

## Synthesis of Isomelamines and Isocyanurates and Their Biological Evaluation

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Received April 26, 1996; accepted July 22, 1996

The reaction of cyanogen bromide (**1**) with primary amines (**2a–p**), including arylmethanamines (**2l–p**), gave the corresponding cyanamides (**3a–p**). Trimerization of **3a–p** gave 1,3,5-trisubstituted 2,4,6-triimino-1,3,5-triazines (isomelamines) (**4a–p**), which were treated with hydrochloric acid to give the corresponding 1,3,5-trisubstituted 2,4,6-trioxohexahydro-1,3,5-triazines (isocyanurates) (**5a–c, f**) and 1,3,5-trisubstituted 2-imino-4,6-dioxohexahydro-1,3,5-triazines (**5b'–e'**). Biological evaluation of **4a–p**, **5a–c, f**, and **5b'–e'** was carried out, and some of these compounds showed bronchodilator and positive inotropic activities.

**Key words** cyanamide; trimerization; isomelamine; isocyanurate; bronchodilator; positive inotropic activity

Extensive studies have been done on the reaction of cyanogen bromide (**1**) with alkylamines (**2**) to give alkylcyanamides (**3**),<sup>1–7</sup> some of which trimerize to give the corresponding 1,3,5-trialkyl-2,4,6-triimino-1,3,5-triazines (trialkylisomelamines) (**4**).<sup>2,6,7</sup> In 1885, Hofmann<sup>2</sup> obtained ethylcyanamide (**3b**) from the reaction of mercury(II) oxide (or lead(II) oxide) with ethylthiourea, and reported that **3b** thus obtained trimerized readily to triethylisomelamine (**4b**) at room temperature. Mukaiyama *et al.*<sup>7</sup> and Kitawaki and Sugino<sup>8</sup> reported independently that cyanogen bromide (**1**) reacted with amines (**2a, b**) to give cyanamide (**3a, b**). Compounds **3a, b** trimerized in the presence of a basic catalyst to give **4a, b**. It has also been reported<sup>9</sup> that **4a** is obtained in 40% yield by treating 10% cyanamide with 40% caustic soda and dimethyl sulfate. However, only a few reports<sup>10,11</sup> are available concerning such reactions with arylmethanocyanamides. For example, Friedrich and Heimut<sup>10</sup> synthesized tribenzylisomelamine (**4l**) from *N*-cyano-*N*-benzylacetamide.

In view of the above results, we have investigated the trimerization of cyanamides (**3**), in particular those derived from hetarylaminomethylamines. Compounds **3** were subjected to further reaction without purification (Chart 1). First, according to the procedure reported by Hofmann,<sup>2</sup> we carried out the conversion of **3a** to **4a**. When **3a** was allowed to stand at room temperature in ethanol, it was easily transformed to **4a** in a good yield. Similarly, triazines (**4b–p**) were also obtained by the same treatment of cyanamides (**3b–p**). The results are summarized in Table 1. The IR spectra showed the absorption band due to

the imino group at 1590–1620 cm<sup>-1</sup>. In the <sup>1</sup>H-NMR spectra, the signals due to imino protons were observed at 6.06–7.68 ppm (3H, brs). The <sup>13</sup>C-NMR spectra of **4a–p** also supported the triazine structures. Elemental analyses and spectral data for triazines (**4a–p**) are shown in Table 3. Compounds **4a–p** were treated with an acidic catalyst such as hydrochloric acid in water to give the corresponding 1,3,5-trisubstituted 2,4,6-trioxohexahydro-1,3,5-triazines (isocyanurates) (**5a–c, f**), and 1,3,5-trisubstituted 2-imino-4,6-dioxohexahydro-1,3,5-triazines (**5b'–e'**). The above results are summarized in Table 2. The IR spectra of **5a–c, f**, and **5b'–e'** showed the absorption band at 1660–1690 cm<sup>-1</sup>. The <sup>13</sup>C-NMR spectra of **5a–c, f**, and **5b'–e'** also supported the structures. Elemental analyses and spectral data for **5a–c, f**, and **5b'–e'** are shown in Table 3.

