REACTIVITY OF TRIFORMYLMETHANE. I. REACTIONS OF TRIFORMYLMETHANE WITH SELECTED TYPES OF AMINO COMPOUNDS

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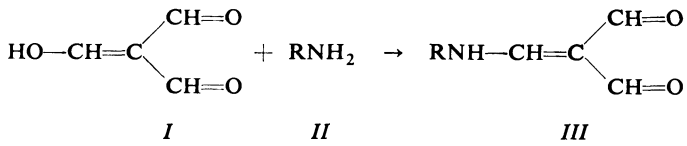
Dedicated to the memory of Professor František Šorm.

Reactions of triformylmethane with various types of amino compounds were investigated. Besides with ammonia, triformylmethane reacts spontaneously with primary amines, amino acids and their esters, urea and related compounds including carbamic acid derivatives. Reactions with amides of carboxylic and sulfonic acids require catalysis with Lewis acids. Primary products are aminomethylenemalonaldehyde derivatives *IIIa*—*IIIv*. Reactions of triformylmethane with excess of selected primary amines and two secondary amines (dimethylamine and morpholine) were also studied.

Triformylmethane (TFM), synthesized for the first time more than thirty years ago[1], has received increased attention during the last two years[2-5]. In the present communication we summarize our studies of reactions of triformylmethane (*I*) with various types of amino compounds; most of the results relate to derivatives with a primary amino group NH_2, the only exception being the secondary amines,mentioned in the end of this discussion.

The reaction of TFM (*I*) with ammonia (R = H, see Scheme 1) in an inert solvent, such as chloroform, proceeds smoothly already at room temperature under formation of product *IIIa* (for properties and ^{1}H NMR structural proof of this and further products see below).

The course of reaction of TFM with primary amines depends both on the character of the amine and the reaction conditions. Essential for a facile formation of compounds *III* is an equimolecular ratio of both reactants, or only a slight excess (e.g. 5%) of one of them. In the first reaction step triformylmethane forms a salt (pK_a of TFM amounts to 2·0, ref.[6]) which in some cases precipitates from the solution and which is gradually converted into the desired product *III*. In this manner we obtained compounds *IIIb*—*IIId* from aniline, tert-butylamine and benzylamine. Reaction with excess of amine results in formation of higher-substituted products.



I *II* *III*

II, III	R	*II, III*	R
a	H	*l*	$OH(COOCH_3)CH_2C_6H_5$
b	C_6H_5	*m*	$CH(COOCH_3)CH_2$—3-indolyl
c	$C(CH_3)_3$	*n*	$CONH_2$
d	$CH_2C_6H_5$	*o*	$CSNH_2$
e	CH_2COOH	*p*	$CONHCONH_2$
f	$CH(COOH)CH_3$	*r*	$COOCH_2CH_3$
g	$CH(COOH)CH_2C_6H_5$	*s*	$COOC(CH_3)_3$
h	$CH(COOH)CH_2COOH$	*t*	$COCH_3$
i	*p*-C_6H_4COOH	*u*	SO_2—*p*-$C_6H_4CH_3$
j	$CH(COOH)CH_2OH$	*v*	CH_2CONH_2
k	CH_2COOCH_3		

SCHEME 1

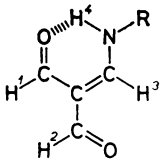
Already small excess of aniline leads to formation of the tris-derivative *IV*. No product containing two aniline moieties in the molecule has been detected even by TLC; however, as reported earlier[1], the bis-derivative can be obtained as the trimethinium salt *Va* when TFM is reacted with a solution of aniline in dilute hydrochloric acid. Contrary to aniline, tert-butylamine reacts with TFM to give the bis-derivative *VIa* even at elevated temperature; the structure *VIa* was confirmed by analysis, ^{1}H NMR spectrum and by conversion into the trimethinium salt *Vb*. From the reaction of TFM with excess of benzylamine we isolated also a bis-derivative which was assigned the structure *VIb* on the basis of its ^{1}H NMR spectrum.

A significant group of compounds reacting with TFM under formation of compounds *III* are amino acids, either free or in the form of esters. The reaction with free amino acids was performed in an aqueous medium: under these conditions the reaction took place not only with glycine, L-alanine, L-phenylalanine and L-aspartic acid but also with *p*-aminobenzoic acid and (with lower yields) D-serine leading to products *IIIe*–*IIIj*. Also the methyl esters of glycine, L-phenylalanine and L-tryptophane afforded the expected products (*IIIk*–*IIIm*).

