STRUCTURE OF AMIDOMALONALDEHYDES AND SOME RELATED COMPOUNDS*

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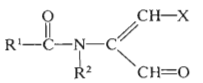
A set of amidomalonaldehyde derivatives *Ia* to *Io* was examined by means of ^{1}H-NMR, IR, and UV spectra; in the case of compounds containing an enol group, the pK_a values were also determined. The detailed structure and behaviour of these compounds in various media was discussed. In the case of amidomalonaldehydes (and probaly also compounds *II* and *Io*) a slow interconversion takes place of two equivalent forms characterised by a seven-membered hydrogen bond.

The first amidomalonaldehydes were reported in 1948 by Cornforth[1]. Nevertheless, a simple and convenient synthesis of this type of compounds has been developed in this Laboratory quite recently[2]. In the present paper, we wish to report on the physico-chemical behaviour of amidomalonaldehydes and some related compounds *Ia* to *Io*.

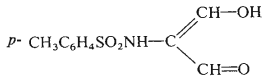


I

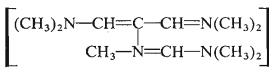
	R^1	R^2	X		R^1	R^2	X
Ia	H	H	OH	*Ii*	CH_3	H	OCH_3
Ib	CH_3	H	OH	*Ij*	C_2H_5O	H	OCH_3
Ic	CF_3	H	OH	*Ik*	CH_3	CH_3	OCH_3
Id	C_6H_5	H	OH	*Il*	H	H	$N(CH_3)_2$
Ie	C_2H_5O	H	OH	*Im*	CH_3	H	$N(CH_3)_2$
If	C_2H_5O	H	$OCOOC_2H_5$	*In*	H	CH_3	$N(CH_3)_2$
Ig	H	CH_3	OH	*Io*	C_2H_5O	H	$NHCH_2C_6H_5$
Ih	CH_3	CH_3	OH				

* Part XXXVI in the series Synthetic Reactions of Dimethylformamide; Part XXXV: This Journal *42*, 1175 (1977).

The amidomalonaldehydes *Ib* to *Id*, the dimethylamino derivatives *Il* and *Im*, and the *p*-toluenesulfonamidomalonaldehyde *II* were obtained by the earlier reported procedure[2]. The formamido derivative *Ia* was prepared by reaction of the crude sodium salt of aminomalonaldehyde with formyl acetyl anhydride and the derivative *Ie* resulted from treatment of the alkaline solution of aminomalonaldehyde with ethyl chloroformate. In the latter case, the intermediate *If* with a protected acidic hydroxylic function can be isolated under certain work-up conditions; compound *If* readily decomposes with the formation of the derivative *Ie*. In the preparation of the two N-methylamidomalonaldehydes *Ig* and *Ih* and of the dimethylamino derivative *In*, the formylation product of sarcosine, namely, N,N-dimethyl-N--(2-N-methyl-N-dimethylaminomethyleneammonio-3-dimethylamino)prop-2-enylideneammonium diperchlorate[2] (*III*), was used as the starting material. The dimethylamino derivative *In* and the formamido derivative *Ig* were obtained by a gradual hydrolysis of the salt *III*; in the preparation of the N-acetyl derivative *Ih*, the salt *III* was completely hydrolysed in aqueous sodium hydroxide to the salt of the parent N-methylaminomalonaldehyde which was then acetylated with acetic anhydride. The acidic hydrogen of amidomalonaldehydes may be readily replaced by a methyl group on treatment with ethereal diazomethane. By this route, the O-methyl derivatives *Ii*, *Ij*, and *Ik* were obtained. Compound *Io* was prepared by reaction of the O-methyl derivative *Ij* with benzylamine.



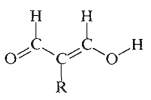
II



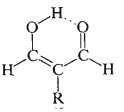
III

In the course of the preparation of compounds *Ia* to *Io* some peculiarities were observed. *1*) When chromatographed in various solvent systems, the O-methyl derivatives *Ii* and *Ij* travel more slowly than the starting dialdehydes *Ib* and *Ie*. As indicated by such an unexpected increase of polarity due to replacement of the acidic hydrogen by a methyl group, a stabilizing interaction preferring the less polar undissociated form asserts itself in the starting hydroxy derivative. In accordance with this idea, the free dialdehydes sublime considerably more readily than the corresponding O-methyl derivatives. *2*) The extraction of N-methylamidomalonaldehydes *Ig* and *Ih* with organic solvents from aqueous media is strikingly more difficult than extraction of the corresponding NH derivatives *Ia* and *Ib*. These two types of compounds differ in their distribution coefficient values between dichloromethane and water by more than one order of magnitude. Both the N-methyl derivatives *Ig*

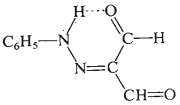
and *Ih* exhibit an increased acidity and their chromatographic behaviour suggests a strong polarity. Contrary to the above anomalous observations, replacement of the acidic hydrogen in the dialdehyde *Ih* by a methyl group with the formation of the O-methyl derivative *Ik* results in the usual decrease of polarity as shown by chromatography. It may be thus inferred from the above qualitative results that the presence of a methyl group on the nitrogen atom of compounds *Ig* and *Ih* removes the interaction by which the less polar form is stabilised in the case of dialdehydes with a NH group.



IV



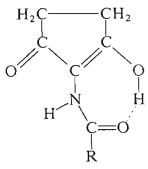
V



VI

As concluded some time ago from physico-chemical investigations on malonaldehyde and some further compounds of this type, the spatial arrangement depends not only on the substitution but also on the medium. Thus for example the unsubstituted malonaldehyde, the IR and ^{1}H-NMR spectra of which led in the earlier papers to contradictory conclusions[3,4], exists in an aqueous solution mainly in the *trans* configuration *IV* according to a later paper[5] while in nonpolar media a form is preferred with the six-membered ring containing an intramolecular hydrogen bond (formula *V*), characteristic of many 1,3-dicarbonyl compounds. Structure *V* is also ascribed to some alkylated malonaldehydes (*e.g.* to 1- and 2-adamantyl derivatives[6]) while in the case of tert-butylmalonaldehyde such a structure predominates only in highly dilute solutions or at low temperatures[7]. On the other hand, the cycloalkyl derivatives[8] (R = cyclopropyl to cyclohexyl) prefer (as inferred from ^{1}H-NMR spectra) the *trans* structure *IV* stabilised by intermolecular hydrogen bonds. The same structure *IV* is ascribed to halomalonaldehydes (R = F, Cl, Br, I) on the basis of the X-ray analysis of the bromo derivative[9] and confrontation of ^{1}H-NMR and IR spectra[10-12]. By the absence of any dialdehydic or hydrated form, these malonaldehydes markedly differ from other 1,3-dicarbonyl compounds as demonstrated *e.g.* on comparison of malonaldehyde with the structurally closely related acetylacetaldehyde[5]. The exclusive existence of the dialdehydic form stabilised by a strong hydrogen bond (formula *VI*) could be regarded as an exception in the case of phenylazonaldehyde[13]. However, this form more likely represents the phenylhydrazone of mesoxalic dialdehyde, *i.e.*, the derivative of a 1,2,3-tricarbonyl compound. From 1,3-dicarbonyl compounds substituted at position 2 by an amino function, the amido

derivatives of 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclopentanedione[14,15] are closely related to the present compounds of type *I*. In the amides mentioned, the existence of a seven-membered ring with a hydrogen bond was established and the stability of this structure (*VII*) was examined[15].



VII

In order to obtain a detailed knowledge on structures of compounds *Ia* to *Io* and explain the above mentioned observations, the ^{1}H-NMR, IR, and UV spectra of compounds *Ia* to *Io* were examined and dissociation constants of compounds with a free enolic hydroxylic functions (formula *I*, X = OH) were measured.*

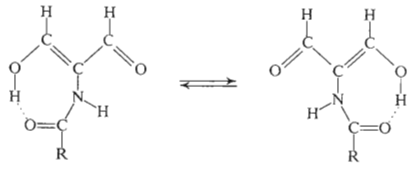
^{1}H-NMR *Spectra*

The examined compounds can be divided into three structural types differring also in the character of ^{1}H-NMR spectra: type *A*, amidomalonaldehydes *Ia* to *Id* with —OH and —NH— groups (*I*, R^2 = H, X = OH); type *B*, N-methylamidomalonaldehydes *Ig* and *Ih* with —OH and —N(CH$_3$)— groups; and type *C*, derivatives in which the enolic hydroxyl of malonaldehydes is replaced by —OCH$_3$, —N(CH$_3$)$_2$, and the like.

