SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME DERIVATIVES RELATED TO 2-METHYLENEBUTANEDIOIC ACID

Miroslav VEVERKA[a] and Eva KRÁĽOVIČOVÁ[b]

[a] *Institute of Biotechnology, Slovak Technical University, 812 37 Bratislava and*
[b] *Research Institute of Chemical Technology, 831 06 Bratislava*

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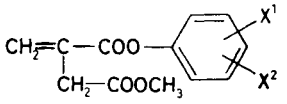
Nucleophilic reactions of methyl 3-chloroformyl-3-butenoate with N-substituted anilines and substituted phenols, and also preparation of 2-methylenebutanedioic acid monoanilides and their dehydration to the corresponding N-arylimides are described.

Pesticidal properties of 2-methylenebutanedioic acid were first reported in the forties[1] and since then a series of derivatives related to this acid, as e.g. esters[2], amides[3] and imides[3] were prepared; most of them showed a remarkable growth-regulatory, fungicidal, herbicidal and insecticidal effects.

This paper concerns the preparation of fungicidally active derivatives of the title acid obtained by introducing structural fragments of compounds already utilized in pest-control specialities into its molecule.

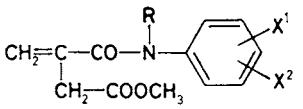
Nucleophilic reaction of methyl 3-chloroformyl-3-butenoate[4] with substituted phenols and anilines afforded compounds *Ia–Id*, and *IIa–IIm*, respectively. 2-Methylenebutanedioic anhydride[4] yielded *IIIa–IIIk* with substituted anilines, the dehydratative cyclization of which led to the corresponding N-arylimides *IVa–IVj*.



	X^1	X^2
Ia	2-Cl	4-CH_3
Ib	2-NO_2	4-NO_2
Ic	4-$COOC_2H_5$	H
Id	4-Cl	H

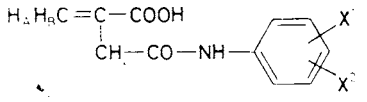
Structures of these products were verified by spectral means. The C-3 proton signals of 2-methylenebutanedioic acid were observed at δ 3·05–3·54, whilst a downfield shift to δ 3·75–3·49 was recorded with imides *IVa–IVj*. Due to asymmetry

at the multiple bond, proton signals of the methylene group appeared at δ 6·53 to 5·84 (H_A) and 6·00–5·50 (H_B). Substitution by an amino group at the carboxylic carbon C-1 resulted in an upfield shift of the methylene proton signals, which were mostly pronounced with compounds *IIj–IIm* (δ 5·2–5·3 and 5·09–5·83).

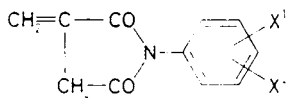


	X^1	X^2	R		X^1	X^2	R
IIa	2-CH_3	6-CH_3	H	*IIh*	3-F	H	H
IIb	2-Cl	4-NO_2	H	*IIi*	2-F	H	H
IIc	4-NO_2	H	H	*IIj*	2-CH_3	6-CH_3	$CH_3OCH_2(CH_3)CH$
IId	2-CH_3	6-C_2H_5	H	*IIk*	2-CH_3	6-C_2H_5	$CH_3OCH_2(CH_3)CH$
IIe	2-Cl	3-Cl	H	*IIl*	2-CH_3	6-CH_3	$CH_3OCO(CH_3)CH$
IIf	2-C_2H_5	6-C_2H_5	H	*IIm*	2-C_2H_5	6-C_2H_5	$CH_3OCO(CH_3)CH$
IIg	2-CH_3	6-Cl	H				

Wave numbers associated with the ν(C=O) vibration of carboxylic group of compounds *IIIa–IIIk* appeared at 1 698–1 600 cm^{-1}, those corresponding to amide I and amide II bands at 1 675–1 647 and 1 635–1 627 cm^{-1}, respectively. The ν(C=O) of methoxycarbonyl groups of compounds *IIa–IIe* were seen between 1 740 and 1 720 cm^{-1}, the amide I and II bands at 1 695–1 640 and 1 630 to 1 608 cm^{-1}, respectively.



