Review Article

Synthesis, Properties and Prodrug Potential of 2-Methyl-2-oxy- and 2-Methyl-2-thio-4*H*-1,3-benzodioxin-4-ones

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The fifty-four known title compounds are fully documented and their chemical and biological properties discussed in detail. Special attention is devoted to their potential as aspirin and salicylic acid prodrugs, respectively.

The salicylates, i.e. compounds or mixtures which after administration furnish therapeutic *in vivo* concentrations of aspirin (*O*-acetylsalicylic acid) **1** and/or salicylic acid **2**, constitute a group of qualitatively and quantitatively important drugs with, *inter alia*, antiinflammatory, analgesic, antipyretic, and antithrombotic properties.[1] They include the esters **3**, the thioesters **4**, and the title compounds **5** and **6**. The last two are the only known examples of the prototype **7**, in which both the carboxy and the acetoxy group of **1** are latent, i.e. present as an ortho ester type compound which yields **1** and/or **2** upon hydrolysis. Compounds **5** and **6** could thus function as prodrugs of **1** and/or **2**.[1-3] A known drug of the type **3** is Benorylate **3**-17,[1,3] while **5**-14 has been presented as the experimental drug MR 693[4-6] and **5**-17 as

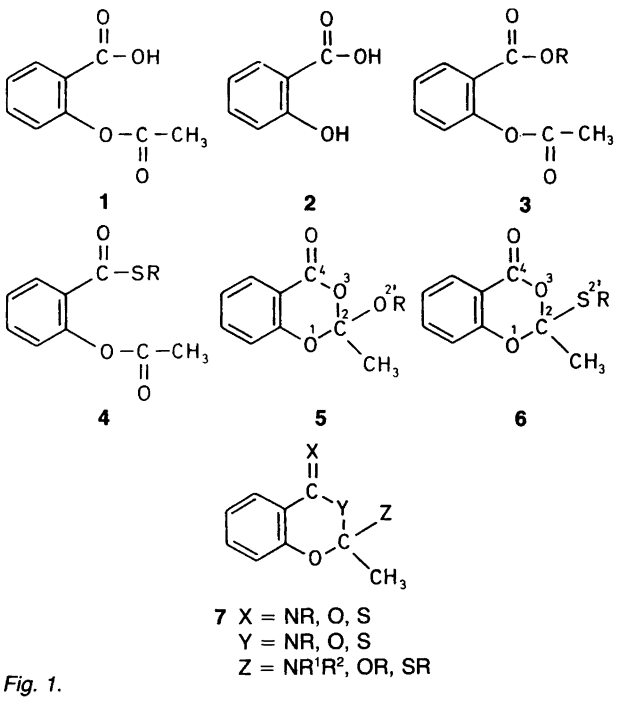
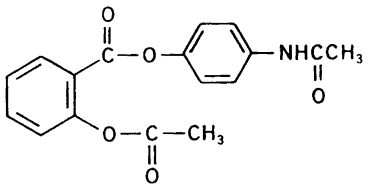
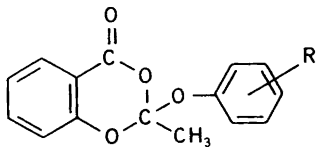


Fig. 1.





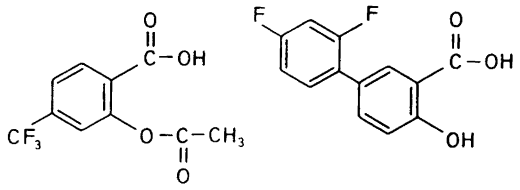


Fig. 2.

the experimental drug MR 897.[7] Drugs such as Triflusal **8**[1,8] and Diflunisal **9**[1,9] (together with Flufenisal,[1] Meseclazone,[1] 4-aminosalicylic acid,[10] 5-aminosalicylic acid,[1] and others with a wide spectrum of pharmacological activities and applications) belong to a parallel series of compounds in which a *C*-substituent is present on the salicylic acid moiety and which are often, in the broader sense, included in the generic term salicylates.

This review covers all compounds **5** and **6** reported up to mid-1988 and presents the state of the art with regard to their synthesis, structural features and chemical properties with special emphasis on their value or otherwise as potential prodrugs.

