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# A Synthesis of 1,2-Tetramethylene-3,4-dihydro-β-carboline.

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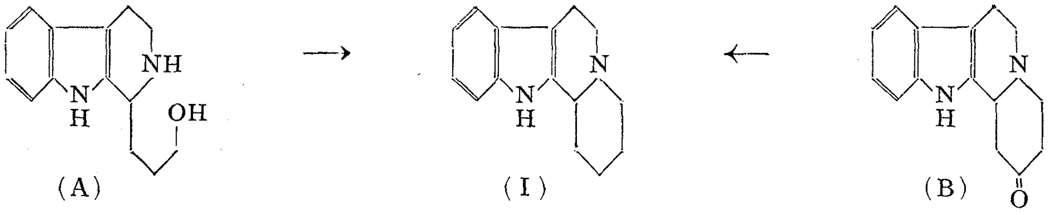
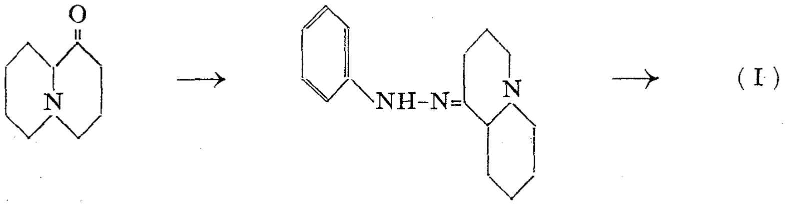
The importance of the ring system (I), 1,2-tetramethylene-3,4-dihydro-β-carboline, in corynantheine and in the yohimbine, alstonia, and serpentina alkaloids has already been discussed in the paper by Groves and Swan,[1] who first described the synthesis of (I) and its derivative. (I) was synthesized from (A) and also from (B), of which the first is the method of choice, because the Wolff-Kishner reduction of (B) is attended with a poor yield.



(A) (I) (B)

A little later, Reckhow[2] published a more direct and simple method of synthesis of (I) : The phenylhydrazone of 4-oxo-1,2,3,4,6,7,8,9-octahydroquinolizine was subjected to the Fischer method.



We are now describing the third method. For the synthesis of (I) itself the second method appears to be the best, but the present method may be useful for the synthesis of some derivatives of (I) and the scope of this method is now being investigated.

2-(2′-Pyridyl)indole (II), which was prepared in a good yield from 2-acetylpyridine phenylhydrazone by the Fischer synthesis, was treated with formaldehyde and diethylamine, giving the corresponding gramine-type compound (III), which was best converted into the methiodide (V) through the methylmethosulfate (IV). When (III) was treated directly with methyl iodide the yield of (V) could not exceed 30%.[3] An aqueous solution of alkali cyanide converted (V) into the acetonitrile (VI) in a fair yield, which was then hydrolyzed to the acid (VII) by heating with alkali. The acid was esterified to give (VIII), from which the alcohol (IX) was obtained by the agency of lithium aluminum hydride in a good yield, whereas the acid (VII) gave the alcohol only in ca. 30% yield, probably due to its sparing solubility in the solvent.

When (IX) was treated with phosphorus tribromide in boiling benzene there separated a crystalline solid, which was found tobe th quaternary bromide (X) and not the hydrobromide of 2-(2′-pyridyl)-3-β-bromoethylindole (Br instead OH in IX), as

