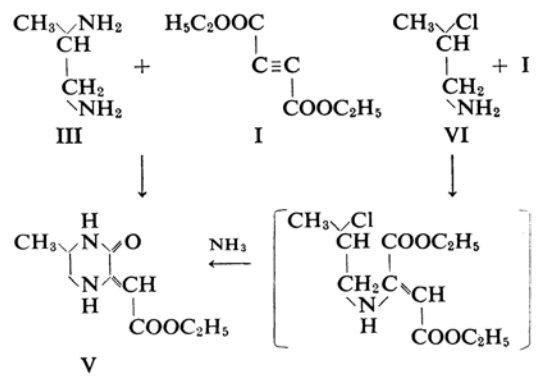
The Reaction of Acetylenecarboxylic Acid with Amines. XII.[1] *On the Hydrolysis of the Products Obtained by the Reactions of Diethyl Acetylenedicarboxylate with Amines*[*1]

By Yasuo IWANAMI, Yoshihisa KENJO,[*2] Koji NISHIBE,[*3] Makoto KAJIURA[*3] and Seiko ISOYAMA

(Received April 11, 1964)

In the preceding papers of this series, the products of the reactions of diethyl acetylenedicarboxylate (I) with amines, diethyl *N*-substituted-aminofumarates (type A),[2-4] 2-oxo-3-ethoxycarbonylmethylene-3,4,5,6-tetrahydro-2*H*-1,4-oxazines (type B),[4,5] 2-oxo-3-ethoxycarbonylmethylene-3,4-dihydro-2*H*-1,4-benzoxazines (type C),[4,5] and 2-oxo-3-ethoxycarbonylmethylene-1,2,3,4-tetrahydroquinoxalines (type E)[6-9] have been reported. It has been shown[3-9] that the compounds of types A, B and C are hydrolyzed into pyruvic acid (VII), carbon dioxide, and amines by the cleavage of the heterocyclic rings of types B and C, while the quinoxaline rings of the copomunds of type E remain unchanged, with only a decarboxylation of the side chain.

The present paper deals with the synthesis 2-oxo-3-ethoxycarbonylmethylenepiperazines (type D), and with the different behaviors of types D and E in hydrolysis. When ethylenediamine (II) and propylenediamine (III) were added to I, exothermic reactions occurred, and 2-oxo-3-ethoxycarbonylmethylenepiperazine (IV) and its 6-methyl derivative V were obtained respectively. While the 5-methyl derivative also seemed to have been produced in the reaction of I with III, only the 6-methyl derivative V could be isolated from the reaction mixture. The structural assignment of V was



1) Part XI: Iwanami, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 600 (1962).

*1 Presented in part at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1963.

*2 Present address: Research Laboratory of Resource Utilization, Tokyo Institute of Technology, Meguro-ku, Tokyo.

*3 Present address: Research Laboratory, Yokohama Rubber Co., Ltd., Hiratsuka City.

2) Y. Iwanami, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 632 (1961).

3) Y. Iwanami, ibid., **82**, 634 (1961).

4) Y. Iwanami, ibid., **83**, 593 (1962).

5) Y. Iwanami, ibid., **82**, 780 (1961).

6) Y. Iwanami, ibid., **82**, 778 (1961).

7) Y. Iwanami, ibid., **83**, 161 (1962).

8) Y. Iwanami, ibid., **83**, 316 (1962).

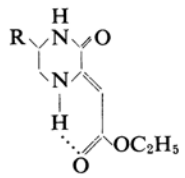
9) Y. Iwanami, ibid., **83**, 590 (1962).

supported by a successful conversion of the reaction product from I and 1-amino-2-chloropropane (VI) into a substance which was identical with V.

The chelate structure[4] of IV and V is suggested by their infrared spectra, the main absorption maxima of which are shown in Table I.

