[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

# Action of N-Chlorourethan on Derivatives of Diethyl Aminomalonate

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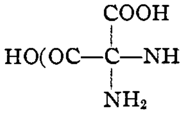
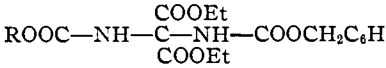
The action of N-chlorourethan on diethyl N-carbomethoxyaminomalonate gave, depending on conditions, diethyl N-carbomethoxy-N′-carboethoxydiaminomalonate, or *sym*-bis-(N-carbomethoxydicarboethoxy)-ethane. With diethyl N-carbobenzyloxyaminomalonate, N-chlorourethane yielded diethyl N-carbobenzyloxy-N′-carboethoxydiaminomalonate, ethyl hydrogen N-carbobenzyloxy-N′-carboethoxydiaminomalonate, *sym*-bis-(N-carbobenzyloxydicarboethoxy)-ethane or ethyl N-carbobenzyloxy-N′-carboethoxydiaminoacetate.

In the course of experiments on the synthesis of polydiaminomalonic acid (I), on which we shall report shortly, it was necessary to prepare compounds of the general formula II. Curtiss and Stracham[1] studied the action of urethan on diethyl mesoxalate which resulted in the formation of diethyl N-carboethoxyaminotartronate (III). The disubstitution product II in which two nitrogen atoms are linked to the central atom of malonic ester seems to be hitherto unknown.



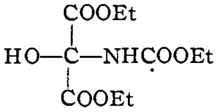
$$\mathrm{HO(OC{-}\underset{\underset{NH_2}{|}}{\overset{\overset{COOH}{|}}{C}}{-}NH)_nH}$$

I



$$\mathrm{ROOC{-}NH{-}\underset{COOEt}{\overset{COOEt}{C}}{-}NH{-}COOCH_2C_6H_5}$$

II R = benzyl or ethyl



$$\mathrm{HO{-}\underset{\underset{COOEt}{|}}{\overset{\overset{COOEt}{|}}{C}}{-}NHCOOEt}$$

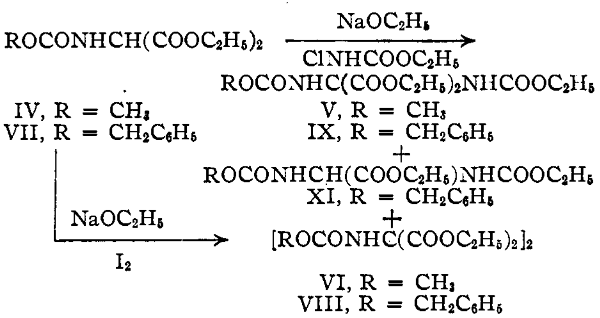
III

Experiments designed to obtain a compound of this type by condensation of diethyl mesoxalate with benzyl carbamate under various conditions were unsuccessful. It appears that in conformity with the results of Curtiss and Stracham only one mole of benzyl carbamate reacted.

The compounds required were obtained by the interaction of N-chlorourethan and derivatives of sodioaminomalonic ester. The action of one mole of N-chlorourethan on the sodium derivative of diethyl N-carbomethoxyaminomalonate (IV) gave in cold or boiling absolute ethanol diethyl N-carbomethoxy-N′-carboethoxydiaminomalonate (V) in 60% yield, while the action of 2 moles of chlorourethan produced in the cold mainly *sym*-bis-(N-carbomethoxy dicarboethoxy)-ethane (VI). The structure of VI was verified by the action of iodine on IV which yielded the same substance.

With diethyl N-carbobenzyloxyaminomalonate (VII) the course of action of N-chlorourethan varies depending on the experimental conditions. Equimolecular amounts of these components yielded in cold absolute ethanol di-(N-carbobenzyloxydicarboethoxy)-ethane (VIII) (10–20%), diethyl N-carbobenzyloxy-N′-carboethoxydiaminomalonate (IX) (30–40%), and ethyl hydrogen N-carbobenzyloxy-N′-carboethoxydiaminomalonate (X) (5%). When the reaction is carried out in boiling ethanol, but otherwise under conditions similar to the above, only the decarboxylation product ethyl N-carbobenzyloxy-N′-carboethoxydiaminoacetate (XI) was isolated. In the reaction of 2 equivalents of chlorourethan and 1 equivalent of diethyl N-carbobenzyloxyaminomalonate (VII) in cold ethanol, VIII was obtained in rapid reaction (80% yield), in addition to a small amount of diethyl N-carbobenzyloxy-N′-carboethoxydiaminomalonate (IX). The structure of VIII was confirmed in analogy to VI by the action of iodine on the sodium derivative of diethyl N′-carbobenzyloxyaminomalonate (VII), and that of the semiester X by partial hydrolysis of the diester IX.

TABLE I



An attempt to synthesize diethyl N-acetylaminomalonate directly from N-chloroacetamide and diethyl sodiomalonate yielded *sym*-tetracarboethoxyethane only.

