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Heteroarylalkanoic Acids with Possible Antiinflammatory Activities, III[1)]

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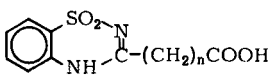
A series of (1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-propanoic acids **B** or -butanoic acids **C** has been synthesized. Their antiinflammatory activities were studied and compared with those of the lower homologues **A**. Some of the compounds examined showed pronounced activities against carrageenan-induced plantar oedema.

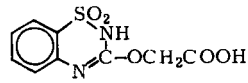
Heteroarylalkansäuren als Potentielle Entzündungshemmer, 3. Mitt.

Es wurde eine Reihe von (1,2,4-Benzothiadiazin-1,1-dioxid-3-yl)-propionsäuren **B** oder -buttersäuren **C** synthetisiert und ihre entzündungshemmende Wirkung im Vergleich mit den niedrigeren Homologen **A** untersucht, die früher schon getestet wurden. Einige dieser Verbindungen zeigten eine deutliche Wirkung auf das durch Carrageen induzierte Rattenpfotenödem.

Within the limits of research aimed at studying heteroarylalkanoic acids of possible antiinflammatory action, it was possible to reveal an interesting grade of antiinflammatory activity[1)] in some derivatives of (1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-acetic acids **A**.



A: n = 1
B: n = 2
C: n = 3



D

The antiinflammatory activity was found also in derivatives of structure **D**[2)], but in this case the experimentation has been limited to a few terms, because of the difficulty in preparing this type of compound.

Continuing our research in this field, we turned our attention to derivatives of structure **B** which are at the same time higher homologues of **A** and isosteres of **D**; our studies have been extended also to the butanoic derivatives **C** which, in turn, are higher homologues of

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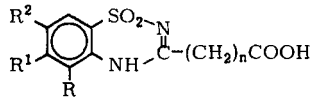
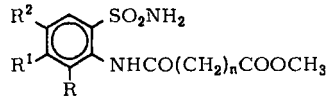
B. Thus a series of bz.substituted derivatives of type **B** has been prepared (compounds **1–10**) as well as the corresponding higher homologues (compounds **11–20**); in both series the substituents have been chosen in such a way as to be able to make a useful comparison with the compounds studied previously.



1-20

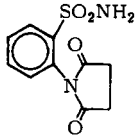


21-40

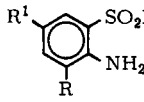
	R^2	R^1	R	n	
1	H	H	H	2	21
2	H	Cl	H	2	22
3	Cl	H	H	2	23
4	Cl	H	Cl	2	24
5	Cl	Cl	H	2	25
6	Br	H	H	2	26
7	Br	H	Br	2	27
8	H	CH_3	H	2	28
9	H	OCH_3	H	2	29
10	H	CF_3	H	2	30
11	H	H	H	3	31
12	H	Cl	H	3	32
13	Cl	H	H	3	33
14	Cl	H	Cl	3	34
15	Cl	Cl	H	3	35
16	Br	H	H	3	36
17	Br	H	Br	3	37
18	H	CH_3	H	3	38
19	H	OCH_3	H	3	39
20	H	CF_3	H	3	40

Compounds **1–20** were prepared by cyclization and simultaneous alkaline hydrolysis of the methyl esters of the ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acids **21–40.** In turn, the compounds **21–40** were obtained from the corresponding 2-aminobenzenesulfonamides by reaction with the chloride of the 1,4-butanedioic or 1,5-pentanedioic acid monomethyl ester.

In the reaction between 2-aminobenzenesulfonamide and the chloride of the 1,4-butanedioic acid monomethyl ester, small quantities of N-[2′-(aminosulfonyl)phenyl]-2,5-pyrrolidinedione **(41)**[3] can be isolated along with the 4-{[2-(aminosulfonyl)phenyl]amino}-4-oxo-butanoic acid methyl ester) **(21).**



41



	R^1	R
42	Cl	Cl
43	Br	Br

According to the reaction conditions, in the treatment of the methyl esters of bihalogen- (**24, 25, 27** and **34, 35, 37**) or of trifluoromethyl substituted (**30** and **40**) ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acids with alkalies, a secondary product can form alongside the corresponding arylalkanoic acid (**4, 5, 7, 14, 15, 17** and **10, 20**) which it has been possible to isolate in the case of **14** and **17** and to identify as 5-[(2'-amino-3',5'-dichlorophenylsulfonyl)-amino]-**(42)** and 5-[(2'-amino-3',5'-dibromophenylsulfonyl)-amino]-5-oxo-pentanoic acid **(43)**.

