46. 2 : 4-*Diarylpyrroles. Part IV. The Formation of Acylated* 5-*Amino*-2 : 4-*diphenylpyrroles from* β-*Benzoyl*-α-*phenylpropionitrile and Some Notes on the Leuckart Reaction.*

By W. H. Davies and Maurice A. T. Rogers.

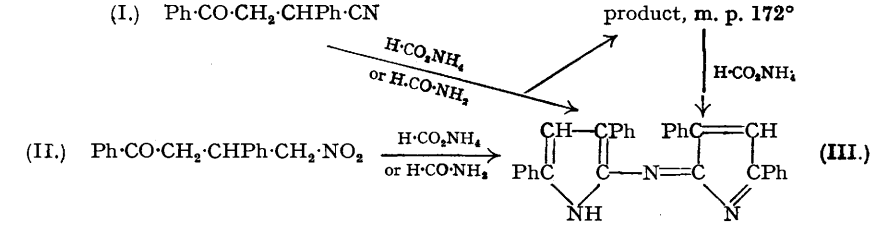
In Part I (Rogers, J., 1943, 590), the isolation of a colourless compound from the action of formamide on β-benzoyl-α-phenylpropionitrile (I) was described. This is now shown to be a formylated 5-amino-2 : 4-diphenylpyrrole. The mechanism of this reaction and of the formation of the azamethine (III) from (I) and ammonium formate or formamide are discussed and inter-related.

The mechanisms of the Leuckart reaction ($COR_2 + H{\cdot}CO_2NH_4 \longrightarrow CHR_2{\cdot}NH_2 + CHR_2{\cdot}NH{\cdot}CHO$) and of its Ott–Ingersoll modification ($COR_2 + H{\cdot}CO{\cdot}NH_2 \longrightarrow CHR_2{\cdot}NH{\cdot}CHO$) are shown to involve different intermediates which may, in the case of certain ketones, result in different products.

The *formyl* and the *acetyl* derivative of 5-amino-2 : 4-diphenylpyrrole have each been isolated in two, and the *acetyl-formyl* derivative in three, readily interconvertible isomeric forms.

In Part I (*loc. cit.*), it was shown that, when γ-nitro-β-phenylbutyrophenone (II) was heated with ammonium formate or formamide under the conditions of the Leuckart reaction, 2 : 2′ : 4 : 4′-tetraphenylazadipyrromethine (III) was formed in yields up to 33%. β-Benzoyl-α-phenylpropionitrile (I), heated with ammonium formate, also gave (III), but with formamide, only small amounts of azamethine were isolated, the main product being a colourless compound, m. p. 172°, which has now also been isolated from the action of (I) on ammonium formate. As this compound on treatment with fresh ammonium formate gave small amounts of azamethine

(III), it seemed to be a possible intermediate in the conversion of (I) into (III). It has therefore been studied in more detail in an attempt to elucidate the mechanism of these remarkable reactions.



