# Synthesis of Isomelamines and Isocyanurates and Their Biological Evaluation

Ryuji NIWA,*,[a] Hitoshi KAMADA,[a] Eiki SHITARA,[b] Jiro HORIUCHI,[b] Nobuyuki KIBUSHI,[b] and Tetsuzo KATO[b]

*Institute for Life Support Technology,[a] Yamagata Technopolis Foundation, 683 Kurumanomae, Numagi, Yamagata 990, Japan and MECT Co.,[b] 1780 Kitano, Tokorozawa, Saitama 359, Japan.*
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**The reaction of cyanogen bromide (1) with primary amines (2a—p), including arylmethylamines (2l—p), gave the corresponding cyanamides (3a—p). Trimerization of 3a—p gave 1,3,5-trisubstituted 2,4,6-triiminohexahydro-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**),[1-7] some of which trimerize to give the corresponding 1,3,5-trialkyl-2,4,6-triiminohexahydro-1,3,5-triazines (trialkylisomelamines) (**4**).[2,6,7] In 1885, Hofmann[2] 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.*[7] and Kitawaki and Sugino[8] 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[9] that **4a** is obtained in 40% yield by treating 10% cyanamide with 40% caustic soda and dimethyl sulfate. However, only a few reports[10,11] are available concerning such reactions with arylmethylcyanamides. For example, Friedrich and Heimut[10] 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 hetarylmethylamines. Compounds **3** were subjected to further reaction without purification (Chart 1). First, according to the procedure reported by Hofmann,[2] 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 $cm^{-1}$. In the $^1$H-NMR spectra, the signals due to imino protons were observed at 6.06—7.68 ppm (3H, br s). The $^{13}$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 $cm^{-1}$. The $^{13}$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. $^1$H- and $^{13}$C-NMR spectra were recorded by using tetramethylsilane as an internal standard on JEOL JNM FX-60 spectrometers at 60 MHz. Chemical shifts ($\delta$) are quoted in parts per million, and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (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.

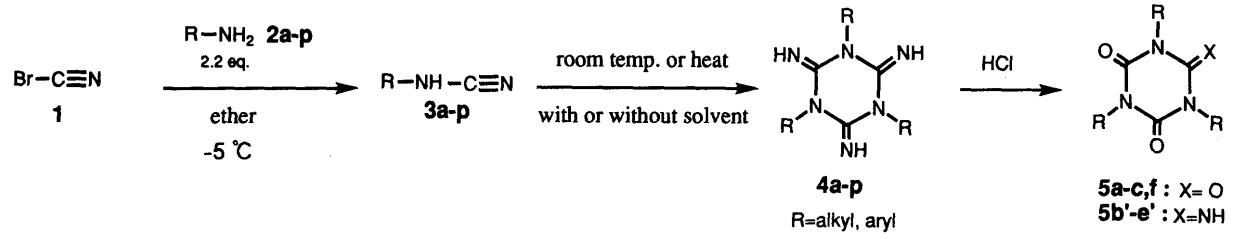


Chart 1

* To whom correspondence should be addressed.

