LXIII.—*Pheno- α -ketoheptamethylene and its Derivatives.*

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THE intramolecular condensation of phenylpropionic chloride in presence of anhydrous aluminium chloride results, as previously shown (Kipping, Trans., 1894, **65**, 680) in the formation of the cycloid ketone, α -hydrindone, and by an exactly analogous reaction, phenylbutyric chloride is converted into α -ketotetrahydronaphthalene (Kipping and Hill, Trans., 1899, **75**, 144).

This method of obtaining cycloid ketones has now been applied to the next higher homologue of this series of acid chlorides, and it is shown in this paper that phenylvaleric chloride, $C_6H_5 \cdot [CH_2]_4 \cdot COCl$, can be converted into a ketone which has been named pheno- α -ketoheptamethylene.

The relationship between the three closed chain compounds which have thus far been prepared with the aid of this reaction is shown by the following formulæ :

α -Hydrindone. α -Ketotetrahydronaphthalene. Pheno- α -ketoheptamethylene.

Pheno- α -ketoheptamethylene, as will be seen from its formula, contains a closed chain of *seven* carbon atoms condensed with a benzene nucleus, and when briefly described about nine months ago by Kipping and Hall (Proc., 1899, 15, 173),* it was the first compound of this type which had been prepared; very shortly afterwards, however, Dieckmann gave a short account (*Ber.*, 1899, 32, 2247) of a closely related compound, namely, pheno-1 : 5-diketoheptamethylene,

which he had obtained by condensing ethyl phthalate with ethyl glutarate,

and then boiling the product with dilute sulphuric acid, which first hydrolyses the ester, and then eliminates the two carboxyl groups; it seems probable, therefore, that compounds of this type will soon be familiar to chemists.

Pheno- α -ketoheptamethylene is a colourless oil and has only a slight smell at the ordinary temperature, but when warmed it gives off a vapour having a strong odour of peppermint. The property of affecting the olfactory organs in the same way as does menthol seems to depend partly, in the case of these aromatic-fatty cycloid ketones, on the number of methylene groups in the reduced ring; hydrindone, for example, has an odour recalling that of jasmine, but the vapour of ketotetrahydronaphthalene has a distinct, although not a very strong, smell of peppermint, and that of the next higher homologue, as just stated, is very marked.

The constitution of pheno- α -ketoheptamethylene is established by its method of formation, which is almost certainly analogous to that of

* Miss Hall was unable to continue this investigation; the authors desire to thank her for the work which she did in connection with it.

α -ketotetrahydronaphthalene (*loc. cit.*); that it is a ketone is shown by the formation of an oxime and a semicarbazone, which are described later; that it contains the heptamethylene ring condensed with the benzene nucleus in the *ortho*-position is proved by the fact that on oxidation with nitric acid it yields, among other products, *o*-phthalic acid.

Just as the oxime of α -ketotetrahydronaphthalene gives on reduction α -aminotetrahydronaphthalene, so the oxime of pheno- α -ketoheptamethylene is reduced to an α -amino-derivative of the following constitution:

Pheno- α -aminoheptamethylene.

This base is a colourless liquid, having the normal properties of a primary amine, and with acids it forms well-defined salts; when its hydrochloride is submitted to dry distillation, it is decomposed, giving a non-basic product which is, in all probability, an unsaturated hydrocarbon, formed from the base by a reaction analogous to that by which indene is produced from hydrindamine hydrochloride (Kipping and Hall, *Trans.*, 1900, 77, 469); this product is being investigated.

Preparation of Phenylvaleric Acid.

The preparation of phenylvaleric acid in considerable quantity for the purpose of this investigation proved to be a rather troublesome process, and we have not been able to improve on the method originally employed by von Baeyer and Jackson (*Ber.*, 1880, 13, 122).

The first step consists in the synthesis of cinnamylidenemalonic acid, a compound which is easily obtained in large quantities by the condensation of cinnamaldehyde with malonic acid in the presence of glacial acetic acid or acetic anhydride,

the reduction of this acid is also readily accomplished in alkaline solution with the aid of sodium amalgam; and on subsequently acidifying the ice-cold solution, hydrocinnamylidenemalonic acid,

is precipitated in colourless crystals (compare Thiele and Meisenheimer, *Annalen*, 1899, 306, 260).

