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Colorimetric Determination of 4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide with 3,5-Dibromosalicylaldehyde. II.[1] Reaction Mechanism of Coloration

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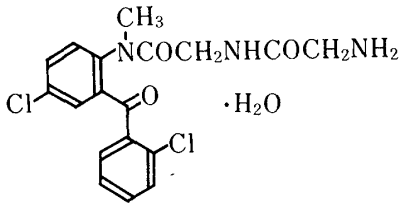
In connection with our studies to develop an assay method for 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide (**1**), a colored substance formed by the reaction of **1** with the reagent 3,5-dibromosalicylaldehyde (DBSA) was isolated and its chemical structure was investigated.

Another colored substance formed by the same reaction of glycinemonomethylamide (**3**) with DBSA was also isolated, and the chromophoric structure was shown to be essentially the same as that of the compound formed in the reaction of **1** with DBSA.

On the basis of spectrometric and chemical evidence, the colored compounds were determined to be *N*-substituted 5-(3,5-dibromo-2-hydroxybenzylidene)-2-(3,5-dibromo-2-hydroxyphenyl)-1-imidazoline-4-ones. The reaction mechanism of the coloration in the assay of **1** is discussed.

Keywords——open-ring benzodiazepine; 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide; coloration reaction mechanism; acid–base equilibria; glycinemonomethylamide; 3,5-dibromosalicylaldehyde; Schiff-base of glycinemonomethylamide

In the previous paper, a colorimetric method was established for the determination of 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide (**1**), a minor tranquilizer. The method was established on the basis of the color reaction of **1** with 3,5-dibromosalicylaldehyde (DBSA) in the presence of piperidine in dimethylsulfoxide (DMSO).



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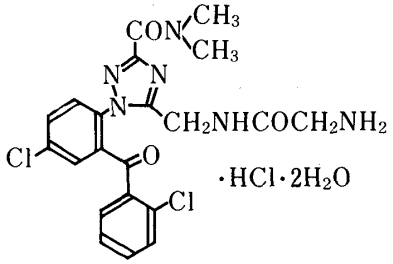


2

$CH_3NHCOCH_2NH_2$

3

Chart 1

In an extension of this work, 1-(2-*o*-chlorobenzoyl-4-chlorophenyl)-5-glycylaminomethyl-3-dimethylaminocarbonyl-1*H*-1,2,4-triazole hydrochloride dihydrate (**2**), newly de-

veloped as a sleep inducer in our laboratories, was assayed by the same method.[2] In addition, it was confirmed that many compounds having a glycinamide group (including **1** and **2**) could also be determined. The structure of the colored substance was not elucidated, although it was found that the Schiff base of **1** with DBSA (**4**) was an intermediary product in the formation of the final colored substance. Because of the importance of the glycinamide group in drugs and biological materials, we decided to examine the structure of the colored substance and the reaction mechanism of the coloration, and to determine whether the assay method is generally applicable to such a system. The colored substances were isolated from the reactions of **1** and glycinemonomethylamide (**3**) with DBSA. It was found that **3** afforded a colored product similar to that prepared from **1**, and that the colored substances had a common chromophoric structure. In the present paper, the structure of the colored substance is reported and the reaction mechanism is discussed.

It is known that DBSA reacts with active methylene compounds such as benzoylacetonitrile in the presence of base to give various types of cyclic compounds.[3-5] It was thus also of interest to us to study a new type of reaction of the glycinamide group analogous to those of active methylene compounds.

Results and Discussion

Reaction of Glycinamide Derivatives with DBSA

Previously it was found that the site of the color reaction with DBSA was the glycylglycinamide residue in the side chain of **1**. The end amino group in the side chain was essential for the color reaction. Since the Schiff base of **1**, which was easily obtainable with 1 mol of DBSA (**4**), reacted further with DBSA, to give the same colored substance as did **1**, it was assumed the Schiff base was an intermediate in the formation of the colored substance. Since no coloration took place with an analogous compound 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-alanylglycinanilide (**8**), the methylene group adjacent to the amino group was also assumed to be essential.