The ^{1}H-NMR spectra of the type *A* compounds exhibit characteristic signals shown in Table I. To our opinion, the structure of these compounds is best represented by an equilibrium between two (chemically identical) structures *VIIIa* and *VIIIb* with a seven-membered hydrogen bond structure and *trans* configuration of the malonaldehyde grouping. The ^{1}H-NMR spectra depend on the rate of the interconversion (from the standpoint of the NMR time scale). When the interconversion is slow, well resolved spectra are obtained whereas more or less averaged spectra result in the case of a rapid interconversion. This conclusion is based on *a*) ^{1}H-NMR spectra in various solvents and *b*) double resonance saturation experiments. The spectra of compounds of the type *A* are exemplified by the ^{1}H-NMR spectrum of the

* While this work was in progress, Professor C. Reichardt from the Phillipps-Universität, Marburg/Lahn, kindly informed us on the thesis of K. Schagerer[16] describing a different synthesis and an independent examination of compounds *Ib* and *Id* also involved in our investigations. In principle, the observations and conclusions given in the above Thesis are in accordance with our findings.

first member, the N-formyl derivative *Ia* (Fig. 1). The spectrum is formed by signals of five different protons and the figure shows not only their positions and shapes but also the observed interactions between these protons. The lowest signal of the enolic H_c proton (signal centered at 12·59 ppm) is split by interaction with the H_b methine proton ($J_{b,c}$ = 12·7 Hz) as well as with the H_e proton on the nitrogen atom ($J_{c,e}$ = 1 Hz). The aldehyde group H_a proton (8·98 ppm) interacts with the N-formyl group H_d proton ($J_{a,d}$ = 0·9 Hz) and with the nitrogen atom H_e proton ($J_{a,e}$ = = 0·3 Hz). The nitrogen atom H_e proton forms a broad signal centered at about 8·25 ppm. The signal of the N-formyl group H_d proton forms a broadened singlet at 8·08 ppm with a distinct interaction with the H_a proton. The methine H_b proton signal lies in the double bond region (signal centered at 6·89 ppm) and, in addition to the



VIIIa *VIIIb*

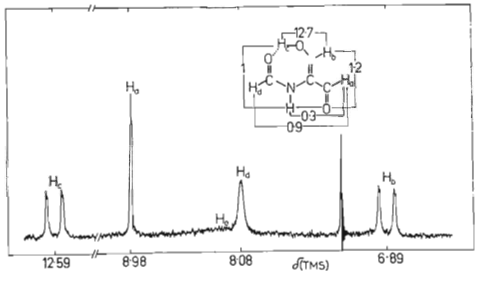


FIG. 1

^{1}H-NMR Spectrum of Formamidomalonaldehyde (*Ia*) in Deuteriochloroform (Varian HA-100 apparatus). The carbon atom carrying the H_b atom is not shown in the formula.

TABLE I

^{1}H-NMR Spectra of Amidomalonaldehyde Derivatives

The spectra were measured on a Varian HA-100 instrument; data from first-order analysis; tetramethylsilane as internal standard; chemical shifts in the δ scale, splittings in Hz; multiplicity given as follows: dd, doublet of doublets; bs, broad singlet; bd, broad doublet and the like.

Compound	Solvent	CHO (H_a)	CHX (H_b)	X (H_c)	R^1 (H_d)	R^2 (H_e)	Note
Ia	$CDCl_3$	8·98 dd	6·83 dd	12·59 dd	8·08 bs	8·25 vbs	*a,b*
	$(CD_3)_2SO$	8·21		—	8·01	9·62	*c*
	CD_3CN	8·97 bs	6·95 bs	12·59	8·01 bs	8·50 vbs	*c,d*
	CD_3CN	7·97		—	8·02	—	*c,e*
	H_2O	8·37		—	8·18	9·00 bs	*f*
	H_2O, Na salt	8·50 d		—	8·13	—	*f,g*
		8·48		—	7·93	—	
Ib	$CDCl_3$ [h]	8·92	6·85 dd	13·21 d	2·24	8·16 bs	*h,i*
	$CDCl_3$ [j]	8·92	6·85	13·11	2·24	7·81 bs	*j*
	$(CD_3)_2SO$	8·13 bs		—	2·10	9·24 bs	*c*
	CF_3COOH	8·17		—	2·48	8·61 bs	*c,k*
	CD_3CN, D_2O	7·95		—	2·16	—	*c*
	H_2O	8·32		—	2·14	8·77	*f*
	H_2O, Na salt	8·45		—	2·28	—	*f,l*
		8·49		—	1·85	—	
Ic	$CDCl_3$	9·05	6·96	11·47 bd	—	8·7 vbs	*m*
Id	$CDCl_3$	9·02	6·94	13·41 d	7·4—8 m	8·52 bs	*n*
	$(CD_3)_2SO$	8·38 bs		—	7·3—8 m	9·07	*c*
Ie	$CDCl_3$ [o]	8·85	6·70 dd	11·98 d	1·32 t	7·13 bs	*o,p*
					4·24 q		
	$CDCl_3$ [r]	8·85	6·68	12·00	—	7·04 bs	*r*
	$(CD_3)_2SO$	8·25 bs		—	1·18 t	7·71	*c*
					4·01 q		
If	$CDCl_3$ [s]	9·23	7·68	*u*	*u*	6·44 bs	*s,u*
	$CDCl_3$ [t]	9·30	7·64	—	—	6·24 bs	*t*
Ig	$CDCl_3$	8·32		—	7·86	2·98	*v*
		8·30		—	8·09	3·10	*y*
	CD_3CN	8·37		—	7·79	2·88 d	*v*
		8·29		—	8·07	3·03	*y*
Ih	CD_3CN	8·31		—	1·77	2·87	
		8·21		—	2·12	3·07	*z*
Ii	$CDCl_3$	9·12	6·91	4·03	2·09	6·93 bs	

TABLE I
(*Continued*)

Compound	Solvent	CHO (H_a)	CHX (H_b)	X (H_c)	R^1 (H_d)	R^2 (H_e)	Note
Ij	$CDCl_3$	9·10	6·84	4·02	1·25 t 4·15 q	6·06	
Il	$CDCl_3$	8·74 8·88	6·82 6·72	3·17 3·14	8·30 8·30	7·47 —	*aa*
Im	$CDCl_3$	8·72	6·73	3·15	2·13	7·55 bs	
In	$CDCl_3$	8·92 8·81	6·81 6·86	3·13 3·10	7·94 8·20	3·01 3·14	*v* *bb*
Io	$CDCl_3$	8·61	6·42 d	7·59 b	1·25 t 4·12 q	6·82	*cc*
II		8·79	6·98 bd	9·25 bd	—	6·55 bs	*dd,ee*

[a] $J_{b,c} = 12·7$; $J_{b,e} = 1·2$; $J_{a,d} = 0·9$; $J_{c,e}$ = about 1; $J_{a,e} = 0·3$. [b] Decrease of intensities in saturation experiments (irradiated proton given in brackets): $H_b - \{H_a\}$ 50%; $H_c - \{H_e\}$ 35%. [c] Hexamethyldisiloxane as internal standard; $\delta = 0·06$. [d] $J_{b,c} = 12$; saturation experiments: $H_b - \{H_a\}$ 100%; $H_c - \{HDO\}$ 100%; signal corresponding to HDO: 2·17 bs. [e] One drop of deuterated pyridine was added. [f] Sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. [g] The major conformer to which the conformation *E* is tentatively ascribed. [h] 10% solution of compound *Ib*. [i] $J_{b,c} = 12·5$; $J_{b,e} = 1·3$. [j] 10% solution of compound *Ib* in $CDCl_3$ was diluted in the ratio 1 : 9. [k] Correction for hexamethyldisiloxane in CF_3COOH, 0·49 ppm. [l] The major conformer to which the conformation *Z* is tentatively ascribed. [m] $J_{b,c} = 13·5$. [n] $J_{b,c} = 12·25$; $J_{b,e} = 0·95$; saturation experiment: $H_b - \{H_a\}$ 28%; when the 10% solution was diluted to a 1% solution, the signals did not change. [o] 10% solution. [p] $J_{b,c} = 12·4$; $J_{b,e} = 1·3$. [r] 10% solution of compound *Ie* diluted in the ratio 1 : 9 (deuteriochloroform). [s] 12% solution. [t] 12% solution diluted in the ratio 1 : 9 with deuteriochloroform. [u] Signals of two ethoxy groups; the signal in the higher field (4·18 q, 1·28 t) is ascribed to the N-(ethoxycarbonyl) group; the signal in the lower field (4·36 q, 1·40 t) is attributed to the O-(ethoxycarbonyl) group. [v] Form *E*; $J_{e,CH_3-N} = 0·6$. [y] The minor form *Z*, 17%. [z] The minor form *Z*, 11%. [aa] The spectrum indicates the presence of two forms, obviously *E* and *Z*. An unambiguous determination was not performed (approximate ratio, 80 : 20). [bb] Form *Z*; content, about 20%. [cc] $J_{b,c} = 13·0$; signals of the benzyl group: CH_2 4·45 d (2 H); $J_{e,CH_2} = 6$, C_6H_5 7·20–7·40 m (5 H). [dd] $J_{b,c} = 12·0$. [ee] Signals of the *p*-toluenesulfonyl group: CH_3 2·42 s; C_6H_4 (AA′XX′) 7·70 (2 H), 7·30 (2 H).

above mentioned interaction with the enolic H_c proton, is split by the H_e proton ($J_{b,e} = 1·2$ Hz).

