into the 7-position in place of the aldehyde residue results in the bronchiolytic activity reappearing.

Continued search for new 7,8-disubstituted derivatives of xanthine having a bronchiolytic activity appears to be promising.

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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ACYLATED BENZOXA- AND BENZODIOXAHETEROCYCLES AND THEIR ACYCLIC ANALOGS

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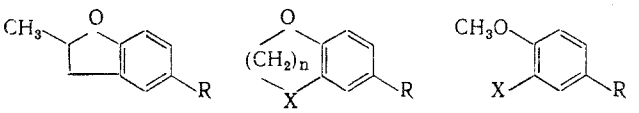
UDC 615.276:[547.56+547.72+547.814+547.841+547.89].012.1.07

Some benzoylated benzoxa- and benzodioxaheterocycles have been found to possess antiinflammatory activity [5]. With the aim, therefore, of investigating structure–activity relationships and of identifying novel antiinflammatory drugs, we have synthesized and tested benzoxa- and benzodioxaheterocycles and their acyclic analogs, containing an acyl substituent of the aliphatic series (Ib-f, i, IIc, i, IIIc, i, IVc, i, Vc, f-j, VIc, i, VIIi, VIIIi, IXc, f, i) or cinnamoyl (IIk-VIIk, IXk) which have either not previously been reported, or the antiinflammatory activity of which was not known.



I II — VII VIII, IX

II, V: $n = 1$; III, VI: $n = 2$; IV, VII: $n = 3$; II — IV $X = CH_2$; V — VII: $X = O$; VIII: $X = C_2H_5$; IX: $X = OCH_3$; Ia — IXa: $R = H$; Ib — IXb: $R = COCH_3$; Ic — IXc: $R = COCH_2CH_3$; Id — IXd: $R = CO(CH_2)_2CH_3$; Ie — IXe: $R = COCH(CH_3)_2$; If — IXf: $R = CO(CH_2)_2Cl$; Ig — IXg: $R = CO(CH_2)_3Cl$; Ih — IXh: $R = COCH_2N(CH_3)_2 \cdot HCl$; Ii — IXi: $R = CO(CH_2)_2N(CH_3)_2 \cdot HCl$; Ij — IXj: $R = CO(CH_2)_3N(CH_3)_2 \cdot HCl$; Ik — Ik: $R = COCH{=}CHC_6H_5$.

The ketones and chloroketones (Ib-f), (IIc, k), (IIIc, k), (IVc, k), (Vc, f, g, k), (VIc, k), (VIIk), (IXc, f, k) were obtained by the Friedel–Crafts acylation of the benzoxa- or benzodioxaheterocycles (Ia-VIIa) or 1,2-dimethoxybenzene (IXa) with acid chlorides in the presence of anhydrous $AlCl_3$ of $SnCl_4$, the β-aminoketone hydrochlorides (Ii-IXi) by the Mannich reaction of the appropriate acetyl compounds (Ib-IXb) with dimethylamine hydrochloride and paraformaldehyde, and the γ-aminoketone (Vj) by treatment of the chloroketone (Vg) with dimethylamine.

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TABLE 1. Properties of Compounds Obtained

