蓮之化學成分研究

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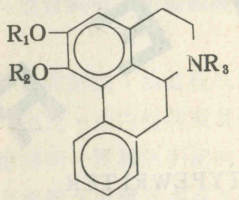
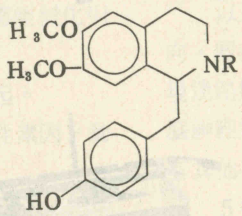
蓮（Nelumbonucifera Gaertn，Nymhaeceae）原產於熱帶亞細亞爲一多年生草本植物，台灣各地普遍栽植於水田邊或公園池塘，供觀賞或採食之用，其根莖（蓮藕）及種子（蓮子）有清涼，止渴，滋養，强壯之效；蓮房可治肺及腎臟之疾患；至於蓮葉及蓮柄則有抗菌，止血及解毒之作用兼治產後口渴，心煩諸症；蓮子蕊爲蓮子中味苦之胚芽，有清心，去熱之效，可治勞心，吐血之疾。

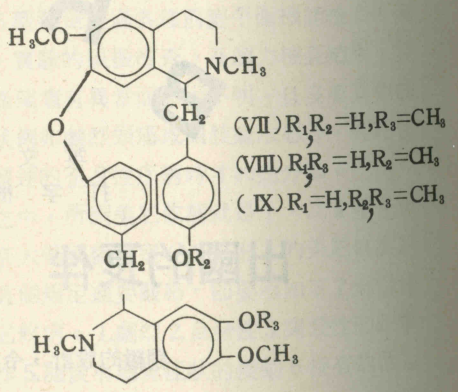
至於蓮之化學成分除蓮子含維生素丙，raffinose，胚芽含 asparagine，蓮藕含維生素丙，asparagine之外，主要有生物鹼存在，關於Nelumbo屬植物生物鹼之化學研究，1899年Greshoff，Boorsma等從蓮之子葉初次分離得一種物質曰Nelumbine，但其性狀未詳，1959年Arthur等從Asiatic Lotus之葉分離得nuciferine（Ⅰ），其後日本富田等從日本產蓮單離出nuciferine（Ⅰ）之外，還證明有roemerine（Ⅱ）與nornuciferine（Ⅲ）以及dl-armepavine（Ⅵ），1962年，美Kupchan等由美國產同屬植物N. lutea，除確認有armepavine（Ⅵ），nuciferine（Ⅰ）之存在，尙新單離出L－(－)－N－norarmepavine（Ⅴ）及(－)－N－norarmepavine（Ⅳ）等生物鹼，同年高怡生等自中國大陸的蓮子蕊分離出一種新型生物鹼曰liesinine（Ⅶ）；而後我們從本省產的蓮子蕊單離兩種新成分，lsoliensinine（Ⅷ）與lotusine（Ⅹ）並證明蓮葉含Nuciferine（Ⅰ），roemerine（Ⅱ）及nornuciferine（Ⅲ），葉柄有nuciferine（Ⅰ）的存在。1965年日本古川由香港產的蓮子蕊分離另一種新物質neferine（Ⅳ）並證明有nuciferine（Ⅰ）以及pronuciferine（Ⅺ）之存在；最近著者等更由本省的蓮子蕊再分離得Neferine（Ⅸ）與新的微量塩基性成分，命名爲methylcorypalline（Ⅻ），後者經化學合成證明其構造爲6.7-dimethoxy-2-methyl-tetrahydroisoquinoline，這次主要關於新成分之單離方法，構造決定及合成概略介紹。



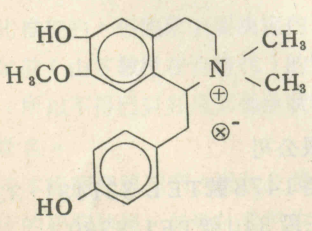
（Ⅰ）R_1，R_2，R_3=CH_3
（Ⅱ）R_1，R_2=CH_2，R_3=CH_3
（Ⅲ）R_1=H，R_2，R_3=CH_3
（Ⅳ）R_1，R_2=CH_3，R_3=H



