Synthesis and Physicochemical Properties of Novel Substituted Malonic Acid Bis(*N*-alkylamides)

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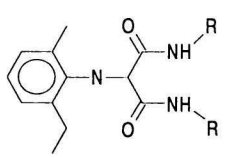
A synthesis of novel substituted bis(*N*-alkylamides) of malonic acid is described. All title compounds were tested for pesticidal activity.

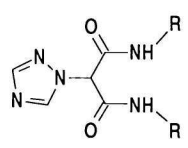
N-Substituted diethyl aminomalonates have served as starting compounds in the synthesis of various pyrrolidones — precursors to antibacterial drugs based on *C*-acetylazetidinones or on thienamycine [1—3]. An assortment of substituted diethyl amino- and anilinomalonates was used as starting material for 5,6-dihydroxy-3,4-dihydrocarbostyryl derivatives [4], aziridines [5], as well as some anticoagulants [6, 7]. Also well known is the use of title malonic derivatives in the synthesis of γ-lactones [8], β-lactames [9] and in the preparation of azo dyes [10].

Some substituted acylaminomalonates have been used as contact herbicides [11—13]. *Pellicciari* and coworkers were the first to prepare the diethyl 1-imidazolylmalonate by the reaction of diethyl diazomalonate with 1,3-imidazole [14], and used it to prepare other bioactive imidazoles. We thus set out to prepare diethyl esters of the 2-ethyl-6-methylanilinomalonic acid, 1*H*-1,2,4-triazolylmalonic acid, and 1*H*-1,3-imidazolylmalonic acid as starting material for the synthesis of title malonic acid bis(*N*-alkylamides).

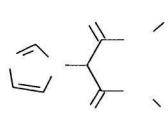
The substituted malonic acid diethyl esters were approached by two synthetic routes — one based on the reaction of the potassium salt of 1*H*-1,2,4-triazole or 1*H*-imidazole with monobromomalonic acid diethyl ester in acetonitrile. Monitoring of the course of reaction showed that whilst the triazole salt reacted fast, giving in a high yield and with a high selectivity the desired product, the potassium salt of imidazole reacted much slower (more than 30 h at reflux) and gave a low yield of product, which was contaminated with impurities stemming from the thermal decomposition of the diethyl 1-imidazolylmalonate.



Ia—Ie



IIa—IIg



IIIa—IIIe

The reason for the vastly different reactivity of the above heterocycles is probably the consequence of the different respective dissociation constants (pK_a = 2.55 for triazole and pK_a = 6.95 for imidazole) [15]. Therefore, other methods, excluding those using the salt, were sought. Indeed, the reaction of monobromomalonic acid diethyl ester with an excess of 1*H*-imidazole or 1*H*-1,2,4-triazole in acetonitrile afforded the desired products in high yields and with a high selectivity.

The reaction of 2-ethyl-6-methylaniline with monobromomalonic acid diethyl ester was carried out as described in the literature [9], *i.e.* at reduced pressure (4.6—5.3 kPa) and temperature 70—80 °C without solvent, since working at atmospheric pressure and the above temperature caused very long reaction times (in excess of 50 h) in addition to low yields of products contaminated with side products. It turned out that the diethyl 1-imidazolylmalonate decomposed during vacuum distillation, so that its purification was done by column chromatography on SiO_2 instead. The obtained (2-ethyl-6-methylanilino)- and (1*H*-1,2,4-triazolyl)malonic acid diethyl ester were purified by distillation.

The physicochemical parameters of the prepared compounds are given in Experimental.

