Synthesis of 4-Amino-6-phenyl-3(2*H*)-pyridazinones: A General Procedure

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A method for the synthesis of 3,4-dichloro-6-phenylpyridazine **5** was described. The compound **5** was used as an intermediate for the synthesis of a series of 4-amino-6-phenyl-3(2*H*)-pyridazinones.

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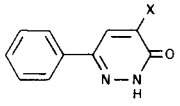
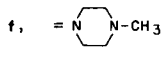
As part of our ongoing research on new cardiovascular agents, a general synthetic procedure for the preparation of 4-amino-6-phenyl-3(2*H*)-pyridazinones **1a-h** was required. A literature search revealed the synthesis of 4-amino-6-methyl-3(2*H*)-pyridazinone **2b** by Hoffman degradation [1] of the corresponding carboxamide **2a**. This procedure is suitable only for the synthesis of the compound **1a** and



1a, X = NH_2
b, = $CONH_2$
c, = $N(CH_3)_2$
d, = $NH(CH_2)_3N(CH_3)_2$
e, = $NH(CH_2)_3CH_3$

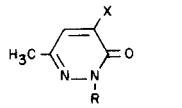


f, =

g, =

h, =

i, = H
j, = Br
k, = Cl



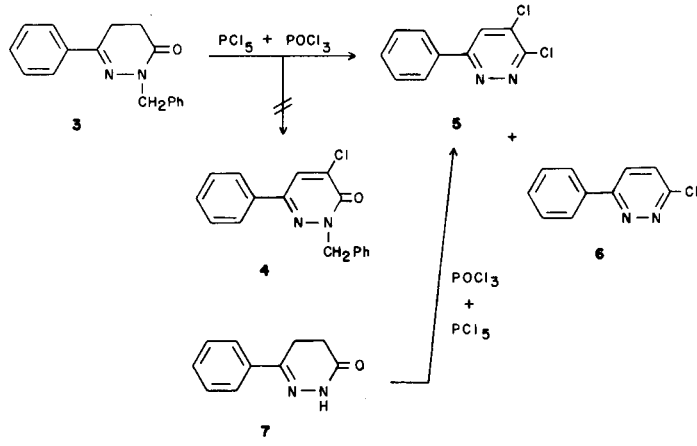
2a, R = H, X = $CONH_2$
b, R = H, X = NH_2
c, R = Ph, X = H
d, R = Ph, X = Cl

cannot be applied for the preparation of other analogs, such as **1c-h**. Since there was no general method available for the synthesis of **1a-h**, the 4-chloro **1j** or 4-bromo **1k** intermediates were considered ideal precursors for such a synthesis. Attempted halogenation of **1i** using bromine and sodium hydroxide, pyridinium perbromide hydrobromide, and sulfuryl chloride failed to give the desired product, **1j** or **1k**, respectively.

It has been repeated that treatment of 6-methyl-2-phenyl-3(2*H*)-pyridazinone **2c** with phosphorus pentachloride [2] or phosphorus pentachloride/phosphoryl chloride mixture [3] leads to the formation of 4-chloro-6-methyl-2-phenyl-3(2*H*)-pyridazinone **2d**. This procedure is limited to the synthesis of 4-amino-2,6-disubstituted-3(2*H*)-pyridazinone and is not applicable to the synthesis of 4-amino-6-substituted-3(2*H*)-pyridazinones **1a-h**.

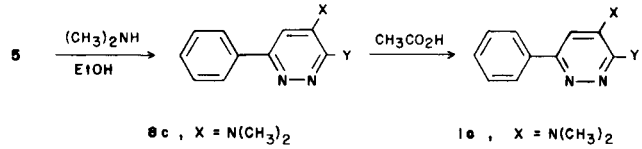
We wish to report in this paper that compound **3**, when reacted with a mixture of phosphorus pentachloride and phosphoryl chloride gave 3,4-dichloro-6-phenylpyridazine **5** along with a small amount of 3-chloro-6-phenylpyridazine **6** [2,3] and not the 4-chloro-6-phenyl-2(phenylmethyl)-3(2*H*)-pyridazinone **4**, as would be expected from the results mentioned above.

Scheme 1



Under similar reaction conditions compound **7** gave a very poor yield (*ca.* 10%) of **5** (Scheme 1). Compound **5** was found to be a very useful intermediate for the synthesis of a variety of 4-amino-6-phenyl-3(2*H*)-pyridazinones. Treatment of **5** with an ethanolic solution of dimethylamine afforded **8c** [4] which upon hydrolysis gave 4-(dimethylamino)-6-phenyl-3(2*H*)-pyridazinone **1c** (Scheme 2).

