Chem. Pharm. Bull. 23(9)2169—2172(1975)

UDC 547.892.04

Benzodiazepines. X.[1] Oxidation of Tetrahydro-1,4-benzodiazepine Derivatives

Kikuo Ishizumi, Kazuo Mori, Shigeho Inaba, and Hisao Yamamoto

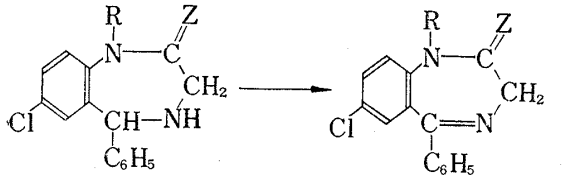
Pharmaceuticals Division, Sumitomo Chemical Co., Ltd.[2]

(Received February 7, 1975)

By ultraviolet (UV) irradiation in dimethyl sulfoxide (DMSO) or acetone tetrahydro-1,4-benzodiazepines of type **1** and 6-chloro-1-cyclopropylmethyl-4-phenyl-1,2,3,4-tetrahydroquinazolin-2-one (**3**) were oxidized to the corresponding dihydro compounds (**2** and **4**). 7-Chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**1b**) was prepared from 4-acetyl-7-chloro-1-methyl-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine (**5**) by oxidation with potassium permanganate followed by acid hydrolysis. Oxidation of other types of 4-acylbenzodiazepine derivatives was also examined.

In the course of other studies connected with the synthesis of tetrahydro-1,4-benzodiazepine derivatives, it was noticed that 7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**1b**) was slightly converted to 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**2b**) on prolonged standing in acetone. This conversion was considered to be effected by a photo-oxidation reaction.[3] The conversion of tetrahydro-1,4-benzodiazepine derivatives (**1**) to the corresponding dihydro derivatives (**2**) by the use of oxidants such as chromium trioxide or ruthenium tetroxide has been described.[4] The effect of light on compounds (**1**), however, has not been investigated. We now report our findings on ultraviolet (UV) irradiation of compounds (**1**).

When a solution of **1b** in acetone was irradiated, the reaction was slow and in the reaction mixture two unknown compounds other than **1b** and **2b** were detected by thin-layer chromatography. The use of dimethyl sulfoxide (DMSO) as solvent, however, facilitated the photo-oxidation reaction, giving **2b** in 48% yield. The photo-oxidation of **1b** to **2b** in DMSO solution was also achieved when exposed to sun light. Also, by the UV irradiation of the 1-unsubstituted tetrahydrobenzodiazepin-2-one (**1a**) the corresponding dihydro compound (**2a**) was obtained in 59% yield, whereas the irradiation of the tetrahydrobenzodiazepine (**1c**) gave a



a: R=H, Z=O
b: R=CH_3, Z=O
c: R=CH_3, Z=H_2

Chart 1

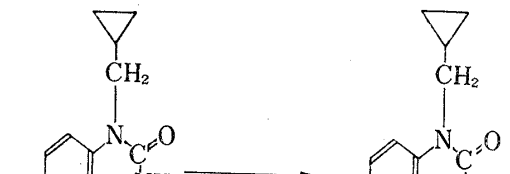


Chart 2

1) Part IX: K. Ishizumi, K. Mori, S. Inaba, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 1027 (1973).
2) Location: *2-1, Takatsukasa-4-chome, Takarazuka-shi, Hyogo.*
3) For an example of the photo-oxidation of amines to imines, see H.J. Roth, E. Schumann, H. George, and F. Assadi, *Tetrahedron Letters*, **1968**, 3433.
4) *a*) R.I. Fryer, G.A. Archer, B. Brust, W. Zally, and L.H. Sternbach, *J. Org. Chem.*, **30**, 1308 (1965); *b*) A.M. Felix, J.V. Earley, R.I. Fryer, and L.H. Sternbach, *J. Heterocyclic Chem.*, **5**, 731 (1968).

complex reaction mixture, from which the corresponding dihydro compound (**2c**) was isolated only in 4% yield.