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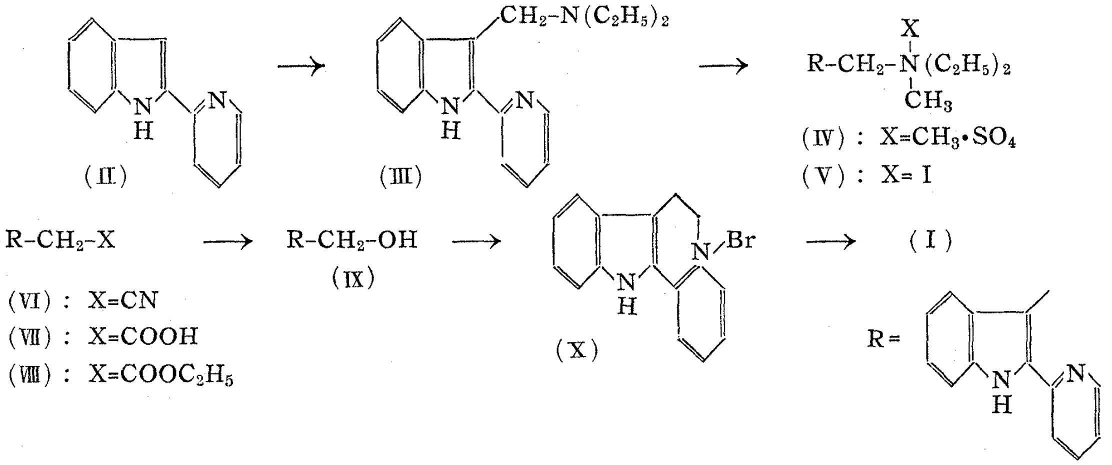
[1] L. H. Groves, G. A. Swan : J. Chem. Soc., **1952**, 650. They named this compound "1,2,3,4,-6,7,12,12b-octahydroindolo[2,3-a]pyridocoline." For the sake of simplicity we adopted the name mentioned in the title.

[2] W. A. Reckhow, D. S. Tarbell : J. Am. Chem. Soc., **74**, 4961 (1952).

[3] cf. C. Schöpf, J. Thesing : Z. Angew. Chem., **63**, 377 (1951).

was first expected. Catalytic reduction of (X) over Adams' catalyst proceeded smoothly, yielding (I) in quantitative yield. The compound (I) thus prepared was identified with the authentic specimen synthesized according to the Reckhow's method.



This method requires many stages to go, but each stage proceeds with fairly good yield. To our knowledge, this is the first example of synthesizing a $\beta$-carboline ring by spanning -$CH_2$-$CH_2$- bridge starting from 3-position of indole to N to form the ring.

Search of the literature revealed that both 2-(3′-pyridyl)- and 2-(4′-pyridyl)-indoles are not yet recorded, so these were synthesized from the phenylhydrazones of $\beta$- and $\gamma$-acetylpyridines in good yields; the cyclizations were best effected by heating with polyphosphoric acid(P.P.A.).

All three pyridyl-indoles are indifferent towards Ehrlich's reagent, only the $\beta$-derivative responded faintly when warmed. The nitrogen atom of the pyridine ring is probably responsible for this inertness of indole-3-position to the color test.

The methosalts of these pyridyl-indoles underwent smooth hydrogenation, giving the correponding 2-piperidylindoles, all of which now gave distinct Ehrlich and pine splinter color tests.

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## Experimental

**2-(2′-Pyridyl)indole (II)**—2-Acetylpyridine phenylhydrazone was prepared by warming the mixture of 2-acetylpyridine (5 g.) in EtOH (3 cc.) and phenylhydrazine (4.47 g.) on a steam bath for 1 hr. On cooling, faint yellow crystalline solid was obtained, which was purified from EtOH, forming faint yellow rhombic pillars of m.p. 155°.

The indole cyclization was best effected by P. P. A. Thus 1.5 g. of the foregoing hydrazone was mixed with 4.5 g. of P. P. A. and the whole was heated in an oil bath, stirring with a thermometer. At 100~120° the mixture became homogeneous, giving a viscous liquid. The temperature was raised to 180~190° and kept there for 5 mins., stirring being continued all the time. On cooling, ca. 25 cc. of $H_2O$ was added, separating (II)-phosphate as a crystalline solid, which was washed with water and decomposed with NaOH solution, giving a brownish solid. The free base was taken up in AcOEt, washed with water, dried, and evaporated. The residual brownish solid was purified from benzene, forming colorless rhombic pillars of m.p. 154°; yield 1.2 g. or 88%. *Anal.* Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.3; H, 5.5; N, 14.1. U.V. (in 95% EtOH): $\lambda_{max}$ 326.5 m$\mu$ (log $\epsilon$ 4.41).

