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Syntheses and Antiinflammatory Activity of Malonamic Acid, Malonamate and Malonamide Derivatives of Some Heterocyclic Compounds

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Malonamate, malonic acid and malonamide derivatives of heterocyclic compounds were synthesized as part of a search for new biologically active compounds, *e.g.*, those having antiinflammatory activity. Malonamates (**1**—**17**) were prepared by the reaction of amines containing heterocycles with malonic acid monoethyl ester. Hydrolysis of the malonamates gave the malonamic acids (**18**—**24**) in good yields. Malonamides (**25**—**43**) were synthesized by condensing amines with *N*-substituted malonamic acids. The antiinflammatory activity of these compounds was examined against carrageenin-induced rat paw edema. *N*-[2-(6-Methoxy)benzothiazolyl] malonamic acid (**23**) and its ethyl ester (**7**) showed significant activity.

Keywords——2-aminothiazole; 2-aminobenzothiazole; 2-aminothiadiazole; 6-aminoindazole; malonamate; malonamic acid; malonamide; antiinflammatory

A number of 2-aminothiazole derivatives having antiinflammatory,[1] local anesthetic,[2] hypoglycemic[3] and fungicidal[4] activities have recently appeared in the literature. Further, some derivatives of malonamic acid and malonamide have antihypertensive,[5,6] sedative and anticonvulsant,[7] analgesic[6,8] and central-nervous-system-stimulating activities.[9] *N*-Acyl or *N*-arylglycine derivatives with structures similar to malonamate were found to possess analgesic and antiinflammatory activities.[10] We first prepared ethyl *N*-2-thiazolylmalonamate (**1**), which is structurally related to the above-mentioned glycine derivatives, and found that it showed moderate suppression of carrageenin-induced paw edema in rats. Based on this observation, we prepared a series of the title compounds and examined them for antiinflammatory activity. The present paper describes the syntheses and discusses the structure–activity relationships on the basis of the screening data.

Chemistry

Although malonamate derivatives of thiazole can be produced by condensing 2-aminothiazole with ethyl malonate in the presence of sodium ethoxide,[11] we were able to prepare them in higher yields by methods A, B, and C shown in Chart 1.

In methods A and B, the malonic acid monoethyl ester was allowed to react with thionyldiimidazole (TDI) (method A) or carbonyldiimidazole (CDI) (method B) in tetrahydrofuran (THF), followed by aminolysis to give the malonamates. When a substituent, such as a methoxy, ethoxy or chloro group, was attached at the 4- or 6-position of the benzothiazole ring, the yields of the desired compounds were poor, because the activated nitrogen atom in the thiazole ring also reacted with *N*-(ethoxycarbonylacetyl)imidazole to give a side-reaction

