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Bromination of N,N'-Substituted Malonodiamides

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Abstract—Aiming at preparation of biologically active compounds a bromination of N,N'-substituted malonodiamides in a glacial acetic acid was carried out. The use of one equiv of bromine provided monobromo derivatives, with two equiv of bromine dibromo-substituted products were obtained. Among the *N*,*N*'-dibenzylamides of alkylmalonic acids only the methyl homolog underwent bromination. The structure of compounds was proved by IR and ^{1}H NMR spectroscopy. The effect of the compounds synthesized on the central nervous system was investigated.

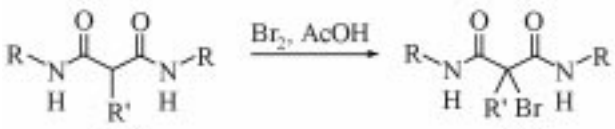
We established formerly that numerous malonic acid derivatives, both with unsubstituted and substituted methylene group, possessed high anticonvulsant properties and we promising substances for further purposeful synthesis of potential anticonvulsants. It is known that one way of introducing substituents into the methylene group of malonic acid derivatives consists in reacting its bromo derivatives with compounds of various classes (alcohols, amines, etc.). Therefore the bromo derivatives of malonic acid are important semiproducts for preparation of potential biologically active compounds.

The bromination of diethyl malonate is known to occur in a very good yield without solvent giving diethyl bromomalonate at the use of one equiv of bromine, and dibromomalonate with two equiv of the halogen. The halogenation of the malonic acid is commonly carried out in ethyl ether as solvent.

However we established that further reaction of diethyl bromomalonate with nucleophilic reagents, namely, with alcohols and especially with aliphatic amines, proceeded in several directions affording as a rule a mixture of crystalline products which required chromatographic separation. As a result the target products were obtained in a low yield, and their isolation is lengthy and laborious. Although the diethyl arylaminomalonates are formed in a fair yield, their amidation is achieved with difficulty.

It was established that the biological activity was characteristic of symmetrical N,N'-substituted malonodiamides with alkyl [1], aromatic [2], and arylmethylene [3] substituents in the methylene group. The bromination of N,N'-substituted malonodiamides may open a way of introducing into these molecules of the other substituents and simultaneously may increase the yield of target products and eliminate the losses accompanying the purification of halogenated esters. Besides this procedure permits avoiding the nucleophilic side reactions at the ester groups.

Taking into account the high anticonvulsant activity of symmetrical alkyl- [1–3] and arylamides [4] of malonic acid, and also analeptic properties of some alkylamides [5] we chose for bromination symmetrical *N*,*N*'-dibutyl-, *N*,*N*'-dibenzylamides, and also certain *N*,*N*'-dianilides of malonic acid.



Ia–i **IIa–i**

R = C_4H_9 (**a**), $CH_2C_6H_5$ (**b, h, i**), 2-$CH_3C_6H_4$ (**c**), 4-$CH_3C_6H_4$ (**d**), 2,4-$(CH_3)_2C_6H_3$ (**e**), $CH_2C_6H_4OCH_3$-4 (**f**), piperonyl (**g**), R' = H (**a**–**g**), CH_3 (**h**), Br (**i**).

As initial compounds were used symmetrical alkyl- and arylamides of malonic acid **Ia–g**, and also dibenzylamides of methylmalonic (**Ih**) and bromomalonic (**Il**) acids prepared along known procedures [2, 4].

We showed before that the methylene group in the molecule of malonic acid dibenzylamide remains very labile as followed from the high yields of its alkylation products [1] and products of Knoevenagel reaction with aromatic aldehydes [6]. Therefore it seemed probable that this compound would readily undergo bromination.

We used the glacial acetic acid as solvent. The bromination was carried out at room temperature.

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Table 1. Yields, melting points, R_f values, and elemental analyses of N,N'-substituted bromomalonodiamides **IIa**–**i**

Compd. no.	Yield, %	mp, °C	R_f [a]	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIa	94	98–100	0.68	45.2	7.3	9.6	$C_{11}H_{21}N_2O_2Br$	45.1	7.2	9.6
IIb	96	170–172	0.66	56.6	4.7	7.7	$C_{17}H_{17}N_2O_2Br$	56.5	4.7	7.8
IIc	77	118–120	0.49	56.5	4.7	7.6	$C_{17}H_{17}N_2O_2Br$	56.5	4.7	7.8
IId	72	180–182	0.51	56.6	4.8	7.8	$C_{17}H_{17}N_2O_2Br$	56.5	4.7	7.8
IIe	76	190–192	0.46	58.7	5.5	7.2	$C_{19}H_{21}N_2O_2Br$	58.6	5.4	7.2
IIf	84	161–162	0.53	54.1	5.1	6.6	$C_{19}H_{21}N_2O_4Br$	54.2	5.0	6.7
IIg	65	123–125	0.71	50.9	3.7	6.3	$C_{19}H_{17}N_2O_6Br$	50.8	3.8	6.2
IIh	68	138–140	0.56	57.7	5.0	7.6	$C_{18}H_{19}N_2O_2Br$	57.6	5.1	7.5
IIi	77	198–200	0.58	46.3	3.7	6.3	$C_{17}H_{16}N_2O_2Br_2$	46.4	3.7	6.4

[a] R_f values were determined on Silufol UV-254 plates, eluent hexane–2-propanol, 80 : 20, development in iodine vapor.