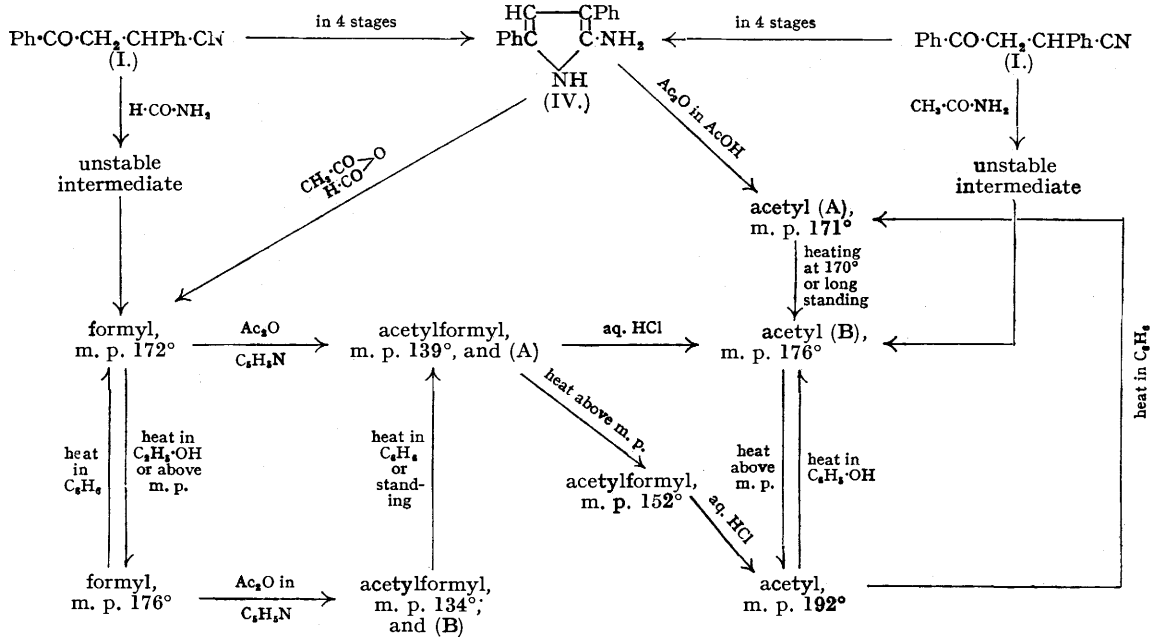
The compound, m. p. 172°, has now been identified as a *formyl* derivative of 5-amino-2 : 4-diphenylpyrrole and has been synthesised in good yield by treating 5-amino-2 : 4-diphenylpyrrole (IV) with the mixed anhydride of formic and acetic acids. A precursor of the compound, m. p. 172°, has also been isolated by working up the reaction mixture of the keto-nitrile (I) with formamide under anhydrous conditions, but owing to the ease with which this is converted into the formyl derivative, m. p. 172°, in the presence of a trace of water or even in moist air, it has not been identified with certainty.

Treatment of (I) with acetamide under anhydrous conditions similarly gave a very unstable compound which, in the presence of moisture, was rapidly converted into an acetyl derivative of 5-amino-2 : 4-diphenylpyrrole, which was also prepared by direct acetylation of the authentic amine obtained from (I) by the four-stage synthesis described in Part I (*loc. cit.*).

Hydrolysis of either of the acyl derivatives with strong mineral acid surprisingly gave β-benzoyl-α-phenylpropionic acid. This recalls the hydrolysis of 2 : 6-diaminopyridine with 70% sulphuric acid to give glutaconic acid (Titov and Levin, *J. Gen. Chem. Russ.*, 1941, **11**, 9).

The identification of the acyl derivatives of (IV) was complicated by the fact that they and the acetylformyl derivative exist in more than one form. In the case of the formyl compound, for example, crystallisation from benzene or chloroform gave fine needles, m. p. 172°, which, on heating above their m. p. or on crystallising from alcohols, gave rather stouter needles, m. p. 176°, which gave no mixed m. p. depression with the material, m. p. 172°, and were readily converted into it on heating in benzene. Two isomers of the acetyl derivative were obtained and probably a third : the acetyl-formyl derivative was also obtained in three forms. The interrelationship of these isomers is summarised in the chart.

Acyl derivatives of 5-*amino*-2 : 4-*diphenylpyrrole.*

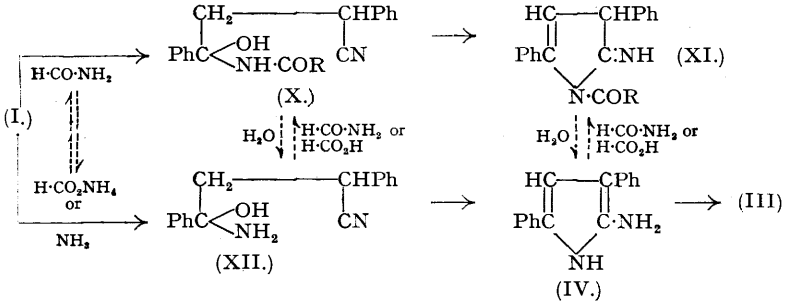


Because of the ease of isomerisation of these acyl derivatives, attempts to determine their precise structure by examining their chemical properties and ultra-violet absorption spectra were unsuccessful. (It may be mentioned that sixteen formulæ are possible for a monoacyl derivative of IV.)

We turn now to the mechanism of the formation of these acyl derivatives from the keto-nitrile (I) and amides.