Compound	Yield, %	mp, °C (solvent), or bp, °C (1 mm), n_D^{20}	UV spectrum λ_{max}, nm	UV spectrum lg ε	IR spectrum, $\nu C{=}O$, cm^{-1}	Found, % C	Found, % H	Found, % Cl	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % Cl	Calculated, % N
Ic	70	123—5, 1.5479	208 228 285	4.02 3.95 3.96	1675	75.51	7.40	—	—	$C_{13}H_{14}O_2$	75.77	7.42	—	—
Ic*	—	55—56 (cyclohexane)	—	—	—	70.16	7.49	—	6.96	$C_{12}H_{15}NO_2$	70.22	7.37	—	6.82
Id	75	128—9, 1.5420	208 228 286	4.01 4.00 4.05	1675	76.14	8.02	—	—	$C_{13}H_{16}O_2$	76.44	7.90	—	—
Id*	—	78—9 (cyclohexane)	—	—	—	71.05	7.88	—	6.50	$C_{13}H_{17}NO_2$	71.21	7.81	—	6.39
Ie	65	127—8, 1.5350	208 228 285	4.03 3.95 3.98	1655	76.18	7.96	—	—	$C_{13}H_{14}O_2$	76.44	7.90	—	—
Ie*	—	120—1 (cyclohexane)	—	—	—	71.08	7.89	—	6.47	$C_{13}H_{17}NO_2$	71.21	7.81	—	6.39
If**	68	—	209 228 290	3.98 3.81 3.65	1670	64.01	5.87	17.67	—	$C_{12}H_{13}ClO_2$	64.15	5.83	17.78	—
IIi	75	170—1 (2-propanol)	206 229 298	4.10 4.05 4.01	1655	60.86	7.17	14.9	25.49	$C_{13}H_{17}NO_2\times$ $\times HCl$	61.06	7.09	13.86	5.48
IIk	90	117—8 (ethanol)	208 232 332	4.31 4.04 4.43	1645	81.64	5.74	—	—	$C_{17}H_{14}O_2$	81.58	5.64	—	—
IVk	95	77—8 (ethanol)	208 229 320	4.24 4.07 4.45	1645	81.76	6.69	—	—	$C_{19}H_{18}O_2$	81.98	6.52	—	—
Vc	58	45—6 (hexane)	207 229 277 310	3.43 3.58 3.39 3.28	1670	67.33	5.61	—	—	$C_{10}H_{10}O_3$	67.40	5.66	—	—
Vf	55	67—8 (ethanol)	207 231 277 312	3.90 4.08 3.69 3.75	1665	56.37	4.29	16.76	—	$C_{10}H_9ClO_3$	56.48	4.27	16.67	—
Vj	65	168—9 (ethanol)	208 230 275 310	4.26 4.46 4.06 4.12	1670	57.29	6.82	12.86	4.86	$C_{12}H_{17}NO_3\times$ $\times HCl$	57.46	6.68	13.05	5.15
Vk	63	97—8 (ethanol)	209 236 328	4.39 4.19 4.33	1640	76.31	4.83	—	—	$C_{16}H_{12}O_3$	76.19	4.76	—	—
VIIk	76	86—7 (ethanol)	209 228 322	4.35 4.07 4.36	1645	76.89	6.03	—	—	$C_{19}H_{16}O_3$	77.12	5.75	—	—

*Oxime.

**Viscous oil, decomposed by means of distillation in vacuo (1 mm).

TABLE 2. Toxicity and Antiinflammatory Activity of Compounds Examined

Compound	LD_{50}, mg/kg	Dose, mg/kg	% inhibition of inflammation, induced by:	
			carrageenan	bentonite
Ib	739 (690—814)	50	9,7	32,7
Ic	1250 (1120—1380)	50	33,7	27,7
Id	...	50	—	—
Ie	...	50	18,0	5,6
If	...	50	—	—
Ii*	235 (210—251)	50	53,7	39,2
IIc	...	50	—	—
IIi*	156 (120—202)	50	60,7	32,5
IIk	...	50	6,9	—
IIIc	...	50	7,0	—
IIIi*	350 (320—393)	50	50,1	36,1
IIIk	...	50	2,8	2,2
IVc	...	50	—	—
IVi*	325 (220—375)	50	76,6	58,5
IVk	...	50	—	—
Vc	2150 (1840—2420)	50	31,5	55,7
Vf	...	50	—	8,6
Vg	...	50	—	—
Vh*	511 (478—543)	50	12,6	—
Vi*	338 (260—439)	50	56,0	63,1
Vj*	...	50	2,1	—
Vk	...	50	—	5,5
VIc	...	50	—	—
VIi*	>1000	50	15,3	—
VIk	...	50	—	—
VIIi*	>800	50	37,7	37,2
VIIk	2652 (2481—2816)	50	38,3	32,8
VIIIi*	345 (278—389)	50	38,5	44,1
IXc	1520 (1415—1690)	50	16,7	35,3
IXf	...	50	—	1,1
IXi*	541 (492—583)	50	41,6	58,3
IXk	...	50	13,2	16,8
Phenacetin	1638 (1366—1965)	200	—	9,1
Acetylsalicylic acid	1000 (743—1382)	200	28,1	6,5
Lysine acetylsalicylate*	1000 (890—1130)	150	37,4	9,8
Ibuprofen	800 (647—936)	80	30,8	22,0
Amidopyrine	625 (583—675)	100	42,6	40,2
Voltaren	172 (108—274)	25	46,7	24,3
Indomethacin	35 (25—42)	5	70,1	28,4

Note. A dash indicates increased edema; range of variation given in brackets; data statistically significant ($P < 0.05$), apart from (Ie). An asterisk denotes subcutaneous, and the remainder oral, administration.

