The condensation of aromatic aldehydes with acyl derivatives of glycine has, in its various modifications, furnished the most useful method available for the synthesis of compounds which may in turn be converted into aromatic amino and ketonic acids such as tyrosine, tryptophane, and thyroxine. The reaction was first studied by Plochl (1) who condensed hippuric acid with benzaldehyde and salicylic aldehyde. The correct interpretation of this reaction and the demonstration of its ability for amino acid synthesis was furnished later by Erlenmeyer (2). Instead of hippuric acid, later investigators (3) have used other derivatives of glycine such as hydantoin and glycine anhydride. In connection with an investigation of aldehyde derivatives of amino acids, peptides, and proteins it became of interest to examine the behavior of glycine itself when condensed with benzaldehyde and acetic anhydride. The reaction was first studied by Plöchl (1) who stated that: “Es konnten jedoch daraus auf keine Weise zur Untersuchung einladende Körper sondern nur Schmieren erhalten werden.” In fact it was this failure to effect the condensation of glycine that led Plöchl to use hippuric acid in its place. Later on Erlenmeyer and Früstück (4) succeeded in isolating the azlactone of $$\alpha$$-acetaminocinnamic acid and subsequently Bergmann and Stern (5), by varying the conditions, obtained 44 to 50 per cent yields and showed how valuable this and the related derivative from $$p$$-hydroxybenzaldehyde were for the synthesis of amino acids and peptides.

A reinvestigation of the condensation just referred to has shown that the reaction is complicated by a competing reaction taking place between glycine and benzaldehyde with formation of a non-
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acetylated derivative possibly of a type resembling a Schiff base. The two reactions may be represented as follows:

\[
\begin{align*}
\text{I.} & \quad \text{II.} \\
\text{CH}_2 \cdot \text{NH}_2 & \quad \text{CH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_2 \\
\text{COOH} & \quad \text{COOH} \\
\text{C}_6\text{H}_5 \cdot \text{CH} = \text{C} & \quad \text{C}_6\text{H}_5 \cdot \text{CH} = \text{C} \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_2 \\
\text{OC} \quad \text{C} \cdot \text{CH}_3 & \quad \text{COOH} \\
\text{O} & \\
\end{align*}
\]

This substance (III) which may be called benzylidene glycine was isolated and analyzed. By analogy and in view of its relative stability it would appear not unlikely that the substance is polymerized though accurate molecular weight determinations are lacking. It is also possible that the alternative structure (IV) containing the same ring as the azlactones may demand consideration. Analogous compounds have been obtained from other amino acids and will be described later.

In view of the fact that this second product of the condensation of glycine and benzaldehyde with acetic anhydride is not an acetylated compound, it appeared likely that its formation could be largely suppressed by acetyling the glycine before subjecting it to reaction with the benzaldehyde. This proved to be the case and correspondingly larger yields of the azlactone of \(\alpha\)-acetaminocinnamic acid were obtained. The acetylation of glycine is not an entirely simple matter. Boiling with glacial acetic acid is ineffective, while warming on the water bath with excess of acetic anhydride yields colored products for the removal of which Radenhausen (6) advocated the use of chlorine. It was found that the acetylation could be far more conveniently effected by warming glycine suspended in 3 parts of glacial acetic acid with
the theoretical amount of acetic anhydride until solution is just effected. This only takes a minute or so with moderate quantities of materials and on cooling a virtually theoretical yield of acetyl-
glycine (aceturic acid) crystallizes out. This method offers by far the easiest method of preparation of the substance. The 
acetylated glycine was then condensed with a variety of typical aldehydes as described in the experimental part of this paper. 
The only product of the reaction calling for any comment is that derived from salicylic aldehyde. While the product first 
formed is the normal acetylated azlactone (V), on treatment with