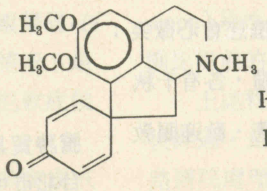
（Ⅴ）R=H
（Ⅵ）R=CH_3



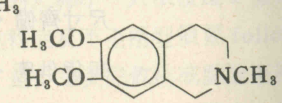
（Ⅶ）R_1，R_2=H，R_3=CH_3
（Ⅷ）R_1，R_3=H，R_2=CH_3
（Ⅸ）R_1=H，R_2，R_3=CH_3



（Ⅹ）

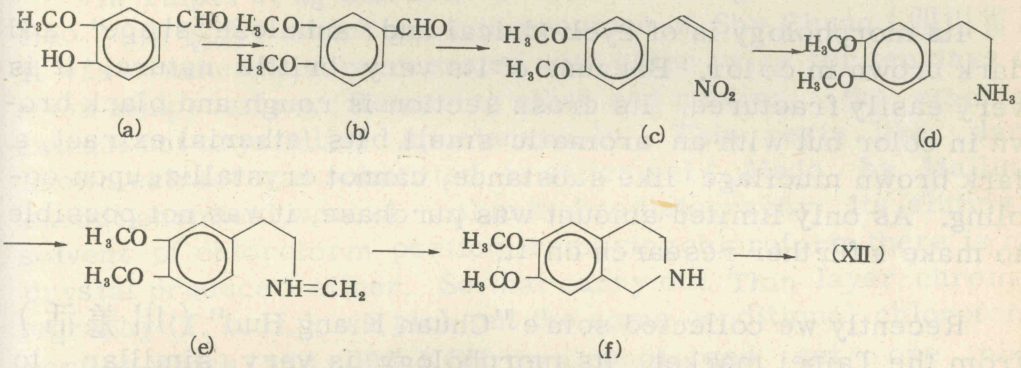


（Ⅺ）



（Ⅻ）

市售蓮子蕊以酒精抽取數次，其抽出液經減壓濃縮得黑色油狀物，以3%的醋酸溶液溶解，過濾之濾液，用乙醚振盪除去非鹽基性物，酸性層加氨水鹼化後，析出的生物鹼以氯仿抽取，合併氯仿抽取層，加NaOH 溶液分離酚性及非酚性塩基，氯仿層用酸鹼處理，水洗，脫水乾燥得精製非酚性的塩基，經Al_2O_3 Column Chromatography從Benzene elution 得粗結晶，用N-hexane再結晶得白色羽狀結晶，量微m.p. 58－60°，T.L.C. 1 Spot，$[\alpha]_{20}^{0}$，±0，$FeCl_3$（－），Labat（－），塩酸塩mp. 216～217°，苦味酸塩mp 152～153°，Methiodide，mp. 242°。由 IR Spectrum 顯示有$-OCH_3$ 基及 1,2,4,5 - tetrasubstituted benzenoid，UV 之極大吸收（λ_{max}）在281mμ，285mμ，290mμ（Sh.），Mass Spectrum $M^+=207$，NMR Signals在 6,18τ（6H，2×OCH_3），7.582（3H,-NCH_3），3.40及 3.48τ（2H，Aromatic H）綜合以上的性質，推定爲dimethoxy，N-methyltetrahydro-isoquinoline derivatives，本結晶性物質直接與我們合成如下之6,7 dimethoxy - 2 - methyltetrahydroisoquinoline以 IR，T.L.C. 比較結果完全一致，且m.p. 混融不下降，此生物鹼之 -HCl，picrate，methiodide 等衍生物與合成品之諸衍生物mp混融亦一致，故證明由蓮子蕊抽取的塩基之構造式爲（Ⅺ），因爲構造上是Manske （1937）所分離的Corypalline之 7 - O - Methyl衍生物，故命名爲Methylcorypalline（Ⅻ）。