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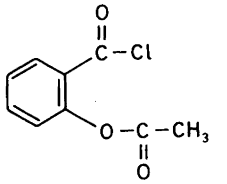
Synthesis of **5** *and* **6.** Table 1 lists the methods which have actually been used in the synthesis or at least appear to be immediately applicable. It should be noted that the acyclic isomer **3** is often formed together with **5** and that the **5**:**3** ratio in the crude reaction products is notoriously unpredictable.[2,11] In a number of cases **5** has only been obtained as **5**/**3** mixtures. It is widely held that **5** is the kinetically and **3** the thermodynamically controlled product.[2,11] *O*-Acetylsalicylic acid chloride **10** is an important starting material for **5** (methods I, II, III and IV) and **6** (method I). In solution its cyclic isomer **11** (which could be expected to be the immediate precursor of **5**) is not observed in equilibrium concentrations above the detection limits of IR[12,13] and NMR[14] spectroscopy. Its intermediacy in some reactions of **10** has, however, been inferred from ^{18}O labeling experiments.[13] The question of whether **11** is present in the solid state has not been addressed specifically, but it is also irrelevant from a synthetic point of view. The salts **12**[14,15] do possess a preformed cyclic structure, but have not yet been used as starting materials for **5** and **6** (Table 1). Under suitable circumstances (for instance in the presence of base) **10** $\rightleftharpoons$ **11** could conceivably eliminate hydrogen chloride and form the ketene acetal **13** as a reactive intermediate which in turn could form **5** by the addition of ROH.[16] The mixed anhydrides undoubtedly formed in method V have not yet been characterized as **14** or **15**, or equilibrium mixtures of both.

Tables 2 and 3 contain relevant data concerning the fifty compounds **5** reported so far. With respect to **5**-2 the discrepancy between the recorded boiling points: 120–122 °C/

Table 1. Synthetic methods for **5** and **6**.

Method	Starting materials	Reaction conditions	Key references
I	**10** + ROH	Solvent a) None[22,24] b) SO_2(l)[16,24] c) CH_2Cl_2[5,11] d) $CHCl_3$[28,29] e) CCl_4[28] f) $CHCl_2CHCl_2$[5] g) CH_3CN[19,23,25,26] h) THF[11] i) CH_3CN/THF[2] j) $C_6H_5CH_3$[5]	11
II	**10** + ROH + weak base	Solvent/base a) None/Et_3N[11] b) None/2,6-$Me_2C_5H_3N$[11] c) CH_2Cl_2/C_5H_5N[6,29] d) $CHCl_3$/C_5H_5N[7,28,29,30,31] e) CCl_4/Et(*i*-Pr)$_2$N[11] f) CCl_4/C_5H_5N[11,29] g) CCl_4/NEt_3[29]	11
III	**10** + RO^-	Solvent CCl_4[11]	11
IV	**10** + $ROSiMe_3$	Solvent/catalyst THF/Et_3N[2]	2
V[a]	**1** + $(R'CO)_2O$ + ROH	Solvent/R' a) C_6H_6/CH_3[5] b) C_6H_6/CF_3[5,29,30] c) C_6H_6/CCl_3[5] d) $C_6H_5CH_3$/CF_3[31] e) $C_6H_5CH_3$/CCl_3[5] f) $C_6H_5CH_3$/C_2H_5[5]	5, 29
VI[b]	**2** + $CH_3C(OR)_3$	Solvent/catalyst C_6H_6/4-$MeC_6H_4SO_3H$[20]	20
VII	**2** + RO–C≡CH	Solvent/catalyst CH_2Cl_2/$Hg(MeCO_2)_2$[17,18,20]	18
VIII[c]	**12** + ROH		14, 15

[a]Probable intermediates: **13** $\rightleftharpoons$ **14**. [b]Only examples with *C*-substituted **2** known; $CH_3C(OR)_3$ with bulky R not readily available; wasteful of expensive alcohols/phenols. [c]Only proposed,[14] no examples known.



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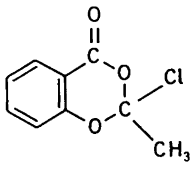

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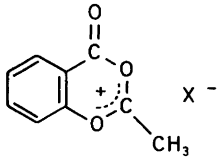
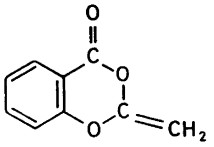


12 **a**: X = $SbCl_6^-$
b: X = ½ $SnCl_6^{2-}$

Fig. 3.

2 mmHg[17] and 105 °C/0.1 mmHg[11] vs. 250–255 °C/0.01 mmHg[18] should be noted. The value given in Ref. 18 is probably in error. Compound **5**-14 has been assigned CAS RN [81674-79-4] (Refs. 5, 6), the equivalent (±)-**5**-14 has RN [89053-43-0] (Ref. 4), while (*S*)-**5**-14 has RN [114926-70-4] (with no references in *Chemical Abstracts*). Similarly, **5**-21 has been assigned RN [52602-13-8] [Refs. 2, 11), the equivalent (±)-**5**-21 RN [81323-76-4] (Ref. 19), and (*R*)-**5**–21 RN [114926-71-5] (again with no references in *Chemical Abstracts*). Obviously, the two pure enantiomers stem from the same anonymous source and have been entered in the *Chemical Abstracts* database without being documented.



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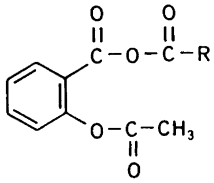

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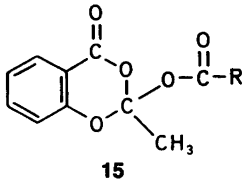

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Fig. 4.

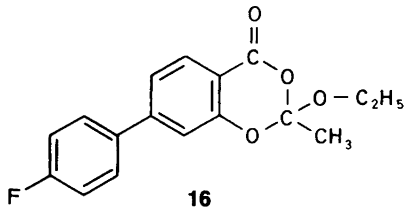

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Fig. 5.

