ETHERS OF 5-HALOGENOSALICYLIC AND THIOSALICYLIC ACIDS

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New alkyl and benzyl ethers of 5-halogenosalicylic and 5-halogenothiosalicylic acids were prepared as intermediates for the production of acylated amines and guanidines and of 2-phenylbenzimidazoles. The compounds were tested for anthelminthic and coccidiostatic efficiency.

In connection with investigating the derivatives of 5-halogenosalicylic and 5-halogenothiosalicylic acids as compounds with a potential biological efficiency and further as intermediates for the synthesis of acylated amines and guanidines with possible antiviral activity and of benzimidazoles with expected anthelminthic efficiency we prepared a greater number of alkyl and benzyl ethers of these acids and subjected them to anthelminthic and coccidiostatic screening. The alkylations known from the literature carried out usually in an aqueous–ethanolic solution of sodium hydroxide or in acetone in the presence of potash did not provide satisfactory results in the present case. On replacing acetone with dimethylformamide (method *A*) it was possible to prepare all the compounds mentioned in Table I with the exception of *XIX* and *XX* and of derivatives of 5-halogenothiosalicylic acids *XXXI*–*XXXVII* which were formed according to Amoretti and Pagani[1] by alkylation of 5-halogenothiosalicylic acids with an appropriate alkyl bromide or iodide in an aqueous-ethanolic sodium hydroxide.

With the compounds prepared here, the anthelminthic and the coccidiostatic efficiency was evaluated in model experiments. Testing for anthelminthic efficiency was done using rats of the Blackhead strain invaded with larvae of *Nippostrongylus brasiliensis* and using H strain mice invaded with eggs of the tapeworm *Hymenolepis nana*. In both cases the dosage of the compounds was 200 mg/kg. In the first test, a statistically significant activity was found with *IX*, *XIV*, *XXI*, *XXV*, *XXVI*, *XXVII* and *XXIX*. In the second test, compounds *XI*, *XX* and *XXIX* were significantly active. The coccidiostatic effect was tested in a model experiment using chicks at three days of age which were infected with oocysts of the coccidium *Eimeria tenella*. The dosage was 125 mg/kg fodder. In this test, statistically significant effects were found with *XI*, *XIV*, *XXVI*, *XXVIII* and *XXXIII*. However, the results of biological

testing did not permit to derive a clear relationship between structure and anthelminthic and coccidiostatic efficiency.

EXPERIMENTAL

The melting points were determined in a Mettler FP 2 apparatus.

Preparation of Acids

Method A: Anhydrous potassium carbonate (0·55 mol) and 0·55 mol of the corresponding alkyl halogenide or benzyl chloride was added to a solution of 0·5 mol ethyl ester 5-chlorosalicylic acid[2] or of ethyl ester of 5-bromosalicylic acid (which was prepared for this purpose by esterification of 5-bromosalicylic acid[3] with ethanol and sulfuric acid) in dimethylformamide. The mixture was refluxed under stirring for 3 h whereupon the dimethylformamide was evaporated *in vacuo*. The mushy residue was combined with 300 ml 20% NaOH and the ester was saponified by 3 h of refluxing. The precipitated sodium salt was dissolved by adding 1 000 ml water and the free acid was precipitated by acidification with hydrochloric acid to pH 2. After filtration and washing with water the compound was crystallized from a suitable solvent. This was the method used for the preparation of acids *I*—*XVIII* and *XXI*—*XXX* (Table I).

Method B: 0·33 mol of the appropriate alkyl bromide or alkyl iodide was added to a solution of 0·3 mol 5-chloro or 5-bromothiosalicylic acid[4] in a mixture with 330 ml ethanol and 130 ml 20% NaOH. The mixture was refluxed under stirring for 1 h, concentrated *in vacuo*, the residue was dissolved in water, bleached with active charcoal and acidified with hydrochloric acid to pH 2. The precipitated product was filtered, washed with water and recrystallized from a suitable solvent. The method was used for preparing acids *XXXI*—*XXXVII* (Table I).