The biological activities of the above products were investigated. Compounds **4b, c**, and **5b, c, c'** were found to show both bronchodilator and positive inotropic activities. The biological data for these products are summarized in Tables 4 and 5.

### Experimental

Melting points were determined on a Yanaco model MP apparatus and are uncorrected. IR spectra were taken with a JASCO IR-810 spectrophotometer. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded by using tetramethylsilane as an internal standard on JEOL JNM FX-60 spectrometers at 60 MHz. Chemical shifts (δ) are quoted in parts per million, and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or brs (broad singlet). Mass spectra were recorded with a JEOL JMS-OISG-2 mass spectrometer. Wako gel (C-200) was employed for silica gel column chromatography.

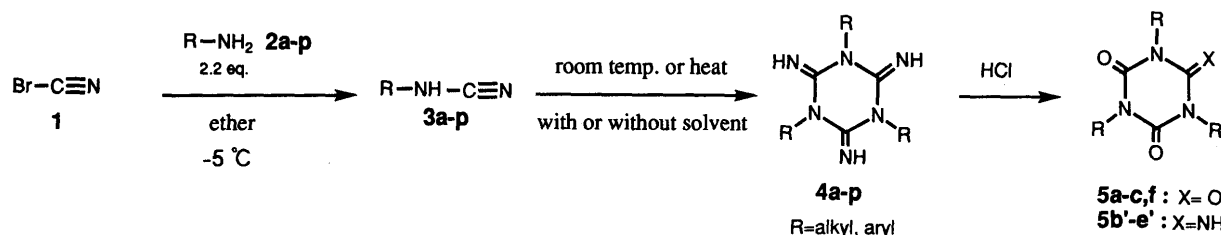


Chart 1

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Table 1. Synthesis of Isomelamines (4) from Cyanamides (3)

| Compd. | R                                                                                   | Reaction conditions   |               |             | Compd.           | Appearance<br>(Recryst. solvent)                 | mp (°C)<br>[lit. mp (°C)]                              | Yield<br>(%) |
|--------|-------------------------------------------------------------------------------------|-----------------------|---------------|-------------|------------------|--------------------------------------------------|--------------------------------------------------------|--------------|
|        |                                                                                     | Solvent               | Temp.<br>(°C) | Time<br>(h) |                  |                                                  |                                                        |              |
| 3a     | Me                                                                                  | EtOH                  | r.t.          | 12          | 4a               | Colorless needles<br>(H <sub>2</sub> O)          | 179—180<br>[178] <sup>9)</sup>                         | 85           |
| 3b     | Et                                                                                  | H <sub>2</sub> O      | 60            | 2           | 4b               | Colorless needles<br>(H <sub>2</sub> O)          | 94—95<br>[ 92] <sup>2)</sup>                           | 74           |
| 3c     | <i>n</i> -Pr                                                                        | EtOH–H <sub>2</sub> O | 50            | 3           | 4c               | Colorless needles<br>(EtOH–H <sub>2</sub> O)     | 87—89                                                  | 61           |
| 3d     | <i>n</i> -Bu                                                                        | EtOH–H <sub>2</sub> O | 50            | 2           | 4d <sup>a)</sup> | Colorless oil                                    |                                                        | 73           |
| 3e     | iso-Bu                                                                              | EtOH–H <sub>2</sub> O | 50            | 3           | 4e               | Colorless needles<br>(Benzene– <i>n</i> -hexane) | 95—96<br>[91—93] <sup>10)</sup>                        | 78           |
| 3f     | CH <sub>2</sub> =CHCH <sub>2</sub>                                                  | EtOH–H <sub>2</sub> O | 50            | 2           | 4f <sup>b)</sup> | Colorless powder                                 | 46—49<br>[bp 105—115 °C/<br>0.026 mmHg] <sup>10)</sup> | 75           |
| 3g     | CH <sub>2</sub> CF <sub>3</sub>                                                     | EtOH–H <sub>2</sub> O | 50            | 3           | 4g               | Colorless prisms<br>(EtOH–H <sub>2</sub> O)      | 163                                                    | 56           |
| 3h     | (CH <sub>2</sub> ) <sub>2</sub> CN                                                  | EtOH–H <sub>2</sub> O | 50            | 1           | 4h               | Pale yellow prisms<br>(Acetone)                  | 160(dec.)                                              | 33           |
| 3i     | (CH <sub>2</sub> ) <sub>2</sub> OEt                                                 | EtOH–H <sub>2</sub> O | 50            | 8           | 4i               | Colorless prisms<br>(AcOEt– <i>n</i> -hexane)    | 56—58                                                  | 26           |
| 3j     | CH <sub>2</sub> CH(OMe) <sub>2</sub>                                                | EtOH–H <sub>2</sub> O | 50            | 4           | 4j <sup>c)</sup> | Colorless oil                                    |                                                        | 86           |
| 3k     | Ph                                                                                  | EtOH                  | Reflux        | 12          | 4k               | Colorless prisms<br>(EtOH)                       | 214—215<br>[210] <sup>12)</sup>                        | 73           |
| 3l     | PhCH <sub>2</sub>                                                                   | EtOH–H <sub>2</sub> O | 50            | 2           | 4l               | Colorless needles<br>(Toluene–cyclohexane)       | 131—132<br>[129—130] <sup>11)</sup>                    | 75           |
| 3m     |   | MeOH                  | Reflux        | 5           | 4m               | Colorless needles<br>(MeOH)                      | 199—200                                                | 52           |
| 3n     |  | EtOH–H <sub>2</sub> O | 50            | 3           | 4n               | Colorless needles<br>(Benzene– <i>n</i> -hexane) | 123—125                                                | 78           |
| 3o     |  | EtOH–H <sub>2</sub> O | 50            | 3           | 4o               | Colorless needles<br>(Benzene–ether)             | 136—137                                                | 94           |
| 3p     |  | EtOH–H <sub>2</sub> O | 50            | 3           | 4p               | Pale yellow needles<br>(H <sub>2</sub> O)        | 157—158                                                | 10           |

