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Synthesis and Analysis of Positive Inotropic Effects of 3-Substituted-2*H*-cyclohepta[*b*]furan-2-one Derivatives

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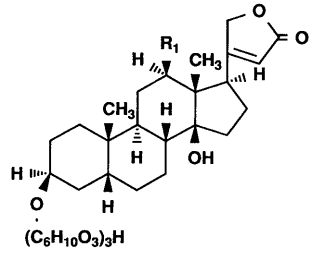
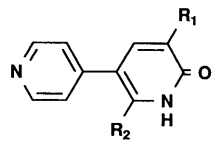
Several 3-substituted-2*H*-cyclohepta[*b*]furan-2-one derivatives were prepared and tested *in vitro* for positive inotropic character. Introduction of an isopropyl group at the 5-position of compound 8a caused an increase of PIC_{50} (negative logarithm of the dosage which increases the contractile force by 50%) from 4.48 to 5.10. Among the 5-isopropyl-8-alkoxy compounds, the isopropoxy compound 12f had the most potent activity with a PIC_{50} value of 5.99. Conversion of the ester group at the 3-position to a methylene group and of the alkoxy group at the 8-position to a substituted amino group caused a decrease in activity. The most active compound, 12f, was also found to have a weaker heart rate (HR)-increasing effect compared to milrinone and amrinone.

Keywords positive inotropic effect; 2*H*-cyclohepta[*b*]furan-2-one; phosphodiesterase

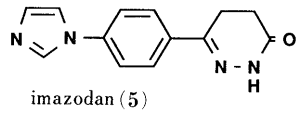
Digitalis glycosides such as digoxin (**1**) and digitoxin (**2**) have been known for centuries as positive inotropic agents that increase heart muscle contraction. The positive inotropic effect of digitalis is beneficial for most patients with congestive heart failure but the ratio between the full therapeutic dose and the toxic dose of digitalis is small, and up to 20% of hospitalized patients receiving digitalis may develop some signs of intoxication.[1] The development of safe and effective positive inotropic agents for treatment of congestive heart failure is required.[2] Amrinone (**3**),[3] milrinone (**4**)[4] and imazodan (**5**)[5] have been reported to improve congestive heart failure (CHF), but side effects such as leukopenia were observed in 20% of patients[6] and more effective and safer cardiotonic agents for CHF are still required. We reported 3-ethyl-7-isopropyl-1-azulenesulfonate (KT1-32)[7] and 3-ethyl-6-isopropyl-1-azulenesulfonate (KT1-785)[8] as potent and chemically stable anti-ulceratives. The precursor of the synthetic azulene, 2*H*-cyclohepta[*b*]furan-2-one (**6**), has a lactone in its molecular structure and a lactone is considered to be essential to the positive inotropic activities of digitalis glycosides.[9] We examined the role of lactone as bioisoster of lactam in the molecules of amrinone and milrinone (having a pyridone moiety) or in that of imazodan (having a pyridazinone moiety). We then synthesized and examined a series of 3-substituted-2*H*-cyclohepta[*b*]furan-2-one derivatives. We describe herein the synthesis and biological characterization of this new class of compounds.



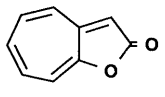
digoxin (**1**) : R_1=OH
digitoxin (**2**) : R_1=H



amrinone (**3**) : R_1=NH_2, R_2=H
milrinone (**4**) : R_1=CN, R_2=CH_3



imazodan (**5**)

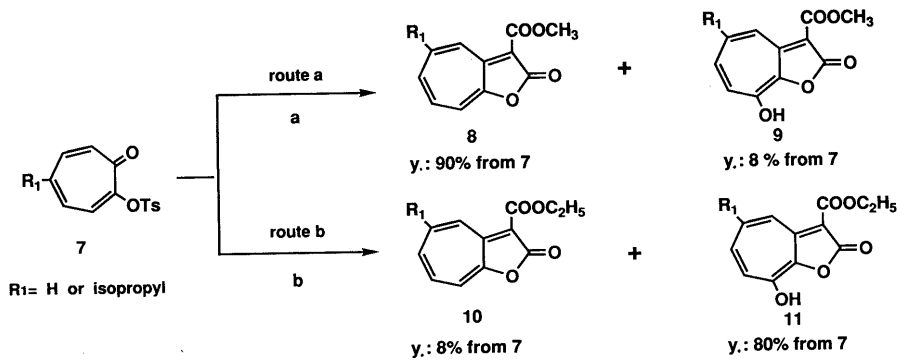


2*H*-cyclohepta[*b*]furan-2-one (**6**)

