PREPARATION OF N,N-DISUBSTITUTED AMINOMALONALDEHYDES*

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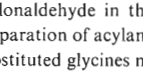
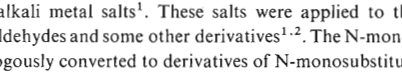
N,N-Disubstituted aminomalonaldehydes were prepared by a general method consisting in alkylation of alkali metal salts of aminomalonaldehyde. Products were characterised by ^{1}H-NMR, IR, and UV spectra.

The chemistry of aminomalonaldehyde (*Ia*) has been developed quite recently. The simplest approach to this compound is based on a two-step synthesis starting from glycine which is treated with a reagent obtained from dimethylformamide and phosphorus oxychloride. Saponification of the resulting salt *II* affords aminomalonaldehyde in the form of alkali metal salts[1]. These salts were applied to the preparation of acylaminomalonaldehydes and some other derivatives[1,2]. The N-monosubstituted glycines may be analogously converted to derivatives of N-monosubstituted aminomalonaldehydes[1]. This route failed in the attempted preparation of N,N-disubstituted aminomalonaldehydes. As the first N,N-disubstituted aminomalonaldehyde, the dimethylamino derivative *Ib* was obtained by formylation of bis(dimethylamino)ethylene[3,4]; the derivatives of cyclic secondary amines (piperidine, morpholine) were prepared analogously[4,5]. However, this route comprises usually several steps since 1,2-bis(dialkylamino)ethylenes are not readily accessible.



Ia, $R^1 = R^2 = H$
Ib, $R^1 = R^2 = CH_3$
Ic — *Im*, see Table I



II

In connection with investigation on the reactivity of the unsubstituted aminomalonaldehyde (*Ia*), the amino group was observed to react with alkylating agents with the predominant formation of N,N-disubstituted aminomalonaldehydes. As a new approach to these compounds, the alkylation has been now examined

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in detail. Various alkylating agents may be used such as alkyl halides, *p*-toluenesulfonates, and dialkyl sulfates; in view of their accessibility, alkyl bromides have been mainly used in the present work. Aminoaldehyde (*Ia*) must be introduced into the reaction mixture in the form of an alkali metal salt, since the attempted liberation is always accompanied by decomposition[1]. The reaction is preferably carried out in an aqueous alcohol (methanol). When the alkyl bromides are less reactive or less accessible, or in order to circumvent hydrolysis, a modification has been developed. In this modification, dry potassium salt of aminomalonaldehyde and excess potassium hydroxide are stirred in anhydrous dimethyl sulfoxide. In this medium, the alkylations are markedly faster. The yields of alkylations depend on the character of the particular bromide and exceed 50% in some cases only; nevertheless, in view of the accessibility of reactant, the present synthesis of N,N-disubstituted aminomalonaldehydes may be regarded as advantageous. Attention has been mainly paid to the scope and limitations of the alkylation. For this reason, optimum reaction conditions for the particular bromides have not been examined.

The alkylations are summarised in Table I. The reactivity of primary alkyl bromides decreased with increasing alkyl groups (ethyl > propyl > n-butyl > n-octyl). The first member of the homologous series, methyl bromide (not shown), is an efficient alkylating agent but the resulting dimethylaminomalonaldehyde readily undergoes a further methylation, *i.e.*, quaternisation of the nitrogen atom. Despite the isolation of a small amount of the dimethylamino derivative under certain condition, this approach is hardly advantageous in view of the reported unambiguous synthesis of dimethylaminomalonaldehyde[3].

Benzyl bromide and allyl bromide reacted readily and in good yields; somewhat lower yields were obtained with the use of propargyl bromide. In order to obtain malonaldehydes substituted by cyclic amines, the application of α,ω-dibromoalkanes was also examined. Under the reaction conditions stated, tetramethylene dibromide and pentamethylene dibromide yielded pyrrolidino- (*Ij*) and piperidinomalonaldehyde (*Ik*), resp. The alkyl bromides may also contain some other functional groups. Thus, the alkylation with 2-bromoethyl acetate in anhydrous dimethyl sulfoxide was quite satisfactory despite the presence of the acetoxy group inclining to hydrolysis.