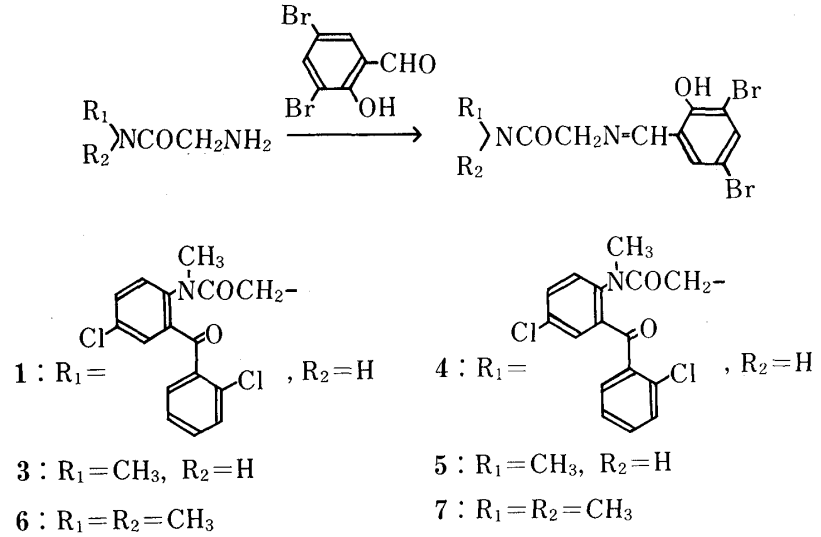
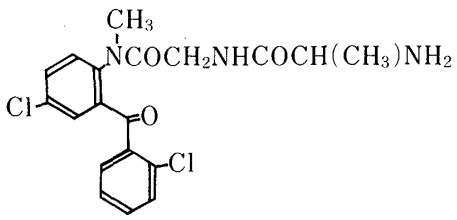


Chart 2

In the present study, two simple glycinamide derivatives, **3** and **6** were chosen and their reactivities with DBSA were investigated. Of the two compounds, **3** formed a colored substance similar to the reaction product of **1** with DBSA. As shown in Fig. 1, the absorption



8

Chart 3

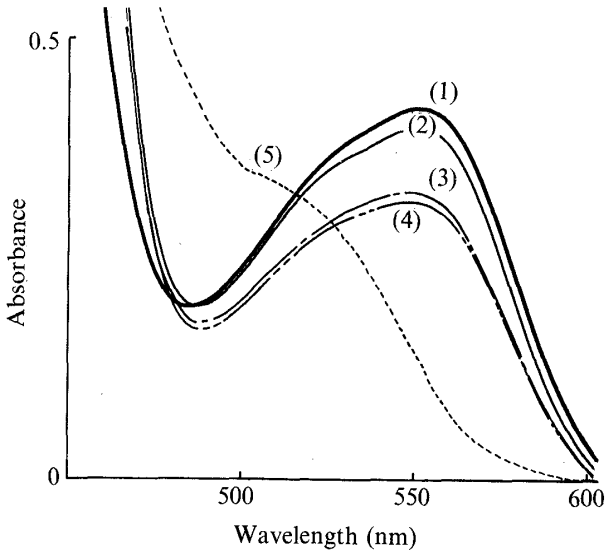


Fig. 1. Visible Absorption Spectra of the Colored Substances Obtained from Glycinamide Derivatives

1, compound **1**; 2, compound **4**; 3, compound **5**; 4, compound **3**; 5, compound **6**.

spectrum of the reaction solution was quite close to that of the colored substance from **1**. The Schiff base (**5**) of **3**, separately prepared in the same manner as described in the previous paper,[1] also underwent the color reaction with DBSA, finally giving the same product as did **3** itself. The results show that the colored product from **3** is not essentially different from that obtained from **1**. On the other hand, an analogous compound **6** showed no coloration, suggesting that the hydrogen atom ($R_2=H$ in **1** or **3**) in the amide group participates in this reaction. Since **3** seems to be a suitable model, we intended first to examine the structure of the product from **3**, and then that of the product from **1**.

Physico-Chemical Characteristics of the Colored Substance

Compound **3** was allowed to react with DBSA (2 eq) in the presence of excess piperidine. A mixture of **3**, DBSA, piperidine and DMSO was heated at 100 °C for 2 h. The reaction mixture was chromatographed over silica gel, followed by recrystallization of the product from EtOH to give a yellow powder, mp 267—271 °C (dec.), $C_{17}H_{10}Br_4N_2O_3$ (*m/z* 606, M^+). The DMSO solution of the isolated material was yellow-colored but changed to red when piperidine was added, exhibiting the same absorption at 550 nm as observed for the original reaction mixture.

Elemental analysis data showed that the compound was composed of two molecules of salicylaldehyde and one molecule of glycinemonomethylamide.

The infrared (IR) spectrum of the product suggested the presence of associated hydroxyl (3274 cm^{-1}) and carbonyl (1714 cm^{-1}) groups. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum gave doublet signals assignable to four aromatic ring protons (δ 7.76, 7.87, 8.07 and 8.21 (1H, d, $J=2.5$ Hz for each signal)), as shown in Fig. 2.

