Application of Methyl Iodide to Uncarine-A in the Presence of Sodium Methoxide (N-Methyluncarine-A)—To MeOH solution of NaOMe, prepared from 0.13 g. of metallic Na and 10 cc. MeOH, 1 g. of uncarine-A and 1.5 g. MeI were added and the mixture was warmed on a water bath for 30 mins. After leaving over night, the solvent was distilled off, the residue was extracted with ether, and ether was evaporated from the extract after drying over anhyd. Na_2SO_4. Recrystallization of the ether residue from MeOH gave 0.1 g. of crystals, m.p. 160°. *Anal.* Calcd. for $C_{21}H_{23}O_3N_2(OCH_3)$: C, 69.09; H, 6.8; N, 7.35; OCH_3, 8.12. Calcd. for $C_{22}H_{27}O_3N_2(OCH_3)$: C, 69.32; H, 7.59; N, 7.03; OCH_3, 7.79. Found: C, 68.79; H, 6.8; N, 7.0; OCH_3, 8.68.

Application of Methyl Iodide to Uncarine-B in the Presence of Sodium Methoxide (N-Methyluncarine-B Methiodide)—To a solution of 1 g. of uncarine-B dissolved in MeOH solution of NaOMe, prepared from 0.13 g. of metallic Na and 10 cc. MeOH, 1.5 g. of MeI was added and the mixture was warmed on a water bath for 1 hr. The solvent was distilled off, the residue was extracted with ether, and ether was evaporated after drying over anhyd. Na_2SO_4. There was no residue. The ether-insoluble substance was recrystallized from MeOH and 1.2 g. of crystals of m.p. 228°(decomp.) was obtained. *Anal.* Calcd. for $C_{21}H_{23}O_3N_2 \cdot CH_3I(OCH_3)$: C, 52.65; H, 5.58; N, 5.35; OCH_3, 5.92. Calcd. for $C_{22}H_{27}O_3N_2 \cdot CH_3I(OCH_3)$: C, 53.31; H, 6.17; N, 5.18; OCH_3, 5.74. Found: C, 52.32; H, 5.85; N, 5.20; OCH_3, 6.27.

Summary

A spiro-type ring was found to be attached to the 3-position of the oxindole ring in uncarine-A and -B from the fact that lithium aluminum hydride reduction of these compounds afforded indoline derivatives and that the application of methyl iodide in the presence of sodium methoxide afforded 1-methyluncarine-A and 1-methyluncarine-B methiodide. Examination was made as to which carbon in the uncarine molecule this spiro bonding existed and the possibilities of the formulae (XIV) and (XV) were considered. However, measuremnt of pK revealed that N_b and the carbonyl in the oxindole were in very close proximity in the uncarine-A molecule. Relationship between uncarine-A and -B would be well explainable by assuming 4-epimeric structures and conformational formulae (XXI) for uncarine-A and (XXII) for uncarine-B were forwarded.

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UDC 547.759

54. Toshikazu Nozoye: Studies on Uncaria Alkaloid. XIX.[1] On Mitraphylline.

(*ITSUU Laboratory**)

When extracting uncarine from *Uncaria Kawakamii* HAYATA, a minute quantity of an alkaloid, sparingly soluble in acetone, is obtained. A fair amount of this alkaloid was accumulated and its repeated recrystallization from methanol afforded a substance of single unity as needle crystals, m.p. 266°, $[\alpha]_D^{23.5}$ +3.8°, and composition of $C_{21}H_{24\sim26}O_4N_2$ was suggested from its analytical values.

This composition and physical constants were in good agreement with those of mitraphylline, obtained first from *Mitragyna macrophylla*[2] and then from *Mit. stipulosa*.[3] Mixed fusion of this substance with the sample, m.p. 265°, kindly sent by Dr, Raymond-Hamet to Dr. Tetsutaro Ikeda, then of this Laboratory, and comparison of ultra-

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1) Part XVIII: This Bulletin, **6**, 300(1958).
2) L. Michiels: J. pharm. Belg., **13**, 719(1931) (C. A., **26**, 3070(1932)).
3) Raymond-Hamet, L. Millat: Bull. sci. pharmcol., **42**, 602(1935) (C. A., **30**, 1379(1936)).

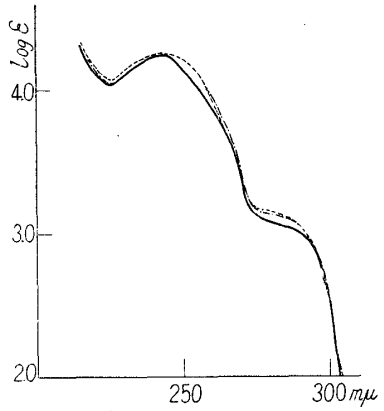


Fig. 1. Ultraviolet Spectra (in MeOH)

—— Mitraphylline
····· Compound of m.p. 266°
-·-·- Uncarine-B

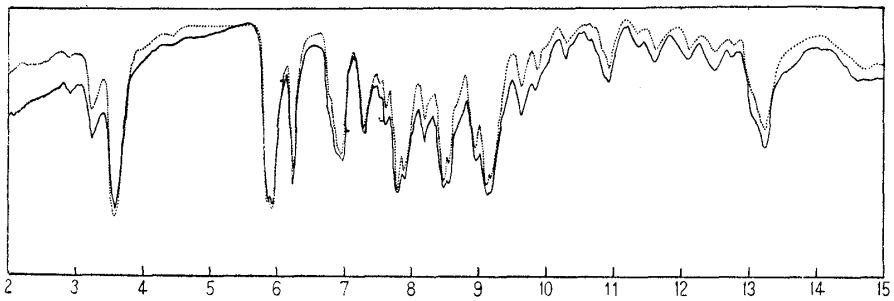
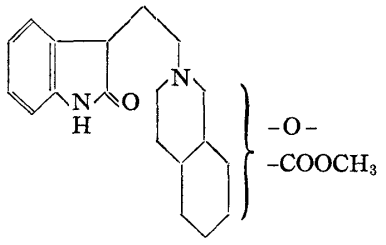


