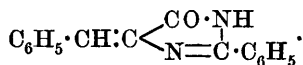


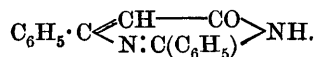
XXIV.—*The Formation of Heterocyclic Compounds.*

By SIEGFRIED RUHEMANN and H. E. STAPLETON, Scholar of St. John's College, Oxford.

THE research on the formation of α -pyrone compounds (Ruhemann, *Trans.*, 1899, **75**, 245, and 411), by the action of ethyl phenylpropiolate on the sodium derivatives of β -diketones and the ethyl esters of β -ketonic acids, induced one of us and A. V. Cunnington to examine the behaviour of organic bases towards the ethyl esters of the acids of the acetylene series, with the view of ascertaining whether in those cases also additive substances were formed which subsequently lost alcohol, and condensed to heterocyclic compounds. A few months ago (*Trans.*, 1899, **75**, 954) we published the first part of our investigations in this direction, and were able to show that by the interaction of benzamidine and ethyl phenylpropiolate a cyclic compound was produced. The constitution of this substance we represented by the symbol,

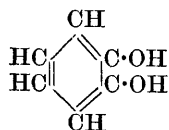


A closer examination of the reaction has led the authors of the present paper to the discovery of the following interesting fact. At the ordinary temperature, benzalphenylglyoxalidone is formed almost exclusively, but on digesting the mixture of the ethyl ester and the amidine on the water-bath, besides this substance another is produced which has been identified as *diphenylpyrimidone*,

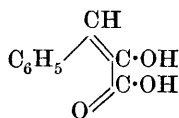
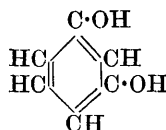


The first grouping could readily change into phenylglycidic acid, whilst the second might be expected to be the more stable. Moreover, the formation of phenylglycidic acid takes place by the action of cold caustic potash on α -chlorophenyllactic acid, that of α -hydroxycinnamic acid, on the other hand, under the influence of the boiling reagent from compounds of the cinnamyl series. These facts are in full agreement with the researches of Fittig and his pupils on the transformation of unsaturated acids into their stereoisomerides, and suggest that boiling caustic potash would partially change phenylglycidic acid into α -hydroxycinnamic acid.

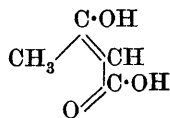
The fact that ferric chloride gives a green colour with α -hydroxycinnamic acid (p. 246) whilst it gives a violet with esters of β -ketonic acids, such as ethyl acetoacetate, seems to indicate that the structure of the former is similar to that of catechol, just as the structure of acetoacetic acid is similar to that of resorcinol. This similarity is shown by the formulæ :



Catechol.

 α -Hydroxycinnamic acid.

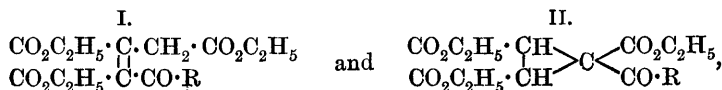
Resorcinol.



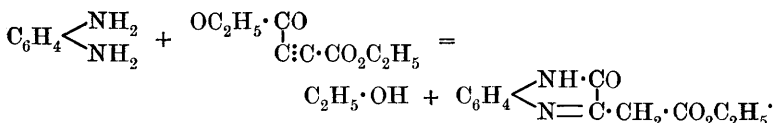
Acetoacetic acid.

Thiourea and guanidine react with ethyl phenylpropiolate in a manner analogous to urea and yield respectively *benzalthiohydantoin* and *benzalimidohydantoin*. These substances are similarly decomposed by caustic potash, and yield α -hydroxycinnamic acid. The destruction of the ring takes place in these cases with the same readiness, and is accompanied by the production of benzaldehyde. Benzalphenylglyoxalidone, on the other hand, is more stable, only partial decomposition being effected by boiling with the alkali, but a small quantity of the hydroxy-acid is certainly formed.

