SYNTHESIS OF METHOXY-HYDROXY-N-METHYL-3·4-DIHYDROISOQUINOLINIUM SALTS.

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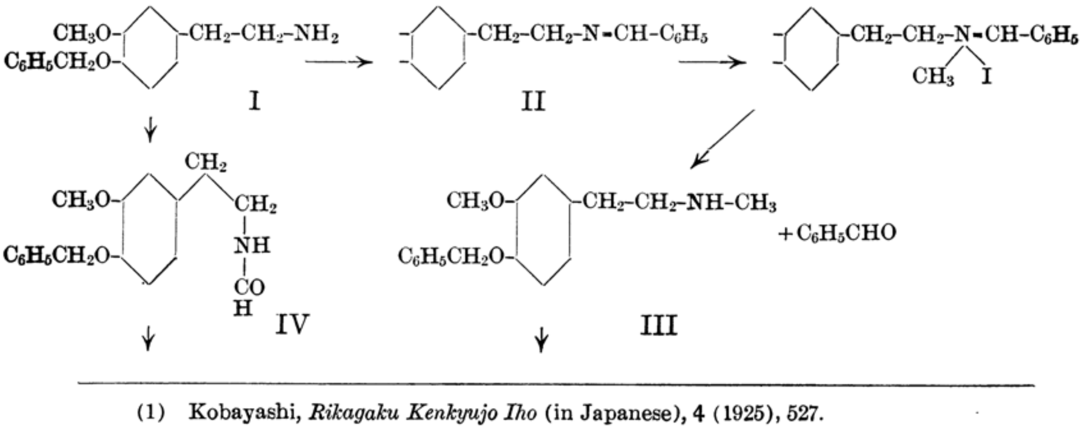
In the dihydroisoquinoline series there are two compounds of much importance from the pharmaceutical point of view. These are hydrastinine and cotarnine, and their hydrochlorides are regarded as having the constitution of 6·7-methylenedioxy-2-methyl-3·4-dihydroisoquinolinium and 6·7-methylenedioxy-8-methoxy-2-methyl-3·4-dihydroisoquinolinium chloride respectively, as is well known. Each of them had first been obtained as an oxidation product of the natural alkaloid hydrastine and of narcotine; later their total synthesis was also successfully achieved.

The present writer has succeeded in preparing several other compounds of this series, namely, 6-methoxy-7-hydroxy-2-methyl-3·4-dihydroisoquinolinium and 6-hydroxy-7-methoxy-2-methyl-3·4-dihydroisoquinolinium salts, as well as their benzylethers. The starting substance is β-[3-methoxy-4-benzyloxyphenyl]-ethylamine (I) which has recently been synthesized by S. Kobayashi.(1)

The method of synthesis which was undertaken and applied successfully in the preparation of 6-methoxy-7-hydroxy-2-methyl-3·4-dihydroisoquinolinium salt (VIII) is expressed by the scheme below.



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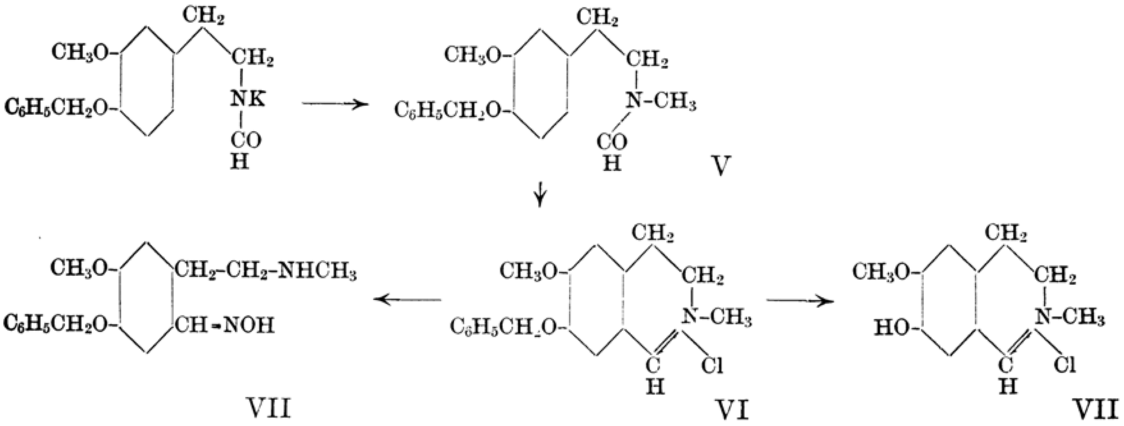
(1) Kobayashi, *Rikagaku Kenkyujo Iho* (in Japanese), 4 (1925), 527.

