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THE STRUCTURE OF MITRAPHYLLINE[1]

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ABSTRACT

Mitraphylline ($C_{21}H_{24}O_4N_2$) contains a carbomethoxyl group, and on hydrolysis gives rise to mitraphyllic acid. Spectroscopic evidence shows that the alkaloid contains two chromophores, one characteristic of an oxindole and one corresponding to the grouping $CH_3OOC—C(=CH.OR)$. On treatment with dilute mineral acid the alkaloid gives rise to mitraphyllal ($C_{19}H_{24}O_3N_2$), which is a hemiacetal that no longer contains the isolated double bond and the carbomethoxyl group originally present in the alkaloid. Reduction of mitraphyllal by the Wolff–Kishner reaction gives mitraphyllane ($C_{19}H_{26}O_2N_2$). The dehydrogenation of mitraphyllal produced 3,4-diethylpyridine and 3-ethyloxindole. The action of lithium aluminum hydride on mitraphylline under mild conditions gave rise to mitraphyllol by reduction of the carbomethoxyl group, and under more vigorous conditions to dihydrodesoxy-mitraphyllol by reduction of the oxindole carbonyl as well. This last product has the properties of an aromatic amine. On the basis of the new experimental evidence, a total structure of mitraphylline is derived.

Mitraphylline has been isolated from *Mitragyna rubrostipulacea* Havil. (= *Adina rubrostipulata* K. Schuman)[3] by Michiels (1), by Denis (2), and also by Raymond-Hamet (3). Michiels (4) also isolated it from *M. stipulosa* Kuntze (= *M. macrophylla* Hiern.). In all cases except one (5) the alkaloid has been isolated in the laevorotatory form. It has been assigned the formula $C_{21}H_{24(26)}O_4N_2$, and assumed to contain a carbomethoxyl group and one C-methyl group (6). Distillation of mitraphylline hydrochloride from zinc dust under reduced pressure yields a neutral substance $C_{10}H_9ON$, 3,4-diethylpyridine, and isoquinoline (6, 7). The same neutral substance has also been obtained from rhyncophylline (8) and uncarine-A (9). It has been converted to 3-ethyloxindole by hydrogenation (7). Wenkert and Reid (10) have suggested that it was probably spiro-3,3-cyclopropyloxindole, and the identity has since been established by Kondo *et al.* (11) by direct comparison with a synthetic specimen. A monoacetyl derivative has been reported (7). Mitraphylline gives a yellow color with tetranitromethane, forms an amorphous dibromide, and when hydrogenated over Adams' catalyst absorbs 3 moles of hydrogen, but over a palladium catalyst, it is reported to absorb only 1 mole (5).

Mitraphylline has now been re-examined and sufficient additional evidence obtained to make it possible for us to advance a total structure for the alkaloid. Although many references to mitraphylline in the literature (6) include an expanded formula showing a

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[2]*National Research Council of Canada Postdoctorate Fellow.*
[3]*The identity of this species seems to be controversial. Certain authors include it in the genus Mitragyna. Botanically, the two genera are very close, but it has been claimed that there are sufficient criteria to include the species in the genus Adina. The plant has been studied successively under several names. For a botanical description of the plant see J. Lebrun, Les essences forestières du Congo Belge, Publication INEAC, Vol. 2, p. 220, Brussels, 1939.*

carbomethoxyl group, the presence of such a group does not seem to have been demonstrated experimentally before. The analysis of mitraphylline and its degradative products confirm the formula $C_{21}H_{24}O_4N_2$. The base was hydrolyzed with potassium hydroxide to the crystalline mitraphyllic acid, $C_{20}H_{22}O_4N_2$. When re-esterified with methanol and hydrogen chloride the acid was partially reconverted to mitraphylline which, however, was contaminated with another product and could not be completely purified. Its X-ray powder diagram contained all the lines present in the X-ray diagram of pure mitraphylline, but a few additional faint lines were also present.

