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Yoshio Ban and Osamu Yonemitsu: The Enamine–Immonium Cation System of 9,10–Dimethoxy–1,2,3,4,6,7–hexahydrobenzo[*a*]quinolizinium Salt.

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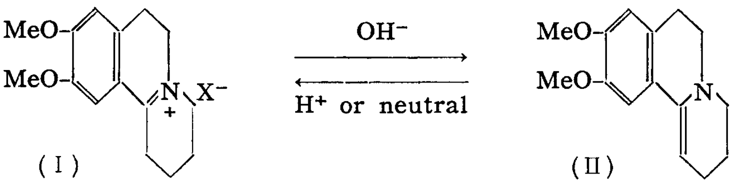
In preliminary experiments for the stereochemistry of emetine,[1] 9,10–dimethoxy–1,2,3,4,6,7–hexahydrobenzo[*a*]quinolizinium iodide (I : X = I), which had been prepared according to the method of Sugasawa,[2] was shown to have the $\nu_{C=\overset{+}{N}}$ band at 1644 cm^{-1} in its infrared spectrum[1b] and its ultraviolet spectrum in 85% ethanol solution is shown by (1) in Fig. 1. This iodide was converted to the corresponding chloride (I, X = Cl) in the usual way, the solution of which was made alkaline with 10% sodium hydroxide solution, separating the fairly unstable base as a white solid. This was collected by filtration at once, washed with water, and recrystallized from 30% hydrous ethanol to afford white needles, m.p. 89~90°, to which was assigned 9,10–dimethoxy–3,4,6,7–tetrahydro–2*H*–benzo[*a*]quinolizine (II) both by the elemental analyses carried out immediately after recrystallization and by observation[3,4] of the $\nu_{C=C}$ band at 1626 cm^{-1} in place of the $\nu_{C=\overset{+}{N}}$ band at 1644 cm^{-1} in the initial iodide[*2] (I : X = I), but the ultraviolet absorption



(I) (II)

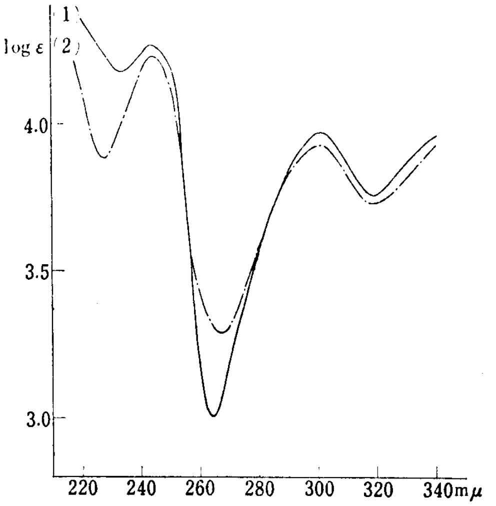


Fig. 1. Ultraviolet Absorption Spectra (in 85% EtOH)

(1) ——— (I) X=I
(2) —•—•— (II)

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1) *a*) Y. Ban, M. Terashima, O. Yonemitsu : Chem. & Ind. (London), **1959**, 568, 569. *b*) Y. Ban, O. Yonemitsu, M. Terashima : This Bulletin, 8, 183,194(1960). *c*) M. Terashima : *Ibid.*, 8, 517 (1960).

2) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 359(1958), and references cited therein.

3) B. Witkop : J. Am. Chem. Soc., **78**, 2873(1956).

4) N. J. Leonard, V. W. Gash : *Ibid.*, **76**, 2781(1954), and numerous papers by N. J. Leonard and coworkers.

[*2] S. Sugasawa and N. Itoh chemically established the structure of 6,7-dimethoxy-1-methylene-2-benzyl-1,2,3,4-tetrahydroisoquinoline which is converted to 6,7-dimethoxy-1-methyl-2-benzyl-3,4-dihydroisoquinolinium iodide by treatment with hydrochloric acid in the presence of potassium iodide, and its oxidation with potassium permanganate in pyridine solution, furnishing N-benzylcorydaldine (Tetrahedron, **1**, 45(1957)).

spectrum ((2) in Fig. 1) of this tertiary base (II) in 85% ethanol solution was quite similar to that of the iodide (I : X=I), and the solution was found to be alkaline to litmus paper.

Thus, the mother liquor of the second recrystallization of this free base was reexamined and proved to be pH 11.95, which undoubtedly suggests that the tertiary base in solid state changed to a quaternary hydroxide (I : X=OH) when it was dissolved in neutral hydrous ethanol to the concentration of ca. $10^{-4}M$. Contrary to this observation, a good separation of the tertiary base (II) on recrystallization from 30% hydrous ethanol is interpreted as the result of equilibrium between (I : X=OH) and (II), in which the latter is predominant by the basicity of the former itself at such a high concentration (ca. $4\times10^{-2}M$).

The ultraviolet absorption spectra of the tertiary base in ether solution and in sodium hydroxide solutions of various pH values are shown in Fig. 2 (1~4).

