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# Studies on Positive Inotropic Agents. V.[1] Synthesis of 1-Heteroaroylpiperazine Derivatives

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A series of 1-heteroaroylpiperazines (V—VII, XI) was synthesized and examined for positive inotropic activities on the canine heart. The key intermediates, heteroarenecarboxylic acids (III, X), were prepared by two different methods, and were condensed with substituted piperazines to give 1-heteroaroylpiperazines V—VII and XI. Among them, quinazoline derivatives (XI) were found to have potent positive inotropic activities.

**Keywords**——positive inotropic activity; congestive heart failure; 2,3-dihydro-2-oxo-benzothiazole-6-carboxylic acid; 2,4-dioxo-3-methyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid; 3-methyl-6-[4-(4-oxo-4-phenylbutyl)-1-piperazinylcarbonyl]-2,4(1*H*,3*H*)-quinazolinedione; biological activity

As a part of an ongoing project to discover novel compounds bearing a potent positive inotropic activity with little chronotropic effect for the treatment of congestive heart failure, we have recently reported the synthesis and the biological activities of a new series of 1-piperazinylcarbonyl-2(1*H*)-quinolinone[2] derivatives. Some of them showed desirable activity on the canine heart.

In order to define the structural requirements for positive inotropic activity in this series, we have prepared various heteroaroylpiperazine derivatives. We now present details of the synthesis and the biological activities of these lactam analogues.

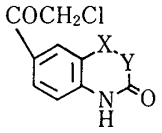
## Chemistry

The key intermediates, heteroarenecarboxylic acids (III, X), were prepared by two different methods. The acids obtained were condensed with substituted piperazines to give the desired 1-heteroaroylpiperazines (V—VII, XI).

Friedel–Crafts reaction of the heteroarenones (I)[3] with chloroacetyl chloride in 1,2-dichloroethane afforded chloroacetylheteroarenones (II) in 76—96% yield (Table I). Conversion of II into the acids III was accomplished by the reaction with excess pyridine followed by hydrolysis with aqueous sodium hydroxide[4] (Table II). Compounds IIa, b were converted into the heteroaromatic carboxylic esters (IVa, b) in order to elucidate the position of the chloroacetyl group. Thus, the esters IVa, b were conveniently obtained by heating of compounds IIa, b with excess pyridine, followed by treatment with alcohol in the presence of $K_2CO_3$.

The position of the carboxy or methoxycarbonyl group of compounds IIIc and IVa[5] was confirmed by the use of the nuclear Overhauser effect (NOE) which was observed between the N(1) proton and vicinal aromatic proton. Compound IVb was identified by comparison of the spectral data with those given by Gassmann *et al.*[6a] and Decodts and Wakselman.[6b] The preparation of amides (V—VII) was achieved through the activated ester method using

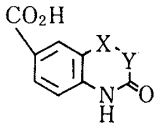
TABLE I. Chloroacetylheteroarenones



II

| Compd. No. | -X-Y- | Yield (%) | mp (°C) (Recrystn. solv.) | Formula | NMR (DMSO-$d_6$) | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| IIa | -S- | 76 | 281—284 (dec.) (DMF-EtOH) | $C_9H_6ClNO_2S$ | 5.01 (2H, s), 7.11 (1H, d, $J$=8.5 Hz), 7.82 (1H, dd, $J$=2, 8.5 Hz), 8.12 (1H, d, $J$=2 Hz), 11.17 (1H, s) | 47.48 (47.24 | 2.66 2.74 | 6.15 5.87) |
| IIb | $-CH_2-$ | 77 | 245—248 ($CHCl_3$-MeOH) | $C_{10}H_8ClNO_2$ | 3.57 (2H, s), 5.08 (2H, s), 6.93 (1H, d, $J$=8 Hz), 7.74—8.03 (2H, m), 10.83 (1H, s) | 57.29 (57.01 | 3.85 3.94 | 6.68 6.55) |
| IIc | $-CH_2-N(Me)-$ | 95 | 208—211 (DMF-MeOH) | $C_{11}H_{11}ClN_2O_2$ | 2.85 (3H, s), 4.44 (2H, s), 5.02 (2H, s), 6.81 (1H, d, $J$=8.3 Hz), 7.61—7.88 (2H, m), 9.67 (1H, s) | 55.35 (55.08 | 4.65 4.54 | 11.74 11.51) |