Herbst and Martell (*J. Org. Chem.*, 1941, **6**, 878) showed that the action of amides, $R \cdot CO \cdot NH_2$, on ketones, COR_2, involves direct addition to give $CR_2(OH) \cdot NH \cdot COR'$, which may then react further in various ways, according to the nature of the ketone used. In some cases, loss of water occurs; *e.g.*, in the reaction with acetamide, α-ketoglutaric acid gives an addition compound which is dehydrated to an internal lactone, whereas phenylpyruvic acid gives α-acetamidocinnamic acid as the main product (Shemin and Herbst, *J. Amer. Chem. Soc.*, 1938, **60**, 1954). Applying a similar mechanism to the present case, we consider that the first intermediate in the reaction between (I) and formamide is (X), which may indeed be the highly unstable water-sensitive product isolated by working up the reaction mixture under anhydrous conditions. By cyclising and eliminating water (cf. cyclisation of acyl derivatives of *o*-aminophenylacetonitrile to 2-aminoindoles; Pschorr and Hoppe, *Ber.*, 1910, **43**, 2543), this intermediate is converted into the acylated aminopyrrole (XI), or an isomer, which is an observed product from the reaction.

The reaction of (I) with ammonium formate, on the other hand, takes a somewhat different course. In his work on the mechanism of the Leuckart reaction, Wallach (*Annalen*, 1905, **343**, 54) showed that the reaction between ammonium formate and ketones involved dissociation of the ammonium salt, followed by formation of the ketone-ammonia $CR_2(OH) \cdot NH_2$. In the case of (I), this would lead to the formation of (XII), which, by cyclisation and dehydration, would give 5-amino-2 : 4-diphenylpyrrole (IV). It was shown, however, in Part I that this amine is readily converted into the azamethine (III) on heating in air [the yield in this conversion has now been shown to be not more than 50%; the mechanism, involving oxidation and elimination of ammonia between two moles of (IV), is still obscure]. The final product from the ammonium formate reaction is therefore not the amine (IV), but the azamethine (III).



On this view, the formation of (III) in the formamide reaction is due partly to hydrolysis of (X) to (XII) and of (XI) to (IV), but mainly to the direct reaction of (I) with free ammonia formed by the thermal decomposition of formamide ($H \cdot CO \cdot NH_2 \longrightarrow CO + NH_3$). The formation of (XI) in the ammonium formate reaction is also a secondary reaction due mainly to reaction of (I) with formamide formed by dehydration of the ammonium salt on heating and to the formylating action of formamide (Hirst and Cohen, J., 1895, **67**, 829).

In agreement with this, it has been found that, from formamide and the keto-nitrile (I), the best yield of (III) is obtained by long heating at relatively low temperatures (about 120—140°). Under such conditions, formamide appears to show little tendency to react with ketones, whereas the ammonia formed by the thermal decomposition of the amide slowly gives (XII) and hence (III). At higher temperatures (above 160°), only traces of (III) can be isolated : this is because of the fairly rapid action of formamide with (I) to give (X) and hence (XI), so that the azamethine (III) is formed in such small amounts that its slow decomposition by boiling formamide (a reaction which has been observed) becomes a serious factor. The conversion of the formyl derivatives of (IV) into (III) on heating with ammonium formate is considered to be due to hydrolysis to the free amine (IV) by the water eliminated from the formate on heating. This is confirmed by the observation that the leuco-derivative of (III) is formed when the formyl compound is heated with water in a sealed tube at 180° : in the presence of air, the leuco-compound is rapidly oxidised to (III).

The hypothesis that ammonia is essential for converting (I) into (III) is supported by other results. When (I) is heated with salts which liberate ammonia, *e.g.*, ammonium phosphate or acetate, the azamethine is formed. Although the reaction was first discovered during dry heating with ammonium formate, it now appears that side reactions are set up, probably due to the reducing action of the free formic acid in the mixture. Better yields of the azamethine (III) are obtained by heating the reactants in alcohol, but by using the acetate in place of the formate in the dry-melt process the yields are raised to nearly 50%. A yield of 50% of (III), it should be noted, corresponds to the intermediate formation of 5-amino-2 : 4-diphenylpyrrole (IV) in theoretical yield.