The four known compounds **6** listed in Tables 4 and 5 were all prepared from **10** and the appropriate thiols in the absence of base (i.e. method I).

Finally, the Flufenisal derivative **16**[20] has been obtained by method VII.

Structural data. The assigned structures of **5**-1 through **5**-50 rest firmly on the X-ray structure determinations in **5**-14[4] and **5**-21.[19] In these structures the three C–O single-bond lengths involving C(2) are especially interesting since they might give an indication of the 'weak spot', i.e. the order in which the corresponding bonds are broken in the course of the hydrolysis of **5**, an important factor in the reaction sequence according to which **5** acts as pro-**1** or pro-**2**, respectively (*vide infra*). In **5**-14 these three bond lengths are: C(2)–O(1) 1.402 Å, C(2)–O(3) 1.425 Å, C(2)–O(2′) 1.417 Å. In **5**-21 the following bond lengths have been determined: C(2)–O(1) 1.427 Å, C(2)–O(3) 1.366 Å, C(2)–O(2′) 1.376 Å. More data must be accumulated before significant trends can be detected. In both cases the 2-organyloxy group occupies an axial position on the somewhat flattened heterocycle (the 2-methyl group thus being equatorial) as a consequence of the preference of the conformationally restrained oxygen lone pairs for the antiperiplanar arrangement.

Of special diagnostic value for the distinction between isomeric **5** and **3** are the ^{13}C NMR signals of C(2) and of the 2-methyl group and the ^1H NMR signals of the 2-methyl group of **5**, which are characteristically different from the analogous signals of **3**. In addition, two carbonyl absorptions are present in the IR spectrum of **3**, whereas only one such absorption is observed in that of **5**.[2] The isomers **6**-4 can be discerned similarly.[2] The mass spectra of isomeric **5** and **3** are practically identical.[2] Another useful and intriguing spectral feature of some compounds **5** (and **6**) is the NMR diastereotopy of geminal nuclei in appropriate positions in the 2-organyloxy and 2-organylthio group, respectively, due to the stereogenic centre at C(2).[12,21]

Photochemistry of **5** *and* **6**. Compounds **5**-15 and **6**-2 have been photolyzed in benzene and in methanol solution, and yield a variety of products (including **3**-15 and **4**-2, respectively) which are assumed to be formed via initial cleavage of the starting materials into the radical pairs **17a** and **17b**, respectively.[22]

Compounds **5** *as synthetic intermediates.* Treatment of carbohydrates and carbohydrate derivatives with **10** leads to

Table 2. CAS registry numbers and preparation of **5**.