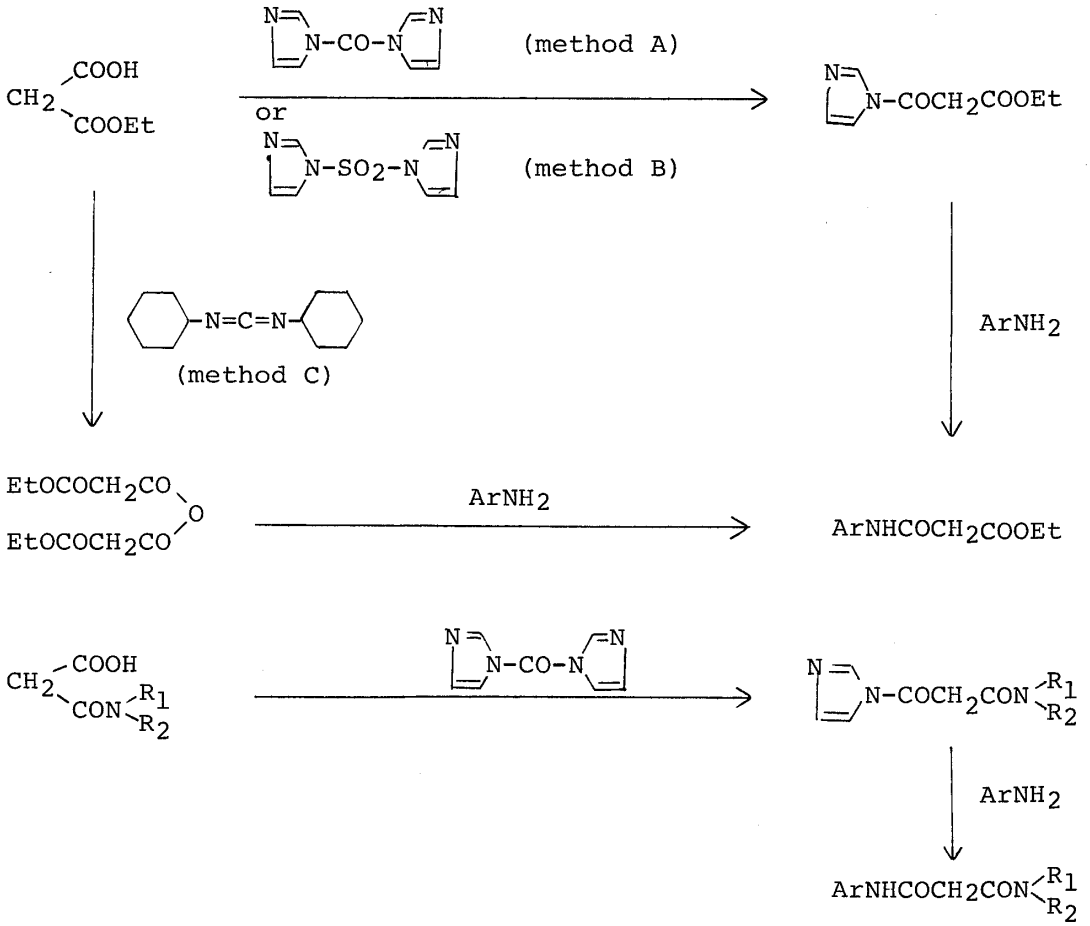


Chart 1

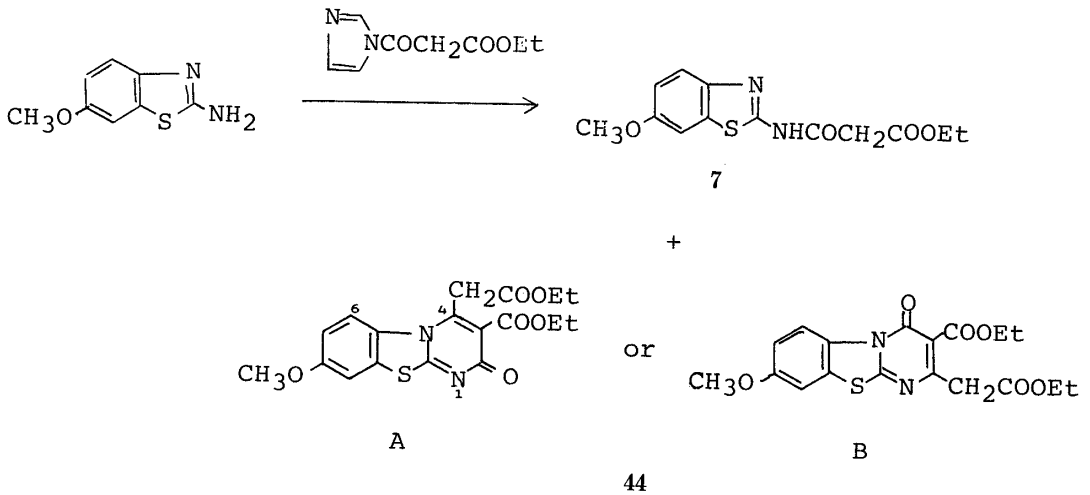


Chart 2

product (**44**). The analytical and spectral data suggested the structure A or B for the by-product (**44**). Structure A was ruled out by the absence of the nuclear Overhauser effect, which was expected between 6-H and 4-CH_2, and we therefore assumed that compound **44** has structure B.

In method C, 2-amino-6-nitrobenzothiazole, which did not afford the corresponding malonamates by method A or B, could be converted to the desired products *via* reaction with

