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## Synthetic Routes to $\beta, \beta$ -Diaryl- $\alpha$ -Amino Acids *via* Nitrogen Heterocycles (I)

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$\beta, \beta$ -Diphenylalanine and its ring-substituted analogs are prepared from oxazolones, thiazolones, imidazolones, hydantoin, thiohydantoin, and piperazine 2,5-diones by alkaline ring opening followed by acid cleavage of the N-benzoyl group. The oxazolone approach, with its variations, offers the most advantageous route to these compounds. Several new amino acids are described.

Although  $\beta, \beta$ -diphenylalanine (I) has been known for over thirty years (3), no general method for the synthesis of this amino acid and its ring-substituted analogs has been described. In an effort to develop such a method, we examined a wide variety of nitrogen heterocyclic systems as potential intermediates. These results are discussed below.

### 1. From saturated azlactones.

We have reported previously (3d) the synthesis of compound I by hydrolytic ring opening of 2-phenyl-4-benzhydryl-5-oxazolone (II), as shown in equation 1.

In similar fashion, chloro, and nitro ring-substituted analogs of I were obtained. The overall yield from II to I was 85-90%.

The main problem was to find the most suitable route to saturated azlactones, such as II. A reasonable approach would seem to be the hydrogenation of the azlactone (III). However, attempts to prepare III *via* the conventional Erlenmeyer synthesis or its modifications, using benzophenone and hippuric acid, have not been successful and, to our knowledge, the compound remains unknown.

In a series of recent papers (4-6), we have described methods for the synthesis of saturated azlactones from the readily available 2-phenyl-4-arylidene-5(4H)-oxazolones (IV), which were prepared from substituted benzaldehydes and hippuric acid.

The reactions involved are summarized below:

(a) Conjugate addition of the elements of benzene under Friedel-Crafts conditions (equation 2).

This reaction is extremely complex and is dependent upon reaction conditions and particularly on the nature of substituents on the arylidene ring (4). Yields are favorable (60-90%) when Ar = C<sub>6</sub>H<sub>5</sub>, *o*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, and 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

(b) Reaction of labile geometric isomers of azlactones with aryl Grignard reagents.

The 4-arylidene-5-oxazolones exhibit geometrical isomerism. Whereas the stable isomers, ordinarily obtained by the Erlenmeyer procedure, react with Grignard reagents to give ring-opened tertiary alco-

hols by attack at the lactone carbonyl (7), the labile isomers exhibit stereoselective behavior toward these reagents and give 35-40% yields of 1,4-addition products (5), identical with those obtained by the method shown in equation 2. These isomers frequently may be obtained from the stable isomers by isomerization with saturated hydrobromic acid under free-radical conditions (5). In general, the configurations of these isomeric pairs have not been clearly established. It is noteworthy that although both the saturated azlactones and the amino acids derived from them possess two different asymmetric centers when Ar  $\neq$  C<sub>6</sub>H<sub>5</sub>, we have isolated but one diastereomer, despite the fact that isomeric azlactones were used as starting materials.

(c) Addition of Grignard reagents in the presence of Cu(I) chloride.

The mode of addition of aryl Grignard reagents to the stable isomers of 4-arylidene azlactones is dramatically reversed by addition of cuprous chloride in the molar ratio of 2:3 = CuCl:ArMgX. Over a wide range of substituents, yields of 25-75% of 1,4-addition products (analogous to II) are obtained (6). This method offers the added feature of furnishing readily amino acids with both phenyl nuclei substituted. The full potentialities of this approach have not been exploited and further studies, both synthetic and mechanistic, are desirable.