The photo-oxidation reaction of another heterocyclic compound, 6-chloro-1-cyclopropylmethyl-4-phenyl-1,2,3,4-tetrahydroquinazolin-2-one (**3**) proceeded more smoothly than of the benzodiazepin-2-ones (**1**). Thus, the tetrahydroquinazolinone (**3**) was oxidized to the dihydroquinazolinone (**4**) in 87% yield in DMSO solution and in 40% yield in acetone solution.[5] The photo-reaction in acetone was accelerated by bubbling air through the solution, giving a 68% yield of **4**. From this result it is clear that the oxidation of benzylic amines to imines is effected by means of atmospheric oxygen in the photo-reaction of **1** and **3**.[6]

As described above, the photo-oxidation reaction in DMSO was fast even without bubbling air through the reaction mixture. Sato, *et al.*[7] have studied the photo-oxidation of benzylic alcohols in DMSO and showed that in the photo-oxidation in DMSO an uptake of oxygen was much facilitated compared with the reaction using other solvents. Although the oxygen uptake was not determined in the present study, the use of DMSO as solvent must result in a fast uptake of oxygen also in the photo-oxidation of benzylic amines.

In a previous publication,[8] it was shown that the preparation of the dihydrobenzodiazepine (**2c**) by diborane reduction of the corresponding 2-one (**2b**) was accompanied by the formation of a small amount of the tetrahydrobenzodiazepine (**1c**), which was isolated as the 4-acetyl derivative (**5**). In connection with the photo-oxidation reaction described above, the conversion of **5** to **1b** was examined. Oxidation of **5** with potassium permanganate gave a 77% yield of 4-acetyl-7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2-one (**7**), which was then hydrolyzed with acid to give the desired compound (**1b**).

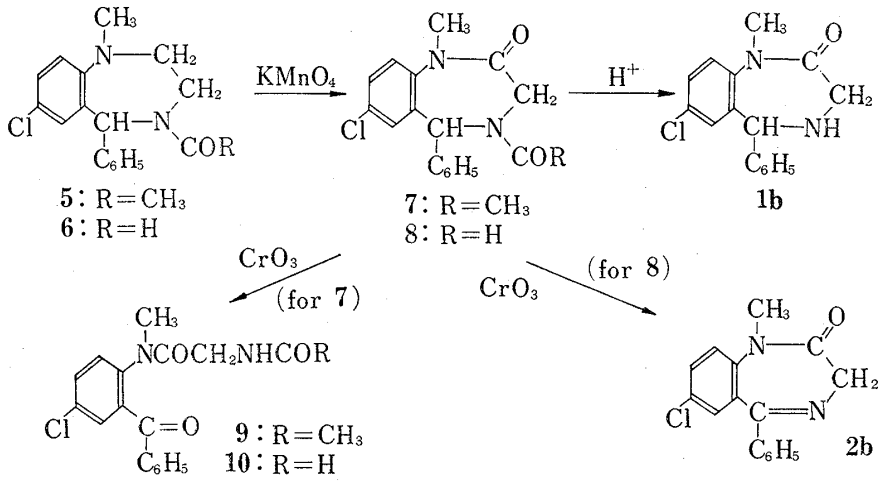


Chart 3

On the other hand, chromic acid oxidation of **5** in acetic acid gave a complex mixture with no obserable formation of **7**.[9] However, chromic acid oxidation of **7** led to the cleavage of the 4,5 N–C bond and the formation of 2-acetamido-2′-benzoyl-4′-chloro-N-methylacetanilide (**9**).

5) The oxidation of tetrahydroquinazolinones of type **3** with potassium permanganate has been described by T. Komatsu, H. Awata, Y. Sakai, T. Inukai, M. Yamamoto, S. Inaba, and H. Yamamoto [*Arzneimittel. Forsh.*, **32**, 1958 (1972)].

