CCXXXII.—*A New Synthesis of Oxazole Derivatives.*

By Robert Robinson.

During the course of a synthetical investigation, the author had occasion to prepare ω-phenylacetylaminoacetophenone,

$$COPh\cdot CH_2\cdot NH\cdot CO\cdot CH_2Ph,$$

and noticed that this substance, under the influence of concentrated sulphuric acid, readily loses the elements of water with the production of a feeble base of the formula $C_{16}H_{13}ON$. The probable explanation of this interesting change is that this compound, reacting in its enolic form,

$$OH\cdot CPh{:}CH\cdot N{:}C(OH)\cdot CH_2Ph,$$

loses water from the two hydroxy-groups, and the base obtained would then be 5-phenyl-2-benzyloxazole,

$$O\begin{matrix}<\\ \\ \end{matrix}\begin{matrix}CPh{=}CH\\ C(CH_2Ph)\end{matrix}\begin{matrix}>\\ \\ \end{matrix}N.$$

That the reaction really does take this course was proved by examining ω-benzoylaminoacetophenone, a substance which was easily obtained by benzoylating ω-aminoacetophenone. On treatment with concentrated sulphuric acid, this compound was found to yield 2 : 5-diphenyloxazole, identical with the base prepared by Emil Fischer (*Ber.*, 1896, **29**, 205) by the condensation of benzaldehyde with its cyanohydrin under the influence of hydrochloric acid. The same base is also obtained by heating bromophenylacetaldehyde with benzamide (E. Fischer, *Ber.*, 1896, **29**, 213).

The production of 2 : 5-diphenyloxazole from ω-benzoylaminoacetophenone is a clear proof that in the synthesis of oxazoles from bromo-ketones or aldehydes and acid amides, the hydrogen of the amino-group condenses with oxygen of the carbonyl group rather than with the bromine. Thus, for instance, the reaction between bromoacetophenone and benzamide does not involve the intermediate formation of benzoylaminoacetophenone, since it is the 3 : 5- and not the 2 : 5-diphenyloxazole which is produced (Blümlein, *Ber.*, 1884, **17**, 2580; Lewy, *Ber.*, 1887, **20**, 2579).

The synthesis may be represented as follows if both the bromoacetophenone and the benzamide are assumed to react in the enolic form:

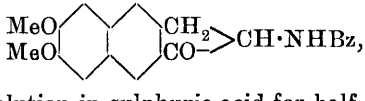
$$\begin{matrix} CPh\cdot OH \\ \| \\ CHBr \end{matrix} + \begin{matrix} HO\cdot CPh \\ \| \\ HN \end{matrix} = H_2O + \begin{matrix} CPh\cdot O\cdot CPh \\ \| \quad\quad \| \\ CH{-}{-}N \end{matrix} HBr.$$

2 : 5-Diphenyloxazole and, to a much greater extent, its dimethoxy-derivative (see p. 2172), exhibit blue fluorescence in alcoholic solution.

The introduction of the methylene group between the oxazole ring and the phenyl radicle gives rise to oxazoles which are not fluorescent. Evidently the occurrence of this property is dependent on an uninterrupted chain of conjugate double linkings connecting the aromatic nuclei through the oxazole ring.

The method of synthesising oxazole derivatives described above in the case of 2 : 5-diphenyloxazole has been tested in various cases, and is probably of very general application, but at least one case in which ring formation does not take place has been observed.

2-Benzoylamino-5 : 6-dimethoxyhydrindone,



is unchanged by solution in sulphuric acid for half an hour, and this is remarkable in view of the ease with which the closely allied ω-benzoylaminoacetoveratrone undergoes the transformation. It is the author's intention to apply this method of oxazole formation to the

synthesis, not only of the unknown parent of the group itself, but also of some of its more important derivatives.

In the meantime a number of new substances are described, which it was necessary to prepare in order to test the applicability of the above synthesis.

Experimental.

ω-Benzoylaminoacetophenone, $COPh{\cdot}CH_2{\cdot}NH{\cdot}COPh$.

This compound is very readily obtained under the following conditions: ω-Aminoacetophenone hydrochloride (5 grams) is dissolved in water (50 c.c.), the solution vigorously stirred, and treated with benzoyl chloride (7 grams) and sufficient aqueous potassium hydroxide (40 per cent. solution) to keep the liquid alkaline.