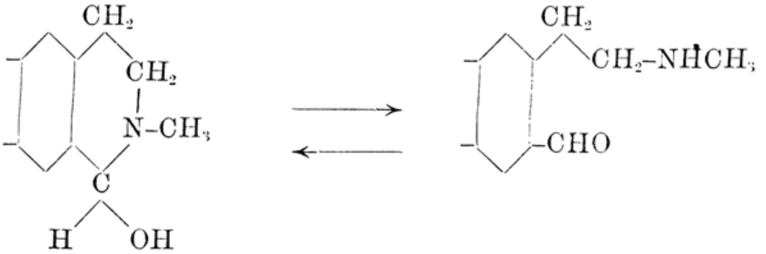


The intra-molecular condensation of formyl-phenyl-ethylamine derivative (V) into dihydroisoquinolinium salt is easily effected by phosphorus oxychloride or thionyl chloride with an exceedingly good yield. Phosphorus pentoxide, however, gives only a poor yield. The most convenient reagent of all is thionyl chloride, for it reacts apparently as follows:—

$$C_{18}H_{21}O_3N + SOCl_2 = C_{18}H_{20}O_2NCl + HCl + SO_2$$

thus directly leading to the formation of the chloride of the expected base. Phosphorus oxychloride, on the other hand, gives the phosphate of the base as an extremely hygroscopic mass, which, therefore, must afterwards be converted into another salt. In spite of the violent evolution of hydrogen chloride at the time of the condensation, the benzyloxyl group remains completely unaffected, while it breaks into benzyl chloride and the free hydroxyl group as a result of the action of concentrated hydrochloric acid.

It is well known that the free bases of hydrastinine and cotarnine react with hydroxylamine to give benzaldoxime derivatives, for they exist in tautomeric forms as below.⁽¹⁾



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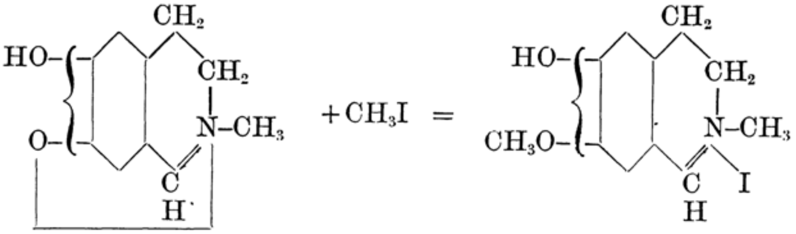
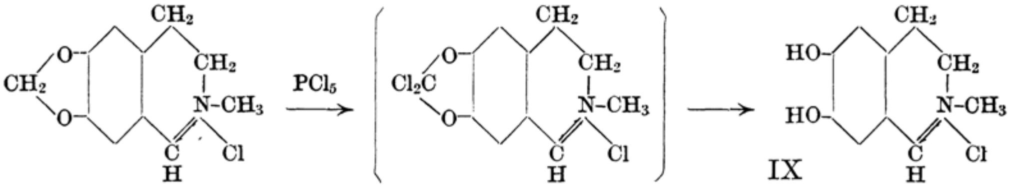
(1) W. Roser, *Ann.*, 249 (1888), 116; 254 (1889), 359.
M. Freund, *Ann.*, 271 (1892), 311; *Ber.*, 22 (1889), 457.
H. Decker, *J. prakt. Chem.*, [2] 47 (1893), 222; *Ber.*, 33 (1900), 2273.
J. Gadamer, *Arch. Pharm.*, 243 (1905), 16.