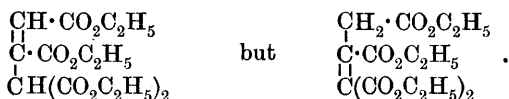
Besides the record of our work in the direction indicated above, this communication contains the results at which we have arrived, up to the present, by using ethyl acetylenedicarboxylate instead of ethyl phenylpropiolate. The study of the action of organic bases on this salt appeared to us to be of especial interest, since it had been found (Ruhemann and Cunningham, *Trans.*, 1899, 75, 784) that α -pyrone derivatives do not result from its union with the ethyl esters of β -ketonic acids. This fact led to the conclusion that both hydrogen atoms of the CH_2 group of the ketonic compound play a part in the reaction. Of the two expressions (R denoting CH_3 or C_6H_5),



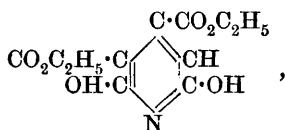
which thus have to be considered, preference had been given to the second, since ammonia does not act on these additive compounds with formation of pyridine derivatives.* On the other hand, the behaviour of *o*-phenylenediamine towards ethyl acetylenedicarboxylate points to the first formula, as we find that the diamine reacts with this salt, forming *ethyl quinoxalidoneacetate*, according to the equation



This result would correspond to the view expressed in formula I regarding the constitution of the products formed by the union of ethyl acetoacetate and ethyl benzoylacetate with ethyl acetylenedicarboxylate. Moreover, this formula is supported by the following considerations. It may be assumed that ethyl malonate would resemble the ester of the β -keto acids in its reaction with ethyl acetylenedicarboxylate. If symbol II were assigned to the former additive products, the conclusion may be drawn that ethyl malonate would also yield a trimethylene derivative with ethyl acetylenedicarboxylate. Michael (*J. pr. Chem.*, 1894, [ii], 49, 20), however, has shown that the additive compound is the ester of an unsaturated acid, since, on hydrolysis, it yields aconitic acid. These facts, whilst indicating that the substances formed by the union of the esters of β -keto acids with ethyl acetylenedicarboxylate are to be represented by formula I, would at the same time lead to the assumption that the constitution of the additive product of ethyl malonate with ethyl acetylenedicarboxylate is not



The latter formula would not be at variance with the formation of aconitic acid from the substance which it represents. It further agrees with the result of the action of ammonia on the ethyl ester of the tetracarboxylic acid. As shown below, there is thus formed *ethyl 2 : 6-dihydroxypyridine-3 : 4-dicarboxylate*,



* As will be shown in a later communication, these esters are identical with those obtained by the action of ethyl chlorofumarate on the sodium derivatives of ethyl acetoacetate and ethyl benzoylacetate (*Trans.*, 1896, 69, 530, 1383; 1897, 71, 323).

which, on hydrolysis with hydrochloric acid, loses carbon dioxide and yields citrazinic acid.

EXPERIMENTAL.

Action of Benzamidine on Ethyl Phenylpropiolate.

As mentioned in the previous paper (Ruhemann and Cunnington, *loc. cit.*), benzamidine hydrochloride and ethyl phenylpropiolate react in the presence of sodium ethoxide to form benzalphenylglyoxalidone. We now find that for the preparation of this compound 1 mol. of the ethoxide is sufficient, but that the reaction takes a different course, if, instead of allowing the mixture to stand at the ordinary temperature, it is heated on the water-bath for 2—3 hours. On adding water and a little acetic acid to the contents of the flask, a yellow solid is precipitated which dissolves in boiling glacial acetic acid, and, on cooling, crystallises out in yellowish needles melting at 284° , whilst the melting point of benzalphenylglyoxalidone is 274° .

The percentage composition of this substance, as ascertained by the following analysis, is, however, identical with that of the compound of lower melting point.

0.2010 gave 0.5695 CO_2 and 0.0910 H_2O . C = 77.15 ; H = 5.02.

0.2871 „ 28 c.c. moist nitrogen at 23° and 767 mm. N = 11.08.

$\text{C}_{16}\text{H}_{12}\text{ON}_2$ requires C = 77.41 ; H = 4.83 ; N = 11.29 per cent.