	X^1	X^2
IIIa	2-CH_3	6-CH_3
IIIb	2-CH_3	6-C_2H_5
IIIc	2-Cl	4-NO_2
IIId	2-CF_3	H
IIIe	3-CF_3	H
IIIf	2-Cl	5-NO_2
IIIg	3-OCH_3	H
IIIh	2-C_2H_5	6-C_2H_5
IIIi	2-CH_3	6-Cl
IIIj	2-F	H
IIIk	3-F	H



	X^1	X^2
IVa	2-C_2H_5	6-C_2H_5
IVb	3-CF_3	H
IVc	2-Cl	3-Cl
IVd	3-Cl	4-Cl
IVe	3-OCH_3	H
IVf	2-CH_3	6-C_2H_5
IVg	2-F	H
IVh	3-F	H
IVi	2-CH_3	6-Cl
IVj	2-CF_3	H

Derivatives of 2-methylenebutanedioic acid were tested for fungicidal activity on agar plates by poisoned food technique at various dilutions and compared with Fundazol and Dithane as standards. The best in vitro antifungal activity was found with compounds *IV*; their $-\log ED_{50}$ values (μg/ml) were close to those of the standards. (*Alternaria alternata* 4; *Botrytis cinerea* 4, 7, *Fusarium nivale* 4, 7). *A. alternata: IVa* 3·85, *IVb* 3·80, *IVc* 4·1, *IVd* 4·0, *IVg* 3·7, *IVh* 3·6, *IVi* 3·95, *IVj* 3·7; *B. cinerea*: *IVa* 4·2, *IVb* 4·3, *IVc* 4·5, *IVd* 4·55, *IVg* 4·2, *IVh* 4·4, *IVi* 4·1, *IVj* 4·0; *F. nivale*: *IVa* 3·85, *IVb* 3·9, *IVc* 4·4, *IVd* 4·5, *IVg* 3·9, *IVh* 4·2, *IVi* 3·8, *IVj* 3·9. A relatively lesser inhibition effect was observed with compounds *I*—*III*.

EXPERIMENTAL

The ^{1}H NMR spectra of hexadeuteriodimethyl sulfoxide solutions (unless stated otherwise) recorded with a Tesla BS 487 C apparatus are relative to hexamethyldisiloxane, the IR spectra in the 500—3 800 cm^{-1} spectral range were taken with a Perkin-Elmer, model 457 spectrometer using a KBr technique.

Methyl 3-(2-Chloro-4-methylphenyloxycarbonyl)-3-butenoate (*Ia*)

Solution of methyl 3-chloroformyl-3-butenoate (1·62 g, 10 mmol) in tetrahydrofuran (5 ml) was added stepwise to a stirred mixture of 2-chloro-4-methylphenol (1·42 g, 10 mmol) and triethylamine (1·01 g, 10 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for additional 24 h, the solvent was distilled off and ethyl acetate (50 ml) was added to the residue. The organic layer was successively washed with hydrochloric acid (0·1 mol l^{-1}), sodium hydrocarbonate solution and water, dried with sodium sulfate, the solvent was removed and the crude product was purified by distillation.

Compounds *Ib*—*Id* (Table I) were prepared in an analogous way.

Methyl 3-(2,6-Dimethylphenylcarbamoyl)-3-butenoate (*IIa*)

Potassium carbonate (1·38 g, 10 mmol) was added to a stirred solution of 2,6-dimethylaniline (1·21 g, 10 mmol) in benzene (10 ml) to which a solution of methyl 3-chloroformyl-3-butenoate (1·62 g, 10 mmol) in benzene (5 ml) was gradually added. The mixture was stirred at an ambient temperature for 24 h, washed with hydrochloric acid (0·1 mol l^{-1}) and water, dried with sodium sulfate, the solvent was distilled off and the crude product was crystallized from benzene–hexane (1 : 2).