6) In contrast Kano, M. Ogata, and H. Yukinaga, Japan Patent 7218857 (1972) [*C.A.*, **78**, 4015*s* (1973)] have reported the photo-oxidation of 2-hydroxy-3-α-methylaminobenzyl-1,4-naphthoquinone in an argon atmosphere to give the corresponding imine in 7% yield.

7) T. Sato, E. Yamada, T. Akiyama, H. Inoue, and K. Hata, *Bull. Chem. Soc. Japan*, **38**, 1225 (1965); T. Sato, H. Inoue, and K. Hata, *ibid.*, **40**, 1502 (1967).

8) K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **37**, 4111 (1972).

9) The oxidation of **1c** by chromium trioxide and dilute sulfuric acid in acetone has been reported to give **1b** in 15% yield.[4a]

In analogy to the 4-acetylbenzodiazepine (**5**), oxidation of 7-chloro-4-formyl-1-methyl-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine (**6**) with potassium permanganate gave the corresponding benzodiazepin-2-one (**8**), which was shown to be identical with the sample prepared by formylation of **1b**. On the other hand, chromic acid oxidation of **8** resulted in the formation of **2b**.[10] The reaction probably proceeds *via* initial oxidation to the formamidoacetanilide intermediate (**10**), followed by removal of the formyl group by chromic acid and subsequent cyclization to give **2b**.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured on a Hitachi Model EPI-G3 spectrophotometer, and NMR spectrum on a Varian A-60D instrument using tetramethylsilane as an internal standard. All solutions were dried over anhydrous sodium sulfate and solvents were evaporated under water-aspirator pressure. The identity of compounds was established by mixture melting point determination and by comparison of IR spectra.

All photochemical reactions were performed at room temperature in an open beaker using a 30 W low pressure mercury lamp (Eikosha Co., PIL-30). During the irradiation the solution was stirred vigorously using a magnetic stirrer and fresh solvent added periodically to keep the volume approximately constant.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**2a**)——A solution of 1.0 g of tetrahydrobenzodiazepinone (**1a**)[11a] in 10 ml of DMSO was irradiated for 24.5 hr. The mixture was diluted with 20 ml of water. The precipitate formed was collected by filtration, washed with water, and recrystallized from isopropyl alcohol to give 149 mg of **2a**, mp 201—206°. The DMSO filtrate was extracted with methylene chloride. The combined extracts were washed with water, dried, and evaporated to dryness. The residue was recrystallized from isopropyl alcohol to give an another 245 mg of **2a**, mp 207—209°. A third crop (188 mg) was obtained from the combined isopropyl alcohol mother liquors to give a total yield of 582 mg (58.6%). The material was identical with an authentic sample.[12]

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**2b**)——A solution of 1.0 g of **1b** in 10 ml of DMSO was irradiated for 27.5 hr. The mixture was diluted with water and extracted with ether and methylene chloride. The extracts were combined, washed with water, dried, and evaporated to dryness. The residue was chromatographed over 50 g of silica gel. Elution with ethyl acetate and recrystallization from isopropyl alcohol gave 0.48 g (48.1%) of **2b**, mp 128—130.5°. The material was identical with an authentic sample.[12]

When the DMSO solution of **1b** was exposed to sun light without stirring for 60 hr, a similar result(a 46.6% yield of **2b**) was obtained.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (**2c**)——A solution of 1.0 g of **1c** in 10 ml of DMSO was irradiated for 24.5 hr. The mixture was diluted with water and the precipitate collected by filtration was chromatographed over 60 g of silica gel. Elution with ethyl acetate gave 38 mg (3.8%) of **2c**, mp 96—100°. The material was identical with an authentic sample.[8]

