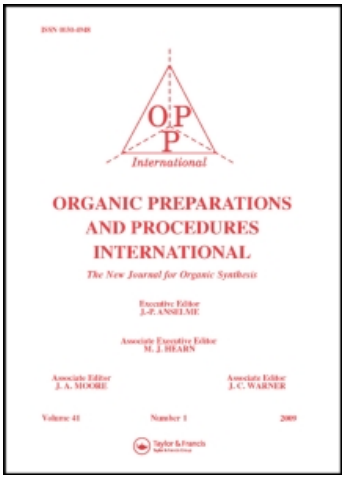

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SYNTHESIS OF 6-(2,2-DIMETHYL-3,4-DIHYDRO-3-OXO-1,4(*2H*)-BENZOXAZIN-7-YL)PYRIDAZIN-3-ONES

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SYNTHESIS OF 6-(2,2-DIMETHYL-3,4-DIHYDRO-3-OXO-1,4(2*H*)-BENZOXAZIN-7-YL)PYRIDAZIN-3-ONES

Submitted by (03/09/04)

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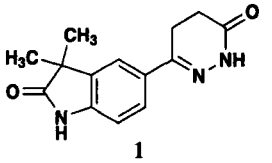
In recent years, a number of highly potent positive inotropes which increase the force of contraction of heart muscle, have been described in the literature.[1-3] These compounds incorporate a 4,5-dihydro-2*H*-pyridazin-3-one ring bearing aromatic nuclei, *e. g.* indolinan (**1**)[4] and

bemoradan (**2**)[5] derivatives. We have thus undertaken the synthesis of 6-(2,2-dimethyl-3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl)-4-hydroxy-4,5-dihydro-2*H*-pyridazin-3-one (**5b**) and 6-(2,2-dimethyl-3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl)-2*H*-pyridazin-3-ones (**7a-d**) in order to extend our knowledge of structure-activity relationships.



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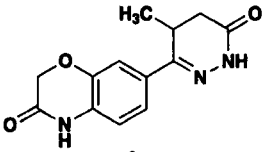
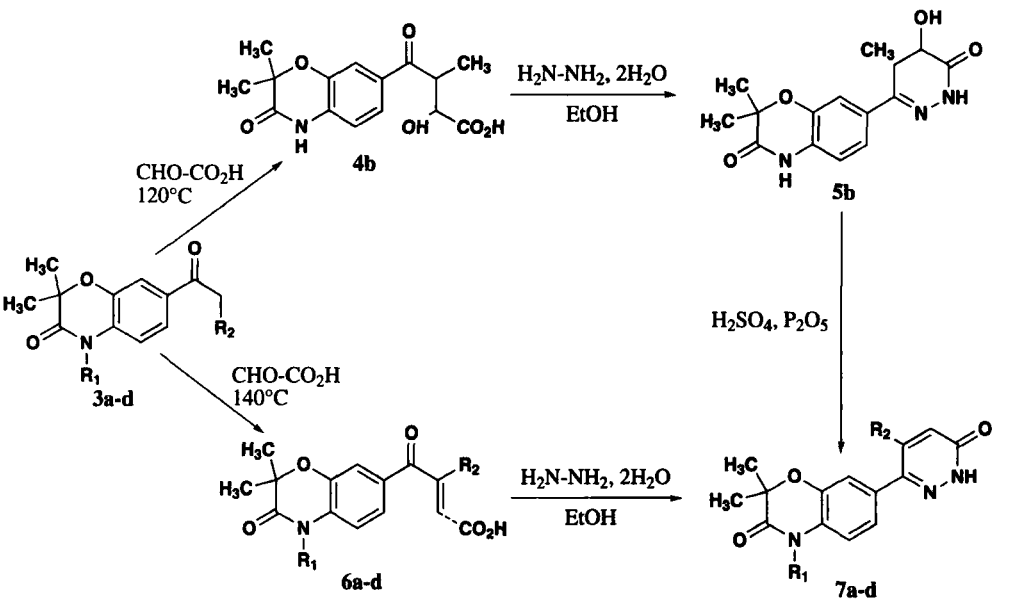


2

The starting 7-acylbenzoxazinones (**3a-d**) were prepared by well known methods.[6-8] Condensation between acetophenone derivatives and glyoxylic acid generally involve the use of acidic[9] or basic[10] catalysts or by sonication with indium chloride.[11] Heating compound **3b** with one equivalent of glyoxylic acid at 120°C, without catalyst and solvent, furnished the corresponding α-hydroxyacid (**4b**) in 60% yield. Cyclization of **4b** to the 4-hydroxypyridazinone (**5b**) was accomplished by treatment of **4b** by hydrazine hydrate[12,13] in 65% yield.