TABLE I. Ethyl Malonamates Ar–$NHCOCH_2COOC_2H_5$

Compd. No.	Ar[a)]	R_1	R_2	Method	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
									C	H	N
1	a	H	—	A	149	18	AcOEt	$C_8H_{10}N_2O_3S$	44.85 (44.76	4.70 4.48	13.07 12.83)
2	a	CH_3	—	A	140.5—142.5	29	AcOEt	$C_9H_{12}N_2O_3S$	47.36 (47.32	5.30 5.45	12.27 12.32)
3	a	CH_2COOEt	—	B	83.5—85	36	EtOH	$C_{12}H_{16}N_2O_5S$	47.99 (47.92	5.37 5.42	9.33 9.21)
4	b	H	H	A	182—184	29	AcOEt	$C_{12}H_{12}N_2O_3S$	54.53 (54.64	4.58 4.48	10.60 10.49)
5	b	H	CH_3	B	219—220	13	Dioxane–benzene	$C_{13}H_{14}N_2O_3S$	56.10 (56.17	5.07 5.14	10.06 9.97)
6	b	OCH_3	H	B	164—165.5	19	AcOEt	$C_{13}H_{14}N_2O_4S$	53.05 (53.04	4.79 4.74	9.52 9.24)
7	b	H	OCH_3	B	197—199	15	AcOEt	$C_{13}H_{14}N_2O_4S$	53.05 (52.96	4.79 4.80	9.52 9.43)
8	b	H	OEt	B	189—190	7	EtOH–Et_2O	$C_{14}H_{16}N_2O_4S$	54.53 (54.69	5.23 5.37	9.08 9.30)
9	b	Cl	H	A	159—160	8	MeOH	$C_{12}H_{11}ClN_2O_3S$	48.24 (48.26	3.72 3.68	9.38 9.46)

10	b	H	NO_2	C	205—206	24	AcOEt	$C_{12}H_{11}N_3O_5S$	46.59 (46.52	3.59 3.45	13.59 13.35)
11	c	—	—	B	145—146	27	EtOH	$C_{16}H_{19}N_3O_4$	60.56 (60.92	6.03 6.08	13.24 12.99)
12	d	—	—	C	115—118	38	MeOH	$C_7H_{10}N_4O_3$	42.42 (42.23	5.09 4.95	28.27 28.09)
13	e	—	—	C	166.5—168	5	EtOH	$C_7H_{10}N_4O_3$	42.42 (42.56	5.09 5.07	28.27 27.95)
14	f	—	—	C	192—193	17	MeOH	$C_8H_{11}N_3O_3S$	41.91 (41.74	4.84 4.94	18.33 18.08)
15	g	—	—	C	138—139	17	EtOH–Et_2O	$C_9H_{11}N_3O_3$	51.67 (51.71	5.30 5.30	20.09 20.15)
16	h	—	—	A	159.5—161	10	AcOEt	$C_{13}H_{15}N_3O_3$	59.76 (59.67	5.79 5.84	16.08 15.98)
17	i	—	—	B	170.5—171.5	15	EtOH–Et_2O	$C_{12}H_{13}N_3O_3$	58.29 (58.21	5.30 5.26	17.00 16.81)

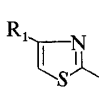
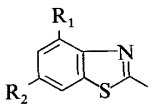
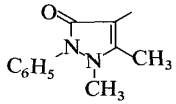
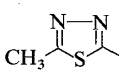
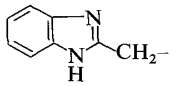
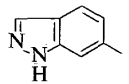
a) Ar=a,  ; b,  ; c,  ; d,  ; e,  ; f,  ; g,  ; h,  ; i, 

Table II. Malonamic Acids Ar–NHCOCH$_2$COOH

Compd. No.	Ar[a]	R_1	R_2	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
18	a	H	—	196—197	70	MeOH	$C_6H_6N_2O_3S$	38.70 (38.81	3.25 3.20	15.05 15.10)
19	a	CH_3	—	165—168	51	MeOH	$C_7H_8N_2O_3S$	41.99 (41.91	4.03 3.97	13.99 14.02)
20	b	H	H	187—189	62	MeOH	$C_{10}H_8N_2O_3S$	50.84 (50.55	3.41 3.38	11.86 11.87)
21	b	H	CH_3	175—177	13	Dioxane–benzene	$C_{11}H_{10}N_2O_3S$	52.79 (52.75	4.03 3.86	11.19 11.11)
22	b	OCH_3	H	208—210.5	48	Dioxane–benzene	$C_{11}H_{10}N_2O_4S$	49.62 (49.82	3.79 3.70	10.52 10.33)
23	b	H	OCH_3	189—190	20	Dioxane–benzene	$C_{11}H_{10}N_2O_4S$	49.62 (49.98	3.79 3.91	10.52 10.38)
24	b	H	OEt	249—251	41	MeOH	$C_{12}H_{12}N_2O_4S$	51.42 (51.19	4.31 4.32	9.99 9.91)

a) See footnote in Table I.

dicyclohexylcarbodiimide (DCC) in dimethylformamide (DMF).