**2-(2′-Pyridyl)-3-diethylaminomethylindole (III)**—To a mixture of formaldehyde solution (2.3 g. of 35%, 1 mole), aq. $Et_2NH$ (8.6 g. of 33%, 1.5 moles), and AcOH (7.8 g., 5 moles) was added 5 g. of (II) and the whole was warmed at 60° on a water bath for 30 mins. with stirring, giving a dark reddish homogeneous solution. On cooling any unreacted starting material (II) was filtered off and the filtrate was basified with 10% NaOH solution with cooling, separating a faint yellow solid, which was filtered, washed with water, and dried. When washed with a little cold EtOH there was obtained nearly colorless prisms of m.p. 88~90°; yield 6.2 g. or 86%. Characterized as a well-defined picrate, which formed yellow pillars of m.p. 182°(decomp.). *Anal.* Calcd. for $C_{18}H_{21}N_3 \cdot C_6H_3ON_3$; C, 56.7; H, 4.7; N, 16.5. Found: C, 56.65; H, 4.7; N, 16.8.

**2-(2′-Pyridyl)-3-diethylaminomethylindole Methiodide** (V)—The foregoing compound (II) (5.2g., 1 mole) was dissolved in a mixture of abs. EtOH-benzene (20 cc. of 1 : 1) acidified with AcOH(2.28 g., 2 moles). To this solution was now added freshly purified $Me_2SO_4$(11.8 g., 5 moles), dissolved in pure benzene (10 cc.) and the whole was kept standing in an ice chest for 40 hrs., separating some faint yellow needle-shaped crystals. The solvent was then evaporated *in vacuo* at room temp. and the remaining solid was washed with benzene, yielding 5.3 g. or 72% of the crude methyl methosulfate (IV). Purified from water, forming faint yellow needles of m.p. 165.5°.

Five grams (1 mole) of (IV) was dissolved in 10 cc. of warm water and to this solution was added a solution of KI(5 g., 2 moles) in water (10 cc.), separating immediately the corresponding methiodide (V) as colorless prism. Yield, 5 g.(nearly theoretical). Purified from hydrous EtOH, forming colorless pillars of m.p. 214°. *Anal.* Calcd. for $C_{19}H_{24}N_3I$: C, 54.2; H, 5.7; N, 10.0. Found: C, 54.0; H, 5.9; N, 9.8.

**2-(2′-Pyridyl)-3-indolylacetonitrile (VI)**—The above-mentioned methiodide (8.8 g., 1 mole) in EtOH(78 cc.) was mixed with an excess of KCN(5.85 g., 4.5 moles) dissolved in $H_2O$(58.5 cc.). The mixture was heated at 65~70° on a steam bath. After about 30 mins.' heating, colorless needles began to separate. Heating was continued for 3 hrs. and on cooling, the crystalline solid was collected, washed first with $H_2O$, and then with a little EtOH. Yield of the crude nitrile amounted to 4.85 g.(nearly quantitative). Purified from hydrous EtOH, forming colorless needles of m.p. 184~185°. *Anal.* Calcd. for $C_{15}H_{10}N_3$: C, 77.25; H, 4.7; N, 18.0. Found: C, 76.8; H, 4.7; N, 17.75. Gives yellow needle-shaped picrate of m.p. 242~243°(decomp.).

When the methosulfate (IV) was reacted with KCN under similar conditions there was recovered the Mannich base (III) and none of the nitrile (VI) was obtained.