The two compounds differ, not only in their melting points, but also in their other properties. Whilst benzalphenylglyoxalidone, when treated with concentrated hydrochloric acid, at first dissolves although the solution immediately sets to a solid, the second substance, which is also soluble in the concentrated acid, remains in solution. This fact, as well as the readiness with which the latter dissolves in caustic potash, agrees with the statements of the behaviour of *diphenylpyrimidone*. The compound differs from the pyrimidone as it has a yellow colour and evolves benzaldehyde when boiled with caustic potash. A closer examination has shown, however, that these properties are due to benzalphenylglyoxalidone contained in the above product, as the solution of the latter in concentrated hydrochloric acid, on standing for a day, gives a separation which, after crystallisation from glacial acetic acid, melts at 274° and has all the properties of this compound. The presence of diphenylpyrimidone in the substance melting at 284° is established by its behaviour towards bromine. On adding the halogen to a solution of the product in concentrated hydrochloric acid, a white precipitate is at once formed which crystallises from glacial acetic acid in colourless needles melting at $297\text{--}298^{\circ}$, and has the composition $\text{C}_{16}\text{H}_{11}\text{ON}_2\text{Br}$.

0.2498 gave 0.1420 AgBr. Br = 24.20.

0.2310 „ 16.8 c.c. moist nitrogen at 16° and 765 mm. N = 8.53.

$C_{16}H_{11}ON_2Br$ requires Br = 24.46 ; N = 8.56 per cent.

Diphenylpyrimidone, which we have prepared according to Pinner's directions (see "Die Imidoäther und ihre Derivate," 1892, p. 254 ; we find the melting point to be 287—288°, compared with 284° as found by Pinner), yields, under similar conditions, a bromo-derivative which in every respect is identical with our compound. Its composition, $C_{16}H_{11}ON_2Br$, has been verified by the following nitrogen determination :

0.2303 gave 16.5 c.c. moist nitrogen at 16° and 765 mm. N = 8.40.

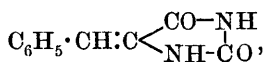
After having thus proved that benzamidine reacts with ethyl phenylpropionate at a higher temperature to form a mixture of benzalphenylglyoxalidone and diphenylpyrimidone, we were anxious to effect their complete separation. Although the solution of the mixture in concentrated hydrochloric acid deposits the glyoxalidone derivative on standing, yet a certain amount remains in the filtrate, and, on the addition of water, is precipitated along with the diphenylpyrimidone. Even on boiling the mixture with caustic potash for some hours, only partial decomposition of the glyoxalidone takes place. The product obtained on acidifying the alkaline solution and recrystallising the precipitate from glacial acetic acid still has a yellow colour, and even after prolonged boiling with alkali the odour of benzaldehyde is still perceptible. Diphenylpyrimidone can, however, be isolated from the mixture in a pure state by making use of the fact that it is very stable, whilst benzalphenylglyoxalidone, although only partially decomposed by alkalis and acids, is readily destroyed by oxidising agents. Fuming nitric acid is especially convenient for this purpose, for, as we have ascertained, it does not give rise to nitro-compounds when added to the solution of diphenylpyrimidone in glacial acetic acid, whilst the glyoxalidone is thus transformed into readily soluble substances. In order to isolate the pyrimidone from the mixed product which is formed by digesting a mixture of benzamidine and ethyl phenylpropionate on the water-bath, it is sufficient to treat its solution in glacial acetic acid with fuming nitric acid, and then to add water. By this means, a solid is precipitated which crystallises from glacial acetic acid in colourless prisms, and has all the properties characteristic of diphenylpyrimidone. Its composition has been verified by the following nitrogen determination :

0.2252 gave 22 c.c. moist nitrogen at 18° and 767 mm. N = 11.32,

$C_{16}H_{12}ON_2$ requires N = 11.29 per cent.