The IR spectra of ketones (Ib-e), (IIb, c), (IIIb, c), (IVb, c), (Vb, c), (VIb, c), (VIIb), (IXb, c), the chloroketones (If), (Vf, g), and (IXf), and the aminoketones (Ii-VIi), (Vh, i, j), (VIi), (VIIi), and (IXi) showed carbonyl stretching vibrations at higher frequencies (1655-1675 cm^{-1}) than in the chalcones (IIk-VIIk) and (IXk) (1640-1645 cm^{-1}), and the UV absorption of the chalcones (IIk-VIIk) and (IXk), which possess longer conjugated chains than the above-mentioned ketones, chloroketones, and aminoketones, was shifted to longer wavelengths. The long wavelength absorption in the UV spectra of the acylated benzodioxaheterocycles (Vb, c, f-i), (VIb, c, i), (VIIb, i) and the 1,2-dimethoxybenzenes (IXb, c, f, i) were shifted to longer wavelengths than those of the corresponding benzoxaheterocycles (Ib-f, i), (IIb, c, i), (IIIb, c, i), and (IVb, c, i). This band is shifted to shorter wavelengths when the number of methylene groups n in the heterocyclic ring is increased, owing to the reduction of the electron-donor capacity of the oxygen atoms with respect to the aromatic ring, as a result of the rotation of the alkoxy-substituents around the C—O bond [3].

The structures of the compounds obtained were confirmed by their PMR spectra. Compounds (Ib) [9], (Ii) [3], (IIb, c), (IIIc) [12], (IIIb, i) [3], (IIIk) [5], (IVb, i) [3],

(IVc) [10], (Vb, i) [7], (Vg) [6], (Vh) [11], (VIb, c, i) [2], (VIk) [8], (VIIb, i) [4], (VIIIb, i) [3], (IXb, i) [14], (IXc) [13], and (IXf, k) [16] have been reported previously.

EXPERIMENTAL CHEMICAL

UV spectra were obtained on a Specord UV-VIS (East Germany) in ethanol, and IR spectra on a UR-20 instrument (East Germany) in Vaseline oil.

The properties and yields of the compounds obtained are shown in Table 1.

5-Acyl-2-methyl- and 5-Acylcoumarans (Ib-f, IIb, c, k), 6-Acylchromans (IIIb, c, k), 7-Acyl-1-benzoxazepanes (IVb, c, k), 5-Acyl-1,3-benzodioxolanes (Vb, c, f, g, k), 6-Acyl-1,4-benzodioxanes (VIb, c, k), 7-Acyl-1,5-benzodioxepanes (VIIb, k), and 1-Acyl-3,4-dimethoxybenzenes (IXb, c, f, k). To a mixture of 25 ml of dry CH_2Cl_2, 37 mmole of the appropriate acid chloride, and 35 mmole of (Ia-IVa), (VIa), (VIIa), or (IXa) was added at −10°C over 0.5 h 5.4 g (40 mmole) of anhydrous $AlCl_3$. The mixture was stirred for 1 h at 20°C, then poured onto ice, acidified with hydrochloric acid, extracted with CH_2Cl_2, the extract washed with water, dried, and the solvent removed. In the acylation of 1,3-benzodioxolane (Va), 10.4 g (40 mmole) of anhydrous $SnCl_4$ was added at 0°C.

Hydrochlorides of β-Dimethylaminopropionyl Compounds (Ii-IXi). A mixture of 40 mmole of the ketone (Ib-IXb), 3.8 g (47 mmole) of dimethylamine hydrochloride, 1.8 g (60 mmole) of paraformaldehyde (trioxymethylene), two drops of concentrated hydrochloric acid, and 30 ml of ethanol was boiled for 10 h, and the ethanol removed.