The results suggest that the product possesses two phenol moieties. This is supported by the fact that two methyl groups were easily introduced into the compound by methylation with CH_3I and K_2CO_3 in dry acetone. The ^{1}H-NMR spectrum of the methylated species showed the presence of two methoxyl groups (δ 3.80, s, 3H and δ 3.87, s, 3H).

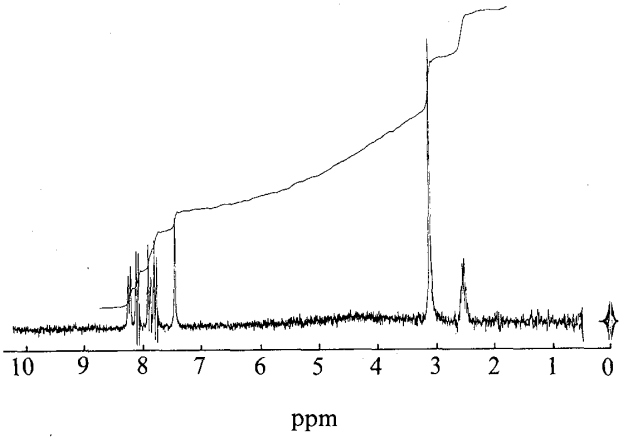
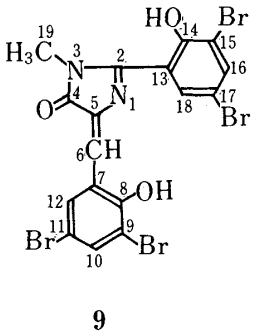


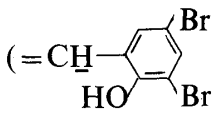
Fig. 2. ^{1}H-NMR Spectrum of the Colored Substance **9**



9

Chart 4

The signal at δ 3.08 (3H, s) in the ^{1}H-NMR spectrum in Fig. 2 is assignable to the *N*-methyl group in the glycinemonomethylamide moiety. The signal at δ 7.43 (1H, s) is attributable to an olefinic proton, which seems likely to be that of the salicylaldehyde residue



(=CH—). Based on these data, we assumed the chemical structure of the isolated colored product to be **9**.

The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum exhibited the presence of an imidazolone ring and two benzene rings. As shown in Fig. 3, the signals at 159.1 and 167.8 ppm are assignable to C_2 and C_4 in the imidazolone ring, respectively, and those at 27.9 and 124.3 ppm are assignable to C_{19} and C_6 attached to the ring, respectively. Two sets of signals at 152.2 and 153.5 ppm are assignable to either C_8 or C_{14} and those at 118.7 and 123.6 are assignable to either C_7 or C_{13}. The other eight signals due to the other eight carbons in the benzene rings, although they were not individually assigned, were separated into two groups, according to whether or not the carbons are linked to bromine. The ^{13}C-NMR spectral data are consistent with the structure **9**.

When **1** was treated with DBSA under the same conditions as for the reaction of **3**, a similar colored product was isolated, though in poor yield due to losses during the process of purification, as a yellow powder, $C_{32}H_{19}Br_4Cl_2N_3O_5 \cdot 1/2H_2O$, mp 220° (dec.) (*m/z* 911, M^+). A solution of this compound in DMSO changed color from yellow to red upon addition of piperidine, as did **9**. The IR spectrum showed three bands at 1645—1750 cm^{-1}, suggesting the presence of carbonyl groups. The ^{1}H-NMR spectrum showed signals similar to those observed in **9**, *i.e.*, four aromatic protons, and one olefinic proton, suggesting common structural features. Complicated signals corresponding to seven protons were observed at δ 7.4—7.8 (multiplet), possibly due to the benzophenone moiety, as shown in Chart 5. Also, the signal at 4.08 (2H, s) was assigned to the methylene proton in the side chain. The spectral data for the colored substance obtained from **1** are consistent with the structure **12**.

Reaction Mechanism

Based on the structure of **9** the following mechanism of the color reaction can be postulated. Compound **3**, as the initial step, forms the Schiff base **5** by reaction with 1 mol of DBSA. One more mole of DBSA attacks the methylene group which was activated by the Schiff base formation to give an adduct **10** by condensation. Cyclization then proceeds by means of an intramolecular nucleophilic attack of the amide nitrogen on the azomethine

