Synthesis of 6-Substituted-4,5-dihydro-3(2*H*)-pyridazinones

P. G. Baraldi*, A. Chiarini and A. Leoni

Dipartimento di Scienze Farmaceutiche, Università di Bologna,
via Belmeloro 6, 40126 Bologna, Italy

S. Manfredini, D. Simoni and V. Zanirato

Dipartimento di Scienze Farmaceutiche, Università di Ferrara,
via Scandiana 21, 44100 Ferrara, Italy

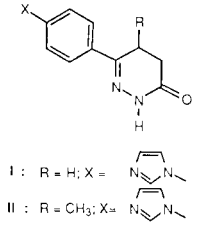
Received August 9, 1989

A convenient synthetic method for the pharmaceutically important 6-substituted-4,5-dihydro-3(2*H*)-pyridazinones is described. The synthetic strategy is based on Δ^2-isoxazolines chemistry which were in turn unmasked by N-O bond cleavage and cyclized to the target compounds.

J. Heterocyclic Chem., **27**, 557 (1990).

Since Curran and McEvoy [1] have reported that many 6-substituted-phenyl-4,5-dihydro-3(2*H*)-pyridazones exhibited considerable and long lasting activity as hypotensive agents, great chemical and pharmacological interest toward compounds containing this pharmacophore moiety has been developed.

In recent reports [2], antiagregatory and antiulcer activity coupled with hypotensive action for 4,5-dihydro-3(2*H*)-pyridazones analogues have also been described. More recently, Bristol *et al.* [3] have reported a new class of potent positive inotropic agents, incorporating the 4,5-dihydro-3(2*H*)-pyridazinones **I** and **II**. The same authors pointed out a five-points model in order to rationalize the structural features required for positive inotropic activity, stressing the role of a basic or hydrogen bond acceptor site opposite the dipole (carbonyl) at the other end of the



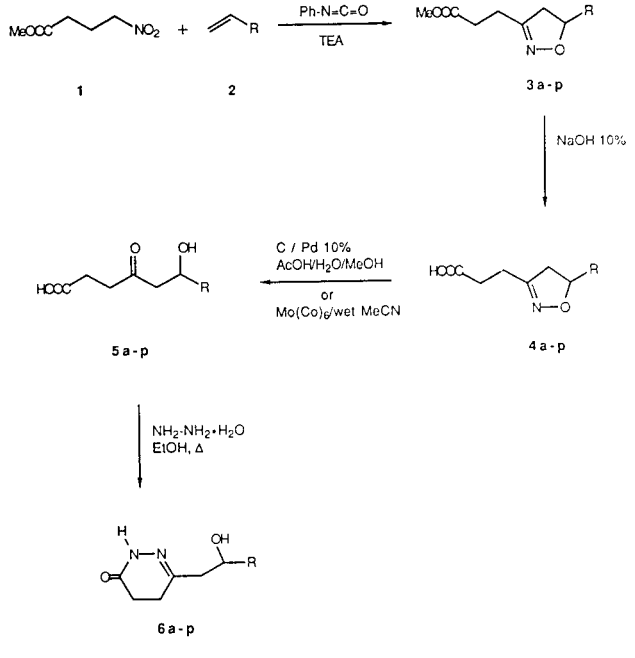
molecule. The inotropic activity of both of these latter compounds is thought to be due to inhibition of a cardiac c-AMP phosphodiesterase (*PDE III*), an enzyme responsible of the hydrolysis of cyclic adenosine monophosphate to its ring-opened form.

In order to investigate the flexibility of the structural requirements delineated from the model, we undertook a program aimed to synthesize a series of compounds **6a-p** analogues of **I** and **II** featured by the introduction of an alkyl or an aralkyl hydroxylated side chain in the C6 position of the nucleus.