Two approaches were used to prepare novel bis(*N*-alkylamides) of malonic acid. In the first one the above-described malonic acid diethyl esters were subjected to ammonolysis at elevated pressure (thick-walled glass vessels) at 40—80 °C, or, in the case of higher amines the reaction was carried out

Table 1. Physicochemical Data of the Prepared Bis(*N*-alkylamides) of Malonic Acid

Compound	Alkyl	Formula M_r	w_i(calc.)/% w_i(found)/% H	C	N	Yield %	M.p./°C Solvent
Ia	CH_3	$C_{14}H_{23}N_3O_2$ 263.14	7.97 8.05	63.90 64.10	15.96 15.99	69	142—143 Heptane
Ib	C_2H_5	$C_{16}H_{25}N_3O_2$ 291.16	8.60 8.63	66.00 66.22	14.42 14.44	86	124—126 Hexane
Ic	C_3H_7	$C_{18}H_{29}N_3O_2$ 319.20	9.09 9.19	67.42 68.11	13.16 13.32	48	93—95 Heptane
Id	i-C_3H_7	$C_{18}H_{29}N_3O_2$ 319.20	9.09 9.19	67.42 68.20	13.16 13.18	62	125—126 Heptane
Ie	C_4H_9	$C_{20}H_{33}N_3O_2$ 347.20	9.50 9.59	69.16 69.25	12.09 12.19	77	85—87 Hexane
IIa	CH_3	$C_7H_{11}N_5O_2$ 197.06	5.58 5.48	42.66 42.00	35.52 35.03	78	170—173 CH_3CN
IIb	C_2H_5	$C_9H_{15}N_5O_2$ 225.09	6.66 6.71	48.02 48.28	31.09 30.68	66	145—147 CH_3OH
IIc	C_3H_7	$C_{11}H_{19}N_5O_2$ 253.11	7.50 7.53	52.19 52.24	27.66 27.13	79	105—107 CH_3CN
IId	i-C_3H_7	$C_{11}H_{19}N_5O_2$ 253.11	7.50 7.57	52.19 52.61	27.66 27.38	54	169—170 CH_3OH
IIe	C_4H_9	$C_{13}H_{23}N_5O_2$ 281.13	8.18 8.26	55.54 55.96	24.89 24.80	88	103—105 CH_3CN
IIf	C_7H_{15}	$C_{19}H_{35}N_5O_2$ 365.30	9.58 9.45	62.46 62.50	19.16 18.95	87	78—79 Heptane
IIg	H	$C_5H_7N_5O_2$ 169.05	4.23 4.14	36.44 36.92	40.82 41.40	83	133—135 Ethanol
IIIa	CH_3	$C_8H_{12}N_4O_2$ 169.10	6.12 6.07	48.99 49.10	28.55 28.00	40	200—203 Acetone
IIIb	C_2H_5	$C_{10}H_{16}N_4O_2$ 224.10	7.14 7.06	53.59 54.02	24.98 24.35	80	180—183 Acetone/acetate
IIIc	C_3H_7	$C_{12}H_{20}N_4O_2$ 252.12	7.93 7.79	57.16 57.52	22.21 21.32	27	133—135 Acetone/acetate
IIId	i-C_3H_7	$C_{12}H_{20}N_4O_2$ 252.12	7.93 7.85	57.16 57.14	22.21 21.72	79	210—215 Acetone/acetate
IIIe	C_4H_9	$C_{14}H_{24}N_4O_2$ 280.20	8.56 8.32	60.00 59.60	19.99 19.10	46	125—129 Acetone

under intense stirring with excess of amine, or with its methanolic solution.

The second approach to dialkylamides of monobromomalonic acid was based on procedures previously described in the literature [16, 17], followed by the reaction with the potassium salt of 1*H*-imidazole or 1*H*-1,2,4-triazole in acetonitrile.

The comparison showed that the first procedure gave both higher (by 15—20 %) overall yields and better selectivity (Table 1).

Structures of the prepared compounds were suggested based on ^{13}C NMR and IR spectra and elemental analysis. Spectral data are given in Table 2.

The central CH carbon of malonic acid was designated C-2. Neither substituents R^1, nor the presence of 1,2,4-triazole or 2-ethyl-6-methylaniline affected its chemical shift. Infrared spectra of bis(*N*-alkylamides) of malonic acid displayed absorption bands of amidic group at $\tilde{\nu}$ = 3290—3348 cm^{-1}, in addition to very intense bands at $\tilde{\nu}$ = 1650—1685 cm^{-1}, belonging to the carbonyl group.

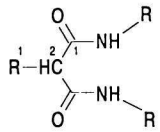
The prepared compounds were screened for pesticidal activity, none of them showed activity comparable with standard compounds.