The structure *VIII* is mainly based on a vicinal interaction, the value of which ($J_{b,c} = 12·7$) is characteristic of the *trans* configuration of the appropriate protons.

Despite similar relations of these protons, the structure *V* (R = —NHCH=O) is regarded as less probable since in such a case both signals would be rapidly averaged due to a ready shift of the proton in the six-membered ring. The structure *VIII* is to our opinion also supported by the observed long-range couplings indicating the optimum coupling paths; these paths can be of the „zigzag" type for $J_{a,d}$ = = 0·9 Hz, "W" with $J_{b,e}$ = 1·2 Hz). Further arguments for structure *VIII* and against structure *V* may be inferred from considerations on the conformational forms of the formamido group. In structure *VIII*, the formamido group is a part of a cycle and consequently the shape and motion of this group depend on this fact; one the other hand, the formamido group is almost free in structure *V*. Most formamido derivatives are known[17] to be a mixture of conformational isomers. The conformational homogeneity indicated by the ^{1}H-NMR spectrum of compound *Ia* is in accordance with structure *VIII* whereas structure *V* would with a great probability require the occurrence of *Z* and *E* forms. These forms virtually assert themselves when the hydrogen bond is removed by conversion of compound *Ia* into an alkali metal salt (*vide infra*). The ^{1}H-NMR spectrum of compound *Ia* in dry trideuterioacetonitrile is also well resolved and exhibits signals analogous to those observed in the spectrum taken in deuteriochloroform (Table I).

Regarding the state of molecules of compound *Ia* in solutions applied to measurements of ^{1}H-NMR spectra, the saturation experiments are worth of mention. These experiments were performed in non-degased solutions under amplitudinal conditions usual with the Nuclear Overhauser Effect (NOE) measurements. Irradiation of the position of the aldehyde H_a proton results (in $CDCl_3$) in a decreased intensity of the methine H_b proton by about 50% (without decoupling); irradiation of the NH proton position was accompanied by a 35% decrease of the —OH group signal. In the acetonitrile solution there was observed a 100% saturation of the methine proton signal and also a complete saturation of the signal corresponding to the —OH group after irradiation of the signal belonging to the HOD molecule. These experiments confirm the existence of a distinct *VIIIa* ⇄ *VIIIb* interconversion in both solvents under the conditions stated. For the above mentioned saturation effects two processes are responsible. The first one is the interconversion (*VIII*, $a \rightleftarrows b$) transforming the irradiated aldehyde protons (H_a) into the methine protons (H_b), raising in this manner the population on the higher level at this position and bringing about saturation of the observed H_b signal. On the contrary, the relaxation processes of the methine protons tend to eliminate the effect of the first process. Now, if the rate of the interconversion is slow in comparison with that of the relaxation processes mentioned, the saturation of the observed signal (H_b) may be only partial (or even negligible). In the opposite case, when the rate of the interconversion becomes dominating (but when the slow exchange conditions still exist) the relaxation processes are no more able to eliminate the saturation so that this process can be complete. According to our opinion, the partial saturation observed in the chloroform solu-

tion corresponds to the former case while the complete saturation in the acetonitrile solution holds for the latter one. As the rate of the interconversion is sensitive to the base-catalysis (see below), we ascribe the different degree of saturation to the different basicity of the two solvents used.

A good structural resolution of ^{1}H-NMR spectra of compounds of the type *A* depends on the anhydrous state and purity of solvents since even small admixtures of water and some other substances (hydrogen chloride and the like) result in more or less averaged spectra (Figs 2–4). This effect is characteristic of the exchange process and may be readily interpreted in terms of the interconversion *VIII*, $a \rightleftarrows b$. This idea is supported by an experiment consisting in addition of water from a graduated capillary in increasing portions (Fig. 3) into a solution of the sample in anhydrous acetonitrile. While the position of the signal of the N-formyl group H_d proton remains almost intact during this gradual addition of water, the other signals are broadened to such an extent that they are difficult to observe. A further addition of water results in an averaged signal of H_a and H_b protons which first coincides with the H_d signal but then gradually shifts downfield; the resulting spectrum finally resembles the spectrum of compound *Ia* in pure water. The spectrum of the aqueous solution of compound *Ia* (Fig. 4*a*) is markedly changed when this dialdehyde is transformed to the alkali metal salt (Fig. 4*b*). Two signals may be identified in the region of the N-formyl group proton. These signals are ascribable to conformational isomers differring in the geometry on the formamido group (*Z* and *E* forms, see also Table 1).

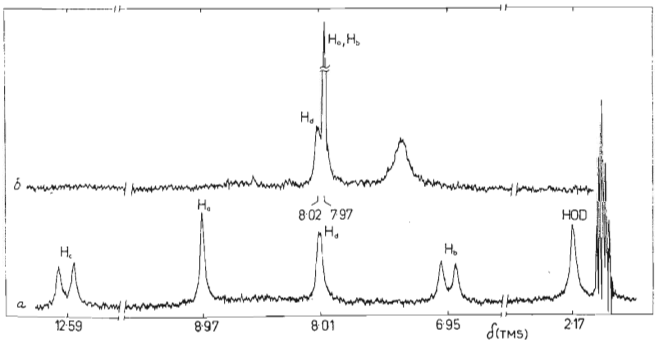


FIG. 2

^{1}H-NMR Spectrum of Formamidomalonaldehyde (*Ia*)

a In trideuterioacetonitrile; *b* after the addition of a trace of pentadeuteriopyridine.

According to our idea, the addition of water to the anhydrous solution of compound *Ia* catalyses the interconversion (*VIII*, $a \rightleftarrows b$) resulting in averaged signals of H_a and H_b protons. A further shift of the averaged signal in the course of the progressing dilution is ascribed to a different process, namely, to the advancing dissociation of the dialdehyde. However, the formamido group does not appear quite "free" even in the aqueous solution of the concentration stated. The formamide group becomes conformationally independent when the dialdehyde is transformed to the alkali metal salt, *i.e.*, by removal of the proton which is capable to form the hydrogen bond. The picture on the nature of compound *Ia* is completed by an experiment consisting in addition of a droplet of deuteriopyridine to the acetonitrile

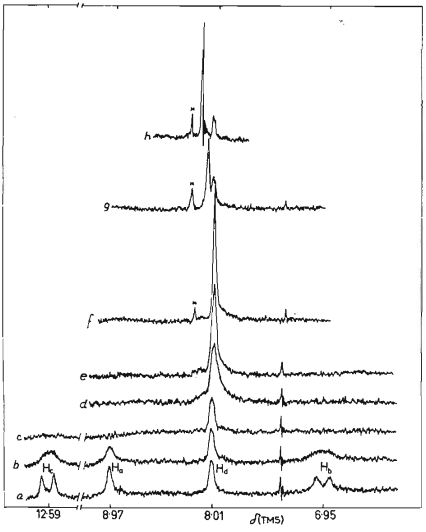


FIG. 3

Dependence of the ^{1}H-NMR Spectrum of Formamidomalonaldehyde (*Ia*) in Acetonitrile on the Content of Water

The lowest trace (*a*) is the spectrum taken in dry acetonitrile with the use of the CH_3-signal as a lock. The shifts indicated correspond to those in Fig. 2*a*. The upper traces (*b*—*h*) were measured after the addition of the following amounts of water to 0·5 ml of a 5% solution of compound *Ia* in dry acetonitrile: *b* 1 mg, *c* 5·5 mg, *d* 25·5 mg, *e* 45·5 mg, *f* 85·5 mg, *g* 185·5 mg, and *h* 485·5 mg. The signal marked with an asterisk probably corresponds to some decomposition products.

solution of compound *Ia*. This addition results in an instantaneous collapse of signals of H_a and H_b protons (Fig. 2*b*) and the position of the resulting signal very exactly corresponds to the averaged values of the original chemical shifts of H_a and H_b protons. The extremely rapid formation of averaged signals is ascribed in this case to the catalytic effect of pyridine as the base on the rate of the interconversion. The ^{1}H-NMR spectra of other compounds of the type *A*, the amidomalonaldehydes *Ib*–*Ie*, exhibit signals analogous to those of the formamido derivative *Ia*. In aprotic solvents ($CDCl_3$, CD_3CN), the —OH group protons formed doublets in the 11·47 to 13·21 ppm region ($J_{b,c}$ = 12·25–13·0 Hz), the methine group protons formed doublets in the 6·69–6·94 ppm region with the same splitting (this splitting is removed by replacement of the enolic proton by deuterium), and the aldehyde group protons formed singlets in the 8·85–9·05 ppm region. Protons of the NH group form a broad signal centered in the 8·16–8·52 ppm region except for the urethane type derivative *Ie*, the distinct upfield shift (7·11 ppm) of which is obviously due to the presence of the alkoxyl group exhibiting the electron-donor mesomeric effect. All compounds of the type *A* obey the Scheme 1 with the indicated interconversion which was also established by saturation experiments with compound *Id*. On the basis of the ^{1}H-NMR spectrum of *p*-toluenesulfonamidomalonaldehyde (*II*), this compound is ascribed a structure analogous to that (*VIII*) proposed for amidomalonaldehydes of the type *A* except for the role of the proton-acceptor in the seven-membered hydrogen bond which is taken over by the oxygen atom of the sulfonyl group.