This structural modification should confer more conformational freedom to the substituent in C6 position, still retaining the hydrogen bond acceptor property through the hydroxyl function. Preliminary studies designed to examine the inotropic and chronotropic effects of some representative compounds **6b**, **6h** and **6m** on isolated cardiac preparations from guinea pig hearts showed no significant activity with respect to reference compounds **I** or **II**. Detailed biological activity of these new series of 3(2*H*)-pyridazinones will be reported in due course.

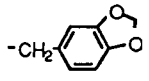
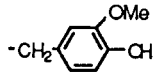
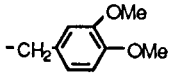
The synthesis of the new series of 4,5-dihydro-3(2*H*)-pyridazinones **6a-p** was carried out by the general methodology depicted in Scheme 1. Ring closure of the requisite β-keto acid **5a-p** was readily accomplished in high yield with hydrazine in refluxing ethanol according to standard procedures [1]. Therefore, the main synthetic problem emerging from the retrosynthetic analysis of the target compounds **6a-p** was the construction of the functionalized carbon chain of **5a-p**.

These intermediates were obtained through a two-step sequence involving a 1,3-dipolar cycloaddition reaction



R = a: n-C_3H_7; b: n-C_4H_9; c: i-C_4H_9; d: n-C_6H_{13}; e: n-C_8H_{17}; f: n-C_9H_{19}; g: n-$C_{10}H_{21}$; h: n-$C_{11}H_{23}$; i: n-$C_{12}H_{25}$; l: n-$C_{14}H_{29}$; m: -CH_2-Ph; n: -CH_2-Ph-3,4-methylendioxy; o: -CH_2-Ph-3-methoxy, 4-hydroxy; p: -CH_2-Ph-3,4-dimethoxy.

Table 1. Experimental data for 3,5-disustituted-4,5-dihydroisoxazoles **4a-p**

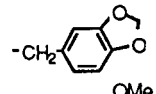
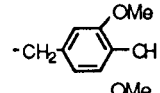
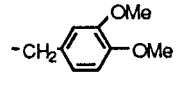
Comp	Product	M.p.°C	Yield (%)	Empirical formula	Analysis (%) calcd./(found) C	H	N	Ref
a	n-C_3H_7	52-53[a]	71	$C_{10}H_{17}NO_3$	20.28	8.6	7.03	
					20.30	8.6	7.03	
b	n-C_4H_9			$C_{10}H_{17}NO_3$				[4]
c	i-C_4H_9			$C_{10}H_{17}NO_3$				[4]
d	n-C_6H_{13}			$C_{12}H_{21}NO_3$				[4]
e	n-C_8H_{17}			$C_{14}H_{27}NO_3$				[4]
f	n-C_9H_{19}			$C_{16}H_{29}N0_3$				[4]
g	n-$C_{10}H_{21}$			$C_{17}H_{31}N0_3$				[4]
h	n-$C_{11}H_{23}$	92-93[b]	90	$C_{17}H_{31}NO_3$	68.64	10.51	4.71	
					68.70	10.51	4.72	
i	n-$C_{12}H_{25}$	95-96[b]	93	$C_{18}H_{33}NO_3$	69.41	10.68	4.50	
					69.41	10.68	4.50	
l	n-$C_{14}H_{29}$	101-102[b]	91	$C_{20}H_{37}NO_3$	70.75	10.99	4.13	
					70.78	10.99	4.12	
m	-CH_2-Ph	80-81[b]	87	$C_{13}H_{15}NO_3$	66.93	6.48	6.01	
					66.95	6.48	6.02	
n		100-102[b]	91	$C_{14}H_{15}NO_5$	68.55	6.16	5.71	
					68.55	6.16	5.71	
o		oil	85	$C_{14}H_{17}NO_5$	--	--	--	
p		104-105[a]	90	$C_{14}H_{19}NO_5$	68.94	7.33	5.36	
					68.94	7.32	5.37	

[a]= ethyl acetate-light petroleum; [b]= chloroform-light petroleum;

between the nitrile oxide generated from 4-nitrobutyric acid methyl ester (**1**) and the appropriate alkenes **2a-p** followed by reductive ring opening of the formed heterocycle. The chosen methodology is based on the central assumption that a 3,5-disubstituted-4,5-dihydroisoxazoline can be easily transformed into a β-hydroxyketone through well-established procedures providing the required functions in the correct position.