The ultraviolet spectrum of mitraphylline is identical with that of rhyncophylline, which has been shown to be made up of contributions from an oxindole chromophore and the grouping $CH_3O_2C—\acute{C}=CH.OR$ (12). The infrared absorption spectrum in chloroform shows a band at 3415 cm.$^{-1}$ indicative of an imino group, and in nujol mull it contains bands at 1725 and 1704 cm.$^{-1}$ attributable to an ester carbonyl and an oxindole carbonyl respectively, at 1626 and 755 cm.$^{-1}$ due to a benzene ring, and at 1105 cm.$^{-1}$ indicative of a cyclic ether. The intensity of the absorption at 1626 cm.$^{-1}$, however, is greater than that expected for a benzene ring, and it is probable that it also includes a contribution from a polarized double bond.

Hydrogenation of the alkaloid in acetic acid solution over a platinum catalyst yielded a hexahydroderivative $C_{21}H_{30}O_4N_2$. The absence of a band at 755 cm.$^{-1}$ in the infrared absorption spectrum of this product indicated that the benzene ring had been hydrogenated. The fact that the ultraviolet spectrum did not contain the usual absorption of an oxindole chromophore confirmed this, while the retention of the strong absorption at 239 mμ, due to the grouping $CH_3OOC—\acute{C}=CH.OR$, showed that the isolated double bond had not been affected (cf. 5). The presence of a band at 1626 cm.$^{-1}$ in the infrared spectrum of the product is also probably due to this double bond.

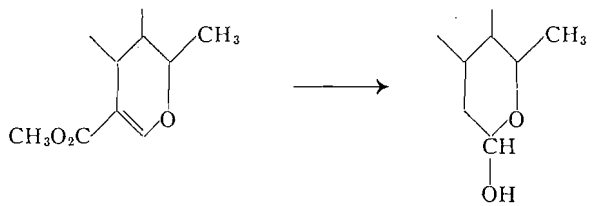
Reduction of mitraphylline with lithium aluminum hydride at room temperature gave rise to an alcohol, $C_{20}H_{24}O_3N_2$, that we propose to designate as mitraphyllol. Its infrared absorption spectrum contained a split oxindole carbonyl at 1730–1708 cm.$^{-1}$, and a band at 1654 cm.$^{-1}$ indicating that the enol–ether grouping was still present. The shift of the last absorption band from 1626 cm.$^{-1}$ (in the spectrum of mitraphylline) was to be expected because reduction of the ester to a primary alcohol group would remove the conjugation. The ultraviolet spectrum of mitraphyllol is that of a simple oxindole.

Under more vigorous conditions, the reduction of mitraphylline with lithium aluminum hydride produced dihydrodesoxy-mitraphyllol, $C_{20}H_{26}O_2N_2$. The infrared spectrum of this product showed no carbonyl absorption, but still contained a band at 1660 cm.$^{-1}$ due to the absorption of the enol–ether double bond. The ultraviolet spectrum was that of an aromatic amine, and indeed, dihydrodesoxy-mitraphyllol coupled with diazotized sulphanilic acid to form an indicator-type dye. Since this reduction of the oxindole carbonyl produced an amine and not an indole derivative it can be concluded that the 3-position of the oxindole system in the alkaloid must be disubstituted (13).

Acid hydrolysis of mitraphylline gave rise to a basic product (cf. 12) which could not be crystallized, but formed a crystalline picrate in methanol. The base regenerated from the picrate was a well-defined crystalline substance, $C_{20}H_{26}O_3N_2$, containing one methoxyl group. The presence of a methoxyl seemed to indicate that the expected aldehyde had, in the presence of methanol, been converted to a hemiacetal. That this was actually so became apparent when the crystalline base was obtained on treatment of the amorphous hydrolysis product with 1% methanolic hydrogen chloride. The ultraviolet spectrum of the crystalline product was that of a simple oxindole, thus indicating that the enol–ether