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

| Compd. | R | Reaction conditions: Solvent | Temp. (°C) | Time (h) | Compd. | Appearance (Recryst. solvent) | mp (°C) [lit. mp (°C)] | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **3a** | Me | EtOH | r.t. | 12 | **4a** | Colorless needles ($H_2O$) | 179—180 [178][9] | 85 |
| **3b** | Et | $H_2O$ | 60 | 2 | **4b** | Colorless needles ($H_2O$) | 94—95 [92][2] | 74 |
| **3c** | *n*-Pr | EtOH–$H_2O$ | 50 | 3 | **4c** | Colorless needles (EtOH–$H_2O$) | 87—89 | 61 |
| **3d** | *n*-Bu | EtOH–$H_2O$ | 50 | 2 | **4d**[a] | Colorless oil | | 73 |
| **3e** | iso-Bu | EtOH–$H_2O$ | 50 | 3 | **4e** | Colorless needles (Benzene–*n*-hexane) | 95—96 [91—93][10] | 78 |
| **3f** | $CH_2=CHCH_2$ | EtOH–$H_2O$ | 50 | 2 | **4f**[b] | Colorless powder | 46—49 [bp 105—115 °C/ 0.026 mmHg][10] | 75 |
| **3g** | $CH_2CF_3$ | EtOH–$H_2O$ | 50 | 3 | **4g** | Colorless prisms (EtOH–$H_2O$) | 163 | 56 |
| **3h** | $(CH_2)_2CN$ | EtOH–$H_2O$ | 50 | 1 | **4h** | Pale yellow prisms (Acetone) | 160(dec.) | 33 |
| **3i** | $(CH_2)_2OEt$ | EtOH–$H_2O$ | 50 | 8 | **4i** | Colorless prisms (AcOEt–*n*-hexane) | 56—58 | 26 |
| **3j** | $CH_2CH(OMe)_2$ | EtOH–$H_2O$ | 50 | 4 | **4j**[c] | Colorless oil | | 86 |
| **3k** | Ph | EtOH | Reflux | 12 | **4k** | Colorless prisms (EtOH) | 214—215 [210][12] | 73 |
| **3l** | $PhCH_2$ | EtOH–$H_2O$ | 50 | 2 | **4l** | Colorless needles (Toluene–cyclohexane) | 131—132 [129—130][11] | 75 |
| **3m** |  | MeOH | Reflux | 5 | **4m** | Colorless needles (MeOH) | 199—200 | 52 |
| **3n** |  | EtOH–$H_2O$ | 50 | 3 | **4n** | Colorless needles (Benzene–*n*-hexane) | 123—125 | 78 |
| **3o** |  | EtOH–$H_2O$ | 50 | 3 | **4o** | Colorless needles (Benzene–ether) | 136—137 | 94 |
| **3p** |  | EtOH–$H_2O$ | 50 | 3 | **4p** | Pale yellow needles ($H_2O$) | 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: Temp. (°C) | Time (h) | Compd. | X | Appearance (Recryst. solvent) | mp (°C) [lit. mp (°C)] | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **4a** | Me | Reflux | 4 | **5a** | O | Colorless prisms ($H_2O$) | 173—175 [175—176][1] | 87 |
| **4b** | Et | Reflux | 24 | **5b** | O | Colorless needles (EtOH) | 94—95 [95][2] | 58 |
| **4b′** | Et | 80 | 6 | **5b′**[a] | NH | Colorless needles (MeOH–ether) | 247—249 | 64 |
| **4c** | *n*-Pr | Reflux | 5 | **5c**[b] | O | Colorless oil | | 52 |
| **4c′** | *n*-Pr | Reflux | 5 | **5c′** | NH | Colorless needles (Benzene–*n*-hexane) | 41 | 33 |
| **4d′** | *n*-Bu | Reflux | 6 | **5d′**[a] | NH | Colorless needles (Benzene–*n*-hexane) | 220—222 | 71 |
| **4e′** | iso-Bu | Reflux | 5 | **5e′** | NH | Colorless prisms (Benzene–*n*-hexane) | 79—80 | 80 |
| **4f** | $CH_2=CHCH_2$ | Reflux | 5 | **5f**[b] | 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