No.	Substituent	Registry No.	Method[a]	Temp./°C	Time/h	Yield/% (ratio **5**:**3**)	Ref.
5-1	Methyl	[52667-93-3]	III	0	5	(1:2)	11
			VII	25	3		18
5-2	Ethyl	[21519-97-1]	II f	60		29 (2:1)	11
			II e	70		100 (6:5)	11
			VII	25	3		18
			VII	Amb.	24	33	17
5-3	n-Butyl	[52602-15-0]	I h	70		(8:2)	11
5-4	*t*-Butyl	[52602-20-7]	I i	Amb.		72 (6:1)	2
			II a	50	4	60	11
5-5	*t*-Butoxy	[52602-02-5]	I a	25	1	62	11
5-6	Neopentyl	[88353-96-2]	IV	Amb.		90 (9:1)	2
5-7	*t*-Amyloxy	[52602-03-6]	I a	25	1	65	11
5-8	2-Chlorophenyl	[52602-06-9]	I h	70	5	68 (2:1)	11
5-9	4-Chlorophenyl	[52602-11-6]	I h	70		87 (3:1)	11
			I i	Amb.		78 (4:1)	2
			IV	Amb.		95 (5:1)	2
5-10	Phenyl	[52602-04-7]	I h	70	5	95 (13:1)	11
			I i	Amb.		85 (6:1)	2
			IV	Amb.		95 (4:1)	2
5-11	Benzyl	[52602-18-3]	IV	Amb.		90 (8:1)	2
			I h	70		67	11
5-12	*o*-Tolyl	[52602-07-0]	I h	70	5	63 (19:1)	11
5-13	*p*-Tolyl	[52602-09-2]	I h	70	5	87 (9:1)	11
5-14	2-Methoxyphenyl	[81674-79-5]	I c	Reflux	48	58	5
			I f	100	48	60	5
			I j	Reflux	36	57	5
			V c	Amb.	10	55	5
			V a	Amb.	10	41	5
			V e	Amb.	24	61	5
			V b	Amb.	10	56	5
			V f	Amb.	10	39	5
			II c	20	16	28	6
5-15	4-Methoxyphenyl	[90998-03-1]	I a	Amb.	4	72	22
5-16	1,3-Diacetoxy-2-propyl	[64630-47-3]	II d	Reflux	15	65	28
			I e	Reflux	15	(1:1)	28
			II d	Reflux	24	65	29
5-17	4-(Acetylamino)phenyl	[87549-36-8]	II d	20	15	28	7
5-18	2-[(3-Pyridinecarbonyl)amino]ethyl	[88353-97-3]	I i	Amb.		78 (9:1)	2
5-19	(±)-1-Phenylethyl	[88353-98-4]	IV	Amb.		95 (1:1)	2
5-20	[3-(4-Chlorobutanoyloxy)]-2-butyl	[95200-41-2]	V b	Amb.	3/2		30
5-21	2-Naphthyl	[52602-13-8]	I i	Amb.		62 (6:1)	2
			I h	70		52 (6:1)	11
			I g	−20			19
5-22	Adenosin-5′-yl	[63244-53-1]	I b	−20	2/3	73	16, 24
5-23	(−)-Bornyl	[88353-99-5]	IV	Amb.		90 (3:1)	2
5-24	(±)-Menthyl	[88354-00-1]	IV	Amb.		90 (3:1)	2
5-25	3-(Hexanoyloxy)-2-butyl	[95200-54-7]	V b	Amb.	3/2	37	30
5-26	[3-(4-Methylpentanoyloxy)]-2-butyl	[95200-40-1]	V b	Amb.	3/2		30
5-27	{3-(Acetyloxy)-2,3,3a,9a-tetrahydro-6-oxo-6*H*-furo[2′,3′:4,5]oxazolo-[3,2-*a*]pyrimidin-2-yl]methyl}	[63283-85-2]	I b	−20	2	80	16
5-28	[3-(4-Chlorobenzoyloxy)]-2-butyl	[95200-46-7]	II d	Reflux	27		30
5-29	{3-(Acetyloxy)-2,3,3a,9a-tetrahydro-[6-imino-6*H*-furo[2′,3′:4,5]oxazolo-[3,2-*a*]pyrimidin-2-yl]methyl} (monohydrochloride)	[64667-46-5]	I g	Amb.			25, 26
5-30	3-(Benzoyloxy)-2-butyl	[95200-43-4]	V b	Amb.	3/2		30
5-31	[2-*O*-Acetyl-3-chloro-3-deoxy-1-(6-oxo-6*H*-purin-9-yl)-5-*O*-β-D-xylofuranosyl]	[74437-66-4]	I g	Amb.	72	67	23
5-32	[2-*O*-Acetyl-3-chloro-3-deoxy-1-(6-amino-9*H*-purin-9-yl)-5-*O*-β-D-xylofuranosyl]	[61773-75-9]	I g	Amb.	72	80	23

contd

Table 2. (contd)

No.	Substituent	Registry No.	Method[a]	Temp./°C	Time/h	Yield/% (ratio 5:3)	Ref.
5-33	[3-*o*-Acetyl-2-chloro-2-deoxy-1-(6-amino-9*H*-purin-9-yl)-5-*o*-β-D-arabinofuranosyl]	[61773-76-0]	I g	Amb.	72	80	23
5-34	3-(4-Methylbenzoyloxy)-2-butyl	[95200-44-5]	V b	Amb.	3/2		30
5-35	3-(2-Phenylethanoyloxy)-2-butyl	[95200-47-8]	II d	Reflux	27		30
5-36	3-(4-Methoxybenzoyloxy)-2-butyl	[95200-45-6]	II d	Reflux	27		30
5-37	3-[3-(4-Chlorophenyl)-2-propenoyloxy]-2-butyl	[95200-51-4]	II d	Reflux	27		30
5-38	3-(3-Phenyl-2-propenoyloxy)-2-butyl	[95200-48-9]	II d	Reflux	27		30
5-39	1-Decanoyloxy-2-propyl	[89076-29-9]	V d	Amb.	1/12	67	31
			II d	Reflux	24		31
5-40	3-Nonanoyloxy-2-butyl	[95200-37-6]	V b	Amb.	3/2		30
5-41	3-(2-Cyano-3-phenyl-2-propenoyloxy)-2-butyl	[95200-52-5]	II d	Reflux	27		30
5-42	3-[3-(*p*-tolyl)-2-propenoyloxy]-2-butyl	[95200-49-0]	II d	Reflux	27		30
5-43	3-[3-(4-Methoxyphenyl)-2-propenoyloxy]-2-butyl	[95200-50-3]	II d	Reflux	27		30
5-44	3-Decanoyloxy-2-butyl	[95200-38-7]	V b	Amb.	3/2		30
5-45	3-(10-Undecenoyloxy)-2-butyl	[95200-42-3]	V b	Amb.	3/2		30
5-46	Hexadecyl	[72155-31-8][b]	I d	Reflux	17	35	29
5-47	3-(2,3-Diphenyl-2-propenoyloxy)-2-butyl	[95200-53-6]	II d	Reflux	27	36	30
5-48	3-Hexadecanoyloxy-2-butyl	[95200-39-8]	V b	Amb.	3/2		30
5-49	1,3-Didecanoyloxy-2-propyl	[64630-46-2]	II d	Reflux	24	31	28, 29
			V b	Amb.	1	76	29
			II c	Reflux	24	35 (8:2)	29
			II c	25	24	35 (6:4)	29
			II c	Reflux	24	35 (4:6)	29
			II f	Reflux	24	55 (3:7)	29
			II g	Reflux	24	30 (5:5)	29
			II f	Reflux	24	90 (1:9)	29
5-50	1,3-Dipalmitoyloxy-2-propyl	[64630-45-1]	II d	Reflux	15	36	28
			II d	Reflux	24	36	29

