MENISINE, ISOMERIC WITH TETRANDRINE

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From the Chinese drug, Mu-fang-chi, the writer [Chou, 1935] reported the isolation of two alkaloids, menisine, C₁₉H₂₂NO₃ and menisidine, C₃₆H₄₁N₂O₆. The former has a m.p. of 127°, containing one molecule of water of crystallisation and a m.p. of 152°, when anhydrous. The empirical formula of menisine, if written with one hydrogen atom less, as $C_{19}H_{21}NO_3$ and doubled, would have the composition $C_{38}H_{42}N_2O_6$, identical with that of tetrandrine [Kondo and Yano, 1932; Chen and Chen, 1935]. Besides the melting points, menisine and tetrandrine were found to be similar in general properties such as solubilities in organic solvents and specific rotations and in their pharmacological action [Chen and Chou, 1937]. On degradation by Hofmann's method, both menisine and tetrandrine gave also same resulting products, consisting of a methine base, m.p. 171°, another substance, m.p. 247° and a nitrogenfree substance, m.p. 221° as previously described by Kondo and Yano [1929] except the substance melting at 247°. These facts led the writer to think that menisine is isomeric with tetrandrine and would probably have the molecular formula of $C_{38}H_{12}N_2O_6$ as assigned to the latter by Kondo and Yano [1932]. In fact, when menisine was heated to a temperature of 150° for 3 hours, it has been found to be transformed completely into tetrandrine, only partial conversion being obtained at lower temperatures It is interesting to point out that during the extraction of menisine from Mu-fang-chi [Chou, 1935], the operations were carried out at room temperatures instead of hot alcohol extracts, processes employed by different workers for the isolation of tetrandrine.

EXPERIMENTAL

For comparison, the degradative experiments by Hofmann's method have been carried out with menisine and tetrandrine separately under

similar conditions. Since the resulting products were found to be exactly the same in both cases, only those experiments with menisine will be described as follows. The tetrandrine used has been generously supplied by Hsu who isolated an alkaloid named Hanfangchin A [1935] and found that latter to be identical with the tetrandrine of Kondo and Yano [1928] in all respects by comparing with an authentic specimen [Hsu, 1937].

Degradation of menisine by Hofmann's method.

Pure menisine, m.p. 127°, in the quantity of 10 g was converted into its methiodide as described previously [Chou, 1935] and then into its corresponding metho-chloride by warming with an excess of AgCl in water on the water bath for sometime. The aqueous solution was filtered, concentrated to 30 cc and then boiled with 3 g of sodium hydroxide for one hour with reflux condenser. The alkaline solution and insoluble gum were extracted repeatedly with hot benzol, leaving undissolved a portion of amorphous residue which was taken up easily with chloroform. The benzol extract was called fraction A and the chloroform extract fraction B. The fraction A was shaken up with a sufficient quantity of N/10 hydrochloric acid and the aqueous layer separated. On standing, the acid solution gave an abundant quantity of the hydrochloride of a methine base in fine needles. It was filtered, dissolved in hot water, made alkaline and extracted with an excess of ether in which it was soluble with difficulty. The ethereal solution, when dried and concentrated, gave a deposit of the methine base in rhombic prisms. When recrystallised pure from methyl alcohol, it formed colourless prisms, melting at 171°, identical with that of α – methine base from tetrandrine as described by Kondo and Yano [1929] and differing from the latter in being optically inactive in methyl alcohol solution.

Analysis: 0.0520 g sub. gave 0.140 g CO_2 and 0.0344 g H_2O_3 C=73.90; H=7.40

Calculated for the methine base, $C_{40}H_{46}N_2O_6$, C=73.85; H=7.08.

Its methiodide, prepared by warming the methine base with methyl iodide in methyl alcohol solution, formed yellowish orange prismatic needles, m.p. 257° with a previous lightening in colour at about 230°.

From the acid mother liquor, after the removal of the crystalline hydrochloride of the methine base as described above, there has been

isolated another base in the form of its methiodide, large bluish rhomboids, m.p. 217° and also optically inactive.