### 2. From thiazolones.

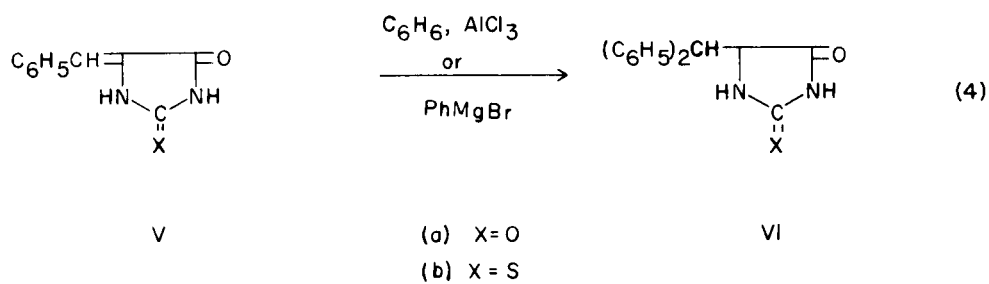
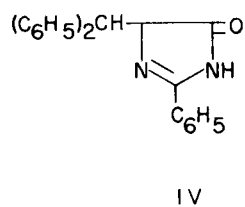
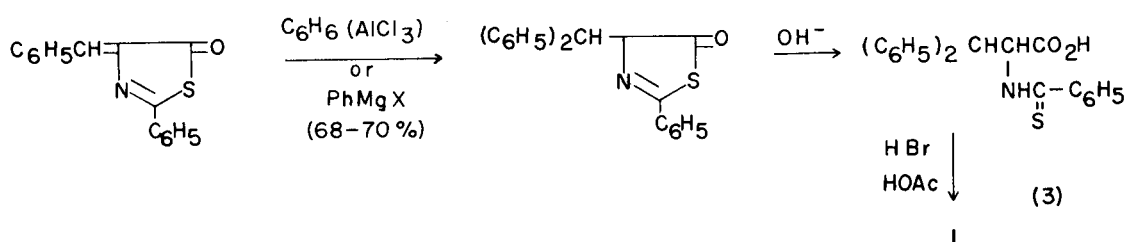
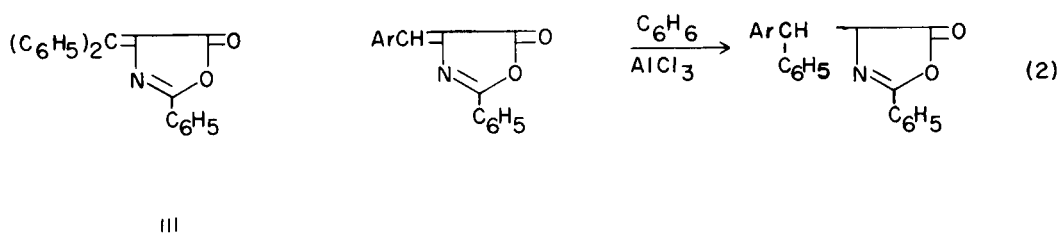
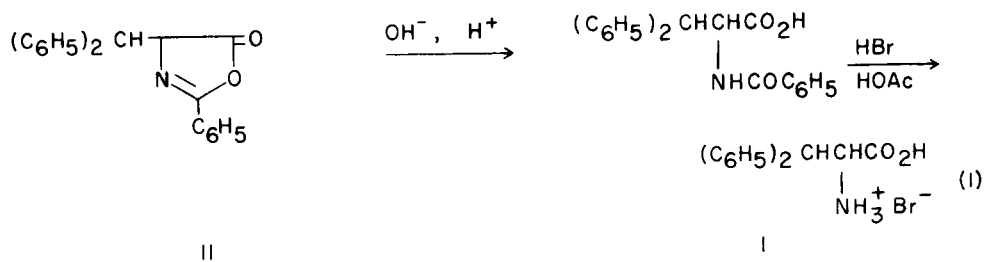
The  $\beta, \beta$ -diaryl amino acids may also be prepared from appropriately substituted thiazolones (8), as shown in equation 3.