Vanillin (a)以 dimethylsulfate methylation 得淡黃色針狀結晶，veratraldehyde (b) m.p. 40～40.5°。(b)於甲醇中與 nitromethane 及微量之methylamine室溫反應得黃色片狀結晶之 3,4，dimethoxy - ω - nitrostyrene (c)，mp 139～140°。(c) 之溶液中，以 lit h.ium Aluminum hydride還原得白色結晶之 3. 4 - dimethoxy phenylethylamine Oxalate (d) mp 178－179°。由(d) oxalate 製成游離的塩基，加 formalin 溶液（37%）formylation 反應得油狀物(e)，再於酸中Cyclization 得 6,7 dimethoxytetrahydroisoquinoline - HCl (e)結晶，mp 254～255°。(e)化成游離塩基，以甲酸（85%）及 formalin（37%）反應，經 hydroxymethylation得白色羽狀結晶之 6,7 - dimethoxy - 2 - methyltetrahydroisoquinoline（Ⅺ），mp 58－59°，HCl，白色顆粒狀結晶mp. 214～5°；picrate，黃色微針狀結晶，mp 152～3°；methiodide，白色片狀結晶，mp 243～4°。

Methylcorypalline的合成雖 Buck 曾製備過，但由自然界單離發現，今次爲首次，此物質與 bisbenzylisoquinoline，benzylisoquinoline，aporheine等生物鹼共存於蓮子蕊，在生合成觀點上，methylcorypalline 很可能爲合成這些更複雜生物鹼之前驅物質（biogenetic precussor）或者爲它之代謝分解物，1953年C. Hanna 和 J.H. Shutt報告 substitute isoquinoline衍生物包括 6,7 dimethoxy - 2 - methyltetrahydroisoquinoline（methylcorypalline）（Ⅺ）類似 Papaverine之作用，具有擴張冠狀動脈的效能。

綜合以上所述，蓮之生物鹼分佈在化學上可分爲(1) aporheines：（Ⅰ），（Ⅱ），（Ⅲ），（Ⅳ），(2) benzyltetraisoquinolines：（Ⅴ），（Ⅵ），（Ⅹ）(3) bisbenzyltetra hydroisoquinoline：（Ⅶ），（Ⅷ），（Ⅸ）(4) apomorphine protobase：（Ⅺ），(5) tetrahydroisoquinoline：（Ⅺ）等五類；於蓮葉柄，胚芽各部所含之成分亦有所差異，葉含（Ⅰ）～（Ⅳ），葉柄含（Ⅰ），（Ⅱ），蓮子蕊有（Ⅶ）～（Ⅺ），故以植物分類學及生理學上與化學構造互相關係的觀點而言，蓮之生物鹼成份的差異頗具興趣的。

A STUDY ON THE CHEMICAL CONSTITUENT OF CHINESE HERB " KIANG HUO"

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"Kiang Huo" (羌活) was originally grown in China. In former times, Dr. Kimura and Nakao[1] ascertained that it belonged to the *Angelica* genus *(Umbelliferae)*. Author was studying at Kyoto University (Japan), we purchased some amount of "Kiang Huo" from a Chinese herb drug market in Osaka for the study of its chemical constituents.[2]

Its morphology is of cyclindrical and annulose shape and dark brown in color. Because of its very brittle nature, it is very easily fractured. Its cross section is rough and black brown in color but with an aromatic smell. Its etherial extract, a dark brown mucilage like substance, cannot crystallize upon cooling. As only limited amount was purchase, it was not possible to make a further research on it.

Recently we collected some "Chuan Kiang Huo" (川羌活) from the Taipei market. Its morphology is very simillar to that of "Kiang Huo". In order to give a systematic study of the umbelliferous drugs, a further research on it was carried out once more.

As the etherial extract did not crystallize upon cooling, it was submitted to silica gel column chromatography. Then by applying the Thin layer chromatography (T. L. C.), we collected the same portion of chloroform and removed the chloroform. But no crystal produced either. However, when treated by saponification as shown in chart I, a crude crystal was obtained. After recrystallization with ethyl alcohol, its melting point raised to 189-190°C The composition of the white needle crystalline (I) is $C_{12}H_{18}O_4$ When the Infra-red spectra of (I) were tested at 1725 cm^{-1}, it showed lactone and carbonyl group.

Based on the foregoing-mentioned melting point, composition and IR spectra, it is presumed that (I) is Bergapten when it was mixed with authentic sample, its melting point did not depress. This fact further strengthened our conviction that (I) is

Bergapten.

Bergapten is isolated from this herb drug by saponification. Ordinarily, *Angelica* genus posses blue fluorescent spots. It shows that this plant contains Umbelliferone. However, merely based on the above-mentioned factors, it still can hardly be determined whether it belongs to the family of *Angelica* genus or not.

