LXXXV.—*Condensation of Acid Chlorides with the Ethyl Ester of (a) Cyanoacetic Acid, (b) Malonic Acid, and (c) Acetoacetic Acid. Part II. Some Experiments on Ethyl Phthaliminoacetoacetate and Ethyl γ -Ethoxyacetoacetate.*

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IN the first part of this research (T., 1913, **103**, 1855) it was shown that the condensation of phthaliminoacetyl chloride with ethyl sodiomalonate gave different products, according to the method of procedure. It was found there that if the condensation took place under the conditions stated by Gabriel (*Ber.*, 1913, **46**, 1319), ethyl phthaliminoacetylmalonate was formed, but if the method described by the authors was employed, the keto-modi-

fication of ethyl phthaliminoacetoacetate was produced, and from this substance the corresponding enol-modification was obtained.

Gabriel and Colman (*Ber.*, 1909, **42**, 1244), and later Pfaehler (*Ber.*, 1913, **46**, 1702), found that on boiling ethyl phthaliminoacetylmalonate with water, ethyl phthaliminoacetoacetate was produced, which melted at 110°. The ketonic modification of this substance, obtained as stated above, melted at 119°, and gave no coloration with ferric chloride; these properties do not agree with those recorded of the substance, m. p. 110°. The latter develops a deep red coloration with ferric chloride, whilst the enolic form of the ester, which melts at 70°, produces an intense violet. It has since been established that the three substances react with phenylhydrazine under similar conditions to produce the same pyrazolone,

The condensation of phthaliminoacetyl chloride with ethyl sodiomalonate according to the method described in the former communication can lead to the formation of ethyl bisphthaliminoacetylmalonate, as well as of ethyl phthaliminoacetylmalonate. The separation of these two substances was effected, since the former was less readily soluble in ethyl alcohol than the latter.

The action of phenylhydrazine on each of these substances leads to some interesting results. In the case of the bis-derivative, the action of phenylhydrazine was the same as that described by Scheiber and Reckleben (*Ber.*, 1913, **46**, 2412) for ethyl bis-succiniminoacetylmalonate; in the present instance, a mixture of the pyrazolone of ethyl phthaliminoacetylmalonate and the phenylhydrazide of phthaliminoacetic acid was obtained, these substances being separated by treatment with sodium hydroxide solution, in which the former alone is soluble. The same hydrazide was also obtained by the action of phenylhydrazine on phthaliminoacetyl chloride.

Ethyl phthaliminoacetylmalonate, on treatment with phenylhydrazine, yields the pyrazolone mentioned above. The action of hydrolysing agents on the various condensation products has been further investigated, with the following results. When the pure keto-form is distilled in a current of steam during half an hour, the residual oil, which solidifies on cooling, gives a distinct deep red coloration with ferric chloride, but after recrystallisation from ethyl alcohol the product was found to melt at the same temperature as the original substance; the mother liquor, however, still showed the ferric chloride reaction. It is evident that enolisation had taken place. Under similar conditions, the enolic form partly dissolved and partly remained as an oil, which solidified on cool-

ing, and, after twice recrystallising from ethyl alcohol, melted at 110° , and was identical with the substance obtained by Gabriel and Colman (*loc. cit.*). From the aqueous solution, on cooling, crystals of phthaliminoacetic acid were deposited, which, after being recrystallised from hot water, melted at 192° . By treatment of these substances with steam for several hours, phthaliminoacetone was obtained in the first instance, and phthaliminoacetic acid in the other case, together with a small amount of phthaliminoacetone, which was separated from the acid by means of sodium carbonate. A result similar to that first mentioned was obtained by the action of steam for a long period on ethyl phthaliminoacetylmalonate, phthaliminoacetone being obtained.

The treatment of the bis-derivative by the same method gave a mixture of phthaliminoacetic acid and phthaliminoacetone, the former being produced, probably, by the elimination of a phthaliminoacetyl group during the hydrolysis.