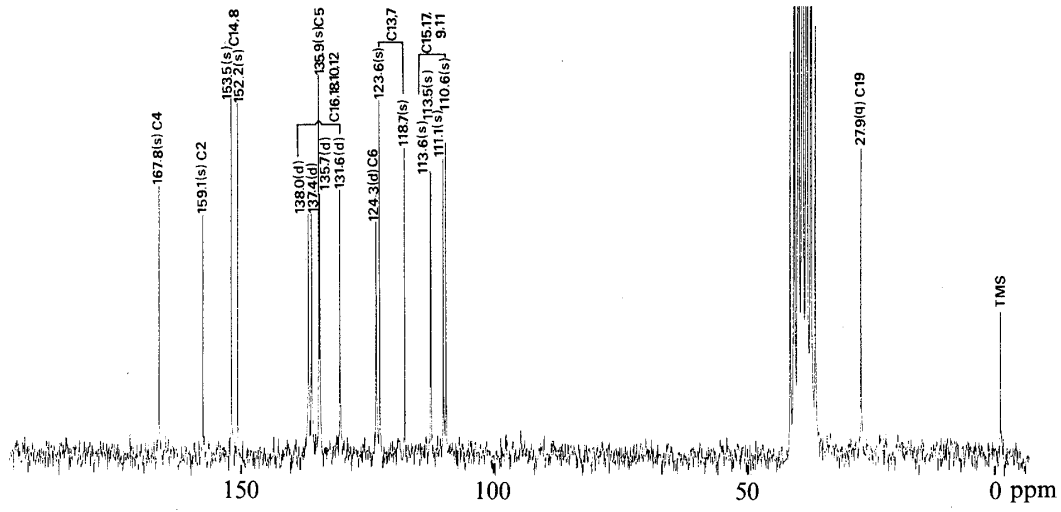


Fig. 3. ^{13}C-NMR Spectrum of the Colored Substance **9**

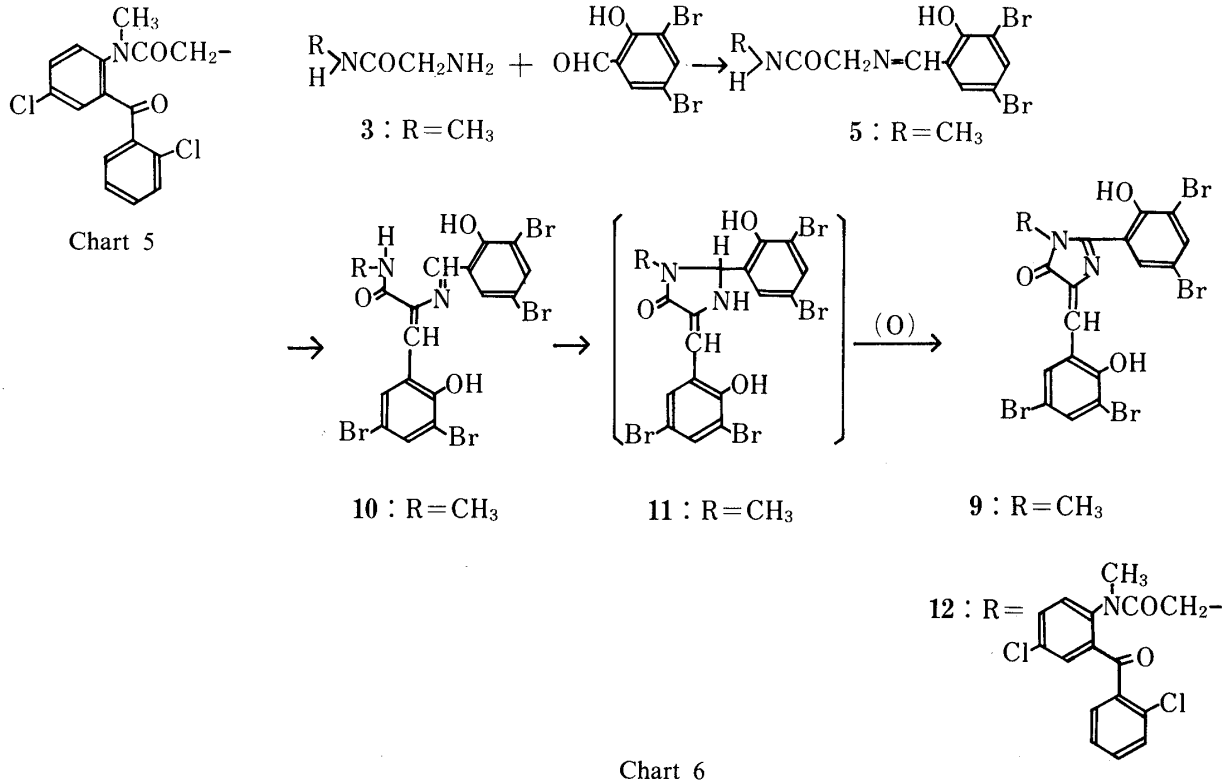


Chart 5

Chart 6

carbon in the presence of piperidine, followed by the oxidation of **11** to give the final product **9**.