Apart from Bergapten, we still continue to study very deliberately other substances.

Experimental Section

Isolation of Bergapten:

Via Taipei drug market, we collected 5kg "Chuan Kiang Huo" (川羌活) which grow in province of Shy Chuan (四川省). It was crushed and mercerated with ether twice for ten days at room temperature. Removing ether and cooling, the etherial extract not crystallized spontaneously. This resin like dark brown extract was submitted to silica gel (Made by Mallinckrodt chemical works) column chromatography. Its eluting solvent of chloroform portion, removing chloroform, there is no crystal produced either. So that carry out Thin layer chromategraphy (T. L. C.), we pick out the same conditional chloroform portion which add 10% KOH in alcohol and set one night for saponification. Then added enough water and removed alcohol by vaccum. Shaking with ether to remove the unsaponification portion.

The water layer, acidified by dil. H_2SO_4 and shake out the coumarin fraction by ether. This ether solution is shaked by the following solution: saturated $NaHCO_3$, 5% NaOH. Removing the acidic portion and phenolic portion.

In the neutral portion, dehydration and removing ether, a crude crystall obtained. It treated recrystallization with ethanol, a white needle crystal, mp. 189-190°C (I).

$C_{12}H_{18}O_4$ *Anal.* Calcd : C, 66.67% ; H, 3.70%
Found : C, 66.80% ; H, 3.80%

The I R spectrum of (I) was identical and exhibited characteristic peak at 1725 cm^{-1} assignable to lactone, carbonyl group. Mixed with authentic sample of Bergapten no depressed melting point.

Chart I. Etherial extract of "Chuan Kian-Huo"

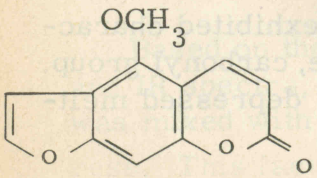
Column chromat. on silica gel
n-Hexane

- eluting-(1)
- Column
  - *n*-Hexane : $CHCl_3$ 2 : 1
    - eluting (2)
    - Column
      - *n*-Hexane : $CHCl_3$ 1 : 1
        - eluting (3)
        - Column
          - $CHCl_3$
            - eluting(4)
            - Column

Saponification the same chloroform portion

evaped.+10% EtOH-KOH(at room temp. for 1 day) + H_2O ; EtoH evap in vacuum.
Et_2O add.

- Et_2O layer
  unsaponificated fraction
- aq. layer
  acidify c̄ 30% H_2SO_4
  Et_2O add.
  - Et_2O layer
    saturated $NaHCO_3$
    - aq. layer
      acidify c̄ 30% H_2SO_4
      +Et_2O add
      acidic portion
    - Et_2O layer
      +5% NaOH solu.
      - aq. layer
        acidify c̄ 30% H_2SO_4
        add Et_2O
        Phenolic portion
      - Et_2O layer
        Neutral portion
        crystal (I)
        mp. 189-190°C
        Bergapten
  - aq. solu.



Bergapten

References

1). M. Nakao, K. Kimura: The Annual Proceeding of Shang-hai Natural Science Laboratory Vol. 1, No. 2, 88 (1929).

2). K. Kimura, K. Hata, K. Yen, S. Cheng: Yakugaku Zasshi (Tokyo): 78, 442 (1958).

〔中文摘要〕

羌活之成分研究(I)

臺北醫學院 生藥化學科

顏焜熒 楊玲玲

臺北市生藥市場收集之大陸產"川羌活"5公斤，用乙醚(Ether)溫浸抽取，移去乙醚通Silica gel Column Chromatography，展開劑順次用*n*-Hexane，*n*-Hexane：$CHCl_3$（2：1），*n*-Hexane：$CHCl_3$（1：1），$CHCl_3$ oney·將$CHCl_3$部分用T.L.C法將具有有相同Spot之部分合併，皂化後得mp. 189～190°C，組成$C_{12}H_{18}O_4$之白色針狀結晶，由紅外光譜（IR）及與標品混融，融點無下降，證實此結晶爲Bergapten。

（台灣藥學雜誌 Vol. 20 投稿中）