[a]See Table 1. [b]In CAS incorrectly indexed as: IN 4*H*-1,3-Benzodioxin-4-one, 2-hexadecyl-; MF C24H38O3.[33]

chemical modifications some of which take place via isolable **5**.[16,23-26] Thus, **5**-22 after treatment with excess **10** and subsequent methanolysis under basic conditions furnishes 9-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)adenine and 2′,3′-*O*-[(methoxycarbonylmethyl)ethylidene]adenosine (the formation of the latter appears to involve the intermediacy of **13**).[24] Methanolysis of **5**-27 under acidic conditions leads to O^2,2′-cyclouridine;[16] under the same conditions **5**-29 can form 1-(3-*O*-acetyl-O^2,2-cyclo-β-D-arabinofuranosyl)cyto-

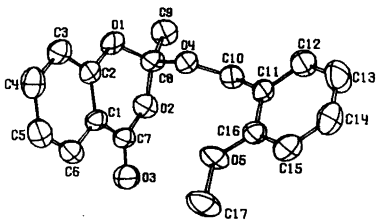


Fig. 6. X-Ray structure of 2-methyl-2-(2-methoxybenzyloxy)-4*H*-1,3-benzodioxan-4-one **5**-14.[32]

Table 3. CAS registry numbers and preparation of **6**.

No.	Substituent	Registry No.	Method[a]	Temp./°C	Time/h	Yield/% (ratio 6:4)	Ref.
6-1	4-Chlorophenyl	[88354-06-7]	I i	Amb.		73 (3:1)	2
6-2	Phenyl	[90998-02-0]	I a	Amb.	4	83	22
6-3	Benzyl	[52602-25-2]	I h	70		(1:1)	11
6-4	*m*-Tolyl	[88354-07-8]	I i	Amb.		54 (1:1)	2

[a]See Table 1.

Table 4. Physical properties of **5**.

No. **5**-	M.p. (b.p.)/ °C (°C)[a]	^{1}H NMR δ_{CH_3}/ppm	^{13}C NMR $\delta_{C(2)}$/ppm	IR $\nu_{C=O}$/cm^{-1}	UV λ_{max}/nm	MS (M^+)	Elemental analysis	Other data
1		1.45 (CCl_4)		1755 (CCl_4)				
2	[b]	1.80 (CCl_4)		1755 (CCl_4)			+	n_D^{20} 1.5129
3	(95)[c]	1.80 (CCl_4)		1755 (CCl_4)			+	
4	(100–115)	1.77 (CCl_4)	112.7 ($CDCl_3$)	1750 (CCl_4)	301		+	
5		1.89 (CCl_4)		1760 (CCl_4)			+	n_D^{20} 1.4941
6	(80–90)	1.85 ($CDCl_3$)	113.4 ($CDCl_3$)	1745 (film)	298			
7		1.91 (CCl_4)		1760 (CCl_4)			+	
8	90–91 (150–170)[c]	1.89 (CCl_4)		1755 (CCl_4)			+	
9	(170–180)	1.87 ($CDCl_3$)	113.2 ($CDCl_3$)	1755 (film)	300		+	
10	(150–160)	1.86 ($CDCl_3$)	113.3 ($CDCl_3$)	1750 (film)	300		+	
11	(110–120) 49–50	1.91 ($CDCl_3$)	113.0 ($CDCl_3$)	1735 (KBr)	300		+	
12	(130–140)	1.84 (CCl_4)		1760 (CCl_4)			+	
13	(145)	1.84 (CCl_4)		1760 (CCl_4)			+	
14	70–74							X-Ray
15	88–90	1.88 ($CDCl_3$)		1760 (Nujol)		286	+	
16	66.5–67					338		
17	102–105	1.8 ($CDCl_3$)		1710 (CH_2Cl_2)			+	
18	98–99	1.82 ($CDCl_3$)		1745 (KBr)		300	+	
19								
20		1.82		1740				
21	88.5–89.5	1.97 ($CDCl_3$)	113.6 ($CDCl_3$)	1745 (KBr)	300		+	X-Ray
22	182–184	1.88 (Me_2SO)		1760 (KBr)	300			
23	(130–140)	1.83 ($CDCl_3$)	113.8 ($CDCl_3$)				+	
24	(130–140)	1.80 ($CDCl_3$)	112.7 ($CDCl_3$)	1740 (film)	304		+	
25		1.84		1745				
26		1.85		1750				
27	190–193	1.68 ($CDCl_3$)		1760 (KBr)			+	R_f 0.15[d]
28		1.80		1750				
29	Amorphous				303			
30		1.85		1760				
31	210–212	1.96 (Me_2SO)		1775 (KBr)			+	$[\alpha]_D^{24}$ −53.3° (*c* 0.6, MeOH) R_f 0.37[d]
32	98–102	1.93 ($CDCl_3$)		1760 (KBr)			+	$[\alpha]_D^{24}$ −20.8° (*c* 1.1, $CHCl_3$) R_f 0.49[d]
33								R_f 0.49[d]
34		1.85		1750				
35		1.80		1740				
36		1.85		1755				
37		1.84		1740				
38		1.87		1740				
39		1.85 ($CDCl_3$)		1730 (neat)			+	
40		1.85		1740				
41		1.85		1750				
42		1.83		1740				
43		1.85		1750				
44		1.85		1750				
45		1.85		1750				
46	36–38	1.80 ($CDCl_3$)				404		
47		1.75		1750				
48		1.85		1750				
49		1.85 ($CDCl_3$)	113.2 ($CDCl_3$)			562		
50	Semisolid					730		