a) Purified by column chromatography [*n*-hexane–ethyl acetate (7:3)]. b) Purified by column chromatography [*n*-hexane–ethyl acetate (1:1)]. c) Purified by column chromatography [chloroform–MeOH (99:1)].

Table 2. Synthesis of Isocyanurates (5) from Isomelamines (4)

| Compd. | R                                  | Reaction conditions |          | Compd.            | X  | Appearance<br>(Recryst. solvent)                 | mp (°C)<br>[lit. mp (°C)]          | Yield (%) |
|--------|------------------------------------|---------------------|----------|-------------------|----|--------------------------------------------------|------------------------------------|-----------|
|        |                                    | Temp. (°C)          | Time (h) |                   |    |                                                  |                                    |           |
| 4a     | Me                                 | Reflux              | 4        | 5a                | O  | Colorless prisms<br>(H <sub>2</sub> O)           | 173—175<br>[175—176] <sup>1)</sup> | 87        |
| 4b     | Et                                 | Reflux              | 24       | 5b                | O  | Colorless needles<br>(EtOH)                      | 94—95<br>[95] <sup>2)</sup>        | 58        |
| 4b'    | Et                                 | 80                  | 6        | 5b' <sup>a)</sup> | NH | Colorless needles<br>(MeOH–ether)                | 247—249                            | 64        |
| 4c     | <i>n</i> -Pr                       | Reflux              | 5        | 5c <sup>b)</sup>  | O  | Colorless oil                                    |                                    | 52        |
| 4c'    | <i>n</i> -Pr                       | Reflux              | 5        | 5c'               | NH | Colorless needles<br>(Benzene– <i>n</i> -hexane) | 41                                 | 33        |
| 4d'    | <i>n</i> -Bu                       | Reflux              | 6        | 5d' <sup>a)</sup> | NH | Colorless needles<br>(Benzene– <i>n</i> -hexane) | 220—222                            | 71        |
| 4e'    | iso-Bu                             | Reflux              | 5        | 5e'               | NH | Colorless prisms<br>(Benzene– <i>n</i> -hexane)  | 79—80                              | 80        |
| 4f     | CH <sub>2</sub> =CHCH <sub>2</sub> | Reflux              | 5        | 5f <sup>b)</sup>  | O  | Colorless oil                                    |                                    | 77        |

a) Isolated as the hydrochloride. b) Purified by column chromatography [*n*-hexane–ethyl acetate (9:1)].

