135. Kohzoh Okada : Studies on the Utilization of Safrole as Medicinal Raw Material. XVII.*¹ Synthesis of 3-Methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7H-pyrrolo[3,2,1-de]phenanthridine.

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1, 2, 3, 3a, 4, 5, 11b, 11c-Octahydro-7H-pyrrolo[3, 2, 1-de]phenanthridine (A) forms the fundamental skeleton of many of the *Amaryllidaceae* alkaloid such as lycorine (I),¹⁻⁴ pseudolycorine (II),^{5,6} pulviine (III),^{7,8} nor-pulviine (IV),⁵ and caranine (V),^{9,10} as have been studied by Uyeo and Wildman and their collaborators.

(A)

(B)

- (I) $\begin{matrix} R \\ R' \end{matrix} \left\{ \begin{matrix} -O \\ -O \end{matrix} \right\} CH_2, R''=OH$
 (II) $R=OH, R'=OCH_3, R''=OH$
 (III) $R, R'=OH, R''=H$
 (IV) $R=OCH_3, R'=OH, R''=H$
 (V) $\begin{matrix} R \\ R' \end{matrix} \left\{ \begin{matrix} -O \\ -O \end{matrix} \right\} CH_2, R''=H$

In the preceding paper*¹ of this series the present author described a synthesis of the compound (B), a crinane type of base, starting from 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone¹¹ readily derivable from safrole. When N, 10b-ethano bridge in this compound is switched over to N, 4 position, so the corresponding lycorane type compound mentioned in the title will be formed. Thus the synthesis of the latter also appeared feasible from the same starting material (VI) and this was realized according to the following scheme :

It was Bachman, *et al.*,¹² who pointed out that 2-phenylcyclohexanone enters into the Mannich type reaction with formaldehyde and dimethylamine to give 2-phenyl-6-dimethylaminomethylcyclohexanone. 2-(3,4-Methylenedioxyphenyl)-5-methylcyclohexanone (VI) behaved similarly and yielded 2-dimethylaminomethyl-3-methyl-6-(3,4-methyl-

*¹ Part XVI : This Bulletin, **10**, 401 (1962).

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enedioxyphenyl)cyclohexanone (VII), a well defined crystal, as a main product, together with a minor amount of an oily substance, which was probably either stereo- or position isomer of (VII), but was not further investigated.

The methyl methosulfate of (VII), when treated with aqueous potassium cyanide solution, gave rise to 2-oxo-3-(3,4-methylenedioxyphenyl)-6-methylcyclohexanecarbonitrile (VIII). Besides the latter there was also obtained a small amount of a solid of m.p. $141\sim 143^\circ$ which was proved to be (IX) produced from (VIII) by Campbell type of cyclization caused by the alkalinity of aqueous potassium cyanide solution.

On being refluxed with conc. methanolic potassium hydroxide in *tert*-butanol according to Campbell¹³⁾ or with aqueous ethanolic sodium bicarbonate solution the acetonitrile (VIII) isomerized to hydro-oxindole derivative (IX), which in conformity with its structure exhibits infrared absorption at 3240, 3070, and 1680 cm^{-1} (NH and CON<) and ultraviolet maxima at 230 and 265 $\text{m}\mu$ ($\log \epsilon$ 4.07 and 4.09, respectively), due to the presence of an ethylene bond conjugated to aromatic ring.

This provide the evidence for the correctness of the structure assigned to (VII), because if this Mannich base had an alternate structure, it should give rise to 1-(3,4-methylenedioxyphenyl)-2-oxo-4-methylcyclohexanecarbonitrile (X); which then should cyclize to the lactam (XI) as already described in the preceeding paper.*¹ The non-

13) A. D. Campbell, I. D. R. Stevens : J. Chem. Soc., 1956, 959.

Fig. 1. Ultraviolet Spectra

- (A) 4-Methyl-7-(3,4-methylenedioxyphenyl)-3a,4,5,6-tetrahydrooxindole (IX).
 (B) 3a-(3,4-Methylenedioxyphenyl)-6-methyl-3a,4,5,6-tetrahydrooxindole (XI).
 (C) 4-Methyl-7-(3,4-methylenedioxyphenyl)-octahydro-2*H*-indol-2-one (XII).

identity of these two lactams is well manifested from their ultraviolet absorption spectra as shown in Fig. 1.