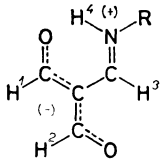
Reaction of TFM with urea and thiourea is very easy. After mixing aqueous solutions of the reactants, the crystalline products *IIIn* and *IIIo* separated within few minutes. Somewhat lower yields were obtained with biuret (product *IIIp*). Condensation of TFM with ethyl and tert-butyl carbamate (*IIr*–*IIs*) was successful as well, particularly the latter carbamate reacted very smoothly under formation of product

IIIs in a yield higher than 85%. In this, as well as in other cases, we observed a beneficial effect of azeotropic removal of water from reaction mixtures consisting in solutions of the reacting components in dichloromethane, benzene or toluene.

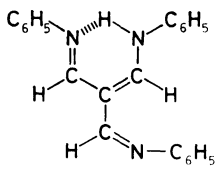
Compared with the above-mentioned cases, the reaction of TFM with amides of carboxylic and sulfonic acids is markedly slower, however, satisfactory results may be achieved by addition of a suitable Lewis-type catalyst, e.g. boron trifluoride etherate, zinc chloride etc., to a solution of both components in an appropriate inert solvent. In this manner we performed the reaction with acetamide (*IIt*) and *p*-toluenesulfonamide (*IIu*).



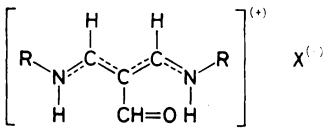
III A



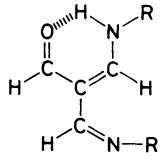
III B



IV



V a, R = C_6H_5; X = Cl
V b, R = $C(CH_3)_3$; X = ClO_4



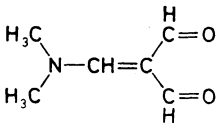
VI a, R = $C(CH_3)_3$
VI b, R = $CH_2C_6H_5$

As expected, the lower reactivity of a primary amide group $CONH_2$ than that of an amino group NH_2 manifested itself in the attempted condensation of TFM with glycine amide (*IIv*) containing in its molecule both these functionalities. The formation of product *IIIv* is the result of a selective attack by the more basic amino group.

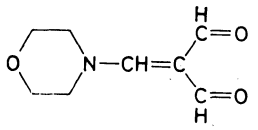
As observed already earlier[1], treatment of TFM with secondary amines leads mostly to salts. Within the framework of this study we describe a condensation of TFM with dimethylamine and morpholine under conditions that had been recommended already earlier[7,8], i.e. using a water-removing reagent, e.g. anhydrous sodium sulfate in toluene. We obtained thus the already known dimethylamino derivative *VII a* and the hitherto undescribed morpholino derivative *VII b*.

The structure of the synthesized products follows unequivocally from their ^{1}H NMR spectra. Almost all compounds of the type *III* show four characteristic signals proving the presence of two protons in two different formyl groups, a trisubstituted double bond methine proton and an NH proton. The downfield formyl

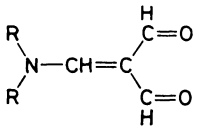
proton exhibits mostly long-range coupling ($^4J \approx 3-4$ Hz) with the methine proton whose signal is in most cases split by coupling with proton on the nitrogen atom (^3J(NH, CH) $\approx 12-16$ Hz); this splitting disappears on exchanging the NH proton for deuterium. No long-range coupling with the methine proton is observed with the second formyl proton, probably due to free rotation of this formyl group. On the basis of these facts the mentioned compounds are assigned the conformation *IIIA*.



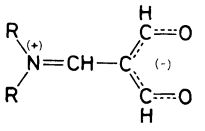
VII a



VII b



VII A



VII B

The ^{1}H NMR spectrum of compound *IIIa* is of interest. The presence of two protons on the nitrogen atom (R = H) is reflected in the mutliplicity of the methine proton signal and apparently also in the great solvent-sensitivity of the spectrum. The spectrum in CD_3CN is analogous to spectra of other compounds *III*, except that the methine proton signal is split by two nonequivalent protons on the nitrogen atom (^3J = 16 or 8 Hz), that are *trans*- and *cis*-oriented towards the methine proton (see conformation *IIIA*). The signals of both protons on nitrogen are extremely broad and their position depends on concentration. Spectrum of *IIIa* in CD_3SOCD_3 retains the basic features of the above-mentioned spectrum but the coupling of the methine proton with the cis NH proton disappears; this may be due to the enhanced mobility of this proton which is not stabilized by intramolecular hydrogen bonding. On the contrary, on addition of trifluoroacetic acid to this solution the methine proton signal reflects, besides interactions with both types of the NH protons (^3J = = 15·9 Hz and 9·1 Hz), also the long-range coupling with two protons (^4J = 1·5 Hz and 1·5 Hz), obviously belonging to the formyl groups. With increasing content of the acid the signals of the aldehyde protons broaden until they merge into one broad signal. We explain these spectral changes by an increasing population of the dipolar structure expressed by formula *IIIB*.