**General Procedure for the Synthesis of Cyanamides (3a–p)** To a solution of cyanogen bromide (1) (10.0 g, 94 mmol) in anhydrous ether (200 ml) was added dropwise 2.2 eq of the appropriate amine (2a–p) in anhydrous ether (100 ml) at –5 °C. The mixture was stirred for 1 h under a nitrogen atmosphere at the same temperature, then the precipitate (amine hydrobromide) was filtered off, and the filtrate was concentrated *in vacuo* below 15 °C. The residual cyanamides (3a–p) were used without purification for the next reaction.

**General Procedure for the Synthesis of 1,3,5-Trisubstituted 2,4,6-Triiminohexahydro-1,3,5-triazines (4a–p)** A solution of a cyanamide (3) in the solvent indicated in Table 1 was stirred. The solvent was evaporated off under reduced pressure. The residue was subjected to silica gel column chromatography, and the resulting crystalline product was recrystallized to give 4. The results are summarized in Table 1.

**1,3,5-Trisubstituted 2,4,6-Trioxohexahydro-1,3,5-triazine (5a, b)** A solution of 4a, b (20 mmol) in water (20 ml) was treated with 10 ml of

Table 3. Analytical and Spectral Data for **4a–p**, **5a–c**, **f** and **5b'–e'**