## Experimental

**Diethyl N-Carbomethoxy-N′-carboethoxydiaminomalonate (V).**—To an ice-cold solution of 20 g. (84.5 millimoles) of diethyl N-carbomethoxyaminomalonate (IV)[2] in 60 ml. of absolute ethanol a solution of 1.95 g. (85 millimoles) of sodium in 25 ml. of absolute ethanol was added and then during 2 minutes with stirring and ice-cooling a solution of 10.42 g. (84.5 millimoles) of N-chlorourethan[3] in 30 ml. of absolute ethanol.[4] During the addition of chlorourethan an exothermic reaction sets in accompanied by the appearance of a sodium chloride precipitate. After refluxing for 14 hours, or, preferably, after allowing the mixture to stand for 2–3 days at room temperature, the ethanol was distilled off *in vacuo* and 200 ml. of water was added to dissolve the sodium chloride. At the same time V precipitated in crystalline form; it was filtered and washed with water; yield 16.4 g. (60%). After two recrystallizations from ethanol the m.p. was 113–114°.

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(1) R. E. Curtiss and E. K. Stracham, *Am. Chem. J.*, **33**, 399 (1911); f. A E. Martell and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941).

(2) M. Frankel, M. Harnik and Y. Levin, *Experientia*, **8**, 98 (1952).

(3) W. Traube and H. Gockel, *Ber.*, **56**, 387 (1923).

(4) In this and the following experiments the freshly prepared solution of N-chlorourethan in ethanol must be used immediately after its preparation, otherwise a violent decomposition of the chlorourethan occurs.

*Anal.* Calcd. for $C_{12}H_{20}N_2O_8$: C, 45.0; H, 6.2; N, 8.8. Found: C, 44.8; H, 6.2; N, 8.5.

***sym*-Bis-(N-carbomethoxydicarboethoxy)-ethane (VI). Procedure A.**—The experiment was conducted as above except that 20.84 g. (169 millimoles) of chlorourethan was added instead of one equivalent. A heavy crystalline precipitate appeared almost immediately. After 2–3 days at room temperature it was collected, washed with water free of chloride ion, and recrystallized from a large amount of ethanol, m.p. 162–163°, and the yield 12.3 g. (70%). From the mother liquor a small quantity of diethyl N-carbomethoxy-N′-carboethoxydiaminomalonate (V) was isolated.

The filtered original reaction mixture was distilled *in vacuo* to dryness. Two hundred ml. of water was added, and a further 4.1 g. (15%) of V was obtained.

**Procedure B.**—To a cold solution of 1.18 g. (5 millimoles) of diethyl N-carbomethoxyaminomalonate (IV) in 6 ml. of absolute ethanol a solution of 0.12 g. of sodium in 5 ml. of absolute ethanol was added, followed by 0.63 g. (5 millimoles) of iodine. The mixture was shaken for 30 minutes, after which a dilute solution of sodium bisulfite was added to complete decoloration. The precipitate was collected by filtration and recrystallized from a large amount of ethanol. The yield was 0.5 g. (42%), m.p. 161.5°. The substance gives no depression with a sample prepared by procedure A.

*Anal.* Calcd. for $C_{18}H_{28}N_2O_{12}$: C, 46.5; H, 6.0; N, 6.0. Found: C, 46.6; H, 5.9; N, 6.0.

It is slightly soluble in cold, but readily soluble in hot benzene, acetone and ethanol.

**Diethyl N-Carbobenzyloxyaminomalonate (VII).**—72.5 g. (0.425 mole) of carbobenzyloxy chloride was added with stirring dropwise to an ice-cooled mixture of 70 g. (0.4 mole) of diethyl aminomalonate, 64 ml. (0.8 mole) of pyridine and 320 ml. of water. The stirring was then continued for 30 minutes. The lower oily layer was separated and the solvent distilled off. The substance distilled at 201–207° (5–6 mm.), m.p. 32–33°, yield 70.2 g. (57%).

*Anal.* Calcd. for $C_{15}H_{19}NO_6$: C, 58.3; H, 6.2; N, 4.5. Found: C, 58.9; H, 6.1; N, 4.4.

For further synthetic work with this substance only highly purified crystalline preparations of it should be used.

***sym*-Bis-(N-carbobenzyloxydicarboethoxy)-ethane (VIII). Procedure A.**—To a solution of 5 g. (16.2 millimoles) of diethyl N-carbobenzyloxyaminomalonate (VII) in 20 ml. of absolute ethanol a solution of 0.38 g. (16.2 millimoles) of sodium in 8 ml. of absolute ethanol was added, followed by a solution of 4.0 g. (32.4 millimoles) of N-chlorourethan in 10 ml. of absolute ethanol (cooling and stirring). A heavy crystalline solid precipitated immediately which was collected after standing overnight at room temperature and washed with water until free of chloride; yield 4.0 g. (80%). After recrystallization from a large amount of ethanol the m.p. was 147–148°. The substance is sparingly soluble in ether and separates from hot benzene as a gel.

*Anal.* Calcd. for $C_{30}H_{36}N_2O_{12}$: C, 58.4; H, 5.8; N, 4.6. Found: C, 58.7; H, 6.1; N, 4.5.

