# Synthesis of New 1,2,4-Triazolo[4,3-*b*]pyridazines and Related Compounds



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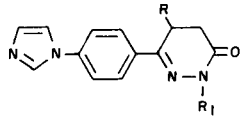
Received December 14, 1984

The synthesis of novel 6-[4-(1*H*-imidazol-1-yl)phenyl]-1,2,4-triazolo[4,3-*b*]pyridazines **8a-f** and related compounds is described. Although the intermediate hydrazine derivatives **7** and **9** possess good positive inotropic activity, the fused bicyclic pyridazines **8a-f** are significantly less potent than the 3(2*H*)-pyridazinone **5**. Compounds **8a-f** are potent but nonselective inhibitors of cardiac phosphodiesterase.

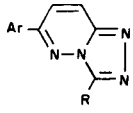
*J. Heterocyclic Chem.*, **22**, 1045 (1985).

In our ongoing cardiotonics program, we have discovered a series of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones and 6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones which are a novel class of orally active positive inotropic agents [1,2]. Two members of this class, **1a** and **1b**, are presently under development for the treatment of congestive heart failure. We have also shown that substitution at the amide nitrogen in the 4,5-dihydro-3(2*H*)-pyridazinone ring **1c** reduces the potency of the inotropic activity [3]. In order to fully evaluate the contribution of the amide function to the inotropic activity as well

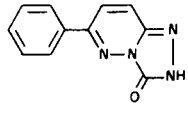


1a, $R_1$ = R = H (CI-914)
1b, $R_1$ = H, R = Me (CI-930)
1c, $R_1$ = Me, R = H

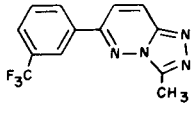
as to other biological activity we have synthesized some fused triazolo and imidazolo pyridazine derivatives. Fused triazolo heterocycles are also of interest because of their interesting biological activity. Triazolo[4,3-*b*]pyridazine derivatives **2a** and **2b** are useful as anxiolytic agents [4] and antihypertensive agents [5,6]. Some of these agents are also useful for treatment of asthma [7,8]. CL 218,872 (**3**), a novel triazolo[4,3-*b*]pyridazine, has been a useful probe in labeling the benzodiazepine receptor in rat brain [9]. Certain of the triazolo[4,3-*a*][1,4]benzodiazepines **4** are reported to be potent central nervous system depressents [10]. This paper discusses synthesis and biological activity of some of the fused 1,2,4-triazolo[4,3-*b*]pyridazine and imidazo[1,2-*b*]pyridazine derivatives.



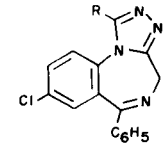
**2a** R = H, $CH_3$
Ar = 2 or 3-pyridyl