Structure of the products *IV*, *V* and *VI*, obtained in the reactions of TFM with

excess of amines, also follows from the ^{1}H NMR spectra. The structure of dimethylaminomethylenemalonaldehyde (*VIIa*) was discussed already earlier[5]; since ^{1}H NMR spectrum of the morpholino derivative *VIIb* corresponds to that of *VIIa*, the structure of the former (*VIIb*) can be described by the dipolar form *VIIB*. Whereas the groups on the nitrogen atom are not equivalent, the protons of both formyl groups appear as a single split by the long-range coupling with the methine proton.

As follows from the above-mentioned results, TFM is capable of reacting with various types of amino compounds, some of which are of key importance for processes occuring in the living matter. Some of the obtained products may be used as intermediates for further syntheses, particularly of heterocyclic compounds (*IIIn* and *IIIo*).

EXPERIMENTAL

The melting points were determined on a Koffer block and are uncorrected. NMR spectra were obtained with a Tesla BS-497 (100 MHz) instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. The spectra of compounds *IIIa*—*IIIv* are given in Table II. Triformylmethane (*I*) was prepared according to ref.[4] except that the required intermediate, 2-dimethylaminomethylene-1,3-bis(dimethylamino)propane bisperchlorate, was obtained as described recently[5]. Analytical samples were dried at 25 Pa for 6 h, unless stated otherwise. The analytical data for *IIIa*—*IIIv* are listed in Table I.

Aminomethylenemalonaldehyde (*IIIa*)

Triformylmethane (1·0 g, 10 mmol) was added with stirring to chloroform (100 ml) saturated with gaseous ammonia. After 4 h, anhydrous magnesium sulfate (1 g) was aded to the almost clear reaction mixture and the stirring was continued overnight. Charcoal (1 g) was added, the mixture was filtered and the solvent was evaporated in vacuo, leaving 0·95 g (95%) of crude crystalline product, m.p. 117—122°C. An analytical sample was obtained by low-temperature crystallization from methanol, m.p. 122—124°C.

Phenylaminomethylenemalonaldehyde (*IIIb*)

A solution of aniline (93 mg, 1 mmol) in acetonitrile (1 ml) was added dropwise to a stirred solution of TFM (100 mg, 1 mmol) in acetonitrile (1·5 ml). After 1 h the solvent was distilled off in vacuo and the residue was mixed with ether. The product *IIIb* was filtered; m.p. 105 to 106°C, yield 125 mg (71%).

Triformylmethane Trianil (*IV*)

Aniline (0·93 g, 10 mmol) was added to a solution of TFM (100 mg, 1 mmol) in dichloromethane (3 ml). After 15 min the reaction mixture contained only one product (TLC on Silufol in ethyl acetate). The solvent was evaporated in vacuo and the product *IV* was crystalized from methanol at −65°C, yield 110 mg (33%), m.p. 89—92°C. For $C_{22}H_{19}N_3$ (325·4) calculated: 81·20% C, 5·89% H, 12·91% N; found: 81·49% C, 5·91% H, 12·63% N. ^{1}H NMR spectrum ($CDCl_3$): 13·15 b, 1 H (N—H); 8·46 s, 2 H (2 × CH of the chelate ring); 8·08 s, 1 H (CH=N); 7·25 m, 15 H (3 × C_6H_5).