When treated with hydroxylamine 6-methoxy-7-benzyloxy-2-methyl-3•4-dihydroisoquinolinium salt (VI) is also easily converted into 2-[ω-methylamino-ethyl]-4-methoxy-5-benzyloxy-1-benzaldoxime (VII).

6-Methoxy-7-hydroxy-2-methyl-3•4-dihydroisoquinolinium salt (VIII) is not a new compound, because it has been obtained by F. L. Pyman(1) by the action of methyl iodide on the phenolbetaine of 6•7-dihydroxy-2-methyl-3•4-dihydroisoquinolinium hydroxide (X). But without making any attempt to establish the relative position of the methoxyl and hydroxyl groups, he expressed the reaction as follows:—



For the purpose of identifying the two substances—Pyman's and the present writer's,—the latter has repeated the former's experiments. 6•7-Dihydroxy-2-methyl-3•4-dihydroisoquinolinium chloride (IX), from which the above mentioned phenolbetaine is readily obtained by treatment with the aqueous solution of sodium carbonate, is prepared by the demethylation of compound VIII, or by the action of phosphorus pentachloride on hydrastinine.



IX

The product of the action of methyl iodide on the phenolbetaine was proved to be absolutely identical with 6-methoxy-7-hydroxy-2-methyl-3•4-dihydroisoquinolinium iodide, having the same decomposition point. The reaction between methyl iodide and the phenolbetaine may, therefore, be more reasonably expressed as follows:—

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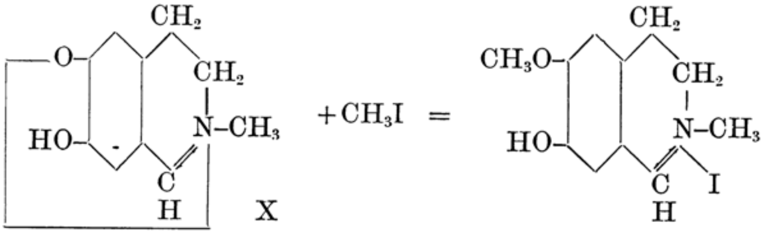
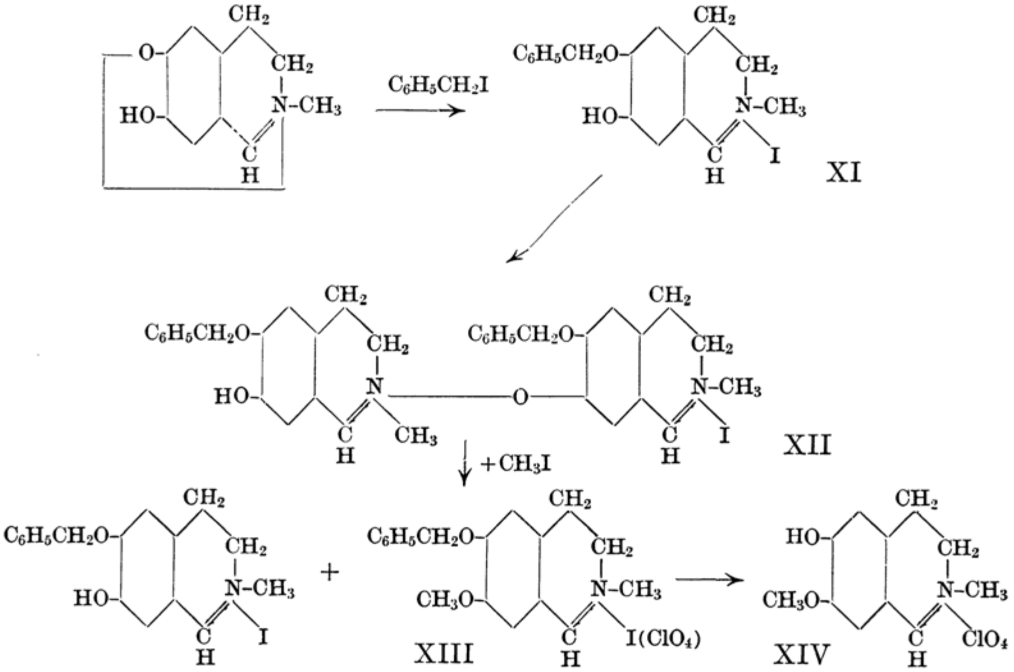
(1) Pyman, *J. Chem. Soc.*, 97 (1910), 268.