**2b**



**3** CL 218,872



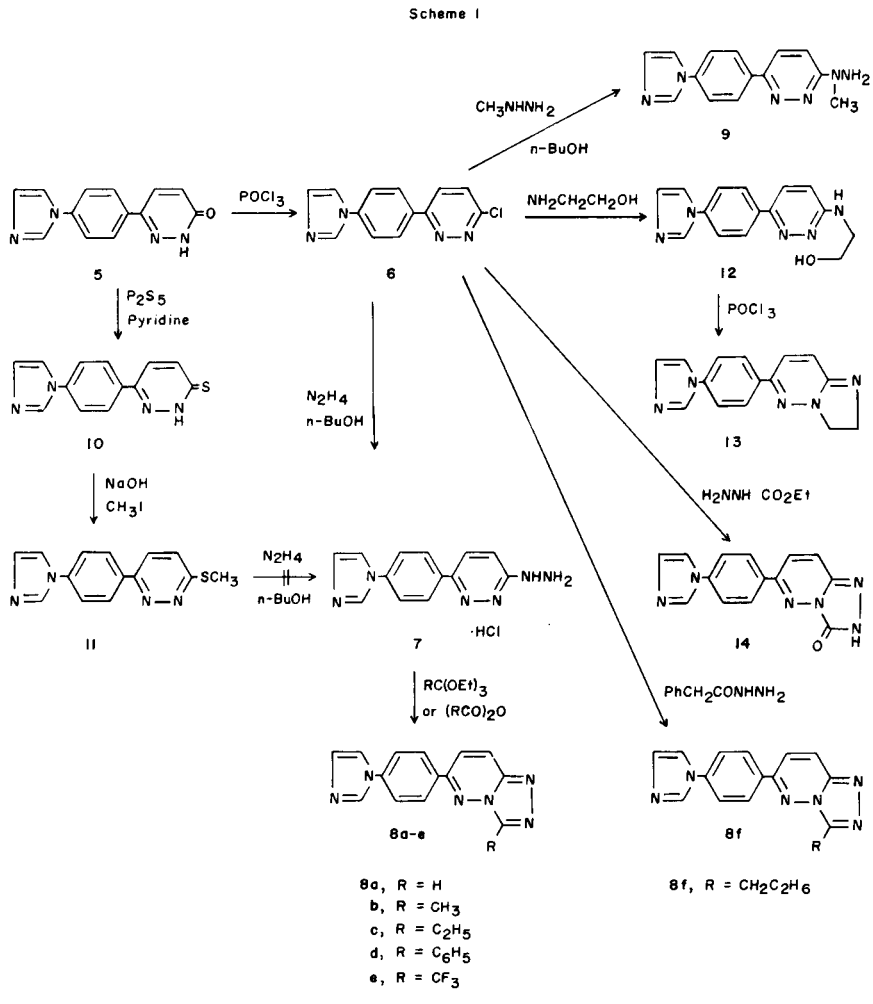
**4a** R = H
**4b** R = $CH_3$

The triazolopyridazines **8a-f** were synthesized from **5** according to Scheme 1.

The pyridazinone **5** was converted to the chloropyridazine **6** by treatment with phosphorus oxychloride at 90°. Substantial polymerization was observed at higher temperature. Compound **6** was reacted with hydrazine hydrate in 1-butanol to yield **7**. A second route for the synthesis of **7** was also investigated. The amide **5** was converted to the thioamide **10** by treatment with phosphorus pentasulfide in pyridine. Direct displacement of the thioxo group with hydrazine failed. Compound **10** was converted to the methylthio derivative **11** by treatment with iodomethane in presence of base. Compound **11** on treatment with hydrazine hydrate also failed to give the hydrazine **7**. The reaction of **6** with methyl hydrazine gave **9** [4]. The structure of **9** was proven from elemental analysis and spectral data. The ir spectrum showed bands at 3310 $cm^{-1}$ and 3420 $cm^{-1}$ and 3420 $cm^{-1}$ ($NH_2$). The nmr spectrum in DMSO-$d_6$ showed a multiplet at $\delta$ 3.4 ppm (3H, Me), broad hump at $\delta$ 4.3-5.3 ppm (2H, $NH_2$, exchangeable) and another multiplet at $\delta$ 7-8.5 ppm (9H, aromatics). The mass spectrum showed ions corresponding to masses 266 (M), 250 (M-$NH_2$), and 221 (M-45).

Compound **7** was converted to triazoles **8a-d** by treatment with requisite orthoesters under acid catalyzed conditions. Compound **8e** was obtained by reacting **7** with a mixture of trifluoroacetic anhydride and trifluoroacetic acid. Condensation of **6** with benzeneacetic acid hydrazide in 1-butanol produced **8f**. For the synthesis of **13**, the chloride **6** was reacted with ethanolamine to produce the (hydroxyethyl)amino compound **12** which was cyclized

Scheme I




with phosphorus oxychloride to **13**. Reaction of **6** with ethyl carbazate gave **14**. The ir spectrum of **14** showed bands at 1715 $cm^{-1}$ (C=O) and 3410 $cm^{-1}$ (NH) confirming the structure. The structure of **14** was also confirmed by nmr spectrum in DMSO-$d_6$ which showed a singlet at $\delta$ 10.7 (1H, NH).

The properties of these compounds are summarized in Table 1.

Compounds **7** and **9** showed good positive inotropic activity, although a log less potent than the pyridazinone **5** [1]. All the fused pyridazine derivatives showed relatively weaker activity. This finding seems to demonstrate the structural requirement of the amide moiety (NH-CO) in substituted phenyl 3(2*H*)-pyridazinones, namely, **5** for potent positive inotropic activity. Compounds **8a-b** have also shown weak CNS activity.

Since inhibition of cardiac phosphodiesterase (PDE) fraction III is believed to be the mechanism of positive inotropic activity of pyridazinones **1a-b** [2], some of the fused triazolo[4,3-*b*]pyridazines **8a,b,d,f** were evaluated for the PDE inhibitory activity. All of these agents demonstrate potent but nonselective inhibitory effects. Compound **8d** is the most potent in this series and the PDE inhibitory activity is comparable to that of papaverine [11].