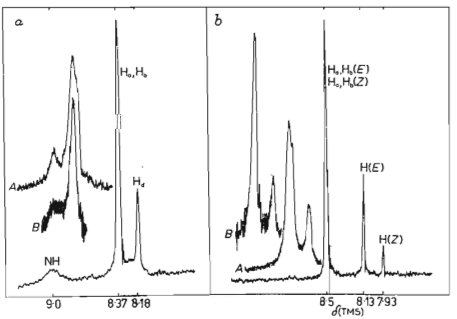
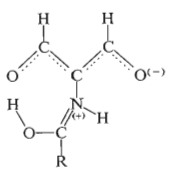


FIG. 4

^{1}H-NMR Spectrum of Formamidomalonaldehyde (*Ia*)

a In an aqueous solution; *A* expanded signal of H_a, H_b; *B* after irradiation of the position of H_d. *b* the sodium salt of formamidomalonaldehyde in an aqueous solution; *A* expanded signal of H_a, H_b; *B* after irradiation of the position of H_d (the *E* form tentatively).

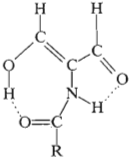
The interconversion of forms *VIIIa* and *VIIIb* may proceed by various mechanisms. Nevertheless, the final result must correspond to the rotation of the formamido group around the central C—N bond and to the shift of the hydrogen bond proton (*VIII*, $a \rightleftarrows b$). An averaging of signals of methylene groups adjacent to carbonyls (see formula *VII*) was observed by Tschesche and coworkers[15] in the case of 5,5-dimethyl-1,3-cyclohexanedione 2-acylamino derivatives at increased concentrations; this effect is ascribed to reorganisation of the molecule occurring in the stage of intermolecular associates. The relatively low solubility of compound *Ia* did not permit investigations in a wider concentration range; the investigation was therefore performed with the use of the acylamino derivatives *Ib* and *Ie*, but the effect of concentration on chemical shifts of signals in question was poorly significant (Table I). To our opinion, the interconversion of the type *A* compounds in aprotic solvents is mainly intramolecular, the most probable transition state of the slow uncatalysed interconversion being the dipolar structure *IX*. The formation of this structure *IX* consists in an intramolecular shift of the proton from the original hydrogen bond to the formamide group and forcing of this protonated group by 90° out of the plane of the malonaldehyde anion. The base-catalysed interconversion could proceed analogously except for the acceptance of the proton by another acceptor; consequently, the planes of the negatively charged anion and of the neutral formamido group would be forced from each other. In this case, the rotation should be easier than with the dipolar structure *IX* which is obviously prevented from such a rotation by attractive forces. The base-catalysed interconversion must be therefore expected to be always faster. This idea is in full accordance with experimental observations. The above considerations on the behaviour of compounds of the type *A* are also supported by measurements in some other solvents such as hexadeuteriodimethyl sulfoxide and trifluoroacetic acid (Table I) affording typical averaged spectra.



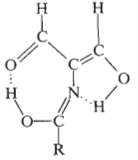
IX

The ^{1}H-NMR spectra of both compounds of the type *B*, the N-methylamidomalonaldehydes *Ig* and *Ih*, markedly differ from those of the type *A* compounds. Under all conditions, the ^{1}H-NMR spectra of compounds *Ig* and *Ih* exhibit identical chemical shifts of both aldehydic protons and the presence of *Z* and *E* forms which

differ in configuration on the amido group. The assignment of signals to the *Z* and *E* forms was unambiguously effected in deuterioacetonitrile. In both cases (*Ig* and *Ih*), the same distribution was observed of chemical shifts of aldehydic protons ($\delta H_a = \delta H_b)_Z < (\delta H_a = \delta H_b)_E$ and N-methyls $(\delta(N{-}CH_3))_Z > (\delta(N{-}CH_3))_E$ and relative signal intensities of *Z* and *E* forms (with a minor proportion of the *Z* form: 17% in compound *Ig* about 11% in compound *Ih*). The assignment of signals of the N-methyl group was performed on the basis of the finding that the major signal was split by the corresponding proton with the coupling constant $J = 0{\cdot}6$ Hz which is indicative (analogously to known amides) of the transoid configuration of the N-methyl group and the N-formyl proton, *i.e.*, of the *E* configuration. The marked preference of the *E* form is in accordance with the analogous situation in the case of N-methylated N-acylanilines[18] in which the plane of the acylamine grouping is considerably forced out of the plane of the aromatic system, sometimes by as much as 90°. With both N-methyl derivatives *Ig* and *Ih*, the preference of the *E* form and equivalence of chemical shifts of both aldehydic forms indicate the absence of the intromolecularly stabilised form *VIII* which is characteristic of all compounds of the type *A*. The plane of the N-methylated acylamino group in compounds *Ig* and *Ih* thus appears to be markedly forced out of the plane of the rest of the molecule. However, no information can be inferred from ^{1}H-NMR spectra on the shape of the malonaldehyde grouping; it cannot be therefore determined if this portion of molecule exists in the *trans* form of the type *IV* with a rapid prototropic exchange on both oxygen atoms or in the chelate structure of the type *V*. It cannot be excluded that both these structures may assert themselves in dependence on the medium as it was proposed for the case of the unsubstituted malonaldehyde.



X



XI

It is a question whether the striking differences between structures of compounds of the type *A* and the two N-methyl derivatives of the type *B* can be explained by steric effects only, *i.e.*, by forcing of the amide group out of the plane due to methylation of the nitrogen atom or if another interaction was interrupted in which the proton of the NH group was specifically engaged. In the approximately planar arrangement of the seven-membered hydrogen bond structure present in compounds of the type *A*,

the proton of the NH group is located in the neighbourhood of the aldehyde group. An additional five-membered hydrogen bonding could thus result with the formation of the bicyclic structure *X* capable of interconversion into the tautomer *XI*. In order to obtain experimental foundation for the above considerations, chemical shifts of NH protons in ^{1}H-NMR spectra of compounds *Ib*, *Id*, and *Ie* were examined under various concentrations (Table I). It has been observed that this signal (positions of the other signals did not practically change) is shifted by dilution (1 : 10) to a higher field; this shift is rather significant with compound *Ib* (about 0·35 ppm) and considerable less marked in the case of the derivative *Ie* (0·1 ppm) while the benzamido derivative *Id* does not exhibit any appreciable shift. Depending on the nature of the substituent R^1, an intermolecular hydrogen bonding can be thus formed in the case of compounds of the type *A* (compare with the same conclusion on the basis of IR spectra); notwithstanding, an involvement of the bicyclic structure *X* cannot be excluded. The data of Table I also allow to confront the spectra of compounds of the type *A* with derivatives (*If*, *Ii*, *Ij*) in which the formation of an intramolecular hydrogen bond is made impossible by a covalent substitution of the enolic proton. Since these derivatives display in principle a similar distribution of signals, their structures cannot be expected to be too different. A marked difference is observed only with signals corresponding to the NH group in view of a shift to a higher field by about 1 ppm with respect to the type *A* compounds. Since the position of this NH signal was found to depend on the nature of the R^1 substituent (compare the above comparison of compound *Ie* with other compounds of the type *A*), the encountered shift could be also in this case attributed to the different electronic effect of the group X (*i.e.* the intramolecularly bound hydroxylic group with compounds of the type *A* on the one hand, and the methoxyl group with derivatives *Ii*, *Ij*, and the like on the other hand).