X

But the present writer has still some doubt about the constitution of the phenolbetaine.

6-Hydroxy-7-methoxy-2-methyl-3·4-dihydroisoquinolinium salt (XIV), which has the hydroxyl and methoxyl groups in alternate positions as compared with compound VIII, was obtained by the following reactions:—



XI

XII

XIII

XIV

On account of its analogous behaviour, the intermediate compound (XII) is assumed to have a similar constitution to that of Pyman's 6-methoxy-7-[6-methoxy-7-hydroxy-2-methyl-3·4-dihydroisoquinoliniumoxy]-2-methyl-3·4-dihydroisoquinolinium chloride.(1) The method of synthesis adopted by the present writer may be available as a general method for the preparation of any compound of the following general type:—

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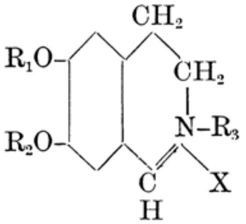
(1) Pyman, *J. Chem. Soc.*, 97 (1910), 269.



Experimental part.

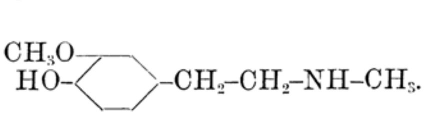
Methyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine, (III). The synthesis of this new base was carried out according to the method, which H. Decker and P. Becker⁽¹⁾ employed in their synthesis of methyl-homo-piperonylamine from homo-piperonylamine. β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine and benzaldehyde, brought together in molecular proportion, react, under spontaneous heating, to give benzal-β-[3-methoxy-4-benzyloxy-phenyl-ethylamine (II). This was purified by recrystallization from a mixture of benzene and petroleum ether; m.p. 57–59°. It crystallizes in light yellow leaflets having a silky lustre.

0.1464 gr. subst. gave 0.4298 gr. CO_2 and 0.0849 gr. H_2O. (Found: C=80.07; H=6.49. $C_{23}H_{23}O_2N$ requires C=79.96; H=6.72%).

The benzal-derivative gives iodemethylate on being heated for about half an hour at 50–60° with methyl iodide in a reflux apparatus perfectly protected from moisture. The iodemethylate is readily hydrolysed in moist alcohol into methyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine hydroiodide and benzaldehyde. The hydrochloride was obtained by passing dry hydrogen chloride into an ethereal solution of the free base. This hydrochloride is easily soluble in water, but moderately so in alcohol, from which it crystallizes in large prisms; m.p. 157–158°. Yield 80%.

0.1303 gr. subst. gave 0.0597 gr. AgCl. 0.1326 gr. subst. gave 0.3213 gr. CO_2 and 0.0844 gr. H_2O. (Found: C=66.08; H=7.12; Cl=11.33. $C_{17}H_{21}O_2N \cdot HCl$ requires C=66.31; H=7.21; Cl=11.53%).

The picrate crystallizes in yellow needles from alcohol; m.p. 163.5–165°. The free base boils under reduced pressure without decomposition; b.p. 200–202° (3.5 mm.)

Methyl-homo-vanillylamine,  $(CH_3O)(HO)C_6H_3\text{–}CH_2\text{–}CH_2\text{–}NH\text{–}CH_3$. This amine plays no part in the course of the synthesis, but is somewhat interesting in constitution being closely related to adrenaline. The hydrochloride

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(1) Decker u. Becker, *Ann.*, 395 (1913), 336.

was obtained by the action of concentrated hydrochloric acid on methyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine; m.p. 149.5–151°.

0.1011 gr. subst. gave 0.0684 gr. AgCl. 10.08 mg. subst. gave 0.540 c.c. nitrogen (11.5°, 756.5 mm.) (Found: Cl=16.74; N=6.40. $C_{10}H_{15}O_2N \cdot HCl$ requires Cl=16.30; N=6.44%).

