point was recognized without purification.

Transformation of the Double Bond in the Lower-melting Hydrochloride (VIII)—The substance (VIII)(20 mg.) was mixed with 10% HCl (0.3 cc.) and, after 1 hr.'s refluxing, the acid solution was evaporated *in vacuo* and the colorless oily residue was obtained. This crude hydrochloride was dissolved in acid solution, filtered, and basified with dil. alkali. The separated free base was collected in ether, washed, dried, and evaporated. The residue was characterized as its picrate, which was purified from conc. AcOH. This picrate was proved to be identical in every respect with a specimen prepared from (VII), as yellowish brown crystals of m.p. 225°(decomp.).

Summary

In the preceding paper it was shown that two kinds of pyrimidinoisoquinoline of a higher and lower melting point were obtained by the cyclization of N-(*p*-nitrobenzoyl-β-alanyl)-β-3,4-dimethoxyethylamine. Later, the structure of two were examined through the infrared spectra and some conclusions were drawn from them. A newer method for their mutual transformation method was found and successfully achieved by boiling the lower-melting substance with 10% hydrochloric acid. Furthermore, the same reaction was found to occur between compounds having no nitro group.

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50. **Tetsuji Kametani and Toyoyuki Katagi**: Studies on the Syntheses of Isoquinoline Derivatives and their Analogs. XXXVI. Deamination of 2′-(*p*-Aminophenyl)pyrimidinoisoquinoline Derivatives.

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In the preceding paper[1] Kametani and Katagi described that two kinds of isomers having a double bond in different positions of piperidine moiety were obtained by the cyclization of N-(*p*-nitrobenzoyl-β-alanyl)-β-veratrylethylamine and their structures were examined by their infrared absorption spectra.

Based upon this assumption, the structure of 2′-aminophenylpyrimidinoisoquinoline derivative (II) obtained by the reduction of the nitro compound (I) was investigated chemically by its deamination.

The nitro compound of higher melting point (I), which was stable in 10% aqueous solution of HCl, was reduced catalytically over Adams' Pt, 3 molar equivalents of hydrogen being absorbed. The amino derivative (II) was obtained, leaving the pyrimidine moiety intact. It is certain that this free bese with m.p. 64° is different from the product (III) with m.p. 124~126°, the hydrogenation product of the same starting material (I) with 5 molar equivalents of hydrogen according to Kametani and Katagi.[2]

This amino derivative (II) was diazotizod by $NaNO_2$ as usual and the product was deaminated by standing it with hypophosphorous acid in ice for a few days, yielding the compound (IV). The picrate of this substance (IV) was purified from conc. acetic acid, giving a brownish yellow crystals, m.p. 223~225°(decomp.). This picrate was found to be identical with the one described in the earlier paper of Kametani and Katagi.[2]

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[1] Part XXXV: This Bulletin, 3, 235(1955).

[2] Kametani, Katagi: J. Pharm. Soc. Japan, **75**, 709(1955).

Consequently, it was proved that the deaminated product (IV) obtained from the hydrochloride (I) was identical with the pyrimidinoisoquinoline derivative of higher melting point without a nitro group in the 2′-phenyl ring.

As is obvious from the above, it was presumed that the hydrochloride of lower melting point obtained by another method[1,2)] would become the corresponding product by the same diazotization described above. There is however a possibility that the double bond migrates from the reduced product of lower melting substance to the higher one (IV) via the diazotized compound. Future studies in this regard are being planned.

A synthesis of the amino derivative (III) hydrogenated by 5 molar equivalents of hydrogen has already been reported. After the diazotization of (III) by the above-mentioned procedure and deamination in the presence of hypophosphorous acid, a substance (V) was obtained. The infrared absorption spectrum of the picrate of (V) was examined and two absorptions out of three that were observed, in the 3.0 μ region of the starting material (III), disappeared, giving only an absorption at 2.9 μ.