Further decomposition of the above substances was obtained by treatment in the following way. The ester under consideration was heated for two hours in a sealed tube at 250° , and the results were as follows. Ethyl phthaliminoacetylmalonate gave a mixture of phthaliminoacetic acid and phthaliminoacetone, ethyl phthaliminoacetoacetate (ketonic form) gave a similar mixture, whilst ethyl phthaliminoacetoacetate (enolic form) yielded phthaliminoacetic acid as the chief product. The bis-derivative behaved as stated above. The action of mineral acids, such as hydrochloric, hydrobromic, or hydriodic acid, is to cause a more complete decomposition of these substances, resulting in the decomposition of the phthalimino-group, as has been shown by Gabriel. In a similar way, the action of alkalis is to attack the phthalimino-group, with the formation of phthalamic acids.

The action of sodium nitrite on ethyl phthaliminoacetylmalonate and on the two acetoacetic ester derivatives gives the same product, namely, α -oximino- γ -phthaliminoacetone. Attempts to prepare α -amino- γ -phthaliminoacetone by reduction of the previous substance with tin or stannous chloride and hydrochloric acid were without result, the hydrochloride of the amino-ketone being unstable, and no salts could be obtained.

In the first part of these investigations a method has been given by which ethyl γ -ethoxyacetoacetate can be obtained, and several derivatives of this substance are now described. α -Oximino- γ -ethoxyacetone, which has been obtained previously, was investigated with a view to its reduction by stannous chloride in acid solution to the corresponding amino-compound. Several attempts were made to obtain this substance, but without results of a

definite value. The course of the reduction seems to be normal, and it is in the isolation of the hydrochloride of the base from the acid solution where the process fails, owing to the fact that the ethoxy-group in the molecule is attacked by the acid during the concentration of the solution, even when the evaporation takes place under diminished pressure. The preparation of such derivatives as the platinum or gold salts or the picrate was impossible from the very impure product obtained, as stated above. It was evident, however, that the amino-ketone had been formed, as the solution reduced Fehling's solution in the cold, and liberated silver from an ammoniacal solution of silver nitrate, and mercury from an alkaline solution of mercuric chloride (compare Gabriel and Pinkus, *Ber.*, 1893, **26**, 2197).

The instability of α -amino- γ -ethoxyacetone is to be considered, therefore, as due to the presence of the ethoxy-group in the molecule. Further instances of this effect will be found in the later experimental work of this paper, but in studying the reactions of α -oximino- γ -ethoxyacetone an interesting case came under observation. On condensation of this substance with *o*-phenylenediamine, the formation of 2-ethoxymethylquinoxaline takes place, and this substance, on oxidation with potassium permanganate, gives pyrazine-2:5:6-tricarboxylic acid; in no case could 2-ethoxymethylpyrazine-5:6-dicarboxylic acid be obtained.

EXPERIMENTAL.

Ethyl Bisphthaliminoacetylmalonate,

This was obtained in the condensation of phthaliminoacetyl chloride and ethyl sodiomalonate, and was separated from the ethyl phthaliminoacetoacetate by extracting the latter with ethyl alcohol, in which the above substance is only sparingly soluble. The product was then crystallised from ethyl acetate, and was obtained in small, white needles, melting at 176° , which are soluble in acetone and in a mixture of chloroform and light petroleum:

0.1057 gave 0.2372 and 0.0438 H_2O . $\text{C}=60.91$; $\text{H}=4.62$.

0.1734 „ 8.4 c.c. N_2 at 17° and 745 mm. $\text{N}=5.5$.

$\text{C}_{27}\text{H}_{22}\text{O}_{10}\text{N}_2$ requires $\text{C}=60.74$; $\text{H}=4.13$; $\text{N}=5.2$ per cent.

1-Phenyl-3-phthaliminomethyl-5-pyrazolone,

This substance was obtained by the treatment of the enolic or ketonic form of ethyl phthaliminoacetoacetate with phenylhydrazine.

5.5 Grams of the ester were mixed with 2.5 grams of phenylhydrazine. After a short time the mixture became warm, and liquefied. The reaction was completed by warming in the steam-bath for an hour, at the end of which time the product had solidified to a hard cake. This was crystallised from methyl alcohol, and obtained as a fine, crystalline powder, which melted and decomposed at 192°:

0.1870 gave 0.4571 CO₂ and 0.0768 H₂O. C=66.66; H=4.5.

0.1244 „ 15.8 c.c. N₂ at 17° and 758 mm. N=13.85.

