# XVI.—Tetraketopiperazine.

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THE formation of ring compounds by the action of sodium alkyloxides on various phenylglycinoacetic esters has been investigated by one of us (*Ber.*, 1900, 33, 2467; Trans., 1905, 87, 435). The ease with which alcohol is eliminated in these cases has led us to apply the reaction to esters of the type of ethyl oxamate, in the hope that by the elimination of a molecule of alcohol between an  $\cdot$ OR group and an  $\cdot$ NH<sub>2</sub> group, ring compounds containing an imino-group might be produced.

In general, the reaction might be expected to be as follows:

$$\mathbf{R}'' <_{\mathbf{CO}}^{\mathbf{CO} \cdot \mathbf{NH} | \mathbf{H}} \xrightarrow{\rightarrow} \mathbf{R}'' <_{\mathbf{CO}}^{\mathbf{CO}} > \mathbf{NH} + \mathbf{R} \cdot \mathbf{OH}$$

Ethyl oxamate would by such a reaction give rise to the threemembered cyclic compound, oxalimide,  $\stackrel{CO}{\underset{CO}{}}$  NH, the existence of which has not yet been clearly established. The only reference to this compound is in a paper by Ost and Mente (Ber., 1886, 19, 3228). The authors describe the preparation of oxalimide from oxamic acid by the action of phosphorus pentachloride, the yield being very small. It is described as crystallising in colourless, well developed monoclinic prisms. No reference is made to the melting point, and the results of analysis given apply equally well to a substance with twice the molecular weight, such as tetraketopiperazine. On boiling with water, the substance decomposed into oxamide and oxalic acid, and Ost and Mente thought it might be dioxaldiamide, CO·NH·CO CO·NH·CO' but they rejected this hypothesis on the ground that such a compound ought on hydrolysis to yield equal molecules of oxamide and oxalic acid, which they found not to be the case. This, however, is not to be expected, as any oxamide formed by the hydrolysis of the parent substance would, in its turn, be equally liable to saponification to oxamic and oxalic acids. We found that during hydrolysis of tetraketopiperazine, ammonia was evolved, and that the relative

proportions of the products depended on the time of reaction and on the concentration of the hydrolyser.

Ost and Mente supposed that the simple oxalimide was obtained by them and that this reacted with water to form oxalic acid and ammonia; the latter then reacted with more oxalimide to form oxamide. It seems improbable that a compound of the configuration of oxalimide would have the stability ascribed to it by these authors. The present paper contains an account of the preparation and properties of tetraketopiperazine, and there seems to be but little doubt that this is the substance which they obtained and which is described in textbooks as oxalimide. Further, their work has recently been repeated,\* and no trace of either oxalimide or tetraketopiperazine could be detected.

We first applied our method to methyl succinamate; this, on treatment with sodium alkyloxide in benzene solution, lost a molecule of alcohol and gave succinimide,

although in no great quantity.

In the case of ethyl malonamate, no ring formation took place as far as the main reaction is concerned, but the preferential saponification of the carboxyalkyl group in regard to the amino-group was brought about. Malonamic acid was not, however, isolated, but an acid resulting from the loss of one molecule of water from two molecules of the malonamic acid :

The use of theoretical amounts of sodium alkyloxides in dry benzene solutions seems to be a method of general application for the preferential saponification of carboxyalkyl groups occurring in the same compound with acid amide groups. In the ordinary way, a •CO•NH, group is readily saponified by alkali and always more easily than an accompanying 'CO<sub>2</sub>R group. Thus, in the case of ethyl oxamate, treatment with caustic soda causes an evolution of ammonia in the cold. Using the theoretical amount of sodium ethoxide in benzene solution, a good yield of sodium oxamate is obtained. We believe this method will be found to be of general application. In addition to oxamic acid, the latter reaction yields, after treatment with water, filtration and acidification with hydrochloric acid, a substance which analysis showed to have the formula  $C_4H_2O_4N_2$  and a molecular weight of 142. This is the dioxaldiamide of Ost and Mente, or tetraketopiperazine. A better yield is obtained if ethyl oxamate is treated directly with the theoretical amount of sodium ethoxide in absence of