a) R_1, R_2 = H; b) R_1, R_2 = CH_3; c) R_1 = CH_3, R_2 = H; d) R_1, R_2 = CH_3

Dehydration of **5b** to the pyridazinone (**7b**) was performed with sulfuric acid and phosphorus pentoxide as dehydration agent. These pyridazinones (**7a-d**) can be more easily obtained in two steps from 7-acylbenzoxazinones (**3a-d**). Condensation and dehydration by melting at 140°C acyl benzoxazinones (**3a-d**) with glyoxylic acid provided acrylic acid derivatives **6a-d** in 55-75% yield. Treatment of the resultant keto acrylic acids with hydrazine hydrate afforded pyridazinones (**7a-d**) with good yields (55-80%).

EXPERIMENTAL SECTION

Mps were determined on a BÜCHI B-540 apparatus and are uncorrected. Infrared spectra were recorded as thin films on potassium bromide plates on a BECKMAN ACCULAB IV spectrophotometer. ^{1}H NMR spectra were obtained on a BRUKER AC 300 P (LARMN, Université de Lille 2), using TMS as internal standard. Elemental analyses were performed by C.N.R.S. – Vernaison.

4-(2,2-Dimethyl-3,4-dihydro-3-oxo-1,4(*2H*)-benzoxazin-7-yl)-2-hydroxy-3-methyl-4-oxo butanoic acid (4b).- A mixture of 4.6 g of **3b** (0.02 mol) and 1.85 g (0.02 mol) of glyoxylic acid was melted at 120°C for 2 h. The reaction mixture was cooled to room temperature and 200 mL of 1% sodium hydroxide solution was added. The resulting precipitate was filtered off and the aqueous filtrate was acidified with 10% hydrochloric acid to pH 3. The white precipitate was collected, washed with water and recrystallized from cyclohexane to yield 3.7 g (60%) of white solid, mp 80-82°C ; IR (cm^{-1}): 3500-3200 (OH, NH), 1750, 1720, 1660 (C=O); ^{1}H NMR ($CDCl_3$): d 1.35 (d, 3H, J = 8.5 Hz), 1.60 (s, 6H), 4.45 (m, 1H), 4.70 (m, 1H), 6.90 (m, 1H), 7.50-7.75 (m, 3H), 9.45 (s, 1H), 9.60 (s, 1H).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.57; N, 4.55; Found: C, 58.83; H, 5.60; N, 4.26

General Procedure for 6a-d.- A mixture of 0.02 mol of **3a-d** and 1.5 g (0.02 mol) of glyoxylic acid was melted at 140°C for 4 h. The reaction mixture was cooled to room temperature and 200 mL of 1% sodium hydroxide was added. The resulting precipitate was filtered off and the aqueous filtrate was acidified with 10% hydrochloric acid to pH 3. The white precipitate was collected, washed with water, dried and recrystallized from the appropriate solvent (*Tables 1 and 2*).

General Procedure of 5b and 7a-d.- A mixture of 0.02 mol of **4b** or **6a-d** was dissolved in 100 mL of ethanol and 2.05 g (0.03 mol) of hydrazine hydrate was added. The reaction mixture was heated at reflux for 3 h, cooled and the white crystals were collected, washed with ethanol, dried and recrystallized from the appropriate solvent (*Tables 1 and 2*).

6-(2,2-Dimethyl-3,4-dihydro-3-oxo-1,4(*2H*)-benzoxazin-7-yl)-4-hydroxy-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (5b).- Yield: 65%; mp 258-260°C (ethanol); IR (cm^{-1}): 3500-3400 (OH, NH), 1770, 1680 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.00 (d, 3H, J = 8.5 Hz), 1.45 (s, 6H), 4.25 (m, 1H), 5.40 (m, 1H), 6.95 (s, 1H), 7.30-7.50 (m, 3H), 10.60 (s, 1H), 10.80 (s, 1H).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.64; N, 13.85; Found: C, 59.61; H, 5.60; N, 13.55

Dehydration of 5b into 7b.- A solution of 3.05 g (0.01 mol) of **5b** in 100 mL of 97% H_2SO_4 and 500 mg of phosphorus pentoxide (0.001 mol) was stirred at 50°C for 3 h. The reaction mixture was cooled to room temperature, poured into cold water and the resulting precipitate was collected and recrystallized from ethanol to afford colorless crystals in 85% yield. mp > 300°C (ethanol).

