

Products of the Reaction of Diethylmalonate with Formaldehyde and Methylamine

by

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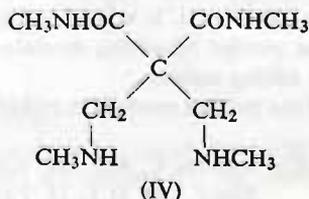
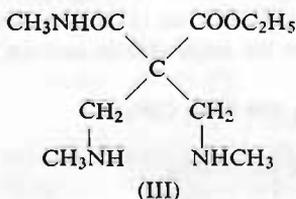
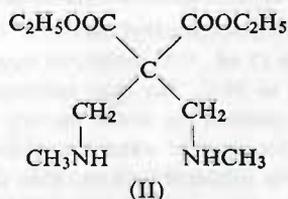
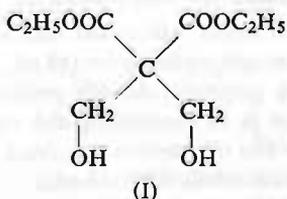
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Numerous experiments have so far shown that primary nitroparaffins on reaction with formaldehyde and primary amines or ammonia can yield various cyclic compounds. Tetrahydro-1,3-oxazine [1]—[9] and hexahydropyrimidine derivatives [10]—[11] are among the most common products. Derivatives of 1,5-diazacyclo-octane also can be obtained [2], [12]—[13].

At present we examined the products formed by reaction of ethyl malonate with formaldehyde and methylamine, in an attempt to obtain cyclic products similar to those formed from primary nitroparaffins under analogous experimental conditions. We were particularly concerned with obtaining tetrahydro-1,3-oxazine derivatives in view of the interest which they have aroused as potential drugs [14]—[17]. Ethyl malonate is known to react with formaldehyde in alkaline medium to form diethyl-2,2-di(hydroxymethyl)malonate (I) [18]. When diethyl malonate or substance (I) was made to react with formaldehyde in the presence of 1—2 moles of methylamine, diethyl 2,2-di(N-methylaminomethyl)malonate (II) was obtained.

In the presence of 4 and 6 moles of methylamine the methylamide (III) and di(methylamide) (IV) were formed, respectively.

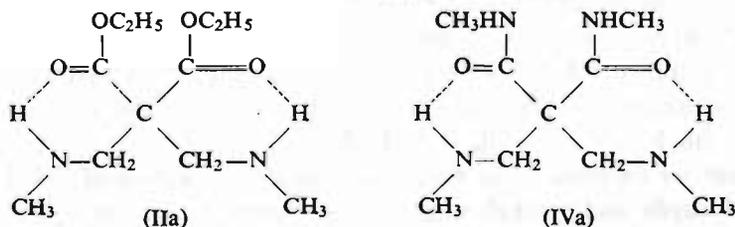
When methylamine was replaced by ammonia, no aminomethylation occurred, and the only identified product was hexamethylenetetramine.



The products (II)—(IV) formed N-nitroso derivatives which on heating with hydrochloric acid gave bases (II)—(IV). They also formed di-N-benzoyl derivatives under the action of benzoyl chloride.

All attempts to substitute only one hydroxyl group of (I) with a methylamino group failed to produce the required amino-alcohol, which could serve to obtain a tetrahydro-1,3-oxazine derivative. Also all attempts to produce hexahydropyrimidine derivatives by cyclization of (II) with an aldehyde (such as formaldehyde — in the form of paraformaldehyde — benzaldehyde or *p*-nitrobenzaldehyde) in benzene or toluene solution were unsuccessful: compound (II) was recovered unchanged from the solution. Also an attempt to cyclize product (III) by boiling it with a solution of *p*-nitrobenzaldehyde in benzene or toluene failed to produce the desired cyclization.

To explain this failure we suggest the existence of internal hydrogen bonds between C=O and NHCH₃ groups, viz. (IIa) and (IVa):



Our preliminary investigations on infrared absorption spectra seem to support the structures with hydrogen bonds. A more detailed study will be undertaken to verify the existence of the hydrogen bonds.

Experimental

Diethyl-2,2-di(hydroxymethyl)malonate

Diethyl-2,2-di(hydroxymethyl)malonate was prepared according to the method described in [18]. However, the oily product did not crystallize and was purified by filtering the solution in ethanol through a column filled with silica gel wetted by ethanol. Then the product was eluted with benzene. The solution in benzene was evaporated to yield crystals, m.p. 50—52°C. Twelve gram of the oil gave 3.8 g. of the crystalline product.

Diethyl di(N-methylaminomethyl)malonate (II) dihydrochloride

Diethyl 2,2-di(hydroxymethyl)malonate (11 g., 0.05 mole) was mixed with aqueous 30 per cent formaldehyde (5 ml., 0.05 mole) and aqueous 30 per cent methylamine (10 ml., 0.1 mole). The temperature rose to 58°C. The clear solution was kept overnight. An oily product precipitated. To complete the reaction the whole mixture was heated in an evaporating dish on a steam bath for c. 3 hours. This removed water almost completely. The oily residue was dried for a few days in a desiccator over sulphuric acid and then dissolved in alcoholic HCl (15 ml.).

After a few days the crystalline precipitate of the dihydrochloride of diethyl di(N-methylaminomethyl)malonate (II) formed. It was soluble in water and insoluble in alcohol, acetone, benzene and ether. It was purified by adding dropwise water to the suspension in acetone, filtration and precipitation by adding acetone.

The yield of the purified product, m.p. 164—167°C, was 3.1 g. (20%).

