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Studies on 1,4-Benzothiazines. I. Synthesis of 2,3-Dihydro-3-imino-4*H*-1,4-benzothiazines and Acetylation of the N-Methyl Derivative

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o-Amino-S-cyanomethylthiophenol (**1**) obtained by the reaction of *o*-aminothiophenol with monochloroacetonitrile was converted to 2,3-dihydro-3-imino-4*H*-1,4-benzothiazine (**2**). Furthermore, the N-methyl derivative (**6**) was prepared from *o*-(formyl-methylamino)-S-cyanomethylthiophenol (**5**) which was obtained by the reaction of benzothiazolium iodide (**4**) with monochloroacetonitrile under basic conditions. Acetylation of **6** was attempted. The compound **6** (base) was acetylated with acetic anhydride in pyridine at room temperature to give the acetylimino compound (**9**) by the usual reaction. Unexpectedly, heating under reflux of the hydrochloride of **6** in acetic anhydride afforded a new ring system compound, 8,15-diazaphenothiazino[8,7-*h*]phenothiazine derivative (**10**) in fair yield. The last reaction gave a small amount of two by-products, which proved to be *o*-(acetyl-methylamino)-S-acetylcarbamoylmethylthiophenol (**11**) and 2,3-dihydro-4-methyl-4*H*-1,4-benzothiazin-3-one (**12**), respectively.

Keywords——benzothiazolium salt; 3-imino-1,4-benzothiazine derivatives; acetylation; acetylation accompanied with dimerization; new ring-system compound; diazaphenothiazinophenothiazine derivative; by-product; hydrolysis

During the course of an investigation of the synthesis and reaction of 1,4-benzothiazines, 2,3-dihydro-3-imino-4*H*-1,4-benzothiazine derivatives were prepared and acetylation of the N-methyl derivative (**6**) was investigated.

In 1955, Riolo[2] reported obtaining a product by the reaction of *o*-aminothiophenol with monochloroacetonitrile in alkali medium which was assumed to be 2,3-dihydro-3-imino-4*H*-1,

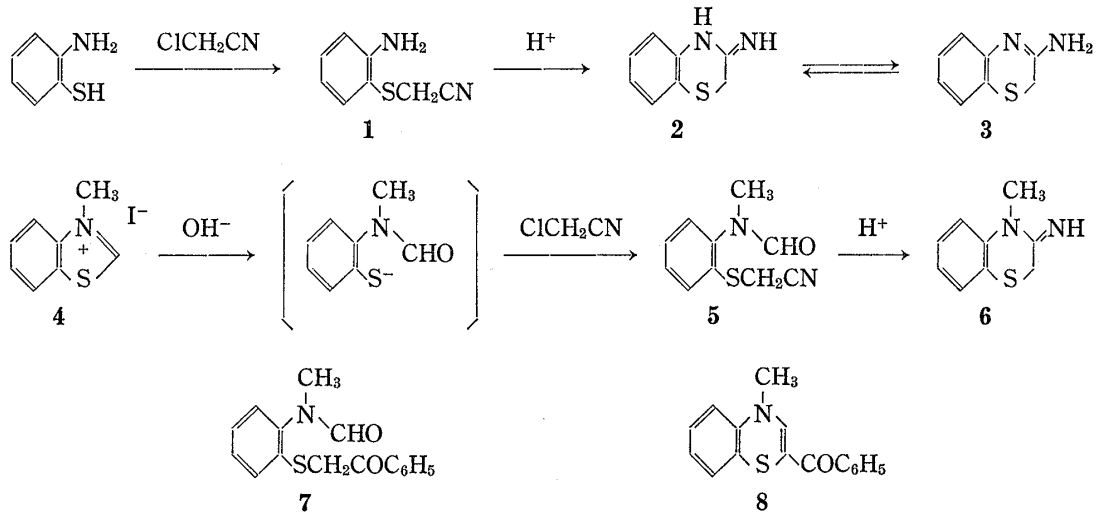

Chart 1

1) Location: *2-10-65, Kawai, Matsubara, Osaka*; *a*) Present address: *Shizuoka College of Pharmacy, 2-2-1, Oshika, Shizuoka.*

2) C.B. Riolo, *Ann. Chim.* (Rome), **45**, 1174 (1955) [*C.A.*, **51**, 5094*f* (1957)].