\[
\begin{align*}
\text{V.} & : \quad \begin{array}{c}
\text{N} \equiv \text{C} \cdot \text{CH}_3 \\
\text{HC} = \text{C} \cdot \text{CO} \\
\text{O} \cdot \text{CO} \cdot \text{CH}_3 \\
\end{array} \\
\text{VI.} & : \quad \begin{array}{c}
\text{NH} \cdot \text{CO} \cdot \text{CH}_3 \\
\text{CH} = \text{C} \cdot \text{COOH} \\
\text{OH} \\
\end{array} \\
\text{VII.} & : \quad \begin{array}{c}
\text{NH} \cdot \text{CO} \cdot \text{CH}_3 \\
\text{CH} = \text{C} \cdot \text{CO} \\
\end{array}
\end{align*}
\]

alkali and subsequent acidification the expected o-hydroxy-\(\alpha\)-acetaminocinnamic acid (VI) has only a transient existence and passed over to a neutral substance giving no phenolic reactions, which is doubtless \(\alpha\)-acetaminocoumarin (VII).

A word may be added as to the use of the reaction just described for preparative purposes. As regards the synthesis of aromatic amino acids and peptides, their utility has been admirably shown by Bergmann and Stern. For the preparation of \(\alpha\)-ketonic acids the reaction should prove of real value. The ordinary Erlenmeyer method of preparation by the action of strong alkali or azlactones derived from hippuric acid is always complicated by the simultaneous formation of benzoic acid, the complete separation of which from the \(\alpha\)-ketonic acid is often a matter of doubt and difficulty. This objection is entirely avoided by the use of the azlactones derived from acetylglycine. These compounds on treatment with alkali give \(\alpha\)-ketonic acids and acetic acid very smoothly in good yield and their separation offers no difficulty.
EXPERIMENTAL.

Direct Condensation of Glycine with Benzaldehyde.—Glycine (2 gm.), anhydrous sodium acetate (2 gm.), benzaldehyde (5 gm.), and acetic anhydride (10 cc.) were heated in a water bath for 2 hours. Water was then added and the excess of benzaldehyde blown off with steam. Sulfuric acid was then added until acid to Congo red and the clear aqueous solution poured off from the yellow-brown solid material. This solution on standing deposits a considerable amount of $\alpha$-acetaminocinnamic acid. The solid matter was then dissolved in half normal sodium hydroxide and filtered from a trace of residue. The filtrate is acidified and the precipitate filtered off, washed, and dried. It is made up of a large amount of $\alpha$-acetaminocinnamic acid with a smaller amount of benzylidene glycine. The latter is separated by dissolving the mixture in a minimum amount of absolute alcohol and precipitating with dry ether. A brownish precipitate separates out which may be purified by repeating the precipitation. The yield of this product is about 10 per cent but undoubtedly much is lost. A yield of about 50 per cent of $\alpha$-acetaminocinnamic acid is obtained from the ether mother liquors. Its properties are identical with those previously described.

Benzylidene glycine forms a buff-colored powder which gives a brown solution in alcohol. Its alcoholic solution reacts acid to phenolphthalein but only requires about half the theoretical amount of alkali to neutralize it. It is insoluble in water, ether, chloroform, and petroleum, but when freshly prepared is freely soluble in alcohols and in aqueous sodium hydroxide. It has not been possible to crystallize it and the analytical data constitute the only evidence of its purity. Several preparations of identical properties were made. On heating, the substance darkens at about 180° and melts somewhat indefinitely at about 207°. As stated in the introduction it is not unlikely that the substance is polymerized and its structure cannot be regarded as settled. For analysis the product was dried in a vacuum at 80° over phosphorus pentoxide. It does not appear to be hygroscopic.