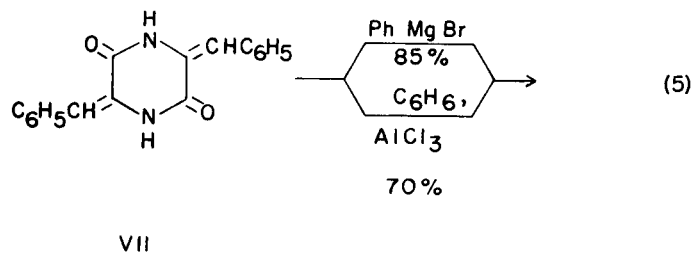
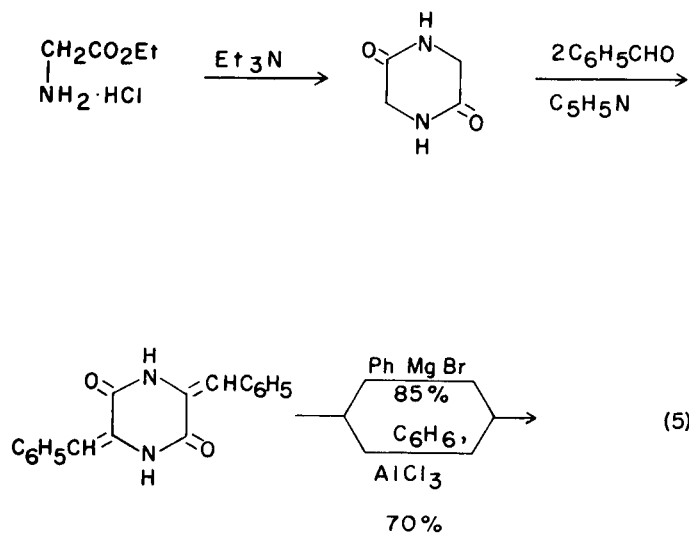
Since the thiazolones are generally prepared from oxazolones, this method does not appear to offer any material advantage over the azlactone route.

### 3. From imidazolones.

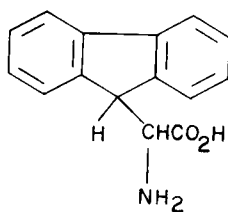
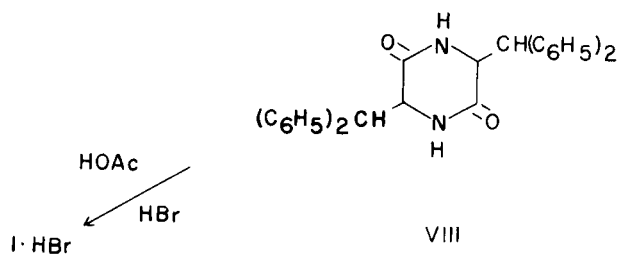
Imidazolones provide convenient starting materials for the synthesis of amino acids (9).

The imidazolone IV was obtained by reaction of II with aqueous ammonia and potassium carbonate. It has been prepared previously by conjugate ad-



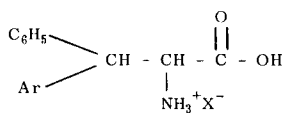


VII



IX

TABLE I  
β,β-Diaryl-α-amino Acids



Ar	X <sup>-</sup>	m. p.	Formula	% Carbon		% Hydrogen	
				Calcd.	Found	Calcd.	Found
C <sub>6</sub> H <sub>5</sub>	Cl	180°	C <sub>15</sub> H <sub>16</sub> NO <sub>2</sub> Cl	-----	-----	-----	-----
2-Cl-C <sub>6</sub> H <sub>4</sub>	Cl	178°	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> Cl <sub>2</sub>	57.70	56.59	4.84	4.80
2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	Cl	213°	C <sub>15</sub> H <sub>14</sub> NO <sub>2</sub> Cl <sub>3</sub>	51.97	52.01	4.07	3.99
4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Br	217°	C <sub>15</sub> H <sub>15</sub> N <sub>2</sub> O <sub>4</sub> Br	49.06	48.95	4.12	3.80
2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Br	206°	C <sub>15</sub> H <sub>15</sub> N <sub>2</sub> O <sub>4</sub> Br	49.06	49.26	4.12	3.78
2-C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	Br	219°	C <sub>21</sub> H <sub>20</sub> NO <sub>2</sub> Br	63.32	62.66	5.06	5.40
4-ClC <sub>6</sub> H <sub>4</sub>	Cl	204°	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> Cl <sub>2</sub>	57.70	57.42	4.84	5.02
4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Br	201°	C <sub>16</sub> H <sub>18</sub> NO <sub>2</sub> Br	57.14	57.32	5.36	5.18
4-HOC <sub>6</sub> H <sub>4</sub>	Br	195°	C <sub>16</sub> H <sub>16</sub> NO <sub>3</sub> Br	53.25	52.94	4.73	4.91

dition of phenylmagnesium bromide to 2-phenyl-4-benzylidene-5(4H)-imidazolone (10).

Compound IV gave  $\beta,\beta$ -diphenylalanine on hydrolysis with red phosphorus, phosphoric acid, and potassium iodide (11). The difficulty in isolating the imidazolone in pure form due to low solubility, limits the utility of this approach.