Chemistry

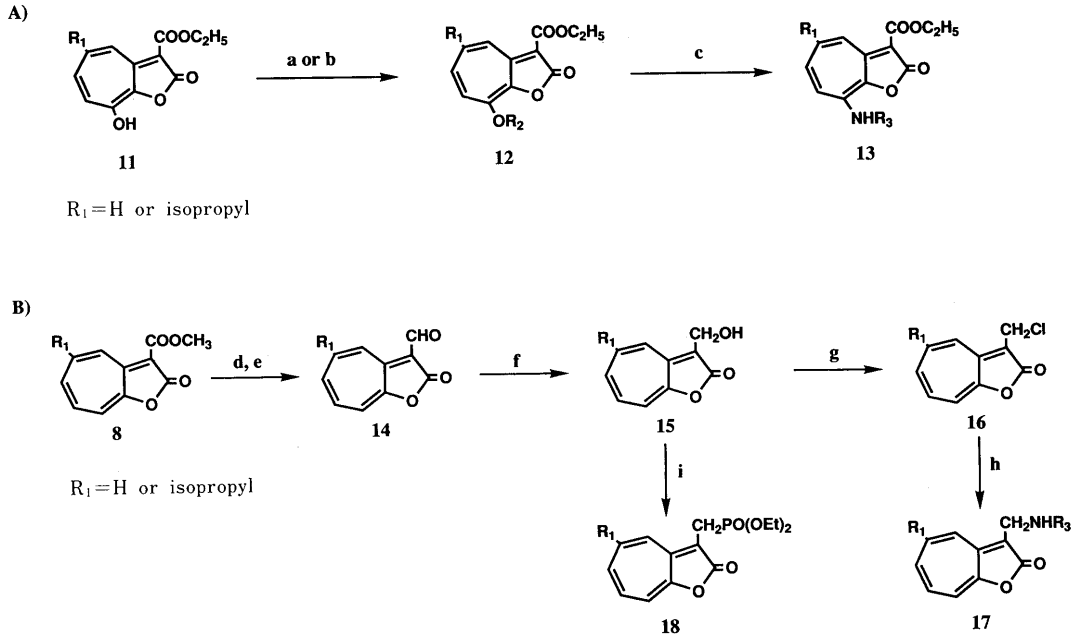
The synthesis of these compounds proceeded from the known 5-substituted-3-methoxycarbonyl-2*H*-cyclohepta-[*b*]furan-2-ones **8** and 5-substituted-8-hydroxy-3-ethoxy-carbonyl-2*H*-cyclohepta[*b*]furan-2-ones **11**[10] (Chart 1). The reaction of the known tosyl tropolones **7** with dimethyl malonate and sodium methoxide yielded a mixture of compounds **8** and **9** in a ratio of 90:8 (route a). The 8-hydroxy compounds **11** were obtained more efficiently by route b. The reaction of **7** with diethyl malonate and sodium ethoxide yielded a mixture of 5-substituted-3-ethoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one **10** and 5-substituted-8-hydroxy-3-ethoxycarbonyl-2*H*-cyclohepta-[*b*]furan-2-one **11** in a ratio of 8:80. In route a, the arylsulfonyloxy group is eliminated *via* a protonated intermediate to give a tropone-type intermediate,[10] which subsequently cyclizes to the 2*H*-cyclohepta[*b*]furan-2-one **8** as the major product. On the other hand, in route b the arylsulfonyl group of the intermediate is eliminated as arenesulfinate ion with the aid of a strong base (NaOEt) to produce a tropolonate type intermediate,[10] which subsequently cyclizes to the 8-hydroxy-2*H*-cyclohepta[*b*]-furan-2-one **11** as the major product. After recrystallization, **8** and **11** were obtained in pure form. Alkylation and subsequent amination of the 8-hydroxy group of **11** are shown in Chart 2. Compounds **11** were alkylated with diazomethane in ether or alkyl halide with potassium carbonate to yield compounds **12**, which were aminated with appropriate amines, yielding the amino compounds **13**. The ester **8** was demethoxycarbonylated with 75% sulfonic acid, followed by formylation *via* the Vilsmeier–

synthesis of 2*H*-cyclohepta[*b*]furan-2-one



(a) dimethyl malonate (DMM), CH_3ONa, MeOH, 0°C; (b) diethyl malonate (DEM), C_2H_5ONa, EtOH, 0°C

Chart 1



(a) CH_2N_2/ether; (b) alkyl halide, K_2CO_3/toluene, r. t,; (c) NHR_2/EtOH, reflux;
(d) 75% H_2SO_4, 100°C; (e) $POCl_3$/DMF, 0°C; (f) $NaBH_4$, MeOH, r.t.; (g) $SOCl_2/C_6H_6$, reflux;
(h) NHR_2/MeOH, r. t.; (i) $P(EtO)_3$, 150°C

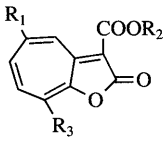
Chart 2

Haack reaction to give the corresponding aldehyde **14**. Reduction of **14** with $NaBH_4$ in methanol, followed by chlorination of the resulting 3-hydroxymethyl compound **15** with thionyl chloride yielded **16**. Amination of **16** with appropriate amines yielded **17**. Phosphorylation of **15** with triethylphosphate yielded the phosphoryl esters **18**.