The assumption that the final step in formation of the colored substance involves oxidation by oxygen present in the solvent was proved to be reasonable. When **3** was allowed to react with DBSA in oxygen-free DMSO deaerated by flushing with argon, the reaction solution did not develop its final color and remained yellow-colored, as observed at the initial step of the reaction. When this yellow solution was allowed to stand in contact with the atmosphere, the color changed to red. As shown in Fig. 4, the absorption intensity increased with time and the resulting spectrum had the maximum wavelength to 550 nm, in accord with that of **9**. This suggests that the increase of the colored substance was brought about by air-oxidation. When the reaction of **3** with DBSA was carried out without piperidine, no

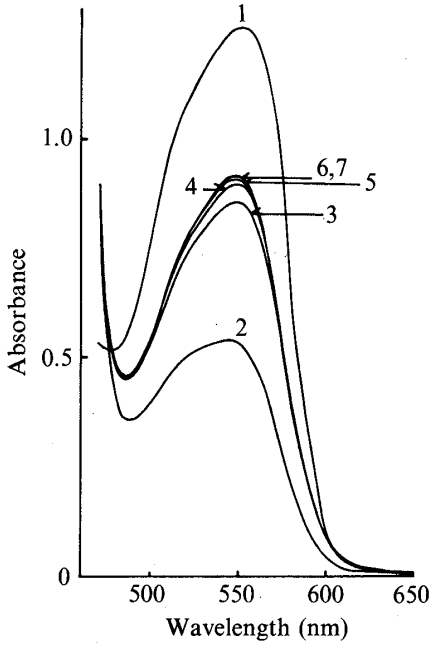


Fig. 4. Visible Absorption Spectra of Compound **3** in Contact with the Atmosphere

1, according to the assay method for compound **1**; 2, after standing for 2 min; 3, after standing for 5 min; 4, after standing for 10 min; 5, after standing for 20 min; 6, after standing for 30 min; 7, after standing for 45 min.

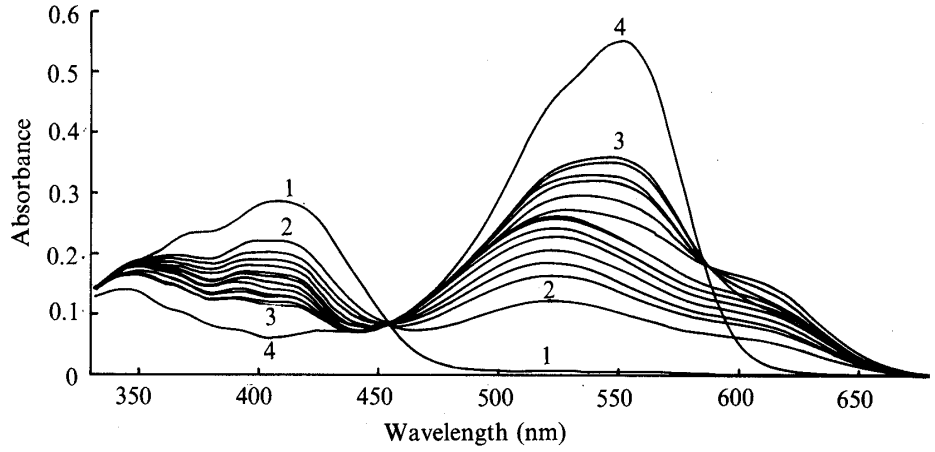


Fig. 5. Visible Absorption Spectra of the Colored Substance **9** in DMSO

1, without *N*-ethylmorpholine; 2, 3, in the presence of *N*-ethylmorpholine ranging from $C_B = 5 \times 10^{-5}$ M to $C_B = 2.5 \times 10^{-1}$ M; 4, in the presence of morpholine ($C_B = 1 \times 10^{-1}$ M).

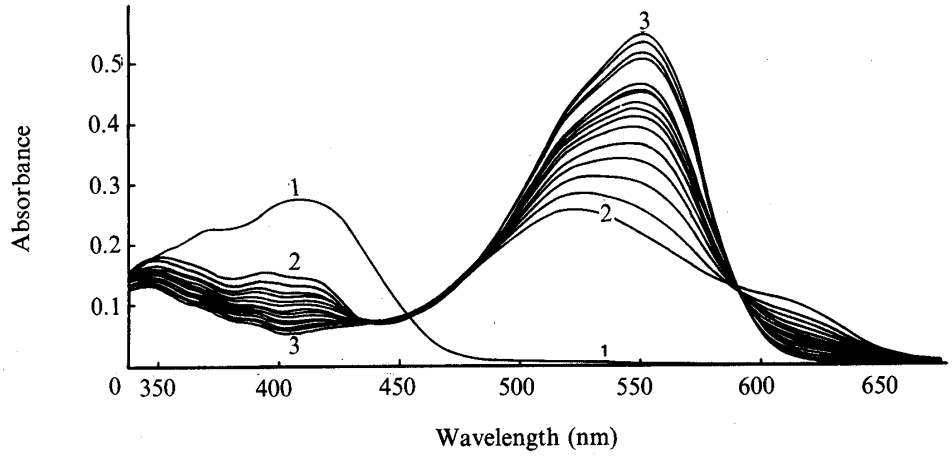


Fig. 6. Visible Absorption Spectra of the Colored Substance **9** in DMSO

1, without morpholine; 2, 3, in the presence of morpholine ranging from $C_B = 1 \times 10^{-4}$ M to $C_B = 1$ M.