[a]At 0.01 Torr, except as specified. [b]B.p. 120–122 °C at 2 Torr, see Ref. 16. B.p. 105 °C at 0.01 Torr, see Ref. 17. B.p. 250–255 °C at 0.01 Torr, see Ref. 18. [c]at 0.05 Torr. [d]($CHCl_3$/C_2H_5OH, 9:1).

Table 5. Physical properties of **6**.

No. **6-**	M.p. (b.p.) /°C[a]	^{1}H NMR δ_{CH_3}/ppm	^{13}C NMR $\delta_{C(2)}$/ppm	IR $\nu_{C=O}$/cm^{-1}	UV λ_{max}/nm	MS (M^+)	Elemental analysis
1	60–61	2.00 ($CDCl_3$)	112.4 ($CDCl_3$)	1745 (KBr)	304		+
2	71–73	2.00 ($CDCl_3$)		1750 (Nujol)		272	+
3	(130–150)	1.94 (CCl_4)		1760 (CCl_4)			
4							

[a]at 0.01 Torr.

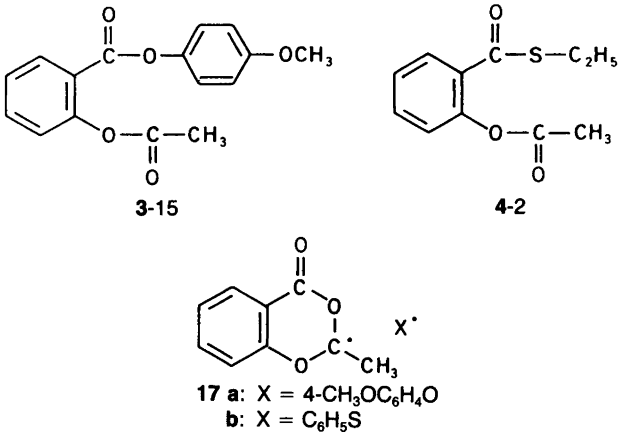


Fig. 7.

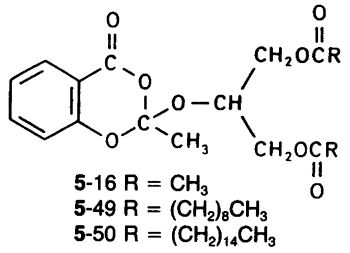


Fig. 9.

sine or 1-(O^2,2-cyclo-β-D-arabinofuranosyl)cytosine hydrochloride.[25,26] Methanolysis of **5**-31 yields 9-β-D-(3′-chloro-3′-deoxyxylofuranosyl)hypoxanthine as well as 9-β-D-(2′-chloro-2′-deoxyarabinofuranosyl)hypoxanthine.[23] Reduction of **5**-32 with tributylstannane under radical conditions leads to 3′-deoxyadenosine, while its basic methanolysis affords 9-β-D-(3′-chloro-3′-deoxyxylofuranosyl)-9*H*-purin-6-amine; under the same conditions **5**-33 yields 9-β-D-(2′-chloro-2′-deoxyarabinofuranosyl)-9*H*-purin-6-amine.[23]

Hydrolysis of **5** *and* **6**. Scheme 1 shows a variety of pathways along which **5** can be hydrolysed to **1** or **2**. Obviously