#### 4. From hydantoins and thiohydantoins.

Mumford and coworkers (12) have prepared  $\beta,\beta$ -dialkyl  $\alpha$ -amino acids by hydrolysis of 5,5-dialkylhydantoins and thiohydantoins.

We have found that the hydantoins VIa and VIb are conveniently prepared as shown in equation 4.

Addition proceeds exclusively 1,4, in yields of 70-82%. Acid hydrolysis of VIa or VIb gave diphenylalanine. A disadvantage of this method is the relatively poor solubility of the benzylidene hydantoins (V) in non-polar solvents.

#### 5. From diketopiperazines.

3,6-Dibenzylidenepiperazine-2,5-dione (VII) prepared from piperazine-2,5-dione and excess benzaldehyde (13), adds the elements of benzene 1,4 exclusively to form 3,6-dibenzhydrylpiperazine-2,5-dione (VIII) in 70-85% yield, as shown in equation 5. Compound VIII may be hydrolyzed to  $\beta,\beta$ -diphenylalanine. Although this method possesses the advantage that two molecules of amino acid are derived from one molecule of diketopiperazine, the poor solubility characteristics of these compounds seriously detract from its general use.

When all factors are taken into account, it appears that the oxazolone approach, with its variations, offers the most advantageous method for the synthesis of these amino acids.

We have also prepared (14) 9-fluorenylglycine (IX), the *o,o'*-bridged analog of  $\beta,\beta$ -diphenylalanine, by reductive hydrolysis of 2-phenyl-4-(9'-fluorenylidene)-5(4H)-oxazolone (15).

#### Biological Testing.

dl- $\beta,\beta$ -Diphenylalanine hydrobromide was screened at the Mead Johnson Research Center. It was found to have no antibacterial activity and to be ineffective as an amino acid antagonist for bacteria.

#### EXPERIMENTAL (16)

##### 2-Phenyl-4-benzhydryl-5(4H)-oxazolone (ID).

This compound and ring-substituted analogs were prepared from 2-phenyl-4-arylidene-5(4H)-oxazolones, according to procedures described previously (4-6).

##### Hydrolysis of oxazolones to N-benzoyl amino acids.

Compound II (8.4 g.), dissolved in 50 ml. of 95% ethanol, was treated with a solution of 30 g. of sodium hydroxide in 250 ml. of water. The mixture was heated under reflux for 24 hrs., after which 100 ml. of 3N hydrochloric acid was added to precipitate the N-benzoyl derivative, which was crystallized by dissolving in 5% sodium hydroxide and reprecipitating with hydrochloric acid. N-Benzoyl- $\beta,\beta$ -diphenylalanine (8.8 g.), m.p. 193°, was obtained.

*Anal.* Calcd. for  $C_{22}H_{18}NO_3$ : C, 76.52; H, 5.51. Found: C, 76.47; H, 5.44.

The following N-benzoyl amino acids were prepared similarly:  $\beta$ - $C_6H_5$ ,  $\beta$ -(*o*-Cl $C_6H_4$ ), m.p. 210°;  $\beta$ - $C_6H_5$ ,  $\beta$ -(2,4-Cl $_2C_6H_3$ ), m.p. 195°;  $\beta$ - $C_6H_5$ ,  $\beta$ -(*p*-NO $_2C_6H_4$ ), m.p. 181°.

The N-benzoyl derivatives of the other amino acids were converted directly to the amino acids without characterization.

Acid hydrolysis of the N-benzoyl derivative to the amino acid (17).

The N-benzoyl derivative of I (8 g.) was placed in a round-bottomed flask, equipped with a side arm provided with a thermometer. Fifty milliliters of 48% hydrobromic acid and 100 ml. of glacial acetic acid were added. The mixture was heated under reflux for six hrs. at 115°. The acid mixture was then distilled under reduced pressure and the residue dissolved in water and extracted with ether. The ethereal solution, on evaporation, gave crystals of benzoic acid (m.p. 121°). The aqueous solution was distilled under reduced pressure. The residual amino acid hydrobromide was dissolved in water, decolorized with animal charcoal, and concentrated, to give 7.6 g. of colorless crystals of  $\beta,\beta$ -diphenylalanine hydrobromide, m.p. 205°.