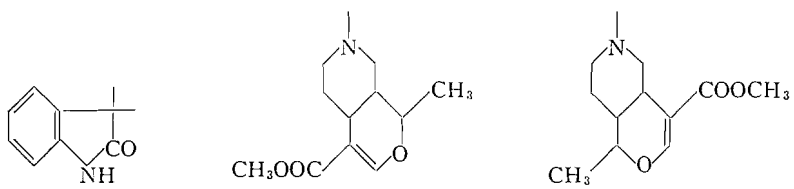
system was no longer present. The infrared absorption spectrum contained a split oxindole carbonyl band at 1695–1730 cm.$^{-1}$, bands at 1625 and 750 cm.$^{-1}$ due to the benzene ring, and three new bands at 1180, 1140, and 1060 cm.$^{-1}$ which are reported to be characteristic of an acetal (14). The crystalline product $C_{20}H_{26}O_3N_2$, for which we suggest the name methylmitraphyllal, gave on hydrolysis a base which could not be induced to crystallize. This base contained no methoxyl group, it slowly reduced Tollens' reagent, and could be methylated in almost quantitative yield to methylmitraphyllal. Its infrared spectrum contained no absorption attributable to an aldehyde, but did contain an absorption band in the hydroxyl region, and therefore the amorphous substance must be a hemiacetal and will be designated as mitraphyllal. Further evidence that mitraphyllal was a hemiacetal was provided by the Wolff–Kishner reduction, which yielded mitraphyllane ($C_{19}H_{26}O_2N_2$), an amorphous product isolated as its crystalline picrate. As expected, the infrared absorption spectrum of mitraphyllane in chloroform contained a peak at 3600 cm.$^{-1}$ indicating the presence of a hydroxyl group.

The formation of mitraphyllal and methylmitraphyllal is consistent with the presence in the alkaloid of the cyclic system I since hydrolysis of the ester and the enol–ether group followed by decarboxylation and cyclization would result in the formation of a hemiacetal II.



I II

Dehydrogenation of mitraphyllal with palladium–charcoal produced 3,4-diethylpyridine and 3-ethyloxindole. Hence the experimental evidence indicates the presence in the alkaloid of fragment III and either fragment IV or V. It was hoped to distinguish between IV and V by means of the dehydrogenation product of mitraphyllol, which was expected

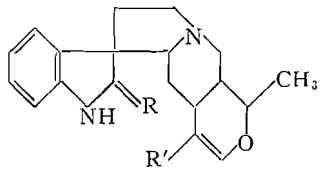


III IV V

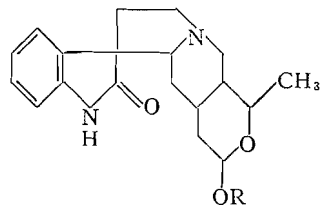
to be 3-ethyl-4-isopropylpyridine. Unfortunately, this dehydrogenation either with selenium or with palladium produced 3,4-diethylpyridine. Biogenetically, however, structural element IV is more likely than V. Furthermore, structure IV occurs in a number of carboline alkaloids (15–18) whereas structure V has not yet been found. Also, IV definitely corresponds to the structure of rhyncophylline (12) and may legitimately be assumed to be present in mitraphylline.

The biogenetic derivation of mitraphylline is probably similar to that suggested for rhyncophylline (12) involving the same starting materials. As for rhyncophylline, the α-position of the piperidine ring would be linked to the 3-position of the oxindole system,

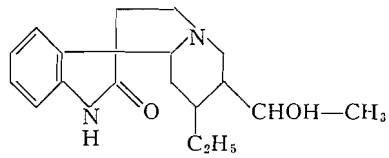
and therefore, the structure of mitraphylline must be that shown in formula VI (R = O, R′ = CO_2CH_3). On the basis of this formula, the structures of the various derivatives



VI (R = O; R′ = CO_2CH_3)
VII (R = O; R′ = CH_2OH)
VIII (R = H_2; R′ = CH_2OH)



IX (R = H)
X (R = CH_3)



XI

of mitraphylline became obvious. Thus mitraphyllol is represented by VII, dihydrodesoxymitraphyllol by VIII, mitraphyllal by IX, methylmitraphyllal by X, and mitraphyllane by XI.

Just as rhyncophylline is the oxindole analogue of corynantheine, mitraphylline is the oxindole analogue of the four stereoisomerides ajmalacine (δ-yohimbine, tetrahydroserpentine) (15), mayumbine (16), akuammigine (17), and tetrahydroalstonine (18).

EXPERIMENTAL

The ultraviolet spectra were determined in absolute ethanol, unless otherwise stated, on a Beckmann DU spectrometer. The infrared absorption spectra were recorded with a Perkin–Elmer double beam instrument model 21. The peaks are indicated by a wave number and the percentage absorption (in parenthesis). The compounds were dispersed in mulls in nujol unless otherwise mentioned. All melting points were taken on a microscope hot stage and are uncorrected.