Photo-oxidation of 6-Chloro-1-cyclopropylmethyl-4-phenyl-1,2,3,4-tetrahydroquinazolin-2-one (**3**) **to 6-Chloro-1-cyclopropylmethyl-1,2-dihydro-4-phenylquinazolin-2-one** (**4**)——i) In DMSO: A solution of 1.8 g of **3**[13] in 10 ml of DMSO was irradiated for 49.5 hr. The reaction mixture was left at room temperature for 2 days and the precipitate was collected by filtration to give 582 mg of **4**, mp 171—174°. The filtrate was diluted with water and extracted with methylene chloride. The residue obtained by evaporation of the solvent was crystallized from isopropyl alcohol to give an additional 284 mg of **4** for a combined yield of 866 mg (87.0%). The material was identical with an authentic sample.[14]

ii) In Acetone: A solution of 0.50 g of **3** in 20 ml of acetone was irradiated for 57 hr. The solution was evaporated to dryness and the residue was crystallized from isopropyl alcohol to give 0.20 g (40%) of **4**, mp 170—172°.

An examination of the mother liquors by thin-layer chromatography showed the presence of considerable amounts of unchanged **3**.

---

10) The treatment of the 4-acetyl- and 4-formyltetrahydrobenzodiazepine **5** and **6** with sodium hydride has been reported to lead to the dihydrobenzodiazepine **2c**: R.I. Fryer and L.H. Sternbach, U.S. Patent 3625957 (1971); S. African Patent 6800796 (1968)[*C.A.*, **70**, 78029*f* (1969)].

11) *a*) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); *b*) L.H. Sternbach, E. Reeder, and G.A. Archer, *ibid.*, **28**, 2456 (1963).

12) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968).

13) Kindly furnished by Mr. Michihiro Yamamoto.

14) K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **39**, 2587 (1974).

iii) In Acetone under Bubbling Air: A solution of 1.0 g of **3** in 60 ml of acetone was irradiated for 27.5 hr, during which time air was bubbled through the solution. The solution was evaporated to dryness and the residue was crystallized from isopropyl alcohol to give 0.47 g of **4**, mp 173—176°. From the mother liquors, an additional 0.21 g of product was obtained to give a combined yield of 0.68 g (68.4%).

7-Chloro-4-formyl-1-methyl-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine (6)——To 20 ml of acetic anhydride was added 10 ml of 100% formic acid under cooling and the solution was stirred at 50° for 30 min. After cooling, an additional 10 ml of formic acid was added, followed by 8.5 g of **1c** and the mixture was stirred at 1—3° for 2.5 hr. The reaction mixture was diluted with a mixture of 50 ml of ice water and 50 ml of methylene chloride and made basic with aqueous ammonia with stirring. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride. The organic layers were combined, dried, and evaporated to dryness. The residue was crystallized from ether and recrystallized from isopropyl alcohol to give 8.21 g (87.6%) of **6**, mp 117—119°. Further recrystallization from isopropyl alcohol afforded colorless prisms, mp 120—123.5° (lit.[10] mp 121—122°). IR ν_{max}^{Nujol} cm^{-1}: 1670. *Anal.* Calcd. for $C_{17}H_{17}ON_2Cl$: C, 67.88; H, 5.70; N, 9.31; Cl, 11.79. Found: C, 67.87; H, 5.88; N, 9.27; Cl, 11.87.

4-Acetyl-7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (7)——To a cooled solution of 130 g of **5**[8] in 3 liters of dioxane was added a solution of 98 g of potassium permanganate in 1.05 liters of water at 8—21°. After the addition of 40 ml of formic acid, the reaction mixture was neutralized with aqueous ammonia. The insoluble material was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in chloroform. The solution was washed with water, dried, and evaporated to dryness. The residue was crystallized from isopropyl alcohol to give 71.8 g of **7**, mp 183—187°. From the filtrate, an additional 32.2 g of product was obtained for a combined yield of 104 g (76.6%). Recrystallization from ether afforded colorless prisms, mp 188.5—192°. IR ν_{max}^{Nujol} cm^{-1}: 1660. *Anal.* Calcd. for $C_{18}H_{17}O_2N_2Cl$: C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.72; H, 5.22; N, 8.47; Cl, 10.70.