EXPERIMENTAL

Melting points were determined with the Kofler hotstage. ^{13}C NMR spectra were measured with the JX-100 (Jeol) spectrometer in deuterochloroform or methanol (*IIIa—IIIe*) solutions, with tetramethylsilane as internal standard. Infrared spectra were taken with the PU 9800 FTIR instrument (Philips) either of films on KBr, or of KBr pellets. The progress of reactions was monitored with Silufol (Lachema) silica gel plates carrying a 254 nm fluorescence indicator, eluted with the chloroform–methanol mixture (φ_r = 95 : 5).

Contact insecticidal activity was tested for *Musca domestica* and *Aphis fabae*, using Fenitrothion and Malathion as standards. Acaricidal activity was tested on female *Tetranychus urticae* Koch, ovicidal activ-

Table 2. Spectral Characteristics of Substituted Bis(*N*–alkylamides) of Malonic Acid



Compound	^{1}H NMR, δ		IR, $\tilde{\nu}$/cm^{-1}	
	C-1	C-2	ν(NH—R)	ν(C=O)
Ia	169.68	66.20	3292	1678
Ib	169.34	66.63	3296	1680
Ic	169.00	66.26	3319	1653
Id	167.91	66.16	3290	1660
Ie	169.09	66.26	3298	1680
IIa	164.21	65.14	3308	1659
IIb	163.53	65.28	3302	1659
IIc	164.01	65.49	3330	1655
IId	162.78	65.53	3296	1676
IIe	163.63	65.47	3312	1660
IIf	163.55	65.48	3330	1660
IIIa	165.76	62.89	3348	1655
IIIb	165.02	62.90	3308	1687
IIIc	165.18	62.92	3310	1687
IIId	164.14	62.88	3290	1645
IIIe	164.89	62.78	3319	1684

ity on its ova, using Carbophenthion as standard [18]. The herbicidal activity was assessed on *Avena fatua*, *Echinochloa cruss-gallii*, *Fagopyrum vulgare,* and *Sinapis alba* [18], fungicidal activity by the *in vitro* method on *Tilletia foetida*, *Botrytis cinerea*, *Fusarium avenaceum,* and *Alternaria alternata*, by the *in vivo* method on *Erysiphe graminis* [19].

Diethyl 2-Ethyl-6-methylanilinomalonate

2-Ethyl-6-methylaniline (0.25 mol) was mixed at laboratory temperature with monobromomalonic acid diethyl ester (0.125 mol), the reaction flask was closed, kept under aspirator vacuum of 4.6—5.3 kPa and stirred at 70 °C for 8 h. After cooling the separated 2-ethyl-6-methylanilinium bromide was filtered off. Chloroform was added to the filtrate, the chloroform solution washed with water (2 × 50 cm^3) and then with 5 % hydrochloric acid. The organic layer was separated, dried with sodium sulfate and chloroform was removed. The crude product was purified by vacuum distillation. Yield = 20 g (55 %), b.p. (3.3 kPa) = 110—115 °C. For $C_{16}H_{23}NO_4$ (M_r = 293.16) w_i(calc.): 65.54 % C, 7.84 % H, 4.7 % N; w_i (found): 64.95 % C, 7.26 % H, 4.51 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1} = 1738. ^{1}H NMR spectrum ($CDCl_3$), δ: 6.9 (m, 3H, H_{arom}), 4.6 (s, 1H, CH), 4.2 (m, 4H, C_2H_5, 1H, NH), 2.7 (q, 2H, C_2H_5*), 2.3 (s, 3H, CH_3*), 1.2 (m, 9H, C_2H_5).

*Substituents at an aromatic ring.

2-Ethyl-6-methylanilinomalonic Acid Bis(*N*-alkylamides) *Ia—Ie*

Diethyl 2-ethyl-6-methylanilinomalonate (0.1 mol) was mixed with the amine (0.22 mol) in a glass autoclave at –10 to 0 °C. The autoclave was closed, the mixture stirred and heated at 70 °C without solvent for 6 h. The excess amine was then distilled off and crude amine purified by crystallization.