TABLE I

Analytical data of compounds *IIIa*—*IIIv*

Compound	Formula (M.w.)	Calculated/Found		
		% C	% H	% N
IIIa	$C_4H_5NO_2$ (99·1)	48·49 48·31	5·09 4·97	14·14 14·31
IIIb	$C_{10}H_9NO_2$ (175·2)	68·56 68·30	5·18 5·11	8·00 7·89
IIIc	$C_8H_{13}NO_2$ (155·2)	61·91 61·92	8·44 8·29	9·03 8·94
IIId	$C_{11}H_{11}NO_2$ (289·2)	69·83 69·81	5·86 5·81	7·40 7·26
IIIe	$C_6H_7NO_4$ (157·1)	45·86 46·16	4·49 4·52	8·91 9·08
IIIf	$C_7H_9NO_4$ (171·2)	49·12 49·19	5·30 5·34	8·18 8·26
IIIg	$C_{13}H_{13}NO_4$ (247·3)	63·15 62·87	5·30 5·42	5·67 5·87
IIIh	$C_8H_9NO_6$ (215·2)	44·66 44·63	4·22 4·17	6·51 6·40
IIIi	$C_{11}H_9NO_4$ (219·2)	60·27 60·61	4·14 4·23	6·39 6·48
IIIj	$C_7H_9NO_5$ (187·2)	44·92 44·62	4·85 4·78	7·48 7·53
IIIk	$C_7H_9NO_4$ (171·2)	49·12 49·40	5·30 5·37	8·18 8·27
IIIl	$C_{14}H_{15}NO_4$ (261·3)	64·36 64·61	5·79 5·43	5·36 5·65
IIIm	$C_{16}H_{16}NO_4$ (300·3)	63·99 63·61	5·37 5·41	9·33 9·06
IIIn	$C_5H_6N_2O_3$ (142·1)	42·26 42·33	4·26 4·13	19·71 19·82
IIIo[a]	$C_5H_6N_2O_2S$ (158·2)	37·97 37·93	3·82 3·73	17·71 17·98
IIIp	$C_6H_7N_3O_4$ (185·1)	38·93 38·88	3·81 3·92	22·70 22·41
IIIr	$C_7H_9NO_4$ (171·2)	49·12 49·14	5·30 5·18	8·18 8·32

TABLE I
(*Continued*)

Compound	Formula (M.w.)	Calculated/Found		
		% C	% H	% N
IIIs	$C_9H_{13}NO_4$	54·26	6·58	7·03
	(199·2)	53·94	6·53	7·21
IIIt	$C_6H_7NO_3$	51·07	5·00	9·92
	(141·1)	50·74	5·07	9·87
IIIu[b]	$C_{11}H_{11}NO_4S$	52·16	4·38	5·53
	(253·3)	51·87	4·30	5·50
IIIv	$C_6H_8N_2O_3$	46·15	5·16	17·94
	(156·1)	46·03	5·21	17·93

[a] Calculated: 20·20% S, found: 20·15% S; [b] calculated: 12·66% S, found: 12·56% S.

Tert-butylaminomethylenemalonaldehyde (*IIIc*)

Tert-butylamine (0·125 ml, 1·2 mmol) was added to a solution of TFM (100 mg, 1 mmol) in dichloromethane (2 ml). The immediately formed white precipitate (for isolation vide infra) dissolved slowly on further stirring at room temperature. After 3 h, another portion of dichloromethane (3 ml) was added together with anhydrous magnesium sulfate. After further 1 h the solution was filtered, the solvent distilled off in vacuo and the residue crystallized from cyclohexane. Yield 110 mg (71%) of *IIIc*, m.p. 63–70°C. An analytical sample was sublimed in vacuo at 25 Pa, m.p. 68–70°C.

Salt of Triformylmethane with tert-Butylamine

The precipitate, obtained as described in the preceding experiment, was isolated by filtration and dried; m.p. 103–108°C, yield 130 mg (75%). For $C_8H_{15}NO_3$ (173·2) calculated: 55·47% C, 8·73% H, 8·09% N; found: 55·22% C, 8·68% H, 8·11% N.

Tert-Butylaminomethylenemalonaldehyde tert-Butylimine (*VIa*)

a) A solution of triformylmethane (100 mg, 1 mmol) in tert-butylamine (1·5 ml, 14·3 mmol) was allowed to stand at room temperature for 24 h. The amine was evaporated, the residue dissolved in ethyl acetate (15 ml), the solution washed with water (3 × 2 ml) and dried. After evaporation of the solvent, the residue was crystallized from cyclohexane (2 ml), yielding 105 mg (50%) of *VIa*, m.p. 105–109°C.

b) Tert-butylamine (0·25 ml, 2·4 mmol) was added to a stirred mixture of TFM (100 mg, 1 mmol) and water (1 ml). From the originally homogeneous mixture a white solid began to precipitate. After 24 h, the product *VIa* was collected and dried; yield 180 mg (86%) of product, m.p. 107·5–110°C, identical with that obtained by procedure *a*). For $C_{12}H_{22}N_2O$ (210·3) cal-

TABLE II

^{1}H NMR parameters of compounds *IIIa*—*IIIv*. Chemical shifts in ppm (coupling constants in Hz). For other conditions see Experimental