These results throw light on the mechanism of the normal Leuckart reaction. Leuckart and co-workers showed that, when ketones or aldehydes were heated with ammonium formate at high temperatures, mixtures of primary, secondary and tertiary amines and their formyl derivatives were obtained (*Ber.*, 1885, **18**, 2341; 1886, **19**, 2128; 1887, **20**, 104; 1889, **22**, 1851, 2409; *J. pr. Chem.*, 1890, **41**, 330). Wallach (*loc. cit.*) found that the reaction could be carried out at much lower temperatures (100—150°) and that the addition of acid (formic or acetic) tended to give the amine formates instead of the formyl-amines. He showed that the mechanism involved formation of the ketone-ammonia, which was then reduced by the free formic acid in the

melt to give the primary amine, which might then be formylated or might react with more ketone and so give the secondary amine.

$$COR_2 \xrightarrow{NH_3} CR_2\begin{matrix}OH\\NH_2\end{matrix} \xrightarrow{H\cdot CO_2H} CHR_2\cdot NH_2 \underset{COR_2}{\overset{H\cdot CO_2H}{\rightleftharpoons}} \begin{matrix}CHR_2\cdot NH\cdot CHO\\CR_2(OH)\cdot NH\cdot CHR_2\end{matrix}$$

A similar mechanism was postulated by Davidson, Weiss, and Jelling (*J. Org. Chem.*, 1937, **2**, 319, 328) for the reaction between ammonium acetate or formate and benzoin or benzil in acetic acid solution, though in these cases no reduction takes place because the ketone-ammonia rearranges to desylamine, the acyl derivatives of which are amongst the observed products.

$$\begin{matrix}Ph\cdot CO\\|\\Ph\cdot CH\cdot OH\end{matrix} \xrightarrow{NH_3} \begin{matrix}Ph\cdot C{:}NH\\|\\Ph\cdot CH\cdot OH\end{matrix} \longrightarrow \begin{matrix}Ph\cdot CH\cdot NH_2\\|\\Ph\cdot CO\end{matrix} \xrightarrow{R\cdot CO_2H} \begin{matrix}Ph\cdot CH\cdot NH\cdot COR\\|\\Ph\cdot CO\end{matrix}$$

Ott (*Annalen*, 1931, **488**, 186) found that in certain cases formamide could replace ammonium formate in the reaction and gave improved yields of the formyl derivative of the primary amine: this he considered to be due to the good solvent action of the amide. Ingersoll and co-workers (*J. Amer. Chem. Soc.*, 1936, **58**, 1808) showed that this formamide modification was of general application and gave products remarkably free from secondary and tertiary amines and their derivatives. As ammonium formate is known to be dehydrated to formamide above 160° (*i.e.*, under the conditions of the normal Leuckart reaction), they postulated that formamide was the active agent in the formate reaction.

Wegler and Rüber (*Ber.*, 1935, **68**, 1053) discovered that formomethylamide also reacted with ketones and gave formyl derivatives of secondary amines. This was confirmed and extended by Novelli (*J. Amer. Chem. Soc.*, 1939, **61**, 520), who, in a later paper on the action of *N*-substituted formamides on benzoin (*Anal. Asoc. Quím. Argentina*, 1939, **27**, 151), agreed with Ingersoll's hypothesis that formamide was the active agent in the formate reaction and suggested that the mechanism for both forms of the Leuckart reaction involved addition of the amide to the ketone, to give $CR_2(OH)\cdot NH\cdot CHO$.

From the present work, it seems clear that, although formamide reacts in the way suggested by Novelli to give $CR_2(OH)\cdot NH\cdot CHO$, ammonium formate can, to some extent at least, give $CR_2(OH)\cdot NH_2$ as suggested by Wallach. It therefore follows that Ingersoll's hypothesis that formamide is the active agent in both cases is incorrect. This dual mechanism is in agreement with the fact that the formation of free amines has not been reported by the workers on the formamide reaction * (Ott, Ingersoll, Novelli, *locc. cit.*), whereas the formation of free amines in the ammonium formate reaction is well established (Leuckart, Wallach, *locc. cit.*). Further, the formamide reaction gives almost entirely the formyl derivative of the primary amine only: the frequently reported formation of secondary and tertiary amines and their derivatives in the ammonium formate reaction is undoubtedly due, as shown by Wallach, to the formation of the non-volatile amines, $CR_2(OH)\cdot NH_2$ and $CHR_2\cdot NH_2$, which compete with ammonia in the reaction with more ketone.

It should, however, be emphasised that when the Leuckart reaction is carried out above the temperature at which ammonium formate is dehydrated to formamide (*i.e.*, above about 150°), the ketone is reacting with a mixture of the amide and the ammonium salt so that both reaction mechanisms are involved, giving $CR_2(OH)\cdot NH_2$ and $CR_2(OH)\cdot NH\cdot CHO$.

