Summary

The bisected phenolic base, m.p. 205~207°(decomp.) (A-base) obtained by the fission of cepharanthine by sodium in liquid ammonia has positively been proved to be *d*-1-(4′-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II).

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49. **Tetsuji Kametani and Toyoyuki Katagi**: Studies on the Syntheses of Isoquinoline Derivatives and their Analogs. XXXV. Migration of the Double Bond of Pyrimidinoisoquinolines and Presumption of their Structures by the Infrared Absorption Spectra.

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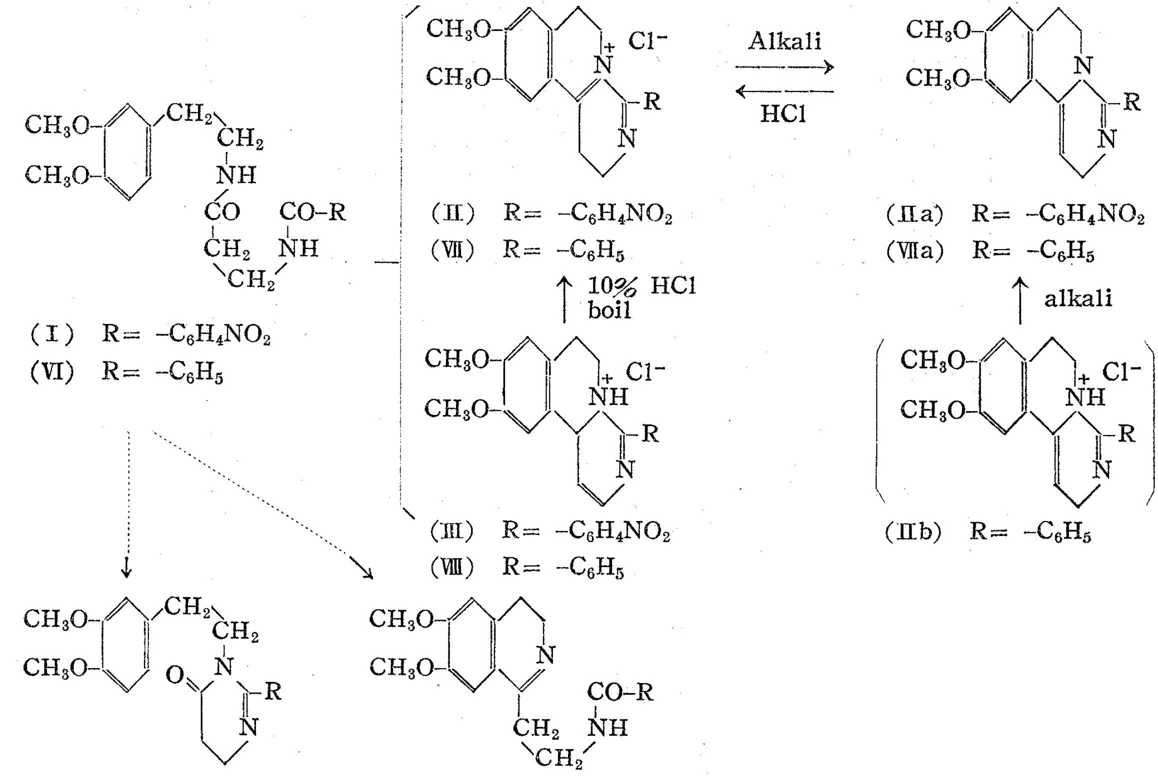
In the preceding paper[1] we reported that two kinds of isomers having higher and lower melting point were obtained by the cyclization of N-(*p*-nitrobenzoyl-β-alanyl)-β-3,4-dimethoxyphenylethylamine (I) by the Bischler-Napieralski reaction. In this paper we present the assumed structure of both substances by the infrared absorption spectra and revealed the migration mechanism of double bond between them.

