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Synthesis of lactams with potential cardiotonic activity

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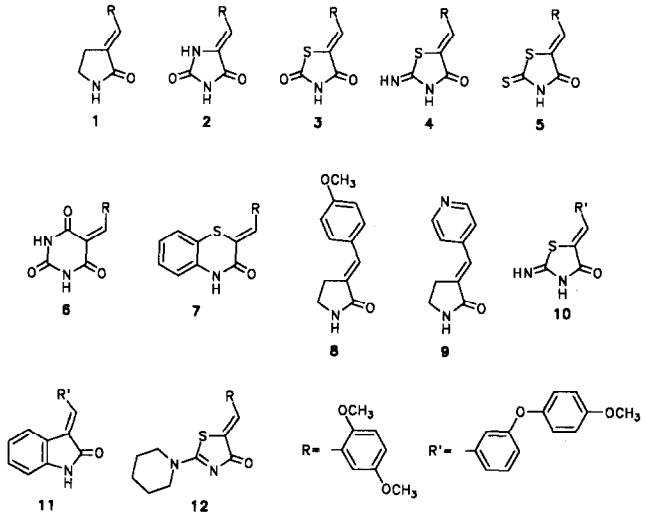
Introduction

In our previous papers on the synthesis of potential cardiotonic agents, we established that methoxyphenyl (in particular 2,5-dimethoxyphenyl) and pyridyl groups may be useful pharmacophores when connected to imidazothiazoles [1–5] and indolinones [6–8]. In order to study the effect of other heterocycles on the pharmacological activity, we synthesized and evaluated 2,5-dimethoxybenzylidene lactams different from 2-indolinone (**1–7**). Two analogs arising from pyrrolidin-2-one (**8**, **9**) and two 4-methoxyphenoxybenzylidene derivatives (**10–11**) were also prepared (scheme 1).

Chemistry

Compounds **2–6**, **10**, **11** were obtained *via* the Knoevenagel reaction between the appropriate unsubstituted lactam and an aldehyde (RCHO or R'CHO) in the presence of piperidine. It is known that aldol condensation of 2-pyrrolidinone with aromatic aldehydes cannot be carried out under these experimental conditions: the method used [9–11] involves protection of the lactam nitrogen function with an electron-withdrawing group which simultaneously enhances the acidity of the hydrogens α to the carbonyl. For this reason, compounds **1**, **8**, **9** were prepared from *N*-acetyl-2-pyrrolidinone [12] in the presence of sodium hydride. Compound **7** was prepared from 4*H*-benzo[1,4]thiazin-3-one and 2,5-dimethoxybenzaldehyde in sodium methoxide solution.

As far as the geometrical isomers are concerned, in every case we isolated 1 isomer only and we believe that compounds **1–12** belong to the configuration depicted in scheme 1: *E* for compounds containing the pyrrolidine ring (**1**, **8**, **9**, **11**) and *Z* for the others. Our postulate is supported by the results published in a recent series of interesting papers dealing with physical and spectroscopic measurements on 5-arylmethylene-hydantoins [13–16], 5-pyridylmethylene-hydantoins [17–19] and 5-furyl/5-thienylmethylene-hydantoins [20].



Scheme 1.

In 2 cases we found that piperidine had taken part in the above reactions: in the case of compound **6**, piperidine gave a white salt, but the expected orange compound precipitated by simply treating its methanol solution with hydrochloric acid. In the case of compound **5**, piperidine reacted at the 2-position of the thiazole ring with elimination of hydrogen sulfide and the resulting derivative was **12** (scheme 1). From a literature survey we found that analogs of compound **12** have already been obtained by refluxing 5-arylidenerhodanines (prepared in turn by means of the sodium acetate–acetic acid method [21]) with piperidine in ethanol [22–24]. It was possible to obtain compound **5** simply by carrying out the Knoevenagel reaction in the presence of triethylamine instead of piperidine.