Mitraphylline

The alkaloid was obtained from the bark of *Mitragyna rubrostipulacea* Havil.[4] Mitraphylline consisted of colorless needles, m.p. 275–276°, $[\alpha]_D^{24}$ −3° (*c*, 1.3 in chloroform), −39° (*c*, 2.4 in 0.1 *N* hydrochloric acid), pK_a 4.6 (by titration in 80% methylcellosolve with 0.02 *N* hydrochloric acid). Found: C, 68.60; H, 6.69; N, 7.59; OCH_3, 8.46; act. H, 0.29. Calcd. for $C_{21}H_{24}O_4N_2$: C, 68.46; H, 6.57; N, 7.60; 1 OCH_3, 8.41; 1 act. H, 0.27%. Ultraviolet absorption: shoulder at 280 mμ, log ε 3.18, λ_{max} 243 mμ, log ε 4.22, λ_{min} 224 mμ, log ε 4.02. Infrared absorption: 3260(32), 1725(85), 1704(84), 1626(74), 1105(74), 755(46). In chloroform: 3415(20), 1715(81), 1625(68).

The base formed a perchlorate that crystallized from alcohol–ether as long prismatic needles, softening at 214° and melting at 240°, $[\alpha]_D^{22}$ −26°±6 (*c*, 1 in 95% ethanol). A

[4]*Collected in the Northeast section of the Experimental Station (Mulungu) of the Institut pour l'étude agronomique du Congo (INEAC) in whose chemical laboratory the isolation of the alkaloids was carried out. The extraction of the bark was done in the plant of the Cooperative Congokina, Costermansville, Belgian Congo.*

hydriodide was also prepared that consisted, after crystallization from absolute methanol, of silky needles, m.p. 233–236°, $[\alpha]_D^{22}$ −13.5° (*c*, 1.2 in absolute ethanol). Found: C, 51.31; H, 5.14. Calcd. for $C_{21}H_{24}O_4N_2.HI$: C, 50.80; H, 5.08%.

Alkaline Hydrolysis of Mitraphylline

The base (0.35 g.) was refluxed for 1 hour in methanol (9 ml.) containing water (1 ml.) and potassium hydroxide (0.5 g.). The methanol was distilled off and the aqueous solution neutralized with dilute hydrochloric acid. The mixture was then extracted with chloroform, and the extract was dried and evaporated to dryness. The residual mitraphyllic acid (150 mg.) partially crystallized when benzene was added. After several recrystallizations from ethanol, it consisted of colorless prisms (45 mg.), m.p. 301° (decomp.). $[\alpha]_D^{22}$ +21.4° (*c*, 1.17 in pyridine). Found: C, 67.66; H, 6.28; N, 7.73. Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91%.

Esterification of Mitraphyllic acid

The acid (66 mg.) was refluxed for 10 minutes in a saturated solution of methanolic hydrogen chloride (3 ml.). The solvent was evaporated and the base liberated with ammonium hydroxide was extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness. It left a residue (49 mg.) which was chromatographed on alumina (grade II). Elution with chloroform containing 1% methanol gave mitraphylline (28 mg.), which after crystallization from methanol, melted at 257–259° either alone or in admixture with pure mitraphylline. The X-ray powder photograph confirmed the identity with mitraphylline.

Acetylmitraphylline

Mitraphylline (190 mg.) was acetylated in pyridine (2 ml.) and acetic anhydride (0.5 ml.). The acetylated product (68 mg.) after crystallization from methanol–water, melted at 171–173°. $[\alpha]_D^{23}$ −6.2 (*c*, 1.0 in ethanol). Found: C, 67.33; H, 6.21; N, 6.54; $COCH_3$, 9.96. Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.39; N, 6.83; 1 $COCH_3$, 10.49%. pK_a 4.3 (by titration with 0.02 *N* hydrochloric acid in 80% methylcellosolve).