Thus, cycloaddition of the nitrile oxide generated *in situ* from **1** according to Mukaiyama conditions to alkenes **2a-p** proceed smoothly affording the 3,5-disubstituted-4,5-dihydroisoxazolines **3a-p** in good yield (70-80%) [4]. These cycloadducts can quickly be purified either by flash chromatography as esters or by hydrolytic conversion to the corresponding acids **4a-p** depending on the employed reductive opening of the labile N-O bond. Recently, tak-

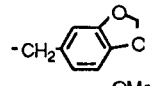
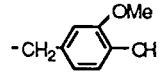
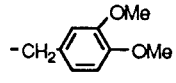
Table 2. Experimental data for ß-substituted-ß-hydroxyketones **5a-p**

Comp	Product	M.p.°C	Yield (%)	Empirical formula	Analysis (%) calcd./(found) C	H	Ref
a	n-C_3H_7	40-42[a]	61	$C_9H_{16}O_4$	57.43	8.57	
					57.54	8.55	
b	n-C_4H_9	58-59[a]	77	$C_{10}H_{18}O_4$	59.39	8.97	
					59.62	9.00	
c	i-C_4H_9	45-47[b]	68	$C_{10}H_{18}O_4$	59.39	8.97	
					59.43	8.94	
d	n-C_6H_{13}	76-77[c]	72	$C_{12}H_{22}O_4$	62.58	9.63	
					62.60	9.64	
e	n-C_8H_{17}	87-88[d]	73	$C_{14}H_{26}O_4$	65.09	10.14	
					65.12	10.14	
f	n-C_9H_{19}	84-85[d]	71	$C_{15}H_{28}O_4$	66.14	10.36	
					66.10	10.35	
g	n-$C_{10}H_{21}$	--	-	--	--	--	[6]
h	n-$C_{11}H_{23}$	93-94[d]	81	$C_{17}H_{32}O_4$	67.96	10.74	
					67.97	10.74	
i	n-$C_{12}H_{25}$	97-98[d]	79	$C_{18}H_{34}O_4$	68.75	10.90	
					68.80	10.91	
l	n-$C_{14}H_{29}$	103-104[d]	71	$C_{20}H_{38}O_4$	70.13	11.18	
					70.14	11.18	
m	-CH_2-Ph	oil	62	$C_{13}H_{16}O_4$	--	--	
n		oil	65	$C_{14}H_{16}O_4$	--	--	
o		oil	67	$C_{14}H_{18}O_4$	--	--	
p		oil	70	$C_{15}H_{20}O_4$	--	--	

[a]= pentane; [b]= hexane; [c]= light petroleum; [d]= diethyl ether-light petroleum;

ing advantage of the Nitta's studies [5] on molybdenum hexacarbonyl, we have developed a general procedure based on this reagent to promote the conversion of 4,5-dihydroisoxazoline to β-hydroxyketones [6] and applying it successfully to some of the esters here described **3g,i**. However, in this work we have generally employed the catalytic hydrogenation [7] which was performed in a mixture of methanol, water and acetic acid 4:2:4 in the presence of 10% palladium/charcoal affording the β-ketols **5a-p** in high yield without detectable elimination products.