Hydrochloride of 5-Chloro-2-(2-diethylaminoethoxy)benzoic Acid (*XIX*)

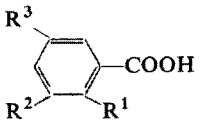
A solution of 2·3 g sodium in 100 ml ethanol was gradually combined with 20·1 g ethyl ester of 5-chlorosalicylic acid[2], 18·9 g hydrochloride of 2-diethylaminoethyl chloride and with 2·5 g sodium in 100 ml ethanol. The mixture was refluxed for 5 h, the precipitated sodium chloride was filtered, washed with ethanol and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in 500 ml 50% ethanol and refluxed for 4 h with 30 g sodium carbonate. After concentration to half the original volume and acidification with hydrochloric acid, the product was salted out from the emulsion with ammonium sulfate. By dissolving it in 100 ml boiling ethanol and filtration, the insoluble fraction was removed and the compound was precipitated from the filtrate by adding 700 ml ether. After filtration, washing with ether and drying, a total of 21·4 g (69·6%) compound melting at 159—167°C was obtained. A sample for analysis was crystallized from ethanol and 98% acetone. The m.p. and the elementary composition are shown in Table I.

By an analogous procedure, hydrochloride of 5-bromo-2-(2-diethylaminoethoxy)benzoic acid (*XX*) was prepared from the ethyl ester of 5-bromosalicylic acid. The yield, m.p. and elementary composition are shown in Table I.

The anthelminthic and coccidiostatic screening of compounds prepared here was done at the Research Institute for Biofactors and Veterinary Drugs (director Dr B. Ševčík). The elementary analyses were done at the analytical department of this institute (directed by Dr J. Körbl.)

TABLE I

Ethers of 5-Halogenosalicylic and 5-Halogenothiosalicylic Acids



Compound (yield, %)	R^1	R^2 R^3	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl (Br)	% N (S)
I (93·2)	n-C_3H_7O	H Cl	51·0—53·3 light petroleum	$C_{10}H_{11}ClO_3$ (214·7)	55·95 55·60	5·17 4·97	16·52 16·51	—
II[a] (97·6)	n-C_3H_7O	H Br	63·7—64·3 light petroleum	$C_{10}H_{11}BrO_3$ (259·1)	46·35 46·54	4·28 4·42	(30·84) (30·73)	—
III[a] (93·0)	i-C_3H_7O	H Br	101·0—101·8 light petroleum	$C_{10}H_{11}BrO_3$ (259·1)	46·35 46·59	4·28 4·15	(30·84) (30·60)	—
IV (98·6)	n-C_4H_9O	H Br	63·1—64·1 light petroleum	$C_{11}H_{13}BrO_3$ (273·1)	48·37 48·36	4·80 4·90	(29·26) (29·52)	—
V (43·9)	i-C_4H_9O	H Cl	68·8—69·8 [b]	$C_{11}H_{13}ClO_3$ (228·7)	57·77 57·65	5·73 5·96	15·51 15·64	—
VI (63·8)	i-C_4H_9O	H Br	65·6—66·2 [b]	$C_{11}H_{13}BrO_3$ (273·1)	48·37 48·37	4·80 4·90	(29·26) (29·52)	—
VII (89·3)	n-$C_5H_{11}O$	H Br	81·2—82·2 light petroleum	$C_{12}H_{15}BrO_3$ (287·2)	50·19 50·17	5·26 5·50	(27·83) (27·56)	—
VIII (97·1)	n-$C_6H_{13}O$	H Cl	40·0—40·8 light petroleum	$C_{13}H_{17}ClO_3$ (256·7)	60·81 60·97	6·68 6·75	13·80 13·75	—
IX (97·3)	n-$C_6H_{13}O$	H Br	65·8—66·4 light petroleum	$C_{13}H_{17}BrO_3$ (301·2)	51·84 51·99	5·69 5·99	(26·53) (26·61)	—