When all the benzoyl chloride has been decomposed, the oil solidifies. The almost colourless, crystalline mass is collected, washed with water, and a small quantity of oily impurity removed by contact with porous porcelain.

The colourless substance may be recrystallised from alcohol, and separates in beautiful needles, melting at 123°:

0·1202 gave 0·3322 CO_2 and 0·0608 H_2O. C = 75·4; H = 5·6.

$C_{15}H_{13}O_2N$ requires C = 75·3; H = 5·4 per cent.

2:5-*Diphenyloxazole*, $O<\begin{matrix}CPh{:}CH\\ |\\ CPh{:}N\end{matrix}$.

Benzoyl-ω-aminoacetophenone (1 gram) was dissolved in concentrated sulphuric acid (5 c.c.), and the solution warmed on the water-bath for two minutes and then poured into water.

The colourless, crystalline precipitate, after collection and crystallisation from light petroleum (b. p. 50—70°), melted at 73°, whilst the melting point of 2:5-diphenyloxazole, prepared from benzaldehyde and benzaldehydecyanohydrin, is 74° (E. Fischer, *Ber.*, 1896, **29**, 207). The identity of the two substances was further proved by a careful comparison of the products, as well as by the fact that a mixture of them melted at 73°.

Since 2-phenyl-5-veratryloxazole exhibits marked blue fluorescence in benzene solution, it was of interest to examine 2:5-diphenyloxazole in this respect.

It was found that, although this property is difficult to observe in ordinary light, yet by the light of burning magnesium the alcoholic or benzene solution of this substance shows strong violet-blue fluorescence.

ω-Phenylacetylaminoacetophenone, $COPh\cdot CH_2\cdot NH\cdot CO\cdot CH_2Ph$.

This substance was prepared in considerable quantities for some synthetical experiments, and the following process was found to be expeditious.

ω-Aminoacetophenone stannichloride (50 grams) is dissolved in hot water (250 c.c.) and the solution cooled, and treated with phenylacetyl chloride (30 grams) and then with aqueous potassium hydroxide (175 c.c. of a 40 per cent. solution). The rise in temperature is checked by the addition of small pieces of ice, and the liquid must be thoroughly stirred by mechanical means. The end of the reaction is indicated by the crystallisation of the product, and, after dilution with water, the pale yellow crystals are collected and crystallised from benzene, ether, or alcohol.

The purest product is obtained from ether; colourless needles or prisms, melting at 104°:

0·1235 gave 0·3424 CO_2 and 0·0680 H_2O. C = 75·6; H = 6·1.

$C_{16}H_{15}O_2N$ requires C = 75·9; H = 5·9 per cent.

The *oxime* crystallises from benzene or dilute alcohol in prisms, or from ethyl acetate and light petroleum as a highly characteristic mass of balls of minute threads. It melts at 154°, and was found to be unaltered by solution in concentrated sulphuric acid for a short time. Longer action induces some change, but it was not found possible to isolate the expected six-membered, heterocyclic substance.

On analysis, after drying in a vacuum:

0·1217 gave 10·9 c.c. N_2 at 12° and 765 mm. N = 10·7.

$C_{16}H_{16}O_2N_2$ requires N = 10·4 per cent.

The *phenylhydrazone*, when recrystallised from alcohol, forms a beautiful, satiny powder, which under the microscope is seen to consist of curious crystals, shaped like a flower with four large petals. This derivative melts at 184—185°, and shows a great tendency to change into a yellow oil, especially under the influence of heat:

0·1222 gave 12·8 c.c. N_2 at 150° and 754 mm. N = 12·2.

$C_{22}H_{21}ON_3$ requires N = 12·2 per cent.

5-Phenyl-2-benzyloxazole, $O<\begin{matrix}CPh=CH\\C(CH_2Ph)\end{matrix}>N$.

ω-Phenylacetylaminoacetophenone (2 grams) was dissolved in cold concentrated sulphuric acid (10 c.c.), and the solution kept for two hours. On adding water in excess, a crystalline precipitate is obtained, but time must be allowed for the milky fluid to deposit the

whole of the substance in a solid condition. On crystallisation from light petroleum, magnificent long, flat needles, melting at 89°, separate.