Compounds **2**, **5**, **6** and **8** reported in the literature (see table I) have not been evaluated as potential cardiotonic agents.

The spectroscopic data of compounds **1–12** are in agreement with the assigned structures. The IR spectra (table I) show the NH groups in the range 3250–3100 cm^{-1} and the carbonyl groups between 1780–1660 cm^{-1}. Features common to the ^{1}H-NMR spectra (table II) are the singlets of the methoxy groups (3.7–3.8 ppm) and the peaks of the methine group: these are singlets in the range 6.6–8.5 ppm, except in the pyrrolidinones (**1**, **8**, **9**) where they are triplets (7.0–7.4 ppm) because of coupling with the protons at position 4. The molecular ion peak (table II) is always detectable in the mass spectrum; it is the base peak in compounds **3–5**, **9**, **11** and a prominent peak (25–98%) in all the others.

Table I. Compounds **1–12**.

Comp	*Formula (mw)*	*Mp (°C)*	ν_{max}[a], *cm*$^{-1}$
1	$C_{13}H_{15}NO_3$ (233.3)	-177–180	1695,1305, 1280, 1210
2	$C_{12}H_{12}N_2O_4$ (248.2)	247–250[b]	1780, 1725, 1665, 1495
3	$C_{12}H_{11}NO_4S$ - (265.3)	280–284 dec	1730, 1680,1590, 1345
4	$C_{12}H_{12}N_2O_3S$ (264.3)	244–246 dec	1660, 1500, 1240, 1145
5	$C_{12}H_{11}NO_3S_2$ (281.3)	253–255[c]	1700, 1570, 1495, 1225
6	$C_{13}H_{12}N_2O_5$ (276.2)	274–276[d]	1755, 1675, 1570, 1260
7	$C_{17}H_{15}NO_3S$ (313.4)	199–204	1660, 1590, 1280, 1015
8	$C_{12}H_{13}NO_2$ (203.2)	203–205[e]	1675, 1640, 1600, 1250
9	$C_{10}H_{10}N_2O$ (174.2)	210–214	1690, 1650, 1595, 1285
10	$C_{17}H_{14}N_2O_3S$ (326.4)	269–273 dec	1675, 1570, 1500, 1230
11	$C_{22}H_{17}NO_3$ (343.4)	132–133	1710, 1610, 1500, 1205
12	$C_{17}H_{20}N_2O_3S$ (332.4)	175–178	1680, 1600, 1560, 1490

[a]The NH groups give broad signals in the range 3250–3100 cm^{-1};[b]lit [25], mp: 249–251°C; [c]lit [26], mp: 257–259°C; [d]lit [27], mp: 270–272°C dec; [e]lit [9], mp: 200–201°C.

Pharmacological results

Compounds **1–12** were tested on spontaneously beating guinea-pig atria according to the procedure described under *Experimental protocols*. Table III shows the results obtained in comparison with sulmazole.

Of all the 2,5-dimethoxybenzylidene lactams investigated, compound **4** was the most potent inotropic agent. The weak positive inotropism of barbituric acid derivative **6** is interesting in view of a very recent report on the negative inotropic effects of barbiturates [28]. The contrast may be similar to that for the 1,4-dihydropyridines (a well-known family of calcium antagonists displaying negative inotropic activity). These heterocycles may be modified in order to produce positive inotropic agents: for example, changing 2 substituents in the nifedipine molecule leads to BAY K 8644, which shows effects that are diametrically opposite to those of the calcium antagonists [29].

In the search for a new lead in the field of compounds different from 2,5-dimethoxybenzylidene lactams (**8–12**), the activity of 3-pyridin-4-ylmethylene-pyrrolidin-2-one **9** may be promising.