X	n-$C_{12}H_{25}O$	H	47·4—48·8	$C_{19}H_{29}ClO_3$	66·94	8·58	10·40	
(67·6)		Cl	80% acetic acid	(340·9)	66·95	8·63	10·63	
XI	n-$C_{12}H_{25}O$	H	61·7—62·5	$C_{19}H_{29}BrO_3$	59·22	7·58	(20·74)	—
(98·8)		Br	light petroleum	(385·3)	59·18	7·71	(20·92)	
XII	$CH_2{=}CHCH_2O$	H	79·2—79·8	$C_{10}H_9ClO_3$	56·48	4·27	16·68	—
(96·5)		Cl	[c]	(212·6)	56·92	4·31	16·74	
XIII	$CH_2{=}CHCH_2O$	H	73·3—74·2	$C_{10}H_9BrO_3$	46·71	3·53	(31·09)	—
(95·3)		Br	[b]	(257·1)	46·52	3·62	(31·05)	
XIV	$CH{\equiv}CCH_2O$	H	105·1—105·6	$C_{10}H_7ClO_3$	57·02	3·35	16·83	—
(96·6)		Cl	water	(210·6)	57·18	3·36	16·90	
XV	$CH{\equiv}CCH_2O$	H	121·5—122·4	$C_{10}H_7BrO_3$	47·08	2·77	(31·33)	—
(55·8)		Br	30% methanol	(255·1)	47·05	2·76	(31·48)	
XVI	$CH_3{-}CCl{=}CHCH_2O$	H	126·3—126·8	$C_{11}H_{10}Cl_2O_3$	50·60	3·86	27·16	—
(94·9)		Cl	[d]	(261·1)	50·75	3·58	27·15	
XVII	$CH_3OCH_2CH_2O$	H	69·8—70·3	$C_{10}H_{11}ClO_4$	52·07	4·81	15·37	—
(90·0)		Cl	[e]	(230·7)	52·61	5·01	15·46	
XVIII	$CH_3OCH_2CH_2O$	H	67·0—67·4	$C_{10}H_{11}BrO_4$	43·66	4·03	(29·05)	—
(96·0)		Br	[b]	(275·1)	43·63	3·81	(29·23)	
XIX	$(C_2H_5)_2NCH_2CH_2O$	H	176·6—178·3	$C_{13}H_{19}Cl_2NO_3$	50·66	6·21	23·01	4·55
(46·5)	HCl	Cl	98% acetone	(308·2)	50·85	6·13	23·17	4·29
XX	$(C_2H_5)_2NCH_2CH_2O$	H	170·3—171·8	$C_{13}H_{19}BrClNO_3$	44·27	5·43		3·97
(48·4)	HCl	Br	95% acetone	(352·7)	44·14	5·54		3·83
XXI	$C_6H_5CH_2O$	H	120·6—121·5	$C_{14}H_{11}ClO_3$	64·01	4·22	13·50	—
(83·2)		Cl	[f]	(262·7)	64·32	4·11	13·40	

TABLE I
(*Continued*)