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The $^1H$ nmr spectra were recorded (DMSO-$d_6$ unless otherwise stated) on a Varian EM 390 and XL 200 spectrometer with TMS as an internal standard. The ir spectra were recorded on a Nicolet FT-IRMX-1 as FT-IR2 OSX spectrophotometer. Mass spectra were obtained on a Finnigan 1015 Quadrupole mass spectrometer. The uv spectra were recorded in methanol on a Carry 118 UV-Visible recording spectrophotometer. The tlc were performed on silica gel G (Stahl) plates with dichloromethane/methanol (9:1), and the plates were visualized with uv light and/or iodine vapor.

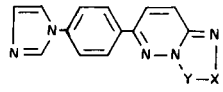
3-Chloro-6-[4-(1*H*-imidazol-1-yl)phenyl]pyridazine (**6**).

A suspension of 20 g of 6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (**5**) [1] in 200 ml of phosphorus oxychloride was heated gradually in an oil bath to 90-92°. The reaction mixture was held at that temperature for three additional hours, cooled, and filtered. The residue was dissolved in water, the *p*H of the solution was adjusted to 7.0 and the product filtered. The orange solid was recrystallized from methanol to yield 12 g of **6**, mp 229-230° dec.

*Anal.* Calcd. for $C_{13}H_9ClN_4$: C, 60.83; H, 3.53; N, 21.83; Cl, 13.81. Found: C, 60.44; H, 3.71; N, 21.81; Cl, 14.06.

Table 1

Fused Pyridazine Derivatives



| No. | X | Y | Yield % | Crystn Solvent | mp, °C | Formula | Analyses % Calcd/Found C | H | N | Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| **8a** | N | CH | 75 | Methanol | 293-294 | $C_{14}H_{10}N_6$ | 56.23 | 3.68 | 28.11 | 11.88 |
| | | | | | | HCl | 56.26 | 3.82 | 28.30 | 11.81 |
| **8b** | N | $C(CH_3)$ | 75 | THF/Ethanol | 209-210 | $C_{15}H_{12}N_6 \cdot$ | 64.31 | 4.43 | 30.01 | |
| | | | | | | $0.2\ H_2O$ | 64.07 | 4.57 | 29.60 | |
| **8c** | N | $C(C_2H_5)$ | 60 | 2-Propanol | 178-179 | $C_{16}H_{14}N_6$ | 66.19 | 4.86 | 28.95 | |
| | | | | | | | 65.88 | 5.08 | 28.78 | |
| **8d** | N | $C(C_6H_5)$ | 70 | 2-Propanol | 238-239 | $C_{20}H_{14}N_6 \cdot$ | 69.52 | 4.28 | 24.33 | |
| | | | | | | $0.4\ H_2O$ | 69.60 | 4.33 | 23.93 | |
| **8e** | N | $C(CF_3)$ | 50 | Ethanol | 237-238 | $C_{15}H_9F_3N_6 \cdot$ | 49.06 | 2.51 | 21.93 | |
| | | | | | | $0.5\ CF_3CO_2H$ | 49.41 | 2.45 | 21.70 | |
| **8f** | N | $C(CH_2C_6H_5)$ | — | Methanol | >280 | $C_{21}H_{16}N_6 \cdot$ | 64.26 | 4.43 | 21.42 | |
| | | | | | | $HCl \cdot 2H_2O$ | 64.10 | 4.33 | 21.37 | |
| **13** | $CH_2$ | $CH_2$ | 40 | | 202-203 | $C_{15}H_{13}N_5$ | 68.42 | 4.98 | 26.60 | |
| | | | | | | | 68.05 | 4.99 | 26.65 | |
| **14** | NH | CO | 13 | DMF | 358-359 | $C_{14}H_{10}N_6O$ | 60.42 | 3.62 | 30.20 | |
| | | | | | | | 60.03 | 3.96 | 29.88 | |

3-Hydrazino-6-[4-(1*H*-imidazol-1-yl)phenyl]pyridazine Monohydrochloride (**7**).

A mixture of 1.2 g of **6** and excess hydrazine hydrate (1.2 ml) in 1-butanol (12 ml) was heated under reflux for three hours. The reaction mixture was cooled, filtered, and the residue was washed with ethanol and air-dried to give 1 g of **7** as the hydrochloride, mp 214-216° dec.

*Anal.* Calcd. for $C_{13}H_{12}N_6 \cdot HCl$: C, 54.02; H, 4.50; N, 29.08; Cl, 12.29. Found: C, 53.62; H, 4.67; N, 29.35; Cl, 12.24.