Compounds *IIb*—*IIi* (Table I) were obtained in an analogous way.

Methyl 3-[N-(2,6-Dimethylphenyl)-N-(1-methoxy-2-propyl)carbamoyl]-3-butenoate (*IIj*)

A solution of 3-chloroformyl-3-butenoate (1·62 g, 10 mmol) in acetone (10 ml) was added stepwise to a stirred mixture of N-(1-methoxy-2-propyl)-2,6-dimethylaniline (1·93 g, 10 mmol) in acetone (30 ml) at room temperature. After 24 h of stirring the solvent was distilled off and the remaining residue was dissolved in benzene (50 ml). The insoluble portion was filtered off, the filtrate was washed with hydrochloric acid (0·1 mol l^{-1}), dried with sodium sulfate and the solvent was removed under diminished pressure. The crude product was purified by distillation.

Compounds *IIk*—*IIm* (Table I) were synthesized in an analogous way.

TABLE I

Derivatives of 2-methylenebutanedioic acid

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found % C	% H	% N	% halogen
Ia	$C_{13}H_{13}ClO_4$	142/500[a]	58·11	4·88		13·19
	(268·7)	75	57·89	4·61		13·03
Ib	$C_{12}H_{10}N_2O_8$	120–121/1[a]	46·46	3·25	9·03	
	(320·2)	69	46·12	3·18	9·07	
Ic	$C_{15}H_{16}O_6$	135/1[a]	61·64	5·52		
	(292·3)	64	61·45	5·37		
Id	$C_{12}H_{11}ClO_4$	132/5[a]	56·60	4·35		13·92
	(254·7)	73	56·28	4·16		13·71
IIa	$C_{14}H_{17}NO_3$	143/6[a]	68·00	6·93	5·66	
	(247·3)	59	67·94	6·81	5·51	
IIb	$C_{12}H_{11}ClN_2O_5$	67	48·26	3·71	9·38	11·87
	(298·7)	54	48·03	3·59	9·21	11·77
IIc	$C_{12}H_{12}N_2O_5$	121–122	54·55	4·62	10·60	
	(264·2)	64	54·13	4·51	10·43	
IId	$C_{15}H_{19}NO_3$	76–78	68·94	7·33	5·36	
	(261·3)	63	68·44	7·21	5·27	
IIe	$C_{12}H_{11}Cl_2NO_3$	24	50·02	3·87	4·86	24·61
	(288·1)	67	49·87	3·71	4·59	24·55
IIf	$C_{16}H_{21}NO_3$	113	69·79	7·69	5·09	
	(275·4)	61	69·19	7·48	4·87	
IIg	$C_{13}H_{14}ClNO_3$	140/4[a]	58·32	5·27	5·23	13·27
	(267·7)	72	58·07	5·01	5·14	13·03
IIh	$C_{12}H_{12}FNO_3$	132/5[a]	60·76	5·09	5·90	
	(237·2)	68	60·04	5·01	5·87	
IIi	$C_{12}H_{12}FNO_3$	131/5[a]	60·76	5·09	5·90	
	(237·2)	67	60·37	4·99	5·81	
IIj	$C_{18}H_{25}NO_4$	164/6[a]	67·69	7·89	4·39	
	(319·4)	54	67·58	7·71	4·21	
IIk	$C_{19}H_{27}NO_4$	142/6[a]	68·44	8·16	4·20	
	(333·4)	49	68·31	8·12	4·07	
IIl	$C_{18}H_{23}NO_5$	176/6[a]	64·85	6·50	3·93	
	(333·4)	57	64·44	6·39	3·71	
IIm	$C_{20}H_{27}NO_5$	178/6[a]	66·46	7·53	3·88	
	(361·4)	48	66·31	7·44	3·74	
IIIa	$C_{13}H_{15}NO_3$	187–189	66·94	6·48	6·00	
	(233·3)	91	66·55	6·17	5·86	
IIIb	$C_{14}H_9Cl_2NO_3$	156–157	48·20	3·31	5·11	25·87
	(274·1)	87	48·03	3·29	5·09	25·55