Experimental protocols

Chemistry

The melting points are uncorrected. Analyses (C, H, N) were within ± 0.4% of the theoretical values. TLC was performed on Bakerflex plates (silica gel IB2-F); the eluent was a mixture of petroleum ether/acetone in various proportions. The IR spectra were recorded in Nujol mulls on a Perkin–Elmer 298. The NMR spectra were recorded on a Varian EM-390 (90 MHz) or on a Varian Gemini (300 MHz) using TMS as internal standard. The EI–MS were recorded at 70 eV on a VG 7070E. Compounds **1–12** were prepared from commercially available lactams: pyrrolidin-2-one (**1**, **8**, **9**), imidazolidine-2,4-dione (hydantoin) (**2**), thiazolidine-2,4-dione (**3**), 2-iminothiazolidin-4-one (pseudothiohydantoin) (**4**, **10**), 2-thioxothiazolidin-4-one (rhodanine) (**5**, **12**), pyrimidine-2,4,6-trione (barbituric acid) (**6**) 4*H*-benzo[1.4]thiazin-3-one (**7**) and 1,3-dihydroindol-2-one (indolinone) (**11**). These compounds were reacted with 2,5-dimethoxybenzaldehyde (**1–7**, **12**), 4-methoxybenzaldehyde (**8**), 4-pyridinecarboxaldehyde (**9**) or 3-(4-methoxyphenoxy)benzaldehyde (**10**, **11**). Three general procedures were employed:

Table II. ^{1}H-NMR and MS of compound **1–12**.

Comp	^{1}H-NMR in DMSO-d_6[a]: δ, ppm J, Hz	MS. m/z (%)
1	3.04 (2H, dt, pyr, J=3, J=6) 3.35 (2H, t, pyr, J=6) 3.75 (3H, s, OCH_3) 3.79 (3H, s, OCH_3) 6.91 (1H, dd, ar, J=3, J=9) 6.99 (1H, d, ar, J=9) 7.01 (1H, d, ar, J=3) 7.37 (1H, t, —CH=, J=3)	233 (M^+, 64) 202 (100) 175 (15) 161 (17)
2	3.77 (3H, s, OCH_3) 3.78 (3H, s, OCH_3) 6.59 (1H, s, —CH=) 6.89 (1H, dd, ar, J=3, J=9) 6.97 (1H, d, ar, J=9) 7.07 (1H, d, ar, J=3)	248 (M^+, 54) 217 (14) 162 (100) 119 (13)
3	3.76 (3H, s, OCH_3) 3.85 (3H, s, OCH_3) 6.96 (1H, m, ar) 7.11 (2H, m, ar) 7.99 (1H, s, —CH=)	265 (M^+, 100) 194 (75) 179 (78) 151 (12) 136 (13)
4	3.80 (3H, s, OCH_3) 3.85 (3H, s, OCH_3) 7.08 (3H, m, ar) 7.88 (1H, s, —CH=)	264 (M^+, 100) 233 (31) 194 (59) 179 (48)
5	3.77 (3H, s, OCH_3) 3.85 (3H, s, OCH_3) 6.89 (1H, m, ar) 7.11 (2H, m, ar) 7.76 (1H, s, —CH=)	281 (M^+, 100) 194 (97) 179 (88) 151 (15) 136 (16)
6	3.72 (3H, s, OCH_3) 3.84 (3H, s, OCH_3) 7.06 (1H, d, ar, J=9) 7.14 (1H, dd, ar, J=3, J=9) 7.78 (1H, d, ar, J=3) 8.51 (1H, s, —CH=)	276 (M^+, 54) 245 (100) 202 (57) 175 (39) 119 (20)
7	3.78 (3H, s, OCH_3) 3.80 (3H, s, OCH_3) 7.05 (4H, m, ar) 7.20 (2H, m, ar) 7.31 (1H, m, ar) 7.93 (1H, s, —CH=)	313 (M^+, 43) 282 (100) 239 (16) 189 (30) 148 (51)
8	3.02 (2H, dt, pyr, J=3, J=6) 3.36 (2H, t, pyr, J=6) 3.80 (3H, s, OCH_3) 7.04 (2H, d, ar, J=9) 7.10 (1H, t, —CH=, J=3) 7.52 (2H, d, ar, J=9)	203 (M^+, 98) 146 (100) 131 (22) 115 (13) 103 (25) 77 (19)
9	3.11 (2H, dt, pyr, J=3, J=6) 3.39 (2H, t, pyr, J=6) 7.05 (1H, t, —CH=, J=3) 7.49 (2H, d, py, J=6) 8.61 (2H, d, py, J=6)	174 (M^+, 100) 145 (8) 130 (12) 117 (56) 90 (14)
10	3.77 (3H, s, OCH_3) 6.96 (1H, dd, ar1, J=2, J=8) 6.99 (2H, d, ar2, J=9) 7.07 (2H, d, ar2, J=9) 7.14 (1H, t, ar1, J=2) 7.29 (1H, d, ar1, J=8) 7.48 (1H, t, ar1, J=8) 7.55 (1H, s, —CH=)	326 (M^+, 76) 256 (100) 241 (7) 228 (6) 213 (6) 133 (8) 89 (22)
11	3.75 (3H, s, OCH_3) 6.80 (1H, t, ind) 6.85 (1H, d, ind) 7.0 (3H: 2H, d, ar2, J=9 + 1H, m, ar1) 7.12 (2H, d, ar2, J=9) 7.16 (1H, t, ar1, J=2) 7.22 (1H, t, ind) 7.37 (1H, d, ar1, J=8) 7.39 (1H, d, ind) 7.50 (1H, t, ar1, J=8) 7.55 (1H, s, —CH=)	343 (M^+, 100) 191 (11) 165 (10) 144 (11) 45 (23)
12	1.70 (6H, s, pip) 3.50 (2H, s, pip) 3.72 (3H, s, OCH_3) 3.76 (3H, s, OCH_3) 3.91 (2H, t, pip) 6.83 (2H, m, ar) 6.98 (1H, m, ar) 7.99 (1H, s, —CH=)	332 (M^+, 25) 301 (100) 194 (41) 179 (30)