Table 2. IR and ^{1}H NMR spectra of compounds **IIa**–**g**

Compd. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm			
	C=O	CH–Br	NH, 2H	H arom	CH–Br, d, 1H	Proton signals from the other functional groups
IIa	1662, 1630	3012	8.12 t	–	4.40	3.02 m (4H, $2NHC\underline{H}_2$); 1.30 m [8H, $2CH_2(C\underline{H}_2)_2CH_3$)]; 0.92 t (6H, $2CH_3$)
IIb	1670, 1640	3015	8.82, t	7.29 s, 10H	4.42	4.34 d (4H, $2C\underline{H}_2C_6H_5$)
IIc	1670, 1640	3020	9.09 s	7.43–7.12 m, 8H	5.03	2.31 s (6H, $2CH_3$)
IId	1648, 1608	3026	9.22 s	7.46–7.14 d.d, 8H	4.80	2.26 s (6H, $2CH_3$)
IIe	1650, 1620	3022	9.20 s	7.42–7.02 m, 6H	4.21	2.15 s (12H, $4CH_3$)
IIf	1644, 1612	3018	8.82 t	7.28 d.d, 8H	4.32	4.42 d (4H, $2C\underline{H}_2$Ar); 1.96 s (6H, OCH_3)
IIg	1660, 1624	3020	8.64 t	7.22–7.64 m, 6H	4.48	4.24 d (4H, $2C\underline{H}_2$Ar); 2.96 s (4H, $2CH_2$)
IIh	1650, 1610	–	7.92 t	7.29 s, 10H	–	4.47 d (4H, $2C\underline{H}_2C_6H_5$); 2.12 s (3H, CH_3)
IIi	1653, 1625	–	8.67 t	7.25 s 10H	–	4.24 d (4H, $2C\underline{H}_2C_6H_5$)

The reaction was started by initiation with the light of an incandescent lamp. An equivalent amount of bromine was gradually added dropwise as the reaction mixture lost color. These reaction conditions ensured formation of the final products in short time and in high yield. The higher yields (Table 1) were obtained in bromination of dialkyl- (**IIa, b**) and dialkylarylamides (**IIf, g**). With dianilides a side reaction of aromatic ring bromination is presumable. However the mild bromination conditions permitted avoiding formation of a large amount of side products, and the impurities were efficiently removed by crystallization.

The bromination of methylmalonic acid *N*,*N*'-dibenzylamide (**Ih**) was successfully performed evidencing its relatively high reactivity. The bromination of further homologs (R' = C_2H_5, C_3H_7) did not give satisfactory results apparently due to steric hindrances.

The bromination of monobromomalonic acid dibenzyl amide (**Ii**) resulted apparently in a mixture of mono- and dibromo derivatives. However the repeated crystallization provided dibromo derivative **IIi** in pure state as shown by TLC and ^{1}H NMR spectrum. The product **IIi** was obtained in a fair yield, but a better yield was attained at bromination of malonic acid *N*,*N*'-dibenzylamide (**Ib**) with a double excess of bromine.

The attempt to obtain compound **IIb** by independent synthesis, amidation of alkyl bromomalonate, was unsuccessful presumably to amine reaction not with the ester groups but with more

labile halogen atom in agreement with the published data [7].

The success of the synthesis can be preliminary checked by a positive Beilstein's test and higher melting point of the product than that of the initial compound (Table 1).

The structures were proved by elemental analyses and spectral methods.

The analysis of ^{1}H NMR spectra of compounds synthesized showed that the common signal of proton from the substituted methylene group in the spectra of compounds **IIa–g** was shifted downfield as compared with the spectra of the initial compounds (Table 2). The displacement originates from the introduction into the molecule of electronegative bromine atom which induces paramagnetic shift of the neighboring protons [8]. The signals from aromatic and aliphatic substituents in amide groups and from the methyl attached to the methylene group of the acid skeleton in **IIh** compound remain the same as in the initial compounds [2, 4].

In the IR spectra of compounds **IIa–i** the absorption bands of stretching vibrations of the methylene group shift to larger wave numbers because of the halogen atom, and the maxima of these bands appear in the region over 3000 cm^{-1} (Table 2) evidencing the presence of bromine atom in the molecule [9].

Although the target of our work was the synthesis of semiproducts for preparation of biologically active compounds, we tested also their proper pharmacological effect.

The pharmacological activity of compounds synthesized was investigated by V. N. Savchenko in Karazin Kharkov National University.

The presence of bromine in the molecules of organic compounds is known to induce appearance of sedative properties. Therefore the pharmacological screening was directed to testing the effect of compounds synthesized on the central nervous system.

The results of the pharmacological screening revealed weak protective properties of the compounds obtained against convulsions caused by corazole. As was expected, all the compounds provide synergistic soporific effect with phenobarbital.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Bruker WP-100 SY at operating frequency 100 MHz, solvent DMSO-d_6, internal reference TMS, chemical shifts were presented in δ scale. IR spectra were measured on Specord M-80 instrument from KBr pellets, substance concentration 1%.

N,N'-Substituted bromomalonodiamides IIa–i (general procedure). To a solution of 0.01 mol of N,N'-substituted malonodiamide **Ia–g**, methylmalonodiamide **Ih**, or bromomalonodiamide **Ii** in 20 m of glacial acetic acid was added dropwise while stirring 0.52 ml (0.01 mol) of bromine. The reaction was started by irradiation with light. After stirring for 1 h the reaction mixture which became colorless was poured into 100 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol.

Dibromomalonic acid *N,N'*-dibenzylamide (IIi). To a solution of 2.8 g (0.01 mol) of malonic acid *N,N'*-dibenzylamide (**Ib**) in 20 ml of glacial acetic acid was added dropwise while stirring 1.04 ml (0.02 mol) of bromine. The reaction was started by irradiation with light. After stirring for 1 h the reaction mixture that became colorless was poured into 100 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 3.4 g (77%), mp 198–200°C (from water). Yields, melting points, R_f values, and elemental analyses for compounds **IIa–i** are listed in Table 1, IR and ^{1}H NMR spectra in Table 2.

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