The hydrochloride with a higher melting point is more difficult to dissolve in water and methanol than the one of lower melting substance and the former was difficult to be purified from methanol and could be recrystallized from hot water or acetic acid. By the results of elemental analysis of both compounds, they corresponded respectively to the calculations of the objective pyrimidinoisoquinoline hydrochloride containing 3 moles



(I) R= $-C_6H_4NO_2$
(VI) R= $-C_6H_5$

(II) R= $-C_6H_4NO_2$
(VII) R= $-C_6H_5$

(IIa) R= $-C_6H_4NO_2$
(VIIa) R= $-C_6H_5$

(III) R= $-C_6H_4NO_2$
(VIII) R= $-C_6H_5$

(IIb) R= $-C_6H_5$

(IV) R= $-C_6H_4NO_2$

(V) R= $-C_6H_4NO_2$

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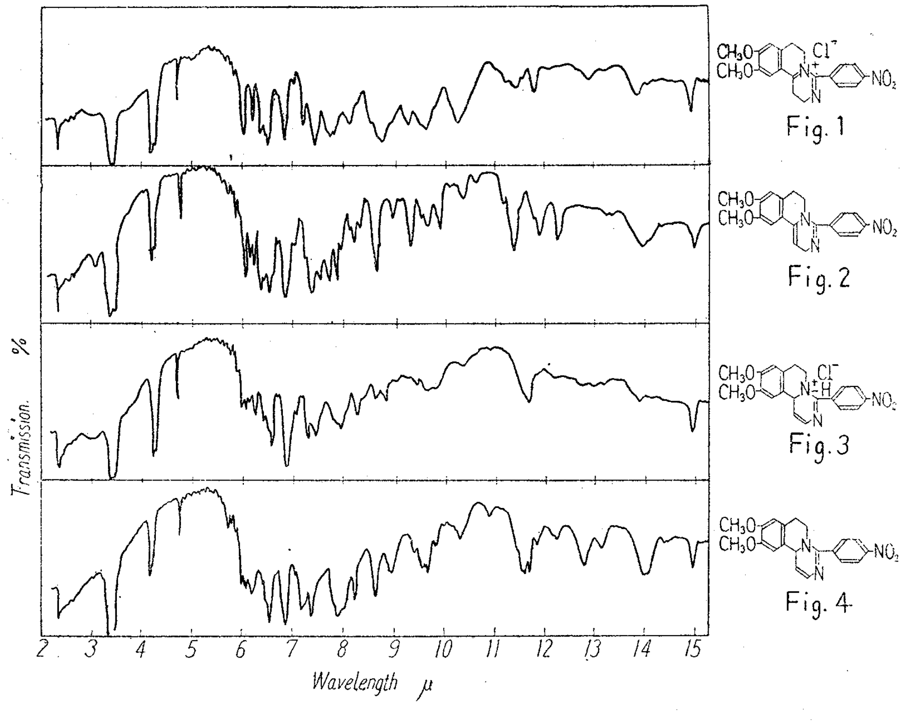
[1] Part XXXIV: Kametani, Katagi: J. Pharm. Soc. Japan, **75**, 709(1955)

(in case of a higher melting substance) or 2 moles (in case of a lower melting one) of the water of crystallization and they were thought to be (II) or (III) from the examination of their infrared absorption spectra as will be described later. Judging from only the results of elemental analyses, the formation of isoquinoline derivative (V) or pyrimidone derivative (IV), besides the pyrimidinoisoquinoline derivative (II) or (III), may be supposed. Especially the probability of the formation of (V) is supposed, but we cannot help recognizing the formation of the structure (II) or (III), as the absorption band of amide linkage was not observed in their infrared absorption spectra and it absorbed catalytically 3~5 moles of hydrogen as reported in the preceding paper[1] or later.

The infrared absorption spectra of the compounds of higher (Fig. 1 or 2) and lower melting point (Fig. 3 or 4) were compared. The intense maximum observed for the salt of the higher melting one (II) (Fig. 1) lies in a frequency range of 6.05 μ, which has been apparently thought to be an absorption of the carbonyl group, but should be the absorption of $>C=\overset{+}{N}<$ linkage in the above-mentioned structure (II), since the absorption of NH band was not observed.[2~5] Moreover, Goulden[6] has shown that the presence of a positive charge on the nitrogen atom gives rise to a higher C=N frequency value, for example, by 13 cm^{-1} in the case of 2-phenyl-N-piperonylidene-ethylamine and its methiodide. According to Witkop,[2] it has now been found that myosmine is best expressed by the Δ^1-pyrroline structure. As Eddy and Eisner observed independently,[7] there is no band in the NH region in the infrared spectrum of myosmine. Moreover, Witkop and Patrick[8] revealed that the infrared spectrum of 2,3-di(3-indyl)-ψ-indole hydrochloride shows the characteristic indolenine band, usually at 6.10~6.30 μ, displaced to almost 6.40

