SYNTHETIC REACTIONS OF DIMETHYLFORMAMIDE. XXV.*

PREPARATION OF DIMETHYLAMINOMALONALDEHYDE, 2-METHOXY-, 2-ETHOXY-, AND 2-DIMETHYLAMINOTRIMETHINIUM SALTS

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Formylation of 1,2-bis(dimethylamino)ethylene afforded the 2-dimethylaminotrimethinium salt *III*, the saponification of which with alkali led to dimethylaminomalonalaldehyde. Formylation of dimethylaminoacetaldehyde dimethylacetal and diethylacetal proceeds under the formation of 2-methoxy- and 2-ethoxytrimethinium salts. This observation confirms the formation *in situ* of olefinic derivatives in formylations of acetals and ketals of aliphatic carbonyl compounds with reagents of the Vilsmeier type.

In earlier papers[1-5] of this Series we have been interested in reactions of selected types of aliphatic compounds with formylating agents obtained from dimethylformamide by the action of carbonyl chloride or phosphorus oxychloride. In connection with these investigations we have reported preparation of numerous β-dialdehydes and their derivatives[1], *inter alia* various 1,3-bis(dimethylamino)trimethinium salts of the type *Ia*.

$$[(CH_3)_2N{-}CH{=}CR{-}CH{=}N(CH_3)_2]\,ClO_4$$

Ia, R = alkyl, aryl or halogen
Ib, R = OC_2H_5
Ic, R = OCH_3

As a continuation of investigations on aminomalonaldehyde, the simple synthesis of which has been recently worked out in our Laboratory[6], we have now prepared dimethylaminomalonaldehyde (*V*) with the use of 1,2-bis(dimethylamino)ethylene (*II*) as the starting compound (Scheme 1). Treatment of compound *II* with N,N-dimethylchloromethyleneammonium chloride[7] afforded 1,2,3-tris(dimethylamino)-trimethinium perchlorate (*III*). The alkaline saponification of the salt *III* led to 2,3-bis(dimethylamino)acraldehyde (*IV*) in the first step and to the alkali salt of dimethylaminomalonaldehyde in the second step. The amphoteric character of the aldehyde *V* manifests itself by the formation of salts with both acids and bases.

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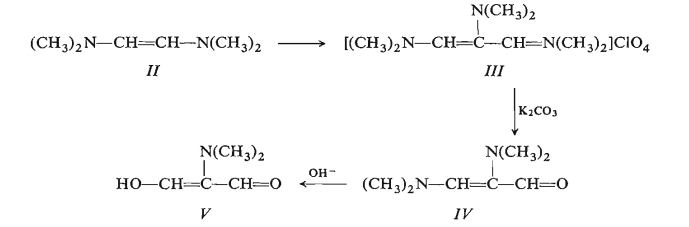
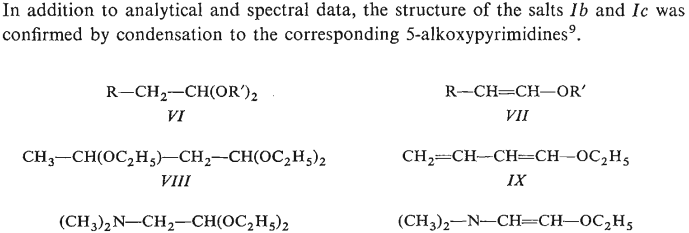


SCHEME 1

The starting 1,2-bis(dimethylamino)ethylene (*II*) has been in our preliminary experiments prepared by reaction of dimethylamine with chloroacetaldehyde[8]. It is however more advantageous to prepare first dimethylaminoacetaldehyde diethylacetal, saponify the latter compound by the action of hydrogen chloride in formic acid, and treat the liberated intermediary dimethylaminoacetaldehyde with dimethylamine.

An interesting contribution to elucidation of the mechanism of the earlier reported formylation reactions has been now obtained by formylation of dimethylaminoacetaldehyde diethylacetal. This reaction affords 77·5% yield of the 1,3-bis(dimethylamino)-2-ethoxytrimethinium salt *Ib*. Dimethylaminoacetaldehyde dimethylacetal reacts analogously, *i.e.*, under the formation of the 2-methoxytrimethinium salt *Ic*. In addition to analytical and spectral data, the structure of the salts *Ib* and *Ic* was confirmed by condensation to the corresponding 5-alkoxypyrimidines[9].