From the different mechanisms involved in the Leuckart reaction and in the Ott–Ingersoll modification, it is therefore to be expected that the two methods may sometimes give rise to different products. Furthermore, "abnormal" products may be formed when the primary addition compound from either reaction is of such a type that it may be dehydrated or cyclised instead of being reduced by the free formic acid or formamide in the usual way (cf. Emerson *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 972). In cases in which the reducing action is undesirable, acetamide or ammonium acetate may show considerable advantage over the lower homologues, as has been shown in the present work with the keto-nitrile (I).

Experimental.

Melting points were taken in Pyrex tubes and are uncorrected.

The analyses are by Mr. E. S. Morton, who found that, owing to the tendency for low carbon values in this series (see Part III; Rogers, J., 1943, 598), it was advisable to mix the compounds with freshly ignited coarse copper oxide before combustion.

1. *Reactions of 5-Amino-2 : 4-diphenylpyrrole* (IV).—5-Nitroso-2 : 4-diphenylpyrrole (2 g.) in methyl alcohol (50 c.c.) was catalytically reduced to the amine (IV) as described in Part I, and the catalyst filtered off.

(a) *Formylation.* The alcoholic solution of (IV) was treated with the mixed anhydride of formic and acetic acids (5 c.c.) (cf. Béhal, G.P. 113,165, from Friedländer, vol. 6, p. 1279) and poured into water after ½ hour. The purple solid was crystallised from methyl alcohol, a small amount of azamethine (III) being removed by hot filtration. Needles of the high-melting form of formylated 5-amino-2 : 4-diphenylpyrrole separated on cooling; m. p. 173—175° (yield 1·3 g., 66%). Further crystallisation from methyl or ethyl alcohol raised the m. p. to 175—176°; crystallisation from benzene, however, gave the low-melting isomer in white felted needles, m. p. 171—172°. A mixture of the two forms had m. p. 175—176°.

(b) *Conversion into azamethine* (III). The crude amine (IV) (1·0 g.), isolated as in Part I, was heated in methyl

* An exception to this is the preparation of free amines by heating ketones with formo-β-hydroxyethylamide (Gen. Aniline, U.S.P. 2,25[illegible],245). As the amide itself is known to lose carbon monoxide readily on heating (Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079), it is probable that the intermediate $CHR_2\cdot N(C_2H_4\cdot OH)\cdot CHO$ is first formed and, under the unusually drastic reaction conditions employed in the patent example, loss of carbon monoxide follows to give the secondary amine, $CHR_2\cdot NH\cdot C_2H_4\cdot OH$.

alcohol in air for ½ hour and kept for 6 hours. The precipitated azamethine (III) was collected, washed with methyl alcohol, and dried (0·37 g., 40%). Evaporation of the red alcoholic filtrate left a resin, from which no crystalline material could be obtained.

2. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *with Formamide.*—(a) *At various temperatures.* (I) (3 g.) (cf. Hann and Lapworth, J., 1904, **85**, 1355) and formamide (10 c.c.), heated for 17 hours, gave the following yields of azamethine (III): at 120°, 17·5%; at 140°, 18%; at 160°, 1·5%; at 180°, 0%. The yields at the higher temperatures were improved by reducing the time of heating.

(b) *At* 190°. (i) *Worked up with addition of water.* (I) (100 g.) was added to boiling formamide (100 c.c.) and heated at 185—195° (bath temperature) for 3 hours. After cooling, the paste was ground with water, collected, washed successively with very dilute hydrochloric acid, very dilute sodium hydroxide solution, and water. The purple solid was dried (107 g., m. p. 152—160°) and crystallised from benzene to give white needles (64 g.), m. p. 168—170°, identical with the *formyl* derivative of 5-amino-2 : 4-diphenylpyrrole obtained *via* the nitroso-derivative. [The benzene liquors had the purple-blue colour typical of the azamethine (III).] Further crystallisation from benzene raised the m. p. to 171—172° (Found: C, 77·45; H, 5·15; N, 10·5. $C_{17}H_{14}ON_2$ requires C, 77·85; H, 5·3; N, 10·7%).

Crystallisation of either the crude or the pure product from ethyl or methyl alcohol gave the high-melting *isomer* in coarser needles, m. p. 175—176° (Found: C, 77·45; H, 5·35; N, 10·8%).