Another group of our set of compounds consists of substances *Il*, *Im*, and *In* derived from the corresponding amidomalonaldehydes on replacement of the enolic hydroxyl by the dimethylamino group. With both formamido derivatives *Il* and *In*, the presence of two forms was indicated by ^{1}H—NMR spectra. As inferred on the basis of identification by long-range coupling of the N-methyl group and confrontation of chemical shifts and signal intensities with the appropriate data of the above discussed dialdehyde *Ig*, these two forms were concluded in the case of compound *In* to represent most likely the conformational isomers *Z* and *E* differring in configuration on the formamido group, the *Z* form being less abundant (20% with the derivative *In* and 17% with the dialdehyde *Ig*). In the case of the acetamido derivative *Im*, only one form was identified; this case might be analogous to that of acetanilide[17,18] in which the *Z* form is extremely favoured. A free rotation of the amido group in all the three 3-dimethylaminoacrolein derivatives *Il*, *Im*, and *In* is assumed.

The benzylamino derivative *Io* contains an enamine proton which may form a six-membered or seven-membered hydrogen bonding analogously to the enolic

TABLE II

Infrared Spectra of Amidomalonaldehydes and Related Compounds (in cm^{-1})

Compound	Deuteration	ν(NH)	ν(OH)		ν(C=C)	Amide-I	ν(C=O)	Amide-II
Ia	H	3 354 s	2 870 m, vbr		1 685 m	1 641 vs		1 530 s
	D	2 491 m	2 060 w, vbr		1 678 m	1 641 vs		1 082 s
	(H/D)[a]	(1·35)	(1·39)					(1·41)
Ib	H	3 365 s	2 850 w, vbr		1 680 m	1 634 vs		1 535 s
	D	2 494 m, br	2 030 w, bvr		1 675 m	1 635 vs		1 069 s
	(H/D)	(1·35)	(1·40)					(1·43)
Ic	H	3 329 s	2 900 w, vbr	1 709 w	1 693 w, sh	1 664 m	1 641 m	1 555 m
Id	H	3·366 m	2 770 w, vbr		1 677 m	1 637 vs		1 539 s
	D	2 501 m	2 010 w, vbr		1 669 vw	1 634 s		1 083 m
	(H/D)	(1·34)	(1·38)					(1·42)
Ie	H	3 375 s	2 950 m, vbr		1 692 s	1 661 vs, sh	1 641 vs	1 536 vs
	D	2 507 m	2 160 w, vbr		1 687 m	1 655 vs	1 643 vs	1 063 s
	(H/D)	(1·35)	(1·37)					(1·44)
Io	H	3 376 m	3 284 w, br[b]	1 713 s, sh	1 682 s, sh	1 705 vs	1 618 vs, br	1 534 s
	D	2 508 m	2 438 w, br[b]	1 715 m, sh	1 666 m	1 702 s	1 614 vs, br	1 137 m
	(H/D)	(1·35)	(1·35)					(1·35)
II	H	3 295 w	[c]		1 684 w, br	—	1 642 m	[c]
Ig	H	—	2 830 m, vbr		1 686 s	1 668 s, sh	1 632 vs	—
	D	—	2 210 w, vbr		1 686 m	1 668 m	1 632 s	—
	(H/D)		(1·28)					
Ih	H	—	2 790 m, vbr		1 683 m	1 648 s	1 611 vs	—
	D	—	2 180 w, vbr		1 683 m	1 648 s	1 611 s	—
	(H/D)		(1·28)					
In	—	—	—		1 680 m	1 667 s, sh	1 615 vs	—

[a] The wavenumber ratios ν(NH)/ν(ND), ν(OH)/ν(OD) or amide-II/amide-II′; [b] ν(NH) of the benzylamino group; [c] The solubility of the compound is very low, the less intensive bands cannot be determined.

proton. The ^{1}H-NMR spectrum indicated a single form with a broad signal of the enamine proton at 7·59 ppm and a relatively sharp doublet of the methine proton ($J_{NH,OH}$ = 13·0 Hz). A vicinal interaction of this kind convincingly indicates the *trans* configuration of the appropriate protons and simultaneously, a very slow exchange of the NH proton. For the broad NH signal, there is obviously responsible life-time broadening by quadrupol relaxation of ^{14}N. Conclusively, compound *Io* is assumed to exhibit with a great probability a seven-membered hydrogen bonding analogous to that in structure *VIII*.

IR *Spectra*

Most measurements of IR spectra were performed in chloroform solutions (Tables II and III) and with some selected compounds, the effect of the solvent was examined in detail (Table IV). A majority of compounds was also measured after the exchange of hydrogen in —OH and —NH— groups by deuterium in order to verify the shape of the broad band of the —OH group after removal of the interfering effect of ν(CH) submaxima and furthermore, in order to examine participation of bending vibrations β(NH) or β(OH) on absorption bands in the carbonyl region. The IR spectra were confronted with conclusions based on ^{1}H-NMR spectra as well as with the reported data mentioned in introduction[5,8,9,10,14,15].

The IR spectrum of amidomalonaldehydes *Ia*–*Ie* (compounds of the type *A*) exhibits a very broad ν(OH) band. Position, nature (shape), and concentration independence of this band indicates the presence of an intramolecularly bound —OH group. Such a bond would suggest structures expressed by formula *V* (R = —NH. .COR[1]) as well as *VIII*. By removal of the free proton from the hydroxylic group by methylation (*i.e.*, by conversion of compounds *Ib* and *Ie* into the methoxy derivatives *Ii* and *Ij*, resp.), the frequency of the amide-I band ($\Delta\nu$ about 65 cm^{-1}) is markedly increased. This effect indicates to our opinion that the amide carbonyl of compounds *Ia* and *Ie* is a component of the intramolecular hydrogen bonding as exemplified by formula *VIII*.

A further information on the behaviour of compounds of the type *A* in chloroform solutions was inferred from the concentration dependence of bands belonging to the NH bond. The data shown in Tables were obtained from dilute (0·003M) solutions free of any marked association in all cases. In more concentrated (2%) solutions, two compounds (*Ia* and *Ib*) exhibit a markedly high association. The $\nu(NH)_{assoc.}$ band of compound *Ia* (3298 cm^{-1}) and compound *Ib* (3305 cm^{-1}) is shifted by about 60 cm^{-1} downwards with respect to the ν(NH) band observed in more dilute solutions. In 2% chloroform solutions, the content of associated forms amounts tens of percents with compounds *Ia* and *Ib* while the percentage of those forms in other compounds of the type *A* is almost negligible. It may be inferred from comparison of some data shown in Tables II and III that the ν(NH) band of compounds *Ia*

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TABLE III

Infrared Spectra of Amidomalonaldehyde Derivatives (in cm^{-1})

Compound	Deuteration	ν(NH)	ν(C=O) carbonate	Amide-I	ν(C=C)	ν(C=O) aldehyde	Amide-II
Ii	H	3 428 w[a], 3 412 m[a], 3 394 w[a]		1·696 s	1 659 s, sh	1 650 s	1 500 m, br
	D	2 550 m 2 515 w, sh		1 690 s, sh		1 645 vs, br	1 087 m
	(H/D)[b]	(1·34) (1·35)					(1·38)
Ij	H	3 420 m, br		1 731 s, br	1 686 m	1 654 vs	1 506 s, br
	D	2 529 w, br		1 726 s, br	1 686 m	1 653 vs	1 110 s, br
	(H/D)	(1·35)					(1·36)
If	H	3 423 w, sh, 3 401 m	1 778 s	1 747 s, 1 730 m, sh	1 696 m, sh	1 676 s	1 514 s 1 505 s, sh
	D	2 555 w, sh [c]	1 776 s	1 739 m, 1 729 m, sh	1 691 m, sh	1 675 s	1 108 m
	(H/D)	(1·34)					(1·37)
Il	H	3 390 s[a] 3 374 m[a]		1 699 m	1 669 w	1 610 s	1 522 m, sh, 1 508 m, sh
	D	2 506 m[a] 2 492 w[a]		1 694 m	1 668 w	1 609 s	1 101 w 1 087 w
	(H/D)	(1·35) (1·35)					(1·38) (1·39)
Im	H	3 400 s[a] 3 377 w[a]		1 695 m, sh, 1 689 m	1 668 m	1 608 vs	1 494 m, br
	D	2 519 m[a] 2 494 w[a]		1 684 m	1 667 m	1 607 vs	1 096 m, sh, 1 087 m
	(H/D)	(1·35) (1·35)					(1·36) (1·37)

[a] The values were obtained by separation of the asymmetric ν(NH) or ν(ND) band on a Hewlett-Packard 9830 calculator; [b] the wavenumber ratios ν(NH)/ν(ND) or amide-II/amide-II′; [c] the band cannot be determined due to interference of the absorption of hydrolytical products.

and *Ie* is shifted with respect to that of the corresponding methoxy derivatives *Ii* and *Ij* to lower wavenumbers by about 50 cm^{-1}; on the other hand, the amide-II band (in principle an in plane bending vibration of the NH bond) is shifted to higher wavenumbers by about 30 cm^{-1}. This difference between NH data belonging to the ring system *VIII* and open-chain structure of the methoxy derivatives could be ascribed to the different electronic effect of the residue X in formula *I* (*i.e.*, to the intramolecularly bound hydroxylic group in the case of compounds of the type *A* and to the methoxy group in compounds *Ii* and *Ij*). However, it cannot be excluded that this difference indicates in the case of compounds of the type *A* a weak interaction between the remaining aldehydic group and the NH bond; the character of such an interaction would suggest a weak intramolecular hydrogen bond (as present in the bicyclic structure *X*) which would be in equilibrium with a stronger intermolecular hydrogen bond. The explanation of the above observation must be therefore adjourned.