Results and Discussion

The compounds described herein were examined for positive inotropic activity. They were tested for their effects on isolated guinea pig atria and papillary muscle according to the method previously reported.[11] The contractile activities of these compounds were expressed as the negative logarithm of the dosage which increases the contractile force by 50% (PIC_{50}) and the maximal change of contractile force (CF) and percentage increase in the heart rate (HR) were also recorded. The results for the 3-alkoxycarbonyl compounds (**8a, b, 12a—i**) are presented in Table I. The introduction of the isopropyl group at the C-5 position of compound **8a** increased the PIC_{50} value from 4.48 to 5.10. The compound having an 8-methoxy group (**12a**) also showed an increased the PIC_{50} value, from 4.48 (**8a**) to 4.75 (**12a**). The introduction of an isopropyl group at the 5-position of compound **12a** resulted in an increase of the PIC_{50} value from 4.75 to 5.70. The effect of a 5-isopropyl group on the PIC_{50} value was also seen in compound **8b** as compared to the unsubstituted **8a**. In the 5-isopropyl compounds, the 8-hydroxy group of compound **12b** was replaced with OMe (**12c**) up to O-*n*-butyl (**12h**) groups. The maximal activity

TABLE I. 8-Unsubstituted and 8-Substituted-3-alkoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-ones



Compd.	R_1	R_2	R_3	mp (°C)[a]	Formula[b]	Analysis (%) Calcd (Found)		Atria			
						C	H	Inotropic PIC_{50}[c]	Max change CF (%)[d]	Max change HR (%)[e]	PMI[f]
8a	H	Me	H	172—173	$C_{11}H_8O_4$	64.71 (64.38)	3.95 (3.90)	4.48	93	26	10
8b	iso-Pr	Me	H	119—120	$C_{14}H_{14}O_4$	68.28 (68.39)	5.73 (5.70)	5.10	70	16	NE[g]
12a	H	Et	OMe	139—140	$C_{13}H_{12}O_5$	62.90 (62.89)	4.87 (4.66)	4.75	124	13	NE
12b	iso-Pr	Et	OH	130—132	$C_{15}H_{16}O_5$	65.21 (64.90)	5.84 (6.18)	3.58	53	10	NE
12c	iso-Pr	Et	OMe	170—171	$C_{16}H_{18}O_5$	66.20 (66.19)	6.25 (6.23)	5.70	113	45	20
12d	iso-Pr	Et	OEt	182—184	$C_{17}H_{20}O_5$	67.09 (66.74)	6.62 (6.77)	6.20	142	19	16
12e	iso-Pr	Et	O-*n*-Pr	130—132	$C_{18}H_{22}O_5$	67.91 (68.30)	6.96 (7.04)	5.60	140	−14	51
12f	iso-Pr	Et	O-iso-Pr	119—120	$C_{18}H_{22}O_5$	67.91 (68.17)	6.96 (7.07)	5.99	173	17.5	95
12g	H	Et	O-*n*-Bu	127—129	$C_{16}H_{18}O_5$	66.20 (66.60)	6.25 (6.29)	5.13	111	3	NE
12h	iso-Pr	Et	O-*n*-Bu	121—123	$C_{19}H_{24}O_5$	68.66 (68.70)	7.28 (7.29)	5.30	48	0	NE
12i	H	Et	OAc	134—136	$C_{14}H_{12}O_6$	60.87 (60.87)	4.38 (4.36)	3.60	60	9	NE

a) Melting points were measured without correction. *b*) Analytical values for C, H were within 0.4% of calculated values. *c*) Negative logarithm of the dose which increases contractile force of isolated guinea pig left atria by 50%. *d*) Maximum change (%) of contractile force of isolated guinea pig left atria. *e*) Maximum change (%) of heart rate of isolated guinea pig right atria. *f*) Change (%) of contractile force of isolated guinea pig papillary muscle at 3×10^{-5} g/ml. *g*) NE indicates no effect.

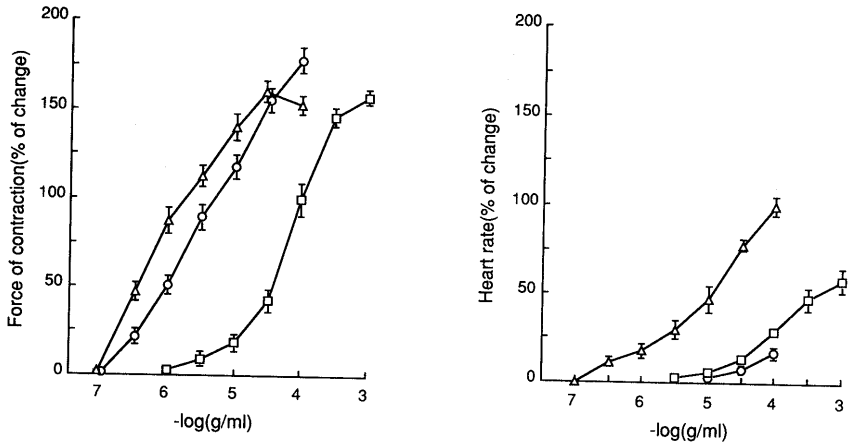
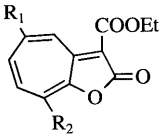
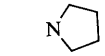
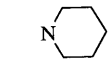
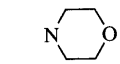
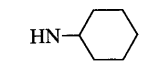
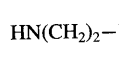