Infrared Absorption of Pyrimidinoisoquinoline Derivatives



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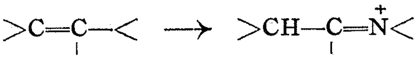
[2] Witkop: J. Am. Chem. Soc., **76**, 5597(1954).
[3] Evans: *Ibid.*, **73**, 5230(1951).
[4] Pickard, Polly: *Ibid.*, **76**, 5169(1954).
[5] Leonard, Gash: *Ibid.*, **76**, 2781(1954).
[6] Goulden: J. Chem. Soc., **1953**, 997.
[7] Eddy, Eisner: Anal. Chem. (in press).
[8] Witkop, Patrick: J. Am. Chem. Soc., **73**, 713(1951).

μ, an effect probably caused by the conjugation of the $>C=N-$ bond with the two indyl substituents.

Judging from the foregoing facts, it was thought that the higher melting hydrochloride (II) (Fig. 1) was likely to undergo conjugation more than the lower melting one (III) (Fig. 3), since the absorption spectrum in the 6.0 μ region shifted a little in going from the latter to the former. In fact, the absorption spectrum of (III) (Fig. 3 or 4) at 6.0 μ is observed in going to the one of (II) (Fig. 1 or 2). So the higher melting hydrochloride (II) was assumed to be an isoquinolinium chloride derivative having a $>C=\overset{+}{N}<$ bond. Comparing the difference between the hydrochloride (II) (Fig. 1) and the free base (IIa) (Fig. 2), both compounds have the absorption of $>C=N-$ at 6.05~6.17 μ and the deformation vibration of $>C=C<$ observed in the 6.17 μ region in Fig. 2 disappears in Fig. 1. Accordingly, the double bond of the free base (IIa) is located between 5′ and 6′ positions, whereas the double bond migrates to that between 1′ and 6′ positions in the hydrochloride. This fact is found in other examples reported by many researchers.[9~12] As can be judged from the spectra in Figs. 1 and 2, and in the above-mentioned literatures, it was thought that a substance (IIa) would be obtained by basifying (II) with alkali and a migration of the double bond would occur. Accordingly, if a similar transformation were to occur between the lower- and higher-melting substances, the former ought to be a structure of (III) with the double bond at 5′—6′ position. On the contrary, the free base of (III) ought to be identical in every respect with (IIa) by mixed melting point test and infrared absorption spectra, if the double bond of the lower-melting substance were in 5′—6′ position, as in the free base (IIa). However, no agreement was found between the free base of (II) (namely, IIa) and the lower melting substance (III), so that the double bond of (III) must exist in 4′—5′ position.

According to Chakravarti *et al.*,[13] the above-mentioned assumption on the formation of (III) is approved in the following example. An instance of the shift of a double bond into conjugation between two aromatic rings is found in the synthesis of dibenzoquinolizines from N-formyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines. In these compounds the double bond appears in the 3—4 position of the isoquinoline ring. Recently, Leonard and Gash[5] reported the determination of the proximity of nitrogen to a double bond by the infrared absorption spectra. The infrared spectra have been determined for a series of α,β- and β,γ-unsaturated tertiary amines and their salts. A method is thus provided for differentiating between an α,β-unsaturated tertiary amine and one in which the double bond is further removed from nitrogen. So the application of this method to the location of the unsaturation in the pyrimidine moiety of the pyrimidinoisoquinoline (II or III) is very interesting. Accordingly, the structures between (II) and (III), and the transformation of double bond was observed in the case of higher melting substances, because the deformation vibration at 6.17 μ of the free base moves to the $>C=\overset{+}{N}<$ region (6.05 μ) of the hydrochloride and the absorption is piled up. In fact, the absorption of the hydrochloride (II) in the 6.05 μ region was stronger than that of the free base (IIa). On the contrary, there was no distinct difference in the case of the lower melting substance (Fig. 3 or 4) between the hydrochloride (Fig. 3) and the free base (Fig. 4). So the double bond of (III) is supposed to be further removed from the nitrogen in 1-position. Accordingly, the structure of (II), (IIa), and (III) are



