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SYNTHESIS AND CARDIOTONIC ACTIVITY OF 2-ALKYLTHIO-1-ACYL-5,6-DIMETHOXYBENZIMIDAZOLES AND THEIR CYCLIC ANALOGS

A. B. Brukshtus, V. N. Garalene, A. R.-R. Sirvidite, and V. K. Daukshas

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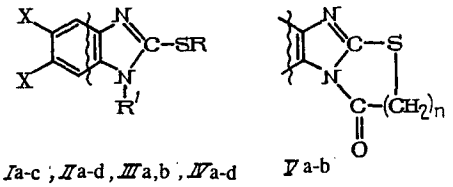
2-Alkylthio-1-acyl-5,6-ethylenedioxybenzimidazoles, as well as their methylenedioxy analog (IVa), display cardiotonic activity [1]. Therefore, to study the dependence of cardiotonic activity on chemical structure, and to search for new drugs, we synthesized and studied previously unknown structural analogs of these compounds, containing two methoxy groups (IIa-d) or a methylenedioxy group (IVb-d) in the aromatic ring.



*I*a-c; *II*a-d, *III*a,b; *IV*a-d *V* a-b

Ia-c, IIa-d, Va, b: X=OMe;
IIIa, b, IVa-d: X_2=OCH_2O;
Ia-c: R^1=H; R=Me (Ia), Et (Ib), CH_2CH_2COOH (Ic);
IIa, b: R=Me; R^1=Ac (IIa), COEt (IIb);
IIc, d: R=Et; R^1=Ac (IIc), COEt (IId);
IIIa, b: R^1=H; R=Me (IIIa), Et (IIIb);
IVa, b: R=Me; R^1=Ac (IVa), COEt (IVb);
IVc, d: R=Et; R^1=Ac (IVc), COEt (IVd);
Va, b: n=1 (Va), 2 (Vb).

2-Alkylthiobenzimidazoles Ib, c and IIIb were synthesized by S-alkylation [2, 3] of the corresponding benzimidazolin-2-thione derivatives with iodoethane or 3-chloropropionic acid in alkaline solution. Compounds Ia, b and IIIa, b were converted to the corresponding 1-acyl derivatives IIa-d and IVb-d by N-acylation with the chloroanhydrides of acetic or propionic acids, and compound Ic was cyclized to Vb by heating in acetic anhydride in pyridine.

Characteristics of new compounds Ib and c, IIa-d, IIIb, IVb-d, and Vb are given in Table 1. Their structures were confirmed by UV, IR, and PMR spectral data. The structure of compounds IIa-d, IVb-d, and Vb as N-acyl derivatives is confirmed by the absence of NH-group bands in the IR spectrum in the region 2400-3200 cm^{-1}, and the presence of carbonyl bands in the region 1700-1720 cm^{-1}. The wavelength of the UV absorption band of dimethoxy derivatives IIa-d is shifted to the short-wavelength side, compared with that of corresponding methylenedioxy derivatives IVa-d, because of a decrease in the electron-donating tendency of the oxygen atoms toward the aromatic ring, due to a repetition of methoxy substituents around the $C_{Ar}-O$ bond [1, 4].

Starting derivatives of benzimidazolin-2-thione [2, 3], as well as compounds Ia [2], IIIa, IVa [1], and Va [2] have been previously described.

EXPERIMENTAL (CHEMICAL)

UV spectra were taken on a Specord UV-VIS instrument (Germany) in 95% ethanol, IR spectra on a Specord M80 (Germany) in Vaseline mull, and PMR spectra on a Tesla BS-487C (Czech Republic, 80 MHz), internal standard—TMS.

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TABLE 1. Characteristics of Compounds Ib and c, IIa-d, IIIb, IVb-d, and Vb

Compound	Yield, %	mp, °C (solvent)	UV spectrum λ_{max}, nm	UV spectrum lg ε	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm: CH_3	PMR spectrum, δ, ppm: CH_2	PMR spectrum, δ, ppm: OCH_3, OCH_2O	PMR spectrum, δ, ppm: ArH	Empirical formula
Ib	76	149—50 (ethanol)	250 300	3,89 4,36	2550—3200 (NH)	1,36 q[a]	3,42 q[a]	3,85 s	7,07 s[b]	$C_{11}H_{14}N_2O_2S$
Ic	72	181—3 (2-propanol)	251 302	3,85 4,27	1624 (C=O) 2300—3200 (NH, OH)	—	2,73 t[a] 3,36 t[a]	3,77 s	7,02 s[c] 12,54 s[d]	$C_{12}H_{14}N_2O_4S$
IIa	45	158—9 (ethanol)	254 310	4,33 4,17	1712 (C=O)	2,70 s 2,75 s	—	3,94 s	7,15 s[b] 7,33 s	$C_{12}H_{14}N_2O_3S$
IIb	47	125—6 (ethanol)	252 307	4,46 4,18	1716 (C=O)	1,38 t[a] 2,70 s	3,01 q[a]	3,88 s	7,10 s[b] 7,28 s	$C_{13}H_{16}N_2O_3S$
IIc	63	134—5 (2-propanol)	257 312	4,42 4,15	1712 (C=O)	1,40 t[a] 2,81 s	3,25 q[a]	3,86 s	7,13 s[e] 7,42 s	$C_{13}H_{16}N_2O_3S$
IId	68	109—10 (ethanol)	252 307	4,41 4,15	1700 (C=O)	1,35 t[a] 1,45 t[a]	3,05 q[a] 3,33 q[a]	3,91 s	7,14 s[b] 7,42 s	$C_{14}H_{18}N_2O_3S$
IIIb	87	238—9 (2-propanol)	250 315	3,87 4,28	2400—3200 (NH)	1,34 t[a]	3,18 q[a]	5,94 s	6,92 s[e]	$C_{10}H_{102}N_2O_3S$
IVb	70	164—6 (ethyl acetate)	251 318	4,28 4,04	1708 (C=O)	1,09 t[a] 2,65 s	2,32 q[a]	5,91 s	6,89 s[e]	$C_{12}H_{12}N_2O_3S$
IVc	59	165—6 (ethyl acetate)	254 320	4,26 4,40	1712 (C=O)	1,44 t[a] 2,73 s	3,30 q[a]	5,99 s	7,05 s[b] 7,32 s	$C_{12}H_{12}N_2O_3S$
IVd	66	155—6 (2-propanol–water)	255 320	4,37 4,28	1720 (C=O)	1,33 t[a] 1,43 t[a]	3,00 q[a] 3,29 q[a]	5,99 s	7,04 s[b] 7,28 s	$C_{13}H_{14}N_2O_3S$
Vb	43	250—2 (benzene)	256 310	4,21 3,97	1720 (C=O)	— —	3,13 t[a] 3,46 t[a]	3,80 s	7,13 s[c] 7,68 s	$C_{12}H_{12}N_2O_3S$