In alkylations with primary alkyl bromides, we did not detect any monosubstituted derivative as the intermediary product. Thus, only the dibenzylamino derivative was found in the reaction mixture with the use of thin-layer chromatography despite very mild reaction conditions and a small proportion of benzyl bromide (about 10%).

As expected, the alkylation of the amino group in the dialdehyde *Ia* with secondary alkyl bromides was much more difficult than with primary alkyl bromides. The steric effect results in retardation of the alkylation and differentiation in the formation

of the mono- and disubstituted derivative. This situation can be illustrated by experiments with isopropyl bromide. When performed in aqueous alcohol, the reaction is very slow and the formation of two products may be observed. After the isolation and separation of these two substances (the yields were low under these special

TABLE I

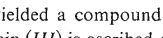
N,N-Disubstituted Aminomalonaldehydes *Ic*—*Im*

Compound R^1, R^2	Method yield, %	M.p., °C solvent	Formula (m.w.)	Calculated/Found % C	% H	% N
Ic	A[a]	194—195·5	$C_7H_{13}NO_2$	58·72	9·15	9·78
C_2H_5	40	subl.	(143·2)	58·88	9·22	9·72
Id	B[b]	156·5—157	$C_9H_{17}NO_2$	63·13	10·01	8·18
n-C_3H_7	46	benzene, subl.	(171·2)	63·11	9·99	8·27
Ie	B[a]	142—143·5	$C_{11}H_{21}NO_2$	66·29	10·62	7·03
n-C_4H_9	40	subl.	(199·3)	66·48	10·61	7·12
If	A[a]	117—118·5	$C_{19}H_{37}NO_2$	73·26	11·97	4·50
n-C_8H_{17}	30	CCl_4	(311·5)	73·54	12·13	4·68
Ig	A[a]	186·5—190	$C_{17}H_{17}NO_2$	76·38	6·41	5·24
$C_6H_5CH_2$	78	$C_2H_4Cl_2$	(267·3)	76·35	6·36	5·23
Ih	A[a]	133—134	$C_9H_{13}NO_2$	64·65	7·84	8·38
$CH_2{=}CHCH_2{-}$	82	acetone	(167·2)	64·61	7·96	8·45
Ii	A[a]	128—129	$C_9H_9NO_2$	66·25	5·56	8·58
$CH{\equiv}CCH_2{-}$	54	ethyl acetate	(163·2)	66·75	5·71	8·76
Ij	B[a]	156·5—159	$C_7H_{11}NO_2$	59·56	7·85	9·92
$-(CH_2)_4-$	46	benzene	(141·2)	59·76	7·79	9·79
Ik	B[c]	195—197[d]	$C_8H_{13}NO_2$	61·91	8·44	9·03
$-(CH_2)_5-$	49	benzene	(155·2)	62·16	8·33	9·06
Il	B[a]	106—107	$C_{11}H_{17}NO_6$	50·96	6·61	5·40
$CH_3COOCH_2CH_2$	21	benzene	(259·3)	50·52	6·77	5·67
Im	B[e]	197—199	$C_9H_{17}NO_2$	63·13	10·01	8·18
i-C_3H_7	30	benzene	(171·2)	63·12	9·93	7·88

[a] See the experimental part; [b] the reaction mixture was processed after 5 h and the product isolated by chromatography on silica gel (200 g) in 10 : 1 dichloromethane–ethanol solvent mixture; [c] the product was purified by chromatography on silica gel (100 g) in 5 : 1 dichloromethane–ethanol solvent mixture; [d] reported[5], m.p. 195°C; [e] the product was purified by chromatography on silica gel (200 g) in 5 : 1 dichloromethane–ethanol solvent mixture, sublimation, crystallisation (benzene), and resublimation.

conditions) by chromatography, the structure of a di(isopropyl) derivative was established for the more mobile product whereas the data of the more polar product are in accord with the structure of a monoisopropyl derivative. The latter compound represents the first monosubstituted aminomalonaldehyde isolated in a pure state. When the isopropyl bromide was allowed to react in dimethyl sulfoxide, the alkylation was considerably faster and afforded the di(isopropyl) derivative in a fair yield.