C₁₈H₁₃O₃N₃ requires C=67.2; H=4.0; N=13.76 per cent.

Attempts to obtain the corresponding aminomethyl derivative from the above substance have so far been unsuccessful, as only a very impure substance was obtained by boiling it with hydrochloric or hydrobromic acid, or by heating it in a sealed tube at 150° for two hours with the same acids.

1-Phenyl-3-phthalaminomethyl-5-pyrazolone,

was obtained by hydrolysing the above substance with an alcoholic solution of potassium hydroxide, and treating the resulting potassium salt with hydrochloric acid. It crystallised from dilute acetic acid as a yellow, crystalline powder, melting and decomposing at 164°. The further hydrolysis of this substance with acids did not lead to any better result than that mentioned above:

0.2116 gave 0.4957 CO₂ and 0.0748 H₂O. C=63.90; H=3.93.

C₁₈H₁₅O₄N₃ requires C=64.09; H=4.15 per cent.

Ethyl 1-Phenyl-3-phthaliminomethyl-5-pyrazolone-4-carboxylate,

This compound was obtained by warming phenylhydrazine and ethyl phthaliminoacetylmalonate in 50 per cent. acetic acid solution for a short time on the steam-bath. The product crystallised from acetic acid as a pale yellow powder, which melted at 215°:

0.1041 gave 0.2472 CO₂ and 0.0428 H₂O. C=64.7; H=4.5.

0.1285 „ 12.0 c.c. N₂ at 23.5° and 763 mm. N=10.78.

C₂₁H₁₇O₅N₃ requires C=64.4; H=4.3; N=10.7 per cent.

The corresponding phthalamino-derivative was obtained as a yellow, crystalline powder, but not in a condition pure enough for analysis. On fusion at 120°, carbon dioxide was evolved, and from the residue, after crystallisation from acetic acid, the above-described phthalaminopyrazolone, melting at 164°, was obtained. By warming an excess of phenylhydrazine with ethyl bisphthaliminoacetylmalonate in a 50 per cent. solution of acetic acid, a mixture of the pyrazolone just described and the phenylhydrazide of phthaliminoacetic acid was obtained. The crude product was treated with cold sodium hydroxide solution, and the residue, consisting of the hydrazide, was filtered from the alkaline solution and crystallised from ethyl alcohol, being thus obtained in small needles, melting at 197°. This substance was identical with that obtained by the action of phenylhydrazine on phthaliminoacetyl chloride, which crystallised from ethyl alcohol in small needles, melting at 198–199°.

On acidifying the alkaline solution, there was obtained the pyrazolone, melting at 215°, and identical with that already described.

Phthaliminoacetyl Phenylhydrazide,

Two grams of phthaliminoacetyl chloride, crystallised from benzene, were treated with 1.5 grams of phenylhydrazine. Reaction took place immediately in the cold, and, after keeping for fifteen minutes, the mixture was warmed on the steam-bath for half an hour. The product crystallised from methyl alcohol in needles, melting at 199°, and gave a violet coloration in the Bülow reaction:

0.1368 gave 0.3260 CO₂ and 0.0519 H₂O. C = 65.00; H = 4.22.

C₁₆H₁₃O₃N₃ requires C = 65.08; H = 4.4 per cent.

α-Oximino-γ-phthaliminoacetone,

Ten grams of ethyl phthaliminoacetylmalonate were dissolved in 7 grams of potassium hydroxide contained in 250 c.c. of water, and the clear solution was treated with 2.8 grams of sodium nitrite dissolved in a small quantity of water. The mixed solutions were kept for twenty-four hours, and then treated with a slight excess of dilute sulphuric acid. The crystals which had separated after the solution had been kept for two days in the ice-chamber were recrystallised from benzene and obtained in prisms, melting and decomposing at 156°:

0.1986 gave 0.4092 CO₂ and 0.0776 H₂O. C=56.62; H=3.46.

0.2266 „ 8.8 c.c. N₂ at 19° and 760 mm. N=4.5.

C₁₁H₈O₄N₂ requires C=57.00; H=3.40; N=3.41 per cent.