*Anal.* Calcd. for  $C_{15}H_{12}NO_2Br$ : C, 55.90; H, 4.96; N, 4.34. Found: C, 56.17; H, 5.16 and N, 4.24.

The hydrochloride, m.p. 180°, was prepared by using dilute hydrochloric acid, in place of water, to dissolve the residue.

The hydrochloride (or hydrobromide) was dissolved in water and titrated with a dilute solution of sodium hydroxide, using a pH meter, until precipitation occurred. The amino acid was filtered and re-crystallized from hot water, containing a trace of ammonia, m.p. 235°, dec.

A similar method was employed for the isolation of other amino acids. (See Table I).

All of these amino acids gave positive ninhydrin tests. The hydrohalide salts exhibited bands at 3150-3030 ( $NH_3^+$  stretching) and 1760-1710  $cm^{-1}$  (-COOH band) in the infrared.

Preparation of  $\beta,\beta$ -diphenylalanine *via* a thiazolone.

The procedure has been described previously (8).

##### 2-Phenyl-4-benzhydryl-5-imidazolone (IV).

A mixture of 2.0 g. of 2-phenyl-4-benzhydryl-5-oxazolone, 10 ml. of ethyl alcohol and 2 ml. of concentrated aqueous ammonia was heated under reflux until all of the solid had dissolved. Concentrated aqueous ammonia (2 ml.) and 1 g. of potassium carbonate were added and heating was continued for another hour. The white product which separated was crystallized from benzene, m.p. 220° (lit. (10) 220-221°), yield, 1.6 g.

##### Hydrolysis of IV.

The imidazolone (1.5 g.) was heated under reflux with a mixture of 8.1 ml. of phosphoric acid, 1.0 ml. of water, 0.18 g. of potassium iodide, and 0.6 g. of red phosphorus for 6 hrs. On cooling, benzoic acid crystallized from solution. The solution was extracted with ether, the ether layer was separated, and the aqueous layer treated with 25 ml. of 2N sodium hydroxide and boiled to expel ammonia. On cooling, 0.6 g. of  $\beta,\beta$ -diphenylalanine separated, m.p. 233°, dec.

##### Hydantoin of diphenylacetaldehyde.

This compound, m.p. 224°, was prepared in poor yield according to a procedure described previously (18).

5-Benzylidene hydantoin (Va), 5-benzylidene-2-thiohydantoin (Vb), and 3,6-dibenzylidenepiperazine-2,5-dione (VII).

These compounds were prepared by condensation of the appropriate starting material (hydantoin, 2-thiohydantoin, or piperazine-2,5-dione) with benzaldehyde in the presence of sodium acetate and acetic anhydride (at 150-160° for 6 hrs.). The compounds were crystallized from glacial acetic acid to give (Va), m.p. 220° (19), Vb, m.p. 258° (20,21) and VII, m.p. ca. 300° (13).

##### Reaction of 5-benzylidene hydantoins with phenylmagnesium bromide.

To a solution of phenylmagnesium bromide, prepared from 1.8 g. of magnesium metal and 11.7 g. of bromobenzene, a suspension of 1.91 g. of 5-benzylidene hydantoin in 50 ml. of ether, 50 ml. of anisole (22) was added over a period of one hr. The reaction mixture was left overnight. It was decomposed with a saturated solution of ammonium chloride, the aqueous layer extracted with ether and the combined anisole-ether layer heated on a water bath to remove the ether. The anisole was removed under reduced pressure. The residue was crystallized from acetic acid to give 2.2 g. (82%) of 5-benzhydryl hydantoin, m.p. 224°. There was no depression on admixture with an authentic sample prepared from diphenylacetaldehyde.

Similarly, 2.6 g. (76.5%) of 5-benzhydryl-2-thiohydantoin, m.p. 205°, was obtained from 2.45 g. of starting material.

*Anal.* Calcd. for  $C_{16}H_{14}OSN_2$ : C, 68.05; H, 4.99. Found: C, 67.83; H, 4.92.

Reaction of 3,6-dibenzylidenepiperazine-2,5-dione (VII) with phenylmagnesium bromide.