TABLE I. MAIN INFRARED ABSORPTION BANDS (KBr disk) (cm^{-1})

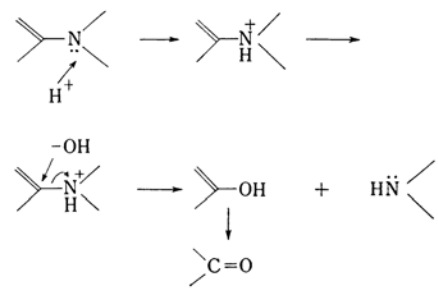
Product	Amine ν_{NH}	Chelated ester $\nu_{C=O}$	Amide $\nu_{C=O}$	Double bond $\nu_{C=C}$
IV	3350	1692	1660	1615
V	3365	1694	1650	1623



IV : R=H
V : R=CH_3

By hydrolysis with hydrochloric acid, both IV and V gave puruvic acid (VII), carbon dioxide, and the amines (II and III), as is shown in Chart 1. The formation of VII and carbon dioxide can be explained by assuming the intermediate formation of oxalacetic acid. Thus, the hydrolysis, followed by the decarboxylation, of the newly-synthesized compounds of type D is quite similar to that of the compounds of types A, B and C reported on in the preceding papers. Diethyl *N*-(*n*-butyl)-aminofumarate (VIII), 4-methyl-2-oxo-3-ethoxycarbonylmethylene-3, 4, 5, 6-tetrahydro-2*H*-1, 4-oxazine (X), 6-chloro-2-oxo-3-ethoxycarbonylmethylene-3, 4-dihydro-2*H*-1, 4-benzoxazine (XII) and 2-oxo-3-ethoxycarbonylmethylene-1, 2, 3, 4-tetrahydroquinoxaline (XIV) were newly hydrolyzed. Their decarboxylation caused by hydrolysis is also similar to that in the above cases, except for that of XIV.

On the other hand, the decarboxylation of XIV through its hydrolysis gave 2-oxo-3-methyl-1, 2-dihydrobenzoquinoxaline (XV), although its structure resembles that of the compounds of type D. In any discussion of the above discrepancy, the breaking of the carbon-nitrogen bond which occurs by hydrolysis in all these compounds except in the compounds of type E seems to be important. The splitting mechanism in the compounds of types A, B, C and D, which have an enamine structure, is probably as follows:



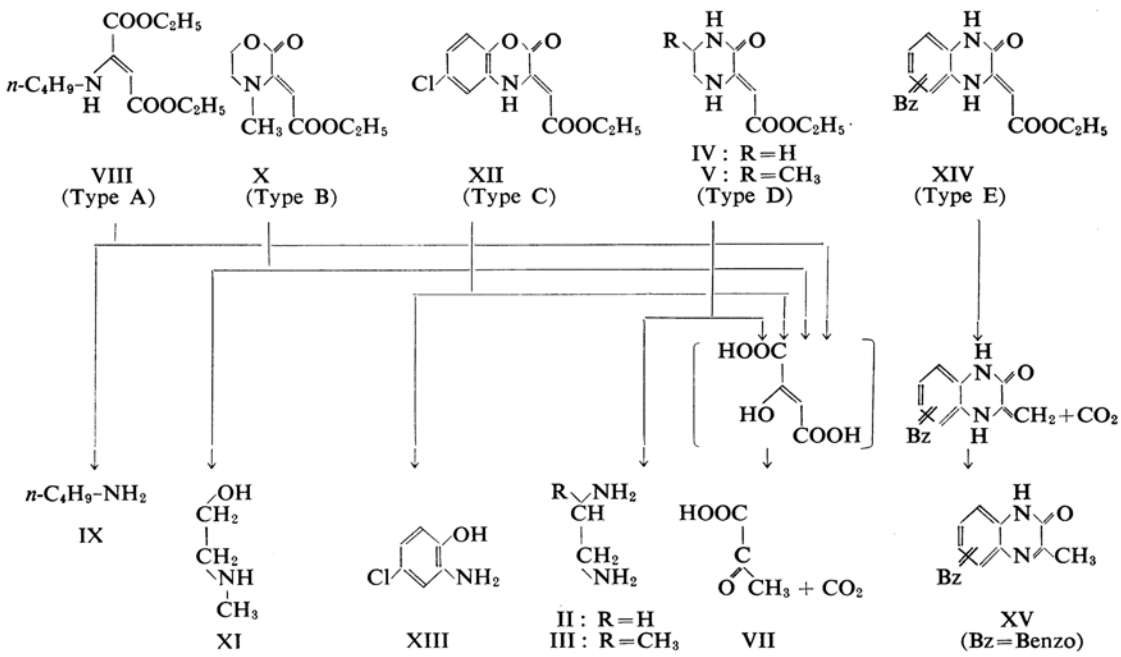
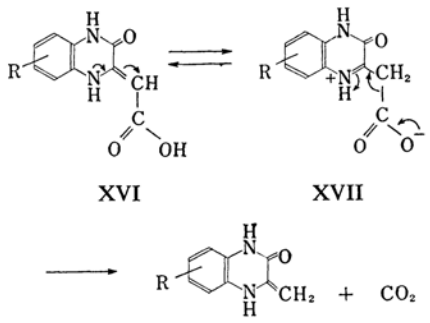