Hexahydromitraphylline

Mitraphylline (108 mg.) was hydrogenated in glacial acetic acid (10 ml.) over Adams' catalyst (50 mg.) at 28° and 755 mm. of mercury. The hydrogen absorbed (23.4 ml.) corresponded to the volume calculated (21.5 ml.) to reduce three double bonds. The catalyst was filtered and the filtrate made basic with sodium carbonate solution and extracted with chloroform. The extract was dried over sodium sulphate, evaporated to dryness, and the residue crystallized from acetone from which it separated as colorless prisms (60 mg.), m.p. 276° (decomp.). $[\alpha]_D^{25}$ +15.3° (*c*, 0.97 in ethanol). Found: C, 67.29; H, 7.96; N, 7.51. Calcd. for $C_{21}H_{30}O_4N_2$: C, 67.35; H, 8.09; N, 7.48%. Ultraviolet absorption: λ_{max} 237 mμ, log ε 4.05, λ_{min} 215 mμ, log ε 3.72. Infrared absorption: 1710(89), 1698(89), 1630(70), 1105(76), 1092(77).

Acid Hydrolysis of Mitraphylline

Mitraphylline (500 mg.) was refluxed with 8% hydrochloric acid (125 ml.) for 3.5 hours, and the cooled solution neutralized with sodium bicarbonate and extracted with ether. The extract was dried over sodium sulphate and evaporated to dryness leaving the crude amorphous mitraphyllal (490 mg.), which was dissolved in absolute methanol (20 ml.). Picric acid (500 mg.) was added and the solution boiled for 30 minutes and then concentrated. The picrate crystallized as yellow prisms which after recrystallization from

methanol melted at 198–200° (decomp.). Found: C, 54.80; H, 5.03. Calcd. for $C_{20}H_{26}O_3N_2$. $C_6H_3O_7N_3$: C, 54.64; H, 5.11%. The base was regenerated on a basic resin (Amberlite IRA, 400) in methanol. The eluate on evaporation left a residue which crystallized from acetone in colorless prisms (methylmitraphyllal, 150 mg.) m.p. 224°, $[\alpha]_D^{25}$ −59.2° (*c*, 1.3 in ethanol). Found: C, 70.26; H, 7.49; N, 8.03; OCH_3, 8.43. Calcd. for $C_{20}H_{26}O_3N_2$: C, 70.15; H, 7.65; N, 8.18; 1 OCH_3, 9.05%. Ultraviolet absorption: shoulder at 780 mμ, log ε 3.18, λ_{max} 253 mμ, log ε 3.86, λ_{min} 228 mμ, log ε 3.33. Infrared absorption: 1730(94), 1696(81), 1625(56), 1183(74), 1140(71), 1060(88), 749(79).

Methylmitraphyllal

A solution of crude mitraphyllal (500 mg.) in 1% methanolic hydrogen chloride (50 ml.) was allowed to stand at room temperature overnight, refluxed for 30 minutes, and evaporated to dryness. Aqueous sodium carbonate was added to the residue and the mixture extracted with chloroform. The extract was dried over sodium sulphate, evaporated to dryness, and the residue was crystallized several times from acetone. The product (140 mg.) melted at 224° either alone or in admixture with a sample of methylmitraphyllal obtained as described above.

Hydrolysis of Methylmitraphyllal

Methylmitraphyllal (100 mg.) was refluxed with 1% hydrochloric acid (20 ml.) for 1 hour. The cooled solution was neutralized with sodium bicarbonate and extracted with ether. The extract was dried over sodium sulphate and evaporated to dryness. The residue consisted of the amorphous mitraphyllal, 95 mg. which contained no methoxyl group. Infrared absorption in chloroform: 3590(38), 3430(52), 1725(99), 1626(81). With Tollens' reagent mitraphyllal slowly formed a silver mirror. When treated with picric acid in methanol it gave an almost quantitative yield (150 mg.) of methylmitraphyllal picrate, m.p. 198–200° (decomp.).