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Experimental Part

Chemical

MP: Büchi capillary apparatus, uncorr. *Elementary analyses:* Carlo Erba Elemental Analyzer Mod. 1106, Microanalysis Laboratory of Dipartimento di Science Farmaceutiche, University of Modena. All compounds were analysed for C, H, N, S and, if present, Cl, Br; the values found fell well within ± 0.3 % of the theoretical values. *I.R. spectra:* Perkin-Elmer model 257 apparatus in solid phase dispersed in nujol.

Methyl esters of ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acids **21–40**

Compounds **21–40** were prepared starting from the corresponding 2-aminobenzenesulfonamides, by reaction in N,N-dimethylacetamide (DMA) with the chloride of the 1,4-butanedioic or 1,5-pentanedioic acid monomethyl ester (1.5 to 2 moles for each mole of original sulfonamide) at 20–25°C, then proceeding as already indicated for other 2-acylaminobenzenesulfonamides[4].

On completion of the reaction, the ethereal layer was separated by decantation and the oily layer was mixed with 2.5 % HCl until complete transformation into a powdery solid which was then washed with 2 % $NaHCO_3$ solution. The insoluble matter, consisting of ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acid methyl ester was crystallized from acetone/petrol ether, b.p. 80–100°C. Table 1 gives the yields, melting points and empirical formulae of the compounds obtained. In the case of the 4-{[2-(aminosulfonyl)phenyl]amino}-4-oxo-butanoic acid methyl ester **(21)**, a crystalline solid separated from the acid and alkaline-bicarbonate wash waters, in percentages varying according to the duration of treatment; it was found to consist of N-[2'-(aminosulfonyl)phenyl]-2,5-pyrrolidinedione **(41)**. **41** was identified on the basis of the results of the elementary analyses ($C_{10}H_{10}N_2O_4S$: C,H,N,S)

and from the melting point (250–259°C, dec. also when mixed with an authentic sample of **41** obtained according to *Kratzl* and *Ruis*[3]), and in addition from comparison of the I.R. absorption spectra.

Table 1: *Methyl esters of* ω-{*[2-(aminosulfonyl)phenyl]amino*}-ω-*oxo-alkanoic acids* **21–40**

Compound	Yield %	m.p. °C	Formula
21	62	102–104	$C_{11}H_{14}N_2O_5S$
22	91	131–133	$C_{11}H_{13}ClN_2O_5S$
23	94	143–145	$C_{11}H_{13}ClN_2O_5S$
24	95	163–164	$C_{11}H_{12}Cl_2N_2O_5S$
25	88	163–165	$C_{11}H_{12}Cl_2N_2O_5S$
26	95	159–161	$C_{11}H_{13}BrN_2O_5S$
27	84	171–173	$C_{11}H_{12}Br_2N_2O_5S$
28	55	121–123	$C_{12}H_{16}N_2O_5S$
29	85	104–105	$C_{12}H_{16}N_2O_6S$
30	89	127–128	$C_{12}H_{13}F_3N_2O_5S$
31	59	127–129	$C_{12}H_{16}N_2O_5S$
32	95	125–127	$C_{12}H_{15}ClN_2O_5S$
33	86	125–126	$C_{12}H_{15}ClN_2O_5S$
34	88	126–127	$C_{12}H_{14}Cl_2N_2O_5S$
35	91	142–144	$C_{12}H_{14}Cl_2N_2O_5S$
36	70	128–130	$C_{12}H_{15}BrN_2O_5S$
37	89	127–129	$C_{12}H_{14}Br_2N_2O_5S$
38	75	126–128	$C_{13}H_{18}N_2O_5S$
39	86	109–111	$C_{13}H_{18}N_2O_6S$
40	65	108–110	$C_{13}H_{15}F_3N_2O_5S$

(1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)-alkanoic acids **1–20**

These were obtained starting from the methyl esters of the corresponding ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acids **21–40** by cyclization and hydrolysis with hot NaOH (method A) or at room temp. (method B).

Method A: the ω-{[2-(aminosulfonyl)phenyl]amino}-ω-oxo-alkanoic acid methyl ester dissolved in 4 % NaOH (10 ml per g of product) was heated on a boiling waterbath for 10 min. After cooling, the alkaline solution, first saturated with a current of CO_2 to separate possible decomposition products, supplied the corresponding arylalkanoic acid on acidification with HCl. The product, washed with H_2O, was successively crystallized from a suitable solvent.

