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-diaminonilino-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

![Chemical structures](chart1.png)


2) This work was presented at the Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Nishinomiya, 1978.

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a major product, accompanied by a small amount of 4-acetyl-3-diacetylamino-4H-1,4-benzo-
thiazine (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 compo-
und 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°C 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-diacyetyl-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_{25}H_{32}N_{5}O_{2}S_{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°C. Its recrystallization from benzene—n-hexane,
however, gave two kinds of crystals: needles, mp 148°C, and prisms, mp 139°C. Even though
the IR spectrum of the crystals of mp 139°C was different from that of the crystals of mp 148°C
in the solid state, the spectra of both samples showed identical absorption bands in chlo-
roform 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-bisacetoxy-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.

![Chart 2](image)

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 hydro-
chloride 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>
<thead>
<tr>
<th>No.</th>
<th>IR ν_{NCOCH_{3}} cm(^{-1})</th>
<th>Solvent</th>
<th>Chemical shift δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1675, 1720</td>
<td>CDCl(_3)</td>
<td>2.09 (3H, s, &gt;NCOCH(_3)), 2.50 (6H, s, -NCOCH(_3))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.46 (1H, s, C(_\alpha)-H)</td>
</tr>
<tr>
<td>5a</td>
<td>1695</td>
<td>CDCl(_3)</td>
<td>2.35 (6H, s, &gt;NCOCH(<em>3)×2), 2.58 (3H, s, C(</em>\alpha)-CH(_3))</td>
</tr>
<tr>
<td>5b</td>
<td>1660</td>
<td>DMSO-d(_6)</td>
<td>2.23 (3H, s, &gt;NCOCH(<em>3)), 2.29 (3H, s, C(</em>\alpha)-CH(_3)), 9.45(^a) (1H, s, &gt;NH)</td>
</tr>
<tr>
<td>5c</td>
<td></td>
<td>Pyridine-d(_5)</td>
<td>2.10 (3H, s, C(_\alpha)-CH(_3)), 9.51(^a) (2H, s, &gt;NH×2), 4.80(^a) (s, weak signal of N-proton at the 6-position of 5d, a tautomer of 5c)</td>
</tr>
<tr>
<td>6</td>
<td>1675</td>
<td>CDCl(_3)</td>
<td>1.92 (6H, s, &gt;NCOCH(<em>3)×2), 2.32 (3H, s, C(</em>\alpha)-CH(_3))</td>
</tr>
</tbody>
</table>

\(^a\) Disappeared on deuterium exchange.

Experimental\(^4\)

Acetylation of 2,3-Dihydro-3-imino-4H-1,4-benzothiazine Hydrochloride (1b) —— \(\Lambda\) — 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\(_2\)SO\(_4\) 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°. \(\text{Anal. Calcd. for C}_{14}H_{13}N_{2}O_{5}S: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.04; H, 4.79; N, 9.68.}\)

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°). \(\text{Anal. Calcd. for C}_{15}H_{14}N_{2}O_{5}S\(_2\)-C\(_6\)H\(_6\): C, 67.57; H, 4.67; N, 8.45. Found: C, 67.26; H, 4.56; N, 8.81. On heating the above crystals at 100° for 1 hr, a colorless powder was obtained. mp 277—281°. \(\text{Anal. Calcd. for C}_{25}H_{18}N_{2}O_{5}S_{2}: C, 62.98; H, 4.09; N, 10.02. Found: C, 62.81; H, 4.03; N, 10.25. MS m/z: 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°. \(\text{Anal. Calcd. for C}_{22}H_{22}N_{2}O_{5}: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.54; H, 5.83; 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 —— The method of Hamana et al.,\(^6\) originally used for 2,6-dianilino-4-picoline, was applied. A mixture of 2,6-dibromo-4-picoline (2.9 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\(_2\)CO\(_3\), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. Recrystallization of the residue from petroleum benzine gave 7 (1.9 g, 86.5%) as colorless prisms, mp 101—102°. \(\text{Anal. Calcd. for C}_{18}H_{14}N_{2}: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.78; H, 6.08; N, 15.28.}\)

\(^4\) Melting points are not corrected.


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°C. Anal. Calcd. for C_{21}H_{21}N_{2}O_{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_{2}CO_{3} and extracted with CHC_{2}l. The CHCl_{3} solution was dried over anhydrous Na_{2}SO_{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°C (dec.). Anal. Calcd. for C_{29}H_{15}N_{3}O_{3}: 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°C. Anal. Calcd. for C_{27}H_{14}ClN_{2}S_{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 precipitate 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°C. Anal. Calcd. for C_{18}H_{12}N_{2}S_{2}: C, 64.45; H, 3.91; N, 12.53. Found: C, 64.20; H, 4.91; N, 12.46.

Prostaglandin F_{2a} from the Japanese Coastal Gorgonian, Euplexaura erecta

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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_{2a}. This is the first report of the isolation of prostaglandins from gorgonians obtained outside the Caribbean area.

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

In 1969, Weinheimer and Spraggins 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, (15R)-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.