In some cases, the chromatography of alkylation products indicated the presence of a small amount of an additional UV-absorbing less polar by-product. The content of this substance increases with increasing amounts of the alkylating agent. In addition to the expected main product *If*, the reaction of aminomalonaldehyde with butyl bromide (3 equivalents) yielded a compound to which the structure of 2-(di-n-butylamino)-3-n-butoxyacrolein (*III*) is ascribed on the basis of elemental analysis and spectral data.



III

The structure of the present aminoaldehyde derivatives was confirmed by elemental analyses and spectra. The character of ^{1}H-NMR spectra corresponds to that of the earlier reported N-substituted compounds[3,4]. Except for the dipropargyl derivative *Ii* (8·20 ppm), both aldehydic groups form a single signal in the 8·48 – 8·7 ppm region while the signal belonging to the acidic hydrogen depends on concentration and temperature[3,4] (in some cases, this signal is so broad that it cannot be identified). The signals of aliphatic groups on the nitrogen atom indicate a restricted rotation, particularly in the case of the di(isopropyl) derivative *Im*. In order to confirm the structure, the ^{1}H-NMR spectrum of compound *Im*, was measured in deuterated dimethyl sulfoxide to obtain averaged and interpretable spectra (Table II).

The assumed structure of the novel aminomalonaldehyde derivatives is also in accordance with their IR spectra which differ in the double bond region to a negligible extent only and are almost identical with IR spectra of the earlier reported derivatives[3,4] (see for example the IR spectra of the diethyl derivative *Ic* and compounds *Ii* and *In* in the Experimental part).

The UV spectra were measured both in ethanol and aqueous media; in the latter media, the expected pH dependence of spectral data was observed. On the basis of dimethylaminomalonaldehyde spectra at various pH values (from 1M-HCl to 1M-NaOH), the following media were used for standard measurements of the other compounds: water, 0·01M-NaOH, and 1M-HCl. The UV spectral data are shown in Table III. In ethanol, the maximum varies from 262 to 267 nm with the extinction ε of about $25 - 30 \cdot 10^3$ (for a striking exception see the spectrum of compound *Ii*). In an aqueous solution, the band position does not hardly change but the band is narrower and higher. In 0·01M-NaOH, the maximum is shifted to about 270 nm

TABLE II

The ^{1}H-NMR Spectra of Aminomalonaldehydes *Ic*—*In*

Compound	Solvent	—CH=O . . (2 H)	—OH[a]	R
Ic	$CDCl_3$	8·73	7·65 vbs	1·13 t (9 H); J = 7 Hz; 2·1—2·8 vbs (4 H)
Id	$CDCl_3$	8·70	8·05 bs	0·90 t (6 H); 1·55 m (4 H); 3·45 bs (4 H)
Ie	$CDCl_3$	8·70	7·80	0·9 t (6 H); 1·45 m (8 H); 3·5 vbs (4 H)
If	$CDCl_3$	8·69	—	0·8—1·7 m (28 H); 3·1—3·9 m (4 H)
Ig	$CDCl_3$	8·48	7·04	7·15—7·35 m (10 H); 4·40 s (4 H)
Ih	$CDCl_3$	8·66	8·37	4·11 d (4 H); J = 6·5 Hz; 5·20—6·0 m (6 H)
Ii	polysol	8·20	6·16	2·33 t (2 H); 3·92 d (4 H); J = 2·5 Hz
Ij	$CDCl_3$	8·64	9·15	2·2—2·4 m (4H); 3·5—3·75 m (4H)
Ik	$CDCl_3$	8·69	7·01	1·6—2·1 m (6 H); 3·67 bs (4 H)
Il	$CDCl_3$	8·55	6·98	2·1 s (6 H); 3·45—3·6 m (4 H); 4·05—4·2 (4 H)
Im	[b]	8·56	—	1·13 d (12 H); 4·15 heptet (2 H); J = 6·5 Hz
In	[b]	8·53	4·50 vbs	1·01 d (6 H); 3·43 heptet (1 H); J = 7 Hz

[a] Position of this proton signal depends on the concentration and temperature; [b] hexadeuteriodimethyl sulfoxide.