According to the infrared absorption spectrum of the free base (III) (Fig. 1), two absorptions of 2.78 and 2.88 μ were recognized as those of the N–H stretching vibrations. These depend upon the presence of the primary amine (aniline has two absorption bands, 2.91 and 2.97 μ) and, further, the absorption of the secondary amine is observed in the 3.05 μ region (piperidine has an absorption at 3.04~3.05 μ). On the contrary, an absorption at 2.89 μ that corresponds to the NH group was observed only in the infrared spectrum of the deaminated product (V) (Fig. 2). At the same time that the NH group of (III) was diazotized, the NH group was substituted with a nitroso group, then on being reduced by the hypophosphorous acid, the NH group seemed to be regenerated. Above conclusion is based on results of elementary analyses and Liebermann test.

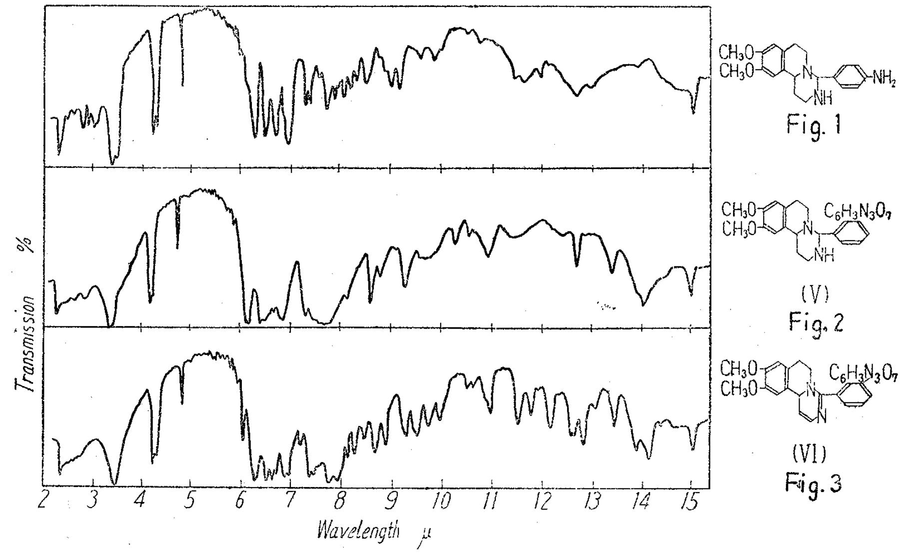
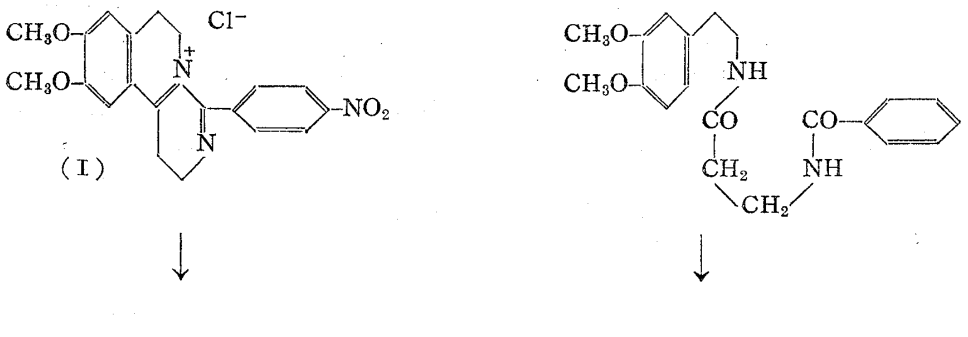