The lactam (IX) readily took up one molar equivalent of hydrogen over palladium on carbon yielding 4-methyl-7-(3,4-methylenedioxyphenyl)-octahydro-2*H*-indol-2-one (XII) in a good yield, which was reduced to 4-methyl-7-(3,4-methylenedioxyphenyl)-octahydroindole (XIII) by the conventional lithium aluminium hydride reduction. The latter gave positive Liebermann test for the basic NH-group, whose presence was also supported from the infrared absorption ($2750\sim 2250$ and 1575 cm^{-1}) measured on its hydrochloride salt.

Pictet-Spengler type cyclization of (XIII) with formaldehyde in hydrochloric acid proceeded smoothly to give 3-methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridine (XIV), which gave negative Liebermann test, and from the infrared spectrum of its hydrochloride ($2700\sim 2250\text{ cm}^{-1}$) (XIV) supposed to be a tertiary base.

Experimental*³

2-Dimethylaminomethyl-3-methyl-6-(3,4-methylenedioxyphenyl)cyclohexanone (VII)—A mixture of 5.9 g. of 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone (VI), 3.1 g. of dimethylamine hydrochloride, and 1.05 g. of paraformaldehyde in 10 cc. of isoamylalcohol containing 3 drops of conc. HCl was refluxed for 30 min., and then allowed to stand at room temperature overnight. The hydrochloride of 2-(3,4-methylenedioxyphenyl)-5-methyl-6-dimethylaminomethylcyclohexanone (m.p. $170\sim 173^\circ$) separated was removed by filtration, and from filtrate additional hydrochloride was obtained by addition of dehyd. Et_2O . Collected hydrochloride was washed with EtOH, dissolved in H_2O , and basified by 10% NaOH solution. The free base solidified and was recrystallized from EtOH. Colorless needles, m.p. $131.5\sim 132^\circ$. Yield, 1.8 g. or 25%. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$: C, 70.56; H, 8.01; N, 4.84. Found: C 70.26; H, 8.22; N, 4.98.

Picrate: m.p. 155° , yellow needles from EtOH. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_{10}\text{N}_4$: C, 53.28; H, 5.05; N, 10.81. Found: C, 53.16; H, 5.29; N, 11.00.

Methiodide: colorless crystals of m.p. 232° (decomp.) from aq. EtOH. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{NI}$: C, 50.24; H, 6.09; N, 3.25. Found: C, 50.38; H, 6.27; N, 3.52.

Methyl methosulfate: To a benzene solution of the base, a slight excess of Me_2SO_4 was added and kept at room temperature overnight. The precipitate was collected and recrystallized from EtOH. Colorless pillars, m.p. $218\sim 220^\circ$ (decomp.). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{29}\text{O}_7\text{NS}$: C, 54.93; H, 7.04; N, 3.37. Found: C, 54.75; H, 7.34; N, 3.16.

2-Oxo-3-(3,4-methylenedioxyphenyl)-6-methylcyclohexanecetonitrile (VIII)—The mixture of the above described methosulfate (5.5 g.) in 25 cc. of EtOH, 20 cc. of H_2O , and aqueous solution (10 cc.) of KCN (2.5 g.) was shaken for 30 min. and then stored at room temperature for 1 hr. The precipitate was collected by filtration and washed three times with each 10 cc. of hot EtOH. The colorless needles recrystallized from benzene-EtOH had m.p. 164° . Yield, 1.67 g. or 46.5% of the theoretical. IR: $\nu_{\text{C}\equiv\text{N}}$ 2250 cm^{-1} . *Anal.* Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.60; H, 6.32; N, 4.82.

*³ All melting points are uncorrected.

The combined EtOH washing was concentrated and the residue was purified by recrystallization from EtOH to give colorless needles, m.p. 141~143°, which was not depressed when admixed with the compound which was obtained by treatment of the above nitrile (VIII) with aqueous NaHCO₃ solution. (cf. the following section).