Compound VII (3.44 g.) reacted with the Grignard reagent prepared from 3.6 g. of magnesium and 23.4 g. of bromobenzene to furnish 4.5 g. (85%) of compound VIII. m.p. above 300°.

#### Friedel-Crafts Reaction of Va with Benzene.

In a 500 ml. three-necked flask, provided with a dropping funnel, stirrer, and a condenser connected to a nitrogen supply, was placed 8.0 g. of anhydrous aluminum chloride and 60 ml. of benzene, dried and distilled over sodium. The flask was cooled in an ice bath and the contents of the flask stirred for one hr. at room temperature. 5-Benzylidene hydantoin (1.91 g.), suspended in 65 ml. of benzene, was added to the reaction mixture, care being taken that the temperature did not rise above 10°. After the addition of the hydantoin suspension, the ice bath was removed and the reaction mixture stirred at room temperature for three hrs. Dilute HCl (1:15) (125 ml.) was added to decompose the complex. The aqueous layer was removed and washed with benzene. The combined benzene layers were washed with water several times and dried over anhydrous magnesium sulfate. The benzene was removed by distillation on a water bath. The residual solid was crystallized from acetic acid, m.p. 224°. The melting point checked with an authentic sample, yield 2.2 g.

#### Friedel-Crafts Reaction of Vb with Benzene.

5-Benzylidene-2-thiohydantoin (2.45 g.) reacted with 125 ml. of benzene and 8 g. of aluminum chloride, using the procedure described above, to give 2.4 g. (70.5%) of product, m.p. 204°.

#### Friedel-Crafts reaction of VII.

Compound VII (3.44 g.) reacted with 150 ml. of dry benzene and 9.6 g. of aluminum chloride to give 3.7 g. (70%) of VIII, m.p. above 300°.

#### Acid Hydrolysis of VIa, VIb and VIII.

One gram of each of the above compounds was hydrolyzed separately with a mixture of 20 ml. of glacial acetic acid and 10 ml. of 48% hydrobromic acid for six hrs. The excess acid mixture was distilled under reduced pressure. The residue, in each case, was dissolved in water and decolorized with charcoal. The hydrobromide melted in the range of 204-205° (lit. (3e) 205°).

*Anal.* Calcd. for  $C_{15}H_{18}NO_2Br$ : C, 55.90; H, 4.96; N, 4.34. Found: C, 56.00; H, 5.10; N, 4.20.

#### 2-Phenyl-4-(9'-fluorenylidene)-5(4H)-oxazolone.

This compound, m.p. 246°, was prepared in 40% yield according to a procedure described previously (15).

#### 9-Fluorenylglycine IX.

2-Phenyl-4-(9'-fluorenylidene)-5-oxazolone (8 g.) 5.4 g. of red phosphorus and 48 ml. of acetic anhydride were heated under reflux. During a period of one hr., 48 ml. of 50% hydriodic acid was added dropwise with stirring. The reaction mixture was refluxed for 4 hrs. and filtered by suction. The unreacted phosphorus was washed on the filter with two 5 ml. portions of glacial acetic acid. The filtrate and washings were evaporated to dryness under reduced pressure at 50°. To the dry residue was added 100 ml. of water and the mixture again evaporated to dryness under reduced pressure at 65°. To this residue was added 100 ml. of water and 100 ml. of ether. The mixture was thoroughly shaken until solution was complete. The water layer was washed four times with 75 ml. portions of ether. The aqueous solution was heated on a steam bath with 2 g. of Norite and a trace of sodium sulfite until all the dissolved ether had been removed. The solution was filtered, the filtrate heated to boiling, neutralized to Congo Red with 50 ml. of 15% ammonium hydroxide and allowed to cool. The white precipitate was washed with 600 ml. of cold water in 150 ml.

portions and recrystallized by dissolving in boiling water and adding 95% ethanol to the filtrate until cloudiness developed.

The recrystallized white product was washed with water and dried. The yield of 9-fluorenylglycine, m.p. 221-222°, dec., was 1.79 g. (36%).

The compound was soluble in strong acid and base and gave a positive ninhydrin test. Infrared (KBr pellet); 1640  $cm^{-1}$ (s) and 3600-2850  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{15}H_{13}NO_2$ : C, 75.29; H, 5.47; N, 5.83. Found: C, 75.08; H, 5.52; N, 6.12.

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