Amines which are slightly soluble in THF, such as 2-amino-5-methyl-1,3,4-thiadiazole and 3-amino-1,2,4-triazole, are unreactive in method A or B, but can be converted into malonamates by method C. The substituted malonamates obtained are listed in Table I. The malonamic acids prepared from the corresponding ethyl malonamates by alkaline hydrolysis are shown in Table II.

According to the literature[12,13] on the preparation of amides by aminolysis of esters, the reaction of ethyl *N*-[2-(6-methoxy)benzothiazolyl]malonamate with diethylamine using sodium hydride in dimethylsulfoxide[12] gives no corresponding malonamide, except for 2-acetamido-6-methoxybenzothiazole, which provides the malonamide (**34**) in a poor yield (0.4%) when treated with *n*-butyl lithium in THF.[13] Preparation of the malonamide was attempted by condensing *N*-[2-(6-methoxy)benzothiazolyl]malonamic acid with diethylamine using DCC or CDI, but the former gave a mixture of 2-amino- and 2-acetamido-6-methoxybenzothiazole and the latter gave an undesired product, which was presumed to be a dimer (**45**)[14] from its mass spectral data and elemental analysis.

The desired malonamides (**34**—**37**) were obtained by the reaction of 2-amino-6-methoxybenzothiazole with *N*,*N*-diethylmalonamic acid, *N*-*n*-butylmalonamic acid, β-oxo-1-piperidinepropionic acid or β-oxo-4-morpholinepropionic acid,[15] using CDI in dry THF. Other malonamides (**25**—**33**, **38**—**43**), listed in Table III, were prepared in the same manner.

Pharmacology

The antiinflammatory activity of the compounds was examined on carrageenin-induced hind paw edema in rats as described in the experimental section. The results in Table IV show that compound **1** was fairly effective in the initial hour (63.4% inhibition), but its effect declined to about 30% inhibition after 2 h. The same tendency was found for the activity of compounds **8**, **14**, **37** and **38**. On the other hand, compound **2** appeared to be ineffective in the initial hour, but became increasingly effective after 2—3 h (about 30% inhibition). Compounds **4**, **7**, **17** and **23** gave similar results.

Among the thiazole derivatives, compound **1** showed moderate antiinflammatory activity. Substitution at position 4 of compound **1** with methyl (**2**) or ethoxycarbonylmethyl

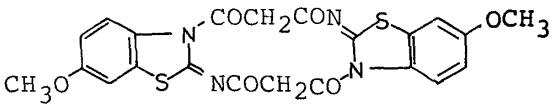


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Chart 3

(**3**) did not improve the activity. Changing the ester moiety (**1**, **2**) to carboxylic acid (**18**, **19**) or amide (**25**—**29**) caused the activity to decrease.

In the benzothiazole series, compound **4** showed a weak antiinflammatory activity. Substitution at position 6 of compound **4** with methoxy (**7**), ethoxy (**8**) and nitro (**10**) resulted in almost no improvement of the activity. On the other hand, introduction of methyl (**5**) at position 6 and of chloro (**9**) at position 4 of compound **4** markedly decreased the activity. Changing the ester moiety to a carboxylic acid (**20**, **22**—**24**) or amide (**31**, **33**—**42**) caused no change or a decrease in activity.

The derivatives of 1,2,4-triazole exhibited slight antiinflammatory activity, and *N*-3-triazolylmalonamate (**13**) was more effective than the *N*-4-triazolyl derivative (**12**).

The local anesthetic action for the amides (**25**—**43**) was examined using guinea pigs as described in the experimental section, but no significant action was found.

The acute toxicity of the compounds showing significant antiinflammatory activity was examined using mice as described in the experimental section. Compound **23** was highly toxic. When given at a dose of 100 mg/kg, writhing was observed, and at a dose of 300 mg/kg, two out of three mice died. It also reduced body weight and caused ulceration with hemorrhage in the glandular stomach. Compound **7** given at 300 mg/kg caused body weight reduction, writhing or erosions in the glandular stomach.

As 2-(6-methoxy)benzothiazolyl derivatives showed significant antiinflammatory activity but also were highly toxic, we are now trying to prepare novel derivatives of 6-methoxybenzothiazole.

Experimental

The structures of the isolated compounds tested for pharmacological experiments were determined by spectral (infrared (IR), mass spectrum (MS) and nuclear magnetic resonance (NMR)) and elemental analyses. All melting points were measured with a Yanaco MP-S3 apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-420 spectrophotometer and mass spectra with a Hitachi RMU-6MG spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL FX-200 spectrometer with tetramethylsilane as an internal standard in chloroform-*d*, methylsulfoxide-d_6 or pyridine-d_5. Amines containing heterocycles were purchased from Aldrich Co.