| Compd.                 | Formula                                            | Analysis (%)     |                |                | IR<br>(KBr) $\text{cm}^{-1}$ | $^1\text{H-NMR}$ ( $\text{DMSO-}d_6$ ) $\delta$                              | $^{13}\text{C-NMR}$ ( $\text{DMSO-}d_6$ ) $\delta$                         | MS $m/z$                          |
|------------------------|----------------------------------------------------|------------------|----------------|----------------|------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------|
|                        |                                                    | Calcd            | (Found)        |                |                              |                                                                              |                                                                            |                                   |
|                        |                                                    | C                | H              | N              |                              |                                                                              |                                                                            |                                   |
| <b>4a</b>              | $\text{C}_6\text{H}_{12}\text{N}_6$                | 42.84<br>(42.48) | 7.19<br>7.22   | 49.97<br>50.07 | 3320, 1620                   | 3.28 (9H, s), 6.44 (3H, brs)                                                 | 31.2 (q), 147.0 (s)                                                        | 168 ( $\text{M}^+$ )              |
| <b>4b</b>              | $\text{C}_9\text{H}_{18}\text{N}_6$                | 51.40<br>(50.99) | 8.63<br>8.67   | 39.97<br>39.84 | 3340, 1600                   | 1.09 (9H, t), 3.68–4.20 (6H, m), 6.37 (3H, brs)                              | 11.8 (q), 38.2 (t), 144.6 (brs)                                            | 210 ( $\text{M}^+$ )              |
| <b>4c</b>              | $\text{C}_{12}\text{H}_{24}\text{N}_6$             | 57.11<br>(57.12) | 9.59<br>9.72   | 33.30<br>33.40 | 3380, 1590                   | 0.86 (9H, t), 0.91–1.83 (6H, m), 3.93–4.26 (6H, m), 6.39 (3H, brs)           | 10.9 (q), 19.8 (t), 45.0 (t), 145.8 (s)                                    | 253 ( $\text{M}^+ + 1$ )          |
| <b>4d</b>              | $\text{C}_{15}\text{H}_{30}\text{N}_6$             | 61.18<br>(61.21) | 10.27<br>10.43 | 28.55<br>28.53 | 3395, 1600                   | 0.88–0.97 (9H, m), 1.38 (12H, m), 3.90 (6H, m), 6.31 (3H, brs)               | 13.6 (q), 19.5 (t), 28.6 (t), 43.1 (t), 145.8 (s)                          | 294 ( $\text{M}^+$ )              |
| <b>4e</b>              | $\text{C}_{15}\text{H}_{30}\text{N}_6$             | 61.18<br>(60.81) | 10.27<br>10.71 | 28.55<br>28.19 | 3350, 1600                   | 0.84 (18H, d), 1.67–2.33 (3H, m), 3.50–4.00 (6H, m), 6.46 (3H, brs)          | 19.6 (q), 26.1 (d), 49.5 (t), 146.6 (s)                                    | 295 ( $\text{M}^+ + 1$ )          |
| <b>4f</b>              | $\text{C}_{12}\text{H}_{18}\text{N}_6$             | 58.51<br>(58.34) | 7.37<br>7.65   | 34.12<br>34.05 | 3375, 1600                   | 4.64 (6H, brs), 5.00–5.26 (6H, m), 5.49–6.15 (3H, m), 6.32 (3H, brs)         | 45.5 (t), 115.9 (t), 132.7 (d), 145.3 (s)                                  | 246 ( $\text{M}^+$ )              |
| <b>4g</b>              | $\text{C}_9\text{H}_9\text{N}_6\text{F}_9$         | 29.04<br>(29.03) | 2.44<br>2.45   | 22.58<br>22.55 | 3410, 3390, 1620             | 5.04 (6H, brs), 7.68 (3H, brs)                                               | 43.3–44.6 (m), 121.3–128.0 (m), 143.7 (brs)                                | 372 ( $\text{M}^+$ )              |
| <b>4h</b>              | $\text{C}_{12}\text{H}_{15}\text{N}_9$             | 50.51<br>(50.78) | 5.30<br>5.01   | 44.19<br>43.99 | 3400, 3360, 1610             | 2.50 (6H, m), 4.22 (6H, m), 7.14 (3H, brs)                                   | 14.9 (t), 39.2 (t), 118.4 (s), 143.7 (s)                                   | 285 ( $\text{M}^+$ )              |
| <b>4i</b>              | $\text{C}_{15}\text{H}_{30}\text{N}_6\text{O}_3$   | 52.61<br>(52.70) | 8.83<br>8.96   | 24.54<br>24.70 | 3350, 1610                   | 1.09 (9H, t), 3.38 (6H, q), 3.51 (6H, m), 4.05 (6H, m), 6.64 (3H, brs)       | 15.1 (q), 44.3 (t), 65.8 (t), 67.3 (t), 146.5 (s)                          | 342 ( $\text{M}^+$ )              |
| <b>4j<sup>a)</sup></b> | $\text{C}_{15}\text{H}_{30}\text{N}_6\text{O}_6$   | 46.14<br>(46.33) | 7.75<br>7.96   | 21.53<br>21.73 | 3350, 1620                   | 3.46 (18H, s), 4.03 (6H, brs), 4.38 (3H, t), 6.65 (3H, brs)                  | 48.9 (t), 54.5 (q), 103.2 (d), 148.1 (s)                                   | 390 ( $\text{M}^+$ )              |