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

| Compd. | Formula | Analysis (%) Calcd (Found) C | H | N | IR (KBr) $cm^{-1}$ | $^1$H-NMR (DMSO-$d_6$) $\delta$ | $^{13}$C-NMR (DMSO-$d_6$) $\delta$ | MS $m/z$ |
|---|---|---|---|---|---|---|---|---|
| **4a** | $C_6H_{12}N_6$ | 42.84 (42.48 | 7.19 7.22 | 49.97 50.07) | 3320, 1620 | 3.28 (9H, s), 6.44 (3H, br s) | 31.2 (q), 147.0 (s) | 168 ($M^+$) |
| **4b** | $C_9H_{18}N_6$ | 51.40 (50.99 | 8.63 8.67 | 39.97 39.84) | 3340, 1600 | 1.09 (9H, t), 3.68—4.20 (6H, m), 6.37 (3H, br s) | 11.8 (q), 38.2 (t), 144.6 (br s) | 210 ($M^+$) |
| **4c** | $C_{12}H_{24}N_6$ | 57.11 (57.12 | 9.59 9.72 | 33.30 33.40) | 3380, 1590 | 0.86 (9H, t), 0.91—1.83 (6H, m), 3.93—4.26 (6H, m), 6.39 (3H, br s) | 10.9 (q), 19.8 (t), 45.0 (t), 145.8 (s) | 253 ($M^+ + 1$) |
| **4d** | $C_{15}H_{30}N_6$ | 61.18 (61.21 | 10.27 10.43 | 28.55 28.53) | 3395, 1600 | 0.88—0.97 (9H, m), 1.38 (12H, m), 3.90 (6H, m), 6.31 (3H, br s) | 13.6 (q), 19.5 (t), 28.6 (t), 43.1 (t), 145.8 (s) | 294 ($M^+$) |
| **4e** | $C_{15}H_{30}N_6$ | 61.18 (60.81 | 10.27 10.71 | 28.55 28.19) | 3350, 1600 | 0.84 (18H, d), 1.67—2.33 (3H, m), 3.50—4.00 (6H, m), 6.46 (3H, br s) | 19.6 (q), 26.1 (d), 49.5 (t), 146.6 (s) | 295 ($M^+ + 1$) |
| **4f** | $C_{12}H_{18}N_6$ | 58.51 (58.34 | 7.37 7.65 | 34.12 34.05) | 3375, 1600 | 4.64 (6H, br s), 5.00—5.26 (6H, m), 5.49—6.15 (3H, m), 6.32 (3H, br s) | 45.5 (t), 115.9 (t), 132.7 (d), 145.3 (s) | 246 ($M^+$) |
| **4g** | $C_9H_9N_6F_9$ | 29.04 (29.03 | 2.44 2.45 | 22.58 22.55) | 3410, 3390, 1620 | 5.04 (6H, br s), 7.68 (3H, br s) | 43.3—44.6 (m), 121.3—128.0 (m), 143.7 (br s) | 372 ($M^+$) |
| **4h** | $C_{12}H_{15}N_9$ | 50.51 (50.78 | 5.30 5.01 | 44.19 43.99) | 3400, 3360, 1610 | 2.50 (6H, m), 4.22 (6H, m), 7.14 (3H, br s) | 14.9 (t), 39.2 (t), 118.4 (s), 143.7 (s) | 285 ($M^+$) |
| **4i** | $C_{15}H_{30}N_6O_3$ | 52.61 (52.70 | 8.83 8.96 | 24.54 24.70) | 3350, 1610 | 1.09 (9H, t), 3.38 (6H, q), 3.51 (6H, m), 4.05 (6H, m), 6.64 (3H, br s) | 15.1 (q), 44.3 (t), 65.8 (t), 67.3 (t), 146.5 (s) | 342 ($M^+$) |
| **4j**[a] | $C_{15}H_{30}N_6O_6$ | 46.14 (46.33 | 7.75 7.96 | 21.53 21.73) | 3350, 1620 | 3.46 (18H, s), 4.03 (6H, br s), 4.38 (3H, t), 6.65 (3H, br s) | 48.9 (t), 54.5 (q), 103.2 (d), 148.1 (s) | 390 ($M^+$) |
| **4k** | $C_{21}H_{18}N_6$ | 71.16 (71.15 | 5.12 4.97 | 23.72 23.92) | 3350, 1620 | 5.05 (3H, br s), 7.49 (15H, br s) | 128.8 (d), 129.7 (d), 129.9 (d), 136.8 (s), 148.1 (s) | 354 ($M^+$) |