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.30; N, 14.72; Found: C, 63.28; H, 5.36; N, 14.54

Table 1. Yields, mps and Elemental Analyses of Compounds **6a-d** and **7a-d**

Cmpd	Yield(%)	mp(°C)	Elemental Analyses (*Found*)		
			C	H	N
6a	60	218-219[a]	61.07(*61.19*)	4.76(*4.56*)	5.08(*5.00*)
6b	70	135-136[b]	62.27(*62.33*)	5.22(*5.17*)	4.83(*4.88*)
6c	75	182-184[a]	62.27(*62.42*)	5.22(*5.15*)	4.83(*4.75*)
6d	55	209-212[b]	63.35(*63.15*)	5.64(*5.72*)	4.61(*4.56*)
7a	55	>300[a]	61.98(*62.01*)	4.83(*4.80*)	15.49(*15.58*)
7b	60	>300[a]	63.14(*63.40*)	5.30(*5.41*)	14.72(*14.48*)
7c	65	>300[a]	63.14(*63.40*)	5.30(*5.45*)	14.72(*14.44*)
7d	80	>300[a]	64.19(*64.41*)	5.72(*5.77*)	14.04(*13.91*)

a) From ethanol; b) From methanol.

Table 2. IR and ^{1}HNMR Data of Compounds **6a-d** and **7a-d**

Cmpd	IR (cm^{-1})	^{1}HNMR (δ)
6a	3500 (OH), 3300 (NH), 1780, 1720, 1650 (C=O)	[a]1.55 (s, 6H), 5.95 (d, 1H, J =15 Hz), 6.25 (d, 1H, J =15 Hz), 7.20-7.50 (m, 2H), 7.90 (d, 1H, J = 8 Hz), 9.80 (s, 1H), 10.20 (s, 1H).
6b	3500 (OH), 3300 (NH), 1775, 1720, 1650 (C=O)	[b]1.55 (s, 6H), 2.25 (s, 3H), 5.95 (s, 1H), 6.95 (d, 1H, J =7.5 Hz), 7.40 (d, 1H, J =2.1 Hz), 7.80 (dd, 1H, J = 7.5, 2.1 Hz), 9.60 (s, 1H), 10.50 (s, 1H)
6c	3500 (OH), 1780, 1720, 1650 (C=O)	[b]1.55 (s, 6H), 3.45 (s, 3H), 5.95 (d, 1H, J =15 Hz), 6.25 (d, 1H, J =15 Hz), 7.50 (m, 2H), 8.00 (dd, 1H, J = 7.5, 2.1 Hz), 10.50 (s, 1H)
6d	3500 (OH), 1780, 1740, 1650 (C=O)	[b]1.55 (s, 6H), 2.30 (s, 3H), 3.45 (s, 3H), 6.00 (s, 1H), 7.00 (d, 1H, J =7.5 Hz), 7.55 (d, 1H, J =2.1 Hz), 8.00 (dd, 1H, J = 7.5, 2.1 Hz), 10.50 (s, 1H)
7a	3500, 3400 (NH), 1780, 1680 (C=O)	[a]1.45 (s, 6H), 6.95 (d, 1H, J = 6.5 Hz), 7.25 (d, 1H, J = 6.5 Hz), 7.50 (m, 2H), 8.00 (d, 1H, J = 7.5 Hz), 10.40 (s, 1H), 10.80 (s, 1H)
7b	3500, 3450 (NH), 1780, 1685 (C=O)	[a]1.45 (s, 6H), 2.15 (s, 3H), 6.75 (s, 1H), 7.00 (d, 1H, J = 7.5 Hz), 7.80 (m, 2H), 10.50 (s, 1H), 10.75 (s, 1H)
7c	3450 (NH), 1760, 1680 (C=O)	[a]1.45 (s, 6H), 3.45 (s, 3H), 6.95 (d, 1H, J = 6.5 Hz), 7.25 (d, 1H, J = 6.5 Hz), 7.50 (m, 2H), 8.00 (d, 1H, J = 7.5 Hz), 10.80 (s, 1H)
7d	3500 (NH), 1750, 1680 (C=O)	[a]1.45 (s, 6H), 2.15 (s, 3H), 3.45 (s, 3H), 6.75 (s, 1H), 7.00-7.30 (m, 3H), 12.90 (s, 1H)

a) In DMSO-d_6; b) in $CDCl_3$.

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