TABLE II. Heteroarenecarboxylic Acids



III

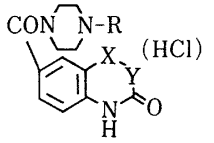
| Compd. No. | -X-Y- | Yield (%) | mp (°C) (Recrystn. solv.) | Formula | NMR (DMSO-$d_6$) | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| IIIa | -S- | 75 | >300 ($MeOH-CHCl_3$) | $C_8H_5NO_3S$ | 7.09 (1H, d, $J$=8.5 Hz), 7.77 (1H, dd, $J$=2, 8.5 Hz), 8.05 (1H, d, $J$=2 Hz), 11.09 (1H, s), 11.30 (1H, br s) | 49.22 (48.94 | 2.58 2.72 | 7.18 7.38) |
| IIIb | $-CH_2-$ | 74 | >300 (DMF-$H_2O$) | $C_9H_7NO_3$ | 3.60 (2H, s), 6.90 (1H, d, $J$=8.5 Hz), 7.65—8.01 (2H, m), 10.73 (1H, s), 11.88 (1H, br s) | 61.01 (61.12 | 3.98 3.81 | 7.90 8.10) |
| IIIc[a] | $CH_2-N(Me)-$ | 69 | >300 (DMF-MeOH) | $C_{10}H_{10}N_2O_3$ | 2.82 (3H, s), 4.41 (2H, s), 6.79 (1H, d, $J$=8.2 Hz), 7.48—7.76 (2H, m), 9.54 (1H, s), 11.58 (1H, br s) | 58.25 (57.97 | 4.89 4.98 | 13.59 13.54) |

a) NOE 12%; NH ($\delta$ 9.54) ----→ $C_8$-aromatic proton ($\delta$ 6.79).

diethyl phosphorocyanidate (DEPC)[7] (Chart 1). The acids III, DEPC and substituted piperazines were reacted in the presence of triethylamine at 0—5 °C, to give the desired amides V—VII (Table III).

Quinazoline-2,4-dione-6-carboxylic acid (X) was obtained from the diester (VIII)[8] through the ring closure reaction (Chart 2). Accordingly, the reaction of VIII with

