate: mp 88–89°; $[\alpha]^{29}D$ −8° (*c* 6.50, EtOH); ν_{max}^{KBr} 3440(32), 2910(13), 2840(14), 2690(24), 1930(80B), 1660(76), 1650(65), 1634(17), 1606(45), 1551(59), 1509(85), 1497(86), 1460-(39), 1445(49), 1436(58), 1410(71), 1392(53), 1384(63), 1333(77), 1301(74), 1286(79), 1261(78), 1236(80), 1204(70), 1174(51), 1140-(30), 1100(0), 1048(36), 1006(67), 935(77), 923(78), 900(80), 880-(76), 851(70), 825(77), 813(85), 792(92), 775(96), 757(96), 720(90), 686(90), 620(43) (Baird Atomic AB-2).

Anal. Calcd for $C_{15}H_{24}ClO_4N$: C, 56.68; H, 7.61; Cl, 11.16; N, 4.41. Found: C, 56.49; H, 7.57; Cl, 10.95; N, 4.25.

Dihydro-α-guaiene (14), $[\alpha]^{30}D$ −32° (*c* 1.86), was prepared from guaiol (**13**) *via* α-guaiene by reduction over Raney nickel W2[18] in dioxane–methanol containing sodium hydroxide.

Partial Synthesis of Dihydroguaipyridine (15) and Dihydroepiguaipyridine (10). In a 100-ml, three-neck flask, fitted with thermometer, dropping funnel, and reflux condenser, which was connected to a gas-measuring column, a mixture of 325 ml of chloroform (Mallinckrodt, analytical reagent), 11 ml of absolute ethanol, and 16 ml of concentrated sulfuric acid was heated at 50°. While the contents of the flask were stirred magnetically a solution of 10.3 g (0.05 mole) of dihydro-α-guaiene (**14**) in 65 ml (0.10 mole) of 1.6 *N* hydrazoic acid in chloroform was added during 1 hr. A total of 12 ml of concentrated sulfuric acid was added in three portions during the following 2 hr; 1500 ml of nitrogen was evolved during the 3-hr period. The reaction mixture was worked up as described in the preparation of **4** and on flash distillation gave 5.8 g of a clear yellow oil. Dehydrogenation over 10% palladium on carbon (733 mg) in 1-methylnaphthalene (18 ml) at 220–270° for 3 hr followed by work-up, combination with the product from an identical reaction, and final distillation (~80° at 0.1 mm) yielded a colorless liquid (3.8 g.). Although thin layer chromatography in one solvent system indicated a single product ($R_f^{4.5\%}$ 0.70), the nmr spectrum was not identical with that of "natural" dihydroepiguaipyridine and suggested the presence of a mixture of 2,3,6-trisubstituted pyridines (δ 7.15 ppm and δ 7.20 ppm). Thin layer chromatography in another solvent system revealed a second product (~20%, $R_f^{20\%}$ 0.60) in addition to the major component ($R_f^{20\%}$ 0.55).

A portion of the crude reaction product was submitted to preparative thin layer chromatography (cyclohexane–ethyl acetate, 80:20). Removal of the back section of the product band and isolation gave a crude residue (184 mg) which was subjected to further separation by eight repetitive column chromatograms on alumina, activity grade I. Fraction 5 (11 mg) of chromatogram 8 contained dihydroguaipyridine (**15**), a colorless liquid: $R_f^{20\%}$ 0.55; mol wt, 217 (mass spectrum); ν_{max}^{neat} 3060(68), 2930(6), 2870(10), 1585(19), 1570-(29), 1455(6), 1435(18), 1388(42), 1378(35), 1360(27), 1340(49), 1322(66), 1310(68), 1280(68), 1268(68), 1248(61), 1207(74), 1160-(45), 1137(78), 1114(73), 1091(62), 1083(69), 1060(72), 1025(60), 1014(67), 1000(75), 960(83), 944(82), 915(86), 904(76), 893(79), 835(59), 826(48), 808(35), 796(79), 763(74), 758(75), 734(78), 688-(82) (P and E 137); nmr 0.96 (2 d, 6 H) (J = 7 cps), 1.27 (d, 3 H) (J = 7 cps), 1.72 (m, 6 H), 2.41 (s, 3 H), 2.87 (m, 3 H), 6.76 (d, 1 H) (J = 7.5 cps), and 7.20 ppm (d, 1 H) (J = 7.5 cps).