*Action of Urea, Thiourea, and Guanidine on Ethyl Phenylpropiolate.
Benzalhydantoin.*

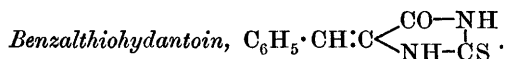
We have already mentioned in the introduction to this paper that the compound which is formed by the action of sodium ethoxide on a mixture of urea and ethyl phenylpropiolate has not the structure $C_6H_5C:C\cdot CO\cdot NH\cdot CO\cdot NH_2$, as has been stated previously (*loc. cit.*), but



This formula, which represents the compound as benzalhydantoin, follows from its behaviour towards alkali. Although it is freely soluble in dilute caustic potash and is precipitated unchanged by hydrochloric acid, yet a concentrated solution of the alkali only gradually dissolves it on boiling, and at the same time, decomposition takes place. At first, the odour of benzaldehyde is perceptible, and, later, an evolution of ammonia sets in, which ceases after the heating has been continued for three hours. The alkaline liquor, on being acidified with hydrochloric acid, yields a solid which readily dissolves in ether and crystallises from chloroform in colourless plates. This compound is characterised as α -hydroxycinnamic acid (phenylpyruvic acid) by its melting point, 154—155°, the green coloration it gives with ferric chloride, and by the following analysis :

0.2206 gave 0.5339 CO_2 and 0.0969 H_2O . C = 66.00 ; H = 4.88.

$C_9H_8O_3$ requires C = 65.85 ; H = 4.87 per cent.



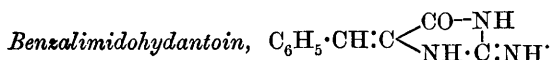
This compound is obtained in a similar manner to benzalhydantoin by mixing alcoholic solutions of sodium ethoxide and thiourea with ethyl phenylpropiolate. After standing for several hours, the alcohol is removed by evaporation, and then water and a little dilute sulphuric acid are added. A yellowish solid is precipitated, which is insoluble in water, and only sparingly soluble in alcohol or boiling glacial acetic acid. From the solution in the latter solvent, it gradually separates, on adding water, as a yellowish powder, which is washed with alcohol and dried at 100°. On slowly heating, it decomposes about 280°, but, when the temperature is rapidly raised, decomposition takes place at 300°. On analysis :

0.2081 gave 23.5 c.c. moist nitrogen at 15° and 764 mm. N = 13.30

0.2740 ,, 31.5 ,, ,, 17° ,, 764 mm. N = 13.40.

$C_{10}H_8ON_2S$ requires N = 13.72.

On boiling this compound with concentrated caustic potash for three hours in a flask fitted with a reflux condenser, it suffers a decomposition analogous to that of benzalhydantoin and yields α -hydroxycinnamic acid. This is isolated by acidifying the alkaline liquor with hydrochloric acid, extracting the solution with ether, and removing the solvent by evaporation. The residue, recrystallised from chloroform, shows all the properties characteristic of α -hydroxycinnamic acid.



When alcoholic solutions of sodium ethoxide, guanidine thiocyanate and ethyl phenylpropiolate (1 mol. of each) are mixed a yellowish-red coloration is produced, and, on slightly warming on the water-bath, the contents of the flask set to a semi-solid mass. The product is almost insoluble in water or alcohol, but dissolves in boiling glacial acetic acid, from which, on carefully adding water, it separates in yellowish, microscopic needles. These darken at about 285° and melt at 295° to a black liquid. On analysis:

0.2030 gave 0.4785 CO_2 and 0.0900 H_2O . C = 64.18 ; H = 4.92.

0.2570 ,, 47.5 c.c. moist nitrogen at 10° and 768 mm. N = 22.36.

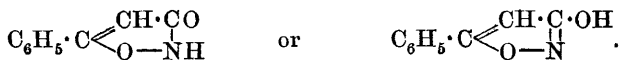
$C_{10}H_9ON_3$ requires C = 64.17 ; H = 4.78 ; N = 22.46 per cent.

This compound possesses both acidic and basic properties. It freely dissolves in hot concentrated hydrochloric acid, and the solution, on cooling, deposits yellowish needles of the hydrochloride; this, however, is unstable, and on drying loses hydrogen chloride.

Its constitution is proved, as in the former cases, by the decomposition which the substance suffers under the influence of caustic potash; when boiled with it, the odour of benzaldehyde is developed, an evolution of ammonia takes place, and an acid is formed which we have proved to be α -hydroxycinnamic acid.

Action of Hydroxylamine on Ethyl Phenylpropiolate 5-Phenyl-3-isoxazolone.