In common with the other oxazole derivatives described in this paper, this substance is readily soluble in most organic solvents, but sparingly so in boiling water or cold light petroleum:

0·1300 gave 0·3891 CO_2 and 0·0639 H_2O. C = 81·6; H = 5·5.

$C_{16}H_{13}ON$ requires C = 81·7; H = 5·5 per cent.

Under no conditions was fluorescence observed in the solutions of this substance.

The *picrate* forms pale yellow prisms, readily soluble in alcohol, melting at 103°:

0·1173 gave 11·6 c.c. N_2 at 10° and 768 mm. N = 12·0.

$C_{22}H_{16}O_8N_4$ requires N = 12·1 per cent.

α-Hydroxy-β-phenylacetylamino-α-phenylethane,

$OH{\cdot}CHPh{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2Ph$.

ω-Phenylacetylaminoacetophenone (10 grams) was dissolved in methyl alcohol (150 c.c.) and water (50 c.c.). The solution was vigorously stirred and treated with sodium amalgam (300 grams of 3 per cent.), added gradually during three hours. A neutral reaction was maintained by a stream of carbon dioxide, and the reduction was completed in four to five hours. The liquid was filtered to remove sodium carbonate, and then diluted with twice its volume of water. A crystalline precipitate slowly separated, which, when recrystallised, first from benzene and finally from dry ether, formed hard, colourless prisms, melting at 99°:

0·1198 gave 0·3291 CO_2 and 0·0747 H_2C. C = 74·9; H = 6·9.

$C_{16}H_{17}O_2N$ requires C = 75·3; H = 6·6 per cent.

Unsuccessful attempts were made to cause this substance to give up the elements of water so as to produce a dihydro-oxazole derivative. Thus the action of concentrated sulphuric acid is either so mild that the compound may be recovered unchanged, or so vigorous at higher temperatures that there is complete decomposition. If a solution in concentrated sulphuric acid is warmed for two minutes on the water-bath, then diluted with water and boiled, a very strong and characteristic odour of phenylacetaldehyde is observed. The formation of this substance is clearly due to the elimination of water so as to form the compound

$CHPh{:}CH{\cdot}NH{\cdot}CO{\cdot}CH_2Ph$,

which, in turn, is further hydrolysed, yielding phenylacetaldehyde, ammonia, and phenylacetic acid.

This alcohol is also surprisingly stable towards phosphoric oxide in boiling benzene solution. In one experiment a 10 per cent. solution in benzene was boiled for one and a-half hours with a large excess of phosphoric oxide. On decomposing the product with ice, a considerable quantity of the unchanged substance was found in the aqueous phosphoric acid solution, from which it was recovered by extraction with ether after the addition of sufficient alkali to neutralise the acid. Under, however, more vigorous conditions, a very small quantity of a base can be isolated. α-Hydroxy-β-phenylacetylamino-α-phenylethane (5 grams) was dissolved in benzene (50 c.c.), and boiled with phosphoric oxide (30 grams) for five hours. The benzene was then decanted, and the residue heated for three hours on the water-bath. The product was dissolved in water, filtered, and, after rendering alkaline with potassium hydroxide, extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, and this aqueous solution treated with picric acid.

The *picrate* so formed crystallises from alcohol in canary-yellow micro-prisms, melting at 176—177°. There is a possibility that this substance is the picrate of benzyl*iso*quinoline, which melts at 184° (corr.) (Decker and Pschorr, *Ber.*, 1904, **37**, 3396). The quantity obtained was, however, very small, and the substance was not further investigated.

2-Phenyl-5-veratryloxazole, $O<\begin{matrix}C[C_6H_3(OMe)_2]\\ CPh\text{———}N\end{matrix}>CH$.