5-(γ-Dimethylaminobutyryl)-1,3-benzodioxolane Hydrochloride (Vj). A solution of 4.5 g (20 mmole) of the chloroketone (Vg) and 9 g (0.2 mole) of dimethylamine in 100 ml of benzene was kept for a week at 20°C, concentrated, extracted with 5% hydrochloric acid, the extract basified with sodium hydroxide, extracted with ether, and dry hydrogen chloride passed into the dried extract.

EXPERIMENTAL PHARMACOLOGICAL

Acute toxicities towards white mice were determined by the Litchfield and Wilcoxon method, as modified by Roth [1]. Antiinflammatory activity was assessed in experimental models of edema induced in the paws of white rats by carrageenin [17] and bentonite [15]. The ketones and chloroketones (Ib-f), (IIc, k), (IIIc, k), (Vc, f, g, k), (VIc, k), (VIIk), and (IXc, f, k), which were insoluble in water, were administered orally as suspensions in 1% carboxymethylcellulose with the addition of Tween-80, and the aminoketone hydrochlorides (Ii-IXi), (Vh, j) subsutaneously as the 1% aqueous solutions. Mongrel mice weighing 18-25 g and rats weighing 150-230 g of both sexes were used.

Table 2 shows the mean arithmetical percentages of reduction in edema, measured 1, 2, 3, and 5 h following administration of the test compound. It was found that some of the propionyl and cinnamoyl compounds (Ic), (Vc), (VIIk), and the hydrochlorides of many of the β-dimethylaminopropionyl compounds (Ii), (IIIi-Vi), (VIIi-IXi) were of low toxicity, possessed antiinflammatory activity, and in the favorable conjunction of these properties they were superior to the drugs in current medical use (Table 2). Varying the number of carbon atoms in the acyl moiety of the propionyl compound (Ic) or the β-dimethylaminopropionyl compound (Vi), or introduction of chlorine into the β-position of the propionyl group in ketones (Ic), (Vc), or (IXc) resulted either in a decrease (Ib, e) or disappearance (Id, f), (Vf, h, j), (IXf) of antiinflammatory activity. The 1,2-dimethoxybenzenes (IXc, i, k) were more active than their heterocyclic analogs, the 1,4-benzodioxanes (VIc, i, k).

These studies indicate a continuation of the search for novel antiinflammatory drugs in propionyl, β-dimethylaminopropionyl, and cinnamoyl derivatives of aromatic systems of this type.

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SYNTHESIS AND PHARMACOLOGICAL EXAMINATION OF POLYFUNCTIONAL MACROHETEROCYCLES.

3.* SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NITROGEN- AND SULFUR-CONTAINING MACROCYCLES

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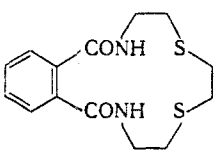
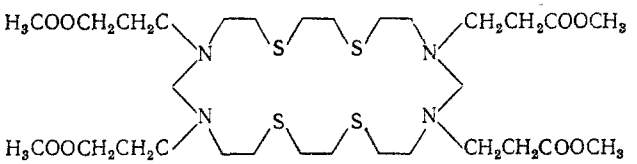
The naturally-occurring macrocyclic antibiotics valinomycin, nigerycin, and other similar compounds possess a wide spectrum of antibacterial activity. However, as a result of their high toxicity and low solubility in water, they have not been used in medical practice [5].

In order to identify synthetic analogs of naturally occurring macrocycles with antimicrobial activity, we have synthesized some nitrogen- and sulfur-containing macroheterocycles, together with open-chain compounds, and examined their antibacterial activity.

1,2-Benzo-3,14-dioxo-7,10-dithia-4,13-diazacyclotetradec-1-ene (I), 1,4,12,15-tetrathia-7,9,18,20-tetrakis-(2-methoxycarbonylethyl)-7,9,18,20-tetraazacyclodocosane (II), and their acyclic heteroanalogs 1,8-bis-(2-methoxycarbonylethylamino)-3,6-dithiaoctane (III) and 1,8-bis-(2-cyanoethylamino)-3,6-dithiaoctane (IV), have been obtained by us previously [1-3].



I



II

$RNHCH_2CH_2SCH_2CH_2SCH_2CH_2NHR$

III, IV

$R = CH_2CH_2COOCH_3$ (III), CH_2CH_2CN (IV)

*For communication 2, see [4].

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