UDC 547.759

55. Toshikazu Nozoye: Studies on Uncaria Alkaloid. XX. Structure of Rhynchophylline. (5).[1] Structure of Rhynchophylline and Isorhynchophylline.

(*ITSUU Laboratory**)

Rhynchophylline, the alkaloid of *Uncaria rhynchophylla* MIQ. (*Ourouparia rhynchophylla* MATSUM.), was first found and named by H. Kondo, Fukuda, and Tomita[2] from the hooked stalks of this plant on the market and the following empirical formula was forwarded.

Rhynchophylline, prisms, m.p. 216°; $[\alpha]_D^{13}$ −14.7°.

$$C_{22}H_{28}O_4N_2=C_{19}H_{21}O\left\{\begin{array}{l}\equiv N\\ =NH\ ?\\ -COOCH_3\\ -OCH_3\end{array}\right.$$

Later, H. Kondo and Tetsutaro Ikeda[3] extracted an amorphous alkaloid, named isorhynchophylline, from fine stalks and leaves of *Uncaria rhynchophylla* and found that it was an isomer of rhynchophylline and that it underwent isomerization on being heated with acetic anhydride. Isorhynchophylline, $[\alpha]_D^{13}$ +8.1°, formed a perchlorate of m.p. 159~160°.

In the present series of experiment, this isomerization was attempted under conditions identical with that of uncarine-A to -B and isomerization of isorhynchophylline

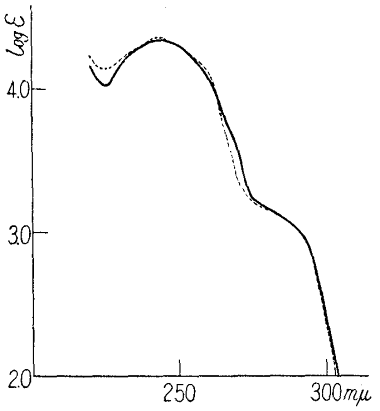


Fig. 1. Ultraviolet Spectra (in MeOH)

—— Rhynchophylline

······ Isorhynchophylline

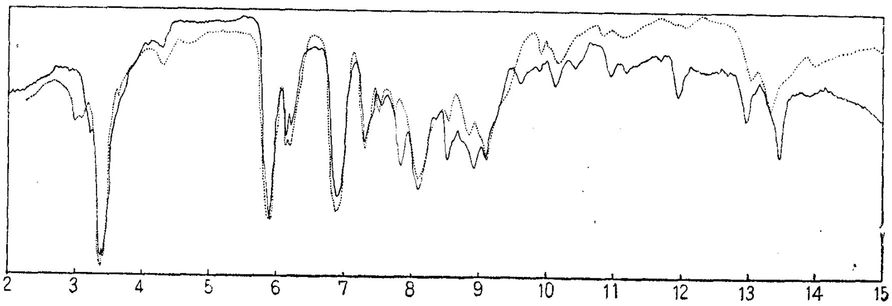


Fig. 2. Infrared Spectra (in Nujol)

—— Rhynchophylline ······ Isorhynchophylline

---

* Konno-cho, Shibuya-ku, Tokyo (野副利一).

[1] Part (4). T. Nozoye: Ann. Rept. ITSUU Lab. (Tokyo), **8**, 46(1957).

[2] H. Kondo, T. Fukuda, M. Tomita: Yakugaku Zasshi, **48**, 321(1928).

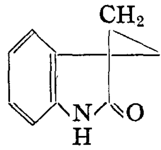
[3] H. Kondo, Tetsutaro Ikeda: *Ibid.*, **57**, 881(1937).

to rhynchophylline was effected in about the same yield. Since their ultraviolet and infrared spectra are closely similar (Figs. 1 and 2), they are considered to be stereoisomers indicated by the same structural formulae.