Fig. 1. Cumulative Concentration–Response Curves for the Effects of Compound **12f** (—○—), Amrinone (—□—) and Milrinone (—△—) on Force of Contraction (Left Panel) and Heart Rate (Right Panel) in Isolated Guinea Pig Atria

was obtained with the isopropyl compound **12f**, with PIC_{50} of 5.99 and CF of 173%. Further elongation of the alkyl chain to *n*-butyl gave no further increase in activity. The activity of the 8-acetyl compound **12i** was weaker than that of the 8-alkylated compound **12a**. Among a series of 2*H*-cyclohepta[*b*]furan-2-one compounds, **12f** had the most potent activity. The results for 8-amino-substituted compounds are shown in Table II. In this series, the diethylamino compound **13a** had the maximal effect, with a PIC_{50} of 5.30. The introduction of a diamino group instead of an amino group at the 8-position of compound **13a** (compound **13g**) caused a decrease of PIC_{50} activity from 5.30 to 4.07. The results for the 3-substituted methyl compounds **17a—g** and **18** are presented in Table III. Replacement of the carbonyl group (=CO) at the 3-position with methylene ($=CH_2$) caused loss of PIC_{50} and CF activity, so the ester carbonyl group at the 3-position of 2*H*-cyclohepta[*b*]furan-2-one is considered

TABLE II. 8-Amino Substituted 3-Ethoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-ones



Compd.	R_1	R_2	mp (°C)[a]	Formula[b]	Analysis (%) Calcd (Found)			Atria			
					C	H	N	Inotropic[c] PIC_{50}	Max change CF^{d} (%)	Max change HR^{e} (%)	PMI^{f}
13a	H	NEt_2	78—79	$C_{16}H_{19}N_1O_4$	66.42 (66.45	6.62 6.59	4.84 4.88)	5.30	129	6	46
13b	H		215—216	$C_{16}H_{17}N_1O_4$	66.89 (66.63	5.96 5.89	4.88 4.91)	4.97	160	0	26
13c	iso-Pr		121—123	$C_{20}H_{25}N_1O_4$	69.95 (69.75	7.34 7.38	4.08 4.46)	4.30	65	2	25
13d	iso-Pr		156—158	$C_{19}H_{23}N_1O_5$	65.98 (66.07	6.71 6.49	4.06 4.20)	4.75	85	2	8
13e	iso-Pr		165—167	$C_{21}H_{27}N_1O_4$	70.56 (70.57	7.61 7.65	3.96 4.14)	4.50	54	−3	NE[g]
13f	H	$HN(CH_2)_2NMe_2$	143 (dec.)	$C_{16}H_{20}N_2O_4 \cdot H_2O$	59.61 (59.52	6.88 6.79	8.69 8.80)	—	18	−16	NE
13g	H	$HN(CH_2)_2NEt_2$	197 (dec.)	$C_{18}H_{24}N_2O_4 \cdot H_2O$	61.70 (61.63	7.48 7.59	7.99 7.91)	4.07	53	6	NE
13h	iso-Pr	$HN(CH_2)_2NMe_2$	228 (dec.)	$C_{19}H_{26}N_2O_4$	65.92 (65.87	7.54 7.56	8.05 8.09)	4.88	38	45	NE
13i	H	$HN(CH_2)_2$– 	210 (dec.)	$C_{18}H_{22}N_2O_4 \cdot H_2O$	62.06 (62.25	6.94 6.79	8.04 7.66)	—	−63	−22	NE

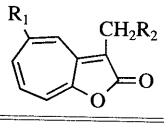
Footnotes, see Table I.

