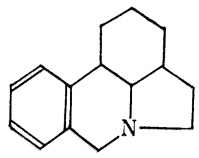
UDC 547.566.2.07

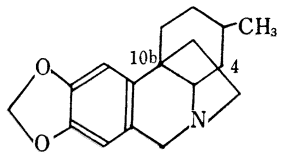
135. Kohzoh Okada : Studies on the Utilization of Safrole as Medicinal Raw Material. XVII.*1 Synthesis of 3-Methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridine.

(*Tokyo Research Laboratory, Fujisawa Pharmaceutical Co., Ltd.**2)

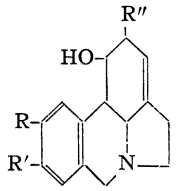
1, 2, 3, 3a, 4, 5, 11b, 11c-Octahydro-7*H*-pyrrolo[3, 2, 1-*de*]phenanthridine (A) forms the fundamental skeleton of many of the *Amaryllidaceae* alkaloid such as lycorine (I),[1~4] pseudolycorine (II),[5,6] pulviine (III),[7,8] nor-pulviine (IV),[5] and caranine (V),[9,10] as have been studied by Uyeo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



(A)



(B)



(I) R, R′ = -O-CH2-O-, R″=OH
(II) R=OH, R′=OCH3, R″=OH
(III) R, R′=OH, R″=H
(IV) R=OCH3, R′=OH, R″=H
(V) R, R′ = -O-CH2-O-, R″=H

In the preceeding paper*1 of this series the present author described a systhesis of the compound (B), a crinane type of base, starting from 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone[11] 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).
*2 Nukui, Koganei, Tokyo (岡田光三).

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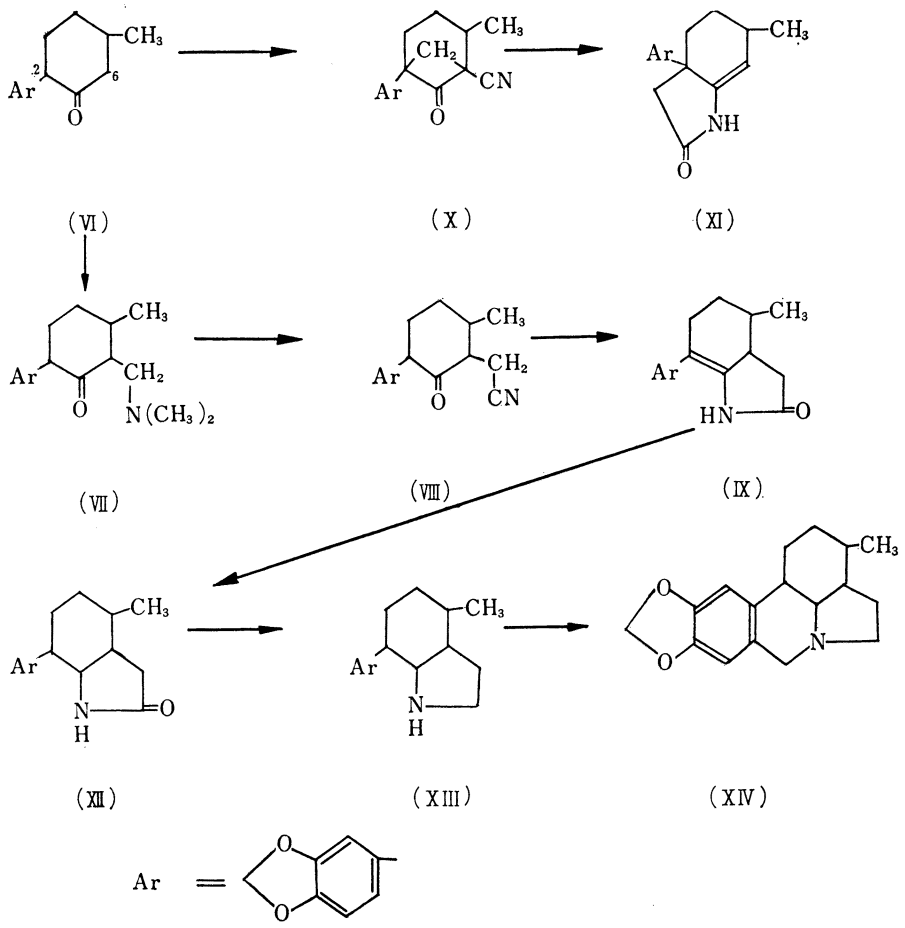