coloration was found. It seems that piperidine is required as a catalyst at the cyclization step from **10** (or **11**) to **9**.

Acid-Base Equilibria of the Colored Substance

Compound **9** does not take its color at 550 nm in DMSO alone, but requires a strong base such as piperidine. It was shown here that piperidine served not only as a catalyst for the color reaction but also as an ionization (or dissociation) promoter of the colored product. The result suggests that ionized forms of the two phenol moieties participate in the coloration.

The absorption spectrum of **9** in DMSO changed on addition of various amounts of *N*-ethylmorpholine (p*K*a 7.67) and a new absorption at 520 nm appeared, as shown in Fig. 5. The absorbance increased with increasing base concentration. The spectra showed an isosbestic point (453 nm), suggesting the presence of an acid-base equilibrium. When another base, morpholine (p*K*a 8.35), was added to the DMSO solution of **9**, the color of the solution became red and developed gradually with increasing base concentration, as shown in Fig. 6. The absorption spectra shifted to much longer wavelength than those observed on *N*-ethylmorpholine addition. As the absorbance increased, another isosbestic point (591 nm) was recognized, suggesting the presence of another acid-base equilibrium. The spectra remained almost constant over 0.1 M morpholine, and were in accordance with that observed in piperidine–DMSO solution. Compound **9** presumably formed two kinds of equilibria in the presence of two bases with different basicities due to the ionization (or dissociation) of the two phenol moieties. The results show that the colored species is the dianion of **9** which is formed by the addition of the strong base piperidine (pK_a 11.2).

Acid-base equilibria of **9** were examined by using the spectral data. When **9** is expressed as a dibasic acid H_2X, the following equilibria may exist.

$$H_2X + B \overset{K_1^i}{\rightleftharpoons} HX^-BH^+ \overset{K_1^d}{\rightleftharpoons} HX^- + BH^+ \qquad \text{(Eq. 1)}$$

$$HX^-BH^+ + B \overset{K_2^i}{\rightleftharpoons} X^{2-}(BH^+)_2 \overset{K_2^d}{\rightleftharpoons} X^{2-} + 2BH^+ \qquad \text{(Eq. 2)}$$

(B: base)

The spectra in Fig. 5 obtained by addition of *N*-ethylmorpholine satisfied the quantitative relation shown in the equation,

$$K_1^i = \frac{[HX^-BH^+]}{[H_2X][B]} = \frac{A - A_{H_2X}}{(A_{HA^-BH^+} - A)C_B} \qquad (1)$$

where A: absorbance of the equilibrium mixture

A_{H_2X}: absorbance of the unchanged species

$A_{HX^-BH^+}$: absorbance of the monoanion

C_B: analytical concentration of *N*-ethylmorpholine

On the other hand the spectra in Fig. 6 obtained by addition of morpholine satisfied the following equation.

$$K_2^i = \frac{[X^{2-}(BH^+)_2]}{[HX^-BH^+][B]} = \frac{A - A_{HX^-BH^+}}{(A_{X^{2-}(BH^+)_2} - A)C_B} \qquad (2)$$

where $A_{X^{2-}(BH^+)_2}$: absorbance of the dianion.

The spectral data were thus explained in terms of two ionizations in two steps. It was concluded that the color of **9** at 550 nm was due to the ionized form ($X^{2-}(BH^+)_2$) which was formed through the two ionization equilibria.

The color reaction mechanism was thus elucidated by using a simple model compound, glycinemonomethylamide. Although the result is not described in this paper, a colored

substance analogous to **9** was isolated from the reaction of glycylglycine ethyl ester and DBSA, and was shown to have the same chromophoric structure as **9**. We consider that the assay method established for the drug **1** is likely to be extensively applicable to other compounds having a glycinamide moiety.

Experimental

Apparatus——The absorption spectra were measured with a Shimadzu UV-190 spectrophotometer. IR spectra were measured with a JASCO DS-403G spectrophotometer. The ^{1}H-NMR spectra were taken with a Varian EM-360 spectrometer operated at 60 MHz and the ^{13}C-NMR spectra were taken with a Varian XL-100-12A spectrometer operated at 25.2 MHz. Chemical shifts are expressed as ppm downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The mass spectra (MS) were recorded with a Hitachi M-68 spectrometer.