Similarly, refluxing a mixture of 1.2 g of **6** and excess methylhydrazine (0.5 ml) in 1-butanol (12 ml) for five hours gave 1 g of 3-[4-(1*H*-imidazol-1-yl)phenyl]-6-(1-methylhydrazino)pyridazine (**9**), mp 229-230° dec.

*Anal.* Calcd. for $C_{14}H_{14}N_6$: C, 63.15; H, 5.26; N, 31.57. Found: C, 62.98; H, 5.46; N, 31.56.

General Procedure for the Synthesis of 1,2,4-Triazolo[4,3-*b*]pyridazine Derivatives **8a-d**.

A mixture of **7** and an excess of requisite triethylorthoester was heated under reflux until tlc shows absence of starting material (*ca.* 30 minutes). The resultant solid was filtered, washed with hexane, and recrystallized to yield **8a-d**.

6-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**8e**).

A mixture of 0.98 g of **7** in 5 ml of trifluoroacetic anhydride and 5 ml of trifluoroacetic acid containing 0.3 g of potassium acetate was heated at 100° for four hours. The solution was concentrated under reduced pressure, the residue was treated with water and the *p*H of the solution was adjusted to 6. The precipitate was filtered, washed with water and recrystallized to give 0.5 g of **8e**.

6-[4-(1*H*-Imidazol-1-yl)phenyl]-3-(phenylmethyl)-1,2,4-triazolo[4,3-*b*]-pyridazine Monohydrochloride (**8f**).

A mixture of 1.2 g (0.005 mole) of **6** and 0.75 g of benzeneacetic acid hydrazide in 15 ml of 1-butanol was heated under reflux for eight hours. Butanol was distilled under *vacuo* and the residue was treated with water. The precipitate was filtered and recrystallized twice from methanol to give **8f**.

6-[4-(1*H*-Imidazol-1-yl)phenyl]-3(2*H*)-pyridazinethione (**10**).

A solution of 4.8 g (0.2 mole) of **5** and 4.5 g (0.2 mole) of phosphorus pentasulfide in 50 ml of pyridine was heated at 95° for six hours. Pyridine was distilled under reduced pressure, and the residue was stirred briefly with 5% aqueous sodium hydroxide and filtered. The filtrate was made slightly acidic (*p*H ~ 6) and filtered. The residue was crystallized from chloroform/ethanol (1:1) to give 2.65 g of **10**, mp 270-271° dec.

*Anal.* Calcd. for $C_{13}H_{10}N_4S$: C, 61.34; H, 3.93; N, 22.01. Found: C, 61.05; H, 4.21; N, 21.85.

3-[4-(1*H*-Imidazol-1-yl)phenyl]-6-(methylthio)pyridazine (**11**).

A solution of 0.45 mole of iodomethane in 3 ml of methanol was added to a solution of 1.46 g of **10** in 5.9 ml of aqueous sodium hydroxide (1*N*). A precipitate appeared instantaneously which was filtered, washed with water and dried to give 1.1 g of **11**, mp 194-196°.

*Anal.* Calcd. for $C_{14}H_{12}N_4S$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.79; H, 4.02; N, 20.71.

2,3-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]imidazo[1,2-*b*]pyridazine (**13**).

A mixture of 3.2 g of **6** in 5 ml of 2-aminoethanol was heated under reflux for six hours. Excess 2-aminoethanol was distilled, the residue was treated with ethanol and filtered to yield 0.8 g of **12**, mp 232-233°. A mixture of 0.8 g of **12** and phosphorus oxychloride (4 ml) was refluxed for three hours. The suspension was poured into water and the solution was adjusted to *p*H 8. The product was filtered, washed with water, and air-dried to give **13**.

6-[4-(1*H*-Imidazol-1-yl)phenyl]-1,2,4-triazolo[4,3-*b*]pyridazin-3(2*H*)-one (**14**).

A mixture of 3.2 g of **6** and 2.5 g of ethyl hydrazinecarboxylate in 1-butanol (30 ml) was heated under reflux for 24 hours. The resultant solid was filtered, washed with ethanol and recrystallized to yield **14**.

Acknowledgement.

The author is thankful to Dr. J. A. Bristol for many helpful suggestions. The author is also thankful to Dr. F. A. MacKellar and his associates for ir and nmr spectra as well as for the elemental analysis. The author would like to acknowledge the technical assistance of Mr. B. L. Duell.

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