Ethyl Ethylidenebis-γ-ethoxyacetoacetate,

Thirty-five grams (2 mols.) of ethyl γ-ethoxyacetoacetate were mixed with 4.5 grams (1 mol.) of freshly distilled acetaldehyde, and the whole was well cooled in a freezing mixture of ice and salt. Two grams of diethylamine were then added gradually, the temperature being maintained at 0°. After keeping at this temperature for two hours, the mixture was left at room temperature for five days, when it had formed a crystalline mass. A portion of this, after being pressed on a porous plate, crystallised from methyl alcohol in colourless needles, melting at 96°:

0.2793 gave 0.6012 CO₂ and 0.1812 H₂O. C=58.71; H=8.00.

C₁₈H₃₀O₈ requires C=59.34; H=8.24 per cent.

1-Ethoxy-4-methyl-2-ethoxymethylcyclohexen-6-one,

Twenty-seven grams of the crude ester obtained in the preceding condensation were hydrolysed by boiling with dilute sulphuric acid for twenty hours, and the product was distilled in a current of steam. The distillate was treated with solid potassium hydroxide, and the oil thus obtained was extracted with ether, dried, and distilled. Five grams of an oil boiling at 149°/12 mm. were obtained. An attempt to improve the yield was made in the following manner. Twenty-two grams of the ester were dissolved in an equal volume of benzene, and the solution was saturated with hydrogen chloride and kept for twelve hours. The mixture was then poured into water, washed several times with a solution of sodium hydrogen carbonate, and finally with water; it was then dried, and the benzene removed by distillation under diminished pressure. Some hydrogen chloride which was still found to be present was removed by boiling the product with diethylaniline (6 grams) in an oil-bath at 140°. The product was then poured into water and extracted with ether, and the ethereal extract, after being washed several times with dilute sulphuric acid, and finally twice with water, was dried and distilled. The product boiled at 157°/15 mm., and had a pleasant, terpene-like odour. The yield by this method was 8 grams:

0.2463 gave 0.6187 CO₂ and 0.2019 H₂O. C=67.4; H=9.11.

C₁₂H₂₀O₃ requires C=67.92; H=9.43 per cent.

The poor yields in the two methods are probably due to the effect of the acid on the ethoxy-groups, since a considerable amount of substance, which decomposes on distillation at a higher temperature, is produced.

The *semicarbazone* of this *cyclohexenone* was obtained by dissolving 2.5 grams of sodium acetate in a small quantity of water, and adding 1.5 grams of semicarbazide hydrochloride and 2 grams of the *cyclohexenone*. The product crystallised from methyl alcohol in plates, melting and decomposing at 232° :

0.1218 gave 16.0 c.c. N_2 at 14° and 760 mm. $N=15.60$.

$C_{13}H_{23}O_3N_3$ requires $N=15.61$ per cent.

Ethyl γ -ethoxy- α -methylacetoacetate, $EtO \cdot CH_2 \cdot CO \cdot CHMe \cdot CO_2Et$.

Johnson (*J. Amer. Chem. Soc.*, 1913, **35**, 582) has already described the preparation of this substance, and of the corresponding ethyl compound, by condensing ethyl ethoxyacetate with ethyl α -bromopropionate and ethyl α -bromobutyrate, respectively, in the presence of zinc.

In the present instance, the following method has been adopted.

4.6 Grams (1 atom) of sodium were dissolved in 60 c.c. of ethyl alcohol, and 35 grams (1 mol.) of ethyl γ -ethoxyacetoacetate were gradually added to the solution, cooled in ice, and then 28 grams (1 mol.) of methyl iodide. The mixture was kept for an hour, and afterwards heated on the steam-bath until the solution gave a neutral reaction towards litmus. The product was treated with water, the ester extracted several times with ether, and the ethereal solution dried and distilled after the evaporation of the ether; the bulk of the liquid distilled at $114-120^{\circ}/14$ mm. After carefully fractionating this product, a substance, boiling at $115^{\circ}/16$ mm., was obtained. This, on analysis, proved to be the above compound, which is a pale yellow liquid, but is colourless immediately after distillation. (Found, $C=57.3$; $H=8.16$. $C_9H_{16}O_4$ requires $C=57.44$; $H=8.51$ per cent.)

Ethyl γ -ethoxy- α -ethylacetoacetate is obtained in a similar way, using ethyl iodide. It is a pale yellow liquid, boiling at $124^{\circ}/15$ mm.