Scheme 2

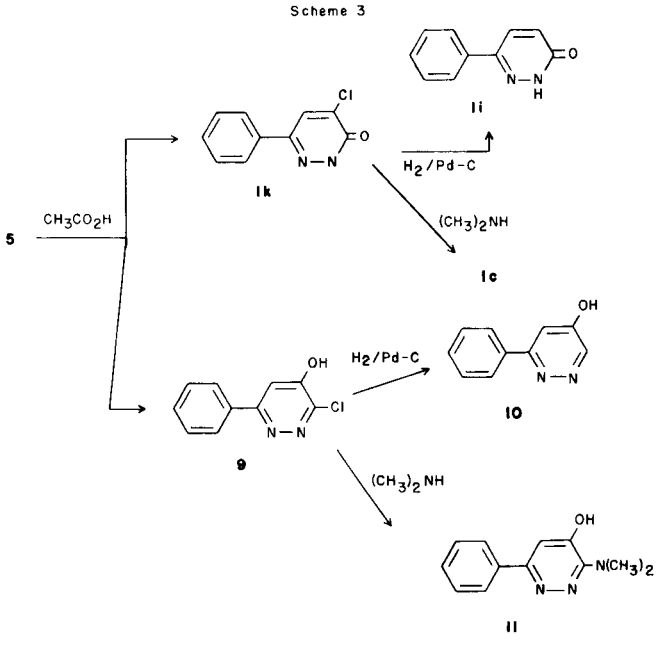


8c, X = $N(CH_3)_2$, Y = Cl
1c, X = $N(CH_3)_2$, Y = OH

The structure of **1c** was confirmed from the analytical and spectral data, and independent synthesis (Scheme 3). Thus, the ir spectra of **1c** in chloroform revealed the presence of a cyclic lactam C=O (1643 cm^{-1}) and a NH

(3480 cm^{-1}) bands. The ^{1}H-nmr spectrum of **1c** (DMSO-d_6) exhibits a singlet at δ 3.1 (6H, $N(CH_3)_2$), a singlet at δ 5.7 (1H, $HC{=}CN(CH_3)_2$), a multiplet at δ 7.3-8.0 (5H, aromatic), and a singlet at δ 13.0 (1H, NHCO).

Scheme 3



Hydrolysis of **5** gave a 3:1 mixture of **1k** and **9**. Catalytic reduction of **1k** gave a known compound, 6-phenyl-3(2*H*)-pyridazinone **1i** [5], whereas catalytic reduction of **9** gave a new compound **10**. Treatment of **1k** with dimethylamine gave **1c**. The analytical and spectral data of **1c** prepared by this route was in agreement with the structure assigned earlier. Similar treatment of **9** with dimethylamine gave **11**.

Other 4-amino-pyridazinones **1d-h** were prepared from **5** by reaction with the desired amine to give **8d-h**, followed by hydrolysis according to Scheme 2. Compound **1a** was synthesized from **1b** by Hoffman degradation. The characteristics of 3-chloro-6-phenyl-4-pyridazinamines and 4-amino-6-phenyl-3(2*H*)-pyridazinones are summarized in Tables 1 and 2, respectively.

EXPERIMENTAL

Melting points were recorded on Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. The ir spectra were recorded on a Nicolet MX-1 IR spectrophotometer and the ^{1}H-nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as the internal standard.

4,5-Dihydro-6-phenyl-2-(phenylmethyl)-3(2*H*)-pyridazinone (**3**).

A mixture of γ-oxobenzenebutanoic acid (60 g, 0.33 mole), 1-(phenylmethyl)hydrazine (65.7 g, 0.33 mole), and sodium acetate (95.6 g, 0.7 mole) in 700 ml of aqueous ethanol (85%) was heated under reflux for 18 hours. Ethanol was removed and the residue was treated with water. The semisolid mass was extracted with chloroform and finally purified by crystallisation from ether/isopropyl ether, mp 63-64°.

Anal. Calcd. for $C_{17}H_{16}NO_2$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.23; H, 6.09; N, 10.51.

3,4-Dichloro-6-phenylpyridazine (**5**).

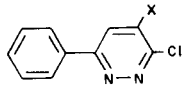
A mixture of 4,5-dihydro-6-phenyl-2-(phenylmethyl)-3(2*H*)-pyridazinone (**3**) (70 g, 0.26 mole), phosphorus pentachloride (350 g), and phosphoryl chloride (150 ml) was heated under reflux for 8 hours. Most of the phosphoryl chloride was distilled under reduced pressure and the residue was decomposed with ice water. The crystalline material which separated upon cooling was filtered, washed with water, and recrystallised from ethanol to give 29 g of the product, mp 164-165° (50%).

Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.33; H, 2.26; N, 12.44; Cl, 31.55. Found: C, 53.53; H, 2.64; N, 12.45; Cl, 31.26.

From the mother liquor a second crop of material was obtained which contained some 3-chloro-6-phenylpyridazine as evidenced from tlc and nmr (*ca.* 10%).

Table 1

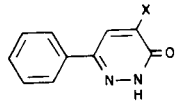
3-Chloro-6-phenyl-4-pyridazinamines



Compound	X	Mp °C	Solvent of Crystallization	Yield (%)	Analysis % Calcd./Found C	H	N	Cl	S	Molecular Formula
8c	$N(CH_3)_2$	89-90	Ethanol	90	61.67 61.62	5.13 5.18	17.98 18.05	15.20 15.27		$C_{12}H_{12}ClN_3$
8d	$HN(CH_2)_3N(CH_3)_2$	89-90	*iso*-Propyl ether	69	61.96 61.92	6.54 6.46	19.27 19.39	12.22 12.56		$C_{15}H_{19}ClN_4$
8e	$HN(CH_2)_3CH_3$	oil	—	77	64.27 64.53	6.11 6.21	16.06 16.20	13.57 13.30		$C_{14}H_{16}ClN_3$
8f	4-Methylpiperazino-	110-111	Ethanol	64	60.14 59.99	6.08 6.12	18.71 18.49	11.86 12.22		$C_{14}H_{17}ClN_4O{\cdot}0.6H_2O$
8g	Morpholino-	148-150	—	90	60.98 60.98	5.05 5.18	15.24 15.19	12.88 12.48		$C_{14}H_{14}ClN_3O$
8h	Thiomorpholino-	86-87	—	86	57.63 57.34	4.80 4.99	14.40 14.18	12.17 12.20	10.97 11.10	$C_{14}H_{14}ClN_3S$

Table 2

4-Amino-6-phenyl-3(2*H*)-pyridazinones



Compound	X	Mp °C	Solvent of Crystallization	Yield (%)	Analysis % Calcd./Found C	H	N	S	Molecular Formula
1a	NH_2	322-323	Acetic acid	80	63.41	4.87	21.76		$C_{10}H_9ON_3$
					63.07	4.90	21.89		
1b	$CONH_2$	312-313	Acetic acid	68	61.39	4.22	19.53		$C_{11}H_9O_2N_3$
					61.08	4.16	19.47		
1c	$N(CH_3)_2$	186-188	Ethanol	60	66.97	5.95	19.53		$C_{12}H_{13}ON_3$
					67.00	5.99	19.63		
1d	$HN(CH_2)_2N(CH_3)_2$	152-153	Dichloromethane	50	66.15	7.40	20.57		$C_{15}H_{20}ON_4$
					66.14	7.47	20.54		
1e	$NH(CH_2)_3CH_3$	150-151	Ethanol	60	69.13	6.99	17.28		$C_{14}H_{17}ON_3$
					69.05	7.16	17.20		
1f	Thiomorpholino-	267-268	DMF	60	58.67	6.19	18.25	11.58	$C_{15}H_{18}ON_4 \cdot HCl$
					58.59	6.51	18.29	11.74	
1g	Morpholino-	187-188	DMF	69	65.35	5.88	16.33		$C_{14}H_{15}O_2N_3$
					65.22	5.62	16.23		
1h	*N*-Methylpiperazino-	190-191	DMF	74	61.53	5.49	15.38	11.72	$C_{14}H_{15}ON_3S$
					61.63	5.71	15.40	12.01	

General Procedure for the Preparation of 3-Chloro-6-phenyl-4-pyridazinamine **8a-h**.

A mixture of **5** (0.59 g, 0.002 mole) in ethanol (5 ml) containing an excess of the desired amine (0.006 mole) was heated on a steam bath for five hours. The ethanol was evaporated and the residue was treated with water. The solid was filtered and crystallised to give the product **8a-h** (see Table 1).

General Procedure for the Preparation of 4-Amino-6-phenyl-3(2*H*)-pyridazinone **1a-h**.

A mixture of **8a-h** (.006 mole) in acetic acid (8 ml) was heated under reflux for six hours. After the removal of the acetic acid the residue was treated with water and the solution was made basic (*p*H 8.0) with aqueous ammonium hydroxide. The product which separated was filtered and crystallised to give **1a-h** (see Table 2).