TABLE III

The UV Spectra of Aminomalonaldehydes *Ia*—*In*, λ_{max} in nm (ε . 10^{-3})

Compound	C_2H_5OH	H_2O	0·01M-NaOH	1M-HCl
Ia	--	—	299 (28·7)[a]	—
Ib	262 (31·8)	262 (32·3)	271 (22·6)[b]	242 (20·0)
Ic	263 (32·6)	263 (32·6)	269 (25·9)	243 (20·3)
Id	263 (30·6)	263 (30·4)	270 (25·1)	244 (19·9)
Ie	264 (31·2)	264 (30·0)	270 (24·8)	244 (19·6)
If	264 (30·6)	266[c]	271[c]	245 (17·8)
Ig	267 (26·0)	267 (24·0)	274 (20·7)	250 (13·6)
Ih	263 (28·4)	263 (28·6)	272 (24·0)	244 (24·0)
Ii	263 (10·9)	263 (21·5)	272 (16·5)[b]	243 (15·5)
Ij	263 (30·9)	263 (30·8)	273 (20·5)[b]	243 (19·2)
Ik	262 (31·4)	261 (31·4)	272 (21·0)[b]	242 (19·8)
Il	263 (23·0)	262 (25·6)	271 (20·4)	243 (16·2)
Im	263 (28·8)	263 (28·1)	268 (22·5)	243 (18·1)
In	264 (31·0)	264 (30·2)	298 (19·4)	244 (19·4)

[a] The value obtained by hydrolysis of trifluoroacetylamidomalonaldehyde in 1M-NaOH (ref.[2]); [b] the absorption band exhibited a weak inflex at 299—300 nm; [c] the value of the molar extinction coefficient was not determined because of the low solubility of compound *If*.

and the extinction coefficient is lower. Some compounds exhibited in this medium an insignificant inflex at about 300 nm. It is interesting that this inflex may be observed only with derivatives, the amino group of which is substituted with residues of low steric requirements (the dimethylamino derivative *Ib*, both cyclic derivatives *Ij* and *Ik*, and the dipropargyl derivative *Ii*). Contrary to N,N-disubstituted aminomalonaldehydes, the UV spectrum of the monoisopropylamino derivative *In* exhibits in alkaline media a distinct band shifted to 298 nm. This value is strikingly similar to that of the unsubstituted aminomalonaldehyde[2]. This phenomenon may be regarded as characteristic of all derivatives bearing at least one hydrogen atom on the amino group. In 1M-HCl, the maxima of all aminomalonaldehyde derivatives examined are shifted to lower values, the corresponding extinction coefficients being also lower.

Substituted aminomalonaldehydes are stable and crystalline substances with properties similar to those of the earlier reported derivatives[3,4]. Worth of mention is the behaviour of isopropylaminomalonaldehyde (*In*) differring by the presence of one hydrogen on the nitrogen atom. This compound was found to undergo readily the oxidation; contrary to N,N-disubstituted aminomalonaldehydes, compound *In* affords an anodic polarographic wave[6]. Consequently, compounds of this type may be regarded as closely related to the group of reductones in accordance with the idea that the parent aminomalonaldehyde represents an amino analogue of the simplest reductone, the hydroxymalonaldehyde (the so called triose reductone), *cf.*[6].

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The ^{1}H-NMR spectra were measured on a Varian HA-100 apparatus. The IR spectra were recorded on a Zeiss UR-20 apparatus. The UV spectra were taken on a Unicam SP 8000 apparatus.