| <b>4k</b>              | $\text{C}_{21}\text{H}_{18}\text{N}_6$             | 71.16<br>(71.15) | 5.12<br>4.97   | 23.72<br>23.92 | 3350, 1620                   | 5.05 (3H, brs), 7.49 (15H, brs)                                              | 128.8 (d), 129.7 (d), 129.9 (d), 136.8 (s), 148.1 (s)                      | 354 ( $\text{M}^+$ )              |
| <b>4l</b>              | $\text{C}_{24}\text{H}_{24}\text{N}_6$             | 72.70<br>(72.77) | 6.10<br>6.00   | 21.20<br>21.39 | 3380, 1600                   | 5.30 (6H, s), 6.59 (3H, brs), 7.28 (15H, brs)                                | 46.9 (t), 126.6 (d), 126.8 (d), 128.3 (d), 137.2 (s), 146.3 (s)            | 396 ( $\text{M}^+$ )              |
| <b>4m</b>              | $\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_6$   | 61.36<br>(61.26) | 4.58<br>4.57   | 15.90<br>16.05 | 3375, 1600                   | 3.40 (6H, s), 5.05, 5.18 (6H, s), 5.39–6.00 (3H, brs), 6.29–6.87 (9H, m)     | —                                                                          | 528 ( $\text{M}^+$ )              |
| <b>4n<sup>b)</sup></b> | $\text{C}_{18}\text{H}_{18}\text{N}_6\text{O}_3$   | 59.01<br>(59.04) | 4.95<br>4.96   | 22.94<br>23.02 | 3380, 1610                   | 5.16 (6H, s), 6.06 (3H, brs), 6.37 (6H, brs), 7.37 (3H, brs)                 | 41.3 (t), 109.0 (d), 110.6 (d), 142.2 (d), 146.8 (s), 149.8 (s)            | 366 ( $\text{M}^+$ )              |
| <b>4o<sup>c)</sup></b> | $\text{C}_{18}\text{H}_{18}\text{N}_6\text{S}_3$   | 52.15<br>(52.11) | 4.38<br>4.41   | 23.20<br>23.01 | 3380, 1600                   | 5.36 (6H, s), 6.21 (3H, brs), 6.95 (3H, brs), 7.08 (3H, brs), 7.23 (3H, brs) | 43.3 (t), 125.8 (d), 126.5 (d), 138.4 (s), 146.4 (s)                       | 414 ( $\text{M}^+$ )              |
| <b>4p</b>              | $\text{C}_{21}\text{H}_{21}\text{N}_9$             | 63.14<br>(63.37) | 5.30<br>5.40   | 31.56<br>31.42 | 3350, 1600                   | 5.33 (6H, s), 6.71 (3H, brs), 7.34 (3H, m), 8.49 (3H, m), 8.54 (3H, m)       | 44.4 (t), 123.5 (d), 132.6 (d), 134.4 (d), 145.6 (s), 147.8 (d), 148.0 (d) | 399 ( $\text{M}^+$ )              |
| <b>5a<sup>b)</sup></b> | $\text{C}_6\text{H}_9\text{N}_3\text{O}_3$         | 42.10<br>(42.33) | 5.30<br>5.50   | 24.55<br>24.51 | 3420, 1670                   | —                                                                            | 28.8 (q), 149.4 (s)                                                        | 171 ( $\text{M}^+$ )              |
| <b>5b<sup>b)</sup></b> | $\text{C}_9\text{H}_{15}\text{N}_3\text{O}_3$      | 50.69<br>(50.53) | 7.09<br>7.31   | 19.71<br>19.43 | 1680                         | 1.12 (9H, t), 3.78 (6H, q)                                                   | 12.7 (q), 37.4 (t), 148.7 (s)                                              | 213 ( $\text{M}^+$ )              |
| <b>5b<sup>d)</sup></b> | $\text{C}_9\text{H}_{17}\text{ClN}_4\text{O}_2$    | 43.46<br>(43.39) | 6.89<br>6.89   | 22.53<br>22.54 | 1760, 1700, 1660, 1590       | 1.26, 1.32 (9H, t), 3.98, 4.10 (6H, q), 4.86 (2H, s)                         | 12.3, 12.7 (q), 40.2, 41.6 (t), 147.8 (s), 153.3 (s)                       | 212 ( $\text{M}^+ - \text{HCl}$ ) |
| <b>5c<sup>e)</sup></b> | $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_3$   | 56.45<br>(56.13) | 8.29<br>8.30   | 16.46<br>16.37 | 1690                         | 0.94 (9H, t), 1.33–2.07 (6H, m), 3.87 (6H, t)                                | 11.2 (q), 21.3 (t), 44.6 (t), 149.2 (s)                                    | 255 ( $\text{M}^+$ )              |
| <b>5c<sup>b)</sup></b> | $\text{C}_{12}\text{H}_{22}\text{N}_4\text{O}_2$   | 56.67<br>(56.44) | 8.72<br>8.75   | 22.03<br>21.95 | 1740, 1700, 1660             | 0.84–1.08 (9H, m), 1.48–1.91 (6H, m), 3.83–4.03 (6H, m), 5.51 (1H, brs)      | 11.2 (q), 20.5, 21.3 (t), 44.3, 45.0 (t), 146.7 (s), 148.9 (s)             | 254 ( $\text{M}^+$ )              |
| <b>5d<sup>b)</sup></b> | $\text{C}_{15}\text{H}_{29}\text{ClN}_4\text{O}_2$ | 54.12<br>(54.19) | 8.78<br>8.85   | 16.83<br>16.84 | 1750, 1700, 1660, 1600       | 0.90–2.03 (21H, m), 3.93, 4.49 (6H, t), 11.08 (2H, brs)                      | 13.8 (q), 19.5, 19.9 (t), 29.2 (t), 44.1, 45.9 (t), 146.6 (s), 150.7 (s)   | 296 ( $\text{M}^+ - \text{HCl}$ ) |
| <b>5e<sup>b)</sup></b> | $\text{C}_{15}\text{H}_{28}\text{N}_4\text{O}_2$   | 60.78<br>(60.76) | 9.52<br>9.56   | 18.90<br>18.89 | 3360, 1730, 1670, 1620       | 0.93 (18H, d), 1.85–2.43 (3H, m), 3.70, 3.82 (6H, d), 6.10 (1H, brs)         | 20.0 (q), 26.6, 27.3 (d), 49.5, 50.0 (t), 147.1 (s), 149.6 (s)             | 296 ( $\text{M}^+$ )              |
| <b>5f<sup>e)</sup></b> | $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$   | 57.82<br>(57.46) | 6.07<br>6.07   | 16.86<br>16.83 | 3075, 1680                   | 4.45, 4.54 (6H, s), 5.10–5.35 (6H, m), 5.59–6.30 (3H, m)                     | 45.0 (t), 119.0 (t), 131.1 (d), 148.5 (s)                                  | 249 ( $\text{M}^+$ )              |