7-Chloro-4-formyl-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (8)——i) From **6**: Compound (**6**) (5.0 g) was oxidized as described above. The crude product obtained was dissolved in methylene chloride and washed with 0.24N HCl and then with aqueous ammonia. The methylene chloride layer was dried and evaporated to dryness. The residue was chromatographed over 70 g of silica gel. Elution with chloroform and crystallization from isopropyl alcohol gave 2.48 g (47.4%) of **8**, mp 165—183°. Recrystallization from isopropyl alcohol afforded colorless prisms, mp 162—164°. IR ν_{max}^{Nujol} cm^{-1}: 1680, 1665. *Anal.* Calcd. for $C_{17}H_{15}O_2N_2Cl$: C, 64.87; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.83; H, 4.84; N, 8.94; Cl, 11.21.

ii) From **1b**: Compound (**1b**) was formylated in a similar manner as described for the formylation of **1c**. The crude product was recrystallized from isopropyl alcohol to give colorless prisms, mp 162—164° in 58.8% yield. The material was identical with the sample obtained above.

7-Chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (1b)——i) From **7**: Compound (**7**) (0.10 g) was dissolved in 2.5 ml of hot ethanol. To the cooled solution was added 1 ml of 6N HCl. The mixture was stirred at 50—60° for 30 hr and allowed to stand for 2 days at 4°. The precipitate that formed was collected by filtration and washed with cold ethanol to give 0.36 g (38.2%) of the hydrochloride of **1b**, mp 266—269° (decomp.). Recrystallization from ethanol afforded colorless needles, mp 270—272° (decomp.). *Anal.* Calcd. for $C_{16}H_{16}ON_2Cl_2$: C, 59.46; H, 4.99; N, 8.67; Cl, 21.94. Found: C, 59.32; H, 5.10; N, 8.69; Cl, 21.96.

The free base was obtained and shown to be identical with an authentic sample.[11b]

ii) From **8**: A mixture of 0.30 g of **8**, 0.3 ml of conc. HCl and 8 ml of ethanol was stirred at 58° for 13.5 hr. After cooling, the precipitate was collected by filtration to give 0.17 g (55.2%) of the hydrochloride of **1b**, mp 270—272° (decomp.). The material was identical with the sample obtained above.

2-Acetamido-2′-benzoyl-4′-chloro-N-methylacetanilide (9)——To a solution of 1.0 g of **7** in 20 ml of acetic acid was added a solution of 2.0 g of chromic anhydride in 2 ml of water at 13—15°. After stirring at 25—27° for 6 hr, the mixture was diluted with 20 ml of water, made basic with 30% NaOH, and extracted with chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to dryness. The residue was chromatographed over 50 g of silica gel with chloroform to give 52 mg of starting material (5.2% recovered **7**) as a first fraction and 80 mg of an unidentified compound, mp 220—223°, as a second fraction. Continued elution with chloroform gave 533 mg (52.8%) of **9**, mp 104—109°, as a third fraction. Recrystallization from a mixture of benzene, ether and ligroin gave colorless prisms, mp 105—108°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1670, 1650. NMR (CCl_4) δ: 1.77 (3H, s, $COCH_3$), 2.97 and 3.23 (3H, NCH_3), 3.50 and 3.74 (2H, CH_2), 7.05 (1H, NH), 7.43—7.83 (8H, m, aromatic H). *Anal.* Calcd. for $C_{18}H_{17}O_3N_2Cl$: C, 62.70; H, 4.97; N, 8.12; Cl, 10.28. Found: C, 62.77; H, 4.94; N, 8.07; Cl, 10.19.

Chromic Acid Oxidation of 8——To a solution of 1.0 g of **8** in 20 ml of acetic acid was added a solution of 2.0 g of chromic anhydride in 1.6 ml of water. After stirring at 29° for 22.5 hr, the mixture was diluted with 50 ml of water, made basic with 30% NaOH, and extracted with methylene chloride. The residue obtained by evaporation of the solvent was dissolved in 15 ml of carbon tetrachloride and extracted with four 10 ml portions of 5% HCl. The organic layer was washed with aqueous ammonia, dried, and evaporated to dryness. The residue was crystallized from a mixture of ethyl acetate and ether to give 0.18 g of unreacted **8**. The filtrate was chromatographed over 50 g of silica gel with ethyl acetate to give an additional 0.12 g of **8**. The total yield of recovered **8** was 30%.