$$>C=\underset{|}{C}-< \longrightarrow >CH-\underset{|}{C}=\overset{+}{N}<$$

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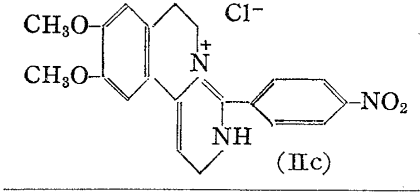
9) Hamilton, Robinson: J. Chem. Soc., **109**, 1029(1916).
10) Kopfli, Perkin: *Ibid.*, **1928**, 2898.
11) Bills, Noller: J. Am. Chem. Soc., **70**, 957(1948).
12) Sugasawa, Mizukami: Japan. J. Pharm. & Chem., **25**, 599(1953).
13) Chakravarti, Haworth, Perkin: J. Chem. Soc., **1927**, 2275.

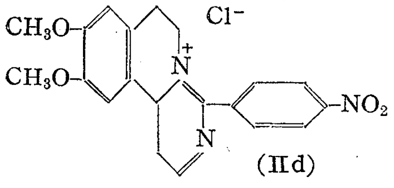
presumed to be correct. Therefore, the structure of (III) reported in the previous paper,1) in which the double bond of lower melting hydrochloride (III) was shown to exist in 5'—6' position must be corrected as shown in the accompanying chart.

In the preceding paper, it was reported that a great deal of higher melting substance was obtained in the case of using a fair amount of $POCl_3$ compared with the solvent and a lower melting one was obtained when using a small amount of $POCl_3$, less than that of the solvent. After examining the various conditions of formation, it was found that the rate of their formation did not depend upon the conditions of temperature and solubility in the solvent or the amount of $POCl_3$, but upon the method of treatment with 10% HCl after the reaction. In fact, when the reaction mixture was treated with 10% HCl with warming or triturated thoroughly with a great deal of 10% HCl for a long time, the higher melting one was obtained when treated with a small amount of 10% HCl for a while or by the petroleum ether treatment. It has been shown in the preceding paper14) that the hydrochloride of (VIII), having a lower melting point of 200°(decomp.), was obtained by the method of Kametani and Kano.14) In this paper the higher-melting hydrochloride of m.p. 240°(decomp.) was proved to be obtained by inspecting cyclization conditions. So the hydrochloride14) previously obtained corresponds to the lower melting one (VIII), containing a double bond in the 4'—5' position. Though the condition of formation was uncertain, an intermediate hydrochloride of m.p. 222°(decomp.) was obtained and this compound was expected to have a structure of (IIb) and convert to (IIa) in case of the free base, but the results of infrared spectra were contrary to such expectations, for the spectrum of this compound having an intermediate melting point agrees with that of the hydrochloride or the free base.

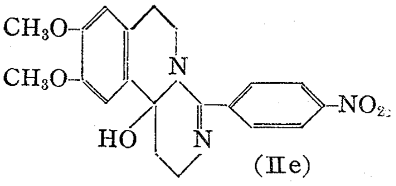
Moreover, the formula of (II) is presumed to be (IIc) or (IId). Namely, it is assumed that (II) exists as the formula (IIc) and a double bond migrates from (IIc) to (IIa) if the former is basified and becomes free. By contrast, the stable higher melting substance is supposed to correspond to (II) and the labile lower melting one is thought to be (IIc) or (IId), but it seems correct to assume that the formula of higher melting substance corresponds to (II), according to the following reasons: (a) From a structural point of view, the chances that the double bond of -C=C- and -C=N- linkage conjugates respectively with two phenyl rings are the same in case of (II) and (IIc), but the chance of conjugation of the formula (IId) is remarkably less than the above. Accordingly, the formula of (IId) is presumed to be incorrect in this case. (b) As described above, the chance of conjugation between a phenyl ring and a double bond is the same in the case of (II) and (IIc), but it is thought that the formula of (II) is the most stable, because the positively charged nitrogen directly attracts electron from the neighboring position and furthermore, the phenyl ring has a nitro group which attracts electrons. It is reasonable that the lack of electron in nitrogen is supplied from the phenyl ring of isoquinoline ring having an electron-releasing group, a methoxyl. Accordingly, the formula of (II) is more probable than (IIc). (c) Judging from the results of infrared spectra, if the formula of (IIc) is correct, the higher-melting hydrochloride ought to have an absorption of NH band and deformation vibration of $>C=C<$, but none of them was observed in the spectra of the higher-melting hydrochloride. Moreover, if the formula of (IId) corresponds to the labile lower melting one, it should have no absorption