**2-(2′-Pyridyl)-3-indolylacetic Acid (VII)**—The nitrile (VI, 1 g.) was suspended in aq. KOH solution (50 cc. of 20%) and the whole was refluxed in an oil bath kept at 150~160°. After 4.5 hrs.' heating, all the nitrile disappeared, giving a yellowish solution. On cooling, the resultant solution was diluted with about an equal volume of water, filtered through a wet filter, and the filtrate was made acid with 30% AcOH, separating yellowish needles, which were collected on a filter and washed. Yield, 1.05 g. or 99% of the crude acid (VII), which formed faint yellow needles of m.p. 194° when purified from hydrous EtOH. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.4; H, 4.8; N, 11.1; Found: C, 71.3; H, 4.8; N, 10.9.

This acid (0.9 g.) was dissolved in hot EtOH (30 cc.) and a stream of dry HCl-gas was passed through this solution for 3 hrs., during which time the mixture was kept refluxing on a water bath. After being allowed to stand over night at room temperature, the solvent was removed *in vacuo*, leaving a yellow transparent syrup, which was dissolved in $H_2O$(ca. 10 cc.), basified with soda solution, and the oil that separated was thoroughly extracted with ether. The ether was washed, dried over $K_2CO_3$, and evaporated. There remained 0.9 g. of needle-shaped crude ester, which was recrystallized from hexane-MeOH, forming yellow prisms of m.p. 93.5~94.5°. *Anal.* Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.9; H, 5.7; N, 10.0. Found: C, 72.8; H, 5.9; N, 10.4.

**2-(2′-Pyridyl)-3-(β-hydroxyethyl)indole(IX)**—An ethereal solution of the foregoing ester(0.8 g., 1 mole) in absolute ether (40 cc.) was added during 20 mins. to an ethereal suspension of $LiAlH_4$ (0.2 g., 1.5 moles in 20 cc. of abs. ether) with cooling and stirring, separating a yellowish solid. After being stirred for 1 hr. at room temperature, the mixture was refluxed on a water bath for 3 hrs. Water (0.42 g. corresponding to $LiAlH_4$ used) was then added to decompose the unreacted $LiAlH_4$, followed by an excess of 10% NaOH solution. The filtrate from the solid was repeatedly extracted with ether, washed, dried, and evaporated, leaving faint reddish, pillar-shaped crystals; yield, 0.5 g. or 73%. This was purified from benzene, forming light brownish rhombic pillars of m.p. 154°. Gives crystalline hydrochloride from EtOH, which did not melt below 290°. *Anal.* Calcd. for $C_{15}H_{14}ON_2 \cdot HCl$: N, 10.2. Found: N, 10.7.

**3,4-Dihydro-5,10-dehydroindolo[2,3-a]quinolizinium Bromide** (X)—The foregoing alcohol (0.1 g., 1 mole) in abs. benzene (15 cc.) was added to benzene solution of $PBr_3$(0.11 g., 1 mole in 10 cc. of benzene) without cooling, separating yellowish solid. The mixture was then refluxed gently on a steam bath, when the solid first became syrupy and solidified again after some time, evolution of HBr being observed. After about 6 hrs.' heating the mixture was cooled and the resultant crystalline solid was collected on a filter, washed with benzene, and then purified from EtOH, forming brilliant yellow needles of m.p. 327~330°(decomp.). Yield, 0.12 g. or 95%. *Anal.* Calcd. for $C_{15}H_{13}N_2Br$: C, 59.8; H, 4.3; N, 9.3; Br, 26.6. Found: C, 59.8; H, 4.8; N, 8.8; Br, 26.2.

**3,4-Dihydro-1,2-tetramethylene-β-carboline** (I)—The foregoing bromide (0.1 g.) in EtOH (20 cc. of 50%) was reduced catalytically with $H_2$ activated over Adams' Pt. In 30 mins., theoretical amount of $H_2$ was consumed, giving a colorless solution. The filtrate from the catalyst was evaporated *in vacuo* to ca. 10 cc. and was basified with 10% $Na_2CO_3$ solution, separating a crystalline solid. Yield, 0.07 g. or nearly theoretical. Purified from hexane, this formed faint yellow rhombic pillars of m.p. 150~150.5°. *Anal.* Calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4. Found: C, 79.2; H, 8.1; N, 12.4.