With planar molecules of amidomalonaldehydes (type *A*), a strong coupling of the in plane vibrations of the whole skeleton must be expected. It appears nevertheless advisable for practical reasons to assign the observed bands to particular vibrations. Thus, in accordance with interpretation of the IR spectrum of bromomalonaldehyde (George and Mansell[10]), the band located in the 1670–1690 cm^{-1} region in spectra of compounds *Ia* to *Ie* (similar to compound *Io*, *vide infra*) was attributed to ν(C=C) despite a different assignment in the case of related β-methoxy-α,β-unsaturated ketones by Dabrovski and Tencer[19]. This band is markedly less intensive than the ν(C=O) band (1620–1640 cm^{-1}) and is more sensitive towards the exchange of free protons by deuterium (contribution of β(NH) or β(OH)) and towards the change of the substituent R^1. The amide-I band of these compounds either overlaps with the malonaldehyde ν(CO) band or lies at higher wavenumbers as an isolated band ($R^1 = CF_3, OC_2H_5$). With compound *Ib*, dependence of IR spectra on the polarity of the solvent and on the state was examined (Table IV). Since the character of the spectrum in the ν(CO) and ν(C=C) region does not markedly change in protic solvents or in the solid state, the *trans* form of the malonaldehyde grouping which is also incorporated into the cyclic structure *VIII*, remains intact in the media stated.

A seven-membered intramolecular hydrogen bonding analogous to that of compounds of the type *A* is also assumed on the basis of the IR spectrum (in accordance with interpretation of ^{1}H-NMR spectra) in the case of *p*-toluenesulfonamidomalonaldehyde (*II*) in which the role of the proton acceptor is taken over by oxygen atom of the sulfonamido group. Also compound *Io* apparently forms a seven-membered intramolecular hydrogen bonding, the proton donor being the benzylamino group ($X = C_6H_5CH_2NH$). However, as indicated by wavenumber values of the ν(NH) and amide-I band, this hydrogen bond is considerably weaker than with compounds of the type *A*.

The IR spectra of N-methylamidomalonaldehydes *Ig* and *Ih* (compounds of the type *B*) also support the occurrence of a strong intramolecular hydrogen bond, but

TABLE IV

Dependence of Infrared Spectra of Compounds *Ib* and *Ih* on Solvents

Compound	Solvent	ν(NH), ν(ND) free	ν(NH), ν(ND) assoc.	ν(OH) ν(OD)	Carbonyl region		
Ib	CCl_4 [a]	3 364 w	3 308 w	2 800 w, vbr	1 682 w	1 642 vs	1 632 vs, sh
	$CHCl_3$ [b]	3 365 m	3 305 w	2 850 w, vbr	1 680 m	1 634 vs, br	
	CH_3CN [b]	3 350 w, br	3 310 w, sh	[h]	1 680 w, sh	1 643 vs	1 635 vs, sh
	CH_3SOCH_3 [c]	[h]		2 585 m, vbr 1 691 m	1 677 m	1 639 vs, br	
	C_2H_5OH [d]	[h]		[h] 1 681 m	1 670 m	1 642 vs	1 633 vs
	[e]	3 290 s		2 610 w, br	1 669 s, sh	1 644 vs	1 631 s, sh
[$^2H_2$]-*Ib*	$CHCl_3$ [b]	2 494 m	2 459 w, sh	2 030 w, vbr	1 675 m	1 635 vs, br	
	CH_3OD [d]	[h]		[h]	1 679 m, sh	1 637 vs, br	
	D_2O [f]	[h]		[h]	1 670 m, sh	1 639 vs, br	
Ih	$CHCl_3$ [b]	—		2 790 m, vbr	1 683 m	1 648 s	1 611 vs, br
	CH_3SOCH_3 [g]	—		2 470 w, vbr	1 681 m,sh	1 643 s, br	
	C_2H_5OH [d]	—		[h] 1 695 w, sh	1 684 m, sh	1 649 s, br	1 633 s, sh
	[e]	—		2 640 m, vbr	1 660 s		1 588 vs, br
[^2H]-*Ih*	$CHCl_3$ [b]	—		2 180 w, vbr	1 683 m	1 648 m	1 611 s
	CH_3OD [d]	—		[h]	1 678 m	1 642 vs, br	
	D_2O [f]	—		[h]	1 666 m, sh	1 631 vs, br	

[a] $c < 2\%$; 0·1 mm. [b] c 2%; 0·1 mm. [c] c 4%; 0·044 mm. [d] c 6%; 0·025 mm. [e] Solid in KBr. [f] c 8%; 0·025 mm. [g] c 3%; 0·044 mm. [h] Absorption of the solvent or the region was not measured.

bands in the carbonyl region are dependent (contrary to the IR spectra of compounds of the type *A*) upon the solvent. The acetamido derivative *Ih* (Table IV) exhibits in chloroform the strongest band in the carbonyl region at about 1 600 cm^{-1} whereas in dimethyl sulfoxide and protic solvents, this strongest band is considerably shifted to higher wavenumbers and the spectra strikingly resemble those of the corresponding type *A* compounds. To our opinion, it may thus be inferred that the malonaldehyde moiety of the N-methyl derivatives *Ig* and *Ih* probably exhibits the *trans* form in protic solvents while the *cis* form is preferred in nonpolar solvents analogously to the proposal of George and Mansell[5] for the case of the unsubstituted malonaldehyde.

While the ^{1}H-NMR spectra and IR spectra of the above discussed derivatives allowed of an about identical interpretation, a somewhat different view is offered in the case of the remaining group of compounds (type *C*) in which the enolic group of malonaldehydes is replaced by a methoxy or dimethylamino group.

With the methoxy derivatives *Ii* and *Ij*, the compound *If*, and the dimethylamino derivatives *Il* and *Im*, the IR spectra exhibit marked inflexes on the ν(NH) bands or this band is at least strikingly broadened (compound *Ij*); this shape does not change even in dilute solutions (0·003M and 0·0015M). Also the amide-I or amide-II bands of these compounds are doubled or broadened. The attempted separation of the ν(NH) bands of compounds *Il* and *Im* (Table III) indicated that these bands may be split into two components, the integrated absorption intensities of which are approximately in an 1 : 1 ratio. Bands at lower wavenumbers exhibit a roughly twofold half-width. At concentrations above 0·01M, compounds *Il* and *Im* strongly associate. Bands due to stretching vibrations of associated NH groups exhibit a shape similar to that of ν(NH) bands of free NH groups, *i.e.*, with an inflex at lower wavenumbers. The structure of the ν(NH) band in the methoxy derivative *Ii* is even more complex; the shape of this band corresponds to superposition of three components. In tetrachloromethane solutions, the complex structure of all these bands is somewhat different.

The difference between the IR and ^{1}H-NMR spectra consists in the fact that the latter spectra (taken of course in more concentrated solutions) indicated the existence of conformers with the formamido derivative only (a different content of the minor component, about 20%, was recorded) while the two acetamido derivatives *Ii* and *Im* appeared homogeneous from the standpoint of conformation. Consequently we assume that the above mentioned shape of the ν(NH) bands does not suggest the occurrence of conformational forms on the acylamino groupings, *inter alia* because the amide-II bands are known to occur at about 1 500 cm^{-1} in the case of the *Z*-conformers only. With the open-chain structures of compounds of the type *C*, the IR spectra thus probably indicate a mixture of geometrical forms differring for example in stereochemistry on the double bond or conformation of functional groups (ref.[19]), these forms being in a rapid equilibrium from the standpoint of the NMR

time scale. It cannot be excluded that some of these forms exhibit a weak intramolecular hydrogen bonding between the amide portion and the acrolein portion of the molecule.