4-Methyl-7-(3,4-methylenedioxyphenyl)-3a,4,5,6-tetrahydrooxindole (IX)—The mixture of the nitrile (VIII) (7.30 g.), 30% KOH-MeOH (12 cc.), and *tert*-BuOH (110 cc.) was refluxed for 2 hr., and, after cool, the solvent was removed *in vacuo*. To the residue H₂O was added to separate a solid, which was collected and purified from EtOH. Colorless needles thus obtained amounted to 5.00 g. (68.5% of the theoretical) and melted 140~142°. For analysis the needles were once again purified from EtOH to yield a specimen of m.p. 144°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3240, 3070, 1680. UV absorption maxima were observed at 230 and 265 m μ (log ϵ 4.07 and 4.09, respectively). *Anal.* Calcd. for C₁₆H₁₇O₃N: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.15; H, 6.34; N, 4.87.

On acidifying the alkaline filtrate of the compound (IX) there was obtained an acid, which formed colorless rhombs of m.p. 164° (yield 0.1 g.) from EtOH and was identified as 2-oxo-3-(3,4-methylenedioxyphenyl)-6-methylcyclohexanecetic acid. *Anal.* Calcd. for C₁₆H₁₈O₅: C, 66.19; H, 6.36. Found: C, 66.30; H, 6.25.

The compound (IX) was obtained by the following method also; the nitrile (VIII) (0.15 g.) was refluxed with EtOH (2 cc.), 10% aqueous NaHCO₃ solution (1 cc.), and H₂O (2 cc.) for 2 hr., concentrated, and added with H₂O. The precipitate was collected, washed with H₂O, and then purified from EtOH. This melted at 141~142°, and was identical with the authentic specimen.

4-Methyl-7-(3,4-methylenedioxyphenyl)-octahydro-2H-indole-2-one (XII)—The compound (IX), (0.88 g.) was dissolved in glacial AcOH and hydrogenated over 10% Pd-C (0.30 g.) at room temperature and atmospheric pressure. During about 6 hr. theoretical amount of H₂ was absorbed. The reduction mixture was filtered and evaporated to give a solid of m.p. 171~173° (0.80 g., 91% of the theoretical). This was purified from EtOH as colorless needles, m.p. 173°. UV λ_{max} m μ (log ϵ): 235 (3.76), 285 (3.74). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3240, 1670. *Anal.* Calcd. for C₁₆H₁₉O₃N: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.33; H, 7.16; N, 4.98.

4-Methyl-7-(3,4-methylenedioxyphenyl)-octahydroindole (XIII)—To the mixture of LiAlH₄ (0.37 g.) and dehyd. dioxane, the solution of the lactam (XII) (0.77 g.) in dioxane (20 cc.) was added dropwise with stirring. The whole was heated to 75~80° with stirring for further 7 hr. After cool, a small amount of H₂O and NaOH solution were added and the mixture was filtered. The residue on the filter was repeatedly washed with hot EtOH. The filtrate and the EtOH washing were combined and concentrated. The residue was mixed with H₂O, acidified with HCl, and shaken with Et₂O. The aqueous layer was basified with NaOH solution and extracted with Et₂O. The combined extract was washed with H₂O and dried over anhyd. Na₂SO₄. The solvent was removed to leave a viscous oily product (0.35 g.), which was purified by distillation (b.p._{0.3} 160~170°). Yield, 0.33 g. For analysis picrate was formed as orange needles from a mixture of AcOH and AcOEt, m.p. 221°(decomp.). *Anal.* Calcd. for C₁₆H₂₁O₂N-C₆H₃O₇N₃: C, 54.09; H, 4.95; N, 11.47. Found: C, 53.76; H, 4.97; N, 11.39.

3-Methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7H-pyrrolo[3,2,1-de]phenanthridine (XIV)—A mixture of (XIII) (0.73 g.) in 2 cc. of H₂O was treated with 5 cc. of HCHO and 1 g. of NaHCO₃. The reaction mixture was heated on a steam bath for 30 min., then cooled. The upper aqueous layer was decanted from the gummy residue, which was washed several times with H₂O. The gum was then dissolved in 5 cc. of 7% HCl, and the solution was heated on a steam bath for 1 hr. and cooled. The solution was diluted with H₂O and extracted with Et₂O. The aqueous solution was basified with NH₄OH and extracted with Et₂O. The combined Et₂O extract was washed with H₂O, dried over Na₂SO₄, and the solvent was evaporated to leave 0.53 g. of a brown basic oil. The crude product was dissolved in benzene and chromatographed over 25 g. of alumina (Merck). Elution with benzene gave 0.32 g. of an oil which was crystallized from Et₂O to colorless needles, m.p. 95~96°. *Anal.* Calcd. for C₁₇H₂₁O₂N: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.39; H, 7.83; N 5.18. Picrate: yellow needles, m.p. 180~183°(decomp., from glacial AcOH). *Anal.* Calcd. for C₁₇H₂₁O₂N-C₆H₃O₇N₃: C, 55.20; H, 4.83; N, 11.20. Found: C, 55.22; H, 4.76; N, 10.73.