| **4l** | $C_{24}H_{24}N_6$ | 72.70 (72.77 | 6.10 6.00 | 21.20 21.39) | 3380, 1600 | 5.30 (6H, s), 6.59 (3H, br s), 7.28 (15H, br s) | 46.9 (t), 126.6 (d), 126.8 (d), 128.3 (d), 137.2 (s), 146.3 (s) | 396 ($M^+$) |
| **4m** | $C_{27}H_{24}N_6O_6$ | 61.36 (61.26 | 4.58 4.57 | 15.90 16.05) | 3375, 1600 | 3.40 (6H, s), 5.05, 5.18 (6H, s), 5.39—6.00 (3H, br s), 6.29—6.87 (9H, m) | — | 528 ($M^+$) |
| **4n**[b] | $C_{18}H_{18}N_6O_3$ | 59.01 (59.04 | 4.95 4.96 | 22.94 23.02) | 3380, 1610 | 5.16 (6H, s), 6.06 (3H, br s), 6.37 (6H, br s), 7.37 (3H, br s) | 41.3 (t), 109.0 (d), 110.6 (d), 142.2 (d), 146.8 (s), 149.8 (s) | 366 ($M^+$) |
| **4o**[c] | $C_{18}H_{18}N_6S_3$ | 52.15 (52.11 | 4.38 4.41 | 23.20 23.01) | 3380, 1600 | 5.36 (6H, s), 6.21 (3H, br s), 6.95 (3H, br s), 7.08 (3H, br s), 7.23 (3H, br s) | 43.3 (t), 125.8 (d), 126.5 (d), 138.4 (s), 146.4 (s) | 414 ($M^+$) |
| **4p** | $C_{21}H_{21}N_9$ | 63.14 (63.37 | 5.30 5.40 | 31.56 31.42) | 3350, 1600 | 5.33 (6H, s), 6.71 (3H, br s), 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 ($M^+$) |
| **5a**[b] | $C_6H_9N_3O_3$ | 42.10 (42.33 | 5.30 5.50 | 24.55 24.51) | 3420, 1670 | — | 28.8 (q), 149.4 (s) | 171 ($M^+$) |
| **5b**[b] | $C_9H_{15}N_3O_3$ | 50.69 (50.53 | 7.09 7.31 | 19.71 19.43) | 1680 | 1.12 (9H, t), 3.78 (6H, q) | 12.7 (q), 37.4 (t), 148.7 (s) | 213 ($M^+$) |
| **5b′**[d] | $C_9H_{17}ClN_4O_2$ | 43.46 (43.39 | 6.89 6.89 | 22.53 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 ($M^+ - HCl$) |
| **5c**[e] | $C_{12}H_{21}N_3O_3$ | 56.45 (56.13 | 8.29 8.30 | 16.46 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 ($M^+$) |
| **5c′**[b] | $C_{12}H_{22}N_4O_2$ | 56.67 (56.44 | 8.72 8.75 | 22.03 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, br s) | 11.2 (q), 20.5, 21.3 (t), 44.3, 45.0 (t), 146.7 (s), 148.9 (s) | 254 ($M^+$) |
| **5d′**[b] | $C_{15}H_{29}ClN_4O_2$ | 54.12 (54.19 | 8.78 8.85 | 16.83 16.84) | 1750, 1700, 1660, 1600 | 0.90—2.03 (21H, m), 3.93, 4.49 (6H, t), 11.08 (2H, br s) | 13.8 (q), 19.5, 19.9 (t), 29.2 (t), 44.1, 45.9 (t), 146.6 (s), 150.7 (s) | 296 ($M^+ - HCl$) |
| **5e′**[b] | $C_{15}H_{28}N_4O_2$ | 60.78 (60.76 | 9.52 9.56 | 18.90 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, br s) | 20.0 (q), 26.6, 27.3 (d), 49.5, 50.0 (t), 147.1 (s), 149.6 (s) | 296 ($M^+$) |
| **5f**[e] | $C_{12}H_{15}N_3O_3$ | 57.82 (57.46 | 6.07 6.07 | 16.86 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 ($M^+$) |