4-benzothiazine (**2**). We attempted the preparation of **2** according to Riolo's method. The resulting product, however, could not be denoted **2** but as an intermediate, *o*-amino-S-cyanomethylthiophenol (**1**) to **2**, because its infrared (IR) spectrum showed the existence of C≡N by the absorption band at 2250 cm^{-1} and acid treatment of the compound **1** readily produced **2**. The structure of **2** was confirmed by IR and nuclear magnetic resonance (NMR) spectral data, elemental analysis and by elemental analysis of the picrate.

The NMR spectrum of the hydrochloride of **2** exhibited three singlets at δ 13.15 (1H), 10.60 (1H) and 9.48 (1H) which disappeared with deuterium exchange. Two of these signals are attributable to two NH groups, while a signal of NH_2 group is not observed. As the result, the hydrochloride of **2** seems to be fixed in imino form (**2**) and not amino form (**3**), a possible tautomer of **2**.

The N-methyl derivative (**6**) was derived from *o*-(formyl-methylamino)-S-cyanomethylthiophenol (**5**) obtained by the reaction of N-methylbenzothiazolium iodide (**4**) with monochloroacetonitrile. Synthesis of 2-benzoyl-4-methyl-4*H*-1,4-benzothiazine (**8**) *via* *o*-(formylmethylamino)-S-phenacylthiophenol (**7**) prepared from **4** and phenacyl bromide has been described as the analogous reaction by Friedlich *et al.*[3] Monochloroacetonitrile instead of phenacyl bromide readily reacted with **4** under basic conditions to give **5**, an analogue of **7**. Although Friedlich *et al.* obtained **8** by alkali treatment of **7**, thin-layer chromatography (TLC) showed that similar treatment of **5** only resulted in several spots of some products without isolation of the corresponding thiazine compound. On the other hand, as expected, refluxing a solution of **5** in HCl–ethanol afforded the hydrochloride of 2,3-dihydro-3-imino-4-methyl-4*H*-1,4-benzothiazine (**6**); the structure of which was evidenced by its spectral data and elemental analysis.

Next, acetylation of **6** was carried out. When **6** (base) was treated with acetic anhydride in pyridine at room temperature, acetylimino compound **9** was obtained. However heating under reflux of the hydrochloride of **6** in acetic anhydride did not afford **9**, but TLC of the reaction mixture showed the unknown compound **10** which appeared as yellow needles, accompanied by two by-products (**11** and **12**) which only appeared as spots. As similar treatment of the base instead of the hydrochloride did not result in **10**, this reaction seems to be catalyzed by a mineral acid such as hydrochloric acid. Mass spectral data (M^+ *m/e* 428) and elemental analysis of **10** agreed with the molecular formula $C_{24}H_{20}N_4S_2$. We think that the 24 carbons represent the addition of 6 carbons from 3 acetyl cations to 18 carbons corresponding to two molecules of the original compound **6**. In the NMR spectrum, there appeared two singlets attributable to two N–CH_3 at δ 3.43 and 3.62, two singlets attributable

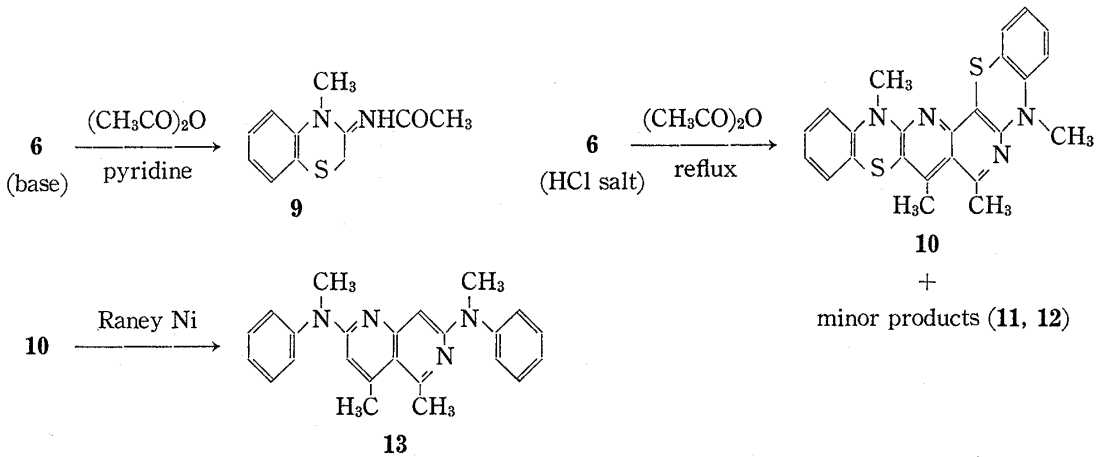

Chart 2

3) W. Friedlich, F. Hröhnke, and P. Schiller, *Chem. Ber.*, **98**, 3804 (1965).

to two C–CH_3 on aromatic rings at δ 2.57 and 2.83, and signals of eight aromatic protons at 6.7—7.4.