1,2,4-Triazolylmalonic Acid Diethyl Ester

To the potassium salt of 1,2,4-triazole (0.1 mol) in acetonitrile the monobromomalonic acid diethyl ester (0.1 mol) was added at laboratory temperature. The reaction mixture was refluxed and stirred for 6 h, cooled, the separated potassium bromide filtered off and the filtrate concentrated. After addition of chloroform the solution was washed with water (2 × 50 cm^3), the organic layer separated, dried by sodium sulfate and concentrated. The crude product was distilled *in vacuo*. Yield = 17.7 g (78 %), b.p. (6.6 Pa) = 108—110 °C. For $C_9H_{13}N_3O_4$ (M_r = 227.09) w_i(calc.): 47.50 % C, 5.72 % H, 18.49 % N; w_i(found): 47.00 % C, 6.1 % H, 18.72 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1} = 1761. ^{1}H NMR spectrum ($CDCl_3$), δ: 8.5 (s, 1H, H-2), 7.9 (s, 1H, H-4), 5.9 (s, 1H, CH), 4.3 (q, 4H, —CH_2—CH_3), 1.3 (t, 6H, —CH_2—CH_3).

Bis(*N*-alkylamides) of 1,2,4-Triazolylmalonic Acid *IIa—IIg*

Method A. Neat diethyl 1,2,4-triazolylmalonate (0.1 mol) and 0.22 mol of the corresponding amine, or their respective methanolic solutions were mixed at −10 to 5 °C in an autoclave, then stirred at 80 °C for 6 h. The reaction mixture was cooled, the excess amine removed and the crude product purified by crystallization.

Method B. A solution of the potassium salt of 1,2,4-triazole (0.1 mol) and the corresponding dialkylamide of monobromomalonic acid (0.11 mol) in acetonitrile was vigorously stirred and refluxed for 7 h. The work-up was similar as in method *A*.

1,3-Imidazolylmalonic Acid Diethyl Ester

To the solution of 1,3-imidazole (0.015 mol) in acetonitrile the diethyl ester of monobromomalonic acid (0.05 mol) was gradually added at 60 °C. Then the reaction mixture was heated up to reflux and stirred for another 3 h. After cooling the separated imidazolium bromide was removed and the filtrate concentrated. The residue was diluted with chloroform, the solution washed twice with 20 cm^3 of water, the organic layer dried by sodium sulfate and evaporated to dryness. The crude product was purified by chromatography on a SiO_2 column eluted with the chloroform—methanol (φ_r = 9 : 1) mixture. Yield = 9.6 g (85.8 %), oil. For $C_9H_{13}N_3O_4$ (M_r = 226.10) w_i(calc.): 53.09 % C, 6.24 % H, 12.38 % N; w_i(found): 53.11 % C, 6.49 % H, 12.81 % N. IR spectrum (KBr) $\tilde{\nu}/cm^{-1}$: 1750. ^1H NMR spectrum ($CDCl_3$), δ: 7.68 (s, 1H, H-2), 7.16 (s, 1H, H-5), 7.09 (s, 1H, H-4), 5.5 (s, 1H, CH), 4.3 (q, 4H, —$\underline{CH_2}$—CH_3), 1.3 (t, 6H, —CH_2—$\underline{CH_3}$).

1,3-Imidazolylmalonic Acid Bis(*N*-alkylamides) *IIIa—IIIe*

Method A. In a glass autoclave diethyl 1,3-imidazolylmalonate (0.1 mol) was mixed with neat amine (0.2 mol) or its methanolic solution at −10 to 5 °C, the reactor closed and heated, with stirring, to 70 °C for 5 h. After cooling to room temperature the unreacted amine (and methanol where applicable) was distilled off and the crude product crystallized.

Method B. In the reaction flask the potassium salt of 1,3-imidazole (0.01 mol) was mixed with acetonitrile and gradually added to the acetonitrile solution of the corresponding bromomalonic acid dialkylamide (0.011 mol). The mixture was stirred and refluxed for 5—9 h, then cooled, the precipitated bromide sucked off and the filtrate concentrated. The solid residue was purified by crystallization.

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