Analysis

C₁₁H₂₄O₄N₄Cl₂ requires C, 41.5; H, 7.5; N, 8.8; Cl, 22.0%;

found C, 41.5; H, 7.4; N, 8.7; Cl, 22.05%.

Dipicrate of (II)

The dihydrochloride of (II) (0.8 g.) was dissolved in water (3 ml.), neutralized with 20 per cent sodium hydrogen carbonate solution and the free base was extracted with ether. The ether was evaporated, the base was dissolved in ethanol and alcoholic solution of picric acid was added. The dipicrate was precipitated and crystallized from alcohol. The product (1.1 g.) had m.p. 176—179°C.

Analysis

$C_{23}H_{38}N_8O_{18}$ requires N, 16.0%;
found N, 16.0%.

Di-(N-nitroso)derivative of (II)

Dihydrochloride of (II) (2.0 g.) was dissolved in aqueous 20 per cent sodium nitrite (10 ml.). The yellow oily product was extracted with ether, the solution was washed with aqueous 10 per cent sodium hydrogen carbonate, finally with water and dried over sodium sulphate. The yield was 1.4 g. (74%).

Analysis

$C_{11}H_{20}N_4O_6$ requires N, 18.4%;
found N, 17.9%.

The oily product gave a positive Liebermann reaction. On heating with conc. hydrochloric acid it yielded a crystalline hydrochloride, identical with the dihydrochloride of (II).

Di(N-benzoyl)derivative of (II)

Dihydrochloride of (II) (0.5 g.) was suspended in benzoyl chloride (0.3 g.) and pyridine (10 ml.) was added. The temperature rose to 40°C. After the reaction had ceased, the suspension was warmed on a steam bath until complete solution of the precipitate (c. 10 min.) and was dissolved in water (30 ml.). Aqueous 10 per cent sodium carbonate was added to obtain $pH = 8.0$. The oily product was extracted with ether, the extract was dried over sodium sulphate.

Analysis

$C_{25}H_{30}N_2O_6$ requires N, 6.1%;
found N, 5.8%.

Monoethyl ester of di(N-methylaminomethyl)-malonic methylmonoamide (III) dihydrochloride Diethyl 2,2-di(hydroxymethyl)malonate (11.0 g., 0.05 mole) was mixed with aqueous (30%) formaldehyde (5 ml., 0.05 mole) and aqueous (30%) methylamine (20 ml., 0.2 mole). The temperature rose to 68°C and the oily product precipitated.

The mixture was left overnight and warmed on a steam-bath for 5 hrs. to evaporate water. The oily product was dried in a desiccator over sulphuric acid. Alcoholic HCl (20 ml.) was added and the dihydrochloride of (III) was collected after a few days. The product is soluble in water and insoluble in ethanol, benzene, acetone, and carbon tetrachloride.

It was crystallized from acetone and water as described above in the case of dihydrochloride of (II). The yield was 0.6 g., m.p. 166—190°C. It gave an oily N-nitroso derivative showing a positive Liebermann test.

Analysis

$C_{10}H_{23}N_3O_3Cl_2$ requires C, 39.3; H, 7.5; N, 13.7; Cl, 22.9%;
found C, 39.2; H, 6.9; N, 13.7; Cl, 22.3%.

Dipicrate of (III)

Dipicrate of (III) was obtained by adding saturated aqueous solution of picric acid to the dihydrochloride of (III). It was crystallized from water, m.p. 183—185°C.

Analysis

$C_{22}H_{27}N_9O_{17}$ requires N, 18.1%;
found N, 18.3%.

Free base (III)

Dihydrochloride of (III) (3.7 g.) was dissolved in water (4 ml.), neutralized with aqueous (10%) sodium hydrogen carbonate solution (15 ml.), extracted with ether and dried over sodium sulphate

After evaporation of ether, the oily product (2 g.) crystallized in time. It was purified by crystallization from alcohol. M.p. 132—135°C.

Analysis

$C_{10}H_{21}N_3O_3$ requires N, 18.1%;
found N, 18.4%.

Di(N-methylaminomethyl)malonic di(methylamide) (IV)

Dihydrochloride of (II) (2.0 g.) was dissolved in water (5 ml.) and aqueous 10 per cent sodium carbonate was added to the alkaline reaction. The oily free amine (II) was extracted with ether, the ether evaporated and the free amine warmed with aqueous (40%) methylamine (4 ml.). The solution was kept for a few days, heated on a steam-bath to evaporate water. The oily product (V) crystallized on standing. It is soluble in water, ethanol, chloroform and insoluble in acetone. Crystallized from benzene, it melted at 156—158°C, yield 0.9 g.

It gave a nitroso derivative showing the positive Liebermann test.

Analysis

$C_9H_{20}N_4O_2$ requires C, 50.0; H, 8.4; N, 25.9%;
found C, 50.1; H, 8.6; N, 25.4%.

The same product was obtained by reacting diethyl di(hydroxamethyl)malonate (11 g., 0.05 mole) with aqueous (30%) formaldehyde (5 ml., 0.05 mole) and aqueous (30%) methylamine (30 ml., 0.3 mole.).

Dihydrochloride of (IV)b

Dry product (IV) was dissolved in ethanolic HCl. Dihydrochloride of (IV) was crystallized from ethanol, m.p. 178—180°C.

Analysis

$C_9H_{22}N_4O_2Cl_2$ requires C, 37.4; H, 7.6; N, 19.7%;
found C, 37.0; H, 7.6; N, 20.1%.

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