<sup>\*</sup> The work has been carried out in these laboratories by Dr. A. W. Titherley and Dr. A. A. Hall in connexion with the attempted synthesis of oxalimide, and they inform us that their results were entirely negative.

benzene. We have also obtained the substance by the condensation of oxamide with ethyl oxalate in presence of sodium ethoxide:

$$\begin{array}{cccc} \text{CO·NH} & \text{H} & \text{C}_2\text{H}_5\text{OOC} \\ \text{CO·NH} & \text{H} & \text{C}_2\text{H}_5\text{OOC} \end{array} \longrightarrow \qquad \text{NH} < \begin{array}{c} \text{CO·CO} \\ \text{CO·CO} \end{array} > \text{NH}.$$

Light is thrown on the configuration of this compound by the fact that it forms a monohydrazone, mono- and di-sodium salts, and a di-silver salt; we were not able to prepare a pure mono-silver salt.

Cold sodium hydrogen carbonate acts on the substance with effervescence to form a white mono-salt; the di-salt is obtained by the use of sodium hydroxide, but the action in this case is complicated by the fact that hydrolysis is concurrent, and we could only obtain the pure salt by using the alkali in the form of the theoretical amount of sodium alkyloxide, all moisture being carefully excluded. These reactions point to the probability of the existence of one hydroxyl group in the molecule reacting directly with sodium hydrogen carbonate to form a mono-sodium salt, and to the possible presence of a second hydroxyl group by tautomeric rearrangement between the CO and NH groups under the influence of stronger alkali. The substance has thus probably the following constitution :

$$N \ll_{CO--CO}^{C(OH) \cdot CO} NH.$$

This formula shows one of the ketonic groups to be different in nature from the others, and this may account for the formation of a monohydrazone. The yield of sodium salt obtained in the preparation of the substance shows the salt to be dibasic. We purpose investigating the reduction products of this substance, the action of alkyl iodides on the sodium and silver salts, and the products of the interaction which takes place with aniline.

#### EXPERIMENTAL.

Succinimide from Methyl Succinamate.—0.68 gram of sodium wire (1 atom) was placed in 100 c.c. of dry benzene, and dissolved in rather more than 1.1 gram (1 mol.) of methyl alcohol by warming on the water-bath. 0.4 gram of methyl succinamate (1 mol.) was added, and the mixture heated on the water-bath for two hours and allowed to cool. Water was then added and the aqueous part separated from the benzene, which was extracted several times with water.

The benzene portion left no residue on evaporation. The aqueous solution was shaken with a little other to remove benzene, and air was bubbled through to remove benzene and ether. The solution, which was slightly alkaline, was acidified with hydrochloric acid and evaporated on the water-bath. The crystalline residue was dried over sulphuric

acid, ground, and extracted three times with alcohol quickly raised to the boiling point. The alcoholic solution gave, on evaporation, a white crystalline solid, which after recrystallisation from absolute alcohol melted at 124° (succinimide m. p. 125°). The yield was small, but the following reaction had evidently taken place to some extent:

$$\begin{array}{ccc} \mathrm{CH}_{2} \cdot \mathrm{CO} \cdot \mathrm{NH} \stackrel{\mathrm{H}}{\mathrm{H}} \\ \mathrm{CH}_{2} \cdot \mathrm{CO} \quad \mathrm{OCH}_{3} \end{array} \longrightarrow \begin{array}{ccc} \mathrm{CH}_{2} \cdot \mathrm{CO} \\ \mathrm{CH}_{2} \cdot \mathrm{CO} \end{array} \\ \mathrm{NH} + \mathrm{CH}_{3} \cdot \mathrm{OH}. \end{array}$$

