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ISOMERIZATION OF MENISIDINE*

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木防己素乙之同質異性化（摘要）

此文證明有些植物鹼在加熱至適當溫度時，即可使之同質異性化 (Isomerization)，不必如普通方法用酸類或鹼類或他種化學藥品以促其實現．在一九三八年，作者曾將木防己素甲加熱至 150°，使之變爲日人近藤及矢野二氏所發現之 Tetrandrine，並證明二者爲同質異性物．今又將木防己素乙加熱至 160° 約五小時，發現所得者已變爲莊長恭氏所發現之 Fangchinoline．最感興趣者，在一九四八年，作者曾利用溫度使常山鹼甲變爲常山鹼丙．前者幾無抗瘧作用，後者抗瘧作用極强，超過奎寧 148 倍之多．此種簡單之同質異性化方法，當可供從事化學研究工作者之試用．

In 1935, the writer reported the isolation from the Chinese drug Mu-fang-chi two alkaloids, menisine, $C_{19}H_{21}NO_3$, m.p. 127° and menisidine, $C_{36}H_{40}N_2O_6$, m.p. 176°. Their pharmacological action was subsequently studied (Chen and Chou, 1937). The formula of menisine, $C_{19}H_{21}NO_3$, if doubled, would have the composition $C_{38}H_{42}N_2O_6$, identical with that of tetrandrine (Kondo and Yano, 1932). In fact, menisine has been found later (Chou, 1938) to be isomeric with tetrandrine, and can easily be transformed into the latter by heating to a temperature of 150° for a few hours. In 1939, Chuang *et al* isolated from the Chinese drug Hang-fang-chi, tetrandrine and another alkaloid, $C_{37}H_{40}N_2O_6$ m.p. 237° to which the name fangchinoline was assigned. They differed from each other by a CH_2 group. Fangchinoline was stated by them to contain three methoxyl and one phenolic hydroxyl groups, and, on methylation, gave rise to tetrandrine. The similarity between fangchinoline and menisidine in general properties, except their melting points, led the writer to think that these two bases are probably isomeric also as in the case of tetrandrine and menisine. This view has now been substantiated by the fact that on heating to a temperature of 160-170° for 5 hours, menisidine was completely converted into fangchinoline, and when methylated with diazomethane, it gave rise to the formation of menisine. In consequence, menisidine is isomeric with fangchinoline, differing from menisine also only by a CH_2 group, and should possess the

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composition $C_{37}H_{40}N_2O_6$ assigned to fangchinoline by Chuang *et al* (1939), instead of $C_{36}H_{40}N_2O_6$ as reported previously.

EXPERIMENTAL

1) *Conversion of menisidine into menisine.*

A mixture of 6 cc. of a 40 percent KOH solution and 20 cc. of ether was cooled to 5° with a freezing mixture. 2 g. of finely powdered nitrosomethylurea was added to it little by little with shaking. The yellow solution so obtained was allowed to remain in the ice mixture for some time, and then the ethereal layer was decanted carefully into a cold solution of 0.5 g. of pure menisidine dissolved in 60 cc. of ether. The whole was allowed to stand at room temperature (about 16°) for 3 days and then washed twice with a dilute solution of acetic acid. The acid solution was separated, made alkaline with sodium carbonate, and the precipitate extracted with a mixture of chloroform and ether. The chloroform-ether solution, when dried and distilled, left behind a basic residue consisting of the menisine required together with some unchanged menisidine. On taking up with a little acetone, menisidine separated out first in the form of its acetone compound in rhombic prisms. Its acetone mother liquor, on concentration, deposited menisine in a rather impure state. When crystallised pure from 95 percent alcohol, it formed fine soft needles, m.p. 127°, containing one molecule of water of crystallization. It was identical to menisine isolated from Mu-fang-chi in all respects and when mixed with the latter, its melting point remained unchanged.

2) *Conversion of menisidine into fangchinoline.*

1 g. of pure menisidine, m.p. 176°, was heated in an oil bath until it completely melted and then maintained at a temperature of 160-170° for 5 hours. The reddish mass was taken up with a little hot alcohol and filtered from any insoluble resinous matter. The alcoholic solution, on concentration, deposited crystals of fangchinoline in small rhombic prisms. Recrystallized from alcohol, it melted at 237°. When mixed with a pure specimen of fangchinoline supplied kindly by Dr. Chuang, no depression in its melting point has been observed. It was identical to fangchinoline in all its chemical and physical properties. Like menisidine, it formed easily an addition compound with acetone in rhombic prisms, melting at about 165°, resolidifying at 180° and finally melting at 237°. When recrystallized from alcohol, this addition compound lost its acetone content and melted directly at 237°. Fangchinoline prepared by Dr. Chuang (1939) formed also an acetone addition compound in a similar way.

DISCUSSION

Conversion of menisidine into fangchinoline as reported above indicates

the fact that certain alkaloids can easily be isomerized by the action of heat alone without the presence of acids or alkalis or any chemical reagents. Similarly, γ-dichroine, the highly active antimalarial alkaloid with a Q-value of 148, has been obtained by simply heating the almost inert alkaloid, α-dichroine, to a suitable temperature. (Chou *et al,* 1948). This interesting property of certain alkaloids deserves to be taken into consideration in dealing with alkaloids or similar products or in synthesising new drugs.

SUMMARY

Menisidine has now been found to be isomeric with fangchinoline isolated from the Chinese drug Han-fang-chi by Chuang *et al*. These two alkaloids differ from each other only in their melting points. When methylated with diazomethane, menisidine gives rise to the formation of menisine, and when heated to a temperature of 160-170° for 5 hours, it is completely transformed into fangchinoline. It forms easily an addition compound with acetone. It should have the composition $C_{37}H_{40}N_2O_6$ assigned to fangchinoline by Chuang *et al* instead of $C_{36}H_{40}N_2O_6$ as reported previously.

REFERENCES

[1] Chen, K. K. and Chou, T. Q. 1937, The Action and Toxicity of Menisine and Menisidine. Chin. Jour. Physiol. **11,** 29.
[2] Chou, T. Q. 1935, The Alkaloids of Chinese Drug, Mu-Fang-Chi. *ibid.* **2,** 267.
[3] ————, 1938, Menisine, Isomeric with tetrandrine. *ibid.* **13,** 167.
[4] Chuang, C. K., Hsing, C. Y., Kao, Y. S. and Chang, K. H. 1939, Untersuchungen über die Alkaloide von Han-fang-chi. Fangchinolin, ein Demethyl-tetrandrin. Ber. D. Deutsch. Chem. Gesellsch. **72,** 519.
[5] Kondo, H. and Yano, K. 1932, Die Konstitution des Tetrandrins. Die Alkaloide von Stephania Tetrandra, S. Moore (IV). Ann. Chem. **497,** 90.
[6] Chou, T. Q., Fu, F. Y. and Kao, Y. S. 1948, Antimalarial Constituents of Chinese drug, Ch'ang Shan, Dichroa Febrifuga Lour. Jour. Amer. Chem. Soc. **70,** 1765.