Chart 1

Hünig, Lücke and Benzing[10] have shown that ordinary simple enamine was easily hydrolyzed into a carbonyl compound and an amine even when such an enamine was titrated with dilute hydrochloric acid.[11]

An independent type of hydrolysis observed in the compounds of type E can be analogously explained by Doering and Pasternak's hypothesis[12] regarding the decarboxylation hydrolysis of ethyl α-pyridylacetates. That is to say, the tautomerization of enamine (XVI) to ketimine (XVII) appears to take place when the compounds of type E are hydrolyzed to the corresponding acid (XVI). Then the spontaneous decarboxylation may be supposed to proceed as follows:

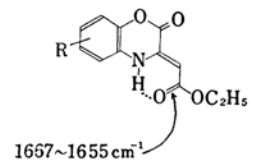


XVI XVII

At least in the case of the compounds of type E, assuming the formation of the intermediate acid (XVI) is fairly satisfactory as a means of interpreting the decarboxylation mechanism, although it is not known whether the corresponding acids of A—E are intermediately formed or not. Probably an insufficient tautomerization of the compounds of types A, B, C and D to their ketimine forms causes them to be hydrolyzed as enamines.

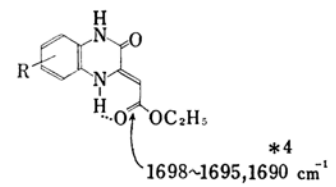
The carbon-carbon double bond of the enamine form conjugates with two carbonyl groups. Furthermore, the chelate ring[4] needs the double bond of the enamine form. The two carbonyl groups and the chelate ring will, therefore, facilitate the adoption of the enamine form shown in Chart 1. In the case of the compounds of type E, however, it is tempting to tautomerize them into the ketimine form, because they have a condensed aromatic ring and the ketimine double bond is stabilized by taking a quinoxaline structure. Thus, the different decarboxylation mechanisms of the compounds of type D and E appears to depend on whether or not they have an aromatic ring.

However, the compounds of type C, which have a condensed aromatic ring, are hydrolyzed to result in the cleavage of a oxazine ring, as in the case of the compounds of type B. This discrepancy may be explained on grounds that the quinoxaline ring of the compounds of type E is more stabilized by an easier mesomerism through its whole ring than through the benzoxazine ring of the compounds of type C. The chelate bond in the compounds of type E is, therefore, weakened for the reason already described. Evidence of such a tendency is given by the shift of the infrared absorption[4,13] of chelated ester-carbonyl groups.



1657~1655 cm^{-1}

Type C
R=H, 6-NO_2 and 6-Cl



1698~1695,1690 cm^{-1} *4

Type E
R=H, 6-CH_3, 7-CH_3, 7-Cl, 6-NO_2 and 6, 7-Benzo

The larger shift towads a lower frequency in the compounds of type C than that in type E is observed. The presence of the more stabilized chelate ring in the compounds of type C appears to support the above hypothetical interpretation.

Experimental

2-Oxo-3-ethoxycarbonylmethylenepiperazine (IV). —Into a solution of I (1.7 g., 0.01 mol.) in ethanol (25 ml.), a solution of II (0.6 g., 0.01 mol.) in ethanol (25 ml.) was dropped with stirring. The mixture became brown, and its temperature rose

10) S. Hünig, E. Lücke and E. Benzing, *Chem. Ber.*, **91**, 129 (1958).
11) S. Hünig, E. Benzing and E. Lücke, ibid., **90**, 2833 (1957).
12) E. Doering and V. Z. Pasternak, *J. Am. Chem. Soc.*, **72**, 143 (1950).