[a]J = 7.8 Hz. [b]In deuterochloroform. [c]In deuterodimethylsulfoxide. [d]COOH. [e]In deuteroacetone.

TABLE 2. Effect of Compounds IIa-d, IVb-d, and Va on Strength of Contraction of Guinea Pig Cardiac Atrium

Compound	Concentration of compounds studied, M: $1 \cdot 10^{-5}$	$1 \cdot 10^{-4}$	$5 \cdot 10^{-4}$
Control*	92,2±4,5[a]	96,4±3,5[b]	100,7±3,5[c]
IIa	136,7±10,7	178,0±30,8	167,0±21,5
IIb	115,4±2,2	136,8±11,3	155,8±13,8
IIc	115,7±2,3	123,7±5,8	164,2±9,6
IId	126,0±13,4	159,0±24,8	214,7±34,4
IVb	108,2±2,3	123,2±7,3	138,2±10,5
IVc	121,0±8,0	136,0±12,0	169,3±13,7
IVd	108,0±4,0	131,3±14,0	165,3±1,7
Va	123,4±6,2	176,2±15,0	222,2±22,0
Milrinone	132,2±4,6	156,8±10,2	162,4±11,7

*Physiologic solution, containing appropriate amount (concentration: [a]$5 \cdot 10^{-4}$ M, [b]$5 \cdot 10^{-3}$ M, [c]$3 \cdot 10^{-2}$M) of dimethylacetamide.

Characteristics and yields of compounds synthesized are given in Table 1. Values found in elemental analysis correspond to those calculated.

5,6-Dimethoxy(or Methylenedioxy)-2-ethylthiobenzimidazoles (Ib, IIIb) and 3-(5,6-Dimethoxybenzimidazol-2-ylthio) Propionic Acid (Ic). To a solution of 20 mmoles of the appropriate derivative of benzimidazolin-2-thione and 0.84 g (21 mmoles) NaOH in a mixture of 15 ml ethanol and 15 ml water, with stirring, at a temperature of 10°C was added a solution of 20 mmoles of iodoethane or 3-chloropropionic acid in 10 ml of ethanol. This was refluxed 1 h, cooled, and the product filtered.

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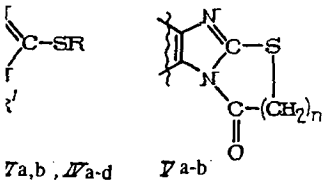

Ia,b, IIa-d IVa-b

OMe;
H_2O;
(Ia), Et (Ib), CH_2CH_2COOH (Ic);
(IIa), COEt (IIb);
(IIc), COEt (IId),
(IIIa), Et (IIIb);
(IVa), COEt (IVb);
(IVc), COEt (IVd);
/b).

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IVb-d, and Va on
Cardiac Papillary

pounds	
	$5 \cdot 10^{-4}$
	101,3±1,4[c]
	283,6±9,7
	199,2±22,0
	176,2±17,6
	184,8±17,7
	119,0±15,5
	159,0±30,7
	107,3±15,0
	176,5±40,4
	260,6±19,6

ppropriate amount
M, [c] $3 \cdot 10^{-2}$M) of

2 mmoles of the appropriate compound (Ia,b or IIIa,
dded dropwise, with stirring at room temperature, a
l $CHCl_3$. This was refluxed 2 h, cooled, washed with
r vacuum.
mixture of 2.3 g (8 mmoles) of compound Ic, 3.3 g
heated at 100°C for 30 min, cooled, poured into ice

ried out on preparations of atria and papillary muscles
ncy of 1 Hz. Physiologic solution had the following
-Cl – 10; $MgCl_2$ – 1; glucose – 5; pH 7.3-7.4.
were dissolved in 0.3 ml of dimethylacetamide (which
ntrations of $5 \cdot 10^{-4} - 3 \cdot 10^{-2}$ M), and this solution was
with the compounds studied was begun after a 60-min
s of rhythmically stimulated atria and papillary muscles
of the results, calculated from 5 experiments for each
studied was compared with that of milrinone [1, 5].
l cyclic analog Va display inotropic activity. However,
. Compounds IId and Va surpass milrinone in positive
onds to milrinone in its effect on strength of papillary
more active than the corresponding methylenedioxy
imethoxy derivative Va also surpasses its ethylenedioxy
l may both decrease (compounds IIa, b and IVc, d) and

drugs among compounds of the type examined.

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