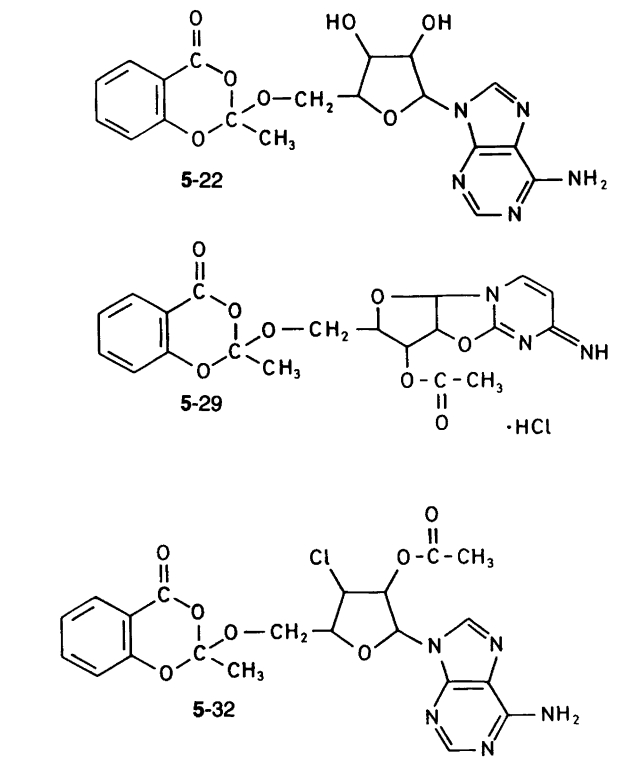
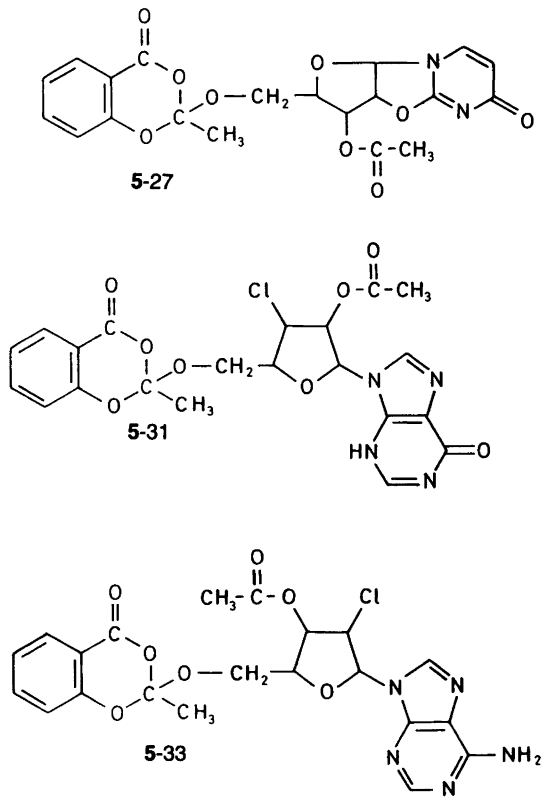
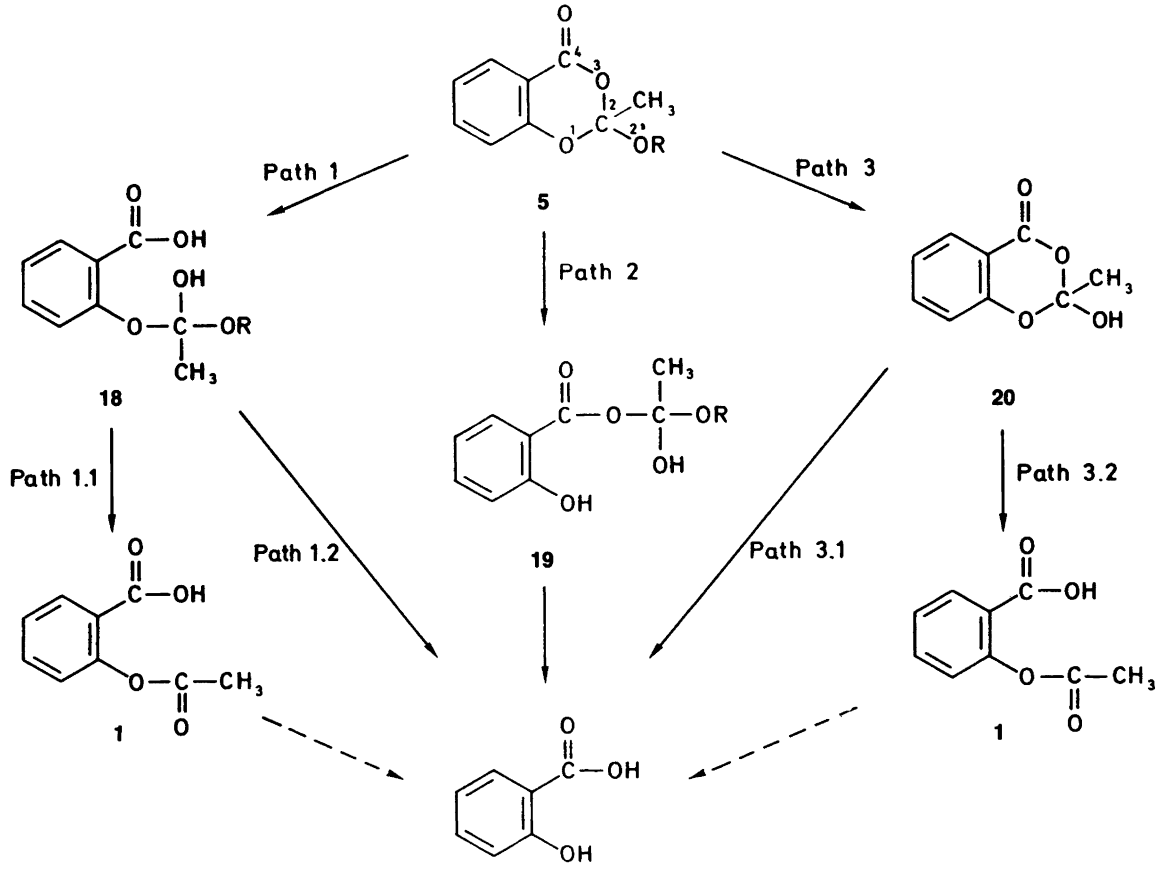