This substance, when boiled with water, decomposes into hydro-

cinnamylideneacetic acid, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, and carbon dioxide.

So far, the yields are almost quantitative, but the reduction of the hydrocinnamylideneacetic acid to phenylvaleric acid has to be done with an aqueous or acetic acid solution of hydrogen iodide in sealed tubes, all other reducing agents which have been tried having failed to bring about the desired change; the contents of the tubes are generally rather dark in colour, and the acid must be purified by recrystallisation from water, in which it is sparingly soluble, and then from light petroleum; it is thus obtained in almost colourless, rhomboidal crystals melting at 59° .

Phenylvaleric chloride was obtained by heating the acid with rather more than the calculated quantity of phosphorus pentachloride in a Wurtz flask, and then heating on the water-bath under greatly reduced pressure until all the phosphorus oxychloride had distilled over; it is a colourless, mobile liquid, which does not fume in the air, and has only a very faint odour.

The Action of Aluminium Chloride on Phenylvaleric Chloride.

The conversion of phenylvaleric chloride into pheno- α -ketoheptamethylene does not take place as readily as that of phenylpropionic chloride into hydrindone, and a rather higher temperature seems to be required to bring about the change; the reaction is also very incomplete, so that the actual yield of ketone is small.

On the other hand, by using the right proportion of aluminium chloride, the formation of tarry products can be almost entirely prevented, and a large proportion of the unchanged acid can be recovered; allowing for this, the yield is by no means unsatisfactory, and amounts on the average to 30 or 40 per cent. of the calculated amount. The following conditions have been found to give the best results: Phenylvaleric chloride (5 parts) is dissolved in about six times its volume of light petroleum (b. p. $60\text{--}80^\circ$); finely powdered aluminium chloride (6 parts) is added slowly, and the mixture is rapidly heated on a bath of boiling water; as soon as the temperature rises to about 70° , the evolution of hydrogen chloride sets in, and a fairly vigorous reaction continues so long as the mixture is heated, and almost constantly shaken; after about 30 minutes, by which time the contents of the flask have separated into two layers, the liberation of hydrogen chloride shows marked signs of abating, and the flask is quickly cooled.

After cautiously adding water, the petroleum is separated by distilling in steam, and the process is continued so long as ketone comes over; the latter is isolated by extracting the distillate with a little

light petroleum or ether, washing with dilute sodium carbonate solution, and then evaporating the dried extract.

The clear aqueous solution left after steaming contains a little regenerated phenylvaleric acid, which can be separated from the small quantity of resinous matter by filtration, and further quantities of the acid may be obtained by repeatedly extracting this bye-product with water.

The crude phenoketone, obtained by evaporating its solution in ether or light petroleum, is an almost colourless, moderately mobile liquid, which seems to be practically free from any appreciable quantity of impurity ; if necessary, it can be purified by distillation under reduced pressure, or by converting it into the crystalline semicarbazone and decomposing the latter with dilute sulphuric acid (see below).

When obtained by the second method, it is a colourless oil, specifically heavier than water, but it turns yellowish on exposure to the air. It does not solidify when cooled to 0° , or when kept for a long time at the ordinary temperature; since hydrindoné melts at 44° , it would seem that the melting points of these cycloid ketones become lower as the number of carbon atoms in the reduced chain increases.

It is practically insoluble in water, but is miscible with all ordinary organic solvents ; it volatilises slowly in steam, and boils at about 270° under atmospheric pressure, apparently decomposing slightly ; when boiled with water, the escaping vapour has a strong odour of peppermint.

It interacts readily with phenylhydrazine, and with *p*-bromophenylhydrazine when it is warmed gently with either of these reagents, but the products do not crystallise at all readily, and are quite unsuitable for purposes of identification or isolation ; they also undergo decomposition, and turn reddish-brown on exposure to the air.