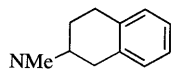
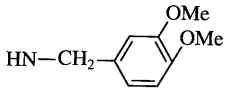
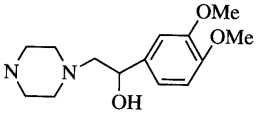
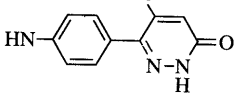
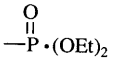
to be essential for the activities. The introduction of pyridazinylmethyl, a constituent of imazodan, at the 3-position (compound **17g**) increased PIC_{50} and CF%, but the activities are not superior to those of **12f**. The activities of amrinone and milrinone as reference compounds are also shown in Table III. From these findings, compound **12f** is the most active compound in this series. As shown in Fig. 1, compound **12f** increased the contractile force of guinea-pig atria from 3×10^{-7} to 3×10^{-5} g/ml in a dose-dependent manner with the maximal change of 173%. The positive inotropic effect of compound **12f** was three times less potent than that of milrinone and 30 times stronger than that of amrinone. In guinea-pig papillary muscle compound **12f** at 3×10^{-5} g/ml increased the contractile force by 95%. The effect of compound **12f** was comparable to those of amrinone and milrinone at the same dose. Positive chronotropic activity in cardiotonic agents is considered undesirable,[12] since an ideal positive inotropic agent should not induce tachycardia, which can lead to cardiac arrhythmias and an increase of myocardial oxygen consumption.[13] Compound **12f** was evaluated for effect on HR. Compared to milrinone, **12f** caused a relatively minor HR increase (17.5%, **12f** *v.s.* 155%, milrinone) and had a more favorable profile, as shown in Fig. 1. To determine the mechanism responsible for the inotropy exhibited by **12f**, the phosphodiesterase III (PDE III)-inhibitory activity of **12f** was tested according to the method of Schuhkmacker *et al.*[13] as shown in Table IV. The IC_{50} of **12f** (7.67×10^{-6} M) was the same as that of milrinone ($IC_{50} = 7 \times 10^{-6}$ M). Thus, the action of **12f** may be due to PDE III inhibition, but other possible explanations include Na^+, K^+-ATPase-inhibitory activity or Ca^{2+}-sensitizing effect, a mechanism first described by Herzig *et al.*[14] The potential interest of this effect is that it does not require an increase in calcium concentration for cardiac contraction, thereby avoiding the risk of calcium overload and arrhythmia.[15] The inotropic effect of digitalis glycosides having lactones in the molecule is due to Na^+,K^+-ATPase-inhibitory effects.[9] Since **12f** also has lactone in the molecule, it may have the same mechanism of inhibitory effect as digitalis glycosides. Another possibility is that **12f** has an additional undefined mechanism of action. These possibilities are currently under investigation. In conclusion, we have demonstrated that in the 3-substituted-2*H*-cyclohepta[*b*]furan-2-one series, ethyl 5-isopropyl-8-isopropyloxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**12f**) showed positive inotropic activity. Furthermore, the chronotropic effect of (**12f**) was less than those of the reference compounds. Therefore, **12f** represents a new structural lead compound.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 90 MHz on a Hitachi R-90H Fourier-transform NMR spectrometer, and date are summarized in Table V. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. Coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; sept, septet; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh)

TABLE III. 3-Aminomethyl Substituted 3-Diethylphosphinomethyl 2*H*-cyclohepta[*b*]furan-2-ones



Compd.	R_1	R_2	mp (°C)[a]	Formula[b]	Analysis (%) Calcd (Found) C	H	N	Atria Inotropic[c] PIC_{50}	Max change CF[d] (%)	Max change HR[e] (%)	PMI[f]
17a	iso-Pr	NMe_2	210—212	$C_{15}H_{19}N_1O_2 \cdot H_2O$	68.42 (68.52	8.04 7.77	5.32 5.31)	—	40	−38	NE[g]
17b	H		233—235	$C_{14}H_{15}N_1O_3 \cdot H_2O$	63.86 (63.83	6.51 6.21	5.32 5.10)	—	3	−2	NE
17c	iso-Pr		153—155	$C_{17}H_{21}N_1O_3 \cdot H_2O$	66.86 (66.97	7.59 7.43	4.59 4.82)	—	45	−37	NE
17d	H		239—241	$C_{21}H_{21}N_1O_2 \cdot H_2O$	75.11 (74.75	6.20 6.27	4.23 4.15)	—	26	35	81
17e	H		183—184	$C_{19}H_{19}N_1O_4$	70.14 (70.13	5.87 5.78	4.31 4.29)	—	−34	−66	NE
17f	H		160—162	$C_{24}H_{28}N_2O_5$	67.91 (68.06	6.65 6.65	6.60 6.39)	4.02	51	−31	NE
17g	H		164—165	$C_{21}H_{17}N_3O_3$	69.88 (70.18	4.70 4.77	11.92 11.70)	5.25	59	38.5	65
18	H		70—71	$C_{14}H_{17}O_5P_1$	56.76 (56.75	5.78 5.75)		—	−44	6	−38
Amrinone								4.43	151	51	95
Milrinone								6.43	155	97	97

Footnotes, see Table I.

TABLE IV. IC_{50} Values for Bovine Myocardiac Phosphodiesterase (Type III)

Compound	IC_{50} (M)
8b	4.27×10^{-5}
12a	$> 10^{-4}$
12f	7.67×10^{-6}
12g	1.30×10^{-5}
Amrinone	1.16×10^{-6}
Milrinone	7×10^{-6} [a]
Papaverine	1.16×10^{-6}

a) Data from N. Komas, C. Lugnier, A. L. Bec, C. S-L. Gal, G. Barthelemy, J. C. Stoclet, *J. Cardiovasc. Pharmacol.*, **14**, 213 (1989).

was used.