Preparation of Glycinedimethylamide Hydrochloride (6)——A solution of *N*-(*tert*-butoxycarbonyl)-glycinesuccinimide ester (0.5 g, 1.8 mM) in acetonitrile (50 ml) was treated with 0.1 ml of 50% aqueous dimethylamine solution. The mixture was stirred at room temperature for 3 h, then the solvent was evaporated off under reduced pressure, and the residue was dissolved in AcOEt (1000 ml). The solution was washed with 0.1 M $NaHCO_3$ (25 ml) and H_2O (100 ml), then dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in AcOEt (5 ml) containing HCl (*ca.* 2 N). The solution was allowed to stand for 2.5 h at room temperature. Ether was added to give a white crystalline precipitate. Recrystallization from absolute EtOH–ether afforded 0.16 g (65%) of **6** as white needles (very hygroscopic). *Anal.* Calcd for $C_4H_{11}ClN_2O \cdot 1/4H_2O$: C, 33.57; H, 8.10; N, 19.58. Found: C, 33.85; H, 7.97; N, 19.72. IR ν_{max}^{Nujol} cm^{-1}: 3440, br, 2700—1980, 1655. ^{1}H-NMR (CD_3OD) δ: 2.97 (3H, s, N–C$\underline{H}_3$), 3.00 (3H, s, N–C$\underline{H}_3$), 3.92 (2H, s, –C$\underline{H}_2$).

Glycinemonomethylamide (**3**) was synthesized in the same manner as described for the preparation of **6**. mp 159—160 °C. *Anal.* Calcd for $C_3H_9ClN_2O$: C, 28.93; H, 7.28; Cl, 28.46; N, 22.49. Found: C, 28.70; H, 7.33; Cl, 28.28; N, 22.62.

Preparation of Schiff-Base of Glycinemonomethylamide (5)——3,5-Dibromosalicylaldehyde (4 mM) was added to a solution of glycinemonomethylamide hydrochloride (4 mM) dissolved in an equivalent amount of 0.1 N CH_3ONa (in MeOH), and the mixture was stirred at room temperature for 1 h. The yellow crystalline precipitate was filtered off. Recrystallization from CH_2Cl_2–EtOH afforded 0.75 g (54%) of yellow needles, mp 174.5—175.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3420, 3296, 1657. ^{1}H-NMR (DMSO-d_6) δ: 2.66 (3H, d, J = 5 Hz, –NHC$\underline{H}_3$), 4.32 (2H, s, –C$\underline{H}_2$), 7.57 and 7.82 (1H, d, J = 2.5 Hz, aromatic ring), 8.12 (1H, br, –N$\underline{H}$CH$_3$), 8.53 (1H, s, –N=C$\underline{H}$–). *Anal.* Calcd for $C_{10}H_{10}Br_2N_2O_2$: C, 34.32; H, 2.88; Br, 45.66; N, 8.00. Found: C, 34.20; H, 2.83; Br, 45.46; N, 7.76.

Isolation of the Colored Substance (9)——A solution of glycinemonomethylamide hydrochloride (2.5 g, 0.02 M) in DMSO (50 ml) was treated with 11.24 g of 3,5-dibromosalicylaldehyde (0.04 M) and piperidine (25 ml). The mixture was heated at 100 °C for 2 h, then the piperidine was evaporated off under reduced pressure. After cooling, the residue was poured into a stirred solution of 1 N HCl (1000 ml). The resulting precipitate was washed with H_2O and chromatographed on a silica gel column, eluting with benzene and $CHCl_3$, successively. The eluate with $CHCl_3$ gave a crude yellow product (0.5 g). Recrystallization from EtOH gave **9** (0.21 g) as an amorphous yellow powder. mp 267—271 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3274, 1714, 1636. ^{1}H-NMR (DMSO-d_6) δ: 3.08 (3H, s, N–C$\underline{H}_3$), 7.43 (1H, s, >C=C$\underline{H}$–), 7.76, 7.87, 8.07, 8.21 (1H, d, J = 2.5 Hz, aromatic ring). ^{13}C-NMR (DMSO-d_6) δ: 27.9 (q, N–$\underline{C}$H$_3$), 110.6 (s), 111.1 (s), 113.5 (s), 113.6 (s), 118.7 (s), 123.6 (s), 124.3 (d, >C=$\underline{C}$H–), 131.6 (d), 135.7 (d), 135.9 (s, >$\underline{C}$=CH–), 137.4 (d), 138.0 (d), 152.2 (s), 153.5 (s), 159.1 (s), 167.8 (s, $\underline{C}$=O). MS m/z: 606 (M^+). *Anal.* Calcd for $C_{17}H_{10}Br_4N_2O_3$: C, 33.48; H, 1.65; Br, 52.41; N, 4.59. Found: C, 33.43; H, 1.72; Br, 52.16; N, 4.66.