The results of our experiments, which are described above, induced us to re-examine the product of the action of hydroxylamine on ethyl phenylpropiolate. A closer study of this substance has shown that it is not a hydroxamic acid, but a cyclic compound of the formula



This constitution follows from the remarkable stability of the

substance towards acids and alkalis. Even on boiling it with these reagents for some hours, hardly any decomposition takes place, although a substance of the formula $C_6H_5 \cdot C : C \cdot C(N \cdot OH) \cdot OH$, might be expected to readily break up into phenylpropionic acid and hydroxylamine.

To the description of the properties of the isoxazolone contained in the previous paper, we add the following cryoscopic determination of the molecular weight, glacial acetic acid being used as the solvent.

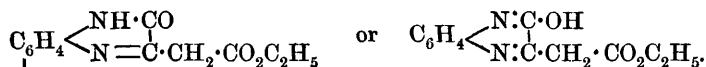
Weight of substance.	Weight of solvent.	Depression.	Mol. wt.
0.625	21.62	0.73°	161

$C_9H_7O_2N$ requires mol. wt. = 169

Further experiments, which we intend to perform, are necessary in order to ascertain whether in the methyl derivative, $C_9H_6O_2N \cdot CH_3$, the alkyl group is united with the nitrogen or with the ketonic oxygen of the isoxazolone.

Action of o-Phenylenediamine on Ethyl Acetylenedicarboxylate.

We have pointed out already that ethyl acetylenedicarboxylate and ethyl phenylpropiolate seem to show differences in their behaviour with organic bases similar to those with esters of β -ketonic acids. Of special interest in this respect is the fact that ethyl phenylpropiolate does not condense with *o*-phenylenediamine whilst ethyl acetylenedicarboxylate, on treatment with the base, yields a compound which is to be regarded as *ethyl quinoxalidoneacetate*.



The formation of this substance takes place on mixing an alcoholic solution of sodium ethoxide (2 mols.) with *o*-phenylenediamine hydrochloride (1 mol.) and ethyl acetylenedicarboxylate (1 mol.), and heating the mixture on the water-bath for 2—3 hours. After removing the alcohol by evaporation, water and a little hydrochloric acid are added, and the resulting yellow solid is washed with dilute spirit. It dissolves in boiling alcohol with great difficulty, and, on cooling, crystallises in yellow needles, which soften at 205° and melt at 210° to a red liquid.

On analysis, the following numbers were obtained :

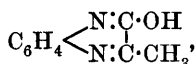
0.2074 gave 0.4714 CO_2 and 0.0968 H_2O . C = 61.98 ; H = 5.18.

0.2713 ,, 28.5 c.c. moist nitrogen at 17° and 763 mm. N = 12.23.

$C_{12}H_{12}O_3N_2$ requires C = 62.04 ; H = 5.17 ; N = 12.06 per cent.

The ethyl ester has both basic and acidic properties. It dissolves

in concentrated hydrochloric acid, but the hydrochloride thus formed is decomposed by water. Whilst the solution of ethyl quinoxalidone-acetate in hydrochloric acid is yellow, its solution in dilute caustic potash is colourless; the compound, therefore, has properties characteristic of the hydroxyquinoxalines. On boiling the ester with concentrated caustic potash for 3 hours and then acidifying the alkaline liquor, carbon dioxide is evolved and a solid is precipitated. This crystallises from boiling water in almost colourless needles melting at 245°, and was found to be identical with hydroxymethylquinoxaline,



previously prepared by Hinsberg (*Annalen*, 1896, 292, 249). The composition of the substance was verified by the following analyses:

0.2184 gave 0.5395 CO₂ and 0.0985 H₂O. C = 67.37; H = 5.01.

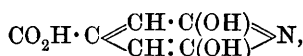
0.2303 „ 34.4 c.c. moist nitrogen at 15° and 759 mm. N = 17.47.

C₉H₈ON₂ requires C = 67.50; H = 5.00; N = 17.50 per cent.

Formation of Ethyl 2:6-Dihydroxypyridine-3:4-dicarboxylate.