[a]The NH groups, when detectable, give broad singlets in the range 8–11 ppm. Abbreviations: pyr = pyrrolidine, py = pyridine, pip = piperidine, ind = indole, ar = aromatic (ar1 near the lactam, ar2 far from the lactam).

Table III. Positive inotropic activity of compounds **1–12**.

Compound	*EC_{50} (μmol)*	*E_{max} (mean of 2–4 atria)*[a]	
		%Δ from baseline value = 0[b]	*Concentration to obtain E_{max} (μmol)*
1		NS[c]	
2		NT[d]	
3		NS	
4	90	62 ± 37	300
5		NT	
6	258	74 ± 5	1400
6•$C_5H_{11}N$	271	71 ± 34	1100
7		NT	
8		NS	
9	318	73 ± 20	2200
10		NT	
11		NT	
12		NS	
Sulmazole	14.6	63 ± 9	350

[a]Chronotropic effect was not significant (± 10%); [b]initial contractile force = 0.4 ± 0.1 g; [c]not significant; [d]not testable due to the poor solubility in the medium.

*Synthesis with sodium hydride: 3-(2,5-dimethoxybenzylidene)pyrrolidin-2-one **1**, 3-(4-methoxybenzylidene)pyrrolidin-2-one (**8**) and 3-pyridin-4-ylmethylene-pyrrolidin-2-one **9***

In a 3-necked flask equipped with a stirrer, thermometer and dropping funnel, 55% NaH dispersion (100 mmol), washed twice with petroleum ether, was added to anhydrous THF (50 ml) and the resulting suspension cooled to 5°C. *N*-Acetyl-2-pyrrolidinone [12] (30 mmol in 50 ml THF) was added from the dropping funnel at a rate that maintained a temperature of 5–10°C. The mixture was kept at ice-bath temperature for 1–2 h and at room temperature for 5–10 h, then it was poured onto ice. THF was evaporated under reduced pressure and the mixture was acidified with 2 N HCl. The expected product was collected by filtration (**1**, **8**: ≈ 90%) or extracted with $CHCl_3$ (**9**: ≈ 15%) and crystallized from methanol.