Action of Sodium Ethoxide on Ethyl Malonamate.—Ethyl malonamate was prepared (Ber., 1895, 28, 479) by the action of a slow stream of hydrochloric acid gas on a well-cooled mixture of ethyl alcohol and ethyl cyanoacetate, and subsequent decomposition by heat of the hydrochloride of iminomalonic ester which is produced. A certain amount of ammonium chloride was formed, and the pure ester was obtained by extracting the product with acetone and allowing the solution to evaporate slowly. The resulting oil crystallised readily on cooling and stirring, and the ester melted at  $49-50^{\circ}$ . Thirteen grams were obtained from 25 grams of ethyl cyanoacetate.

(a) Sodium Ethoxide and Ethyl Malonamate in Benzene Solution.— 2.3 grams (1 atom) of sodium wire were suspended in 100 c.c. of dry benzene and dissolved in 4.6 grams of ethyl alcohol by the aid of heat. After cooling, 13.1 grams (1 mol.) of ethyl malonamate in benzene solution were added, and the whole allowed to stand overnight. The mixture was then heated on the water-bath for two hours, cooled, and the solid which had separated was filtered and dried. Yield about 16.2 grams.

In this and all other similar reactions a deep indigo-blue colour developed, which only disappeared on the addition of water.

The benzene portion was added to iced water, but no precipitation took place and the water remained neutral and colourless. The benzene left no residue on evaporation.

The solid product was white and almost completely soluble in water, from which a buff-coloured substance was precipitated by dilute hydrochloric, though not by acetic acid. The bulk was treated with water, the residue separated, and on adding dilute hydrochloric acid to the filtrate a pale brown amorphous precipitate was obtained; the product burnt without melting on platinum foil, leaving a very slight residue. The yield was 7.2 grams. This substance dissolves readily in warm methyl alcohol, from which it separates as a crystalline powder on cooling; there is some slight decomposition as the mother liquor assumes a reddish tint. It is insoluble in ether, benzene or water, but dissolves readily in aqueous sodium hydrogen carbonate with effervescence. Ammonia was evolved on heating the substance. A neutral solution gave a yellow precipitate with silver nitrate, reduction taking place on warming; salts of copper, lead, and mercury were also obtained, but barium chloride only gave a precipitate on boiling.

The crude product was crystallised from aqueous methyl alcohol.

0.1825 gave 23.2 c.c. moist nitrogen at  $16^\circ$  and 739 mm. N=14.40.

 $C_3H_5O_3N$  requires N = 13.58 per cent.

 $2C_3H_5O_3N - H_2O$  requires N = 14.89 per cent.

Titration with baryta solution  $[1 \text{ c.c.} = 0.00822 \text{ Ba}(\text{OH})_2]$ .

0.1065 required 6 c.c. Equivalent = 185.07.

0.1016 , 5.6 c.c. , = 189.6.

Titration with sodium hydroxide solution (1 c.c. = 0.0040 NaOH).

0.1021 required 5.3 c.c. Equivalent = 190.8.

Mean of three results = 188.49.

 $C_3H_5O_3N$  (Malonamic acid) requires equivalent = 206.

 $2C_{3}H_{5}O_{8}N - H_{2}O$  requires equivalent = 188.

It has been found impossible to hydrolyse ethyl malonamate to malonamic acid by any of the usual methods. Malonic acid is the chief substance obtained together with some decomposition products.

(b) Action of Sodium Ethoxide on Ethyl Malonamate in Absence of Benzene.—0.72 gram of sodium (1 atom) was treated with just sufficient alcohol to convert the metal into sodium ethoxide, and while the latter was still molten 3.9 grams (1 mol.) of ethyl malonamate were added. Reaction appeared to take place immediately. The mixture was heated on the water-bath for half an hour and afterwards in a paraffin bath at 150° for one hour. After cooling it was treated with water, in which it dissolved to a yellow solution, leaving only a trace of insoluble residue. The solution was filtered and acidified with hydrochloric acid, when a buff-coloured precipitate was obtained; this was filtered, washed with cold water until free from chloride, and dried in a vacuum. Yield 0.75 gram.