Route a: Methyl 2-Oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (8a) Sodium methoxide, prepared from sodium metal (1.8 g, 0.8 mol) and anhydrous MeOH (80 ml) was, gradually added to a stirred solution of 2-troponyl *p*-toluenesulfonate **7** (11.0 g, 0.4 mol) and dimethyl malonate (10.5 g, 0.8 mol) in anhydrous MeOH (80 ml) at 0 °C. After being stirred for an additional 6 h at 0 °C, the reaction mixture was poured into H_2O. Crystals were collected, washed with H_2O, dried *in vacuo* and recrystallized from EtOH, giving **8a** (7.3 g, 89%) as yellow needles (mp 172—173 °C, lit.[16] 172.5—173.8 °C). The aqueous filtrate was acidified with 6 N HCl and crystals were collected and recrystallized from EtOH, giving **9** (0.75 g, 8.5%) as yellow needles.

Route b: Ethyl 8-Hydroxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (11) Similar treatment of a solution of **7** (13.8 g, 0.05 mol) and diethyl malonate (16.0 g, 0.1 mol) in anhydrous EtOH (100 ml) with 0.1 M NaOEt gave **10** (1.1 g, 8.3%) as yellow needles (mp 129—130 °C) and **11** (11 g, 79%) as yellow needles (mp 223—225 °C).

Ethyl 8-Methoxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (12a) A suspension of **11** (10.0 g, 0.043 mol) in AcOEt 100 ml was treated with freshly prepared diazomethane in Et_2O (100 ml) with stirring under ice-cooling. After additional stirring for 2 h, the precipitate formed was collected by filtration and recrystallized from MeOH to give **12a** (6.78 g, 63.8%). MS *m/z*: 248 (M^+). IR (KBr): 2960, 1748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz, $-CH_2CH_3$), 4.18 (3H, s, $-OCH_3$), 4.40 (2H, q, J=7.0 Hz, $-CH_2CH_3$), 7.20—7.50 (3H, m, C_5-, C_6-, C_7-H), 8.90 (1H, d, J=10 Hz, C_4-H).

Ethyl 8-Diethylamino-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (13a) A mixture of **12a** (2.5 g, 0.01 mol) and diethylamine (2.2 g, 0.03 mol) in EtOH 10 ml was heated under reflux for 3 h. After removal of the solvent *in vacuo*, the residue was extracted with AcOEt, then the extract was washed with brine, dried and evaporated. The product was recrystallized from EtOH, giving **13a** (1.85 g, 64%) as yellow needles. MS *m/z*: 289 (M^+). IR (KBr): 3400, 2970, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, t, J=7.0 Hz, $-N(CH_2CH_3)_2$), 1.42 (3H, t, J=7.0 Hz, $-CH_2CH_3$), 3.69 (4H, q, J=7.0 Hz, $-N(CH_2CH_3)_2$), 4.38 (2H, q, J=7.0 Hz, $-CH_2CH_3$), 7.10—7.30 (3H, m, C_5-, C_6-, C_7-H), 8.85 (1H, d, J=10 Hz, C_4-H).

2-Oxo-2*H*-cyclohepta[*b*]furan-3-carbaldehyde (14) A mixture of **8a** (23 g, 0.11 mol) and 75% H_2SO_4 (230 ml) was warmed at about 100 °C for 30 min and poured into ice-water. The precipitates were collected by filtration, and recrystallization from EtOH gave 2*H*-cyclohepta[*b*]furan-2-one (11.2 g, 68.8%) as yellow prisms (mp 72 °C). The obtained 2*H*-cyclohepta[*b*]furan (3 g, 0.021 mol) was added to a mixture of $POCl_3$ (22 ml) and dry *N*,*N*-dimethylformamide (DMF) (25 ml) at 0 °C. The mixture was stirred at room temperature for 2 h and then poured into ice-water (100 ml). The aqueous layer was adjusted to pH 8 with 10% NaOH and extracted with $CHCl_3$. The organic layer was washed with water, dried, and then evaporated. The product was recrystallized from