(ii) *Worked up under anhydrous conditions.* (I) (10 g.) was added to boiling formamide (20 c.c.) and heated at 185—195° (bath temperature) for 2 hours. After cooling, the paste was collected under a current of dry nitrogen and washed with benzene (10 c.c.). The light brown solid was dissolved in hot benzene (50 c.c.), decanted from the lower layer of formamide, cleared with kieselguhr, and filtered hot. Large prisms, m. p. 145—150° (softening at 142°), separated. Two crystallisations from benzene gave white prisms, m. p. 151—154°, which after vacuum drying at 50° had m. p. 158—160° (Found: C, 73·8; H, 5·0. $C_{17}H_{14}ON_2$ requires C, 77·85; H, 5·3. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·75%).

Further crystallisation of the product gave formylated 5-amino-2 : 4-diphenylpyrrole, m. p. 171—172°, identical with previous samples (no doubt due to traces of moisture in the solvent). The crude material, m. p. 145—150°, on standing in moist air, or, more rapidly, on treatment with a trace of water, changed its crystalline form and had m. p. 167—169°; mixed m. p. with formylated 5-amino-2 : 4-diphenylpyrrole, 169—171°. No acid was liberated on treatment with water, thus indicating that the unstable intermediate is not a diformyl derivative.

(c) *In ethyl alcohol.* (I) (5·9 g.), formamide (2·5 g.), and ethyl alcohol (95 c.c.) were refluxed in a stream of air for 8 hours. The hot solution, filtered from a trace of (III), deposited (I) unchanged on cooling.

A similar experiment with (I) (3 g.) and formamide (28·7 c.c.) in alcohol (50 c.c.) gave the azamethine (III) (0·3 g., 10·7%).

3. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *with Ammonium Formate.*—(a) *At various temperatures.* (I) (3 g.) and ammonium formate (15 g.) gave the following yields of azamethine (III) on heating in air: at 130° for ½ hour, 2·5%; at 130° for 3 hours, 24%; at 140° for 20 minutes, 7%; at 180° for 4 minutes, 5%; at 220° for 1 minute, 2·5%. In a slow stream of ammonia gas, the following yields were obtained: at 140° for 2 hours, 24%; at 160° for 20 minutes, 10·8%; at 180° for 4 minutes, 8·0%. In all cases above 160°, longer time of heating reduced the yields.

(b) *Under Leuckart conditions.* (I) (10 g.) and ammonium formate (50 g.) were heated in an open flask, allowing the water to distil off. The temperature rose to 200° in about 20 minutes. The product was worked up as in 2(b)(i), separated from the small amount of (III), and crystallised from benzene to give formylated 5-amino-2 : 4-diphenylpyrrole (2·0 g.), m. p. 171—172°.

(c) *In alcohol.* (I) (11·75 g.), ammonium formate (160 g.), and ethyl alcohol (200 c.c.) were refluxed for 20 minutes in a stream of dry air. The solution was filtered hot from the insoluble material, which was then washed twice with hot methyl alcohol to give azamethine (III) (2·36 g.). From the alcoholic filtrates, (I) was recovered (6·7 g.) (yield 21%, corresponding to a 49% conversion).

4. *Reaction of β-Benzoyl-α-phenylpropionitrile with Acetamide.*—(a) *Dry heating.* (i) *Worked up after addition of water.* (I) (10 g.) and acetamide (10 g.) were heated at 180° for 20 minutes and worked up as in 2(b) (i). Repeated crystallisation from benzene or alcohol gave fine white needles which softened at 169—170°, rehardened, and melted sharply at 192° (for details of this isomer, see Section 6b). This did not depress the m. p. of authentic acetylated 5-amino-2 : 4-diphenylpyrrole prepared *via* the nitroso-derivative (see Part I).

(ii) *Worked up under anhydrous conditions.* This was carried out as for the similar reaction with formamide [see reaction 2(b)(ii)], the crude product after purification from carbon tetrachloride having m. p. 133—139°. Repeated crystallisation slowly raised the m. p. to 171°, whereas addition of a trace of water, or standing in moist air gave a product softening at 168—170°, rehardening, and melting clear at 192°. This was identical with the product obtained in (i).

5. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *and Ammonium Acetate.*—(a) *Dry heating.* Ammonium acetate (25 g.) and (I) (5 g.) were heated steadily in an open flask until the temperature rose to 220° (about ½ hour). The product was repeatedly extracted with hot methyl alcohol to leave the insoluble azamethine (III) (2·3 g., 48%).