The oxime and the semicarbazone, on the other hand, crystallise very readily, and are easily purified.

Pheno- α -ketoheptamethylene is readily attacked by bromine and by bromine water, giving crystalline products which, however, have not yet been examined ; its behaviour towards oxidising agents is described later.

Pheno- α -ketoheptamethylene Semicarbazone, $\text{C}_{11}\text{H}_{12} \cdot \text{N} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2$.—This compound is gradually deposited in colourless crystals when a solution of the crude ketone in dilute alcohol is warmed on the water-bath with sodium acetate and semicarbazide hydrochloride, and after some hours the reaction is complete ; for analysis, the product was recrystallised from boiling alcohol and dried at 100° .

0.1506 gave 0.3669 CO₂ and 0.0975 H₂O. C = 66.4; H = 7.2.

0.1434 „ 0.3484 CO₂ „ 0.0896 H₂O. C = 66.3; H = 6.9.

C₁₂H₁₅ON₃ requires C = 66.4; H = 6.9 per cent.

Pheno- α -ketoheptamethylene semicarbazone separates from alcohol in highly lustrous, silky plates, melting at 206—207° if heated slowly from 200°, decomposing and giving off bubbles of ammonia; if heated rapidly, the substance may not melt until 214—215° (219—220° corr.).

It is readily soluble in boiling chloroform, methyl or ethyl alcohol, ethyl acetate, acetone, or acetic acid, but only sparingly so in hot light petroleum, and is practically insoluble in water. It is decomposed by warm dilute hydrochloric or sulphuric acid, the ketone being regenerated; this fact, and the readiness with which the semicarbazone crystallises, make the isolation and identification of the ketone a simple matter, even when only a very small quantity is available.

Although many cycloid ketones afford isomeric semicarbazones, this does not seem to be the case with pheno- α -ketoheptamethylene; its semicarbazone was fractionally crystallised from alcohol, and thus separated into five fractions, but they all melted at the same temperature.

Pheno- α -ketoheptamethylene Oxime, C₁₁H₁₂·N·OH, is obtained when the ketone, regenerated from the semicarbazone, is heated in alcoholic solution with slight excess of hydroxylamine hydrochloride and potash and the mixture allowed to stand for some time. On adding a little water, the separation of a crystalline compound soon commences, and the last portions may be obtained by gently evaporating the solution on the water-bath, and subsequently acidifying it. The oxime is readily purified by recrystallisation from dilute methyl alcohol or light petroleum, from which it is deposited in long needles having a silky lustre, and melting at 108—109°.

Pheno- α -ketoheptamethylene oxime is very readily soluble in methyl or ethyl alcohol, acetone, acetic acid, or ether, but only moderately so in boiling light petroleum; it also dissolves freely in cold potash solution, but is only sparingly soluble in water or dilute acids.

Oxidation of Pheno- α -ketoheptamethylene.

Pheno- α -ketoheptamethylene is only very slowly oxidised by potassium permanganate in presence of sodium carbonate, but on warming, oxidation proceeds fairly rapidly. It is readily attacked by hot dilute nitric acid, but apparently the reaction is not a simple one, as in the case of most of the fatty cycloid ketones, and various products are generated.

In order to try and obtain some evidence in favour of the view

that the ketone contains a closed chain of seven carbon atoms, that is, that it has been produced from the acid chloride by condensation in the ortho-position, as in the cases previously examined, some of the pure substance was treated with dilute (about 5 per cent.) nitric acid; on heating, brown fumes were evolved, and after boiling for about half an hour most of the ketone seemed to be changed.

On cooling, a brownish, flaky mass separated at the surface, and at the bottom of the liquid there was a considerable quantity of oil. These two products were collected separately, the nitric acid solution was concentrated, filtered when cold to remove oily matter, and then evaporated to dryness.

The almost colourless crystalline residue, when purified by recrystallisation from water, melted at about 185° , and was readily soluble with effervescence in dilute sodium carbonate solution; when gently heated, it gave a sublimate which consisted of long needles melting sharply at $127-128^{\circ}$, and did not dissolve immediately in cold dilute sodium carbonate solution.