Compound	Solvent	H-1	H-2	H-3	H-4	Other signals
IIIa	CD_3CN	9·77 d (3)	9·34 s	7·86 ddd (16; 8; 3)	[a]	—
IIIa	CD_3SOCD_3	9·67 d (3)	9·30 s	7·77 dd (16; 3)	[a]	—
IIIa[b]	CD_3SOCD_3	9·46[b]		7·77 ddt (16; 9; 1·5)	[a]	—
IIIb	$CDCl_3$	9·81 d (4)	9·59 s	8·25 dd (14; 4)	12·45 bs	7·34 m, 5 H (C_6H_5)
IIIc	$CDCl_3$	9·58 bs	9·42 s	7·97 d (16)	11·18 bs	1·43 s, 9 H ($(CH_3)_3C$)
IIId	$CDCl_3$	9·66 d (3)	9·43 s	7·85 d (16)	11·02 bs	7·35 m, 5 H (C_6H_5); 4·60 d, 2 H (CH_2, $^3J = 6$)
IIIe	CD_3SOCD_3	9·61 d (3)	9·31 s	7·87 dd (15; 3)	10·45 bs	4·28 d, 2 H (CH_2, $^3J = 7$)
IIIf	CD_3SOCD_3	9·64 d (3)	9·32 s	7·99 dd (15; 3)	10·70 bs	4·50 m, 1 H (CH); 1·48 d, 3 H (CH_3, $^3J = 7$)
IIIg	CD_3SOCD_3	9·57 d (3)	9·21 s	7·74 dd (15; 3)	10·55 m	7·25 m, 5 H (C_6H_5); 3·25 m, 2 H (CH_2); 4·74 m, 1 H (CH)
IIIh	CD_3SOCD_3	9·64 d (3)	9·33 s	7·98 dd (15; 3)	10·75 m	12·82 bs, 1 H (COOH); 4·68 m, 1 H (CH); 2·99 d, 2 H (CH_2, $^3J = 5$)
IIIi	CD_3SOCD_3	9·84 d (3)	9·52 s	8·50 dd (15; 3)	11·79 d (15)	12·93 b, 1 H (COOH); 7·61 m, 4 H (C_6H_4)
IIIj	CD_3SOCD_3	9·63 d (3)	9·33 s	7·99 dd (15; 3)	10·75 m	4·49 m, 1 H (CH); 3·83 m, 2 H (CH_2)
IIIk	CD_3SOCD_3	9·63 d (3)	9·32 s	7·88 dd (15; 3)	10·46 m	4·36 d, 2 H (CH_2, $J = 6$); 3·69 s, 3 H (CH_3O)

IIIl	CD_3SOCD_3	9·58 d (3)	9·23 s	7·74 dd (15; 3)	10·52 m	7·25 m, 5 H (C_6H_5); 4·83 m, 1 H (CH); 3·71 s, 3 H (CH_3O); 3·27 m, 2 H (CH_2)
IIIm	CD_3SOCD_3	9·57 d (3)	9·21 s	7·76 dd (15; 3)	10·62 m	10·96 bs, 1 H (NH of indole); 7·51—6·86 m, 5 H (indole); 4·84 m, 1 H (CH—CO); 3·70 s, 3 H (CH_3O); 3·34 m, 2 H (CH_2)
IIIn	CD_3SOCD_3	9·83 d (3)	9·52 s	8·26 dd (13; 3)	11·24 d (13)	7·87 bs, 7·53 bs, 2 × 1 H (NH_2)
IIIo	CD_3SOCD_3	9·86 d (3)	9·59 s	8·75 dd (13; 3)	11·90 d (13)	9·68 bs, 9·48 bs, 2 × 1 H (NH_2)
IIIp	CD_3SOCD_3	9·87 d (3)	9·61 s	8·28 dd (12; 3)	12·70 bs	10·20 bs, 1 H (NH); 6·98 bs, 2 H (NH_2)
IIIr	$CDCl_3$	10·02 d (3)	9·59 s	8·05 dd (12; 3)	11·07 bs	4·38 q, 2 H (OCH_2, $^3J = 7$); 1·38 t, 3 H (CH_3, $^3J = 7$)
IIIs	$CDCl_3$	10·01 d (3)	9·56 s	7·99 dd (13; 3)	10·96 bs	1·56 s, 9 H ($(CH_3)_3C$)
IIIt	$CDCl_3$	10·03 d (4)	9·59 s	8·18 dd (12; 4)	11·67 bs	2·33 s, 3 H (CH_3)
IIIu	$CDCl_3$	9·89 d (3)	9·53 s	[c]	[c]	7·96—7·28 m, 4 H (C_6H_4); 2·47 s, 3 H (CH_3)
IIIv	CD_3SOCD_3	9·61 bs	9·32 bs	7·87 d (15)	10·45 m	7·61 bs, 7·26 bs, 2 × 1 H (NH_2); 4·15 d, 2 H (CH_2, $^3J = 6$)