Typical Procedures for the Preparation of Ethyl Malonamates——Method A. Ethyl *N*-[2-(4-Methyl)thiazolyl]malonamate (**2**): A mixture of malonic acid monoethyl ester[16] (2.64 g, 20 mmol) and TDI [prepared from imidazole (5.45 g, 80 mmol) and thionyl chloride[17] (2.4 g, 20 mmol)] in THF solution was stirred for 30 min at room temperature. A dry THF (20 ml) solution of 2-amino-4-methylthiazole (2.28 g, 20 mmol) was added to the resulting solution with stirring at room temperature and the reaction mixture was allowed to stand overnight, then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with 5% $NaHCO_3$ and water, then dried over $MgSO_4$. After removal of the solvent, the residual solid was recrystallized from ethyl acetate, giving colorless needles, mp 140.5—142.5 °C, yield 29%. IR ν_{max}^{KBr} cm^{-1}: 3260, 1735, 1630. MS *m/z*: 228 (M^+), 140, 114 (base peak). NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 2.36 (3H, d, J=1.0 Hz, 4-$C\underline{H}_3$), 3.54 (2H, s, $COC\underline{H}_2CO$), 4.27 (2H, q, J=7.1 Hz, $COOC\underline{H}_2CH_3$), 6.55 (1H, q, J=1.0 Hz, 5-H). The crude material from the mother liquor of compound **2** was chromatographed on SiO_2 with AcOEt–C_6H_6 (1 : 9, v/v). An additional crop of this material (0.66 g) was isolated from the third fraction.

Method B. Ethyl *N*-[2-(6-Methoxy)benzothiazolyl]malonamate (**7**): Compound **7** was prepared by method A except for the use of CDI[18] instead of TDI. Compound **7** was obtained as colorless needles of mp 197—199 °C by recrystallization from AcOEt (yield 15%). IR ν_{max}^{KBr} cm^{-1}: 1730, 1660, 1610. MS *m/z*: 294 (M^+), 206, 165 (base peak). NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.3 Hz, $COOCH_2C\underline{H}_3$), 3.58 (2H, s, $COC\underline{H}_2CO$), 3.87 (3H, s, $OC\underline{H}_3$), 4.29 (2H, q,

TABLE III. Malonamides Ar–NHCOCH$_2$CON$<^{R_3}_{R_4}$

Compd. No.	Ar[a)]	R_1	R_2	R_3 R_4	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
25	a	H	—	*N*, *N*-Diethyl	130—131	48	AcOEt–Et_2O	$C_{10}H_{15}N_3O_2S$	49.77 (49.92	6.27 6.38	17.41 17.45)
26	a	H	—	–$(CH_2)_2O(CH_2)_2$–	169—172	33	AcOEt	$C_{10}H_{13}N_3O_3S$	47.05 (47.04	5.13 5.04	16.46 16.32)
27	a	H	—	–$(CH_2)_5$–	172—173	18	AcOEt	$C_{11}H_{15}N_3O_2S$	52.16 (51.90	5.97 5.93	16.59 16.44)
28	a	H	—	R_3=H R_4=*N*-*n*-Butyl	158—159	47	AcOEt	$C_{10}H_{15}N_3O_2S$	49.77 (49.84	6.27 6.28	17.41 17.47)
29	a	CH_3	—	*N*, *N*-Diethyl	118—119.5	52	AcOEt	$C_{11}H_{17}N_3O_2S$	51.74 (51.73	6.71 6.83	16.46 16.31)
30	a	CH_3	—	–$(CH_2)_5$–	135—137	26	AcOEt	$C_{12}H_{17}N_3O_2S$	53.91 (53.88	6.41 6.52	15.72 15.50)
31	b	H	H	*N*, *N*-Diethyl	169—170	48	AcOEt	$C_{14}H_{17}N_3O_2S$	57.71 (57.57	5.88 5.90	14.42 14.19)
32	b	H	H	–$(CH_2)_2O(CH_2)_2$–	226—229	11	AcOEt	$C_{14}H_{15}N_3O_3S$	55.07 (55.28	4.95 4.98	13.76 13.73)
33	b	OCH_3	H	*N*, *N*-Diethyl	158—160	38	AcOEt	$C_{15}H_{19}N_3O_3S$	56.06 (56.01	5.96 5.92	13.07 13.05)