Mitraphyllane

Mitraphyllal (100 mg.) trimethyleneglycol (2.5 ml.) and 95% hydrazine (250 mg.) were heated together at 150° for 1 hour. Potassium hydroxide (0.5 g.) was added and the excess of hydrazine evaporated while the temperature was increased to 200°. After 3 hours the mixture was cooled, water was added, and the solution extracted with ether. The extract was washed with water, dried over sodium sulphate, and evaporated to dryness. The residue was dissolved in methanol and a solution of picric acid (100 mg.) in methanol was added. The picrate was collected and recrystallized from methanol from which it separated in long yellow prisms (70 mg.) m.p. 167–169°. Found: C, 55.13; H, 5.48. Calcd. for $C_{19}H_{26}O_2N_2.C_6H_3O_7N_3$: C, 55.24; H, 5.38%. The base was regenerated on a basic resin (Amberlite IRA, 400) in methanol and was distilled at 0.1 mm. (air bath temperature 170–180°). It consisted of a colorless glass, 35 mg. $[\alpha]_D^{25}$ +39.3° (*c*, 0.89 in ethanol). Found: C, 72.42; H, 8.33. Calcd. for $C_{19}H_{26}O_2N_2$: C, 72.58; H, 8.34%. Ultraviolet absorption: shoulder at 280 mμ, log ε 3.21, λ_{max} 252 mμ, log ε 3.87, λ_{min} 229 mμ, log ε 3.60. Infrared absorption: 3200(55), 1707(92), 1625(61), 752(61). In chloroform: 3600(34), 3435(48), 1710(98), 1625(73).

Mitraphyllol

A solution of mitraphylline (500 mg.) and lithium aluminum hydride (400 mg.) in tetrahydrofuran (250 ml.) was allowed to stand at room temperature overnight. Water (3 ml.) was added, and after 30 minutes the precipitate was filtered off and washed with chloroform. The combined washings and filtrate were dried over sodium sulphate and

evaporated to dryness. The residue was crystallized from acetone from which it separated as colorless prisms (170 mg.), m.p. 227°, $[\alpha]_D^{25}$ −79.7° (*c*, 0.79 in ethanol). Found: C, 70.16; H, 6.81; N, 8.07. Calcd. for $C_{20}H_{24}O_3N_2$: C, 70.56; H, 7.11; N, 8.23%. Ultraviolet absorption: shoulder 280 mμ, log ε 3.11, λ_{max} 252 mμ, log ε 3.88, λ_{min} 230 mμ, log ε 3.57. Infrared absorption: 3270(59), 1730(89), 1708(88), 1655(62), 1626(67), 750(61).

Dihydrodesoxy-mitraphyllol

Mitraphylline (200 mg.) and lithium aluminum hydride (200 mg.) in dioxane were refluxed under nitrogen for 3 hours. Water (2 ml.) was added to the cooled solution, and after 30 minutes, the precipitate was filtered off and washed with chloroform. The combined filtrate and washings were dried over sodium sulphate and evaporated to dryness. The residue, after crystallization from ether, consisted of colorless prisms (105 mg.), m.p. 173–174°, $[\alpha]_D^{25}$ −15.9° (*c*, 1.26 in ethanol). Found: C, 73.44; H, 8.08; N, 8.66. Calcd. for $C_{20}H_{26}O_2N_2$: C, 73.59; H, 8.03; N, 8.58%. Ultraviolet absorption: λ_{max}, 295 mμ, log ε 3.45, λ_{max} 243 mμ, log ε 3.83, λ_{min} 270 mμ, log ε 3.59. Infrared absorption: 3375(48), 3180(50), 1660(56), 1615(56), 745(78).

A few drops of diazotized sulphanilic acid were added to a solution of dihydroxy-mitraphyllol in hydrochloric acid. A red color developed immediately which turned to yellow when the solution was made alkaline. The red color returned on acidification. Neither mitraphylline nor mitraphyllol coupled with diazotized sulphanilic acid.

Dehydrogenation of Mitraphyllal

Mitraphyllal (200 mg.) was heated with palladium–charcoal (30%, 200 mg.) under dry nitrogen to 290° during 1 hour. A distillate was collected which was fractionated into two portions, I, boiling below 210°, and II, boiling above 210°. Fraction I was a colorless basic liquid which formed a picrate crystallizing from methanol in yellow plates, m.p. 140–141°, not depressed on admixture with an authentic specimen of 3,4-diethylpyridine picrate. Found: C, 49.21; H, 4.25. Calcd. for $C_9H_{13}N.C_6H_3O_7N_3$: C, 49.45; H, 4.43%. The infrared spectrum was identical with that of 3,4-diethylpyridine picrate. Fraction II (boiling higher than 210°) was crystallized from hexane. It consisted of colorless prisms, m.p. 101°, not depressed on admixture with a synthetic specimen of 3-ethyloxindole. The X-ray powder diagram was identical with that of the synthetic specimen.

ACKNOWLEDGMENTS

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