The acidic layers that separated from the carbon tetrachloride layer were washed with carbon tetrachloride, neutralized with aqueous ammonia and re-extracted with methylene chloride. The methylene chloride extracts were combined, dried, and evaporated to dryness. The residue was crystallized from a mixture of isopropyl alcohol and ether to give 0.17 g (26.8% based on unrecovered **8**) of **2b**, mp 123—126°. The material was identical with an authentic sample.[12]

[Chem. Pharm. Bull. 23(9)2173—2174(1975)]

UDC 547.831.08 : 543.544

Analysis of 5-Chloro-7-iodo-8-quinolinol Conjugates by High Performance Liquid Chromatography

Ching-Tan Chen, Kazuichi Hayakawa, Toshio Imanari and Zenzo Tamura

Faculty of Pharmaceutical Sciences, University of Tokyo[1]

(Received February 7, 1975)

An analytical method of 5-chloro-7-iodo-8-quinolinol (Clioquinol or Chinoform) (CF) conjugates was established by high performance liquid chromatography.

The chromatographic conditions were as follows: column, SAX (50 cm × 2 mm i.d.); mobile phase, I (0.02M borate buffer–0.1M KCl, pH 9.5), II (0.02M borate buffer–0.5M $NaClO_4$, pH 9.5); gradient, 0→25% $\left(\frac{\text{II}}{\text{I}+\text{II}}\right)$ at 3%/min; column pressure, 500 psi; flow rate, 1 ml/min; detector, ultraviolet-detector at 254 mμ. Urine samples of a man administered CF were injected directly to the column, and the major metabolite, CF glucuronide was determined, while very small amounts of CF sulfate was detected.

Recently, the metabolism of 5-chloro-7-iodo-8-quinolinol (Clioquinol or Chinoform) (CF) in a man and various animals has been studied by many investigators to clarify the cause of SMON (Subacute-Myelo-Optico-Neuropathy). In the course of this study, we developed the micro-analysis of CF and its conjugates in biological fluids by gas chromatography equipped with electron capture detector.[2]

It is a very sensitive and reliable method, but somewhat complicated. Then, the establishment of simple and convenient method was required in the analysis of biological samples which contain comparatively large amounts of CF conjugates such as urine.

It has been shown by Anders, *et al.*[3] that high performance liquid chromatography is very useful for the analysis of glucuronides and sulfates in the study of drug metabolism, because they could be analyzed directly without hydrolysis and derivatization.

In this work, we tried to use high performance liquid chromatography for the analysis of CF glucuronide (CF-G) and CF sulfate (CF-S) in human urine.

Materials and Apparatus

CF-G and CF-S were synthesized according to Matsunaga's[4] and Chen's[5] methods.

Apparatus——DuPont 830 Liquid Chromatograph equipped with ultraviolet detector was used.

Column——"Zipax" SAX (DuPont) was packed in a stainless tube (50 cm × 2 mm i.d.). Other conditions are described in the figures.

1) Location: *Hongo, Bunkyo-ku, Tokyo.*
2) Z. Tamura, M. Yoshioka, T. Imanari, J. Fukaya, J. Kusaka and K. Samejima, *Clin. Chim. Acta*, **47**, 13 (1973); C. Chen, K. Samejima and Z. Tamura, *Igaku no Ayumi* (Japan), **84**, 195 (1973).
3) M.W. Anders and J.P. Latorre, *J. Chromatog.*, **55**, 409 (1971).
4) I. Matsunaga and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1056 (1971).
5) C. Chen, K. Samejima and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **21**, 911 (1973).