34	b	H	OCH_3	*N*, *N*-Diethyl	168—169	71	AcOEt	$C_{15}H_{19}N_3O_3S$	56.06 (56.03	5.96 5.97	13.07 12.89)
35	b	H	OCH_3	$-(CH_2)_2O(CH_2)_2-$	203—205	41	AcOEt	$C_{15}H_{17}N_3O_4S$	53.72 (53.82	5.11 5.08	12.53 12.34)
36	b	H	OCH_3	$-(CH_2)_5-$	207—208	8	MeOH	$C_{16}H_{19}N_3O_3S$	57.64 (57.65	5.74 5.77	12.60 12.68)
37	b	H	OCH_3	$R_3=H$ $R_4=N$-*n*-Butyl	244—245	44	AcOEt	$C_{15}H_{19}N_3O_3S$	56.06 (55.87	5.96 5.94	13.07 12.86)
38	b	H	OEt	*N*, *N*-Diethyl	163—165.5	28	AcOEt	$C_{16}H_{21}N_3O_3S$	57.29 (57.17	6.31 6.35	12.53 12.36)
39	b	H	OEt	$-(CH_2)_2O(CH_2)_2-$	203—205	14	AcOEt	$C_{16}H_{19}N_3O_4S$	55.00 (54.76	5.48 5.47	12.03 11.72)
40	b	H	OEt	$-(CH_2)_5-$	186—188	8	MeOH	$C_{17}H_{21}N_3O_3S$	58.77 (58.82	6.09 6.15	12.09 11.93)
41	b	H	OEt	$R_3=H$ $R_4=N$-*n*-Butyl	239—240.5	31	AcOEt	$C_{16}H_{21}N_3O_3S$	57.29 (57.07	6.31 6.34	12.53 12.38)
42	b	Cl	H	*N*, *N*-Diethyl	168—170	11	AcOEt	$C_{14}H_{16}ClN_3O_2S$	51.61 (51.38	4.95 4.88	12.90 12.81)
43	c	—	—	*N*, *N*-Diethyl	161—162.5	54	MeOH	$C_{18}H_{24}N_4O_3$	62.77 (62.68	7.02 7.07	16.27 16.11)

a) See footnote in Table I.

Table IV. Inhibitory Effect of Ethyl Malonamates of Heterocyclic Compounds on Carrageenin-Induced Paw Edema in Rats

Compd. No.	% inhibition			Compd. No.	% inhibition		
	1 h	2 h	3 h		1 h	2 h	3 h
1	63.4	30.9	33.0	**22**	28.2	13.3	21.3
2	−8.1	32.7	39.0	**23**	−1.3	21.6	62.1
3	22.3	19.5	15.2	**24**	27.9	23.2	22.4
4	−20.5	39.9	44.4	**25**	3.8	12.0	2.3
5	−7.5	8.3	−3.4	**26**	17.5	11.8	4.1
6	23.9	9.6	18.8	**27**	7.8	7.1	−3.2
7	−7.3	35.0	48.0	**28**	20.6	10.1	4.3
8	42.3	27.7	23.8	**29**	18.0	13.2	1.8
9	−3.3	3.4	10.1	**31**	18.4	22.7	11.5
10	15.4	16.6	15.8	**33**	14.8	9.1	−1.6
11	15.4	13.3	17.1	**34**	15.0	18.2	7.4
12	10.5	3.5	4.7	**35**	11.7	22.2	13.8
13	22.1	35.6	23.5	**36**	24.5	13.8	4.1
14	33.4	34.9	24.1	**37**	30.3	24.2	17.2
15	−15.3	18.4	10.4	**38**	31.8	20.1	8.1
16	15.7	5.4	14.2	**39**	27.4	22.6	9.9
17	−14.0	37.1	36.3	**40**	29.4	17.2	12.4
18	14.1	24.3	26.7	**41**	24.8	19.1	11.5
19	17.4	23.2	23.2	**42**	24.5	32.2	13.7
20	13.1	21.8	15.1	**43**	29.4	15.8	8.0
21	18.5	29.5	26.9	Ibuprofen	40.8	60.5	61.9

J=7.3 Hz, $COOC\underline{H}_2CH_3$), 7.02—7.72 (3H, m, ArH). The residue obtained by concentration of the mother liquor was recrystallized from dioxane, giving a white curdy precipitate (**44**), mp 128—129 °C, yield 12.4%. MS m/z: 390 (M^+). NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 1.40 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 3.91 (2H, s, $C\underline{H}_2COOEt$), 4.20 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 4.42 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$). *Anal.* Calcd for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.41; H, 4.68; N, 7.16.