Formyl-methyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine, (V). 3.2 grams of formate of methyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine (m.p. 105–106°) were heated for half an hour at 170–175°. The product was dissolved in benzene, washed with dilute hydrochloric acid, and subsequently with dilute alkali. After expelling the greater part of the solvent some light petroleum was added. When it had been left standing overnight the formyl-derivative was deposited as a white crystalline mass. This was purified by recrystallization from 50% alcohol, from which it separated in white prismatic crystals; m.p. 78–80°. Yield 2.7 gr. The same compound was also obtained from formyl-β-[3-methoxy-4-benzyloxy-phenyl]-ethylamine (IV m.p. 69–71°) by treatment first with metallic potassium and then with methyl iodide according to D.R.P. 332,474. Yield 90%. This formyl-derivative is readily soluble in ordinary organic media, but insoluble in water.

0.1245 gr. subst. gave 0.3287 gr. CO_2 and 0.0835 gr. H_2O. (Found: C=72.01; H=7.51. $C_{18}H_{21}O_3N$ requires C=72.20; H=6.92%).

6-Methoxy-7-benzyloxy-2-methyl-3·4-dihydroisoquinolinium salts, (VI). 4 grams of the above mentioned compound (V) were dissolved in 20 c.c. of toluene, to which 4 grams of thionyl chloride were added. On being gently heated, the clear mixture became turbid, and then followed a copious evolution of gas, the reaction being complete after a few minutes. The resinous mass, which was deposited at the bottom of the vessel, was separated from the supernatant liquid and washed with light petroleum (during this operation the resinous mass gradually became crystalline), and finally recrystallised from a mixture of alcohol and acetone. This chloride crystallizes in two forms,—one light yellow, short prisms, which melt at 135–138°, after sintering at 125°, the other colourless, large prisms, which melt gradually between 70° and 120°. After being dried in a vacuum at 80°, both of them melt at 135–138° and effervesce at 142°. The aqueous solution of this compound exhibits, in a marked degree, the property of fluorescence, and has a strong bitter taste. These properties are exactly similar to those of hydrastinine. Moreover, in a single qualitative test of its physiological behaviour, it contracted the uterus muscle of a rat.

Yellow sample—0.1078 gr. subst. became 0.1023 gr. after being dried in a vacuum at 80°, and gave 0.0443 gr. AgCl. (Found: H_2O=5.10; Cl=10.17. $C_{18}H_{20}O_2NCl \cdot H_2O$ requires H_2O=5.37; Cl=10.54%).

Colourless sample—0.1644 gr. subst. became 0.1477 gr. after being dried in a vacuum at 80°. (Found: $H_2O=10.16$. $C_{18}H_{20}O_2NCl\cdot 2H_2O$ requires $H_2O=10.19\%$).

Anhydrous sample—0.1082 gr. subst. gave 0.2704 gr. CO_2 and 0.0592 gr. H_2O. (Found: $C=68.16$; $H=6.12$. $C_{18}H_{20}O_2NCl$ requires $C=68.01$; $H=6.35\%$).

The picrate crystallizes in golden-yellow plates, which melt at 177–178°.

5.56 mg. subst. gave 0.505 c.c. nitrogen (9.2°, 762.5 mm.) (Found: $N=11.05$. $C_{24}H_{22}O_9N_4$ requires $N=10.98\%$).

2-[ω-methylamino-ethyl]-4-methoxy-5-benzyloxy-1-benzaldoxime, (VII). 1 gram of 6-methoxy-7-benzyloxy-2-methyl-3•4-dihydroisoquinolinium chloride was dissolved in 10 c.c. of water, to which was added 0.3 gram of hydroxylamine hydrochloride in 5 c.c. of water, and the solution was then made alkaline with sodium carbonate. The whole was slightly warmed on a water bath, when the white crystalline oxime was deposited almost quantitatively. A pure sample, recrystallized from alcohol, melts at 166–167°. It turns red on exposure to the daylight.

0.1081 gr. subst. gave 0.2713 gr. CO_2 and 0.0647 gr. H_2O. (Found: $C=68.46$; $H=6.70$. $C_{18}H_{22}O_3N_2$ requires $C=68.78$; $H=7.06\%$).

(To be continued.)