[a] Very broad concentration dependent NH_2 signals; [b] after addition of CF_3COOH; [c] overlapped with aromatic protons at δ 7·96—7·28.

culated: 68·53% C, 10·54% H, 13·32% N; found: 68·40% C, 10·50% H, 13·31% N. ^{1}H NMR spectrum ($CDCl_3$): 11·44 bs, 1 H (NH); 9·05 s, 1 H (CH=O); 8·47 bs, 1 H (CH=N); 7·52 bs, 1 H (CH=C); 1·33 s, 9 H ($(CH_3)_3C$); 1·26 s, 9 H ($(CH_3)_3C$).

1,3-Bis-tert-butylamino-2-formyltrimethinium Perchlorate (*Vb*)

Compound *VIa* was converted into perchlorate *Vb* by treatment with perchloric acid in ethanol; m.p. 173–174°C (ethanol–water 1 : 1). For $C_{12}H_{23}ClN_2O_5$ (310·8) calculated: 46·38% C, 7·46% H, 11·41% Cl, 9·01% N; found: 46·12% C, 7·34% H, 11·54% Cl, 9·07% N. ^{1}H NMR spectrum (CD_3SOCD_3): 10·87 b, 2 H (2 × NH); 9·66 bs, 1 H (CH=O); 8·37 d, 2 H (2 × CH, ^3J(CH, NH) = 16); 1·41 s, 18 H (2 × $(CH_3)_3C$).

Benzylaminomethylenemalonaldehyde (*IIId*)

A mixture of benzylamine (108 mg, 1 mmol), TFM (100 mg, 1 mmol) and dichloromethane (1 ml) was stirred for 2 h. The solvent was distilled off in vacuo and the solid residue was crystallized from methanol to give 110 mg (38%) of *IIId*, m.p. 115–116°C.

Benzylaminomethylenemalonaldehyde Benzylimine (*VIb*)

A mixture of benzylamine (355 mg, 3·3 mmol), dichloromethane (3 ml) and TFM (100 mg; 1 mmol) was set aside for 1 h. Another portion of dichloromethane (2 ml), followed by anhydrous sodium sulfate (0·6 g), was added to the turbid solution. After 24 h the mixture was filtered, the solvent evaporated in vacuo and the residue triturated with light petroleum for 3 h. The crystalline precipitate was collected; m.p. 44·5–46°C. For $C_{18}H_{18}N_2O$ (278·4) calculated: 77·57% C, 6·52% H, 10·06% N; found: 77·32% C, 6·55% H, 9·97% N. ^{1}H NMR spectrum ($CDCl_3$): 9·10 s, 1 H (CH=O); 8·53 bs, 1 H (CH=N); 7·47 bs, 1 H (CH=C); 7·27 m, 10 H (2 × C_6H_5); 4·58 bs, 4 H (2 × CH_2).

N-(Carboxymethyl)aminomethylenemalonaldehyde (*IIIe*)

Triformylmethane (100 mg, 1 mmol) was added to a solution of glycine (100 mg, 1·33 mmol) in water (1 ml). After 5 min, the stirred originally clear solution became turbid and deposited a crystalline precipitate which was filtered after 3 h; yield 100 mg (64%) of *IIIe*, m.p. 185–192°C. An analytical sample was obtained by dissolution of the crude product in water and crystallization from concentrated solution; m.p. 191–193°C.

(*S*)-N-(1-Carboxyethyl)aminomethylenemalonaldehyde (*IIIf*)

A mixture of L-α-alanine (178 mg, 2 mmol), TFM (200 mg, 2 mmol) and water (2 ml) was stirred; the clear solution obtained became geadually turbid and deposited a precipitate. After standing in a refrigerator overnight, the crude product *IIIf* was collected, yield 250 mg (72%), m.p. 158–161°C (water).

(*S*)-N-(1-Carboxy-2-phenylethyl)aminomethylenemalonaldehyde (*IIIg*)

L-Phenylalanine (166 mg, 1 mmol) was dissolved in a warm mixture of water (3 ml) and acetone (2 ml), the solution was cooled and mixed with TFM (100 mg, 1 mmol). The originally clear solution was stirred with occasional removal of acetone vapours with a stream of nitrogen. After about 30 min, the mixture began to deposit crystals which were collected after standing in a refrigerator overnight. Yield of *IIIg* 230 mg (93%), m.p. 143–144°C; an analytical sample was crystallized from water.