Fig. 1

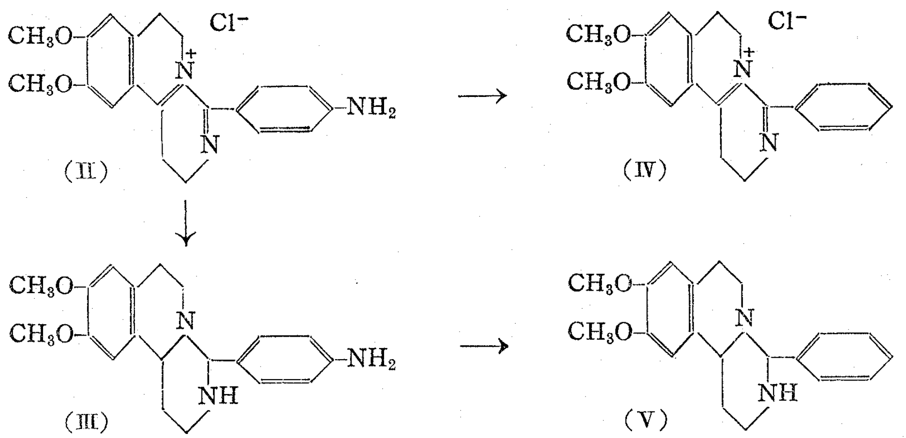
(V)
Fig. 2

(VI)
Fig. 3

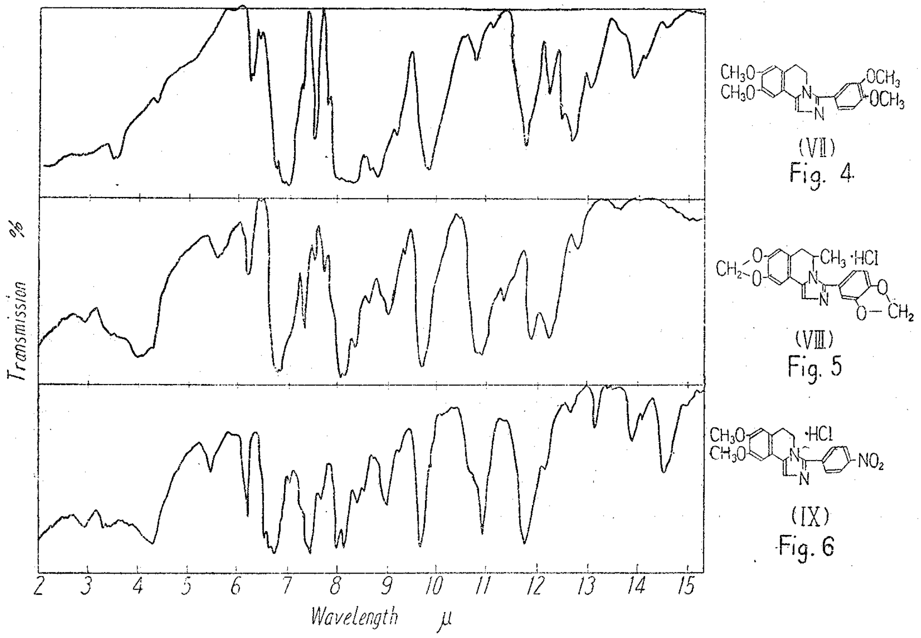
The following illustrates the process of the synthesis :



(I)



The infrared absorption spectra of the picrate of (VI) (Fig. 3) and imidazoisoquinoline derivatives (VII), (VIII), and (IX) are respectively shown in Figs. 4, 5, and 6. All of them have absorption of C=N band which corresponds to the cyclic C=N band of 5.98~6.33 μ. The absorption of —NHCO— linkage was not observed. Consequenthy the structures of various compounds reported in the previous papers were proved to be correct.



(VII) Fig. 4

(VIII) Fig. 5

(IX) Fig. 6

The authors are grateful to Prof. Sugasawa of Tokyo University and Prof. Horii of Osaka University, for their helpful advices and encouragement during the course of this work and also to the Ministry of Education for the Grant in Aid for Scientific Research for the year of 1953. Thanks are also due to Mr. Fukuda of the Central Analysis Room of this Institute for microanalytical data. The authors are also grateful to Mr. M. Yamaguchi of the Osaka Municipal University and Dr. Edward A. May of Samuel P. Stadler & Son, Inc. for the measurement of the infrared absorption spectra.