*4 In most of the compounds of type E, carbonyl groups give rise to absorption bands in regions which do not overlap with those of type D (1694~1692 cm^{-1}), A (1673~1665 cm^{-1}), B (1672 cm^{-1}) and C (1667~1655 cm^{-1}). In the case of R=H, however, the region (1690 cm^{-1}) overlaps with that of type D; this result is not satisfactory for the above interpretation. Nevertheless, there is experimental evidence of a dissimilarity in decomposition between the compounds of types E and D, which may thus come to show clearly different absorption bands in their excited state. At least it should be noted that the absorption band of type E is in the region nearest to that of the normal ester-carbonyl group.
13) Y. Iwanami, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, **83**, 597 (1962).

to 35°C from the room temperature (28°C). After the mixture had been stirred for a further 35 min., the solvent was removed in vacuo, and the residue was allowed to stand overnight in an ice box. The crystals formed (1.0 g., 56%) were then filtered off and recrystallized from ethanol to afford IV as colorless flakes; m. p. 164~165°C (corr.).

Found: C, 51.87; H, 6.68; N, 15.01. Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%.

6-Methyl-2-oxo-3-ethoxycarbonylmethylenepiperazine (V).—Into a solution of I (1.7 g., 0.01 mol.) in ethanol (100 ml.), a solution of III (0.7 g., 0.01 mol.) in ethanol (100 ml.) was added dropwise with stirring. The mixture gradually became yellow, and its temperature reached 23°C from the room temperature (17°C). The crystals deposited (1.8 g., 89%) were recrystallized from ethanol to give V as colorless prisms; m. p. 166~167°C (corr.).

Found: C, 54.52; H, 6.99; N, 13.86. Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%.

The Formation of V by the Amination of the Reaction Product from I and 1-Amino-2-chloropropane (VI).—VI hydrochloride was prepared according to Schaefer's[14] and Ulrich's[15] methods; colorless crystals melting at 179~181°C (lit.[15] m. p. 180~181°C) were obtained. The free amine VI was obtained by treating the hydrochloride with aqueous sodium hydroxide and by distilling the resulting oil under diminished pressure; colorless liquid boiling at 59~61°C/378 mmHg (lit.[14] b. p. about 70°C under slightly reduced pressure) was obtained.

Into a solution of I (5.0 g., 0.03 mol.) in ethanol (100 ml.), a solution of VI (2.5 g., 0.03 mol.) in ethanol (100 ml.) was dropped with stirring. A yellow color developed in the mixture, and the temperature of the mixture rose to 24°C from the room temperature (19°C). After the mixture had been stirred for a further 30 min., the solvent was removed in vacuo. To a solution of residual oil in ethanol (20 ml.), a saturated solution of ammonia in ethanol (30 ml.) was added, and the mixture was heated at 100°C for 4 hr. in a sealed tube. The mixture was then evaporated to dryness, and water was added to the remaining dark red oil. The suspension was extracted with benzene, and the solvent was removed in vacuo. The residue was allowed to stand for two weeks in an ice box, and then a vacuum desiccator. The crystals thereby formed were collected by filtration and repeatedly washed with ether. The recrystallization of the crystals (20 mg., 0.3%) from ethanol gave colorless prisms; m. p. 166~167°C (corr.) (Found: N, 13.82%). No depression of the melting point was observed on admixture with V.

6-Chloro-2-oxo-3-ethoxycarbonylmethylene-3, 4-dihydro-2*H*-1, 4-benzoxazine (XII).—To a solution of I (1.7 g., 0.01 mol.) in ethanol (20 ml.), a solution of 4-chloro-2-aminophenol (XIII) (1.5 g., 0.01 mol.) in ethanol (30 ml.) was added. The temperature of the mixture reached 24°C from the room temperature (21°C). After the mixture had stood overnight, the precipitated crystals (2.5 g., 94%) were collected by filtration and recrystallized from ethanol to afford XII as pale yellow needles; m. p. 122~123°C (corr.).