The fraction B, i.e. the chloroform extract of degradative products, was dried and distilled, leaving behind a reddish residue which, when crystallised pure from methyl alcohol, formed yellowish orthorhombic prisms, m.p. 248° with decomposition. It was only sparingly soluble in ether or benzene but easily soluble in chloroform, alcohol or methyl alcohol. Its methyl alcohol solution was found to be highly dextrorotatory; a 0.5 per cent solution in methyl alcohol in 1 dm tube gave specific rotation of 3.125°; whence $\left[\alpha\right] \frac{18}{10} = +625^{\circ}$, unlike the β -methine base as described by Kondo and Yano [1929], its composition was found to be $C_{42}H_{51}N_2O_{11}$ according to the following analytical data:

- (1) 0.0527 g sub. gave 0.1274 g CO_2 and 0.0326 g H_2O C = 65.93 : H = 6.92
- (2) 0.0547 g sub. gave 0.1325 g CO_2 and 0.0350 g H_2O C = 66.06 : H = 7.16
- (3) 0.1667 g sub. gave 0.007395 g NH_3 by Kjeldhal's method N = 3.66

Calculated for
$$C_{42}H_{54}N_2O_{11}$$
 : $C = 66.14$: $H = 7.08$: $N = 3.67$

Its methiodide was obtained in yellowish rhombic prisms, m.p. 258° with decomposition when recrystallised from methyl alcohol. Its aqueous solution was dextrorotatory; a 0.2 per cent solution in water in 2 dm tube gave specific rotation of 1.47°; whence $[\alpha] \frac{18}{D} = +367.50$

Second stage of the Hofmann degradation.

All residues from the first stage of degradative experiments either in the form of the free base or methiodides were united and boiled again with methyl iodide to ensure complete methylation. The mixed methine methiodides so obtained were converted with AgCl into their corresponding metho-chlorides and then boiled with 10 per cent sodium hydroxide for one hour. The trimethylamine evolved was absorbed by dilute hydrochloric acid and readily gave trimethylamine aurichleride, rhombic prisms, m.p. 250° with decomposition.

Analysis: 0.0723 g sub. gave 0.0355 Au : $\Delta u = 49.10$

Calculated for $(CH_3)_3N.HCl.AuCl_3$: Au = 49.41

The alkaline liquor and the precipitated resinous substance were extracted with chloroform in which the latter readily dissolved. The chloroform solution, when dried and distilled, left behind a gummy residue. When recrystallised repeatedly from chloroform with the addition of alcohol, it formed colourless orthorhombic prisms, m.p. 221°, corresponding to that of the nitrogen-free substance. $C_{36}H_{32}O_6$ obtained from tetrandrine by Kondo and Yano [1932]. When mixed with the latter prepared in our laboratory with tetrandrine, its m.p. remained unchanged. The degradative experiments by Hofmann's method as described above were repeated with tetrandrine under similar conditions and the same resulting products were obtained.

Conversion of menisine into tetrandrine.

I g of pure menisine, m.p. 127°, was heated to a temperature of 150° for 3 hours. The resulting product became highly coloured and was taken up with alcohol in which a part remained undissolved. The alcoholic solution was filtered, distilled and the residue taken up with acetone from which it readily crystallised on concentration. When recrystallised repeatedly from acetone with the addition of a few drops of water, it crystallised out in prismatic needles, m.p. 217°, not depressed by mixing with tetrandrine. Another sample of menisine was heated to a temperature of 120° for 3 hours and the resulting product was found to consist of chiefly unchanged menisine.

SUMMARY

The alkaloid, menisine, isolated from the Chinese drug, Mu-fang-chi, was assigned to the empirical formula $C_{19}H_{22}NO_3$; which, if written with one hydrogen atom less and doubled, would have the composition $C_{38}H_{12}N_2O_6$, identical with that of tetrandrine. It has now been found to be isomeric with the latter, differing from each other only in their melting points. On degradation by Hofmann's method, both menisine and tetrandrine gave same resulting products consisting of a methine base, $C_{10}H_{16}N_2O_6$, m.p. 171° , another in the form of its methiodide, m.p. 217° and a third substance having the composition $C_{12}H_{54}N_2O_{11}$, a m.p. of 248° and a specific rotation of $\pm 625^\circ$. When the Hofmann

degradation was carried a stage further on menisine and tetrandrine, trimethylamine and a nitrogen-free substance m.p. 221° were obtained in both cases. When menisine was heated to a temperature of 150° for 3 hours, it has been found to be transformed completely into tetrandrine

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木防己素甲與TETRANDRINE 為異性同物之證明 趙承嘏

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在國產木防己中,作者曾發現兩種植物蘇,命名為木防己素甲menisine 及木防己素乙menisidine. 前者之分子式為C18H22NO3,如除去一氫原子而倍之,則其分子式變為C38H22N2O6,與日人近藤及矢野二氏由日產木防己中所得之 tetrandrine 之分子式相同·今將木防己素甲及tetrandrine 二物加以繼續研究及比較 覺二物不同之處在熔點,餘如物理化學及藥理三種性質則相類似,盖二者質係異性同物也·如將二物各作 Hofmann 氏之分解,則所得之結果亦相同·分解物取出者共有四種,二者與近藤及矢野二氏所得者相同,餘二者則尚未之前聞·如將木防己素甲熱至150°約三小時,則全部變為 tetrandrine 其熔點亦由 127°變為 217°矣。