ω-Benzoylaminoacetylveratrone (1 gram) (Pictet and Gams, *Ber.*, 1909, **42**, 2948) is warmed with concentrated sulphuric acid (5 c.c.) for five minutes on the water-bath. The solution is cooled, and decomposed by the addition of water. The oxazole derivative separates in colourless crystals, and on recrystallisation from light petroleum, forms groups of very slender needles, melting at 97°. The substance is readily soluble in alcohol or benzene, and the solutions show an intense blue fluorescence. It forms a rather sparingly soluble *hydrochloride*, which dissolves in warm water, and is apparently undissociated in presence of an excess of water. Thus the introduction of methoxy-groups has the effect of increasing the strength of oxazole bases:

0·1194 gave 0·3168 CO_2 and 0·0577 H_2O. C = 72·4; H = 5·4.

$C_{17}H_{15}O_3N$ requires C = 72·6; H = 5·3 per cent.

ω-Phenylacetylaminoacetoveratrone,

$C_6H_3(OMe)_2\cdot CO\cdot CH_2\cdot NH\cdot CO\cdot CH_2Ph$.

A solution of ω-aminoacetoveratrone stannichloride (25 grams) in hot water (150 c.c.) was cooled and treated with phenylacetyl chloride

(25 grams) and an excess of potassium hydroxide. The mixture was mechanically stirred, and cooled with small pieces of ice. The pale yellow, crystalline product was collected, and recrystallised from methyl alcohol, in which solvent it is sparingly soluble in the cold. Flocculent masses of needles are first obtained, and these change in course of time into a powder consisting of stout needles or prisms, melting at 135°:

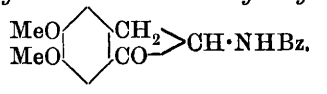
0·1249 gave 0·3171 CO_2 and 0·0687 H_2O. C = 69·2; H = 6·1.
$C_{18}H_{19}O_4N$ requires C = 69·0; H = 6·1 per cent.

2-*Benzyl*-5-*veratryloxazole*, 

ω-Phenylacetylaminoacetoveratrone (1 gram) was dissolved in cold concentrated sulphuric acid (5 c.c.). The solution becomes warm, and at the end of five minutes was diluted with water. The precipitated oxazole derivative, after collection and crystallisation from light petroleum, formed colourless needles, melting at 86°. It is fairly soluble in hot light petroleum, readily so in alcohol or benzene, but the solutions show no trace of fluorescence:

0·1272 gave 0·3410 CO_2 and 0·0703 H_2O. C = 73·1; H = 6·1.
$C_{18}H_{17}O_3N$ requires C = 73·2; H = 5·8 per cent.

2-*Benzoylamino*-5:6-*dimethoxy*-1-*hydrindone*,



2-Oximino-5:6-dimethoxy-1-hydrindone (10 grams) (Perkin and Robinson, Trans., 1907, **91**, 1074) is treated with a solution of stannous chloride (40 grams) in concentrated hydrochloric acid (50 c.c.). In a short time the temperature rises, and the stannichloride of the base separates out. After three hours, the precipitate is collected, dissolved in hot water, and the tin removed by means of hydrogen sulphide. The filtered solution, on evaporation, yields a crystalline mass of 2-*amino*-5:6-*dimethoxy*-1-*hydrindone hydrochloride*. On adding platinic chloride to a hot solution of the hydrochloride, the *platinichloride* is obtained in beautiful, golden needles:

0·1305 gave 0·0310 Pt. Pt = 23·7.
$(C_{11}H_{13}O_3N)_2,H_2PtCl_6$ requires Pt = 23·8 per cent.

2-Amino-5:6-dimethoxy-1-hydrindone hydrochloride (3 grams) was dissolved in water (50 c.c.) and shaken with benzoyl chloride (10 grams), the solution being rendered alkaline by the addition of small quantities of aqueous potassium hydroxide. A colourless, chalky solid separated,

and was collected and washed with alcohol. To effect this it is necessary to grind the substance with the solvent in a mortar.

The product, when dried on porous porcelain, cements together to a very hard and brittle cake. It is sparingly soluble in most organic solvents, and crystallises from benzene, ethyl acetate, or alcohol in needles melting at 224°:

0·1251 gave 0·3175 CO_2 and 0·0646 H_2O. C = 69·2; H = 6·1.

$C_{18}H_{17}O_4N$ requires C = 69·4; H = 5·5 per cent.

This *benzoyl* derivative was found to be unchanged by concentrated sulphuric acid or alcoholic hydrochloric acid, unless the temperature employed is so great that the substance undergoes profound decomposition.

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