Table 3. Experimental data for 6-substituted-4,5-dihydropyridazones **6a-p**

Comp	Product	M.p.°C[a]	Yield (%)	Empirical formula	Analysis (%) calcd./(found)		
					C	H	N
a	n-C_3H_7	59-60	71	$C_9H_{16}N_2O_2$	58.68	8.75	15.20
					58.75	8.71	15.17
b	n-C_4H_9	57-58	82	$C_{10}H_{18}N_2O_2$	60.58	9.15	14.13
					60.67	9.10	14.10
c	i-C_4H_9	133-134	75	$C_{10}H_{18}N_2O_2$	60.58	9.15	14.13
					60.60	9.15	14.13
d	n-C_6H_{13}	65-66	73	$C_{12}H_{22}N_2O_2$	63.69	9.80	12.38
					63.73	9.77	12.34
e	n-C_8H_{17}	72-73	73	$C_{14}H_{26}N_2O_2$	66.11	10.30	11.01
					66.15	10.36	10.97
f	n-C_9H_{19}	73-74	78	$C_{15}H_{28}N_2O_2$	67.13	10.52	10.44
					67.31	10.55	10.41
g	n-$C_{10}H_{21}$	82-83	87	$C_{16}H_{30}N_2O_2$	68.04	10.71	9.92
					68.06	10.70	9.90
h	n-$C_{11}H_{23}$	84-85	83	$C_{17}H_{32}N_2O_2$	68.88	10.88	9.45
					68.90	10.88	9.43
i	n-$C_{12}H_{25}$	90-91	79	$C_{18}H_{34}N_2O_2$	69.63	11.04	9.02
					69.70	11.05	9.00
l	n-$C_{14}H_{29}$	97-98	78	$C_{20}H_{38}N_2O_2$	70.96	11.31	8.27
					70.99	11.30	8.24
m	-CH_2-Ph	144-145	70	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06
					67.23	6.94	12.04
n		121-123	75	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47
					68.85	6.60	11.46
o		138-140	70	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37
					68.30	7.37	11.36
p		117-119	75	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.56
					69.24	7.75	10.54

[a]Crystallization solvent chloroform-diethyl ether.

EXPERIMENTAL

Reaction courses and product mixture were routinely monitored by thin-layer chromatography (tlc) on silica gel precoated F_{254} Merck plates. Infrared spectra (ir) were measured on a Perkin Elmer 257 instrument. Nuclear magnetic resonance (nmr) spectra were determined in deuteriochloroform solution with a Brucker AC 200 spectrometer and peak positions are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Light petroleum refers to the fractions boiling range 40-60°. Melting points were obtained in open capillary tubes and are uncorrected. Column chromatographies were performed with

Merck 60-200 mesh silica gel. All of the products reported showed ir and nmr spectra in agreement with the assigned structures.

3-(2-carbomethoxyethyl)-5-substituted-Δ^2-isoxazolines **3a-p**.

General Procedure.

Phenyl isocyanate (25 ml, 0.23 mole) was slowly added to a mixture of nitro derivative **1** (15 g, 0.1 mole) and the appropriate alkene, **2a-p**, in dry benzene (60 ml) containing several drops of triethylamine. The mixture was stirred overnight at ambient temperature and then refluxed for 2 hours. The precipitated diphenylurea was removed by filtration and the filtrate was concentrated to dryness. The crude residue was reacted, without further purification, in the next step.

3-(2-carboxyethyl)-5-substituted-Δ^2-isoxazolines **4a-p**.

General Procedure.

A solution of the crude residue, **3a-p**, in 20 ml of methanol was added to 0.5 *N* sodium hydroxide (20 ml) and the mixture was stirred overnight. The solvent was concentrated *in vacuo* and the residue, diluted with water (30 ml), filtered through a celite pad, extracted with diethyl ether (2 x 20 ml) and finally acidified with 2*N* hydrochloric acid. The precipitated acid, **4a-p**, was separated by filtration and crystallized. Crystallization solvents, yields and physical data are reported in Table 1. Spectral data of **4h** and **4m** are given as examples:

Compound **4h** had ir (potassium bromide): ν cm^{-1}, 3500, 1720, 1620; ^1H nmr (deuteriochloroform): δ 0.90 (br t, 3H), 1.40 (m, 20 H), 2.6-3.2 (m, 6 H), 4.60 (m, 1 H), 11.00 (br s, 1 H).