In view of these fact, the structure of **10** was determined to be 6,7,9,16-tetramethyl-8,15-diazaphenothiazino[8,7-*h*]phenothiazine. This conclusion suggests that heating of the hydrochloride of **6** in acetic anhydride resulted in dimerization of a probable intermediate formed during the heating process.

On desulfurization with Raney Ni compound **10** afforded, as expected, 2,7-bis(N-methylanilino)-4,5-dimethyl-1,6-naphthyrizine (**13**), whose structure was confirmed by NMR spectral data and elemental analysis.

Acetylation of **6** (HCl salt) failed to isolate the by-products **11** and **12**, however, we found that each of these by-products could be obtained as pure crystals when the reaction condition was suitably altered. When **6** (HCl salt) in a large excess of acetic anhydride was heated in a water bath for 30 min, TLC of the reaction mixture suggested the formation of **11** and **12** rather than formation of **10**. After removal of excess acetic anhydride from the reaction mixture, the residue was dissolved in water and extracted with ethyl acetate. Evaporation of the ethyl acetate left a solid mass, which was fractionated by treatment with benzene. The insoluble substance in benzene was purified and characterized. The NMR spectrum

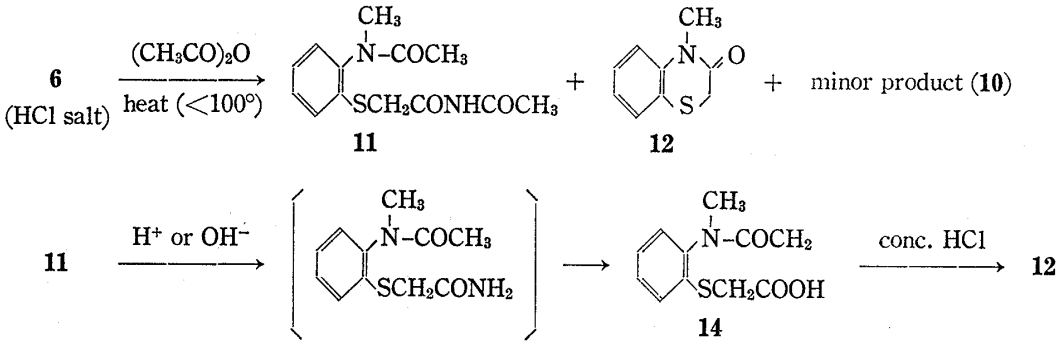

Chart 3

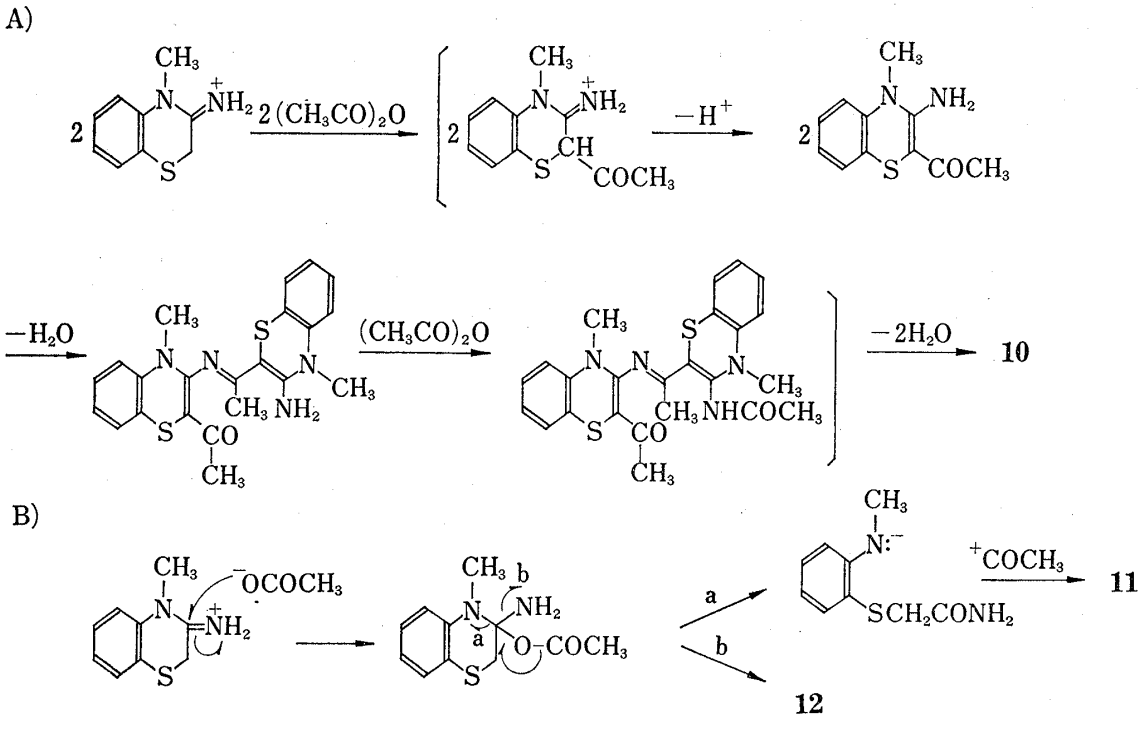

Chart 4

exhibited a singlet attributable to $-CH_2-$ at δ 3.95, and two singlets attributable to two different $-COCH_3$ at δ 1.82 and 2.35, while the IR spectrum exhibited absorption bands at 1735 cm^{-1}, 1640 cm^{-1} and 3150 cm^{-1}; these absorption bands indicate the existence of two carbonyl groups and an imino group. Consequently, compound **11** was assumed to be *o*-(acetyl-methylamino)-S-acetylcarbamoylmethylthiophenol, whose structure was confirmed by elemental analysis and mass spectral data (M^+ *m/e* 280).