Method B: the reaction was performed with 0.5 % NaOH (35 ml per g of product) keeping the reaction mixture at 20–25°C for 24 h, and then proceeding as described in method A. Table 2 gives the methods, yields, melting points, crystallization solvents and empirical formulae of the compounds obtained.

Operating according to method A, a secondary product is obtained from the crystallization waters of the arylalkanoic acids **4, 5, 7, 10, 14, 15, 17, 20** which in the case of **14** and **17** could be identified as respectively 5-[(2'-amino-3',5'-dichlorophenylsulfonyl)-amino]-**(42)** and 5-[(2'-amino-3',5'-dibro-

mophenylsulfonyl)-amino]-5-oxo-pentanoic acid **(43)**. Both compounds were crystallized from acetone/petrolether b.p. 80–100°C and give a positive diazo-reaction:

42 m.p. 168–170°C ($C_{11}H_{12}Cl_2N_2O_5S$: C,H,Cl,N,S)

43 m.p. 176–178°C ($C_{11}H_{12}Br_2N_2O_5S$: C,H,Br,N,S)

In all other cases mentioned above it was impossible, because of the small quantity of product available, to identify the secondary product which presumably consists of the corresponding ω-[(2'-(aminophenylsulphonyl)-amino]-ω-oxo-alkanoic acid, since the crude materials gave a positive diazo-reaction and the relative I.R. absorption spectra are similar to those of **42** and **43**.

Table 2: *(1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)-alkanoic acids* **1–20**

Compound	Method	Yield %	m.p. °C	Cryst. Solvent	Formula
1[a,b]	A	86	215–217	1	$C_{10}H_{10}N_2O_4S$
2	A	92	260–262	2	$C_{10}H_9ClN_2O_4S$
3[a]	A	87	230–232	1	$C_{10}H_9ClN_2O_4S$
4	A(B)	47(96)	291–293	1	$C_{10}H_8Cl_2N_2O_4S$
5	A(B)	47(73)	287–289	3(2)	$C_{10}H_8Cl_2N_2O_4S$
6[a]	A	72	255–257	3	$C_{10}H_9BrN_2O_4S$
7	A(B)	36(97)	287–289	1(2)	$C_{10}H_8Br_2N_2O_4S$
8	A	92	235–238	1	$C_{11}H_{12}N_2O_4S$
9	A	52	242–245	2	$C_{11}H_{12}N_2O_5S$
10	A	77	292–293	4	$C_{11}H_9F_3N_2O_4S$
11[a]	A	81	185–187	1	$C_{11}H_{12}N_2O_4S$
12	A	70	273–274	2	$C_{11}H_{11}ClN_2O_4S$
13	A	76	242–243	4	$C_{11}H_{11}ClN_2O_4S$
14	A(B)	28(79)	261–263	1	$C_{11}H_{10}Cl_2N_2O_4S$
15	A	63	300–302	1	$C_{11}H_{10}Cl_2N_2O_4S$
16	A	75	257–259	1	$C_{11}H_{11}BrN_2O_4S$
17	A(B)	24(78)	257–258	1	$C_{11}H_{10}Br_2N_2O_4S$
18	A	86	236–238	2	$C_{12}H_{14}N_2O_4S$
19	A	95	199–200	1	$C_{12}H_{14}N_2O_5S$
20	A(B)	42(79)	309–312	4	$C_{12}H_{11}F_3N_2O_4S$

1 = acetone/petrol ether b.p. 80–100°C; 2 = DMA/water; 3 = ethanol/water; 4 = methanol/water.

a) The compounds thus marked had already been obtained by other authors, through various procedures: **1**[3,6] **3**[7], **6**[8], **11**[3,9].

b) The compound can be obtained also from N-[2'-(aminosulfonyl)phenyl]-2,5-pyrrolidinedione **(41)** by treatment with NaOH according to method A with practically quantitative yields.

Pharmacology

The antiinflammatory activity of the heteroarylalkanoic acids **1–20** was tested using as the experimental phlogosis model carrageenan-induced plantar oedema in the rat.