(b) *In alcohol.* Ammonium acetate (7·7 g.) and (I) (4·7 g.) in alcohol (80 c.c.) were refluxed in a stream of air for 20 hours, and the azamethine isolated as in (a) (1·5 g., 38%).

6. *Action of Acetic Anhydride on the Formyl Derivatives of 5-Amino-2 : 4-diphenylpyrrole* (IV).—(a) *On formyl derivative, m. p.* 172°. The formyl derivative (crystallised from benzene) (4 g.) in pyridine (16 c.c.) was treated with acetic anhydride (8 c.c.), left overnight, and poured into water. The crude solid (4·07 g., m. p. 120—140°) crystallised from benzene in white prisms, m. p. 171—172° [mixed m. p. with the formyl derivative, 152—160°; mixed m. p. with authentic acetylated (IV) (Part I), 171—172°]. On long storage, this product no longer melted clear at 172° and slowly rehardened at this temperature to melt clear at 192—193°.

The benzene liquors from the purification of the above acetyl derivative, m. p. 172°, were treated with light petroleum (3 vols.); the precipitate crystallised from *cyclo*hexane in stout prisms of an *acetyl-formyl* derivative of (IV), m. p. 138—139° (Found: C, 74·9; H, 5·05; N, 9·1. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3; N, 9·2%). This isomer was hydrolysed with 2N-hydrochloric acid to give the acetyl derivative, m. p. 176° (see below).

After long standing in aqueous alcohol or heating with water, the acetyl-formyl compound melted at 149—151° The same change occurred on maintaining the product at 142° ± 2° for a few minutes; the melt then solidified and re-melted at 150—151°. This product was crystallised from methyl alcohol to give an *acetyl-formyl* derivative of (IV), m. p. 150—151° (alone or mixed with the isomer, m. p. 138—139°) (Found: C, 75·5; H, 5·1; N, 9·45%). On hydrolysis with 2N-hydrochloric acid, this readily gave the acetyl derivative of (IV), m. p. 192° (see below).

(b) *On formyl derivative, m. p.* 176°. The formyl derivative (crystallised from alcohol) (4 g.) was treated as in (a); the crude product (4·1 g.), m. p. 153—176°, clear at 180°, crystallised from benzene to give an *acetyl* derivative of (IV) which on slow heating showed no change before melting at 192—193°, but, when placed in a bath at 176—190°, melted clear and immediately rehardened to melt again at 191—192° (Found: C, 78·4; H, 6·0; N, 10·4. $C_{18}H_{16}ON_2$ requires C, 78·25; H, 5·8; N, 10·1%). The same m. p.'s were observed after crystallisation of the product from alcohols and the product is therefore referred to as the acetyl derivative, m. p. 176°.

This isomer was maintained at 180—185° for 3 minutes, during which time it melted and resolidified with slight

darkening to give the *acetyl* derivative of (IV), m. p. 192°. This had m. p. 189—192° and showed no signs of softening when put in a bath at 178° or 184° (Found : C, 77·9; H, 5·4; N, 10·1%).

The isomer, m. p. 192°, on heating to 200° or on crystallising from alcohol reverted to the acetyl derivative, m. p. 176°; crystallisation from benzene, however, gave the acetyl derivative, m. p. 172°. It was therefore not possible to purify this isomer further.

No mixed m. p. depressions between the isomers were obtained even when they were put in the bath at 170°.

Although it is difficult to be certain that the acetyl derivative, m. p. 172°, is not an impure form of the acetyl derivative, m. p. 176°, we believe them to be separate isomers. The chief distinction between them is the rate at which they are converted on heating into the acetyl derivative, m. p. 192°.

The benzene liquors from the purification of the acetyl derivative, m. p. 176°, were treated with light petroleum (3 vols.) to give a white solid, m. p. 134—136°, mixed m. p. with the acetyl-formyl derivative (m. p. 139°) 99—113°. On storing or on crystallising from benzene, this new acetyl-formyl derivative of (IV) was converted into the acetyl-formyl derivative, m. p. 139°. Repeated crystallisation from ligroin (b. p. 100—120°) surprisingly gave the formyl derivative, m. p. 172°, presumably by hydrolysis with a trace of moisture in the solvent. It was therefore not possible to purify this isomer for analysis.