The product burnt completely on platinum foil, leaving no residue. It dissolved with effervescence in cold aqueous sodium hydrogen carbonate and was reprecipitated on adding hydrochloric acid to the solution. In all its properties it resembled the substance obtained by method (a) in benzene solution.

The acid filtrate was neutralised with sodium carbonate solution, evaporated to a small bulk, and then allowed to stand over concentrated sulphuric acid in a vacuum. A red substance separated, which appeared to be similar to the product obtained from the methyl alcoholic solution after recrystallising the acid. This substance is being further investigated.

# Action of Sodium Ethoxide on Oxamethane.

(a) In Benzene Solution.—3.93 grams of sodium wire (1 atom) were suspended in 100 c.c. of dry benzene and just sufficient absolute alcohol added to convert the metal completely into sodium ethoxide. Twenty grams of oxamethane (1 mol.) were then added, and the mixture was boiled for two hours on the water-bath. Some solid separated which was filtered off. The benzene gave on evaporation a small amount of unchanged oxamethane.

The solid product was treated several times with cold water, when most of it dissolved; the residue consisted of the sodium salt of tetraketopiperazine as described under method (b). The solution was neutralised with aqueous sodium hydrogen carbonate and concentrated on the water-bath. On adding absolute alcohol to the cold solution a voluminous white precipitate was obtained, which was filtered and dried in a vacuum. This sodium salt evolved ammonia when treated with caustic soda in the cold, thus pointing to the probability of its being sodium oxamate.

0.1993 gave 0.1251 Na<sub>2</sub>SO<sub>4</sub>. Na = 20.32.

0.1149 gave 12.7 c.c. moist nitrogen at 23° and 761 mm. N = 12.47. C<sub>2</sub>H<sub>2</sub>O<sub>3</sub>NNa requires Na = 20.72; N = 12.61 per cent.

Thus the reaction in benzene solution yields principally sodium oxamate.

(b) Direct Action in Absence of Benzene.—3.9 grams of sodium (1 atom) were dissolved in just sufficient absolute alcohol to convert the metal into sodium ethoxide. After cooling, 20 grams of oxamethane (1 mol.) were added and the mixture heated in the paraffin bath. At  $125-130^{\circ}$  a violent reaction took place; the mixture became pale brown and alcohol was evolved. This was allowed to escape in order to prevent any hydrolysing action taking place. After heating at  $140^{\circ}$  for about one hour, the mass was cooled and treated several times with hot benzene in order to extract oxamethane, of which a small quantity remained unchanged. The product was then treated with cold water, in which it was only very slightly soluble, filtered, washed with water and alcohol, and dried. The weight of dry sodium salt obtained was 29 grams. (Theory for disodium tetraketopiperazine = 33.4 grams.)

It is a pale yellow powder, only sparingly soluble in cold water, and is decomposed when treated with hydrochloric acid, sodium chloride being formed, together with a substance which on analysis gave figures corresponding to tetraketopiperazine.

The latter substance burnt on platinum foil without melting and left a slight ash which gave an alkaline reaction towards litmus. It did not melt in a capillary tube, but slowly blackened above 250°.

It was insoluble in most organic solvents, but dissolved fairly readily in boiling glacial acetic acid, from which it crystallised in small, almost colourless monoclinic prisms. It dissolved with effervescence in warm aqueous sodium hydrogen carbonate, the sodium salt being precipitated.

The latter appears to be more insoluble than the free tetraketone; the potassium salt is more soluble.

For analysis the recrystallised product was heated for three hours at  $110^{\circ}$  in an air oven, in order to remove any traces of acetic acid.

0 1855 gave 0 2312 CO<sub>2</sub> and 0 0421 H<sub>2</sub>O. C = 33.99; H = 2.52.

0.1819 , 32 c.c. moist nitrogen at  $21^{\circ}$  and 767 mm. N = 20.22.