Table 3: *Antiinflammatory effects of compounds* **1–20**

Compound[a]	Mol.Wt.[b]	% increase in vol. of the paw at 2 h mean ± S.E.	% inhibition at 2 h	Activity index at 2 h	% increase in vol. of the paw at 3 h mean ± S.E.	% inhibition at 3 h	Activity index at 3 h
1	254	56,71 ± 4,53	–	–	64,63 ± 3,54	–	–
2	288,7	38 ± 4,23	23,73	+	45,37 ± 3,54	24,35	+
3	288,7	47,99 ± 5,55	8,73	–	51,92 ± 5,41	17,74	+
4	323	47,11 ± 2,44	–	–	48,07 ± 6,82	12,65	+
5	323	29,34 ± 3,63	42,16	++	43,49 ± 4,35	36,77	++
6	333	46,91 ± 4,78	18,10	+	60,37 ± 4,46	15,23	+
7	412	25,51 ± 2,44	30,05	++	25,08 ± 3,63	54,42	++
8	268	54,78 ± 5,16	–	–	53,42 ± 3,29	–	–
9	284	38,08 ± 4,59	30,10	++	59,83 ± 8,42	16,13	+
10	322	15,16 ± 2,62	58,43	++	21,58 ± 3,35	60,79	+++
11	268	45,23 ± 4,69	6,24	–	47,81 ± 4,23	26,11	+
12	302,7	48,01 ± 5,00	5,36	–	58,15 ± 3,65	15,46	+
13	302,7	45,62 ± 7,98	16,26	+	63,15 ± 8,63	11,48	+
14	337	21,89 ± 3,18	54,60	++	31,33 ± 3,77	45,83	++
15	337	27,59 ± 3,85	45,76	++	42,03 ± 4,37	4,04	–
16	347	48,02 ± 5,31	5,60	–	56,91 ± 4,73	–	–
17	426	33,45 ± 2,41	30,63	++	38,62 ± 3,25	33,23	++
18	282	40,16 ± 2,95	3,07	–	47,74 ± 3,93	6,01	–
19	298	58,26 ± 4,51	–	–	69,39 ± 6,28	2,73	–
20	336	32,75 ± 3,91	10,20	+	38,85 ± 5,15	29,40	+
Indomethacin		21,25 ± 2,31	58,87	++	24,80 ± 2,23	62	+++

a) Ten animals were used for testing each compound except **9** for which nine were used, and indomethacin for which 25 were used. Each substance was used at the constant dose of 0.4 mmol/kg, i.p., indomethacin at the dose of 0.014 mmol/kg, i.p..

b) The molecular weight is referred to the free acid. It should be remembered that the sodium salt was actually used.

– No activity

+ Slight activity (inhibition between 10 and 30 %)

++ Pronounced activity (inhibition between 30 and 60 %)

+++ Very pronounced activity (inhibition over 60 %)

Materials and methods

Female Wistar rats weighing between 140–160 g were used; they were housed for at least one week in airconditioned premises (22 ± 1°C, relative humidity 60 %) and fed a pelletted feed. The substances under study, in the form of the sodium salt, and at the dose of 0.4 mmol/kg for each compound, were injected i.p. after dissolving in distilled water. At the doses used in the antiinflammatory activity tests, no other symptomatologies were observed. Immediately after injection of the substances, tap water was administered by gavage (5 ml per animal), so as to ensure uniform tissue hydration and consequently a more homogeneous phlogistic response according to what has been described by *Winter* et al.[5].

The control animals received an i.p. injection of physiological saline equal in vol. to that of the treated animals. Moreover, the antiinflammatory activity of 0.014 mmol/kg of indomethacin administered i.p. (suspension in 0.5 % methocel) was evaluated as reference, in another group of animals. Treatment with the substances under test was effected 0.5 h before injection into one of the two hind-paws of a 1 % suspension (ml 0.5) of carrageenan in physiological saline. The vol. of the paw was measured with a plethysmometer immediately, 2 and 3 h after the injection of carrageenan.

Results

Table 3 gives the index of antiinflammatory activity of each of the substances tested, 2 and 3 h after the plantar injection of carrageenan. The activity index of indomethacin is also indicated for comparison. Analysis of the results thus obtained shows that some compounds have been found to possess an interesting effect inhibiting the increase in vol. of the paw induced by carrageenan. In fact, compounds **5, 7, 10, 14** and **17** presented marked antiinflammatory activity both 2 and 3 h after injection of carrageenan.

Discussion of the Results

On examining the structure/action relationships it must first of all be pointed out that antiinflammatory activity is present in both the series of compounds examined here (**B** and **C**) and that in this case the length of the alkanoic chain is therefore not a structurally determinant factor for the appearance of this type of activity.

Another observation emerging from this examination is that the effect of lengthening the alkanoic chain is not uniform but may be variously influenced by the substituents present in the benzene ring: in some cases there is a decrease of activity (compare, for instance, **10** with **20**; **9** with **19**; **6** with **16**), in some cases there is an increase (compare, for instance, **4** with **14**) while in other cases the effect is almost nil, especially when considering the activity at 2 h (compare **7** with **17** and **5** with **15**); lengthening in this case leads to a reduction in the duration of action.