Isolation of the Colored Substance (12)——A solution of 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide (1 g) in DMSO (80 ml) was treated with 2.24 g of 3,5-dibromosalicylaldehyde and piperidine (20 ml). The mixture was heated at 70 °C for 2.5 h, then the piperidine was evaporated off under reduced pressure at 100 °C. After cooling, the oily residue was dissolved in benzene (50 ml) and the solution was poured into *n*-hexane (1000 ml) with stirring. The resulting powder was purified by preparative thin layer chromatography on silica gel with benzene–EtOH–*n*-hexane (20 : 1 : 1) as a developer. The colored substance was collected and recrystallized from EtOH–Et_2O–CH_2Cl_2 to give **12** (0.1 g) as an amorphous yellow powder. mp 220 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3440, 3070, 2930, 1730, 1680, 1645. ^{1}H-NMR (DMSO-d_6) δ: 2.73 (3H, d, J = 5 Hz, N–C$\underline{H}_3$), 4.08 (2H, br, –C$\underline{H}_2$–), 7.30 (1H, s, >C=C$\underline{H}$–), 7.44—7.77 (8H, m, aromatic ring), 7.85, 7.93, 8.03, 8.26 (1H, d, J = 2.5 Hz, aromatic ring). *Anal.* Calcd for $C_{32}H_{19}Br_4Cl_2N_3O_5 \cdot 1/2H_2O$: C, 41.54; H, 2.18; Br, 34.54; Cl, 7.66; N, 4.56. Found: C, 41.64; H, 2.18; Br, 34.22; Cl, 7.59; N, 5.19. MS m/z: 911 (M^+).

Methylation of the Colored Substance——A mixture of **9** (0.3 g), 50 ml of acetone, powdered anhydrous K_2CO_3 (0.27 g) and methyl iodide was refluxed for 8 h. After removal of the solvent under reduced pressure, H_2O was poured onto the residue. The suspension was filtered and dried. Chromatography on silica gel using $CHCl_3$ as an eluent gave

the methyl derivative (0.21 g, 66%) as yellow needles. mp 176—178 °C. IR ν_{max}^{KBr} cm^{-1}: 3070, 2930, 1722, 1640. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (3H, s, N–C<u>H</u>$_3$), 3.80 and 3.87 (3H, s, –OC<u>H</u>$_3$), 7.53 (1H, s, >C=C<u>H</u>–), 7.66, 7.71, 7.92, 8.93 (1H, d, J=2.5 Hz, aromatic ring). MS m/z: 634 (M^+). *Anal.* Calcd for $C_{19}H_{14}Br_4N_2O_3$: C, 35.77; H, 2.21; Br, 50.10; N, 4.39. Found: C, 35.53; H, 2.30; Br, 50.13; N, 4.47.

Measurement of Visible Absorption Spectra——a) *N*-Ethylmorpholine: Accurately weigh about 2.5 mg of **9** into a 25-ml volumetric flask, then dissolve it in, and dilute to the mark with, CH_2Cl_2 (stock solution). Pipet 1 ml of the stock solution into a 10-ml volumetric flask and evaporate off the solvent in a stream of nitrogen. Dissolve the residue in DMSO and dilute to the mark with DMSO.

Separately, dissolve a similar evaporation residue in, and dilute to the mark with, *N*-ethylmorpholine–DMSO solution ($5\times10^{-5}-2.5\times10^{-1}$ M) or with 0.1 M morpholine in DMSO. Measure the visible absorption spectra using DMSO as the blank.

b) Morpholine: Proceed as directed for *N*-ethylmorpholine. After evaporation, dissolve the residue in, and dilute to the mark with, morpholine–DMSO solution ($1\times10^{-4}-1$ M).

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References

1) Part I: R. Ikenishi, T. Kitagawa, and E. Hirai, *Yakugaku Zasshi*, **101**, 532 (1981).
2) R. Ikenishi, T. Kitagawa, and E. Hirai, *Chem. Pharm. Bull.*, **32**, 748 (1984).
3) A. Sakurai and H. Midorikawa, *J. Org. Chem.*, **34**, 3612 (1969).
4) A. Fujimoto and A. Sakurai, *Synthesis*, **12**, 871 (1977).
5) R. K. Gupta and M. V. George, *Ind. J. Chem.*, **15B**, 223 (1977).