(IIc)



(IId)



(IIe)

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14) Kametani, Kano: J. Pharm. Soc. Japan, **71**, 1007(1951).

of >C=C< linkage but on the contrary, the absorption spectrum of >C=C< band is observed in it. Besides the foregoing, the formation of a free base having a structure of (Ⅱe) can be presumed in place of the free base of (Ⅱa).

If the structure of (Ⅱe) should be correct, an absorption observed at 3.14 μ for hydroxyl group (Fig. 2) will be clearly explained, but the absorption of 6.17 μ corresponding to >C=C< linkage cannot be explained. Accordingly, even though the formula (Ⅱc) were formed for a time, the dehydration would occur immediately between the 5′ and 6′ positions, and form (Ⅱa) owing to the instability of (Ⅱe). In this case, the absorption at 3.14 μ is presumed to be due to one mole of water of crystallization in the free base (Ⅱa). Therefore, the existence of (Ⅱe) cannot be considered. By contrast, if the absorption of 3.14 μ is due to the hydroxyl group, the free base of the higher-melting substance should be a mixture of both substances (Ⅱe) and (Ⅱa), as shown in the literature.[15] This point is now being examined.

In order to examine the relation between the higher- and lower-melting substances attempts were made to find the transformation method and succeeded in discovering a new procedure of boiling with 10% hydrochloric acid. Recently, Evans[3] reported that, by treatment with Raney nickel in xylene, the compound is converted largely, if not entirely, to the isomeric higher-boiling base. According to the report on Raney nickel-catalyzed isomerization[16] of Δ^3- into Δ^1-pyrroline, the Δ^2-tautomer in this case is very labile and not observed. Therefore, the utilization of the Robinson procedure[16] to the transformation from (Ⅲ) or (Ⅷ) to (Ⅱ) or (Ⅶ) was carried out but the resinification occurred due to overheating that the objective could not be obtained either as a hydrochloride or a free base. On the other hand, the objective compound (Ⅱ) was obtained by boiling with 10% hydrochloric acid. In the case of the compounds containing no nitro group in the phenyl ring, the migration of the double bond from (Ⅷ) to (Ⅶ) was successfully achieved by the same procedure.

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

Experimental

Ring Closure of N-(Benzoyl-β-alanyl)-β-veratrylethylamine (VI)—The results of isoquinoline cyclization by the Bischler-Napieralski reaction under the various conditions are summarized in Table I. In this Table, the treatment is shown as follows: (A) Collecting the hydrochloride obtained by triturating a resinous residue with 10% HCl, which was separated after adding the petr. ether; (B) collecting the one obtained by triturating the residue with 10% HCl with chilling, which was obtained when the solvent and $POCl_3$ were removed *in vacuo*, and (C) collecting the hydrochloride precipitated after standing on cooling from the yellow solution, which was obtained by extracting the residue with 10% hot aq. solution of HCl, after the solvent and $POCl_3$ were removed *in vacuo*.

The principal representative experiments are shown in the following and the Arabic numerals (1,3, etc.) represent the experiment numbers shown in Table I.

(1) The crude hydrochloride of m.p. 240°(decomp.) was obtained by the method (B). Yield, 0.7 g. The crude salt was dissolved in hot water, filtered, and then basified with dil. alkali. The free base was collected in ether, washed, dried, and evaporated, leaving a viscous oil. The picrate of this free base was obtained by standing a mixture of the free base and picric acid in EtOH solution overnight.

The picrate was purified from dil. acetone after recrystallization from dil. EtOH, giving a yel-

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15) Decker: Ber., **37**, 520, 1564, 3809(1904).

16) Chakravarti, Robinson: J. Chem. Soc., **1947**, 78.

TABLE I.