TABLE V. Spectral Data for the 2*H*-Cyclohepta[*b*]furan-2-ones

Product	MS *m/z* (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm) *J* (Hz)
8b	246	1.38 (6H, d, *J*=6.8), 3.14 (1H, sept, *J*=6.8), 4.00 (3H, s), 7.40—7.80 (3H, m), 9.10 (1H, s)
12a	248	1.42 (3H, t, *J*=7.0), 4.18 (3H, s), 4.40 (2H, q, *J*=7.0), 7.20—7.50 (3H, m), 8.90 (1H, d, *J*=10.0)
12c	290	1.32 (6H, d, *J*=6.8), 1.40 (3H, t, *J*=7.0), 3.00 (1H, sept, *J*=6.8), 4.17 (3H, s), 4.40 (2H, q, *J*=7.0), 7.20—7.32 (2H, m), 8.92 (1H, s)
12d	304	1.32 (6H, d, *J*=6.8), 1.40 (3H, t, *J*=7.0), 1.48 (3H, t, *J*=7.0), 3.02 (1H, sept, *J*=6.8), 4.00 (2H, q, *J*=7.0), 4.20 (2H, q, *J*=7.0), 7.20—7.40 (2H, m), 8.95 (1H, s)
12e	318	1.07 (3H, t, *J*=7.0), 1.33 (6H, d, *J*=6.8), 1.42 (3H, t, *J*=7.0), 1.70—2.00 (2H, m), 3.02 (1H, sept, *J*=6.8), 4.20—4.60 (2H, m), 4.38 (2H, q, *J*=7.0), 7.20—7.50 (2H, m), 8.96 (1H, s)
12f	318	1.33 (6H, d, *J*=6.8), 1.41 (6H, d, *J*=7.0), 1.42 (3H, t, *J*=7.0), 3.00 (1H, sept, *J*=6.8), 4.41 (2H, q, *J*=7.0), 5.01 (1H, sept, *J*=7.0), 7.20—7.50 (2H, m), 8.95 (1H, s)
12g	290	1.00 (3H, t, *J*=7.0), 1.40 (3H, t, *J*=7.0), 1.71—2.00 (4H, m), 4.40 (2H, q, *J*=7.0), 4.20—4.60 (2H, m), 7.20—7.60 (3H, m), 8.95 (1H, d, *J*=10.0)
12h	332	0.98 (3H, t, *J*=7.0), 1.32 (6H, d, *J*=6.8), 1.42 (3H, t, *J*=7.0), 1.30—2.00 (4H, m), 3.00 (1H, sept, *J*=6.8), 4.38 (2H, q, *J*=7.0), 4.20—4.60 (2H, m), 7.20—7.40 (2H, m), 8.95 (1H, s)
12i	276	1.41 (3H, t, *J*=7.0), 2.42 (3H, s), 4.41 (2H, q, *J*=7.0), 7.20—7.70 (3H, m), 8.88 (1H, d, *J*=10.0)
13b	287	1.40 (3H, t, *J*=7.0), 1.90—2.20 (4H, m), 3.80—4.00 (4H, m), 4.38 (2H, q, *J*=7.0), 7.00—7.30 (3H, m), 8.85 (2H, d, *J*=10.0)
13c	343	1.29 (6H, d, *J*=6.8), 1.42 (3H, t, *J*=7.0), 1.50—1.90 (6H, m), 3.02 (1H, sept, *J*=6.8), 3.40—3.70 (4H, m), 4.80 (2H, q, *J*=7.0), 7.20—7.40 (2H, m), 8.85 (1H, s)
13d	345	1.31 (6H, d, *J*=6.8), 1.41 (3H, t, *J*=7.0), 3.02 (1H, sept, *J*=6.8), 3.50—3.70 (4H, m), 3.80—4.00 (4H, m), 4.40 (2H, q, *J*=7.0), 7.20—7.40 (2H, m), 8.92 (1H, s)
13e	357	1.30 (6H, d, *J*=6.8), 1.42 (3H, t, *J*=7.0), 1.51—2.20 (10H, m), 3.0 (1H, sept, *J*=6.8), 3.30—3.70 (1H, m), 4.39 (2H, q, *J*=7.0), 5.78 (1H, br s), 7.10—7.30 (2H, m), 8.86 (1H, s)
13f	304	1.39 (3H, t, *J*=7.0), 3.03 (6H, s), 3.30—3.70 (5H, m), 4.30 (6H, q, *J*=7.0), 7.30—7.80 (3H, m), 8.50 (1H, d, *J*=10.0)
13g	332	1.39 (3H, t, *J*=7.0), 1.48 (6H, t, *J*=7.0), 3.20—3.70 (5H, m), 4.30 (6H, q, *J*=7.0), 7.20—7.80 (3H, m), 8.65 (1H, d, *J*=10.0)
13h	346	1.32 (6H, d, *J*=6.8), 1.38 (3H, t, *J*=7.0), 3.00 (1H, sept, *J*=6.8), 3.04 (6H, s), 3.30—3.68 (5H, m), 4.32 (2H, q, *J*=7.0), 7.20—7.35 (2H, m), 8.90 (1H, s)
13i	330	1.38 (3H, t, *J*=7.0), 2.00—2.30 (4H, m), 3.00—3.40 (5H, m), 3.80—4.00 (4H, m), 4.20 (2H, q, *J*=7.0), 7.30—7.70 (3H, m), 8.48 (1H, d, *J*=10.0)
17b	245	1.58 (4H, br s), 2.80 (4H, br s), 4.00 (1H, s), 7.40—7.70 (4H, m), 8.50 (1H, d, *J*=10.0)
17c	287	1.36 (6H, d, *J*=6.8), 1.60 (4H, br s), 2.80 (4H, br s), 3.03 (1H, m), 8.20 (1H, s)
17d	319	1.09—3.05 (7H, m), 3.28 (3H, s), 4.20 (2H, br s), 7.20—8.20 (9H, m)
17e	325	2.18 (6H, s), 2.95 (2H, br s), 3.45 (3H, m), 6.30—7.30 (8H, m)
17f	424	2.30—2.90 (11H, m), 3.49 (2H, s), 3.86 (3H, s), 3.89 (3H, s), 4.66 (1H, m), 6.60—7.70 (8H, m)
17g	359	2.15 (3H, s), 3.30 (1H, br s), 4.10—4.20 (3H, m), 6.40—7.80 (10H, m)

EtOH, giving **14** (2.1 g, 63.3%) as yellow needles. MS *m/z*: 174 (M^+). mp 219 °C. IR (KBr): 1760, 1740, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.30—7.90 (4H, m, C_5-, C_6-, C_7-H), 9.00 (1H, d, *J*=10 Hz, C_4-H), 10.05 (1H, s, CHO).