enedioxyphenyl)cyclohexanone (Ⅶ), a well defined crystal, as a main product, together with a minor amount of an oily substance, which was probably either stereo- or position isomer of (Ⅶ), but was not further investigated.

The methyl methosulfate of (Ⅶ), when treated with aqueous potassium cyanide solution, gave rise to 2-oxo-3-(3,4-methylenedioxyphenyl)-6-methylcyclohexaneacetonitrile (Ⅷ). Besides the latter there was also obtained a small amount of a soild of m.p. 141~143° 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 Campbell[13] 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 mμ (log ε 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-methylcyclohexaneacetonitrile (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.

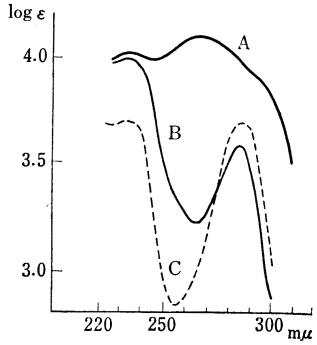

Fig. 1. Ultraviolet Spectra

(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 (2750~2250 and 1575 cm^{-1}) measured on its hydrochloride salt.

Pictét-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 (2700~2250 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. 170~173°) 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. 131.5~132°. Yield, 1.8 g. or 25%. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: 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 $C_{23}H_{26}O_{10}N_4$: C, 53.28; H, 5.05; N, 10.81. Found : C, 53.16; H, 5.29; N, 11.00.
Methoiodide : colorless crystals of m.p. 232°(decomp.) from aq. EtOH. *Anal.* Calcd. for $C_{18}H_{26}O_3NI$: 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. 218~220° (decomp.). *Anal.* Calcd. for $C_{19}H_{29}O_7NS$: 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-methylcyclohexaneacetonitrile (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 : $\nu_{C\equiv N}$ 2250 cm^{-1}. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: 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 $NaHCO_3$ 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 H_2O was added to separate a solid, which was collected and purified from EtOH. Colorless needles thus obtained ammounted 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 ν_{max}^{Nujol} cm^{-1} : 3240, 3070, 1680. UV absorption maxima were observed at 230 and 265 mμ (log ε 4.07 and 4.09, respectively). *Anal.* Calcd. for $C_{16}H_{17}O_3N$: 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-methylcyclohexaneacetic acid. *Anal.* Calcd. for $C_{16}H_{18}O_5$: 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 $NaHCO_3$ solution (1 cc.), and H_2O (2 cc.) for 2 hr., concentrated, and added with H_2O. The precipitate was collected, washed with H_2O, and then purified from EtOH. This melted at 141~142°, and was identical with the authentic specimen.

4-Methyl-7-(3,4-methylenedioxyphenyl)-octahydro-2*H*-indole-2-one (XII)——The compound (Ⅸ), (0.88g.) 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 H_2 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} mμ (log ε) : 235 (3.76), 285 (3.74). IR ν_{max}^{Nujol} cm^{-1} : 3240, 1670. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: 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 $LiAlH_4$ (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 H_2O 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 H_2O, acidified with HCl, and shaken with Et_2O. The aqueous layer was basified with NaOH solution and extracted with Et_2O. The combined extract was washed with H_2O and dried over anhyd. Na_2SO_4. 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 $C_{16}H_{21}O_2N$-$C_6H_3O_7N_3$: 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-7*H*-pyrrolo[3,2,1-*de*]phenanthridine (XIV)——A mixture of (XIII) (0.73 g.) in 2 cc. of H_2O was treated with 5 cc. of HCHO and 1 g. of $NaHCO_3$. 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 H_2O. 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 H_2O and extracted with Et_2O. The aqueous solution was basified with NH_4OH and extracted with Et_2O. The combined Et_2O extract was washed with H_2O, dried over Na_2SO_4, 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 Et_2O to colorless needles, m.p. 95~96°. *Anal.* Calcd. for $C_{17}H_{21}O_2N$: 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 $C_{17}H_{21}O_2N$-$C_6H_3O_7N_3$: C, 55.20; H, 4.83; N, 11.20. Found : C, 55.22; H, 4.76; N, 10.73.