The hydroperchlorate of fractions 4–6 (38 mg) from chromatogram 8 was prepared by titration (congo red) with 10% methanolic perchloric acid. Two recrystallizations gave 29 mg of pure salt: mp 142–143°; $[\alpha]^{30}D$ +6° (*c* 4.83, EtOH); ν_{max}^{KBr} 3270(40), 3010(46), 2940(19), 2900(18), 2840(24), 2610(8), 1909(70), 1640(23), 1608(48), 1552(69), 1457(51), 1436(69), 1384(66), 1373(61), 1363-(66), 1344(74), 1320(84), 1302(65), 1276(89), 1261(86), 1215(82), 1176(43), 1141(2), 1113(2), 1085(2), 1042(60), 1024(70), 1016(76), 991(79), 966(76), 948(84), 937(86), 922(93), 908(81), 887(93), 848-(62), 838(83), 814(87), 771(98), 729(97), 708(90) (Baird Atomic AB-2).

Anal. Calcd for $C_{15}H_{24}ClO_4N$: C, 56.68; H, 7.61; Cl, 11.16; N, 4.41. Found: C, 56.36; H, 7.67; Cl, 10.93; N, 4.39.

A portion (160 mg) of the mixture of products obtained in the dehydrogenation reaction was dissolved in 1-methylnaphthalene (10 ml) and allowed to reflux for 3.5 hr over 10% palladium on carbon (160 mg). Work-up and distillation afforded 127 mg of material which was equilibrated further in Nujol (3 ml) over 30% palladium on carbon (120 mg) at 285–295° during 7 hr. Isolation and distillation gave a product (88 mg) which according to thin layer chromatography was an approximately 1:1 mixture of epimers. Four repetitive preparative thin layer separations (cyclohexane–ethyl acetate, 80:20) gave on removal (water used to make the bands visible) and extraction of the band front, dihydroepiguaipyridine (**10**, 33 mg) as a colorless liquid. Comparison of infrared and mass spectra and $R_f^{20\%}$ value revealed identity with dihydroepiguaipyridine (**10**) prepared by catalytic reduction of epiguaipyridine (**9**). The hydroperchlorate, $[\alpha]^{29}D$ −1° (*c* 1.83, EtOH), of the synthetic base after two recrystallizations from ether (11 mg) had mp 86–89° and was found to be identical with the salt of authentic dihydroepiguaipyridine (**10**) as judged by comparison of infrared spectra. A mixture of the two salts had mp 86–89°.

Equilibration of Dihydroepiguaipyridine (10) and Dihydroguaipyridine (15). Dihydroepiguaipyridine (**10**) of "natural" provenance (260 mg, 1.20 mmoles) was dissolved in Nujol (5 ml) and heated (300–310°) over 30% palladium on carbon for 2 hr. Isolation followed by distillation gave 243 mg of bases of which 157 mg was dissolved in Nujol (1 ml). The mixture was heated to 300° for 24 hr over a 30% Pd-on-C catalyst. Conventional work-up and distillation furnished a mixture of products (78 mg) which according to its nmr spectrum contained approximately equal amounts of the two epimers **10** and **15**. Preparative thin layer separation (700 μg/cm, removal of the rear portion of the band) followed by isolation gave dihydroguaipyridine (**15**) (23 mg). Identity was ascertained by comparison of infrared spectra and $R_f^{20\%}$ values with those of a sample prepared from dihydro-α-guaiene (**14**). The hydroperchlorate, $[\alpha]^{29}D$ +0.5° (*c* 1.57, EtOH), mp 136–38°, exhibited an infrared spectrum identical with that of synthetic dihydroguaipyridine and a mixture of the two salts had mp 138–140°.

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(18) H. R. Billica and H. Adkins, *Org. Syn.*, **21**, 15 (1941).