Method C. Ethyl *N*-[4-(1,2,4-Triazolyl)]malonamate (**12**): DCC (2.47 g, 12 mmol) was added to a solution of malonic acid monoethyl ester (1.58 g, 12 mmol) in dry DMF (10 ml) under ice-cooling. After the mixture had been stirred for 1 h, 4-amino-1,2,4-triazole (0.84 g, 10 mmol) was added, and the entire mixture was kept at 0 °C for 1 h, then at room temperature overnight. The *N,N'*-dicyclohexylurea deposited was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Ethyl acetate (*ca.* 30 ml) was added to the residue, the insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on SiO_2 with AcOEt–C_6H_6 (1:1). From the third fraction, compound **12** was isolated and recrystallized from MeOH as colorless needles, mp 115—118 °C, yield 38%. IR ν_{max}^{KBr} cm^{-1}: 3100, 1740, 1700. MS m/z: 198 (M^+), 111, 85 (base peak). NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 3.59 (2H, s, $COC\underline{H}_2CO$), 4.27 (2H, q, J=7.1 Hz, $COOC\underline{H}_2CH_3$), 8.22 (2H, s, C_3-H, C_5-H of triazole ring).

Typical Procedures for the Preparation of Malonamic Acids——*N*-(2-Benzothiazolyl)malonamic Acid (**20**): A mixture of 1.32 g (5 mmol) of ethyl *N*-(2-benzothiazolyl)malonamate (**4**) and 5% KOH (15 ml) was stirred for 30 min at room temperature, then acidified with 10% HCl under cooling. The white precipitate was obtained by suction filtration, washed with water, and recrystallized from MeOH to give 0.73 g (61.6% from **4**) of **20** as colorless needles, mp 187—189 °C. IR ν_{max}^{KBr} cm^{-1}: 1710, 1560. MS m/z: 236 (M^+), 192, 150 (base peak). NMR (CD_3OD) δ: 4.09 (2H, s, $COC\underline{H}_2CO$), 7.27—7.89 (4H, m, ArH).

N,N-Diethylmalonamic Acid: A mixture of diethylamine (14 g, 190 mmol) in dry ether (100 ml) was cooled to −10 °C, and a solution of ethyl 3-chloroformylpropanoate[19] (13.2 g, 88 mmol) in dry ether (20 ml) was added dropwise with stirring. After 30 min of stirring at the same temperature, the diethylamine hydrochloride which precipitated was removed by suction filtration. The filtrate was washed with water, 5% HCl, 5% $NaHCO_3$, and again with water, then dried over $MgSO_4$, concentrated, and subjected to fractional distillation under reduced pressure to afford ethyl *N,N*-diethylmalonamate[20] as a colorless oil (10.38 g, 63.1%), bp 123—124 °C (4 mmHg). This material (10.38 g, 55 mmol) was taken up in dry EtOH (30 ml), and a solution of KOH (3.64 g, 65 mmol) in dry EtOH (30 ml) was added dropwise with stirring at room temperature. The reaction mixture was stirred for 2 h, left overnight, and then evaporated to dryness. Water was added to the residue, and the aqueous solution was extracted with ether. The

aqueous layer was acidified with conc. HCl (6 ml) under cooling, saturated with KCl, and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to afford a colorless oil (7.94 g), which was crystallized from ether to give *N,N*-diethylmalonamic acid as colorless needles (6.37 g, 72.8%), mp 72—74 °C. MS *m/z*: 159 (M^+). *Anal.* Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.51; H, 8.46; N, 8.92.

The following compounds were prepared similarly.

β-Oxo-1-piperidinepropionic Acid:[21] Yield 46.4%.

β-Oxo-4-morpholinepropionic Acid: mp 109 °C. Yield 40.4%. MS *m/z*: 173 (M^+). *Anal.* Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.74; H, 6.46; N, 8.18.

N-n-Butylmalonamic Acid: mp 56 °C. Yield 89.0%. MS *m/z*: 159 (M^+). *Anal.* Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.53; H, 8.32; N, 8.84.