Alkylation of Aminomalonaldehyde; General Methods

A. *In aqueous methanol.* A mixture of the salt[1] *II* (3·0 g; 0·01 mol) and 2M-NaOH (25 ml) was heated at 60°C with stirring for 4 h and then taken down on a rotatory evaporator to the volume of about 10 ml. To the concentrate, methanol (40 ml) and the appropriate bromide (0·022 mol) was added and the whole mixture stirred at room temperature until the reaction was complete (checked by thin-layer chromatography). The methanol was then evaporated under diminished pressure and the product isolated. For the reaction time, isolation procedure, and deviations (if any) from the general method see the particular derivatives or notes to Table I.

B. *In dimethyl sulfoxide.* A mixture of the perchlorate *II* (3·0 g; 0·01 mol) and 2M-KOH (25 ml) was heated at 60°C for 4 h, diluted with ethanol (50 ml), and cooled down to deposit potassium perchlorate which was filtered off. The filtrate was taken down on a rotatory evaporator at 12 Torr and temperature not exceeding 60°C, the residue dried at 0·25 Torr and about 70°C, cooled down, and diluted with dimethyl sulfoxide (10 ml). The appropriate bromide (0·022 mol) was then added, the mixture maintained at 5—10°C for about 3 h, and kept at 0°C overnight. The dimethyl sulfoxide was evaporated at 0·25 Torr (bath temperature not exceeding 60°C), the residue

dissolved in water, the solution brought to pH 4—5 by the addition of dilute hydrochloric acid, taken down on a rotatory evaporator, and the dry residue extracted with 5 : 1 dichloromethane–ethanol solvent mixture (5 times 25 ml). The combined extracts were dried over anhydrous magnesium sulfate, evaporated, and the residue purified (for details see the particular derivatives or notes to Table I).

Diethylaminomalonaldehyde (Ic). After 24 h, the mixture was processed as follows. Saturated aqueous potassium carbonate (40 ml) was added and the product extracted with 2 : 1 ethanol–benzene solvent mixture (8 times 20 ml). The combined extracts were evaporated, the residue dissolved in water, the aqueous solution neutralised with 1M-HCl, and evaporated under diminished pressure. The residue was extracted with boiling dichloromethane, the extracts were evaporated, and the residue (about 0·75 g) was chromatographed on a column of silica gel (50 g) in 5 : 1 dichloromethane–ethanol solvent mixture. The final purification was effected by sublimation. IR spectrum (chloroform): ν(C=C—C=O) sh 1556 s, 1580 vs, 1640 m; (CH=O) band 2750 w. IR spectrum (KBr): ν(C=C—C=O) 1587 s, sh 1631 s, sh 1644 s; (CH=O) band 2740 m.

Di-n-butylaminomalonaldehyde (Ie). Reaction was performed according to method *B* except for the use of 3 equivalents of n-butyl bromide (3·25 ml). The dimethyl sulfoxide was evaporated, the residue triturated with 2M-NaOH (5 ml), and the insoluble portion removed by extraction with ether (*vide infra*). The aqueous phase was filtered and the filtrate neutralised with dilute hydrochloric acid to deposit crystals which were collected with suction. Yield, 0·8 g (40%); m.p. 142—143°C. The analytical sample was purified by sublimation.

2-(*Di*-n-*butylamino*)-3-n-*butoxyacrolein* (III). The ethereal extract from the preceding experiment was evaporated and the residue (0·6 g) chromatographed on a column of silica gel (40 g) in 5 : 1 dichloromethane–ether solvent mixture to afford 0·35 g (12·5%) of compound *III* boiling at 140°C (bath temperature) and 0·3 Torr. For $C_{15}H_{29}NO_2$ (255·4) calculated: 70·54% C, 11·45% H, 5·48% N; found: 70·32% C, 11·35% H, 5·76% N.

Di-octylaminomalonaldehyde (If). After 3 days, the reaction was interrupted, the methanol evaporated under diminished pressure, the residue distributed between water and ether, the ethereal layer evaporated, and the residue purified by chromatography (in 10 : 1 dichloromethane–ethanol solvent mixture) and crystallisation.