a)  $^1\text{H-NMR}$  ( $\text{CDCl}_3\text{--CD}_3\text{OD}$ ). b)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ). c)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ). In the  $^{13}\text{C-NMR}$  spectra, one signal of the thiophene ring overlapped with the other one. d)  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ). e)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ). IR (neat).

concentrated hydrochloric acid, and the solution was heated to reflux. It was allowed to stand at room temperature overnight, and the precipitate was recrystallized to give the product (**5a, b**).

**1,3,5-Triethyl-2-imino-4,6-dioxohexahydro-1,3,5-triazine (5b')** Employing the procedure described for the above run (**5a, b**), concentrated hydrochloric acid (10 ml) was added to a solution of **4b** (4.20 g, 20 mmol)

in water (10 ml), and the mixture was heated under reflux. It was allowed to stand at room temperature overnight, and the precipitate (**5b**) (0.85 g, 20%) was filtered off. The filtrate was extracted with chloroform (50 ml  $\times$  3), washed with water (50 ml  $\times$  2), and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure, and the crystalline residue was purified by recrystallization from

Table 4. Bronchodilation and Positive Inotropic Activities of **4a**–**p**

| Compound  | R                                                                                 | Bronchodilation    |                | Positive inotropic activity |                |
|-----------|-----------------------------------------------------------------------------------|--------------------|----------------|-----------------------------|----------------|
|           |                                                                                   | g/ml               | Inhibition (%) | g/ml                        | Inhibition (%) |
| <b>4a</b> | Me                                                                                |                    | None           |                             | None           |
| <b>4b</b> | Et                                                                                | $5 \times 10^{-6}$ | 50             | $1 \times 10^{-5}$          | 70             |
| <b>4c</b> | <i>n</i> -Pr                                                                      | $3 \times 10^{-5}$ | 50             | $3 \times 10^{-5}$          | 55             |
| <b>4d</b> | <i>n</i> -Bu                                                                      | $1 \times 10^{-5}$ | 50             |                             | None           |
| <b>4e</b> | iso-Bu                                                                            | $3 \times 10^{-5}$ | 50             |                             | None           |
| <b>4f</b> | CH <sub>2</sub> =CHCH <sub>2</sub>                                                |                    | None           |                             | None           |
| <b>4g</b> | CH <sub>2</sub> CF <sub>3</sub>                                                   |                    | None           |                             | None           |
| <b>4h</b> | (CH <sub>2</sub> ) <sub>2</sub> CN                                                |                    | None           |                             | None           |
| <b>4i</b> | (CH <sub>2</sub> ) <sub>2</sub> OEt                                               |                    | None           |                             | None           |
| <b>4j</b> | CH <sub>2</sub> CH(OMe) <sub>2</sub>                                              |                    | None           |                             | None           |
| <b>4k</b> | Ph                                                                                |                    | None           |                             | None           |
| <b>4l</b> | PhCH <sub>2</sub>                                                                 |                    | None           |                             | None           |
| <b>4m</b> |  |                    | None           |                             | None           |
| <b>4n</b> |  |                    | None           |                             | None           |
| <b>4o</b> |  |                    | None           |                             | None           |
| <b>4p</b> |  |                    | None           |                             | None           |