7. *Action of Acetic Anhydride on the Acetyl Derivative of* (IV).—The acetyl compound (4·7 g.), m. p. 176°, acetic anhydride (27·5 c.c.), and sodium acetate (2·1 g.) were refluxed for 1½ hours and poured into water to give a solid (5·6 g.), m. p. 148—167°. Repeated crystallisation from alcohol or benzene gave a *diacetyl* derivative of (IV) in stout prisms, m. p. 186—188° (Found : C, 75·2; H, 5·6; N, 8·95. $C_{20}H_{18}O_2N_2$ requires C, 75·5; H, 5·7; N, 8·8%). This product shows no tendency to isomerise in different solvents or at 190°. It was not readily hydrolysed by hot 2N-hydrochloric acid.

The alcoholic liquors from the purification of the diacetyl derivative gave a second crop of crystals (0·3 g.), m. p. 106—109°. Recrystallisation from light petroleum (b. p. 40—60°) gave stout prisms of a *triacetyl* derivative of (IV), m. p. 111—112° (Found : C, 73·25; H, 5·55; N, 7·8. $C_{22}H_{20}O_3N_2$ requires C, 73·3; H, 5·55; N, 7·8%). Like the diacetyl derivative, this showed no tendency to isomerise and was resistant to acid hydrolysis.

8. *Action of Acids on the Aminopyrrole* (IV) *and its Acyl Derivatives.*—(a) *Dilute hydrochloric acid on the formyl derivative, m. p.* 172°. The formyl derivative (2·65 g.), methyl alcohol (41·2 c.c.), and 2N-hydrochloric acid (32·5 c.c.) (*i.e.*, N-hydrochloric acid in 50% methyl alcohol) were refluxed for 25 minutes. Water (100 c.c.) was added, and the clear solution treated with sodium hydrogen carbonate (5·5 g.) in water (100 c.c.). The pale yellow precipitate of the aminopyrrole (IV) was rapidly collected and washed. On exposure to air, the base became blue owing to the formation of the azamethine (III). Treatment with acetic anhydride in pyridine gave the acetyl derivative, m. p. 171°; treatment with the mixed anhydride of formic and acetic acids gave the formyl derivative, m. p. 172°, or 176° according to whether benzene or alcohol was used for purification.

(b) *Concentrated hydrochloric acid on the formyl derivative, m. p.* 172°. The formyl derivative (4·0 g.) and 36% hydrochloric acid (20 c.c.) were heated on a steam-bath for 4 hours. Water was added, and the solid collected (3·5 g., m. p. 145—146°), purified by extraction with 2N-sodium carbonate, reprecipitated, and crystallised from benzene to give β-benzoyl-α-phenylpropionic acid (2·8 g., 72%), m. p. 149—150° (decomp.) alone or mixed with authentic acid prepared by hydrolysis of (I) (Hann and Lapworth, *loc. cit.*) (Found : C, 75·45; H, 5·55. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·5%).

(c) *Concentrated hydrochloric acid on the aminopyrrole* (IV). The amine [1 g., prepared as in (a)] was treated with 36% hydrochloric acid as in (b) to give β-benzoyl-α-phenylpropionic acid (0·26 g., 24%), m. p. 150—151° (decomp.).

(d) *Concentrated hydrochloric acid on the acetyl derivative, m. p.* 171°. The acetyl compound (0·5 g.), prepared *via* the nitrosopyrrole, on similar treatment with 36% hydrochloric acid gave β-benzoyl-α-phenylpropionic acid (0·05 g., 9·3%), m. p. 149—150° (decomp.).

9. *Miscellaneous Results.*—(a) When the azamethine (III) (0·5 g.) was heated with boiling formamide (10 c.c.) for 2½ hours, the blue product was completely destroyed, giving a red solution.

(b) The formyl derivative (3 g.), m. p. 172°, was heated with water (10 c.c.) in a nitrogen-filled Carius tube at 180° for 3 hours. The product was pale blue, but, when air was passed in, rapidly became intensely blue owing to oxidation of the leuco-compound to the azamethine (III) (0·14 g., 5%). Some (1·4 g.) of the isomeric formyl derivative, m. p. 176—178°, was recovered and amounts of formic acid (2 mols.) and ammonia (1 mol.) corresponding to the reaction $2{>}CH{\cdot}NH{\cdot}CHO \xrightarrow{2H_2O} {>}CH{\cdot}N{:}C{<} + 2H{\cdot}CO_2H + NH_3 + H_2O$ were detected in the aqueous filtrate.

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