TABLE I
(*Continued*)

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% halogen
IIIc	$C_{11}H_9ClN_2O_5$	173	46·41	3·19	9·84	12·45
	(284·7)	67	46·26	3·01	9·73	12·07
IIId	$C_{12}H_{10}F_3NO_3$	147	52·76	3·69	5·13	
	(273·2)	89	52·15	3·34	5·04	
IIIe	$C_{12}H_{10}F_3NO_3$	136	52·76	3·69	5·13	
	(273·2)	87	52·44	3·51	5·07	
IIIf	$C_{11}H_9ClN_2O_5$	187—189	46·41	3·19	9·84	12·45
	(284·7)	73	46·33	3·08	9·69	12·23
IIIg	$C_{12}H_{13}NO_4$	147	61·27	5·57	5·95	
	(235·2)	88	61·24	5·47	5·85	
IIIh	$C_{15}H_{19}NO_3$	166	68·94	7·32	5·36	
	(261·3)	89	68·43	7·08	5·29	
IIIi	$C_{12}H_{12}ClNO_3$	187	56·81	4·76	5·52	13·97
	(253·7)	78	56·59	4·61	5·29	13·61
IIIj	$C_{11}H_{10}FNO_3$	163	59·19	4·51	6·27	
	(223·2)	88	58·81	4·39	6·01	
IIIk	$C_{11}H_{10}FNO_3$	148	59·19	4·51	6·27	
	(223·2)	86	58·98	4·43	6·09	
IVa	$C_{15}H_{17}NO_2$	83	73·98	7·04	5·76	
	(243·3)	78	73·79	6·94	5·49	
IVb	$C_{12}H_8F_3NO_2$	67	56·48	3·16	5·49	
	(255·2)	57	56·12	3·07	5·44	
IVc	$C_{11}H_7Cl_2NO_2$	96	51·59	2·76	5·47	27·69
	(256·1)	63	51·25	2·49	5·34	27·53
IVd	$C_{11}H_7Cl_2NO_2$	125	51·59	2·76	5·47	27·69
	(256·1)	66	51·13	2·59	5·38	27·41
IVe	$C_{12}H_{11}NO_3$	63	66·35	5·10	6·45	
	(217·2)	54	66·22	5·01	6·34	
IVf	$C_{14}H_{15}NO_2$	109—114	73·66	6·62	6·14	
	(228·3)	63	73·18	6·43	6·01	*
IVg	$C_{11}H_8FNO_2$	76—78	64·39	3·93	6·82	
	(205·2)	69	64·17	3·80	6·61	
IVh	$C_{11}H_8FNO_2$	93—96	64·39	3·93	6·82	
	(205·2)	72	64·22	3·71	6·77	
IVi	$C_{12}H_{10}ClNO_2$	155	61·10	4·27	5·97	15·04
	(235·7)	74	60·93	4·18	5·79	14·98
IVj	$C_{12}H_8F_3NO_2$	87	56·48	3·16	5·49	
	(255·2)	61	56·36	3·04	5·39	

[a] Refers to boiling point (°C/Pa).