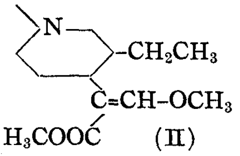
The yield of rhynchophylline from *Uncaria rhynchophylla* is extremely poor and experimental material relied solely on that from *Uncaria Kawakamii* HAYATA. Later, rhynchophylline was discovered from a variety of plants. It was first found in *Mitragyna rotunda*,[4] and then from *Mit. inermis* and *Mit. stipulosa*, the alkaloid from which had first been named mitrinermine[5] but later it was found to be none other than rhynchophylline.[4] It was also found from *Mit. ciliata*[6] and *Ourouparia guianensis*.[7]

Structural studies on this alkaloid began with that by Barger[4] in 1938, who confirmed the empirical formula reported in 1928 by H. Kondo and others,[2] and also showed that rhynchophyllic acid, obtained by the hydrolysis of rhynchophylline, afforded neutral crystals, m.p. 182~184°, $C_{10}H_9ON$, which he presumed to be methylcarbostyril, by dry distillation with calcium oxide under a reduced pressure. Later, in 1953, Cook[8] proved by mixed fusion that the neutral crystals described above and the neutral crystals, m.p. 179~181°, obtained by them by decomposition of mitraphylline and assumed to be 3-vinyloxindole, were identical substance.[9] It was also proved in this Laboratory that the said neutral crystals were identical with the neutral crystals, m.p. 185~186°, $C_{10}H_9ON$, obtained by the decomposition of uncarine, as a result of mixed fusion.[9] It follows, therefore, that rhynchophylline is oxindole-3-spiro-1′-cyclopropane (I).[9,10]

With the progress in the studies on uncarine, attempts were made to establish the structure of this alkaloid, which was considered to belong to the same series. At that time, however, the amount of rhynchophylline available was extremely small that comparison of ultraviolet and infrared spectra, especially of uncarine, and comparison with a model compound were carried out. It was thereby found that the ultraviolet spectrum of rhynchophylline was almost identical with that of uncarine[11] and since they both give the same decomposition product (I), the bonding of the oxindole and piperidine portions in rhynchophylline was the same as that in uncarine. It was also assumed that the difference lay in the substituent in the piperidine portion. From the fact that rhynchophylline possessed one methoxyl more than uncarine, the starting material is recovered by catalytic reduction,[12] presence of one C-methyl group is indicated,[12] and from the comparison of infrared spectral measurements,[11] a partial structure (II) was forwarded for the piperidine portion.[11,12]



(I)



(II)

Now that the structure of uncarine has been established,[13] the structure of rhynchophylline could now be surmised but in order to prove more precisely, rhynchophylline was reduced with lithium aluminum hydride and the ultraviolet spectrum of the reduction product was measured (Fig. 3). As was fully anticipated, the spectrum exhibited

---

[4] G. Barger: J. Org. Chem., **1938**, 418.
[5] Raymond-Hamet: Compt. rend., **199**, 587(1934).
[6] J. W. Cook, *et al.*: J. Chem. Soc., **1950**, 867.
[7] Raymond-Hamet: Compt. rend., **235**, 547(1952).
[8] U. W. Cook, R. M. Gailey, J. D. Loudon: Chem. & Ind. (London), **1953**, 640.
[9] H. Kondo, T. Nozoye, M. Tobita: Ann. Rept. ITSUU Lab. (Tokyo), **5**, 80(1954).
[10] H. Kondo, T. Nozoye, H. Tsukamoto: *Ibid.*, **6**, 53(1955).
[11] H. Kondo, T. Nozoye: *Ibid.*, **7**, 49(1956).
[12] T. Nozoye: *Ibid*, **8**, 46(1957).
[13] T. Nozoye: This Bulletin, **6**, 300(1958).