TABLE III. 4-Substituted 1-Heteroaroylpiperazines




V—VII, XI

| Compd. No. | –X–Y– | R | Yield (%) | mp (°C) (Recrystn. solv.) | Formula | NMR (DMSO-$d_6$)[a] | Analysis (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| Va | –S– | $CH_2Ph$ | 36 | 153—154.5 (EtOH) | $C_{19}H_{19}N_3O_2S$ | 2.16—4.05 (10H, m), 6.85—7.67 (8H, m), 11.50 (1H, br s) | 64.57 (64.65) | 5.42 (5.28) | 11.89 (11.77) |
| Vb | –S– | iso-Bu | 23 | 290—295 (dec.) (MeOH–$Et_2O$) | $C_{16}H_{21}N_3O_2S \cdot HCl \cdot 1/4\,H_2O$ | 0.99 (6H, d, $J$=6.5 Hz), 1.90—2.28 (1H, m), 2.72—4.59 (10H, m), 7.20 (1H, d, $J$=8 Hz), 7.39 (1H, dd, $J$=1.5, 8 Hz), 7.73 (1H, d, $J$=1.5 Hz), 10.46 (1H, br s), 12.21 (1H, s) | 53.32 (53.32) | 6.22 (6.17) | 11.66 (11.65) |
| VIa | $–CH_2–$ | $CH_2Ph$ | 45 | 151—153 (iso-PrOH) | $C_{20}H_{21}N_3O_2$ | 2.23—2.67, 3.35—3.90 (total 12H, m), 6.85 (1H, d, $J$=8.5 Hz), 7.43—7.64 (7H, m), 10.57 (1H, br s) | 71.62 (71.55) | 6.31 (6.26) | 12.53 (12.55) |
| VIb | $–CH_2–$ | iso-Bu | 33 | 285—289 (dec.) (EtOH–MeOH) | $C_{17}H_{23}N_3O_2 \cdot HCl$ | 0.99 (6H, d, $J$=6.5 Hz), 1.89—2.27 (1H, m), 2.72—4.37 (12H, m), 6.88 (1H, d, $J$=8.5 Hz), 7.19—7.44 (2H, m), 10.31 (1H, br s), 10.63 (1H, s) | 60.43 (60.18) | 7.16 (7.28) | 12.44 (12.22) |
| VIIa | $–CH_2–N(Me)–$ | $(CH_2)_3COPh$ | 73 | 189—193 (MeOH) | $C_{24}H_{28}N_4O_3 \cdot HCl \cdot 1/2\,H_2O$ | 1.91—2.26 (2H, m), 2.87 (3H, s), 2.90—4.47 (12H, m), 4.44 (2H, s), 6.82 (1H, d, $J$=8 Hz), 7.18—8.09 (7H, m), 9.47 (1H, s), 11.24 (1H, br s) | 61.86 (61.60) | 6.48 (6.39) | 12.02 (11.97) |
| VIIb | $–CH_2–N(Me)–$ | $CH_2Ph$ | 78 | 233—235 (MeOH) | $C_{21}H_{24}N_4O_2 \cdot HCl$ | 2.74—3.70, 3.84—4.58 (total 8H, m), 2.87 (3H, s), 4.33 (2H, s), 4.43 (2H, s), 6.82 (1H, d, $J$=8 Hz), 7.07—7.78 (7H, m), 9.47 (1H, s), 11.56 (1H, br s) | 62.91 (62.65) | 6.29 (6.22) | 13.98 (13.81) |
| XIa | $–CO–N(Me)–$ | $(CH_2)_3COPh$ | 22 | 186—188 (EtOH–$Et_2O$) | $C_{24}H_{26}N_4O_4$ | 1.62—1.89 (2H, m), 2.13—2.52, 2.85—3.61 (total 12H, m), 3.22 (3H, s), 7.17 (1H, d, $J$=8.5 Hz), 7.41—7.69 (4H, m), 7.84 (1H, d, $J$=1.8 Hz), 7.85—8.00 (2H, m), 11.58 (1H, br s) | 66.34 (66.06) | 6.03 (6.00) | 12.89 (12.63) |
| XIb | $–CO–N(Me)–$ | $CH_2Ph$ | 93 | 223—226 (dec.) (EtOH) | $C_{21}H_{22}N_4O_3$ | 2.80—2.60, 3.35—3.93 (total 8H, m), 3.48 (3H, s), 3.54 (2H, s), 7.19 (1H, d, $J$=8.5 Hz), 7.24—7.35 (5H, m), 7.72 (1H, dd, $J$=2.0, 8.5 Hz), 8.16 (1H, d, $J$=2.0 Hz), 10.53 (1H, br s) | 66.65 (66.64) | 5.86 (5.88) | 14.81 (14.73) |

*a*) Compound XIb was measured in $CDCl_3$.

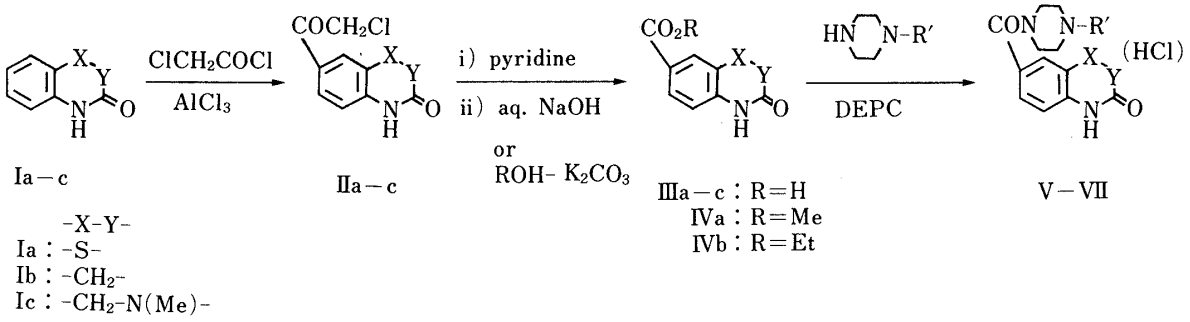



Chart 1

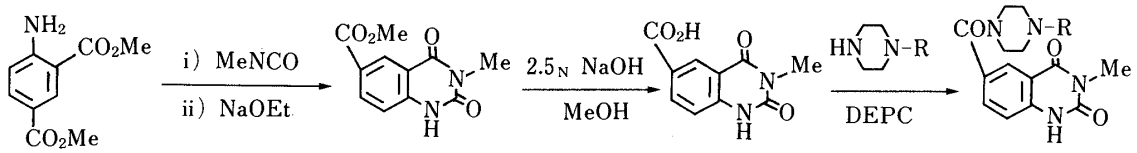



Chart 2

TABLE IV. Biological Activity of Heteroaroylpiperazine Derivatives on the Canine Heart