The picrate forms yellow needles of m.p. 230~232°(decomp.) from EtOH.

**2-Pyridyl-indoles** —2-(3′-Pyridyl)- and 2-(4′-pyridyl)-indoles were prepared in a like manner as their 2′-pyridyl derivative. All three indoles give the corresponding methiodides in good yields on being heated with MeI in MeOH at 100° for 2 hrs., all forming yellow needles from hydrous EtOH.

The methochlorides yield the corresponding N-methylpiperidylindoles on being reduced catalytically over Adams' Pt. Contrary to the pyridylindoles they all give distinct Ehrlich color test (reddish purple) and pine splinter color test (reddish purple).

| | m.p. | Yield (%) | U.V.[a] $\lambda_{max}$ mμ (log ε) | Anal. Found (%) | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| | Phenylhydrazones | | | | | |
| 3-Acetylpyridine | 138°, faint yellow pillars (abs. EtOH) | 80 | | | | |
| 4- 〃 | 150°, faint yellow pillars (abs. EtOH) | 85 | | | | |
| | Indoles | | | | | |
| 2-(3′-Pyridyl)- | 174°, colorless pillars (benzene) | 67 | 317 (4.47) | 80.1 | 5.4 | 14.3[b] |
| 2-(4′-Pyridyl)- | 203.5°, colorless needles (benzene) | 89 | 326.5 (4.43) | 80.8 | 5.2 | 14.4[b] |
| | Methiodides | | | | | |
| 2-(2′-Pyridyl)indole | 194°(decomp.) yellow needles (aq. EtOH) | quantitative | 325 (4.34)[d] | | | |
| 2-(3′- 〃 | 250°(decomp.) yellow needles (aq. EtOH) | 〃 | 324 (4.31)[d] | | | |
| 2-(4′- 〃 | 259~261°(decomp.) yellow needles (aq. EtOH) | 〃 | 253 (3.96)[de]<br>385 (4.29)[de] | | | |
| | Indoles | | | | | |
| 2-(2′-N-Methylpiperidyl)- | 154°, colorless needles (benzene) | quantitative | 271 (3.92) | 78.3 | 8.5 | 13.4[c] |
| 2-(3′- 〃 )- | 129°, colorless prisms (benzene) | 〃 | 271 (3.92) | 78.3 | 8.0 | 13.5[c] |
| 2-(4′- 〃 )- | 182°, colorless prisms (benzene) | 〃 | 271 (3.92) | 78.3 | 8.5 | 13.4[c] |

a) in 95% EtOH.
b) Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4.
c) Calcd. for $C_{14}H_{18}N_2$: C, 78.6; H, 8.3; N, 13.1.
d) in 50% EtOH.
e) Methochloride.

## Summary

3,4-Dihydro-1,2-tetramethylene-β-carboline (I) was synthesized from 2-(2′-pyridyl)indole by a new method. The latter, when treated with fromaldehyde and diethylamine, readily gave the β-diethylaminomethyl derivative (III) in a fair yield. Its methiodide (V), made advantageously via the corresponding methosulfate (IV), was reacted with aqueous alkali cyanide to give the indolylacetonitrile (VI), which was hydrolysed and esterified, giving the indolylacetic ester (VIII). $LiAlH_4$-reduction of this ester yielded the β-hydroxyethyl derivative (IX), which gave directly the β-carbolinium bromide (X) by the agency of $PBr_3$, catalytic reduction of which gave (I) in a smooth reaction.

The hitherto unknown 2-(3′-pyridyl)- and 2-(4′-pyridyl)-indoles, their metho-salts and the corresponding 2-piperidyl indoles were also prepared.

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