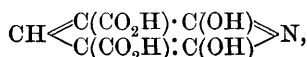
The considerations brought forward in the introduction to this paper point to the formula CO₂C₂H₅·CH₂·C(CO₂C₂H₅):C(CO₂C₂H₅)₂ for ethyl propenetetracarboxylate, the product which Michael (*loc. cit.*; see also Ruhemann and Cunningham, *Trans.*, 1899, 75, 954) obtained by the addition of ethyl malonate to ethyl acetylenedicarboxylate. We have subjected this compound to the action of ammonia with the view of preparing ethyl 2:6-dihydroxypyridine-3:4-dicarboxylate, and thus completing the series of mono- and di-carboxylic acids of 2:6-dihydroxypyridine.

From 2:6-dihydroxypyridine, two mono- and two di-carboxylic acids can be derived. The monocarboxylic acid containing the CO₂H group in the 4-position, namely,



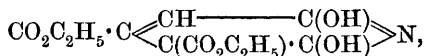
is citrazinic acid, which was discovered by Behrmann and Hofmann (*Ber.*, 1884, 17, 2687), and subsequently obtained by one of us (Ruhemann, *Ber.*, 1887, 20, 3367) in the course of his researches on the action of ammonia on the ethyl esters of unsaturated acids. The ethyl ester of the second or 3-monocarboxylic acid has lately been isolated by Errera (*Ber.*, 1898, 31, 1245).

Of the dicarboxylic acids, only ethyl dihydroxynicotinate,



has, up to the present, been recorded (see Guthzeit, *Ber.*, 1893, **26**, 2795; Ruhemann and Sedgwick, *Ber.*, 1895, **28**, 825; Errera, *Gazzetta*, 1897, **27**, ii, 393; Ruhemann and Browning, *Trans.*, 1898, **73**, 280). On hydrolysis with hydrochloric acid, it loses two mols. of carbon dioxide, and yields 2:6-dihydroxypyridine (Ruhemann, *Trans.*, 1898, **73**, 350; see also Errera, *Ber.*, 1898, **31**, 1246).

We find that the ethyl ester of the remaining dicarboxylic acid,



is readily prepared by placing concentrated aqueous ammonia with ethyl propenetetracarboxylate in a bottle, and agitating the mixture from time to time. In the course of 4—5 days, the oil disappears and the vessel contains a reddish solution, together with a yellowish solid. The latter we have not examined, since its amount is very small. The filtrate is concentrated by heating under diminished pressure on the water-bath, and then acidified with hydrochloric acid. This precipitates a solid, which dissolves readily in hot alcohol, but is only sparingly soluble in boiling water, and separates from the hot aqueous solution in colourless prisms, melting at 161—162°. Ferric chloride gives a reddish-violet coloration with aqueous or alcoholic solutions of the substance. On analysis:

0.2100 gave 0.3975 CO₂ and 0.0993 H₂O. C = 51.62; H = 5.25.

0.2340 „ 11.5 c.c. moist nitrogen at 14° and 745 mm. N = 5.66.

C₁₁H₁₃O₆N requires C = 51.76; H = 5.10; N = 5.49 per cent.

Ethyl 2:6-dihydroxypyridine-3:4-dicarboxylate, besides acidic properties, has also those of a base, since it dissolves in concentrated hydrochloric acid with the greatest ease. On boiling this solution for 3 hours, hydrolysis takes place, accompanied by the removal of 1 mol. of carbon dioxide, and there is formed a monocarboxylic acid, which is precipitated by adding water to the acid solution. This acid has been identified as citrazinic acid by direct comparison of its properties and by the following analyses:

0.1465 gave 0.2485 CO₂ and 0.0405 H₂O. C = 46.26; H = 3.03.

0.2480 „ 18.5 c.c. moist nitrogen at 9° and 769 mm. N = 9.08.

C₆H₅O₄N requires C = 46.45; H = 3.22; N = 9.03 per cent.

The decomposition which ethyl 2:6-dihydroxypyridine-3:4-dicarboxylate suffers on heating with hydrochloric acid is in accordance with the behaviour of the corresponding ester of the 3:5-substituted dicarboxylic acid which, as mentioned before, under the influence of boiling hydrochloric acid, loses 2 mols. of carbon dioxide. These facts show that 2:6-dihydroxypyridinecarboxylic acids with CO₂H groups

in the 3-position readily lose them with elimination of carbon dioxide.

In conclusion, it may be stated that further experiments on the lines indicated in this paper are in progress.

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CAMBRIDGE.