| Compd. No. | Inotropic effect[a)] | Chronotropic effect[a)] |
|---|---|---|
| Va | 0.5 | LE |
| Vb | 0.6 | LE |
| VIa | 0.6 | 0.3 |
| VIb | 0.2 | LE |
| VIIa | 2.4 | 0.8 |
| VIIb | 1.8 | 2.4 |
| XIa | 1.0 | 0.8 |
| XIb | 3.2 | 1.3 |

*a*) The potency of inotropic and chronotropic effects of the test compounds was evaluated at doses (ED 50%) producing the half-maximal response to amrinone as follows. Activity ratio of test compound =ED 50% of amrinone/dose of test compound producing the same response as ED 50% of amrinone. The larger the activity ratio, the more potent is the test drug. The highest dose (1 $\mu$mol) of amrinone used in these experiments increased developed tension by about 50% of the basal tension, and increased sinus rate by about 15 beats/min. LE means lower than 0.1 activity ratio.

methylisocyanate in acetone, followed by treatment with sodium ethoxide, gave the ester (IX). Hydrolysis of IX with 2.5 N NaOH in methanol gave the acid X.

Compounds XIa, b were prepared from X in the same manner as described for the synthesis of V—VII.

## Biological Activity

The results of the *in vitro* screening tests of myocardial contractile force and heart rate are shown in Table IV. The inotropic and chronotropic effects of the heteroaroylpiperazines were compared with those of amrinone.[9)]

We have studied a series of positive inotropic agents bearing a 2(1*H*)-quinolinone nucleus.[2)] These studies have indicated that the agents essentially exhibit positive inotropic actions only when a piperazinylcarbonyl group exists *para* to the N–H group. Therefore, all compounds we synthesized this time had a lactam moiety whose N–H group was located *para* to the piperazinylcarbonyl group.

As for the five-membered lactam analogues V—VI, the benzothiazolones V did not increase the heart rate. However, the inotropic effects were less potent as compared with the parent 2(1*H*)-quinolinone derivatives.[2] In contrast, the six-membered cyclic ureido analogues VII and XI produced potent positive inotropic responses. Among them, compound VIIa had a potent positive inotropic effect with a relatively minor increase in heart rate.

## Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390, Bruker WH-400 or Bruker AC-200 NMR spectrometer using tetramethylsilane or 3-(trimethylsilyl)propionic acid-$d_5$ as an internal standard.

**Preparation of the Chloroacetylheteroarenones (IIa—c). 6-Chloroacetyl-2(3*H*)-benzothiazolone (IIa)**——Chloroacetyl chloride (5.4 ml, 68 mmol) was added dropwise to a suspension of $AlCl_3$ (11.4 g, 85 mmol) in 1,2-dichloroethane (10 ml) with stirring and ice-cooling. Stirring was continued for 1 h, then a suspension of benzothiazolone (Ia) (5.16 g, 34 mmol) in 1,2-dichloroethane (10 ml) was added dropwise to the mixture. The whole was stirred for 2 h with ice-cooling, then warmed to 40—50 °C for 3 h. The reaction mixture was poured into ice-water and the resulting precipitates were collected by filtration. Crude IIa was used without further purification, and a sample for identification was obtained as follows. Crude IIa was recrystallized from dimethylformamide (DMF)–$CHCl_3$ to give IIa as colorless needles, mp 245—248 °C. IR (KBr): 3205, 1705, 1675, 1590 $cm^{-1}$. The NMR spectral data and elemental analysis data are shown in Table I.

Compounds IIb, c were obtained in the same manner as described for IIa. The yields, melting points, NMR spectral data, and elemental analysis data are shown in Table I.