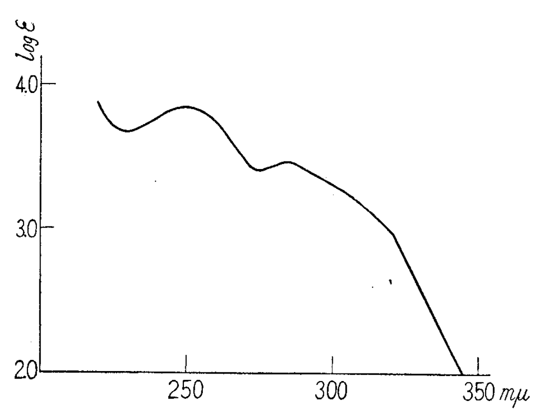
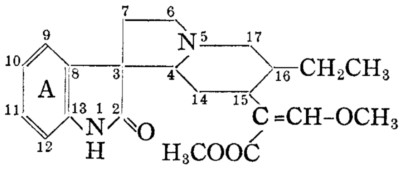


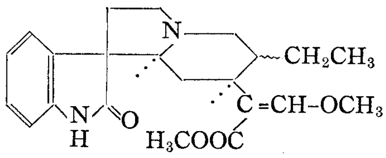
Fig. 3.
Ultraviolet Spectrum (in MeOH) of the Reduction Product of Rhynchophylline with $LiAlH_4$

the absorption of an indoline. It follows, therefore, that it would be appropriate to give the formula (III)[14] to rhynchophylline and isorhynchophylline for the same reasons as considered for uncarine.

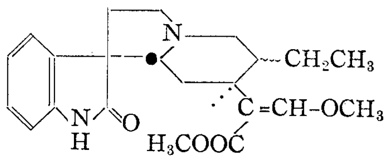
The measurement of pKa gave the values of 6.32 for rhynchophylline and 5.20 for isorhynchophylline. As in the case of uncarine-A and -B, the formula (IV) is proposed for isorhynchophylline with weaker basicity, in which structure the oxygen in the carbonyl in 2-position is closer to N_b at 5-position, i.e. the hydrogen in 4-position taking the α-conformation, while formula (V) with β-conformation for hydrogen in 4-position is forwarded for rhynchophylline.



(III)



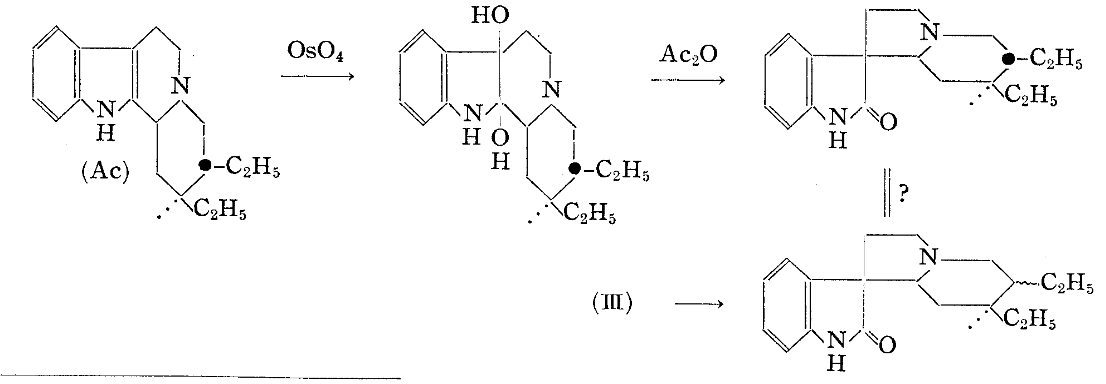
(IV)



(V)

The reason for the α-type hydrogen at 15-position is the same as that in the case of uncarine. If this were β-type, the D-ring in (V) will have to be in boat shape and this would not be able to explain the facile isomerization of isorhynchophylline into rhynchophylline.

Steric configuration at the 16-position is entirely obscure but since the steric configuration of 15—16 juncture in dihydrocorynantheane (VI) had been established,[15] this point will be solved if rhynchophyllane (VII) is formed by the Plant-Robinson conversion[16] of (VI).



