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Studies on 1,4-Benzothiazines. II.[1] Acetylation of 2,3-Dihydro-3-imino-4H-1,4-benzothiazine[2]

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In a previous paper,[1] we described the formation of the 8,5-diazaphenothiazino[8,7-*h*]-phenothiazine derivative (**2**) by acetylation of 2,3-dihydro-3-imino-4-methyl-4H-1,4-benzothiazine (**1a**). This paper deals with the acetylation of the desmethyl derivative (**1b**).

When a suspension of **1b** in acetic anhydride was heated under reflux for 2 hr, the bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine derivative (**5a**) was obtained instead of the expected analog of **2**. The structure of **5a** was assigned on the basis of infrared, nuclear magnetic resonance and mass spectral data, and microanalysis. Treatment of **5a** with Raney Ni afforded the desulfurized compound **6**, which was identical with an authentic sample prepared by acetylation of 2,6-dianilino-4-picoline (**7**).

Deacetylation of **5a** was attempted, and the monoacetyl compound **5b** and the deacetyl compound **5c** were obtained.

Keywords——2,3-dihydro-3-imino-4H-1,4-benzothiazine·HCl; acetylation; acetic anhydride; bis[1,4]benzothiazino[3,2-*b*: 2′,3′-*e*]pyridine derivatives; desulfurization; 2,6-bisacetanilino-4-picoline; deacetylation

We previously studied the acetylation of 2,3-dihydro-3-imino-4-methyl-4H-1,4-benzothiazine (**1a**), and found that heating of the hydrochloride of **1a** in acetic anhydride under reflux afforded a new ring system compound, 6,7,9,16-tetramethyl-8,15-diazaphenothiazino[8,7-*h*]-phenothiazine (**2**).[1] In the present paper, we describe the acetylation of the desmethyl derivative, 2,3-dihydro-3-imino-4H-1,4-benzothiazine hydrochloride (**1b**).[1]

First, a suspension of **1b** in acetic anhydride was heated in a water bath for 30 min. Under these reaction conditions, 2,3-dihydro-4H-1,4-benzothiazin-3-one (**3**) was obtained as

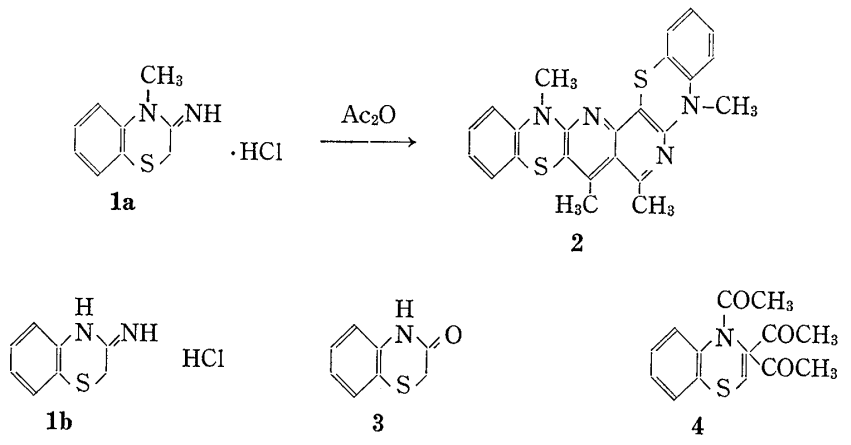


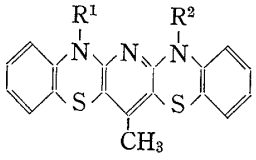
Chart 1

1) Part I: H. Hirano, M. Takamatsu, K. Sugiyama, and T. Kurihara, *Chem. Pharm. Bull.* (Tokyo), **27**, 374 (1979).
2) This work was presented at the Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Nishinomiya, 1978.
3) Location: *2-10-65, Kawai, Matsubara, Osaka, 580, Japan*; *a*) Present address: *Faculty of Pharmaceutical Science, Nagasaki University, 1-14, Bunkyo-machi, Nagasaki, 852, Japan.*

a major product, accompanied by a small amount of 4-acetyl-3-diacetylamino-4H-1,4-benzothiazine (**4**). The infrared (IR) and nuclear magnetic resonance (NMR) spectral data for **4** are shown in Table I.