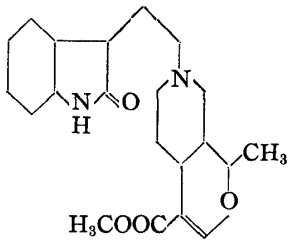
Fig. 2. Infrared Spectra (in Nujol)
—— Compound of m.p. 266° ····· Mitraphylline

violet and infrared spectra established their identity (Figs. 1 and 2).

Studies on the structure of mitraphylline had been made by Cook and his school, and a partial structure (I) was proposed in 1953.[4] Experimental basis for this structure was the fact that the heating of mitraphylline hydrochloride with zinc dust under a reduced pressure afforded neutral crystals of m.p. 179~181°, $C_{10}H_9ON$, which was assumed to be 3-vinyloxindole but was later determined as oxindole-3-spiro-1'-cyclopropane, and that the dehydrogenation of mitraphylline itself gave isoquinoline.



(I)



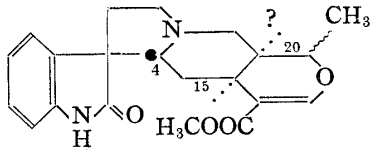
(II)

Later, in 1955, Loudon[5] gave the formula for uncarine *per se* to mitraphylline (II) and stated that it is probably a stereoisomer of uncarine.

Comparison of infrared and ultraviolet absorption spectra of mitraphylline with those of uncarine-B indicated complete identity of their ultraviolet spectra (Fig. 1) and their infrared absorption spectra were also practically identical with the exception of the finger-print region. It may therefore be considered that mitraphylline is a stereoisomer of uncarine and is probably an epimer with the conformation of the hydrogen at 20-position in uncarine different. Since it is more likely that uncarine has the 15—

4) J. W. Cook, R. M. Gailey, J. D. Loudon : Chem. & Ind. (London), **1953**, 640.
5) J. D. Loudon : "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," The Chemical Society, London, 17(1955).

20 juncture in normal type, mitraphylline probably has the allo type. The pKa values of mitraphylline (5.3) and of uncarine-B (5.5) are not greatly different, so that the hydrogen in 4-position of mitraphylline must be in β-form, as in uncarine-B, and the formula (Ⅲ) is proposed for mitraphylline.



(Ⅲ)

The difference between uncarine-B and mitraphylline is thought to be the stereoisomerism at 15–20 conformation, whether it is normal or allo, as in that between alstonine and serpentine. The establishment of the conformation of 15—20 would be obtained as in the case of uncarine, and the Plant-Robinson conversion[6] of tetrahydroalstonine or tetrahydroserpentine should afford a product that would agree with mitraphylline. The latter seems to have greater possibility. Experimental results from workers possessing these materials are awaited with great anticipation.

The author expresses his deep gratitude to Prof. Emeritus Dr. H. Kondo for his kind encouragement during the course of this work and to Prof. E. Ochiai for valuable advices. He is also grateful to Dr. Raymond-Hamet and Dr. Tetsutaro Ikeda of the University of Kanazawa for donation of valuable samples. The infrared spectra were measured by Mr. S. Tanaka, Engineering Faculty, University of Tokyo, ultraviolet spectra and elemental analyses by Mr. K. Watanabe of this Laboratory, and measurement of C-methyl group by Mr. M. Tobita, also of this Laboratory, to all of whom the author's thanks are expressed. The expenses for this work were defrayed by the Grant in Aid for Miscellaneous Scientific Researches provided by the Ministry of Education, which is gratefully acknowlodged.

Experimental

Mitraphylline (from *Uncaria Kawakamii* HAYATA)—*Anal.* Calcd. for $C_{20}H_{21}O_3N_2(OCH_3)$: C, 68.45; H, 6.57; N, 7.61; OCH_3, 8.43. Found : C, 68.05; H, 6.88; N, 7.29; OCH_3, 8.86.

C-Methyl Determination in Mitraphylline—Determination was carried out by the usual procedure, using 8.85 cc. of a 4:1 mixture by volume of 5*N* CrO_3 solution and conc. H_2SO_4.

Sample : 46.4 mg. 0.01*N* NaOH (F=0.9707) : 11.537 cc. Calcd. for $C_{21}H_{24}O_4N_2$: 1 C-CH_3, 4.08%. Found : 3.74%.

Summary

Mitraphylline was extracted from *Uncaria Kawakamii* HAYATA. Mitraphylline was considered to be a steric isomer of uncarine since their compositions were the same and their ultraviolet and infrared spectra showed close similarity. It was assumed that mitraphylline is an isomer with steric configuration of 15—20 positions different from that in uncarine and a β-configuration was presumed for the 4-position by pKa measurement, same as in uncarine-B. From these experimental results, formula (Ⅲ) was given to mitraphylline.

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6) S. G. P. Plant, R. Robinson : Nature, **165**, 26(1950); E. E. Van Tamelen : Chem. & Ind. (London), **1956**, 1145.