Table 5. Bronchodilation and Positive Inotropic Activities of **5b**, **c**, **f**, and **5b'**–**e'**

| Compound   | R                                  | X  | Bronchodilation    |                | Positive inotropic activity |                |
|------------|------------------------------------|----|--------------------|----------------|-----------------------------|----------------|
|            |                                    |    | g/ml               | Inhibition (%) | g/ml                        | Inhibition (%) |
| <b>5b</b>  | Et                                 | O  | $1 \times 10^{-6}$ | 50             | $3 \times 10^{-5}$          | 50             |
| <b>5c</b>  | <i>n</i> -Pr                       | O  | $5 \times 10^{-5}$ | 50             | $3 \times 10^{-6}$          | 70             |
| <b>5f</b>  | CH <sub>2</sub> =CHCH <sub>2</sub> | O  | $5 \times 10^{-6}$ | 50             |                             | None           |
| <b>5b'</b> | Et                                 | NH |                    | None           |                             | None           |
| <b>5c'</b> | <i>n</i> -Pr                       | NH | $3 \times 10^{-5}$ | 50             | $3 \times 10^{-6}$          | 50             |
| <b>5d'</b> | <i>n</i> -Bu                       | NH | $1 \times 10^{-4}$ | 50             |                             | None           |
| <b>5e'</b> | iso-Bu                             | NH |                    | None           |                             | None           |

ethanol to give 3.20 g (64%) of **5b'**.

**2,4,6-Trioxo-1,3,5-tripropylhexahydro-1,3,5-triazine (5c)** and **2-Imino-4,6-dioxo-1,3,5-tripropylhexahydro-1,3,5-triazine (5c')** Employing the procedure described for the preparation of compounds **5a**, **b**, concentrated hydrochloric acid (4 ml) was added to a solution of **4c** (2.00 g, 7.9 mmol) in water (10 ml), and the mixture was heated under reflux. It was allowed to stand at room temperature for 1 h, then extracted with chloroform (50 ml  $\times$  3). The organic solution was washed with water (50 ml  $\times$  3), and dried over anhydrous magnesium sulfate. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (100 g) column chromatography. Elution with *n*-hexane–ethyl acetate (9:1) gave **5c** (1.05 g, 52%) and **5c'** (0.67 g, 33%).

**1,3,5-Tributyl-2-imino-4,6-dioxohexahydro-1,3,5-triazine (5d')** According to the procedure described above, concentrated hydrochloric acid (4 ml) was added to a solution of **4d** (2.00 g, 6.8 mmol) in water (10 ml), and the solution was heated under reflux. Work-up as above gave **5d'** (1.43 g, 71%).

**1,3,5-Triisobutyl-2-imino-4,6-dioxohexahydro-1,3,5-triazine (5e')** Following the same procedure described above, concentrated hydrochloric acid (4 ml) was added to a solution of **4e** (2.00 g, 6.8 mmol) in water (10 ml), and the solution was heated under reflux. Work-up as above gave **5e'** (1.60 g, 80%).

**1,3,5-Triallyl-2,4,6-trioxohexahydro-1,3,5-triazine (5f)** Employing a similar procedure to that used for the preparation of compound **5e'**, concentrated hydrochloric acid (4 ml) was added dropwise to a solution of **4f** (2.00 g, 8.1 mmol) in water (10 ml), and the solution was heated under reflux. Work-up as above gave **5f** (1.56 g, 77%).

**Measurement of Bronchodilator and Positive Inotropic Activity** These compounds were tested on isolated guinea pig right atrium and on isolated

guinea pig trachea by the usual methods.<sup>13,14</sup> They were suspended separately in organ baths which contained 10 ml of Krebs-bicarbonate solution (37 °C) to measure bronchodilator and positive inotropic activity.

**Acknowledgment** The authors are grateful to Prof. N. Katagiri, Pharmaceutical Institute of Tohoku University for valuable advice.

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