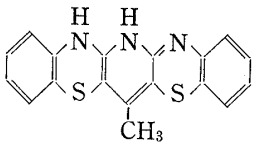
Next, a suspension of **1b** in acetic anhydride was heated under reflux for 2 hr. Thin-layer chromatography of the reaction mixture showed the presence of the unknown compound **5a** and some by-products containing **3**. The unknown compound **5a** was isolated by addition of benzene to the reaction mixture after removal of excess acetic anhydride. It was obtained as colorless prisms with benzene of crystallization. This compound lost the benzene of crystallization on drying at 100° for 1 hr. Previous experiments led us to suspect that **5a** might be an analog of **2**. However, we found that **5a** was not an analog of **2** but was 5,7-diacetyl-13-methyl-5H,7H-bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine, because its mass (MS) spectral data and elemental analysis indicated $C_{28}H_{23}N_3O_2S_2$ as the molecular formula, the IR spectrum exhibited an absorption band due to C=O, and the NMR spectral data showed the presence of a $-CH_3$ group on the aromatic ring and two eq. $-COCH_3$ groups (see Table I). Further experiments were carried out in order to confirm the structure of **5a**. Treatment of **5a** with Raney Ni afforded a desulfurized product **6**, which was recrystallized from benzene to give needles of mp 148°. Its recrystallization from benzene–*n*-hexane, however, gave two kinds of crystals: needles, mp 148°, and prisms, mp 139°. Even though the IR spectrum of the crystals of mp 139° was different from that of the crystals of mp 148° in the solid state, the spectra of both samples showed identical absorption bands in chloroform solutions. Consequently, it was concluded that these two samples were the same compound, notwithstanding the difference in their crystal forms. The structure of **6** was determined to be 2,6-bisacetanilino-4-picoline on the basis of IR and NMR spectral data (see Table I) and comparison with an authentic sample of **6** derived from 2,6-dianilino-4-picoline (**7**).

Although the structure of **5a** was thus confirmed, we cannot account for the difference between the acetylation modes of **1a** and **1b**. Further experiments are in progress.

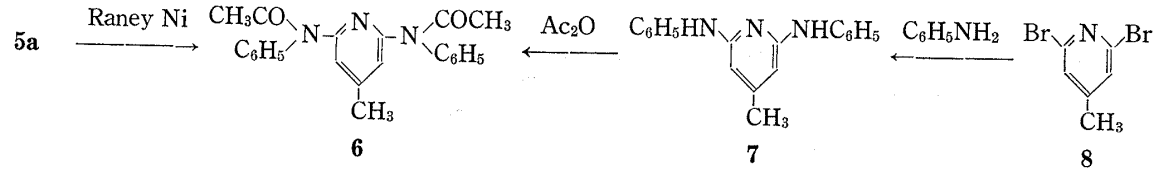


5a—c

5a : $R^1=R^2=-COCH_3$
5b : $R^1=H$, $R^2=-COCH_3$
5c : $R^1=R^2=H$



5d



6 **7** **8**

Chart 2

Finally, deacetylation of **5a** was performed. Treatment of an acetic acid solution of **5a** with hydrochloric acid at room temperature gave a monoacetate, 5-acetyl-13-methyl-5H,7H-bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine (**5b**), while similar treatment of **5a** under heating in a water bath gave 13-methyl-5H,7H-bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine (**5c**). In the latter reaction the hydrochloride of **5c** was crystallized as red needles in the reaction mixture, and its base was obtained as yellow fluorescent needles by treatment of the hydrochloride with triethylamine. The NMR spectrum of **5c** exhibited two singlets at δ 4.80 and 5.91 which disappeared on deuterium exchange. The signal at δ 5.91 (2H) is attributable to the absorption of equivalent N-protons at the 5- and 7-positions. On the other hand,

the signal at δ 4.80 is fairly weak and may be assignable to the N-proton at the 6-position of **5d**, a tautomer of **5c**. This view is supported by the finding that a singlet of the C_{13}–CH_3 group at δ 2.10 is observed as a broad signal (half-width, $w/2=4.5$ Hz).