Analysis. $C_{6}H_{5}O_{2}N$.
Calculated. C 66.4, H 5.52, N 8.59.
Found. " 66.4, 66.6, " 5.74, 5.72, " 8.2, 8.40.
Acetylglycine (Aceturic Acid).—Finely powdered glycine is suspended in 4 cc. of glacial acetic acid and acetic anhydride (2.0 cc.) added. The mixture contained in a small flask is gently rotated over a small flame until the glycine is just dissolved. This requires only about a minute and prolonged heating must be avoided. On cooling, crystals of aceturic acid separate out at once. The product may be sucked off, washed with a little water or ether, and dried. The yield amounts to 2.15 to 2.20 gm., over 90 per cent of the theoretical amount, and requires no further purification. It melts at 206°. On titration with phenolphthalein 0.1 gm. required 8.6 cc. of decinormal sodium hydroxide, indicating a molecular weight of 116 as against a calculated value of 117. It also gave satisfactory results on elementary analysis.

Azlactone of α-Acetaminocinnamic Acid.—Glycine (1.5 gm.) was acetylated as above described by use of 3 cc. of glacial acetic acid and 2.0 cc. of acetic anhydride. Without removing the acetic acid mother liquor from the acetylglycine, 1.6 gm. (1 mol) of anhydrous sodium acetate were added together with benzaldehyde, 2.2 gm. (1 mol), and acetic anhydride, 7 cc. The mixture was heated for 2 hours in a water bath. No separation of crystals takes place during the heating but the color changes to a dark yellowish green. On adding water by degrees to the cooled mixture the azlactone is precipitated as a yellow mass. It is filtered off, spread on porous plates, and dried. The yield of crude product amounts to 70 per cent of the theoretical quantity. It is purified by recrystallization from benzene which leaves behind a trace of insoluble impurity. The substance formed stout yellow needles melting sharply at 154–155°. Bergmann and Stern record 151–152°, while Erlenmeyer and Früstück gave 146–147°. The substance gave satisfactory results on analysis. The preparation of the above compound is unfavorably influenced by too prolonged heating or by using a higher temperature. Acetic acid without acetic anhydride is not effective.

α-Acetaminocinnamic Acid. On dissolving the preceding azlactone in hot 0.5 N sodium hydroxide (3 mols) and acidifying the filtered solution, this compound readily separates. It is recrystallized from boiling water, a little charcoal being used to remove pigment. It is readily soluble in hot water, sparingly in cold, and forms colorless cubes and plates melting at 190–192° as described
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by Bergmann and Stern. It reduces permanganate freely and gives phenylpyruvic acid on boiling with 20 per cent sodium hydroxide.

Azlactone of o-Acetoxy-α-Acetaminocinnamic Acid.—This compound was readily obtained from salicylic aldehyde. The preparation was carried out exactly as for the preceding azlactone except that 10 cc. of acetic anhydride were used and 2.4 gm. of salicylic aldehyde. The yield of crude product amounted to 2.3 gm. It was recrystallized from toluene, too long boiling with the solvent being avoided. It crystallizes in long bright yellow needles, moderately soluble in hot alcohol, sparingly soluble in cold alcohol. It melts at 203–205°.

Analysis.* C_{11}H_{11}O_{4}N.
Calculated. C 63.7, H 4.49, N 5.71.

* The analyses for carbon and hydrogen recorded in this paper were all made in the usual way with 120 to 150 mg. of substance. The nitrogen determinations were made by Kjeldahl's macro method.

α-Acetaminocoumarin.—On dissolving the preceding substance in three molecular proportions of half normal sodium hydroxide and then precipitating the bright red alkaline solution with mineral acid, the initial precipitate which presumably is o-hydroxy-α-acetaminocinnamic acid rapidly changes to a heavy brown neutral compound. It is very sparingly soluble in water but may be recrystallized conveniently from methyl alcohol with a little charcoal. It forms felted masses of long colorless needles melting at 203–204°.

Its aqueous solution reacts neutral to litmus, and it gives no coloration with ferric chloride or Millon's reagent. Its properties and analysis clearly indicate that the substance is α-acetaminocoumarin (VII).