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Summary

A synthesis of 3-methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7H-pyrrolo[3,2,1-de]phenanthridine (XIV) having common hydropyrrolophenanthridine skeleton with several of the *Amaryllidaceae* alkaloid such as lycorine, pulviine, caranine etc.,

was described. 2-(3,4-Methylenedioxyphenyl)-5-methylcyclohexanone (VI) prepared from safrole was used as the starting material. This synthesis had recourse to the fact that the starting ketone underwent the Mannich reaction with formaldehyde and dimethylamine at its 6-position and not at 2-position to give 2-(3,4-methylenedioxyphenyl)-5-methyl-6-dimethylaminomethylcyclohexanone (VII). This fact was evidenced by the ultraviolet absorption data showing the presence of an ethylene bond conjugated to the aromatic ring in the unsaturated lactam (IX) prepared from (VI) *via* the 2-oxo-cyclohexanecarbonitrile (VIII) by Campbell cyclization. Catalytic hydrogenation followed by lithium aluminium hydride reduction converted (VIII) into octahydroindole derivative (XIII) through the saturated lactam (XII). The ultimate base (XIV) was readily obtained from (XIII) by the conventional Pictet-Spengler method.

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**136. Kyosuke Tsuda,^{*1} Susumu Ikuma,^{*2} Masaaki Kawamura,^{*2}
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Über Tetrodotoxin. IV. Mitteilung.^{*3,1)} Die Struktur der
C₉-Base, die sich durch Einwirkung der Alkalilauge
auf Tetrodotoxin gewinnen läßt.

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In einer vorangehenden Mitteilung dieser Reihe¹⁾ wurde eine Methode beschrieben, die durch hydrolytische Abspaltung des Tetrodotoxins^{*4} zu einer heterozyclischen Verbindung, nämlich der C₉-Base, führt, die das Grundgerüst des Tetrodotoxinmoleküls darstellt. Dabei wurde gezeigt, daß sich bei der Kaliumpermanganat-Oxydation dieser C₉-Base die 2-Amino-4,5-pyrimidindicarbonsäure ergibt und daß auf dem an C₄ und C₅ dieses Pyrimidinrings kondensierten Kohlenstoffring neben einer Phenolgruppierung noch eine mit dem Aromatenring nicht verknüpfte Hydroxylgruppe existiert. Dementsprechend wurde dieser C₉-Base eine Teilformel (Ia)^{*5} erteilt.

Im folgenden berichten die Autoren über die Strukturbestimmung der C₉-Base. Aus der Teilformel (Ia) bzw. den UV-Spektren läßt sich für ein mögliches Ringsystem der C₉-Base zuerst das des 2-Aminochinazolins in Betracht ziehen. Die Phenolgruppierung der C₉-Base wurde also durch Einwirkung von Diazomethan methyliert und die UV-Kurve (Fig. 1) des hierbei erhaltenen Methyläthers (Ib), C₁₀H₁₁O₂N₃, Schmp. 223~

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^{*3} Untersuchungen der Eierstockextrakte von Kugelfischen, XIII Mitteil. Vorgetragen bei der monatlichen Versammlung der pharmazeutischen Gesellschaft in Tokio, am 17. März 1962; kurze Mitteilung hat sich als Communication drucken lassen (dieses Bulletin, 10, 247 (1962)).

^{*4} Auf Grund der Analysen- und Titrationsresultate erhält man für das Tetrodotoxin eine Bruttoformel von C₁₂H₁₉O₉N₃ geben, wenn es eine monoacidische Base darstellt.

^{*5} Als Bruttoformel dieser Base wurde früher¹⁾ die Formel C₉H₉₋₁₁O₂N₃ vorgeschlagen; nach mehrmaligen Elementaranalysen der gereinigten Präparate von C₉-Base bzw. von deren Derivaten ließ sich nun die richtige Formel, C₉H₉O₂N₃, eindeutig feststellen.

1) 3. Mitteil.: Dieses Bulletin, 8, 262 (1960).