Found: C, 53.73; H, 4.08; N, 5.49. Calcd. for $C_{12}H_{10}O_4NCl$: C, 53.85; H, 3.77; N, 5.23%.

IR (KBr disk): 3260, 1765, 1655, 1625 cm^{-1}.

2-Oxo-3-ethoxycarbonylmethylene-1, 2, 3, 4-tetrahydro-5, 6(or 7, 8)-benzoquinoxaline (XIV).[*5]—Into a solution of I (1.7 g., 0.01 mol.) in ethanol (50 ml.), a solution of 1, 2-diaminonaphthalene (1.6 g., 0.01 mol.) in ethanol (500 ml.) was added with stirring. After the mixture had been stirred for 1 hr., the precipitated crystals (1.7 g., 60%) were collected by filtration and recrystallized from a large amount of ethanol to give XIV as orange needles; m. p. 227~228°C (corr.).

Found: C, 67.85; H, 5.36; N, 10.06. Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92%.

The Hydrolysis of IV.—One neck of a two necked flask was equipped with a reflux condenser. Into the other neck an inlet tube for bubbling the reaction mixture with a stream of air was fitted. The end of the inlet tube was connected to the outlet of two, in-series-connected scrubbing bottles containing aqueous sodium hydroxide for eliminating carbon dioxide from the air stream. A glass tube joined the top of the condenser to a wash bottle containing water. This was in turn connected to an empty bottle, which served as a trap, and to an absorption bottle containing an aqueous barium hydroxide solution. IV (0.80 g.) was placed in the flask, and 6 N hydrochloric acid (60 ml.) was added. By applying gentle suction (about 750 mmHg) to the outlet of the absorption bottle, a slow stream of air was continuously introduced into the mixture. The mixture bubbled with air was refluxed for 3 hr. During the reflux, IV was gradually dissolved and carbon dioxide was evolved. The precipitated barium carbonate in the absorption bottle was collected by filtration and dried after it had been washed with water (0.65 g., 76%).

A half of the solution containing the hydrolysates was partially concentrated in vacuo, and the crystals thereby formed were recrystallized from water to give the hydrochloride of II as colorless prisms; m. p. 240°C (subl.) (microscopically observed) (the description on its melting point in the literature: sublimes;[16] does not melt at 270°C[17]) (Found: C, 18.30; H, 7.75. Calcd. for $C_2H_{10}N_2Cl_2$: C, 18.05; H, 7.58%).

The remaining half of the solution was diluted with water until the concentration of hydrochloric acid became 2 N, and to the resulting solution the saturated solution of 2, 4-dinitrophenylhydrazine in 2 N hydrochloric acid was added. The precipitated crystals (0.36 g., 62%) were collected and recrystallized from ethanol to give 2, 4-dinitrophenylhydrazone of VII as yellow plates; m. p. 222°C (lit. m. p. 221~222°C) (Found: C, 40.46; H, 3.08. Calcd. for $C_9H_8O_6N_4$: C, 40.30; H, 3.01%).

The Hydrolysis of V.—6 N Hydrochloric acid (80 ml.) was added to V (1.0 g.). In a manner similar

14) F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5929 (1955).
15) H. Ulrich, U. S. Pat. 2163181 (1939).

*5 The infrared absorption of this compound will be reported on in a following paper, together with the structural assignment and the location of its benzo group.
16) A. W. Ipatow, *J. Russ. Phys. Chem. Soc.*, **49**, 302 (1917).
17) T. Curtius and H. Hechtenberg, *J. prakt. Chem.*, **105**, 215 (1920)

to that described above, the mixture was refluxed for 1 hr., and the evolved carbon dioxide was collected as barium carbonate (0.73 g., 73%). Although a half of the hydrolyzed solution was evaporated to dryness, the resulting hygroscopic hydrochloride of III failed to crystallize. The residue was dissolved in alkali, and the presence of III was confirmed by paper chromatography (ascending); solvent: 1-butanol saturated with a 25% aqueous solution of acetic acid; paper: Tōyō Roshi No. 50; location reagent: 0.2% bromophenol blue in ethanol. The same R_f value (0.36) with an authentic specimen was observed. The alkaline solution was then evaporated under diminished pressure, and the vapor was introduced into a solution of picric acid in ethanol. The deposited crystals (0.22 g., 21%) were collected and recrystallized from water to afford the picrate of III as yellow prisms; m. p. 273°C (lit.[18] m. p. 273°C) (Found: N, 21.30. Calcd. for $C_{15}H_{16}O_{14}N_8$: N, 21.05%).