**Preparation of the Heteroarenecarboxylic Acids (IIIa—c). 2,3-Dihydro-2-oxo-benzothiazole-6-carboxylic Acid (IIIa)**——A suspension of IIa (22 g, 0.097 mol) in pyridine (200 ml) was stirred at 80—90 °C for 3 h, then allowed to cool to room temperature. The precipitates were collected by filtration and washed with EtOH. The residue was dissolved in 2.5 N NaOH (190 ml), and the solution was stirred at 70—80 °C for 4 h. The mixture was acidified with concentrated HCl to pH 2, and the resulting precipitates were collected by filtration and washed with MeOH. Recrystallization from $CHCl_3$–MeOH gave IIIa (15.3 g, 81%) as pale yellow needles, mp > 300 °C. IR (KBr): 1695, 1665, 1300 $cm^{-1}$. The NMR spectral data and elemental analysis data are shown in Table II.

Compounds IIIb, c were obtained in the same manner as described for IIIa. The yields, melting points, NMR spectral data, and elemental analysis data are shown in Table II.

**Preparation of the Heteroaromatic Carboxylic Esters (IVa, b). Methyl 2,3-Dihydro-2-oxobenzothiazole-6-carboxylate (IVa)**——A suspension of IIa (1.2 g, 5.3 mmol) in pyridine (10 ml) was stirred at 80—90 °C for 3 h, then allowed to cool. The precipitates were collected by filtration. The residue was dissolved in MeOH (15 ml), and $K_2CO_3$ (0.1 g) was added to the solution. The reaction mixture was refluxed for 2.5 h, and concentrated *in vacuo*. The residue was poured into 0.5 N HCl and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was recrystallized from MeOH to give IVa (0.76 g, 69%) as colorless needles, mp 216—217 °C. IR (KBr): 1730, 1690, 1295 $cm^{-1}$. NMR (400 MHz, DMSO-$d_6$) $\delta$: 3.93 (3H, s, $CH_3$), 7.18 (1H, d, $J$=8.3 Hz, $C_4$-aromatic H, positive NOE (9%) was observed on irradiation at $\delta$ 9.38), 8.00 (1H, dd, $J$=2.0, 8.3 Hz, aromatic H), 8.13 (1H, d, $J$=2.0 Hz, aromatic H), 9.38 (1H, br s, NH). *Anal.* Calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.69. Found: C, 51.40; H, 3.41; N, 6.50.

Compound IVb was prepared in the same manner as described for IVa. Compound IVb was obtained as colorless needles, mp 189—191 °C (EtOH). IR (KBr): 3165, 1715, 1700, 1620 $cm^{-1}$. NMR (200 MHz, $CDCl_3$) $\delta$: 1.39 (3H, t, $J$=7.1 Hz, $CH_3$), 3.58 (2H, s, $CH_2$), 4.36 (2H, q, $J$=7.1 Hz, $CH_2$), 6.92 (1H, d, $J$=8.1 Hz, aromatic H), 7.72—7.91 (2H, m, aromatic H), 8.19 (1H, br s, NH). *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.17; H, 5.45; N, 6.74.

**Preparation of the 1-Heteroaroylpiperazines (Va, VIa, and XIa, b). 6-(4-Benzyl-1-piperazinylcarbonyl)-3-methyl-2,4(1*H*,3*H*)-quinazolinedione (XIb)**——A solution of DEPC (4.96 g, 32 mmol) in DMF (20 ml) was added dropwise to a suspension of X (6.0 g, 27 mmol) and 1-benzylpiperazine (7.1 g, 41 mmol) in DMF (80 ml) at 0—5 °C with stirring, and then a solution of triethylamine (11.4 ml, 80 mmol) in DMF (20 ml) was added dropwise to the cooled mixture. The whole was stirred for 30 min at 0—5 °C, and then at room temperature for 1.5 h. The reaction mixture was poured into ice-water and the resulting precipitates were collected by filtration. The residue was recrystallized from EtOH to give XIb (9.6 g, 93%) as colorless needles, mp 223—224 °C (dec.). IR (KBr): 1720, 1670, 1630 $cm^{-1}$. The NMR spectral data and elemental analysis data are shown in Table III.

Compounds Va, VIa, and XIa were obtained in the same manner as described for XIb. The yields, melting points, NMR spectral data, and elemental analysis data are shown in Table III.

