STUDIES ON THE ALKALOIDS OF *ANONA GLABRA L.* (I). THE ISOLATION OF (−)-*N*-METHYLACTINODAPHNINE.

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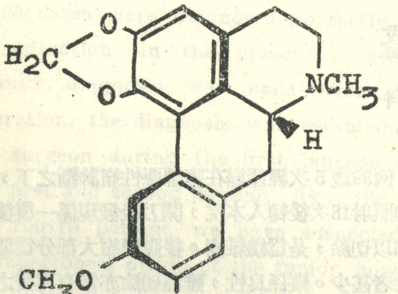
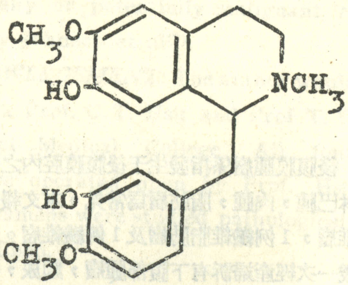
Chemical examination of the leaves of *Anona glabra L.* (Anonaceae) has led to the isolation of a new alkaloid, (−)-*N*-methylactinodaphnine (I) together with reticuline (III) from the alcoholic extract. Characterization of this base (I) by spectral evidence and direct comparison of their infrared spectra (nujol) and tlc were found identical with (+)-*N*-methylactinodaphnine except the optical rotation and mixed melting point.

In the course of our continuing search for the antitumor constituents from Formosan Anonaceous plants, the alcoholic extracts of *A. squamosa* L.[1] and *A. reticulata L.*[2] were found to contain a number of benzylisoquinoline and aporphine alkaloids. In the present paper, we wish to report the isolation and characterization of a new base which clarified as levoratory enantiomer of *N*-methylactinodaphnine (I)[3] together with a known alkaloid, reticuline (III), from the leaves of *Anona glabra L.* (Anonaceae). This new alkaloid was obtained as crystalline hydrobromide salt from the phenolic fraction of the alocholic extract.



(I) R=H (II) R=CH_3



(III)

Base-I, $C_{19}H_{19}O_4N$ was crystallized from methanol as colorless needles, mp. 210-211°, $[\alpha]_D^{31}-61.27°$ (c=0.58, $CHCl_3$). It gave positive ferric chloride and Labat's tests. The mineral acid salt of this base had been prepared as hydrobromide, mp. 224-226° (decomp.) and hydrochloride, mp. 217-220° (decomp.). The ultraviolet spectrum of I shows λ_{max}^{EtOH} $m\mu$ (log ε) at 307 (4.16), 283 (4.14) and λ_{min}^{EtOH} $m\mu$ (log ε) at 292 (4.10), 257 (3.90) indicating a characteristic to 1, 2, 9, 10-tetrasubstituted aporphine alkaloids

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as glaucine[4]. Its infrared band at 3500cm^{-1} and 940, 1050cm^{-1} shows the presence of phenolic hydroxyl and methylenedioxy groups. The nmr ($CDCl_3$) appeared one *N*-methyl group as singlet at 7.49τ (3 protons), one methoxy group as singlet at 6.12τ (3 protons), one methylenedioxy group as two doublets at 3.94, 4.09τ (2 protons) and one extreme downfield singlet at 2.37τ attributed to C_{11}-aromatic proton[4], and the other two one proton singlets at 3.22 and 3.50τ assigned to C_3- and C_8-aromatic proton respectively.

O-methylation of base-I with an excess of diazomethane at room temperature yielded a colorless scales of *O*-methyl derivative (II), $C_{20}H_{21}O_4N$, mp. 168° (Et_2O), $[\alpha]_D^{29}-51.4°$ (c=0.2, $CHCl_3$). ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 940, 1050 (—O—CH_2—O—). nmr($CDCl_3$) τ: 7.46 (3H, one NCH_3), 6.07 (6H, s, two OCH_3), 3.93, 4.08 (2H, —O—CH_2—O—), 3.46, 3.20, 2.33 (3H, C-3, 8, 11 aromatic H). Picrate: orange needles, mp. 179° (decomp.) (Me_2CO). This *O*-methyl compound (II) was identical to dicentrine (mp. 168°, $[\alpha]_D+49.77°$ ($CHCl_3$))[5] in all respects except the optical rotation in the literature. From the above spectral data, base-I was assumed to be *N*-methylactinodaphnine[3] and this was supported by mass spectrum which afforded a molecular ion peak at *m/e* 325 corresponding to the molecular formula $C_{19}H_{19}O_4N$ and other characteristic peaks of aporphine alkaloids[4] at *m/e* 324 (M^+-1), 310 (M^+-15), 282 ($M^+-CH_2=NCH_3$), 165 and 152. The identity was proved by infrared spectrum comparison in solid state but their mixed melting point was depressed to 180-186° on admixture with (+)-*N*-methylactinodaphnine[3] (mp. 206°, $[\alpha]_D^{31}+59°$ (EtOH)), originally isolated from *Neolitsea sericea* (*Blume*) *Koidz* (Lauracea). Comparison their some different physical properties of these two optical isomers of *N*-methylactinodaphnine was shown as follow in Table 1.

Table 1.

	(−)-*N*-methylactinodaphnine	(+)-*N*-methylactinodaphnine
Free base	mp. 210-211° (MeOH) $[\alpha]_D^{31}-61.2°$ ($CHCl_3$)	mp. 206° (210°) (MeOH) $[\alpha]_D^{22}+59°$ ($CHCl_3$)
O-methyl compound	mp. 168° (Et_2O) $[\alpha]_D^{31}-51.4°$ ($CHCl_3$)	mp. 168° (Et_2O) $[\alpha]_D^{17}+49.77°$ ($CHCl_3$)

Consequently, this newly isolated phenolic base-I was assigned to (−)-*N*-methylactinodaphnine, (−)-1, 2-methylenedioxy-9-hydroxy-10-methoxyaporphine (I).