UV *Spectra*

The UV spectra of all the amidomalonaldehyde derivatives examined in the present work are summarised in Table V. The amidomalonaldehydes (compounds of the

TABLE V

Ultraviolet Spectra of Aminomalonaldehyde Derivatives, λ_{max} ($\varepsilon \cdot 10^{-3}$)

Compound	H_2O	0·01M-NaOH	0·01M-HCl	C_2H_5OH
Ia	267 (30·9)	267 (29·7)	251 (15·1)	269 (24·1)
Ib	267 (32·1)	267 (31·5)	251 (18·8)	269 (26·2)
Ic	265 (36·4)	267 (28·7)[a]	249 (22·1)	266 (28·9)
Id	226 (17·4)	226 (16·9)		226 (18·6)
	267 (30·7)	267 (30·7)	248 (20·8)	269 (27·4)
Ie	267 (27·6)	267 (29·3)	251 (15·9)	268 (23·4)
Ig	266 (30·0)	266 (29·6)	252 (15·8)	266 (23·3)
Ih	268 (30·0)	268 (30·0)	252 (15·8)	269 (29·2)
II	228 (15·8)	226 (14·5)	231 (20·3)	227 (15·8)
	267 (23·9)	269 (19·4)	250 (15·1)	267 (sh) (15·3)

	Acetonitrile		Cyclohexane	
Ia	243 (11·2)	264 (11·4)	248 (8·9)	268 (10·5)
Ib	246 (8·8)	270 (10·8)	250 (9·6)	270 (11·8)
Ig	245 (10·9)	263 (11·9)		
Ih	244 (12·1)	266 (9·3)		

	Ethanol			
If	252 (9·8)	*Il*	287 (30·5)	*Io* 287 (35·1)[b]
Ii	253 (17·0)	*Im*	288 (30·4)	
Ij	257 (21·0)	*In*	286 (30·4)	

[a] A slow saponification with the formation of aminomalonaldehyde takes place, resulting in a new band at about 300 nm. In 1M-NaOH, this saponification is completed in the course of about 30 min as indicated by λ_{max} 299 nm (28·7). [b] The same values were obtained in aqueous, alkaline, and acidic solutions.

types *A* and *B*) exhibiting an enolic group, were examined in four solvents, namely, in an aqueous solution, on 0·01M-NaOH, in 0·01M-HCl, and in ethanol. In all these media, identical positions of maxima as well as identical extinction coefficient values were recorded. The fundamental chromophoric group, the malonaldehyde system, is therefore the same in all the above compounds and is not affected by different amido groups as substituents. It may be inferred from accordance of band positions and extinction coefficient values in water and alkaline aqueous solution that compounds of the types *A* and *B* are in aqueous media completely dissociated under the measurement conditions (concentration, about $2 . 10^{-5}$). The spectra taken in ethanol differ only a little from those recorded in aqueous and alkaline solutions, the bands being somewhat broadened and the extinction coefficient values being consequently somewhat lower. On the other hand, all the spectra measured in acidic media exhibit a shift of bands towards about 250 nm and a marked decrease of intensity. Under conditions when the dissociation of the enolic proton is suppressed, there are obviously measured the spectra of undissociated forms that do not differ from each other to any considerable extent. The behaviour of *p*-toluenesulfonamidomalonaldehyde(*II*) in all the above mentioned solvents was analogous to that of the other compounds of the types *A* and *B*.

Two compounds of the type *A* (*Ia* and *Ib*) and the corresponding derivatives of the type *B* (*Ig* and *Ih*) were also examined in an aprotic solvent, namely, in acetonitrile. In this medium, all the four derivatives exhibit two broad overlapping bands, the band at the higher wavelength being most likely attributable to the dissociated form. Concerning the UV spectra of the above four compounds in cyclohexane, the measurement of compounds of the type *B* (*Ig* and *Ih*) failed because of the insufficient solubility of the test substances in this solvent; the UV spectra of compounds *Ia* and *Ib* (type *A*) resembled those taken in acetonitrile (Table V).

Compounds of the type *C* were measured in ethanol. The UV spectra of oxygen-containing compounds of the type *C* (*If*, *Ii*, *Ij*) lacking the enolic proton of the corresponding dialdehydes because of a covalent substitution, resembled the UV spectra of dialdehydes in the undissociated form (*i.e.*, taken in acidic media). The almost identical UV spectra of the dimethylamino derivatives *II*, *Im*, and *In* unambiguously

TABLE VI

pK_a Values of Amidomalonaldehydes

Ia	3·46	*Ig*	2·86	phenylmalonaldehyde[21]	4·40
Ib	3·55	*Ih*	2·88	methylmalonaldehyde[21]	4·99
Ic	2·97	*Ie*	3·66	triformylmethane[22]	2·01
Id	3·56	*II*	3·61		

point out the 3-dimethylaminoacrolein system as the responsible chromophoric group. Also the UV spectrum of the benzylamino derivative *Io*, differring slightly in the extinction coefficient value, indicates the same type of the chromophoric group.

pK_a *Values*

Table VI shows pK_a values of the present aminomalonaldehyde derivatives and some related compounds. The pK_a values of amidomalonaldehydes *Ia* to *Ie*, *i.e.*, compounds containing the —NH— group (type *A*), vary in the range 3·66–3·45 except for the trifluoracetamido derivative *Ic* (2·97). Their acidity is higher than that of methylmalonaldehyde or phenylmalonaldehyde but lower than that of triformylmethane. The influence of the substituent R^1 is in a qualitative accordance with expected results ($CF_3 > C_6H_5 > H > CH_3 > C_2H_5O$); a similar value (3·61) is also shown by *p*-toluenesulfonamidomalonaldehyde (*II*). It is of great interest to note the increased acidity of the N-methyl derivatives *Ig* and *Ih*. As it may be seen from comparison of the formyl derivatives (*Ia vs Ig*) and the acetyl derivatives (*Ib vs Ih*), the introduction of the N-methyl group results in a markedly increased acidity (by 0·60 and 0·68 of the pK_a unit, resp.).

According to the UV spectra, compounds *Ia* and *Ib* are in aqueous solutions completely dissociated and it cannot be thus assumed that the lower acidity of compounds *Ia* and *Ib* (when compared with the corresponding N-methyl derivatives) could be due to intramolecular hydrogen bonds as shown in structures *VIII* or *X*. As observed in connection with investigations on the electronic effect of amido groups on the benzene ring[20], the amido groups become more acidic by introduction of the N-methyl. We ascribe this effect to the formation of an angle between the plane of the aromatic ring and the plane of the amide system; the interferred conjugation results in a weaker mesomeric (electron-donor) effect while the induction (electron-accepting) effect remains in principle intact. An analogous situation is also assumed in the case of N-methylamidomalonaldehydes. The forcing out of the plane results in an increased acidity and occurrence of both conformers.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The UV spectra were measured on a Unicam SP 8000 apparatus.

The IR *spectra* were recorded in chloroform solutions on a Zeiss UR-20 apparatus; ν(NH) bands: $c = 0{\cdot}003$M, $d = 1$ cm; other bands: $c = 2\%$, $d = 0{\cdot}1$ mm. The ν(NH) bands separated on a HP-9830 computer, were measured in concentrations $c = 0{\cdot}0015$M ($d = 4$ cm) on a Perkin-Elmer 621 apparatus. Deuterations were performed by repeated additions of one drop of D_2O to chloroform solutions of the test substances and subsequent removal of the azeotropic mixture by distillation. In the case of substances sensitive to hydrolysis, CH_3OD was used instead of D_2O.

The thermodynamic dissociation constants were determined by potentiometric titration on a Beckman Research pH-Meter. The weighed substances were dissolved in 15·19 ml of redistilled carbon dioxide-free water and the resulting 0·05—0·01M solutions were titrated with 0·1M-KOH under a stream of purified, water-saturated nitrogen. The potassium hydroxide solution (free of potassium carbonate) was added in 0·1 to 0·05 ml portions (manostat Digi-Pet piston burette) and the pH value of the solution was recorded. From the above data (15 to 30 points), the pK_a value was calculated[23] for each point according to the standard computer procedure. Several independent runs were made for each test substance (general reproducibility, $\pm 0{\cdot}02$ pK_a).

Determination of distribution coefficients between dichloromethane and water. The weighed amount of the test substance was distributed at 22·5°C between the two phases and the concentration of the test substance in the aqueous solution was determined spectrophotometrically: *Ia* 0·20, *Ib* 0·46, *Ig* 0·01, *Ih* 0·01.

Thin-layer chromatography on ready-for-use Silufol UV_{254} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets afforded the following R_F values (acetone as eluant): *Ib* 0·65, *Ii* 0·15, *Ie* 0·7, *Ij* 0·57, *Ih* 0·1, *Ik* 0·47.