**Preparation of the Hydrochlorides (Vb, VIb, and VIIa, b). 3,4-Dihydro-3-methyl-6-[4-(4-oxo-4-phenylbutyl)-1-piperazinylcarbonyl]-2(1*H*)-quinazolinone Hydrochloride (VIIa)**——IIIc (1.5 g, 7.3 mmol) was treated with DEPC and

1-(4-oxo-4-phenylbutyl)piperazine dihydrochloride[10] in DMF as described for XIb. The residue obtained was dissolved in methanolic hydrogen chloride and concentrated to dryness. The product was recrystallized from MeOH to give VIIa (2.4 g, 73%) as colorless needles, mp 189—193 °C. IR (KBr): 3445, 2440, 1665, 1620 $cm^{-1}$. The NMR spectral data and elemental analysis data are shown in Table III.

Compounds Vb, VIb,[11] and VIIb were obtained in the same manner as described for VIIa. The yields, melting points, NMR spectral data, and elemental analysis data are shown in Table III.

**Methyl 2,4-Dioxo-3-methyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate (IX)**——A mixture of VIII (43 g, 0.21 mol) and methylisocyanate (36.4 ml, 0.62 mol) in acetone (50 ml) was heated at 70—80 °C for 6 h in a stainless-steel autoclave. After the reaction was completed, the precipitates were collected by filtration, and dried under reduced pressure. The crystals obtained were dissolved in dry EtOH (250 ml), and NaOEt (1 g) was added to the solution. The mixture was heated to reflux for 2 h. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration. Recrystallization from MeOH gave IX (24 g, 50%) as pale grey needles, mp 271—273 °C (dec.). IR (KBr): 3265, 1745, 1725, 1645 $cm^{-1}$. NMR (200 MHz, DMSO-$d_6$) $\delta$: 3.27 (3H, s, $CH_3$), 3.88 (3H, s, $COOCH_3$), 7.26 (1H, d, $J$=8.6 Hz, $C_8$-aromatic H), 8.17 (1H, dd, $J$=2.0, 8.6 Hz, $C_7$-aromatic H), 8.47, (1H, d, $J$=2.0 Hz, $C_5$-aromatic H), 11.62 (1H, br s, NH). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.39; H, 4.07; N, 11.90.

**2,4-Dioxo-3-methyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic Acid (X)**——A mixture of IX (23 g, 98 mmol), 2.5 N NaOH (100 ml), and MeOH (20 ml) was refluxed for 1.5 h. The mixture was poured into ice-water, and acidified with concentrated HCl. The resulting crystals were separated by filtration, and washed with small portions of water. Recrystallization from DMF–$H_2O$ gave X (18 g, 83%) as a white powder, mp > 300 °C. IR (KBr): 1750, 1680, 1645, 1630 $cm^{-1}$. NMR (200 MHz, DMSO-$d_6$) $\delta$: 3.27 (3H, s, $CH_3$), 3.38 (1H, br s, NH), 7.25 (1H, d, $J$=8.5 Hz, $C_8$-aromatic H), 8.16 (1H, dd, $J$=2.0, 8.5 Hz, $C_7$-aromatic H), 8.47 (1H, d, $J$=2.0 Hz, $C_5$-aromatic H), 11.77 (1H, br s, COOH). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55, H, 3.66; N, 12.72. Found: C, 54.36; H, 3.67; N, 12.59.

**Method of Pharmacological Studies**——Inotropic and chronotropic effects of test compounds were examined by the use of isolated, blood-perfused dog heart preparations. The hearts were excised from mongrel dogs of either sex weighing 8—14 kg. The isolated, blood-perfused papillary muscle and sino-atrial node preparations were prepared according to the methods of Endoh and Hashimoto[12] and Kubota and Hashimoto,[13] respectively. The preparations were cross-circulated through the cannulated arteries with blood from a donor dog anesthetized with sodium pentobarbital and receiving heparin. The perfusion pressure was kept constant at 100 mmHg. The papillary muscle was stimulated at a frequency of 2 Hz and tension developed by the muscle was measured with a force displacement transducer (Shinkoh, UL-20-240). Sinus rate was measured by the use of a cardiotachometer (Data Graph, T-149) triggered by developed tension of the right atrium. Blood flow through the cannulated arteries was measured with an electromagnetic flow meter (Nihon Kohden, MF-27). Recording of these parameters was done on an ink-writing rectigraph (Sanei Instrument, 8S). The compounds were injected intraarterially with microsyringes.

## References and Notes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