(*S*)-N-(1,2-Dicarboxyethyl)aminomethylenemalonaldehyde (*IIIh*)

Triformylmethane (100 mg, 1 mmol) was added to a solution of L-aspartic acid (133 mg, 1 mmol) in water (2·5 ml) and the mixture was stirred to homogeneity. After 3 h, the solution was evaporated in vacuo to dryness and the solid residue was crystallized from water to give 160 mg (74%) of *IIIh*, m.p. 186–190°C (decomp.).

N-(4-Carboxyphenyl)aminomethylenemalonaldehyde (*IIIi*)

A solution of TFM (100 mg, 1 mmol) in a tetrahydrofuran–water mixture (1 : 1, 2 ml) was added to a solution of *p*-aminobenzoic acid (138 mg, 1 mmol) in tetrahydrofuran (2 ml). The mixture immediately turned yellow and began to deposit yellowish crystals. After stirring for 3 h, the product was filtered and washed with tetrahydrofuran. Yield 170 mg (78%) of *IIIi*, m.p. 286–290°C.

(*R*)-N-(1-Carboxy-2-hydroxyethyl)aminomethylenemalonaldehyde (*IIIj*)

A solution of D-serine (105 mg, 1 mmol) and TFM (100 mg, 1 mmol) in water (1·5 ml) was stirred for 3 h and then set aside in a refrigerator overnight. The separated crystals were collected and dried; yield 50 mg (27%) of *IIIj*, m.p. 161–163°C.

N-(Methoxycarbonyl)methylenemalonaldehyde (*IIIk*)

Glycine methyl ester hydrochloride (628 mg, 5 mmol) was dissolved with stirring in water (5·5 ml) and TFM (500 mg, 5 mmol) was added immediately after dissolution. After 15 min, the clear solution began to deposit white precipitate and after stirring for further 30 min the product was filtered, washed with very small amount of water and cautiously with cold methanol (1 ml). Yield 750 mg (86%) of *IIIk*, m.p. 116–118°C.

(*S*)-N-(1-Methoxycarbonyl-2-phenylethyl)aminomethylenemalonaldehyde (*IIIl*)

Triformylmethane (100 mg, 1 mmol) was added to a stirred solution of L-phenylalanine methyl ester hydrochloride (216 mg, 1 mmol) in water (1·5 ml). After stirring for 1 h, the precipitate was filtered, washed with very small amount of water and then with cold methanol (1·5 ml). The product *IIIl* was crystallized from methanol (–25°C), m.p. 117–118°C; yield 220 mg (85%).

(*S*)-N-(1-Methoxycarbonyl-2-β-indolylethyl)aminomethylenemalonaldehyde (*IIIm*)

Triformylmethane (100 mg, 1 mmol) was added to a stirred solution of L-tryptophane methyl ester hydrochloride (255 mg, 1 mmol) in water (2 ml). The separated oily product crystallized on addition of methanol (0·5 ml) and after standing for 1 h was collected and crystallized from methanol; yield 280 mg (93%) of *IIIm*, m.p. 130–131°C.

Ureidomethylenemalonaldehyde (*IIIn*)

A mixture of urea (300 mg, 5 mmol), TFM (500 mg, 5 mmol) and water (8 ml) was stirred for 3 h and the separated product was filtered and washed cautiously with a small amount of water, yielding 350 mg (80%) of *IIIn*, m.p. 186–187°C (decomp.).

Thioureidomethylenemalonaldehyde (*IIIo*)

A solution of TFM (300 mg, 3 mmol) in water (6 ml) was added to a stirred solution of thiourea

(300 mg, 5 mmol) in water (6 ml). After 5 h, the yellow precipitate was filtered; yield 360 mg (76%) of *IIIo*, m.p. 189–194°C.

N-(Ureidocarbonyl)aminomethylenemalonaldehyde (*IIIp*)

A solution of biuret (103 mg, 1 mmol) and TFM (100 mg, 1 mmol) in water (4 ml) was stirred at room temperature overnight. The very thick reaction mixture was transferred onto a porous plate and the isolated compound was washed with water and dried. Yield 120 mg (65%) of *IIIp*, m.p. 180–182°C.

N-(Ethoxycarbonyl)aminomethylenemalonaldehyde (*IIIr*)

A solution of ethyl carbamate (468 mg, 5·25 mmol) and TFM (500 mg, 5 mmol) in dichloromethane (30 ml) was stirred for 3 h. Most of the solvent was distilled off (bath temperature about 60°C), dichloromethane was added up to the original volume and after 3 h the whole procedure was repeated. Next day the reaction mixture was filtered through a short column of silica gel, filtered with charcoal and the solvent was evaporated in vacuo. Crystallization of the residue from cyclohexane–benzene (3 : 2, 6 ml) afforded 0·60 g (70%) of *IIIr*, m.p. 90–92°C.