The benzene solution was chromatographed on silica gel, and the eluate gave a product whose structure was identified as 2,3-dihydro-4-methyl-4*H*-1,4-benzothiazin-3-one (**12**) by NMR and IR spectral data and elemental analysis.

Compound **11** was hydrolyzed in dil. HCl to give an acidic compound, *o*-(acetyl-methylamino)-S-hydroxycarbonylmethylthiophenol (**14**). The structure of **14** was confirmed by spectral data and elemental analysis. The residual acetyl group which was not hydrolyzed under the above reaction condition was eliminated by refluxing in conc. HCl for 6 hr and afforded the lactam (**12**), as expected.

Although the reaction process from 6 (HCl salt) to **10** has not been sufficiently elucidated, we posit that acetylation at the 2-position of **6**, formation of an enamine by condensation between two molecules of the resulting acetate and further ring-closure of the enamine by intramolecular dehydration, probably occurred as shown in Chart 4 A). Formation of **11** and **12** may occur *via* the reaction process shown in Chart 4 B).

Our expectation that compound **11** or **12** is a precursor to **10** was negated by the fact that heating of **11** and/or **12** with acetic anhydride did not afford compound **10.**

Experimental[4]

***o*-Amino-S-cyanomethylthiophenol Hydrochloride** (**1**)——Monochloroacetonitrile (18 g) was added drop-wise to a stirred ice-cold solution of *o*-aminothiophenol (25 g) in 10% NaOH and stirring was continued for 2.5 hr. The reaction mixture was extracted with $CHCl_3$, the organic layer washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. Addition of conc. HCl to the residue gave a crystalline product. After washing with EtOH, the product was recrystallized from H_2O to give **1** (30 g, 75%) as colorless leaflets. mp 152°. *Anal.* Calcd. for $C_8H_9ClN_2S$: C, 47.87; H, 4.53; N, 13.96. Found: C, 47.86; H, 4.75; N, 13.76. IR ν_{max}^{KBr} cm^{-1}: 2250 (C≡N). NMR (DMSO-d_6) δ: 4.18 (2H, s, $-C\underline{H}_2-$), 8.85 (3H, s, $^+N\underline{H}_3$ disappeared on deuterium exchange with D_2O).