Compound (yield, %)	R^1	R^2 R^3	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl (Br)	% N (S)
XXII (76·1)	$C_6H_5CH_2O$	H Br	106·1—107·4 [d]	$C_{14}H_{11}BrO_3$ (307·2)	54·74 54·77	3·61 3·49	(26·02) (26·21)	—
XXIII (66·8)	2-$ClC_6H_4CH_2O$	H Cl	150·7—151·9 80% ethanol	$C_{14}H_{10}Cl_2O_3$ (297·1)	56·59 56·46	3·39 3·14	23·86 23·80	—
XXIV (93·5)	2-$ClC_6H_4CH_2O$	H Br	157·8—158·5 80% ethanol	$C_{14}H_{10}BrClO_3$ (341·6)	49·22 49·14	2·95 2·71	(23·40) (23·32)	[g]
XXV (78·5)	3-$ClC_6H_4CH_2O$	H Cl	131·0—131·6 60% ethanol	$C_{14}H_{10}Cl_2O_3$ (287·1)	56·59 56·62	3·39 3·15	23·86 24·22	—
XXVI (82·7)	3-$ClC_6H_4CH_2O$	H Br	136·2—136·8 70% ethanol	$C_{14}H_{10}BrClO_3$ (341·6)	49·22 49·17	2·95 2·91	(23·40) (22·87)	[h]
XXVII (77·6)	4-$ClC_6H_4CH_2O$	H Cl	176·8—177·6 80% ethanol	$C_{14}H_{10}Cl_2O_3$ (297·1)	56·59 56·81	3·39 3·35	23·86 23·94	
XXVIII (80·2)	4-$ClC_6H_4CH_2O$	H Br	169·6—170·1 80% ethanol	$C_{14}H_{10}BrClO_3$ (341·6)	49·22 49·34	2·95 2·97	(23·40) (23·49)	[i]
XXIX (96·7)	3,4-$Cl_2C_6H_3CH_2O$	H Cl	180·6—182·9 80% ethanol	$C_{14}H_9Cl_3O_3$ (331·6)	50·71 51·03	2·74 2·68	32·08 32·09	—
XXX (83·5)	3,4-$Cl_2C_6H_3CH_2O$	H Br	191·9—193·8 80% ethanol	$C_{14}H_9BrCl_2O_3$ (376·0)	44·71 44·50	2·41 2·33	(21·25) (21·17)	[j]

XXXI	CH_3S	H	184·7—186·5	$C_8H_7ClO_2S$	47·41	3·48	17·50	(15·82)
(71·2)		Cl	50% ethanol	(202·7)	47·30	3·47	17·21	(15·64)
XXXII	CH_3S	H	204·8—206·7	$C_8H_7BrO_2S$	38·88	2·86	(32·34)	(12·98)
(91·5)		Br	50% ethanol	(247·1)	39·44	2·94	(32·34)	(12·69)
XXXIII	CH_3S	Cl	150·3—151·6	$C_8H_6Cl_2O_2S$	40·52	2·55	29·91	(13·53)
(55·0)		Cl	tetrachloromethane	(237·1)	40·87	2·56	30·11	(13·63)
XXXIV	$(CH_3)_2CHCH_2S$	H	96·8—97·5	$C_{11}H_{14}O_2S$	62·83	6·71	—	(15·25)
(89·5)		H	light petroleum	(210·3)	62·23	6·58		(14·95)
XXXV	$CH_2{=}CHCH_2S$	H	147·7—149·7	$C_{10}H_9ClOS$	52·52	3·97	15·50	(14·02)
(72·1)		Cl	40% methanol	(228·7)	52·18	4·05	15·27	(14·12)
XXXVI	$CH_2{=}CHCH_2S$	H	161·8—163·6	$C_{10}H_9BrO_2S$	43·97	3·32	(29·26)	(11·74)
(63·2)		Br	60% methanol	(273·2)	44·17	3·31	(29·27)	(11·78)
XXXVII	$CH{=}CCH_2S$	H	205·1—206·5	$C_{10}H_7ClO_2S$	52·98	3·11	15·64	(14·15)
(44·4)		Cl	60% ethanol	(226·7)	52·01	3·27	15·59	(13·95)

[a] Mentioned in ref.[5]; [b] light petroleum–ether (2 : 1); [c] light petroleum–ether (5 : 1); [d] light petroleum–ether (1 : 1); [e] light petroleum–ether (4 : 1); [f] light petroleum–ether (1 : 4); [g] calculated: 10·38% Cl, found: 10·49% Cl; [h] calculated: 10·38% Cl, found: 10·21% Cl; [i] calculated: 10·38% Cl, found: 10·51% Cl; [j] calculated: 18·86 Cl, found: 19·05% Cl.

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