The author wishes to express his hearty gratitude to Prof. Emeritus S. Sugasawa for his guidance also to Dr. Toshiro Fujisawa, the Director of this laboratory for his active interest in this work. Thanks are also due to Mr. Y. Saito for his cooperation, and to Messrs. Ohta and Komuro for analytical data, and to Mr. Kondo for infrared data.

Summary

A synthesis of 3-methyl-9,10-methylenedioxy-1,2,3,3a,4,5,11b,11c-octahydro-7*H*-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 date showing the presence of an ethylene bond conjugated to the aromatic ring in the unsaturated lactam (IX) prepared from (VI) *via* the 2-oxo-cyclohexaneacetonitrile (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 Pictét-Spengler method.

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136. Kyosuke Tsuda,[*1] Susumu Ikuma,[*2] Masaaki Kawamura,[*2] Ryuji Tachikawa,[*2] Yoshihiko Baba,[*2] und Tetsuo Miyadera[*2]: Über Tetrodotoxin. IV. Mitteilung.[*3,1)] Die Struktur der C_9-Base, die sich durch Einwirkung der Alkalilauge auf Tetrodotoxin gewinnen läßt.

(*Institut für angewandte Mikrobiologie der Universität Tokio*[*1] *und Takamine Forschungslaboratorium,*[*2] *Sankyo-AG.*)

In einer vorangehenden Mitteilung dieser Reihe[1)] wurde eine Methode beschrieben, die durch hydrolytische Abspaltung des Tetrodotoxins[*4] zu einer heterozyclischen Verbindung, nämlich der C_9-Base, führt, die das Grundgerüst des Tetrodotoxinmoleküls darstellt. Dabei wurde gezeigt, daß sich bei der Kaliumpermanganat-Oxydation dieser C_9-Base die 2-Amino-4,5-pyrimidindicarbonsäure ergibt und daß auf dem an C_4 und C_5 dieses Pyrimidinrings kondensierten Kohlenstoffring neben einer Phenolgruppierung noch eine mit dem Aromatenring nicht verknüpfte Hydroxylgruppe existiert. Dementsprechend wurde dieser C_9-Base eine Teilformel (Ia)[*5] erteilt.

Im folgenden berichten die Autoren über die Strukturbestimmung der C_9-Base. Aus der Teilformel (Ia) bzw. den UV-Spektren läßt sich für ein mögliches Ringsystem der C_9-Base zuerst das des 2-Aminochinazolins in Betracht ziehen. Die Phenolgruppierung der C_9-Base wurde also durch Einwirkung von Diazomethan methyliert und die UV-Kurve (Fig. 1) des hierbei erhaltenen Methyläthers (Ib), $C_{10}H_{11}O_2N_3$, Schmp. 223~

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*1 Yayoicho, Bunkioku, Tokio (津田恭介).

*2 Nishishinagawa, Shinagawaku, Tokio (生熊 晋, 河村正朗, 太刀川隆治, 馬場義彦, 宮寺哲男).

*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 $C_{12}H_{19}O_9N_3$ geben, wenn es eine monoacidische Base darstellt.

*5 Als Bruttoformel dieser Base wurde früher[1)] die Formel $C_9H_{9\sim11}O_2N_3$ vorgeschlagen; nach mehrmaligen Elementaranalysen der gereinigten Präparate von C_9-Base bzw. von deren Derivaten ließ sich nun die richtige Formel, $C_9H_9O_2N_3$, eindeutig feststellen.

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