2,3-Dihydro-3-imino-4*H*-1,4-benzothiazine (**2**)——A solution of **1** (30 g) in 5% HCl–EtOH (400 ml) was heated under reflux for 1 hr. After evaporation of the solvent, the residue was crystallized by addition of H_2O and the crude crystals were recrystallized from H_2O–EtOH to give the hydrochloride of **2** (18.6 g, 62%) as colorless prisms. mp 168—170°. *Anal.* Calcd. for $C_8H_9ClN_2S$: C, 47.87; H, 4.53; N, 13.96. Found: C, 47.93; H, 4.61; N, 14.03. NMR (DMSO-d_6) δ: 4.06 (2H, s, $-C\underline{H}_2-$), 9.48, 10.50, 13.15 (each 1H, s, $N\underline{H}\times2$, and $\underline{H}Cl$ disappeared on deuterium exchange with D_2O). The base: colorless prisms (from ethyl acetate). mp 161—165°. *Anal.* Calcd. for $C_8H_8N_2S$: C, 58.50; H, 4.92; N, 17.06. Found: C, 58.38; H, 5.00; N, 17.03. NMR (DMSO-d_6) δ: 3.16 (2H, s, $-C\underline{H}_2-$), 6.6—7.2 (4H, m, aromatic protons, and 2H, $N\underline{H}\times2$ or NH_2 disappeared on deuterium exchange with D_2O). The picrate: yellow needles (from $CHCl_3$). mp 227—230°. *Anal.* Calcd. for $C_{14}H_{11}N_5O_7S$: C, 42.74; H, 2.82, N, 17.81. Found: C, 42.83; H, 2.89; N, 17.84.

***o*-(Formyl-methylamino)-S-cyanomethylthiophenol** (**5**)——N-methylbenzothiazolium iodide (**4** 33 g) was dissolved in 10% NaOH (80 ml). Monochloroacetonitrile (7.4 g) was added drop-wise to the above solution, the mixture stirred for 40 min and pH adjusted to 8—10 by the addition of 10% NaOH during the reaction. The crystals formed in the reaction mixture were separated by filtration and recrystallized from EtOH to give **5** (19.5 g, 75.5%) as colorless needles. mp 90°. *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.14; H, 4.89; N, 13.28. IR ν_{max}^{KBr} cm^{-1}: 2260 (C≡N). NMR (DMSO-d_6) δ: 3.25 (3H, s, $N-C\underline{H}_3$), 3.60 (2H, s, $-C\underline{H}_2-$), 8.20 (1H, s, $-C\underline{H}O$).

2,3-Dihydro-3-imino-4-methyl-4*H*-1,4-benzothiazine (**6**)——Compound **5** (20 g) was added to a solution of EtOH (200 ml) containing conc. HCl (20 ml) and the mixture heated under reflux for 30 min. The solvent was evaporated to dryness *in vacuo* and the residual substance recrystallized from EtOH to give **6** (HCl salt, 14.7 g, 70%) as colorless needles. mp 257°. *Anal.* Calcd. for $C_9H_{11}ClN_2S$: C, 50.35; H, 5.16; N, 13.05. Found: C, 50.59; H, 5.05; N, 13.06. NMR (DMSO-d_6) δ: 3.62 (3H, s, $N-C\underline{H}_3$), 4.06 (2H, s, $-C\underline{H}_2-$), 10.50 (2H, s, $N\underline{H}_2$ disappeared on deuterium exchange with D_2O). A solution of **6** (HCl salt, 10 g) in 50 ml water

4) Not all melting points are corrected.

was made alkaline with 10% NaOH under cooling and the solution extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure to give **6** (base, 6.7 g) as a yellow oil. bp_5 148—152°. NMR (DMSO-d_6) δ: 3.40 (3H, s, N–C$\underline{H}_3$), 3.56 (2H, s, –C$\underline{H}_2$–), 7.57 (1H, s, N$\underline{H}$ disappeared on deuterium exchange with D_2O).

Acetylation of 6 (Base)——Compound **6** (base, 2 g) was dissolved in pyridine (10 ml), acetic anhydride (5 ml) was added to the solution and after standing for 24 hr at room temperature, the solvent was evaporated *in vacuo*. The resulting semi-crystalline solid was recrystallized from EtOH to give **9** (1.2 g, 52%) as colorless prisms. mp 99—102°. *Anal.* Calcd. for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.24; H, 5.43; N, 12.46. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O). NMR (DMSO-d_6) δ: 2.15 (3H, s, =NCOC$\underline{H}_3$), 3.45 (3H, s, N–C$\underline{H}_3$), 3.70 (2H, s, –C$\underline{H}_2$–).