*Synthesis with piperidine: 2,5-dimethoxybenzylidene derivatives **2–6**, **12** and 3-(4-methoxyphenoxy)-benzylidene derivatives **10**, **11***

The appropriate lactam (10 mmol) was dissolved in methanol (100 ml) and treated with the appropriate aldehyde (10 mmol) and piperidine (1 ml). The reaction mixture was refluxed for 4–5 h, cooled and concentrated under reduced pressure. The resulting precipitate (70–90%) was collected by filtration and crystallized from methanol. Barbituric acid and rhodanine showed a different behavior from the other lactams: in the reaction with barbituric acid (for the synthesis of **6**) a white piperidine salt was obtained in quantitative yield: 6•$C_5H_{11}N$, mp:180–182°C (CH_3OH); ν_{max}(cm^{-1}): 3520, 3120, 1670, 1585, 1330, 1220, 1035. ^{1}H-NMR (ppm, DMSO–d_6): 1.60 (6H, d, pip); 2.90 (4H, m, pip); 3.67 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.60 (1H, s, -CH =); 6.90 (1H, dd, ar, J = 3, J = 9); 6.99 (1H, d, ar, J = 9); 7.40 (1H, d, ar, J = 3); 9.70 (3H, s, NH).

This compound (1 g) was dissolved in methanol (100 ml) and acidified with 2 N HCl: the orange precipitate, obtained in quantitative yield, was crystallized from methanol (see compound **6** in tables I, II).

In the reaction with rhodanine (for the synthesis of **5**) the product was obtained in the usual high yield but the ^{1}H-NMR spectrum showed the presence of the piperidine ring. Contrary to the above-described salt (6•$C_5H_{11}N$), this compound was colored and did not change by treatment with 2 N HCl; the structure of 5-(2,5-dimethoxybenzylidene)-2-piperidin-l-ylthiazol-4-one **12** was confirmed by IR, ^{1}H-NMR, MS (see tables I, II) and by the following ^{13}C-NMR (ppm, DMSO–d_6 + $CDCl_3$): 23.372, 24.896, 25.565, 49.078, 49.766 (pip); 55.362, 55.624 (OCH_3); 111.907, 113.737, 115.742, 125.547 (CH); 123.729, 128.491, 152.700, 153.305, 174.339, 180.856 (C).

Compound **5** was obtained *via* the above-reported general method by replacing piperidine with Et_3N in a yield of 90%; the other data are reported in tables I, II

*Synthesis with sodium methoxide: 2-(2,5-dimethoxybenzylidene)-4H-benzo[1,4]thiazin-3-one **7***

4*H*-benzo[1,4]thiazin-3-one (10 mmol) was dissolved in methanol (150 ml) and treated with 2,5-dimethoxybenzaldehyde (10 mmol) and CH_3ONa (from 40 mmol Na and 50 ml methanol). The reaction mixture was refluxed for 10 h, cooled and concentrated under reduced pressure. The resulting precipitate (≈ 10%) was collected by filtration and crystallized from methanol.

Pharmacology

The experiments were carried out on spontaneously beating guinea-pig (300–450 g body weight) atria. The preparation was suspended at 37°C in a 20-ml bath of Tyrode solution (composition in g/l: NaCl 8.0, $NaHCO_3$ 1.0, KCl 0.2, NaH_2PO_4 0.005, $MgCl_2$ 0.1, $CaCl_2$ 0.2, glucose 1.0). An initial tension of 1 g was applied to the preparation. Isometric contractions were recorded by strain-gauge transducer connected to a recording microdynamometer. After taking basal responses, the test compounds were added to the preparation at 5–800 μmol on a cumulative basis and the responses recorded. The contact time for each dose was 5 min. Concentrations producing 50% of the maximal effect (EC_{50}) were calculated from concentration–response curves [30].

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