TABLE I. IR Absorption Bands due to Amide Carbonyl Groups and NMR Chemical Shifts for Compounds **4**, **5a**—**c** and **6**

No.	IR ν_{max}^{KBr} cm^{-1} NCOCH$_3$	Solvent	Chemical shift δ (ppm)
4	1675, 1720	$CDCl_3$	2.09 (3H, s, >NCOC<u>H</u>$_3$), 2.50 (6H, s, $-N<^{COCH_3}_{COCH_3}$), 6.46 (1H, s, C_2–<u>H</u>)
5a	1695	$CDCl_3$	2.35 (6H, s, >NCOC<u>H</u>$_3\times2$), 2.58 (3H, s, C_{13}–C<u>H</u>$_3$)
5b	1660	DMSO-d_6	2.23 (3H, s, >NCOC<u>H</u>$_3$), 2.29 (3H, s, C_{13}–C<u>H</u>$_3$), 9.45[a] (1H, s, >N<u>H</u>)
5c	—	Pyridine-d_5	2.10 (3H, s, C_{13}–C<u>H</u>$_3$), 9.51[a] (2H, s, >N<u>H</u>$\times2$), 4.80[a] (s, weak signal of N-proton at the 6-position of **5d**, a tautomer of **5c**)
6	1675	$CDCl_3$	1.92 (6H, s, >NCOC<u>H</u>$_3\times2$), 2.32 (3H, s, C_4–C<u>H</u>$_3$)

a) Disappeared on deuterium exchange.

Experimental[4]

Acetylation of 2,3-Dihydro-3-imino-4H-1,4-benzothiazine Hydrochloride (**1b**)——A) A suspension of **1b** (24.3 g) in acetic anhydride (400 ml) was heated in a water bath for 30 min. After cooling, the crystalline mass formed in the reaction mixture was collected by filtration, washed with water and recrystallized from benzene to give 2,3-dihydro-4H-1,4-benzothiazin-3-one (**3**, 11.9 g, 60%) as colorless needles, mp 178°. The IR spectrum of **3** was identical with that of an authentic sample prepared by Unger's method.[5] The reaction mixture after removal of **3** was concentrated *in vacuo*, then the residue was dissolved in water and extracted with benzene. The benzene extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a solid product which was recrystallized from benzene to give **4** (1.5 g, 4.3%) as colorless prisms. mp 148—150°. *Anal.* Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.04; H, 4.79; N, 9.68.

B) A suspension of **1b** (15 g) in acetic anhydride (200 ml) was heated under reflux for 2 hr. The reaction mixture was concentrated *in vacuo*. Addition of benzene to the resulting residue afforded a brown precipitate which was recrystallized from benzene–EtOH to give **5a** with benzene of crystallization as colorless prisms. Yield, 3.7 g (20%). mp 276—280° (sinters at 85—100°). *Anal.* Calcd. for $C_{22}H_{17}N_3O_2S_2\cdot C_6H_6$: C, 67.57; H, 4.67; N, 8.45. Found: C, 67.26; H, 4.56; N, 8.61. On heating the above crystals at 100° for 1 hr, a colorless powder was obtained. mp 277—281°. *Anal.* Calcd. for $C_{22}H_{17}N_3O_2S_2$: C, 62.98; H, 4.09; N, 10.02. Found: C, 62.81; H, 4.03; N, 10.25. MS *m/e*: 419 (M^+).

Formation of 6 by the Desulfurization of 5a——A mixture of **5a** (0.5 g), Raney Ni (7 g) and benzene (20 ml) was heated under reflux for 10.5 hr. After removal of the catalyst by filtration, the benzene solution was concentrated *in vacuo*. A small amount of ether was added to the resulting residue to give a solid mass which was chromatographed over silica gel and eluted with benzene–ethyl acetate (1: 1). The eluate was concentrated *in vacuo* to give a crude product which was recrystallized from benzene to afford **6** as colorless needles, mp 148°. *Anal.* Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.54; H, 5.85; N, 11.56. Although recrystallization of **6** from benzene–*n*-hexane gave prisms of mp 139° as well as needles of mp 148°, the IR spectra of both samples were identical in $CHCl_3$ solution.

Preparation of 6 from 2,6-Dibromo-4-picoline——i) 2,6-Dianilino-4-picoline (**7**): The method of Hamana *et al.*,[6] originally used for 2,6-dianilinopyridine, was applied. A mixture of 2,6-dibromo-4-picoline (2.0 g) and aniline hydrochloride (3.2 g) was heated at 210—220° in an oil bath for 3 hr. After cooling, water-insoluble material was isolated and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 20% K_2CO_3, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallization of the residue from petroleum benzine gave **7** (1.9 g, 86.5%) as colorless prisms, mp 101—102°. *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.78; H, 6.08; N, 15.28.