Formamidomalonaldehyde (*Ia*)

N,N-Dimethyl-N-(2-dimethylaminomethyleneamino-3-dimethylamino)prop-2-enylideneammonium perchlorate[2] (6 g; 0·02 mol) was added into 2M-NaOH (50 ml), the whole heated at 60°C for 4 h, and evaporated under diminished pressure. The residue was dried (80°C at 0·2 Torr), powdered, and introduced with stirring and ice-cooling into formic acetic anhydride obtained by a dropwise addition (with cooling) of 98% formic acid (30 ml) into acetic anhydride (60 ml), heating of the mixture at 50°C for 15 min, and cooling down. The whole mixture was stirred for 30 min with cooling and for 30 min without cooling, the acids removed at max. 40°C/0·2 Torr, and the residue dissolved in a small volume of water in the presence of sodium hydrogen carbonate. The aqueous solution was made alkaline to phenolphthalein with 2M-NaOH and the impurity removed by extraction with dichloromethane. The aqueous layer was filtered, the filtrate acidified to Congo paper with 1 : 1 sulfuric acid, and the product extracted with fifteen 30 ml portions of dichloromethane. The extracts were combined, the solvent evaporated, the residue dried in a desiccator over sodium hydroxide pellets, and then subjected to sublimation (the first small portion of the sublimate was removed). The sublimate was crystallised from benzene (16 ml) and resublimed. Yield, 1·2 g (52%) of compound *Ia*, m.p. 121·5—122·0°C. For $C_4H_5NO_3$ (115·1) calculated: 41·75% C, 4·38% H, 12·17% N; found: 41·80% C, 4·29% H, 12·06% N.

Ethoxycarbamidomalonaldehyde (*Ie*)

The aqueous solution of the crude sodium salt of aminomalonaldehyde obtained by heating N,N-dimethyl-N-(2-dimethylaminomethyleneamino-3-dimethylamino)prop-2-enylideneammonium perchlorate[2] (15 g; 0·05 mol) with 2M-NaOH (125 ml) at 60°C for 4 h and evaporating the liberated dimethylamine under diminished pressure, was treated with 4M-NaOH (75 ml) and chloroform (150 ml). A solution of ethyl chloroformate (75 ml) in chloroform (150 ml) was then added dropwise at 0°C to 5°C over 30 min. The whole mixture was stirred for 30 min, the organic layer separated, and the aqueous layer extracted with two 100 ml portions of chloroform. The organic solutions were combined, washed with about 20 ml portions of aqueous sodium hydrogen carbonate and water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was washed with light petroleum, dissolved in lukewarm ether (130 ml), the solution filtered with a small amount of active charcoal and anhydrous magnesium sulfate, the filtrate concentrated to the volume of about 50 ml, and the concentrate allowed to

deposit crystals. Yield, 3·8 g (48%) of compound *Ie*, m.p. 81—83°C. The sample for analysis was recrystallised from ether; m.p. 81—83°C. For $C_6H_9NO_4$ (159·1) calculated: 45·28% C, 5·70% H, 8·80% N; found: 45·37% C, 5·72% H, 8·89% N.

2-Ethoxycarbamido-3-ethoxycarbonyloxypropenal (*If*)

The procedure was analogous to the preparation of compound *Ie* but the combined chloroform extracts were not washed with water; the dried (anhydrous magnesium sulfate) extracts were then filtered, the filtrate was evaporated under diminished pressure, the residue dissolved in boiling ether, the solution filtered with a small amount of active charcoal, the filtrate concentrated, and the concentrate allowed to deposit crystals at 0°C. Yield, 40% of compound *If*, m.p. 85—86·5°C (subl.). For $C_9H_{13}NO_6$ (231·2) calculated: 46·75% C, 5·67% H, 6·06% N; found: 46·85% C, 5·70% H, 6·05% N.

2-N-Methylformamido-3-dimethylaminopropenal (*In*)

A mixture of the diperchlorate[2] *III* (4·11 g; 0·01 mol), potassium carbonate (15 g), water (75 ml), benzene (40 ml), and ethanol (20 ml) was heated at 65°C under a reflux condenser on a steam bath for 30 min with stirring, cooled down, and treated with saturated aqueous potassium carbonate (75 ml) and 2 : 1 benzene–ethanol solvent mixture (50 ml). The inorganic salts were filtered off and the organic layer of the filtrate was set aside. The aqueous layer was extracted with five portions of the above solvent mixture. The organic solutions were then combined, dried over anhydrous potassium carbonate, filtered, and the filtrate evaporated under diminished pressure. The residue was dissolved in hot benzene, the solution filtered with active charcoal while hot, and the filtrate evaporated. Yield, 1·25 g (80%) of compound *In*, m.p. 88·5—91·0°C. For $C_7H_{12}N_2O_2$ (156·2) calculated: 53·83% C, 7·74% H, 17·94% N; found: 54·12% C, 7·84% H, 17·89% N.

N-Methylformamidomalonaldehyde (*Ig*)

The derivative *In* (1·25 g; prepared from 4·11 g of the diperchlorate *III*) was dissolved in 2M-NaOH (20 ml) and the mixture heated with stirring at 60°C for 30 min. The liberated dimethylamine was evaporated under diminished pressure, the solution neutralised with hydrochloric acid and acidified with conc. hydrochloric acid (0·85 ml) in water (3 ml). The whole mixture was taken down on a rotatory evaporator under diminished pressure, the residue extracted with boiling benzene (300 ml), the solution filtered with active charcoal, the filtrate concentrated, and the concentrate allowed to deposit crystals. Yield, 260 mg (20%) of compound *Ig*, m.p. 95—98°C. The analytical sample was recrystallised from benzene; m.p. 98·5—100·5°C. For $C_5H_7NO_3$ (129·1) calculated: 46·51% C, 5·46% H, 10·85% N; found: 46·29% C, 5·45% H, 10·55% N.

N-Methylacetamidomalonaldehyde (*Ih*)

A stirred mixture of the diperchlorate *III* (2·05 g; 0·05 mol) and 8M-NaOH (30 ml) was heated at 80°C for 2 h, diluted with water (50 ml), and the liberated dimethylamine removed under diminished pressure. The remaining solution was neutralised to phenolphthalein with dilute (1 : 1) hydrochloric acid, taken down on a rotatory evaporator, the residue dried, and stirred overnight with a mixture of acetic acid (10 ml) and acetic anhydride (10 ml). The acidic portion was removed under diminished pressure at max. 50°C, the residue diluted with water (20 ml), made alkaline to phenolphthalein with 8M-NaOH, acidified with 1 : 1 aqueous sulfuric acid, and treated with 2M-H_2SO_4 (1 ml). The mixture was exhaustively extracted with dichloromethane and the inorga-

nic salts were repeatedly filtered off. Yield, about 70 mg (10%) of compound *Ih*, m.p. 130—132°C. For $C_6H_9NO_3$ (143·1) calculated: 50·35% C, 6·34% H, 9·79% N; found: 50·05% C, 6·31% H, 9·50% N.

2-Acetamido-3-methoxypropenal (*Ii*)

Ethereal diazomethane was added to a solution of compound *Ib* (126 mg; 1 mmol) in acetonitrile (10 ml), the mixture kept at room temperature for 10 min, evaporated, and the residue subjected to sublimation (the first small portion was removed). Yield, 97 mg (68%) of compound *Ii*, m.p. 115—116·5°C (acetone). For $C_6H_9NO_3$ (143·1) calculated: 50·35% C, 6·34% H, 9·79% N; found: 50·55% C, 6·38% H, 9·73% N.

2-Ethoxycarbamido-3-methoxypropenal (*Ij*)

The dialdehyde *Ie* (1·59 g; 0·01 mol) was processed analogously to the preparation of compound *Ii*. Yield (after crystallisation from tetrachloromethane and sublimation), 1·3 g (75%) of compound *Ij*, m.p. 91·5—93·0°C. For $C_7H_{11}NO_4$ (173·2) calculated: 48·55% C, 6·40% H, 8·09% N; found: 48·62% C, 6·46% H, 8·14% N.

2-N-Methylacetamido-3-methoxypropenal (*Ik*)

The reaction product of compound *Ih* (5 mg) with diazomethane was isolated in a sublimation apparatus as an oil and identified by mass spectroscopy on an A.E.I. MS 902 apparatus (high resolution measurements). The observed molecular ion value 157·07415 corresponds to the formula $C_7H_{11}NO_3$ (calculated: 157·0739). For the chromatographic behaviour *vide supra*.

2-Ethoxycarbamido-3-benzylaminopropenal (*Io*)

Benzylamine (120 mg) was added with cooling to a solution of the methoxy derivative *Ij* (173 mg; 1 mmol) in methanol (5 ml). The mixture was evaporated and the residue was crystallised from benzene. Yield, 190 mg (75%) of compound *Io*, m.p. 127·5—129·5°C. For $C_{13}H_{16}N_2O_3$ (248·3) calculated: 62·89% C, 6·50% H, 11·28% N; found: 62·65% C, 6·45% H, 11·30% N.

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