These are properties of phthalic acid and its anhydride, and the fact that this acid is formed on oxidation is confirmatory evidence that the ketone has the constitution assigned to it. Phthalic acid, however, is not the principal product resulting from the above treatment, as a considerable quantity of the ketone is converted into the oily product mentioned above; this oil is soluble in cold dilute sodium carbonate solution, is reprecipitated on the addition of acids, and is apparently unchanged on prolonged heating with nitric acid; as it could not be made to crystallise, it does not seem probable that it could be *o*-carb-oxyphenylbutyric acid, $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, which melts at 138° (Roser, *Ber.*, 1885, 18, 3118), although the formation of this acid under the above circumstances was to be expected.

The second bye-product, namely, the brownish solid referred to above, was easily obtained in a pure state by recrystallising it several times from methyl alcohol, from which it separated in concentrically-grouped prisms melting at $159-160^{\circ}$; this compound was practically insoluble in water or boiling dilute sodium carbonate solution, and it was not changed appreciably by prolonged treatment with hot moderately concentrated nitric acid, in which it was only very sparingly soluble.

The further investigation of these bye-products did not seem to be of sufficient importance to render desirable the sacrifice of a large quantity of the ketone.

This compound is easily obtained by the reduction of the oxime in alcoholic solution with sodium amalgam, keeping the solution slightly acid with acetic acid. After several times the calculated quantity of amalgam had been used, the solution was submitted to distillation in a current of steam, and, as little or no unchanged oxime passed over, the contents of the flask were cooled and made strongly alkaline with potash, and the liquid again distilled in steam. A strongly basic, colourless oil then passed over, and the distillate was collected in dilute hydrochloric acid, the solution being afterwards evaporated to dryness on the water-bath, when a considerable quantity of a white, crystalline salt was obtained.

The amount of amine produced seemed to be practically theoretical, the reduction being rapidly accomplished without any difficulty.

The base is only sparingly soluble in water, but dissolves readily in the ordinary organic solvents; it rapidly absorbs carbon dioxide from the air, giving a crystalline product.

The *hydrochloride* is obtained by crystallisation from hot water in rosette-like aggregations of short, microscopic needles; it is readily soluble in methyl or ethyl alcohol, or in hot water, moderately so in cold water, but only sparingly so in chloroform, acetone, or light petroleum. It did not melt on being heated up to 250°.

The *platinichloride*, $(C_{11}H_{15}N)_2, H_2PtCl_6$, was obtained as a yellow precipitate on mixing strong aqueous solutions of the hydrochloride and platinic chloride. It crystallises from hot water in felted masses of needles of a light orange colour, having no definite melting point, and is very readily soluble in methyl or ethyl alcohol.

The air-dried salt, on being heated at 100° during several hours, did not diminish in weight. On analysis:

0.2998 gave 0.0796 Pt. Pt = 26.54.

$(C_{11}H_{15}N)_2, H_2PtCl_6$ requires Pt = 26.66 per cent.

On ignition, the compound gave off vapours having an odour like that of naphthalene or indene, a behaviour similar to that of the hydrochloride.

The *sulphate*, prepared by neutralising the base with dilute sulphuric acid, is very suitable for the purification of the amine, as it is more sparingly soluble in water than the hydrochloride, and crystallises in thin, transparent plates. It dissolves easily in hot water, but only sparingly in cold water or alcohol; it melts and decomposes at about 227—229°.

The *oxalate*, made in a similar manner, is deposited from water in irregular prisms, which are moderately soluble in water or alcohol, but only slightly so in ethyl acetate.

The *picrate* is deposited in yellow needles when a solution of the oxalate is mixed with an aqueous solution of picric acid ; it crystallises from hot water in felted masses of pale yellow needles, which decompose on being heated ; it is very soluble in hot water, but only sparingly so in cold water.

The *benzoyl* derivative, obtained by the Schotten-Baumann reaction and purified by crystallisation from dilute alcohol, forms felted masses of needles melting at 171—172°. By means of this compound small quantities of the amine may be identified, as it is easily purified, and is practically insoluble in water.

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