Ethyl γ -ethoxy- α -propylacetoacetate, $EtO \cdot CH_2 \cdot CO \cdot CHPr \cdot CO_2Et$, is a colourless liquid, boiling at $137^{\circ}/18$ mm:

0.1554 gave 0.3470 CO_2 and 0.1258 H_2O . $C=60.90$; $H=9.02$.

$C_{11}H_{20}O_4$ requires $C=61.11$; $H=9.26$ per cent.

Ethyl γ -ethoxy- α -isopropylacetoacetate,

$EtO \cdot CH_2 \cdot CO \cdot CHPr^{\beta} \cdot CO_2Et$,

boils at $131^{\circ}/18$ mm.:

0.1215 gave 0.2707 CO_2 and 0.0962 H_2O . $\text{C}=60.77$; $\text{H}=8.80$.

$\text{C}_{11}\text{H}_{20}\text{O}_4$ requires $\text{C}=61.11$; $\text{H}=9.26$ per cent.

Ethyl γ -ethoxy- α -isobutylacetoacetate,

boils at $128^\circ/10$ mm.:

0.1089 gave 0.2489 CO_2 and 0.0911 H_2O . $\text{C}=61.85$; $\text{H}=9.3$.

$\text{C}_{12}\text{H}_{22}\text{O}_4$ requires $\text{C}=62.60$; $\text{H}=9.56$ per cent.

The methyl and ethyl derivatives just described were submitted to hydrolysis in various ways in order to obtain the corresponding ketones, but in every case the acid and the undecomposed ester were also present, so that the yield of the ketone was considerably diminished.

Ten grams of the methyl derivative were heated on the steam-bath for two hours with 100 c.c. of a 10 per cent. solution of potassium hydroxide in water. The product was saturated with potassium carbonate, and extracted with ether. After drying, and evaporation of the ether, an oily residue was left, which gave a violet coloration with ferric chloride, showing the presence of unchanged ester. On distillation, a small fraction was obtained boiling at 140 – 150° , consisting of a colourless liquid having an odour different from that of the original ester. Béhal and Sommelet give the boiling point of α -ethoxybutan- β -one as 146° (*Compt. rend.*, 1904, **138**, 89).

Forty-five grams of the same derivative were divided into three equal portions, and heated in sealed tubes, with twice the volume of water in each case, for one hour at 210° . On opening the tubes, a considerable pressure was observed, and an oily layer, consisting of unchanged ester, was also noted. The contents of the tubes were saturated with potassium carbonate (the first addition produced an effervescence, due to the presence of free acid) and extracted with ether, and, after drying, the ether was evaporated. On distillation, an oil, boiling at 146° , was obtained, which formed a semicarbazone, melting at 87° by Béhal and Sommelet's method (*loc. cit.*).

The corresponding α -ethoxypentan- β -one was obtained from ethyl γ -ethoxy- α -ethylacetoacetate by the method just described, and is an oil boiling at 167° (Béhal and Sommelet give 164 – 165°). The other alkyl derivatives were hydrolysed in the same way, with the result that "acid" hydrolysis chiefly occurs; this was shown by titrating the acid formed with *N*-sodium hydroxide.

One gram of the propyl and the isopropyl derivatives required 5.5 and 6.7 c.c. of *N*-sodium hydroxide respectively (theoretical, 9.2 c.c.), whilst 1 gram of the isobutyl derivative required 7.2 c.c. (theoretical, 8.5 c.c.).

Ethoxyacetamide, $\text{EtO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$.

This has been prepared by Sommelet (*Ann. Chim. Phys.*, 1908, [viii], 9, 493) from the corresponding ester. The same substance was obtained by the reaction of ethoxyacetyl chloride and ammonia in dry ether. It crystallises from benzene in long needles, melting at 80–82°.

2-Ethoxymethylquinoxaline, $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{N}:\text{C}\cdot\text{CH}_2\cdot\text{OEt} \\ \text{N}:\text{CH} \end{smallmatrix}$.