Formylations with agents of the Vilsmeier type are generally assumed to consist in addition of the electrophilic agent to the activated double bond or to a conjugated or aromatic system. In the first paper[1] of this Series, we have described a general synthesis of β-dialdehydes comprising formylation of dialkylacetals, *i.e.*, compounds lacking any double bond, by means of an agent obtained from dimethylformamide and carbonyl chloride. To explain the course of this and related reactions we have proposed that the first stage of the reaction between the dialkylacetal *VI* and the formylating agent consists in elimination of one molecule of the alkanol under the

formation of the vinyl ether *VII* the double bond of which at position β in respect to the alkoxyl group is highly reactive. The proposal of this mechanism was based on the structure of the product; we were aware of the circumstance that it remained to solve the problem of an actual formation of the double bond or involvement of some type of a concerted process, the alkanol elimination being accompanied by an attack of the agent at the vicinal carbon atom. A similar though somewhat more complex situation may be observed with 1,1,3-trialkoxybutanes[4] (*VIII*) which afford exclusively products of an attack at the terminal methyl group; the assumed intermediate is in this case represented by 1-alkoxybutadiene *IX*, resulting on removal of two alkanol molecules. The above mentioned finding confirms the formation *in situ* of activated intermediates in formylations of compounds of the appropriate type. A dimethylaminomalonaldehyde derivative would be formed from dimethylaminoacetaldehyde diethylacetal (*X*) if the elimination of ethanol and the attack of the formylating agent would occur simultaneously. The isolation of the ethoxymalonaldehyde derivative *Ib* as the reaction product is however regarded as a convincing proof of the involvement of 2-ethoxyvinyl-N,N-dimethylamine (*XI*) in the role of the formylation intermediate; in other words, an actual formation of the double bond occurs. From the two activating groups of the disubstituted ethylene, the influence of the ethoxy group is lower than that of the dimethylamino group (mesomeric effect) which consequently controls the further course of the reaction consisting in addition of the electrophilic cation of the formylating agent to that carbon atom which carries the ethoxyl group.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are uncorrected. Ultraviolet spectra were recorded on an Optica Milano CF 4 apparatus. Intrared spectra were measured on a Zeiss Jena UR-10 apparatus. NMR spectra were taken on a Varian HA-100 apparatus (deuteriochloroform; tetramethylsilane as internal standard).

1,2-*Bis(dimethylamino)ethylene* (II). Dimethylaminoacetaldehyde diethylacetal[10] (40·3 g; 0·25 mol) was added dropwise under cooling with ice into 85% aqueous formic acid (100 ml) and the resulting solution was saturated with gaseous hydrogen chloride. The reaction mixture was kept without cooling for 1 h, taken down on a rotatory evaporator to the consistence of a sirup which was added under ice-cooling and stirring into a mixture prepared by the addition of dimethylamine hydrochloride (61 g; 0·75 mol) into a precooled mixture containing saturated aqueous potassium carbonate (250 ml), benzene (250 ml) and potassium hydroxide (42 g). The whole was stirred for 1 hour, the benzene layer separated, and the aqueous phase stirred briefly with benzene (100 ml). The inorganic salts were filtered off, the benzene layer of the filtrate separated, and the aqueous layer extracted with benzene (100 ml). The benzene layers and extracts were combined, dried over magnesium sulfate and the benzene was evaporated under diminished pressure through a short column. Distillation of the residue afforded 21·7 g (75%) of compound *II*, b.p. 34—35°C at 13 Torr, n_D^{20} 1·4657 (reported[8,11], n_D^{20} 1·4643, 1·4658; b.p. 38—40°C/15 Torr, 35°C/13 Torr).

1,2,3-*Tris(dimethylamino)trimethinium perchlorate* (III). The diamine *II* (17·1 g; 0·15 mol) was added dropwise at 5—8°C to a solution obtained by mixing 2·2M chloroform solution of N,N-dimethylchloromethyleneammonium chloride[7] (150 ml) with chloroform (50 ml). The mixture

containing a yellow precipitate was refluxed (1 h), the resulting clear solution cooled down, poured onto ice, treated with light petroleum, the aqueous layer separated, and the organic phase washed twice with a little water. The aqueous phases were combined, neutralised with crystalline sodium carbonate, and the product precipitated by the addition of a solution of sodium perchlorate monohydrate (30 g) in water (15 ml). The mixture was cooled with ice for about 1 h, the precipitate collected with suction, washed cautiously with ice-cold water, dried, and crystallised from 150 ml of ethanol (active charcoal). Yield, 27·15 g (67%) of compound *III*, m.p. 122—123·5°C. For $C_9H_{20}ClN_3O_4$ (269·7) calculated: 40·08% C, 7·44% H, 13·15% Cl, 15·58% N; found: 40·45% C, 7·72% H, 13·26% Cl, 15·55% N. Ultraviolet spectrum (ethanol): λ_{max} 306 nm (log ε 4·45). Infrared spectrum (chloroform): ν 1 588 cm^{-1}. NMR spectrum: 2·58 s (6 H); 3·32 s (12 H); 7·42 s (2 H).