Hydrolysis of **5**.

A mixture of **5** (4.49 g, 0.019 mole) and acetic acid (22 ml) was heated under reflux for six hours. The reaction mixture was cooled. The precipitated product was filtered, washed with water, and subjected to fractional crystallisation to give **9** (0.8 g), mp 283-234°; ir (chloroform): 1670 cm^{-1} (this band was absent in potassium bromide spectrum); ^{1}H-nmr (DMSO-d_6): δ 6.7 (S, 1H), 7.4-7.9 (m, 5H, aromatic) and 13.6 (broad, 1H, NH).

Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 58.11; H, 3.38; N, 13.55; Cl, 17.19. Found: C, 58.33; H, 3.48; N, 13.53; Cl, 17.16.

The filtrate was concentrated to give a second crop of **1k** (2 g), mp 220-221°; ir (potassium bromide): 1663 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 7.3-8.0 (m, 5H, aromatic), 8.35 (S, 1H) and 13.5 (S, 1H, NHCO).

Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 58.11; H, 3.38; N, 13.55; Cl, 17.19. Found: C, 58.32; H, 3.47; N, 13.71; Cl, 17.45.

3-(Dimethylamino)-6-phenyl-4-pyridazinol (**11**).

A mixture of **9** (0.89, 0.004 mole) and 40% aqueous dimethylamine (3 ml, 0.03 mole) in ethanol (12 ml) was heated on a steambath for 18 hours. The ethanol was removed, the residue was diluted with water, filtered, and crystallised to give **11**, mp 231-232°; ^{1}H-nmr (DMSO-d_6): δ 3.0 (S, 6H, $N(CH_3)_2$), 6.23 (S, 1*H*), 7.4-7.8 (m, 5*H*), and 13.8 (S, 1*H*, NHCO).

Anal. Calcd. for $C_{12}H_{13}N_3O \cdot 0.1H_2O$: C, 66.42; H, 6.08; N, 19.37. Found: C, 66.29; H, 5.77; N, 18.94.

Similarly the reaction of **1k** with dimethylamine gave a product which was identical in all respects with **1c**.

Compound **1k** (1.2 g) was dissolved in tetrahydrofuran (20 ml) and hydrogenated using 10% Pd-C. After the usual workup the product was crystallised from ethanol to afford 6-phenyl-3(2*H*)-pyridazinone **1i** [5], mp 198-199°.

Similarly compound **9** was subjected to catalytic hyrogenation to afford 6-phenyl-4-pyridazinol **10**, mp 256-257°; ir (chloroform): 1625 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 5.6 (d, 1H, J = 2 Hz), 7.4-8.0 (m, 6H, aromatic) and 13.5 (S, 1H, NHCO).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.76; H, 4.65; N, 16.27. Found: C, 69.36; H, 4.82; N, 16.30.

2,3-Dihydro-3-oxo-6-phenyl-4-pyridazinecarboxamide (**1b**).

Ethyl 2,3-dihydro-3-oxo-6-phenyl-4-pyridazinecarboxylate [6] was dissolved in methanol (500 ml), saturated with ammonia, and the mixture was allowed to stand overnight at room temperature when the product began to crystallise. Methanol was removed, the solid was filtered, and crystallised to give **1b** (see Table 2).

4-Amino-6-phenyl-3(2*H*)-pyridazinone (**1a**).

Bromine (2 g, 0.025 mole) was added dropwise to an ice-cold solution of sodium hydroxide (2.5 g, 0.062 mole) in water (40 ml). After addition was over the solution was stirred for an additional ten minutes. The above amide **1b** (2.15 g, 0.01 mole) was added portionwise with stirring at 0° until dissolution. The solution was stirred for an additional half an hour at 0° followed by slow heating on a steam bath for 3 hours when a solid crystallised. The product was filtered, washed with water, and crystallised to give **1a** (see Table 2).

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REFERENCES AND NOTES

[1] T. Nakagome, A. Kobayashi and A. Misaki, *Chem. Pharm. Bull.*, **14**, 1074 (1966).

[2] W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 549 (1947).

[3] H. Gregory and L. F. Wiggins, *ibid.*, 2546 (1949).

[4] K. Eichenberger, R. Rometsch and J. Druey, *Helv. Chem. Acta*, **39**, 1755 (1956).

[5] S. Gabriel and G. Colman, *Chem. Ber.*, **32**, 399 (1899).

[6] S. Yurugi, M. Hieda, T. Fushimi and M. Tomimoto, *Chem. Pharm. Bull.*, **19**, 2354 (1971).