*a*) $^1$H-NMR ($CDCl_3$–$CD_3OD$). *b*) $^1$H-NMR ($CDCl_3$). *c*) $^1$H-NMR ($CDCl_3$). In the $^{13}$C-NMR spectra, one signal of the thiophene ring overlapped with the other one. *d*) $^1$H-NMR ($CD_3OD$). *e*) $^1$H-NMR ($CDCl_3$). 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 × 3), washed with water (50 ml × 2), and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure, and the crystalline residue was purified by recrystallization from

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

| Compound | R | Bronchodilation | | Positive inotropic activity | |
|---|---|---|---|---|---|
| | | g/ml | Inhibition (%) | g/ml | Inhibition (%) |
| **4a** | Me | None | | None | |
| **4b** | Et | $5\times10^{-6}$ | 50 | $1\times10^{-5}$ | 70 |
| **4c** | *n*-Pr | $3\times10^{-5}$ | 50 | $3\times10^{-5}$ | 55 |
| **4d** | *n*-Bu | $1\times10^{-5}$ | 50 | None | |
| **4e** | iso-Bu | $3\times10^{-5}$ | 50 | None | |
| **4f** | $CH_2=CHCH_2$ | None | | None | |
| **4g** | $CH_2CF_3$ | None | | None | |
| **4h** | $(CH_2)_2CN$ | None | | None | |
| **4i** | $(CH_2)_2OEt$ | None | | None | |
| **4j** | $CH_2CH(OMe)_2$ | None | | None | |
| **4k** | Ph | None | | None | |
| **4l** | $PhCH_2$ | None | | None | |
| **4m** |  | None | | None | |
| **4n** |  | None | | None | |
| **4o** |  | None | | None | |
| **4p** |  | 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 (%) |
| **5b** | Et | O | $1\times10^{-6}$ | 50 | $3\times10^{-5}$ | 50 |
| **5c** | *n*-Pr | O | $5\times10^{-5}$ | 50 | $3\times10^{-6}$ | 70 |
| **5f** | $CH_2=CHCH_2$ | O | $5\times10^{-6}$ | 50 | None | |
| **5b′** | Et | NH | None | | None | |
| **5c′** | *n*-Pr | NH | $3\times10^{-5}$ | 50 | $3\times10^{-6}$ | 50 |
| **5d′** | *n*-Bu | NH | $1\times10^{-4}$ | 50 | None | |
| **5e′** | 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 × 3). The organic solution was washed with water (50 ml × 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.[13,14] They were suspended separately in organ baths which contained 10 ml of Krebs-bicarbonate solution (37 °C) to measure bronchodilator and positive inotropic activity.

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**References**

1) Cahours A., *Justus Liebigs Ann. Chem.*, **90**, 95—98 (1854).
2) Hofmann A. W., *Chem. Ber.*, **18**, 2781—2782 (1885).
3) Mckee R. H., *J. Am. Chem. Soc.*, **36**, 211—217 (1906).
4) Schmidt H., *Chem. Ber.*, **54**, 2067—2068 (1921).
5) Baum F., *Chem. Ber.*, **41**, 523—525 (1908).
6) Ainley A. D., Curd F. H. S., Rose F. L., *J. Chem. Soc.*, **1**, 98—101 (1949).
7) Mukaiyama T., Ohishi S., Takamura H., *Bull. Chem. Soc. Jpn.*, **27**, 416—422 (1954).
8) Kitawaki R., Sugino K., *J. Org. Chem.*, **25**, 1043—1048 (1960).
9) Miller S. A., Bann B., *J. Appl. Chem.*, **6**, 89—96 (1956).
10) Friedrich L., Heimut Z., Eur. Patent 0087393 A2 (1983) [*Chem. Abstr.*, **99**(24), 196090*r* (1983)].
11) Bivkofer L., *Chem. Ber.*, **75**, 429—430 (1942).
12) Arndt F., *Justsu Liebigs Ann. Chem.*, **384**, 350—351 (1911).
13) Kubota K., "Kiso Yakuri Jikken," Nankodo, Tokyo, 1987, pp. 142—143.
14) Tanabe T., "Shinzo Yakuri Jikkenho," Maruzen, Tokyo, 1981, pp. 1—14.

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