Typical Procedures for the Preparation of Malonamides——*N*-Diethyl-*N'*-[2-(6-methoxy)benzothiazolyl]-malonamide (**34**): CDI (1.94 g, 12 mmol) was added to a solution of *N,N*-diethylmalonamic acid (1.91 g, 12 mmol) in dry THF (20 ml). The mixture was stirred for 1 h at room temperature, then a solution of 2-amino-6-methoxy-benzothiazole (1.80 g, 10 mmol) in dry THF (20 ml) was added dropwise, and stirring was continued for another hour. The reaction mixture was left standing overnight. After evaporation under reduced pressure, the residue was dissolved in AcOEt, washed with water, 10% citric acid, 5% $NaHCO_3$ and water, and dried over $MgSO_4$. The solvent was removed and recrystallization of the residue from AcOEt gave colorless needles, mp 168—169 °C. The crude material obtained from the mother liquor in this recrystallization was chromatographed on SiO_2 with AcOEt–C_6H_6 (1 : 4). The third eluate gave an additional crop of **34** (0.84 g). Total yield 2.27 g (70.8%). IR ν_{max}^{KBr} cm^{-1}: 3150, 1700, 1630. MS *m/z*: 321 (M^+), 206, 180 (base peak). NMR ($CDCl_3$) δ: 1.21 (6H, h, J=7.3 Hz, $NCH_2C\underline{H}_3 \times 2$), 3.42 (4H, h, J=7.3 Hz, $NC\underline{H}_2CH_3 \times 2$), 3.54 (2H, s, $COC\underline{H}_2CO$), 3.87 (3H, s, $OC\underline{H}_3$), 7.00—7.72 (3H, m, ArH). Preparation of compound **34** was attempted by condensing *N*-[2-(6-methoxy)benzothiazolyl]malonamic acid (**23**) and diethylamine using CDI. Recrystallization of the reaction product from benzene gave yellow needles (**45**), mp 260—261.5 °C, yield 21.3%. MS *m/z*: 496 (M^+). *Anal.* Calcd for $C_{22}H_{16}N_4O_6S_2$: C, 53.22; H, 3.25; N, 11.28. Found: C, 53.43; H, 3.30; N, 11.04.

N-n-Butyl-*N'*-[2-(6-methoxy)benzothiazolyl]malonamide (**37**): 2-Amino-6-methoxybenzothiazole (1.80 g, 10 mmol) was treated with a reaction mixture of *N-n*-butylmalonamic acid (1.59 g, 10 mmol) and CDI (1.62 g, 10 mmol) in dry THF solution as described above. The reaction mixture was left overnight, and the precipitate was obtained by suction filtration. Recrystallization from MeOH gave colorless needles, mp 239—240.5 °C. An additional crop of **37** was obtained from the filtrate and recrystallized from MeOH. Total yield 1.42 g (44.1%). IR ν_{max}^{KBr} cm^{-1}: 3300, 1700, 1640. MS *m/z*: 321 (M^+), 206, 180 (base peak). NMR (DMSO) δ: 0.88 (3H, t, J=7.1 Hz, $N(CH_2)_3C\underline{H}_3$), 3.81 (3H, s, $OC\underline{H}_3$), 7.00—7.66 (3H, m, ArH).

Pharmacological Testing——Antiinflammatory activity was examined by the method of Winter, Risley and Nuss.[22] Six to ten male Wistar rats weighing 160—200 g were used for each group. The rat hind paw volume was measured by the displacement method in a water bath, and the test compound at a dose of 25 mg/kg, suspended in 0.5% sodium carboxymethylcellulose (CMC) solution, was administered orally. Thirty minutes later, 0.1 ml of 1% *λ*-carrageenin was injected subcutaneously into the plantar surface of the hind paw, and edema was measured after 1, 2 and 3 h. The increase in paw volume of the drug-treated rats was compared with that of the control group to calculate the percent inhibition. Ibuprofen was used as a reference standard.

Local anesthetic activity was determined using groups of three male Hartley guinea pigs weighing 400—500 g according to the method of Chance and Lobstein.[23] One-tenth milliliter of a 1% suspension of the test compound in 0.5% CMC was instilled into the conjunctive sac with the lid closed for 1 min. Local anesthetic activity was examined 2, 5, 10, 15, 20, 25 and 30 min after instillation in terms of the absence of the blink reflex when the corneal surface was stimulated with the tip of a stylet from a hypodermic needle (pressure loaded, 1 g). Procaine and ibuprofen were used as reference standards.

Acute toxicity was assessed 72 h after a single intraperitoneal injection of 100 or 300 mg/kg of the test compound as a suspension in 0.5% CMC to groups of three male Std-ddy mice weighing 25—30 g. Autopsies were also done.

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