13.2 Grams (1 mol.) of α -oximino- γ -ethoxyacetone were mixed with 10.8 grams (1 mol.) of *o*-phenylenediamine and 12 grams (2 mols.) of glacial acetic acid diluted with 200 c.c. of water. The mixture was warmed on the steam-bath until a clear solution was obtained, and, after cooling, this was made alkaline with potassium hydroxide and distilled in a current of steam. The distillate was saturated with ammonium sulphate, and the quinoxaline extracted with ether. After drying and evaporating the ether, a bright yellow oil remained, which distilled at 237°/760 mm. and 144°/18 mm., yielding a pale yellow liquid. The quinoxaline has a faint, basic odour, becomes darker in colour on keeping, and is completely miscible with water, the solution reacting neutral towards litmus:

0.2262 gave 0.5786 CO_2 and 0.1159 H_2O . $\text{C}=69.38$; $\text{H}=5.70$.

0.2266 „ 29.3 c.c. N_2 at 18° and 738 mm. $\text{N}=14.45$.

$\text{C}_{11}\text{H}_{12}\text{ON}_2$ requires $\text{C}=70.20$; $\text{H}=6.38$; $\text{N}=14.89$ per cent.

On acidifying a solution of the base in water with hydrochloric acid, and evaporating to obtain the crystalline salt, decomposition ensued, and the concentrated solution acquired a deep blue colour. This made the preparation of the platinum salt difficult, and it could only be obtained in the following way.

One gram of the base was dissolved in 15 c.c. of ethyl alcohol (95 per cent.), and treated with 8 c.c. of a 10 per cent. alcoholic solution of platinum chloride. The *platinichloride* was immediately precipitated as a fine, yellow, crystalline powder, which was collected at once, washed with alcohol, and dried for a short time at 80°. It did not melt at 240°, but decomposed at 250°:

0.1621 gave 0.0388 Pt. $\text{Pt}=23.95$.

$(\text{C}_{11}\text{H}_{12}\text{ON}_2)_2\cdot\text{H}_2\text{PtCl}_6$ requires $\text{Pt}=24.52$ per cent.

The *picrate* was obtained by treating a solution of the base in ethyl acetate with a solution of picric acid in the same solvent. It crystallises from methyl alcohol as a yellow powder, melting at 216°.

Five grams of 2-ethoxymethylquinoxaline were dissolved in 500 c.c. of water and 35 c.c. of *N*-potassium hydroxide solution added. This solution was oxidised by the gradual addition of 32.5 grams of potassium permanganate dissolved in $1\frac{1}{2}$ litres of water, the mixture being warmed on the steam-bath during the process. When the oxidation, which required about two hours, was complete, the cold solution was filtered from manganese dioxide, and the filtrate evaporated to 200 c.c. After acidifying with acetic acid, an excess of barium chloride solution was added, the liquid being heated to boiling during the addition. The precipitated barium salt was filtered, washed several times with hot water, suspended in cold water, and decomposed with about the necessary quantity of *N*-sulphuric acid. The barium sulphate was removed, the filtrate neutralised with ammonia, and a concentrated solution of calcium chloride added. The calcium salt of the acid remained in solution, and some calcium oxalate, which was precipitated, was removed by filtration. The filtrate was treated with barium chloride, and the precipitated barium salt was washed with hot water and digested with dilute sulphuric acid. After removing the barium sulphate, the solution was slowly evaporated in a desiccator until the acid crystallised. It was recrystallised from hot water and obtained in silky needles, which melted and decomposed at 191° :

0.4422 gave 0.6359 CO_2 and 0.0748 H_2O . $\text{C}=39.22$; $\text{H}=1.88$.

0.1358 „ 16.05 c.c. N_2 at 17° and 761 mm. $\text{N}=12.91$.

$\text{C}_7\text{H}_4\text{O}_6\text{N}_2$ requires $\text{C}=39.98$; $\text{H}=1.88$; $\text{N}=13.21$ per cent.

The *copper* salt was obtained as a green, crystalline powder by the addition of a solution of copper nitrate to an aqueous solution of the acid. It was crystallised from water containing a little methyl alcohol:

0.1764 gave 0.0700 CuO . $\text{Cu}=31.69$.

$\text{C}_{14}\text{H}_6\text{O}_{12}\text{N}_4\text{Cu}_3$ requires $\text{Cu}=31.30$ per cent.

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