1,2-*Bis(dimethylamino)acraldehyde* (IV). The perchlorate *III* (0·5 g) was added under stirring to a mixture (preheated to 60°C) of potassium carbonate (1·75 g), water (7·5 ml), benzene (2·5 ml), and ethanol (2·5 ml) and the stirring was continued for 1 h. The mixture was then cooled down and added to an excess of saturated aqueous potassium carbonate. The product was extracted with 1 : 1 benzene–ethanol, the extract dried over anhydrous potassium carbonate, and distilled. Yield, 0·23 g (85%) of the hygroscopic compound *IV*, b.p. 90°C/0·4 Torr (bath temperature), n_D^{20} 1·5530. For $C_7H_{14}N_2O$ (142·2) calculated: 59·13% C, 9·92% H, 19·70% N; found: 59·05% C, 10·24% H, 19·60% N. UV spectrum (ethanol): λ_{max} 289 nm (log ε 3·81). IR spectrum (tetrachloromethane): ν(C=C—C=O) 1 665 m, 1 613 vs, ν(C—H(O)) 2 705, sh 2 680 cm^{-1}. NMR spectrum: δ 2·65 s (6 H); 3·21 s (6 H); 6·30 s (1 H); 8·78 s (1 H).

Dimethylaminomalonaldehyde (V). The perchlorate *III* (5·4 g; 0·02 mol) was treated with 2M-NaOH (50 ml), the mixture stirred at 60°C for 70 min, cooled down, and saturated with gaseous carbon dioxide. Saturated aqueous potassium carbonate solution was then added and the product (in the form of the potassium salt) extracted with 2 : 1 ethanol–benzene. The extracts were evaporated, the residue dissolved in a little water, the aqueous solution neutralised with dilute hydrochloric acid, evaporated, the residue dried, and the product extracted with dichloromethane. The extract was evaporated and the residue (2·15 g) crystallised from boiling benzene (90 ml). Yield, 1·8 g (78%) of the aldehyde *V*, m.p. 149°C. The analytical sample was purified by sublimation. For $C_5H_9NO_2$ (115·1) calculated: 52·16% C, 7·88% H, 12·17% N; found: 52·33% C, 7·81% H, 12·17% N. UV spectrum (ethanol): λ_{max} 262 nm (log ε 4·42). IR spectrum (chloroform): ν(C=C—C=O) 1 580, 1 642 cm^{-1}. NMR spectrum: δ 3·16 s (6 H); 8·59 s (2 H); 9·68 s (1 H).

The *hydrochloride* of compound *V* was obtained by passing gaseous hydrogen chloride into a dichloromethane solution of dimethylaminomalonaldehyde, recrystallisation of the precipitate from nitromethane, and sublimation; m.p. 168—176°C (decomp.). For $C_5H_{10}ClNO_2$ (151·6) calculated 39·61% C, 6·65% H, 23·39% Cl, 9·24% N; found: 39·89% C, 6·70% H, 23·22% Cl, 8·96% N.

1,3-*Bis(dimethylamino)-2-ethoxytrimethinium perchlorate* (Ib). A solution of dimethylformamide (75 ml) in chloroform (100 ml) was treated dropwise under ice-cooling with phosphorus oxychloride (50 ml; 0·55 mol) and then over about 40 min with dimethylaminoacetaldehyde diethylacetal (*X*; 40·3 g, 0·25 mol) in such a manner to keep the temperature at about 10°C. The mixture was refluxed for 4 h, cooled down, poured onto ice, diluted with light petroleum, the lower aqueous layer separated, and the organic phase extracted with two 15 ml portions of water. The combined aqueous portions were neutralised with crystalline potassium carbonate and the product precipitated with a solution of sodium perchlorate monohydrate (50 g) in water 25 (ml). The mixture was cooled with ice, the solid collected with suction, washed with ice-cold water, dried, and recrystallised from ethanol (220 ml). Yield, 50·9 g of compound *Ib*, m.p. 119—

121°C. For $C_9H_{19}ClN_2O_5$ (270·7) calculated: 39·93% C, 7·07% H, 13·10% Cl, 10·35% N; found: 39·56% C, 6·81% H, 13·15% Cl, 10·33% N. NMR spectrum δ 1·30 t (3 H); 3·30 s (6 H); 3·41 s (6 H); 3·72 quartet (2 H); 7·34 s (2 H).

1,3-*Bis(dimethylamino)*-2-*methoxytrimethinium perchlorate* (Ic). *A.* Dimethylaminoacetaldehyde dimethylacetal was formylated in the same manner as described in the preceding paragraph. When the reaction mixture was cooled to −15°C to −20°C, the oil solidified. Yield, 20% of the deeply coloured compound *Ic*, m.p. 87–89°C (ethanol).

B. The 2·2M chloroform solution of N,N-dimethylchloromethyleneammonium chloride[7] (30 ml) was diluted with chloroform (10 ml) and saturated with hydrogen chloride. A solution of dimethylaminoacetaldehyde dimethylacetal (4 g; 0·03 mol) in chloroform (4 ml) was then added, the reaction mixture refluxed for 4·5 hours, and processed similarly to the salt *Ib* except for the cooling to −10°C before filtration. Yield, 3·2 g (39%) of compound *Ic*, m.p. 81–89°C. The analytical sample was recrystallised from ethanol; m.p. 88·0–90·5°C. For $C_8H_{17}ClN_2$ (256·7) calculated: 37·43% C, 6·67% H, 13·81% Cl, 10·92% N; found: 37·74% C, 6·96% H, 13·75% Cl, 10·60% N.

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