Application of Methyl Iodide to Uncarina-A in the Presence of Sodium Methoxide (N-Methyl-uncarina-A)—To MeOH solution of NaOMe, prepared from 0.13 g. of metallic Na and 10 cc. MeOH, 1 g. of uncarina-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. Na2SO4. Recrystallization of the ether residue from MeOH gave 0.1 g. of crystals, m.p. 160°. Anal. Calcd. for C17H18O2N2(OCH3): C, 69.09; H, 6.8; N, 7.35; OCH3, 8.12. Calcd. for C26H29O2N2(OCH3): C, 69.32; H, 7.59; N, 7.03; OCH3, 7.79. Found: C, 68.79; H, 6.8; N, 7.0; OCH3, 8.68.

Application of Methyl Iodide to Uncarina-B in the Presence of Sodium Methoxide (N-Methyl-uncarina-B Methiodide)—To a solution of 1 g. of uncarina-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. Na2SO4. 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 C17H17O2N2•CH3(OCH3): C, 52.65; H, 5.58; N, 5.35; OCH3, 5.92. Calcd. for C25H25O2N2•CH3(OCH3): C, 53.31; H, 6.17; N, 5.18; OCH3, 5.74. Found: C, 52.32; H, 5.85; N, 5.20; OCH3, 6.27.

Summary

A spiro-type ring was found to be attached to the 3-position of the oxindole ring in uncarina-A and -B from the fact that lithium aluminum hydride reduction of these compounds afforded indole derivatives and that the application of methyl iodide in the presence of sodium methoxide afforded 1-methyluncarina-A and 1-methyluncarina-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, measurement of pK revealed that N6 and the carbonyl in the oxindole were in very close proximity in the uncarina-A molecule. Relationship between uncarine-A and -B would be well explainable by assuming 4-epimeric structures and conformational formulae (XXI) for uncarina-A and (XXII) for uncarina-B were forwarded.

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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°, [α]D 15 +3.8°, and composition of C11H24•26-O2N2 was suggested from its analytical values.

This composition and physical constants were in good agreement with those of mitraphylline, obtained first from Mitragyna macrophylla2) 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-

* Konno-cho, Shibuya-ku, Tokyo (野周利—).
1) Part VIII: This Bulletin, 6, 300(1958).
2) L. Michiels: J. pharm. Belg., 13, 719(1931)(C. A., 26, 3070(1932)).
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. 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_{16}H_{20}ON, which was assumed to be 3-vinylxindole but was later determined as oxindole-3-spiro-1′-cyclopropane, and that the dehydrogenation of mitraphylline itself gave isoquinoline.

Later, in 1955, Loudon 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 stereo-isomer 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—

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 $\beta$-form, as in uncarine-B, and the formula (III) is proposed for mitraphylline.

![Chemical Structure](image)

(III)

The difference between uncarine-B and mitraphylline is thought to be the stereo-isomerism 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$^5$ 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.

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**Experimental**

**Mitraphylline (from Uncaria Kawakami HAYATA)—Anal.** Calcd. for $C_{25}H_{32}O_{2}N_2(OCH_3)$: C, 68.45; H, 6.57; N, 7.61; OCH$_3$, 8.43. Found: C, 68.65; 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 5N Cr$_2$O$_7$ solution and conc. H$_2$SO$_4$.

Sample: 46.4 mg. 0.01N NaOH (F = 0.9707): 11.537 cc. Calcd. for $C_{25}H_{34}O_4N_2$: 1 C-CH$_3$, 4.08%. Found: 3.74%.

**Summary**

Mitraphylline was extracted from *Uncaria Kawakami 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 $\beta$-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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