Acetylation of 6 (HCl Salt)——i) A suspension of **6** (HCl salt, 1.0 g) in acetic anhydride (30 ml) was heated under reflux for 1.5 hr. After standing overnight at room temperature, the resulting precipitates were collected and recrystallized from $CHCl_3$ to give **10** (0.51 g, 51.2%) as yellow needles. mp 228—230°. *Anal.* Calcd. for $C_{24}H_{20}N_4S_2$: C, 67.29; H, 4.67; N, 13.08. Found: C, 67.47; H, 4.63; N, 13.28. NMR ($CDCl_3$) δ: 2.57 (3H, s, C_6–C$\underline{H}_3$), 2.83 (3H, s, C_7–C$\underline{H}_3$), 3.43, 3.62 (each 3H, s, N–C$\underline{H}_3\times2$), 6.7—7.4 (8H, m, aromatic protons). MS *m/e*: 428 (M^+).

ii) A suspension of **6** (HCl salt, 10 g) in acetic anhydride (800 ml) was heated on a water bath for 30 min, the excess acetic anhydride evaporated *in vacuo*, and the residue dissolved in water. The water solution was extracted with ethyl acetate, and the extract was dried over Na_2SO_4. Evaporation of the solvent left a crystalline substance which was washed with benzene and water. The resulting substance was recrystallized from benzene to give **11** (2.3 g, 17.6%) as colorless prisms. mp 129°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.69; H, 5.75; N, 9.99. Found: C, 55.61; H, 5.73; N, 9.83. IR ν_{max}^{KBr} cm^{-1}: 1690, 1735 (C=O×2), 3150 (NH). NMR (DMSO-d_6) δ: 1.82, 2.35 (each 3H, s, COC$\underline{H}_3\times2$), 3.20 (3H, s, N–C$\underline{H}_3$), 3.95 (2H, s, –C$\underline{H}_2$–), 9.51 (1H, s, N$\underline{H}$ disappeared on deuterium exchange with D_2O). MS *m/e*: 280 (M^+). The above benzene solution used for washing the crude crystals was dried over Na_2SO_4, and concentration of the solution left a brownish residue which was chromatographed over silica gel. Elution with benzene gave a crystalline substance which recrystallized from CCl_4 to give **12** (2 g, 23%) as colorless leaflets. mp 55°. *Anal.* Calcd. for C_9H_9ONS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.36; H, 4.93; N, 7.97. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (DMSO-d_6) δ: 3.40 (2H, s, –C$\underline{H}_2$–), 3.43 (3H, s, N–C$\underline{H}_3$).

2,7-Bis(N-methylanilino)-4,5-dimethyl-1,6-naphthyridine (13)——A mixture of **10** (0.4 g) and Raney Ni (2.0 g) in benzene (15 ml) was heated under reflux for 12 hr. After filtration, the resulting solution was extracted with 2% HCl, the acidic layer was made alkaline to give yellow precipitates which were recrystallized from MeOH to give **13** (0.07 g) as yellow prisms. mp 134°. *Anal.* Calcd. for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.43; H, 6.51; N, 15.21. NMR (DMSO-d_6) δ: 2.51 (3H, s, C_4–C$\underline{H}_3$), 2.82 (3H, s, C_5–C$\underline{H}_3$), 3.40, 3.48 (each 3H, s, N–C$\underline{H}_3\times2$).

Hydrolysis of 11——i) a) A solution of **11** (0.25 g) in dil. EtOH–HCl (50% EtOH 4 ml+10% HCl 4 ml) was refluxed for 15 min, and concentrated *in vacuo*. The resulting crystalline substance was recrystallized from ethyl acetate to give **14** as colorless prisms. mp 146—149°. *Anal.* Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.24; H, 5.26; N, 5.79. IR ν_{max}^{KBr} cm^{-1}: 1700 (CO_2H) NMR (DMSO-d_6) δ: 1.67 (3H, s, COC$\underline{H}_3$), 3.05 (3H, s, N–C$\underline{H}_3$), 3.90 (2H, s, –C$\underline{H}_2$–), 12.90 (1H, s, $CO_2\underline{H}$ disappeared on deuterium exchange with D_2O). b) A suspension of **14** (0.2 g) in conc. HCl (3 ml) was heated under reflux for 6 hr. After cooling, the resulting precipitates were recrystallized from CCl_4 to give colorless leaflets which were identified as **12**.

ii) A solution of **11** (0.2 g) in dil. EtOH–KOH (50% EtOH 2 ml+10% KOH 2 ml) was allowed tc stand for 15 min at room temperature. After evaporation of the solvent, the residue was treated with dil. HCl to yield a crystalline substance which was recrystallized to give colorless prisms identified as **14**.

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