Compound **4m** had ir (film): ν cm^{-1}, 3200, 1720, 1620, 1600; ^1H nmr (deuteriochloroform): δ 2.50-3.20 (m, 8 H), 4.70 (m, 1 H), 7.30 (m, 5 H), 10.70 (br s, 1 H).

4-(β-hydroxy-substituted)-4-oxobutyric Acids **5a-p**.

General Procedure.

A solution of **5a-p** (3.0 mmoles) in methanol/acetic acid/water (9 ml, 5/3/1) mixture was hydrogenated at 1 atmosphere in the presence of catalytic W-2 Raney nickel for 5 hours at ambient temperature. After filtration through a celite pad the solvent was concentrated to dryness and the residue was purified by chromatography on silica gel (eluent, ethyl acetate/methanol/acetic acid, 20/2/0.3). Crystallization solvents, yields and physical data are reported in Table 2. Spectral data of **5h** and **5m** are given as examples.

Compound **5h** had ir (potassium bromide): ν cm^{-1}, 3500, 1700; ^1H nmr (deuteriochloroform): δ 0.90 (br t, 3H), 1.10-1.60 (m, 20 H), 2.30-2.70 (m, 6 H), 4.05 (m, 1 H), 6.00-7.00 (br s, 2 H).

Compound **5m** had ir (film): ν cm^{-1}, 3300-3500, 1700-1600; ^1H nmr (deuteriochloroform): δ 2.30-2.70 (m, 8 H), 4.30 (m, 1 H), 6.80 (br s, 2 H), 7.20 (m, 5 H).

6-Substituted-4,5-dihydro-3(2*H*)-pyridazinones **6a-p**.

General Procedure.

A mixture of **5a-p** (100 mmoles) and 99% hydrazine monohydrate (150 mmoles) in 95% ethanol (50 ml) was heated at reflux for 1 hour. After this period the solution was cooled and treated with water. The precipitated compound was then crystallized. Crystallization solvents, yields and physical data are reported in Table 3. Spectra data of **6h** and **6m** are reported as examples.

Compound **6h** had ir (potassium bromide): ν cm^{-1}, 3500-3100, 1700-1690; nmr (deuteriochloroform): δ 0.90 (br t, 3 H), 1.20-1.70 (m, 20 H), 2.30-2.70 (m, 6 H), 3.20 (br s, 1 H), 4.05 (m, 1 H), 9.05 (br s, 1 H).

Compound **6m** had ir (potassium bromide): ν cm^{-1}, 3500-3100, 1720, 1690; ^1H nmr (deuteriochloroform): δ 2.30-2.60 (m, 6 H), 2.70-2.90 (m, 2 H), 3.90-4.20 (br m, 2 H), 7.20 (m, 5 H), 9.90 (br s, 1 H).

REFERENCES AND NOTES

[1] W. V. Curran and A. Ross, *J. Med. Chem.*, **17**, 273 (1974); F. J. McEvoy and G. R. Allen Jr., *J. Med. Chem.*, **7**, 281 (1974).

[2] T. Yamada, Y. Nobuhara, A. Yamaguchi and M. Ohki, *J. Med. Chem.*, **25**, 975 (1982).

[3] J. A. Bristol, I. Sircar, W. H. Moos, D. B. Evans and R. E. Weishaar, *J. Med. Chem.*, **27**, 1099 (1984); I. Sircar, B. L. Duell, G. Bobowski, J. A. Bristol, R. E. Weishaar and D. B. Evans, *J. Med. Chem.*, **28**, 1405 (1985).

[4] P. G. Baraldi, D. Simoni and P. A. Borea, *Farmaco Ed. Sci.*, **38**, 411 (1983).

[5] M. Nitta, A. Yi and T. Kobayashi, *Bull. Chem. Soc. Japan*, **58**, 991 (1985).

[6] P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini and D. Simoni, *Synthesis*, 276 (1987).

[7] A. P. Kozikowski, *Acc. Chem. Res.*, **17**, 410 (1984).