From the other half of the solution, VII was isolated as its 2, 4-dinitrophenylhydrazone, which was recrystallized from ethanol to give yellow plates; m. p. 221~222°C (Found: N, 20.95. Calcd. for $C_9H_8O_6N_4$: N, 20.89%).

The Hydrolysis of VIII, X and XII.—The syntheses of VIII and X have been reported in the preceding paper.[4]

6 N Hydrochloric acid (100, 100 and 50 ml.) was added to VIII (2.4 g.), X (2.0 g.) and XII (0.50 g.) respectively in the flask of an apparatus similar to that described above, but nitrogen instead of carbon dioxide-free air was bubbled into the mixture under a slightly elevated pressure. In every case, VIII, X and XII, barium carbonate (1.2, 1.7 and 0.32 g. respectively; 61, 72 and 89% respectively) was precipitated in an absorption bottle. From a very small portion of the reaction mixtures, IX, XI and XIII were detected by paper chromatography, and the same R_f values (0.60, 0.26 and 0.18 respectively) with authentic specimens were observed. The separately-formed VII was isolated from the remaining mixtures as its 2, 4-dinitrophenylhydrazone (1.9, 1.5 and 0.46 g.; 75, 56 and 94%), which was recrystallized from ethanol to give yellow plates; m. p. 221~222°C (Found: C, 40.30; H, 3.28, C, 40.61; H, 3.13, and C, 40.17; H, 3.32%).

The Hydrolysis of XIV.—XIV (1.0 g.) was placed in the flask of the above-described apparatus, to which 6 N hydrochloric acid (100 ml.) was then added. The mixture was refluxed 3 hr., and the evolved gas was led into an absorption bottle with a stream of nitrogen. The precipitated barium carbonate (0.54 g., 79%) was separated. After the mixture had stood overnight, dark brown crystals were deposited; they became brown after being washed with water. The dried crystals (0.53 g., 71%) were recrystallized from ethanol with decolorizing carbon to give XV as colorless needles; m. p. 295~296°C (corr.).

Found: C, 74.45; H, 4.99; N, 13.33. Calcd. for $C_{13}H_{10}ON_2$: C, 74.27; H, 5.33; N, 13.54%.

18) A. Windaus et al., *Ber.*, **54**, 2750 (1921).

Summary

2-Oxo-3-ethoxycarbonylmethylenepiperazine (IV) and its 6-methyl derivative (V) have been synthesized by the reactions of diethyl acetylenedicarboxylate with ethylenediamine and propylenediamine. These compounds (IV and V), the previously-reported diethyl *N*-(*n*-butyl)aminofumarate (VIII), 4-methyl-2-oxo-3-ethoxycarbonylmethylene-3, 4, 5, 6-tetrahydro-2*H*-1, 4-oxazine (X), the newly-synthesized 6-chloro-2-oxo-3-ethoxycarbonylmethylene-3, 4-dihydro-2*H*-1, 4-benzoxazine (XII), and 2-oxo-3-ethoxycarbonylmethylene-1, 2, 3, 4-tetrahydrobenzoquinoxaline (XIV) have been hydrolyzed with 6 N hydrochloric acid. The compound XIV has been hydrolyzed, with decarboxylation, to give 2-oxo-3-methyl-1, 2-dihydrobenzoquinoxaline, while all the other compounds have been hydrolyzed into pyruvic acid, carbon dioxide, and the amines by the splitting of the carbon-nitrogen bond.

These two types of hydrolyses shown by the compounds have been discussed in connection with their tautomerism between enamine and ketimine forms.

The authors wish to express their deep gratitude to The late Professor Shin-ichiro Fujise for his valuable instruction and advice.

Department of Chemistry
The Medical Institute of Sasaki Foundation
Kanda-Surugadai, Tokyo