Dibenzylaminomalonaldehyde (Ig). The reaction was complete within about 4 h. The next day, the mixture was diluted with about 30 ml of water, the methanol evaporated under diminished pressure, and the residual liquid extracted with ether. The product was liberated from the alkaline aqueous layer by introduction of carbon dioxide and purified by crystallisation.

Diallylaminomalonaldehyde (Ih). A modification of method *A* was used. A solution of aminomalonaldehyde sodium salt was treated with additional 0·5 g (0·012 mol) of sodium hydroxide; the freshly distilled allyl bromide (1·9 ml; 0·022 mol) was added in methanol (5 ml) under ice-cooling. When the reaction was over (3 h), the methanol was evaporated under diminished pressure and the remaining aqueous solution was washed with ether. Saturated aqueous potassium carbonate (25 ml) was then added to the aqueous layer and the product extracted with 3 : 1 benzene–ethanol solvent mixture (6 times 30 ml). The extracts were combined, filtered with active charcoal, the filtrate evaporated, and the residue dissolved in a minimum volume of water. The aqueous solution was brought to pH 4—5 by the addition of 1M-HCl, evaporated, the residue extracted with boiling acetone, and purified by crystallisation.

Dipropargylaminomalonaldehyde (Ii). The preparation was analogous to that of compound *Ih*. Freshly distilled propargyl bromide (1·73 ml; 0·022 mol) was used. The reaction was completed

within 5 h. The crude product (obtained from extracts) was purified by chromatography on silica gel in 2 : 1 light petroleum–acetone, sublimation, and crystallisation. IR spectrum (KBr): ν(C=C—C=O) 1 578 s, 1 609 s, 1 640 s; ν(C≡C) 2 139; ν(C≡C—H) 3 245 s; $\nu(OH)_{bound}$ 2 560 m, v br.

Pyrrolidinomalonaldehyde (Ij). The residue was purified by chromatography on silica gel (100 g) in 5 : 1 dichloromethane–ethanol, repeated sublimation, and crystallisation.

Di(2-acetoxyethyl)aminomalonaldehyde (Il). The preparation was performed according to method *B* except for the work-up which was completed in anhydrous media. The dimethyl sulfoxide was evaporated, the residue triturated in ether, the alkalinity removed with gaseous hydrogen chloride, the ether evaporated under diminished pressure, the residue extracted with acetonitrile, the extract evaporated, and the residue purified by chromatography on silica gel (80 g) in acetone and by sublimation. Yield, 0·55 g (21%) of compound *Il*, m.p. 106—107°C.

Isopropylaminomalonaldehyde (*In*)

Method *A* was used. The usually prepared solution of aminomalonaldehyde sodium salt (0·01 ml) was treated with methanol (40 ml), 4M-NaOH (10 ml), and isopropyl bromide (5·7 ml; 0·06 mol). The mixture was stirred at room temperature overnight and then methanol (20 ml) and 4M-NaOH (5 ml) was added. The whole was kept for additional 48 h, diluted with water, and evaporated to remove methanol and the excess bromide. The residual solution was neutralised with hydrochloric acid and evaporated. The residue was extracted with boiling acetonitrile (3 times 5 ml) and then with 5 : 1 dichloromethane–ethanol solvent mixture. The acetonitrile extracts deposited on cooling a solid which was combined with the residue obtained by evaporation of the dichloromethane–ethanol extracts. The crude product was purified by repeated sublimation and crystallisation from 10 : 1 acetonitrile–water solvent mixture. Yield, about 150 mg (10%) of compound *In*, m.p. in the range of 159—166°C. For $C_6H_{11}NO_2$ (129·2) calculated: 55·80% C, 8·58% H, 10·84% N; found: 56·10% C, 8·61% H, 10·87% N. IR spectrum (KBr): ν(C=C—C=O) 1 576 s, 1 591 m, sh 1 639 w. Chromatography of the acetonitrile mother liquor (silica gel, 5 : 1 dichloromethane–ethanol) yielded 100 mg of diisopropylaminomalonaldehyde (*Im*).

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