Expt. No.	Amide g.	$POCl_3$ cc.	Solvent[a] cc.	Temperature °C	Time min.	Treatment	Yield g.	m.p. °C
1	1	1.6	16	130~140	60	B	0.7	240
2	1	6	10	130	60	B	0.7	240
3	1	6	10	130	60	C	0.6	—
4	1.5	10	15	110	30	A	1.0	198
5	2.7	20	30	130	40	B	1.1	223
6	3	20	30	130	30	A	1.5	200[14]

lowish brown crystals of m.p. 223°(decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_2N_2 \cdot C_6H_3O_7N_3 \cdot H_2O$ (Picrate): C, 55.02; H, 4.41. Found: C, 55.23; H, 4.48.

(3) After treating by the method (C), the residue was triturated with 10% HCl with warming, but it dissolved in hot HCl and a clear orange solution was formed. After neutralization with dil. alkali, the reaction mixture was extracted with ether, washed, dried, and evaporated. The yellowish oily syrup was obtained in a yield of 0.7 g. The picrate, after purification by the same method as above, was proved to be identical with that of 223°(decomp.) obtained above.

(4) The crude hydrochloride of the lower melting point was obtained by the foregoing procedure (C). This was purified from EtOH, giving yellowish brown crystals of m.p. 198°(decomp.), identical with a specimen prepared from the same starting material according to the method of Kametani and Kano.[14]

Cyclization of N-(*p*-Nitrobenzoyl-*β*-alanyl)-*β*-vertrylethylamine (I)—The results obtained by the methods (A), (B), and (C) are shown in Table II. Several representative experiments are shown below.

TABLE II.

Expt. No.	Amide g.	$POCl_3$ cc.	Solvent[a] cc.	Temperature °C	Time min.	Treatment	Yield g.	m.p. °C
1	1	30	10[c]	140~150	60	C	0.6	246
2	1	20	15[a]	100	75	C	0.7	243
3	3	60	20[b]	100	90	C	0.4	244
4	3	40	20[b]	100	150	C	2.2	246
5	5	12.8	80[c]	140	40	B	1.5	220[e]
6	1	1.6	16	140	60	A	0.5	185~193
7	1	1.6	16[b]	100	60	B	1.0	222[e]
8	1	15	—	130~140	60	B	0.7	185~193
9	2	15	20[b]	100	180	C	1.2	245
10	1	2	16	140	60	B	0.6	220[e]

a) Toluene. b) Benzene. c) Xylene. d) This is a decomposition point and each compound is a hydrochloride. e) The melting point of this hydrochloride is lower, but its picrate is identical with a specimen prepared from higher-melting hydrochloride.

(6) The crude hydrochloride (0.5 g.) was obtained by the method (A). This was purified from EtOH-ether, forming yellowish orange crystals, which sintered at 185° and decomposed at 193°. This hydrochloride was dissolved in hot water and basified with alkali, furnishing a brown precipitate. This was collected on a filter, washed, dried, and purified from dil. EtOH, forming a colorless amorphous powder of m.p. 168°(sint. at 150°). This was identical with a synthetic sample prepared from the same starting substance by the method of Kametani and Katagi.[1]

(8) After treatment by the procedure (B), 5% HCl (3 cc.) was added to the oily residue, vigorous heat generation being recognized owing to the decomposition of $POCl_3$. After a few mins., water was added into the reaction mixture. On cooling, 1.2 g. of faint yellowish brown granular crystals were collected. This was purified from conc. AcOH to faint yellow crystals, m.p. 245° (decomp.). This melting point agrees with that of the substance reported in the previous paper by the method of Kametani and Katagi.[1]

The hydrochloride was dissolved in hot water and basified with alkali, giving a white precipitate. This was collected and purified from EtOH or EtOH-ether, forming colorless needles of m.p. 218°. *Anal.* Calcd. for $C_{20}H_{19}O_4N_3 \cdot H_2O$ (free base): C, 62.65; H, 5.52. Found: C, 62.11; H, 5.58. The picrate, purified from conc. AcOH, formed yellowish brown crystals of m.p. 243~247° (decomp.).

Transformation of the Double Bond in the Lower-melting Hydrochloride (III)—The hydrochloride (III) (25 mg.) was boiled with 10% HCl (1.5 cc.) for 1 hr. The color of the reaction mixture changed to yellow and a faint bluish fluorescence appeared, from which nearly colorless crystals began to separate out after cooling for some time. The crude hydrochloride separated from the above solution was faint yellow crystals of m.p. 235°(decomp.). The raising of the melting 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).