TABLE II

^{1}H NMR spectral data (δ, ppm) of compounds *I*—*IV*

Compound	H_A[a]	H_B[a]	H_{arom}	CH_2[a]	Other protons
Ia	6·03	5·62	6·94 s 6·85 d 6·65 d	3·08	3·18 s
Ib	6·15	5·75	8·86 s 8·67 d 8·38 d	3·35	3·58 s
Ic	6·48	6·00	7·99 d 7·31 d	3·52	3·64 s
Id	6·45	6·00	7·45 d 7·20 d	3·52	3·64 s
IIa[b]	6·04	5·65	7·07 s	3·32	3·59 s
IIb	6·18	5·80	8·38—7·14 m	3·45	3·60 s 9·90 bs
IIc	6·11	5·78	8·25 d 8·00 d	3·49	3·65 s 9·87 bs
IId[b]	6·04	5·66	7·10 s	3·34	3·59 s
IIe	6·08	5·69	7·80—7·31 m	3·25	3·52 s 9·79 bs
IIf	6·00	5·61	7·80 s	3·36	3·55 s 9·38 bs
IIg	5·95	5·54	7·04 s	3·41	3·65 s 2·23 s
IIh	5·89	5·50	7·50—7·00 m	3·38	3·64 s
IIi	5·90	5·56	7·15—6·95 m	3·41	3·65 s
IIj	5·21	4·98	7·11 s	3·09	3·90 m 3·58 s 3·35 d 3·20 s 1·13 d
IIk	5·20	5·09	7·23—7·14 m	3·18	3·63 m 3·56 s 3·32 d 3·16 s 1·15 d
III	5·30	4·91	7·15 s	3·05	3·55 s 3·65 s 4·31 q 1·06 d
IIm	5·29	4·83	7·27 s	3·18	3·56 s 3·67 s 4·31 q 1·06 m
IIIa	6·17	5·77	6·91 s	3·34	9·24 bs
IIIb	6·09	5·96	6·98 s	3·27	9·15 bs
IIIc	6·20	5·79	8·34 d 8·22 d 9·85 s	3·54	9·85 bs
IIId	6·17	5·79	7·76—7·42 m	3·36	9·55 bs
IIIe	6·19	5·77	8·08 s 7·55—7·09 m	3·37	10·35 bs
IIIf	6·19	5·77	8·73 7·98 d 7·75 d	3·48	9·86 bs
IIIg	6·14	5·71	7·27—7·03 m	3·29	9·93 bs
IIIh	6·28	5·84	7·14 s	3·46	8·53 bs 2·57 q 1·10 t
IIIi	6·12	5·72	7·13 s	3·31	9·52 s 2·12 s
IIIj	6·34	5·87	7·23—7·00 m	3·53	9·00 bs
IIIk	6·15	5·51	7·61—7·15 m	3·31	10·19 bs
IVa	6·49	5·74	7·24 s	3·55	2·4 q 1·14 t
IVb	6·25	5·80	7·96—7·55 m	3·64	
IVc	6·19	5·74	7·80—7·38 m	3·58	
IVd	6·09	5·62	7·80—7·38 m	3·58	
IVe	6·07	5·71	7·24—6·70 m	3·49	3·73 s
IVf	6·25	5·73	7·27—7·24 m	3·73	2·49 q 2·01 s 1·03 t
IVg	6·47	5·74	7·37—7·12 m	3·54	
IVh	6·18	5·71	7·66—7·08 m	3·47	
IVi	6·32	5·81	7·38 s	3·68	2·16 s
IVj	6·26	5·80	7·96—7·57 m	3·64	

[a] Singlet; [b] in deuteriochloroform containing tetramethylsilane as an internal reference.

3-(2,6-Dimethylphenylcarbamoyl)-2-methylenepropanoic Acid (*IIIa*)

A solution of 2,6-dimethylaniline (1·21 g, 10 mmol) in benzene (30 ml) was added to a solution of 2-methylenebutanedioic anhydride (1·12 g, 10 mmol) in benzene (20 ml). The mixture was stirred at an ambient temperature for 30 min, the separated compound was filtered off and crystallized from benzene–hexane (1 : 1).

Compounds *IIIb*—*IIIk* (Table I) were obtained by the same procedure.

N-(2,6-Diethylphenyl)-2-methylenebutanedioic Acid Imide (*IVa*)

A mixture of 3-(2,6-diethylphenylcarbamoyl)-2-methylenepropanoic acid (2·61 g, 10 mmol) and sodium acetate (0·7 g, 10 mmol) heated in acetic anhydride (10 ml) at 75°C for 20 min was poured into ice-cold water. The separated precipitate was filtered off and crystallized from hexane.

Compounds *IVb*—*IVj* (Table I) were prepared analogically. The ^{1}H NMR spectral data of compounds *I*—*IV* are listed in Table II.

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