What has been found up to now is made further manifest on comparative examination of Table 3 with Table 4 which reports the data relative to the corresponding compounds of structure **A** studied in previous research[1].

In this case it is possible to observe also an alternation of influence in both the positive (compare, for instance, the series of 5,7-dichloroderivatives **47, 4** and **14**) and negative sense (compare the 6-methoxyderivatives **52, 9** and **19**).

As regards the influence exerted by the substituents present in the benzene ring, it is possible to see that trifluoromethyl-substituion is that which has demonstrated the greatest increasing effect for a value of n = 2 in the alkanoic chain (compound **10**). A notable increasing effect can also be exerted by

the presence of halogens, but this effect is not unequivocal and depends not only on the nature, the number and the position of the halogen, but also on the length of the alkanoic chain present in the molecule. Also the 6-methoxy group presents an increasing influence, but only for a value of n = 2 in the alkanoic chain (compound **9**).

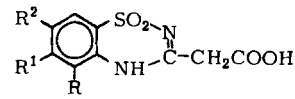

Table 4[a]: *Antiinflammatory effects of compounds* **44–53**

Compound[b]	R^2	R^1	R	Mol.Wt.	Dose mmol/kg i.p.	Activity index at h 2	3
44 (16)	H	H	H	240	0,4	–	+
45 (5)	H	Cl	H	274,7	0,4	–	–
46 (5)	Cl	H	H	274,7	0,4	–	–
47 (5)	Cl	H	Cl	309	0,4	++	++
48 (10)	Cl	Cl	H	309	0,4	++	++
49 (10)	Br	H	H	319	0,4	++	++
50 (10)	Br	H	Br	398	0,4	+	++
51 (10)	H	CH_3	H	254	0,4	+	+
52 (5)	H	OCH_3	H	270	0,4	–	–
53 (5)	H	CF_3	H	308	0,4	–	–
Indomethacin(45)					0,014	+++	+++

a) For the data reported in this table, read[1]

b) The number of animals in brackets

– No activity

+ Slight activity (inhibition between 10 % and 30 %)

++ Pronounced activity (inhibition between 30 % and 60 %)

+++ Very pronounced activity (inhibition over 60 %).

It is possible from all the above to postulate the hypothesis that among the various chemical-physical factors responsible, that represented by a different electronic structure of the benzothiadiazine nucleus for effect of the substituents, plays an important part. By influencing the conformation of the alkanoic chain, this would lead to that structure more or less ideal for the appearance of the biological activity here considered. We promise to effect in-depth investigations in this sense.

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[Ph 976]

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Vinyloge Amidiniumsalze durch Einwirkung von Methyliodid auf sekundäre β-Ketoenamine

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Von Anilin oder Benzylamin abgeleitete sekundäre β-Ketoenamine **1** reagieren beim Erhitzen mit überschüssigem Methyliodid zu *N,N'*-Diphenyl- bzw. *N,N'*-Dibenzyl-4-amino-3-penten-2-iminiumiodiden **2a** bzw. **2b**.

Vinyl Analogous Amidinium Salts from Secondary β-Ketoenamines with Methyl Iodide.

Upon heating with an excess of methyl iodide, secondary β-ketoenamines **1** derived from aniline or benzylamine are converted to the *N,N'*-diphenyl- and *N,N'*-dibenzyl-4-amino-3-pentene-2-iminium iodides **2a** and **2b**, respectively.

Durch überschüssiges Methyliodid in der Siedehitze werden tertiäre Enaminoketone in C_α-methylierte Iminiumsalze übergeführt[1)2)]. Uns interessierte, wie sekundäre β-Ketoenamine unter gleichen Bedingungen reagieren.

Erhitzten wir 4-Phenylamino-3-penten-2-on **(1a)** mit überschüssigem Methyliodid 24 Std. unter Rückfluß, so wurden gelbe, bei 176° schmelzende Kristalle erhalten. Elementaranalyse und Massenspektrum sprachen für die Bruttoformel $C_{17}H_{19}IN_2$. Im ^{1}H-NMR-Spektrum fanden sich je 1 Singulett für 6 Protonen von 2 Methylgruppen bei δ = 2,63 ppm sowie für 1 CH-Proton bei δ = 5.55 ppm, ferner ein zentriertes Multiplett für 10 Aromatenprotonen bei δ = 7.3 und ein breites Signal für 2 NH-Protonen um 11 ppm. Wir

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