4) Melting points are not corrected.
5) O. Unger, Chem. *Ber.*, **30**, 607 (1897).
6) M. Hamana and M. Yamazaki, *Yakugaku Zasshi*, **81**, 574 (1961).

ii) 2,6-Bisacetanilino-4-picoline (**6**): A mixture of **7** (1 g) and acetic anhydride (0.8 g) was refluxed for 2 hr. The reaction mixture was then concentrated *in vacuo*, and the resulting residue was recrystallized from benzene to give **6** (0.6 g, 46%) as colorless needles, mp 148°. *Anal.* Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.44; H, 5.76; N, 11.67. The IR and NMR spectra of this compound were identical with those of the compound obtained by desulfurization of **5a**.

5-Acetyl-13-methyl-5H,7H-bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine (5b)——Compound **5a** (0.5 g) was dissolved in acetic acid (20 ml) with heating in a water bath. The resulting solution was cooled to room temperature and mixed with concentrated HCl (2 ml). After standing for 5 hr, the mixture was diluted with 20 ml of water, neutralized with 30% K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to leave a crystalline mass, which was recrystallized from $CHCl_3$–*n*-hexane to give **5b** (400 mg, 88.9%) as yellow needles, mp 298—300° (dec.). *Anal.* Calcd. for $C_{20}H_{15}N_3OS_2$: C, 63.66; H, 4.01, N, 11.14. Found: C, 63.44; H, 3.95; N, 11.14.

13-Methyl-5H,7H-bis[1,4]benzothiazino[3,2-*b*; 2′,3′-*e*]pyridine (5c)——A mixture of **5a** (1.5 g), concentrated HCl (5.5 ml) and acetic acid (60 ml) was heated on a water bath for 15 min. The hydrochloride of **5c** formed in the reaction mixture was collected by filtration and washed with EtOH and water. Red needles. Yield, 1 g (83.3%). mp 191—193°. *Anal.* Calcd. for $C_{18}H_{14}ClN_3S_2$: C, 58.13; H, 3.79; N, 11.30. Found: C, 58.19; H, 3.53; N, 11.27. A suspension of the hydrochloride of **5c** (500 mg) in triethylamine (5 ml) was allowed to stand overnight. The product was collected by filtration, washed with water and recrystallized from benzene to give the base of **5c** (360 mg, 80%) as yellow needles, mp 219—221°. *Anal.* Calcd. for $C_{18}H_{13}N_3S_2$: C, 64.45; H, 3.91; N, 12.53. Found: C, 64.20; H, 4.91; N, 12.46.

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Prostaglandin $F_{2\alpha}$ from the Japanese Coastal Gorgonian, *Euplexaura erecta*[1]

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A biologically active substance with contracting activity towards isolated guinea-pig ileum has been isolated from the gorgonian *Euplexaura erecta* collected in Japanese coastal waters, and it was identified as prostaglandin $F_{2\alpha}$. This is the first report of the isolation of prostaglandins from gorgonians obtained outside the Caribbean area.

Keywords——*Euplexaura erecta*; prostaglandin $F_{2\alpha}$; Japanese coast; gorgonian; contracting activity; guinea-pig ileum; soft coral; thin-layer chromatography; mass spectrum

In 1969, Weinheimer and Spraggins[3] reported the surprising discovery of the occurrence of relatively large quantities of two unusual prostaglandins in air-dried specimens of a soft coral, the gorgonian *Plexaura homomalla*, occurring in coastal waters off Florida. These prostaglandins, (15*R*)-PGA_2 (**1**, 0.2% of the dried weight) and its acetate methyl ester (**2**, 1.3%), differ from the previously known prostaglandins isolated from mammalian sources in having the "nonmammalian" *R* configuration at the allylic hydroxyl center.

1) A preliminary report of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1976, Abstracts, II, p. 263.
2) Location: *2-3-10 Surugadai, Kanda, Chiyoda-ku, Tokyo 101, Japan.*
3) A.J. Weinheimer and R.L. Spraggins, *Food-Drugs Sea, Proc. Conf. Drugs Sea*, 2nd, **1969**, 311 (1977); *idem*, *Tetrahedron Lett.*, **1969**, 5185.