---

14) The same structural formula was forwarded by J. C. Seaton and Leo Marion (Can. J. Chem., **35**, 1102(1957)) on the basis of the formation of an indoline derivative by $LiAlH_4$ reduction, analogy from corynantheine and biogenesis, and denial of 3-spiro-1′-cyclopropane in uncarine by our work.

15) E. E. Van Tamelen, P. E. Aldrich, T. J. Katz : Chem. & Ind. (London), **1956**, 793.

16) S. G. P. Plant, R. Robinson : Nature, **165**, 36(1950); E. E. Van Tamelen : Chem. & Ind. (London), **1956**, 1145.

The author is deeply grateful for the kind encouragement of Prof. Emeritus Dr. H. Kondo and for valuable advices from Prof. E. Ochiai during the course of this work. Infrared measurements were by Mr. S. Tanaka, Faculty of Engineering, University of Tokyo, ultraviolet spectra and elemental analyses by Mr. K. Watanabe of this Laboratory, measurement of C-methyl group by Mr. M. Tobita, and Miss K. Kobayashi for pK measurement, all of whose kind cooperation is gratefully acknowledged. Expenses were defrayed by the Grant in Aid of Miscellaneous Scientific Researches from the Ministry of Education to which the author is greatly indebted.

Experimental

Isomerization of Isorhynchophylline into Rhynchophylline—A solution of 1 g. of isorhynchophylline dissolved in a dilute solution of AcOH, prepared from 1.6 g. of glacial AcOH and 20 cc. of water, was heated in a boiling water bath for 8 hrs., cooled, neutralized with Na_2CO_3, and extracted with ether. The extract was washed with water, dried over anhyd. Na_2SO_4, and ether evaporated. The residue was recrystallized from acetone to 0.4 g. of crystals melting at 216°, either alone or in admixture with rhynchophylline.

Summary

Reduction of rhynchophylline with lithium aluminum hydride afforded an indoline derivative, which indicated the 3-position of the oxindole ring in its molecule is a spiro type, and the formula (III) was forwarded for rhynchophylline in analogy with uncarine.

Rhynchophylline and isorhynchophylline are considered to be 4-epimers, similar to uncarine-A and -B, because their compositions are the same, their ultraviolet and infrared spectra are in close similarity, and the two easily undergo isomerization. From the measurement of pK, the formula (V) for rhynchophylline and (IV) for isorhynchophylline are proposed.

(Received February 15, 1958)

UDC 547.836.3.07

56. **Kitaro Mizukami**: Synthesis in the Benzoquinolizine Group. XXIV.1) A Synthesis of *rac*-Dihydroisorotundine.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**)

Many years ago, Kondo and Matsuno2) isolated a new alkaloid, $C_{16}H_{21}O_3N$, from the rhizome of *Stephania rotunda* Loureio, indigenous to French Indo-China, which they named rotundine. Chiefly based on the results of degradation works thereof they proposed the structure (A), i.e. 2-methyl-3,9,10-trimethoxy-6,7-dihydro-11b*H*-benzo[*a*]-quinolizine, for rotundine. According to these authors the features of rotundine are the facts that it takes up only one mole of bromine in acetic acid to form dibromo-derivative and absorbs only one mole of hydrogen in the presence of Adams' platinum catalyst to yield dihydrorotundine, which still retains one double bond.

In the course of a projected synthesis of *rac*-dihydrorotundine (B)3) it was found that the compound (C), one of the key intermediates for this synthesis, underwent the ketone fission reaction only with difficulty to yield the ketone (D), which was a rather unstable compound. Therefore it appeared to the present author worthwhile to syn-

---

* Hongo, Tokyo (水上喜太郎).

1) This paper constitutes part of a series entitled "Synthesis in the Quinolizine Group" by Shigehiko Sugasawa. Part XXIII: This Bulletin, **2**, 85(1954).

2) H. Kondo, T. Matsuno: Yakugaku Zasshi, **64B**, 113, 274(1944).

3) This will be the subject of the forthcoming paper.