Experimental

[2′-(*p*-Aminophenyl)-4′,5′-dihydropyrimidino]-1′,6′ : 1,2-(3,4-dihydro-6,7-dimethoxyisoquinolinium Chloride) (II)—The hydrochloride of higher melting point (I) (1.014 g.) was dissolved in 200 cc. MeOH, acidified with a little conc. HCl, and reduced catalytically over Adams' Pt, absorbing about 3 molar portion of H_2 (150 cc.). The product was isolated as usual, yielding ca. 1 g. of a dark brown syrup. This hydrochloride was purified from EtOH-ether, giving an amorphous powder of m.p. 203°(decomp.)(sint. at 197°). The free base was purified from dil. EtOH several times, forming a very hygroscopic yellowish brown crystals, m.p. 94°. This gave a positive diazo reaction(red). *Anal.* Calcd. for $C_{20}H_{21}O_2N_3 \cdot 3.5H_2O$ (Free base) : C, 59.70; H, 6.96. Found : C, 59.58; H, 7.09.

(2′-Phenyl-4′,5′-dihydropyrimidino)-1′,6′:1,2-(3,4-dihydro-6,7-dimethoxyisoquinoline) (IV) (Deamination of the Amine (II))—The foregoing hydrochloride (II) (0.2 g.) was added to the mixture of conc. HCl (0.6 cc.) and water (2 cc.), and warmed on a water bath, giving a clear solution. Cooling with ice and water and stirring vigorously, crystals began to separate. $NaNO_2$ (0.05 g.) dissolved in cold water was added dropwise into the above suspension during ca. 10 mins. All the crystals disappeared after stirring about 30 mins., giving a faint reddish yellow solution. The reaction mixture was filtered and the filtrate was poured into 30% H_3PO_2 (2 cc.). A faint evolution of N_2 gas was observed from the reaction mixture when kept in an ice box for 16 hrs. A white precipitate separated out on the bottom of the container. After a further 48 hrs. in the ice box, the white precipitate was collected on a filter. It weighed 1.2 mg., sintered at 120°, and melted at 160° with decomposition. It was considered to be a crude hydrochloride. The filtrate was basified with 10% NaOH, collected in ether, dried over K_2CO_3, and evaporated, yielding white crystals (70 mg.). The picrate was purified from AcOH, giving a brownish yellow crystals, m.p. 223~225°(decomp.). This picrate was proved to be identical with a specimen prepared from different material according to Kametani and Katagi.1)

(2′-Phenyl-1′,2′,3′,4′,5′,6′-hexahydropyrimidino)-1′,6′ : 1,2-(6,7-dimethoxy-3,4-dihydroisoquinoline) (V) (Deamination of the Amine (III))—(III) (0.22 g.), prepared according to the procedure reported in the previous papers,2) was dissolved in a mixture of conc. HCl (0.6 cc.) and water (2 cc.). $NaNO_2$ (0.05 g.) dissolved in water was added dropwise into the above solution during 10 mins. and the reaction mixture was shaken for about 20 mins. after the addition was completed. After filtration by suction, the filtrate was poured into 30% H_3PO_2 (1.5 cc.), and kept in an ice box for ca. 40 hrs., and subsequently at room temperature for a few days. N_2 gas generated violently, separating a yellowish oily syrup on the bottom of container.

This reaction mixture was basified with 10% NaOH and the separated precipitate was collected in ether, washed, dried, and evaporated. The free base (130 mg.) was obtained as a yellowish oil and gave negative diazo reaction and $FeCl_3$-color tests. The picrate was purified from EtOH, forming a yellowish brown needles of m.p. 205~207°(decomp.). The picrate was obtained only after standing for a considerable time. This compound gave positive Liebermann test for secondary amines.

Summary

In order to establish the structure of 2′-(*p*-aminophenyl)-pyrimidinoisoquinoline derivative, a deaminated substance from a higher melting point was obtained from [2′-(*p*-aminophenyl)-4′,5′-dihydropyrimidino]-1′,6′ : 1,2-(3,4-dihydro-6,7-dimethoxyisoquinolinium chloride). The former was found to be identical with the product obtained by cyclization of N-(*p*-nitrobenzoyl-β-alanyl)-β-veratrylethylamine of higher melting point. Moreover, the hydrogenated prouct of pyrimidine moiety of pyrimidinoisoquinoline derivative was synthesized and successfully deaminated.

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