The absolute configuration of the natural aporphine alkaloids has been studied[6] by the application of sodium-liquid ammonia reduction[7] and determination of their optical rotatory dispersion[8,9]. The *O*-methyl derivative (II) of base-I is a enantiomer of (+)-dicentrine which had been established as (S)-configuration by the high amplitude positive Cotton effect centered at 248 $m\mu$[9]. Base-I was obtained as levoratory isomer and therefore its configuration unambiguously belong to (*R*)-series. The isolation of *R*-(−)-*N*-methylactinodaphnine (I) made the first instance from the natural sources.

EXPERIMENTAL

All melting points are uncorrected and measured on Yanagimoto micromelting point apparatus. The optical rotations and ir spectra were recorded with Rex Photoelectric Polarimeter, model NEP-2 and Hitachi Grating IR Spectrophotometer, model EPI-G2. The nmr spectra were obtained in τ scale with TMS as internal standard in $CDCl_3$. Thin-layer chromatography was performed on silical gel F254 (E. Merck) with $CHCl_3$-MeOH (5-2) as developing solvent and detection by spraying Dragendorff's reagent.

Isolation of alkaloids:

The dried leaves of *Anona glabra L.* (1.57 *kg.*), collected in Taipei were extracted with ethyl alcohol until negative to Mayer's test, and the total alcoholic extract was concentrated to dryness under reduced pressure to give dark syrup. This residue was triturated with 5% AcOH, filtered, and washed with ether to remove the neutral and acidic substances. The acidic solution was made alkaline with concentrated ammonia water and extracted with ether. The combined ether solution was then shaken with 3% aq. sodium hydroxide solution to separate the phenolic and non-phenolic bases. The lower NaOH solution was made weak alkaline with NH_4Cl and extracted with ether. After washing with water and drying over anhyd. $MgSO_4$, the filtrate was concentrated to give a crude phenolic base (4.4*g.*)

This crude phenolic base was dissolved in a small amount of acetone and 38% hydrobromic acid was added until acidic to give crystalline solid (1.2*g.*). Repeated crystallization with ethyl alcohol afforded base-I hydrobromide, mp. 224-226° (decomp.). The mother liquid of this hydrobromide, after acid-alkaline treatment, was chromatographed on silicagel column, eluted with $CHCl_3$ yielded base-I (0.2*g.*). Continued with 10% MeOH in $CHCl_3$ gave colorless oily base-III (20*mg.*), perchlorate, mp. 203-205° (EtOH), $[\alpha]_D^{28} -84.3°$ (c=0.5, EtOH) which shows identical with reticuline as perchlorate in ir (nujol), tlc and no depression mixed melting point.

Base-I. (−)-*N*-methylactinodaphnine (I):

Colorless needles, mp. 210-211° (MeOH), $[\alpha]_D^{31} -61.27°$ (c=0.58, $CHCl_3$), positive Labat's and ferric chloride reactions. uv: λ_{max}^{EtOH} $m\mu$ (log ε): 307 (4.16), 283 (4.14); λ_{min}^{EtOH} $m\mu$ (log ε): 292 (4.10), 257 (3.90). ir ($CHCl_3$) cm^{-1}: 3500 (—OH), 940, 1050 (—O—CH_2—O—). nmr ($CDCl_3$)τ: 7.49 (3H, NCH_3), 6.12 (3H, OCH_3), 3.94, 4.09 (2H, q, —O—CH_2—O—), 2.37, 3.22, 3.50 (3H, aromatic —H). Mass spectrum: M^+ *m/e* 325 ($C_{19}H_{19}O_4N$); base peak, *m/e*

282 ($M^+-C_2H_5N$); other intense peaks at *m/e* 324, 310, 293, 267, 251, 224, 165, 152, 83 and 43. Anal. calcd. for $C_{19}H_{19}O_4N$. C, 70.14; H, 5.89; N, 4.31. Found: C, 70.26,; H, 5.82; N, 4.24. hydrochloride: mp. 217-220° (decomp.) (EtOH). Hydrobromide: mp. 224-226° (decomp.) (EtOH).

***O*-methyl derivative (II) of base-I: (−)-dicentrine (II):**

A solution of base-I (70*mg*.) in $CHCl_3$ was charged with an excess of diazomethane twice and allowed to stand for 5 days at room temperature. The reagent was removed and the residue was treated with acid-alkaline, extracted with ether. The combined ether solution was washed with 5% NaOH solution, dried over anhyd. $MgSO_4$ to leave oily base. Recrystallization with ether yielded colorless scales (44*mg*.) mp. 168°, $[\alpha]_D^{29}-51.4°$ (c=0.2, $CHCl_3$), ir ($CHCl_3$) cm^{-1}: 940, 1050 ($-O-CH_2-O-$). nmr ($CDCl_3$)τ: 7.46 (3H, $-NCH_3$), 6.07 (6H, two OCH_3), 3.93, 4.08 (2H, $-O-CH_2-O-$, two doublets), 3.46 (C_3-aromatic H), 3.20 (C_8-aromatic H), 2.33 (C_{11}-aromatic-H). Anal. calcd. for $C_{20}H_{21}O_4N$. C, 70.78; H, 6.24; N, 4.13. Found: C, 70.91; H, 6.29; N, 4.08. Picrate: orange needles, mp. 179° (decomp) (Me_2CO).

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