N-(Tert-butoxycarbonyl)aminomethylenemalonaldehyde (*IIIs*)

A solution of tert-butyl carbamate (2·46 g, 21 mmol) and TFM (2·0 g, 20 mmol) in dichloromethane (100 ml) was stirred for 1 h and then 10 ml of the solvent was distilled off under atmospheric pressure; this operation was repeated after further 6 h. Next day, anhydrous magnesium sulfate (2·5 g) was added and after 5 h the mixture was filtered with a small amount of charcoal. After evaporation of the solvent in vacuo the residue was crystallized from cyclohexane (about 50 ml; charcoal) to give 3·06 g of *IIIs*. Another crop (0·41 g) was obtained from the mother liquor; total yield 87%. M.p. 83–85°C. An analytical sample was sublimed at 60°C/25 Pa.

Acetylaminomethylenemalonaldehyde (*IIIt*)

A solution of acetamide (0·9 g, 15 mmol) and TFM (1·0 g, 10 mmol) in dichloromethane (30 ml) was set aside for 24 h, half of the solvent was distilled off, another methylene chloride was added up to the original volume and boron trifluoride etherate (3 drops) was added. After 24 h the whole operation was repeated. Next day the solvent was evaporated in vacuo, the residue was partitioned between ethyl acetate (50 ml, 25 ml, 10 ml) and small amount of water (5 ml, 3 ml, 3 ml). The organic layers were combined, dried over anhydrous magnesium sulfate, the solvent was evaporated in vacuo and the residue was crystallized from toluene (60 ml). Total yield 1·12 g (79%) of *IIIt*, m.p. 122–124°C.

p-Toluenesulfonaminomethylenemalonaldehyde (*IIIu*)

A mixture of *p*-toluenesulfonamide (2·14 g, 12·5 mmol), TFM (1·0 g, 10 mmol), three drops of boron trifluoride etherate and methylene chloride (50 ml) was allowed to stand overn:ght. The resulting turbid solution was mixed with anhydrous magnesium sulfate, set aside overnight and washed with water (2 × 100 ml). The product was taken up in 2·5% potassium hydrogen carbonate solution (100 ml, 25 ml), the combined extracts were filtered and acidified (to pH 3) with hydrochloric acid. The product was extracted with dichloromethane (2 × 50 ml), the extract was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. The residue was crystallized from benzene (10 ml) to give 1·5 g (59%) of *IIIu*, m.p. 134–138°C.

N-(Aminocarbonylmethyl)aminomethylenemalonaldehyde (*IIIv*)

Triformylmethane (100 mg, 1 mmol) was added to a stirred solution of glycinamide hydrobromide (155 mg, 1 mmol) in water (1 ml). The clear solution was stirred for 2·5 h and then set aside for 2 days in a refrigerator. The product *IIIv* was filtered, m.p. 178–191°C, yield 130 mg (83%). An analytical sample was crystallized from a small amount of aqueous methanol (1 : 1); m.p. 182–183°C (decomp.).

Dimethylaminomethylenemalonaldehyde (*VIIa*)

A mixture of dimethylamine (0·90 g, 20 mmol), toluene (10 ml), TFM (0·30 g, 3 mmol) and freshly calcined sodium sulfate (about 2·5 g) was stirred overnight, filtered with charcoal and the solvent was evaporated in vacuo. The obtained crystalline product (330 mg, 86%) was identical with the compound obtained in another way[1,5].

Morpholinomethylenemalonaldehyde (*VIIb*)

A mixture of morpholine (1·3 ml, 15 mmol), toluene (20 ml), TFM (300 mg, 3 mmol) and freshly calcined sodium sulfate (2·5 g) was treated similarly as described in the preceding experiment. Yield 480 mg (95%) of crystalline crude *VIIb*, m.p. 94–96°C. An analytical sample, m.p. 97 to 98°C, was obtained by crystallization from cyclohexanone–benzene (3 : 1). For $C_8H_{11}NO_3$ (169·2) calculated: 56·80% C, 6·55% H, 8·28% N; found: 56·72% C, 6·47% H, 8·31% N. ^{1}H NMR spectrum ($CDCl_3$): 9·50 d, 2 H (2 × CH=O, ^4J = 0·8); 7·56 bs, 1 H (CH=); 4·23 m, 2 H and 3·84 m, 6 H (H of morpholine ring).

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