The original ethanolic filtrate gave after the usual treatment a few milligrams of IX.

**Procedure B.**—The substance was prepared from equimolecular amounts of diethyl N-carbobenzyloxysodioaminomalonate and iodine as described in the preparation of the N-carbomethoxy analog VI, procedure B. The yield was 51%. No depression of its melting point occurred on mixing with the substance prepared according to procedure A.

**Diethyl N-Carbobenzyloxy-N′-carboethoxydiaminomalonate IX.**—To 5 g. (16.2 millimoles) of diethyl N-carbobenzyloxyaminomalonate (VII) in 20 ml. of absolute ethanol, a solution of 0.36 g. (16.2 millimoles) of sodium in 6 ml. of absolute ethanol was added. To this mixture during 30 seconds with stirring and cooling a solution of 2.62 g. (20.4 millimoles) of N-chlorourethan in 7.5 ml. of absolute ethanol was added. After 2–3 days at room temperature the solid di-(N-carbobenzyloxydicarboethoxy)-ethane (VIII) was collected and washed with water until free of chloride; m.p. 147–148°, yield 0.5–1.0 g. (10–20%).

The original filtrate was distilled *in vacuo* at 30° and 100 ml. of water was added. On cooling in ice the remaining oil solidified to colorless crystals on standing. After two recrystallizations from ethanol the melting point was 73–74°. The yield was 1.98–2.6 g. (30–40%).

*Anal.* Calcd. for $C_{18}H_{24}N_2O_8$: C, 54.5; H, 6.1; N, 7.1. Found: C, 54.5; H, 6.1; N, 7.4.

The aqueous filtrate yielded on acidification to congo red with concentrated hydrochloric acid a flaky precipitate (0.3 g., 5%) of ethyl hydrogen N-carbobenzyloxy-N′-carboethoxydiaminomalonate (X) which after two recrystallizations from ethanol melted at 149–150° (dec.).

**Ethyl Hydrogen N-Carbobenzyloxy-N′-carboethoxydiaminomalonate (X).**—To a solution of 4.9 g. (12.4 millimoles) of diethyl N-carbobenzyloxy-N′-carboethoxydiaminomalonate (IX) in 40 ml. of absolute ethanol a solution of 0.82 g. (14.6 millimoles) of potassium hydroxide in 40 ml. of absolute ethanol was added. After three days at room temperature the solution was filtered and the ethanol evaporated *in vacuo* over sulfuric acid. The remaining solid was dissolved in 30 ml. of water and extracted twice with ether. The colorless aqueous layer was acidified to congo red with concentrated hydrochloric acid and the precipitated substance was filtered with suction, washed well with water and dried *in vacuo* over sulfuric acid. After recrystallization from ethanol the solid gave no depression of melting point (150°) with the sample obtained as above.

*Anal.* Calcd. for $C_{16}H_{20}N_2O_8$: C, 52.2; H, 5.4; N, 7.6. Found: C, 52.7; H, 5.4; N, 7.6.

**Ethyl N-Carbobenzyloxy-N′-carboethoxydiaminoacetate (XI).**—To 12.5 g. (40.5 millimoles) of diethyl N-carbobenzyloxyaminomalonate (VII) in 50 ml. of absolute ethanol a solution of 0.93 g. (40.5 millimoles) of sodium in 15 ml. of absolute ethanol was added and then with cooling and stirring during one minute a solution of 5 g. (40.5 millimoles) of N-chlorourethan in 15 ml. of absolute ethanol was added. After refluxing for seven hours (protected from moisture with calcium chloride tube) the ethanol was removed *in vacuo* at 40° and 100 ml. of water was added. An oil with suspended solid precipitated. The oil was filtered and the voluminous ball-like aggregates of crystals (3 g., 23%) were recrystallized three times from ethanol, m.p. 136–137°. An additional amount (1–2 g., total yield 30–38%) crystallized out on keeping for two months.

*Anal.* Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.6; H, 6.2; N, 8.6. Found: C, 55.9; H, 6.2; N, 8.6.

**Formation of *sym*-Tetracarboethoxyethane from Diethyl Sodiomalonate and N-Chloroacetamide.**—To a solution of 5 g. (31.3 millimoles) of diethyl malonate in 15 ml. of absolute ethanol, a solution of 0.72 g. (31.3 millimoles) of sodium in 15 ml. of absolute ethanol was added, followed by a solution of 2.93 g. (31.3 millimoles) of N-chloroacetamide in 10 ml. of absolute ethanol (cooling and stirring). After two days at room temperature the solution was filtered and the ethanol removed *in vacuo* at 40°. To the residual oil 100 ml. of water was added. The oil gradually crystallized, and the solid after two recrystallizations from ethanol melted at 75°. It gave no depression of melting point with an authentic sample of *sym*-tetracarboethoxyethane; yield 1.5 g. (30%).

*Anal.* Calcd. for $C_{14}H_{22}O_8$: C, 52.8; H, 6.9. Found: C, 53.0; H, 7.1.

*Note.*—All melting points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England.

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