0.1828 , 32.1 c.c. , , , , 22° , 774 mm. N = 20.26.

 $\rm C_4H_2O_4N_2$  requires  $\rm C=33.80$  ;  $\rm H=1.40$  ;  $\rm N=19.71$  per cent.

The numbers obtained indicate that the substance was not quite pure, but recrystallisation was difficult owing to its insolubility. It is possible that boiling with acetic acid brings about decomposition to some extent.

The substance was dissolved in a large excess of cold water, and titrated with baryta solution, using phenolphthalein as indicator (1 c.c. baryta =  $0.0082 \text{ Ba}(\text{OH})_2$ ).

0.1005 required 7.35 c.c. for neutralisation.

Equivalent found = 142.2.  $C_4H_2O_4N_2$  requires 142.

This corresponds to the formation of a monosodium salt, but the tendency to form a disodium salt was shown by the fact that on standing the red colour disappeared and further baryta was required before it reappeared.

The point of complete neutralisation corresponding to a disodium salt cannot, however, be reached in this way owing to hydrolysis (see sodium salts).

### Sodium Salts of Tetraketopiperazine.

The mono-salt was obtained by treating the tetraketopiperazine with excess of sodium hydrogen carbonate solution in the cold. Partial solution took place with effervescence and reprecipitation on standing.

On isolation the substance was obtained in long, white, silky needles, and proved to be free from carbonate. It dissolved in water with the exception of a small yellow residue which was in every respect like the disodium salt, and the presence of this accounts for the slightly high number obtained on analysis:

The disodium salt cannot be prepared in a pure state by the action of aqueous sodium hydroxide on the parent substance or on the monosalt owing to the fact that a partial hydrolysis takes place as already described. It is best prepared by the method given for the preparation of tetraketopiperazine itself, that is, by treating oxamethane with the theoretical amount of sodium ethoxide. Even in this case a certain amount of hydrolysis is caused by the necessary purification as shown by the figures obtained :

0.1936 dried at  $110^{\circ}$  gave 0.1368 Na<sub>o</sub>SO<sub>4</sub>. Na = 22.88.

 $C_4O_4N_2Na_2$  requires Na = 24.70 per cent.

$$C_4 HO_4 N_2 Na$$
 ,,  $Na = 14.02$  ,, ,,

Silver Salt.—This was obtained from the more soluble potassium salt as a voluminous white precipitate. After drying,

0.1042 gave 0.0632 Ag. Ag = 60.65.

 $C_4O_4N_2Ag_2$  requires Ag = 60.67 per cent.

 $C_4 HO_4 N_2 Ag$  ,, Ag = 43.37 ,, ,,

Hydrazone.—The tetraketopiperazine was dissolved in warm acetic acid and a solution of phenylhydrazine in acetic acid was added. The liquid became yellow and was warmed on the water-bath for five minutes, when fine needles separated. The product was recrystallised from acetic acid and a buff-coloured crystalline substance obtained, which on heating began to sinter at 250° and decomposed without melting completely below 300°.

0.1071 gave 22.4 c.c. moist nitrogen at 20° and 767.5 mm.  $N=24\cdot 15.$ 

 $C_{10}H_8O_3N_4$  (monohydrazone) requires N = 24.13 per cent.

 $C_{16}H_{14}O_2N_6$  (dihydrazone) requires N = 26.08 per cent.

Tetraketopiperazine dissolves sparingly in water, forming a solution which has an acid reaction; on addition of ammonium hydroxide an *ammonium* salt is precipitated which dissolves on dilution. This salt is decomposed by hydrochloric acid with the formation of the parent substance. A *mercury* salt was also obtained.

On boiling with aniline a white crystalline compound is formed which sublimes with great readiness to a voluminous white product, melting between  $210-215^{\circ}$ . It is decomposed on treatment with boiling aqueous caustic potash, aniline being evolved. This product will be further investigated.

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