Analysis. C_{13}H_{9}O_{3}N.
Calculated. C 65.0, H 4.75, N 6.82.
Found. “ 64.9, “ 4.43, “ 6.90.

Azlactone of p-Acetoxy-α-Acetaminocinnamic Acid.—The condensation was carried out as in the case of salicylic aldehyde. The yield was 72 per cent of the theoretical amount. The azlactone
is readily crystallized from methyl alcohol in which it is freely soluble in the boiling solvent but sparingly soluble at room temperatures. It forms glistening golden plates melting at 138-139°+. Bergmann and Stern record 131-132°.

*p-Hydroxy-α-Acetaminocinnamic Acid.*—On dissolving the preceding substance in half normal sodium hydroxide and then acidifying, the free acid separates rather slowly in needles that are apt to retain a little pigment. On recrystallizing from water with charcoal, colorless clear lance-shaped needles are readily obtained. It is sparingly soluble in cold water, freely soluble in hot water or alcohol. The substance dried at room temperature contains water of crystallization and when heated softens around 140° before melting at 207°. On drying at 110°, the clear crystals become opaque and then melt sharply at 203-205° as described by Bergmann and Stern.

*Azlactone of α-Acetaminopiperonylacrylic Acid.*—Piperonal (3 gm.), used in place of benzaldehyde, gave after 3 hours heating on the water bath 2.60 gm. of condensation product. It was well washed with water and then treated with a little ether to remove a trace of oily impurity. It was recrystallized from toluene and forms glistening prisms with a greenish gold color. It is sparingly soluble in methyl alcohol even when hot, freely soluble in acetic acid and ethyl acetate, sparingly soluble in ether. It melts at 183-184°.

*Analysis.* \( \text{C}_{12} \text{H}_{11} \text{O}_{4} \text{N} \).

Calculated. \( \text{C} 62.4, \text{H} 3.89, \text{N} 6.06. \)

Found. \( \text{“} 62.4, \text{“} 4.20, \text{“} 6.10. \)

α-Acetaminopiperonylacrylic Acid.—The free acid was obtained in the usual way from the preceding azlactone. It was recrystallized from water, in which it is sparingly soluble even at the boiling temperature. It separates in the form of nodular masses of needles concentrically arranged and melts at 220-221°.

*Analysis.* \( \text{C}_{12} \text{H}_{11} \text{O}_{4} \text{N} \).

Calculated. \( \text{C} 57.8, \text{H} 4.43. \)

Found. \( \text{“} 57.3, \text{“} 4.59. \)

*Azlactone of α-Acetamino-p-Nitrocinnamic Acid.*—p-Nitrobenzaldehyde (3.22 gm.), when treated as previously described, gave 96 per cent of the theoretical amount of condensation product.
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In the early stage of the reaction, solution is complete but after longer heating on the water bath a solid cake of crystals separates out. This crystallization was not observed in the case of any of the related compounds here described. After an hour of heating, water was added and the compound filtered off. It is sparingly soluble in alcohol or benzene but can be readily crystallized from acetic acid. The crystals have a fine clear orange-yellow color and have the shape of long whetstones. The melting point is 185-186°.

Analysis. \( \text{C}_{11}\text{H}_8\text{O}_4\text{N}_2 \).
Calculated. C 56.8, H 3.45, N 12.0.

α-Acetamino-\(\beta\)-Nitrocinnamic Acid.—The preceding azlactone dissolves in dilute sodium hydroxide with a clear red color and on acidifying the acid is obtained as an almost white granular precipitate. It is very sparingly soluble in water but readily soluble in alcohol. Dilute methyl alcohol is a convenient solvent for recrystallization. It forms sickle-shaped crystals melting at 234–235°.

Analysis. \( \text{C}_{11}\text{H}_8\text{O}_4\text{N}_2 \).
Calculated. C 52.8, H 4.00, N 11.2.

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