3-Chloromethyl-2*H*-cyclohepta[*b*]furan-2-one (16) $NaBH_4$ (8 g, 0.21 mol) was added to a stirred solution of **14** (25 g, 0.14 mol) in MeOH (30 ml) under ice-cooling. The mixture was stirred for 2 h at room temperature, then the solvent was evaporated *in vacuo*. H_2O (30 ml) was added to the residue and the mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried, and then evaporated. The product was recrystallized from EtOH, giving 3-hydroxymethyl-2*H*-cyclohepta[*b*]furan-2-one **15** (23 g, 91%). MS *m/z*: 176 (M^+). mp 143 °C (dec.). IR (KBr): 3450, 1720, 1700 cm^{-1}. A solution of **15** (18 g, 1.01 mol) in benzene (100 ml) was treated with $SOCl_2$ (17 g, 0.15 mol) and refluxed for 2.5 h. The reaction mixture was concentrated *in vacuo*. The residue was washed with Et_2O to afford **16** (14 g, 72%). MS *m/z*: 195 (M^+). mp 208—210 °C (dec.). IR (KBr): 1730, 1700, 1600 cm^{-1}.

3-Dimethylamimomethyl-5-isopropyl-2*H*-cyclohepta[*b*]furan-2-one (17a) A mixture of 5-isopropyl-3-chloromethyl-2*H*-cyclohepta[*b*]-furan-2-one (1.5 g, 6.3 mmol) and dimethylamine (0.61 g, 13.3 mmol) in MeOH (30 ml) was stirred at room temperature for 3 h and evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and this solution was washed with H_2O, dried, and then evaporated. The residue was recrystallized from EtOH, giving **17a** (1.13 g, 72.6%). MS *m/z*: 245 (M^+). IR (KBr): 3450, 3400, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, d, *J*=6.8 Hz, iso-Pr-CH_3), 2.86 (6H, s, $-(CH_3)_2$), 3.15 (1H, sept, *J*=6.8 Hz, iso-Pr-CH), 4.10 (2H, br s, $-CH_2-$), 7.10—7.40 (4H, m, C_6-, C_7-, C_8-H), 8.10 (1H, s, C_4-H).

Diethyl 2-Oxo-2*H*-cyclohepta[*b*]furan-3-ylmethylphosphonate (18) A mixture of **15** (176 mg, 0.1 mol) and $P(EtO)_3$ (70 mg, 0.1 mmol) was stirred for 20 min at 150 °C. After cooling, the reaction mixture was poured into water and extracted with ether. The extract was washed with water, dried, and then evaporated. The residue was recrystallized from ether–hexane to give **18** (200 mg, 71%). MS *m/z*: 296 (M^+). IR (KBr): 2950, 1750, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, t, *J*=7.0 Hz, $-(CH_2\underline{CH_3})_2$), 3.05 (2H, d, *J*=22 Hz, $-CH_2-$), 4.11 (4H, q, *J*=7.0 Hz, $-(\underline{CH_2}CH_3)_2$), 6.60—7.60 (5H, m, Ar-H).

Positive Inotropic Action In this study, atrial muscle of male Hartley guinea-pigs was used. The preparations were dissected and mounted vertically in a 20 ml tissue bath containing Krebs–Henseleit buffer solution of the following composition (millimolar concentrations): NaCl, 118.4; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 2.4; KH_2PO_4, 1.2; $CaCl_2 \cdot H_2O$, 1.9; $NaHCO_3$, 25.0 and glucose 5.6; the solution was bubbled with a gas mixture of 95% O_2 and 5% CO_2 and maintained at 32 °C, pH 7.4. One end of the tissue was connected to a force displacement transducer by a silk ligature while the other was secured to a tissue holder. Tension was recorded isometrically through a force displacement transducer.

Cyclic AMP Phosphodiesterase Assay The reaction mixture for the assay of cyclic AMP phosphodiesterase was composed of (in final concentrations) 250 mM Tris–HCl (pH 7.5), 15 mM $(CH_3COO)_2$ Mg, 10 mM 5′-AMP, 1.25 nCi of [^{14}C]cyclic AMP, test drug and bovine heart cyclic AMP phosphodiesterase in a volume of 0.25 ml. The mixture excluding [^{14}C]cyclic AMP was preincubated for 10 min at 37 °C, then the reaction was started by addition of [^{14}C]cyclic AMP. Incubation was continued for 30 min at 37 °C, and was stopped by the addition of 200 μl of $ZnSO_4$ (170 mM) and $Ba(OH)_2$ (150 mM). After centrifugation (2000 × *g*, 10 min), 300 μl aliquots of the clear supernatant solution were transferred to counting vials, and 7 ml of scintillation fluid was added.

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