Fig. 8.





Scheme 1. The hydrolysis of **5**.

intermediate **18** can be formed in two ways, either by cleavage of the C(2)–O(3) bond or of the C(4)–O(3) bond of **5**. Careful *in vitro* studies in our laboratory[2] have shown that only one of the nine compounds **5** investigated, i.e. **5**-4, hydrolyzes to **1**, while the remaining eight compounds (**5**-6, **5**-9, **5**-10, **5**-11, **5**-18, **5**-21, **5**-23 and **5**-24) yielded only **2**. The only compound **6** examined, i.e. **6**-1, likewise formed **2** upon hydrolysis. Continued investigations[12,21,27] have confirmed our first impression that the majority of compounds **5** are hydrolyzed to **2**, but we have also found additional compounds **5** which are hydrolysed to **1**, typically with R = *t*-alkyl or 2-substituted benzyl. Also, certain compounds **5** which form **1** and **2** simultaneously have been found.[12,21] The question of increasing the half-life of **1**-forming **5** beyond the ultrashort half-life of **5**-4 (4 min) is being addressed.[2,12,21]

Compound **5**-14 has been claimed, though without documentation, to form **1** upon enzymatic *in vitro* hydrolysis, and both **1** and **2** upon *in vivo* hydrolysis.[4,6] Compounds **5**-17 have been claimed to be stable at low pH, again in the absence of documentation.[7] It is truly amazing that no clear-cut *in vitro* data have been presented concerning these experimental drugs. The same is true of the experimental drugs **5**-16, **5**-49 and **5**-50.[28,29]

The pharmacological properties of **5**. A number of compounds **5** has been studied as potential prodrugs of **1** and/or **2**. In most cases the aim was to develop compounds which were equipotent with **1** (especially with respect to plasma levels of **2**), but did not cause gastric lesions as does **1**.

Compound **5**-49 was shown to be inactive in the rat-paw edema test.[28,29] The most thoroughly tested compound appears to be **5**-14. The following pharmacological properties have been described:[4,6] no gastric lesions are observed, pulmonary tropism (considered to be due to the presence of a guaiacol moiety) was noted, the oral antiinflammatory and antipyretic activity in rats closely parallels that of equimolar amounts of **1**, the antitussive effect in guinea pigs of 500 mg kg^{-1} p.o. equals that of 25 mg kg^{-1} p.o. codeine and 100 mg kg^{-1} i.p. is equipotent with 12.5 mg kg^{-1} i.p. codeine. The acute toxicity is low: in mice >3000 mg kg^{-1} p.o., in rats >3000 mg kg^{-1} p.o. and 1750 mg kg^{-1} i.p. All tests for subacute toxicity, chronic toxicity and teratogenicity were negative.

Compound **5**-17 has been shown to be roughly equipotent and equitoxic with **3**-17.[7] Equipotency was shown with respect to its antiinflammatory, analgesic and antipyretic properties. Compounds **5**-17 and **3**-17 share a clear-cut superiority over **1** as far as gastric lesions are concerned. The acute toxicity of **5**-17 is low: the LD_{50} for mice is 2300 mg kg^{-1} p.o., for rats 3500 mg kg^{-1} p.o., much the same as that of **3**-17. In beagle dogs no chronic toxicity is seen below 500 mg kg^{-1}/die p.o. In cynomolgus monkeys dosed with 200 mg kg^{-1} p.o. the plasma **2** level peaks after 8 h

with 112.8 μg ml^{-1} while the corresponding treatment with **3**-17 leads to a similar peak level after only 3 h. Thus, the bioavailability of **5**-17 (expressed as area under the plasma **2** concentration curve) is approximately 2.5 times larger than that of **3**-17.

The antiedema activities of oral **5**-16, **5**-49 and **5**-50 amount to 62–100 % of that of **1**, again without causing gastric lesions at all. The preferred compound is **5**-49.[28,29]

Conclusions

Compounds **5** and **6** are well-documented chemical entities; the potential of compounds **5** to act as prodrugs of **2** and especially of **1** appears far from exhausted since none of the experimental drugs seem to qualify as a true 'superaspirin'. Nonetheless, **5**-14 is already being marketed as Bronteril, while **5**-17 has advanced to phase 2 clinical testing.[34]

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