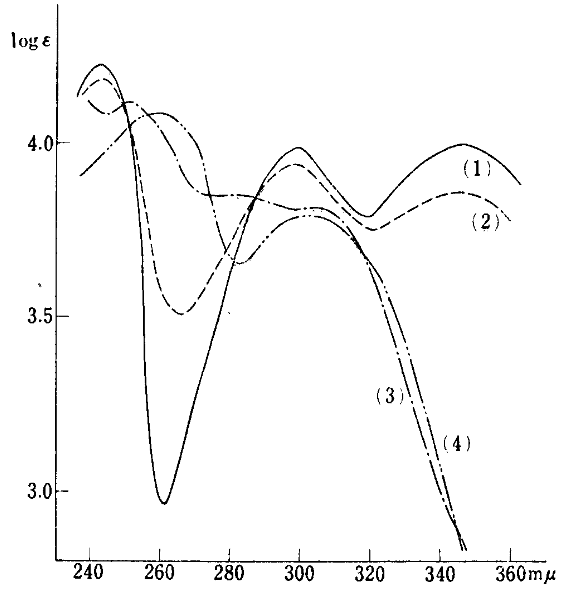

Fig. 2. Ultraviolet Absorption Spectra

(1) ———— (II) in 30% EtOH-H_2O at pH 9.15
(2) ----------- (II) in 30% EtOH-H_2O at pH 11.64
(3) —•—•— (II) in 5% NaOH soln. of 30% EtOH-H_2O
(4) —••—••— (II) in Et_2O

The pKa' of this base, calculated from its ultraviolet spectra (1~3 of Fig. 2), is 12.0, which value reasonably supports the above-described results.

Similar results were already reported by Bills and Noller6) with 1-benzal-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, which is converted in 95% ethanol into the quaternary hydroxide. The tertiary base (II) gradually decomposes on exposure to air, turning yellowish in about 24 hours and brownish in several days, which at last becomes a black resin.

Experimental[*3]

9,10-Dimethoxy-3,4,6,7-tetrahydro-2*H*-benzo[*a*]quinolizine (II)—9,10-Dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quiolizinium iodide,2) m.p. 203~205° (0.5 g.), was converted into the corresponding chloride in the usual way, the chloride was dissolved in 3 cc. of water, and 10 cc. of 10% NaOH solution was added. The white solid that precipitated was collected at once, washed thoroughly with water, and recrystallized from 30% hydr. EtOH to white needles, m.p. 89~90°; yield, 0.3 g. (91%), which was subjected to elemental analyses immediately after recrystallization, since this substance is fairly

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6) J. L. Bills, C. R. Noller : J. Am. Chem. Soc., **70**, 957(1948).

[*3] Koken Model DS-301 double-beam spectrophotometer equipped with two NaCl prisms was used for the determination of infrared spectra and samples were run as Nujol mulls. Beckman Model DK-2 spectrophotometer was used for the determination of ultraviolet spectra. All m.p.s are uncorrected.

unstable on exposure to air. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.79; N, 5.71. Found : C, 73.86; H, 8.25; N, 5.34.

The pKa′ (12.0) of this base was calculated from its ultraviolet absorption spectrum (Fig. 2, 1∼3).

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Summary

The enamine, 9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-benzo[*a*]quinolizine, which was isolated by basifying the aqueous solution of the corresponding immonium chloride, was proved to be reconverted into the immonium cation when dissolved in 85% ethanol to a concentration of ca. $10^{-4}M$. The equilibrium between the two is discussed based on its ultraviolet absorption spectra at various pH values.

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Yoshio Sakurai and Keiichi Itō : Paper Chromatographic Detection of Nitrogen Mustard.

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The detection of nitrogen mustard derivatives on paper chromatogram has hitherto been carried out with the Dragendorff reagent but this method was proved not to be sensitive enough for most biological work. For instance, it was difficult with this reagent to detect less than 50 γ of N-methyl-bis(2-chloroethyl)amine (HN_2).

This paper deals with an improved method, which is based on a rapid and characteristic reaction between nitrogen mustard and compounds having a mercapto group. For this purpose, an alkaline solution containing 6-mercapto-2-naphthol[*2] was used which was prepared immediately before use by reduction of Seligman's reagent (6,6′-dithiodi(2-naphthol)[1]) with sodium amalgam or by alkaline hydrolysis. It was very easy to detect the spots on paper because the combined product as well as the reagent itself could be easily stained on paper by diazo-coupling reaction with diazonium salt.

In practice, ethanol solution of nitrogen mustard hydrochloride was spotted on a paper strip (Toyo Roshi No. 50, 2×40 cm.) and, after drying, just on the same place, one drop of alkaline solution of Seligman's reagent (1.0 g. in 10 cc. of 10% sodium hydroxide solution) was doubly spotted. The chromatogram was immediately run for 15∼17 hours by ascending method, employing the upper layer of a ternary mixture of butanol, acetic acid, and water (80 : 20 : 100) as the solvent system. The paper strips were dried, sprayed with 0.5% *p*-diazobenzenesulfonic acid in 50% ethanol, and then exposed to ammonia gas. Four pink or orange spots appeared instantly, Rf values of which were determined respectively as 0.28 (A), 0.47 (C), 0.58 (D), and 0.90 (E).

In order to identify each spot, the chromatograms obtained under various conditions were examined by comparing the results of staining with three kinds of developing reagent, viz. the diazonium salt, Dragendorff, and sodium nitroprusside reagents, as shown

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[*2] Use of free thiol as a reagent was avoided in this procedure because of its extreme instability during preservation.

1) R. J. Barret, A. M. Seligman : Science, **116**, 324(1952); T. Zincke, R. Derser : Ber., **51**, 354(1918).