

After passage of 100 cubic feet of natural gas through the 20 pounds of char, the latter was again heated at 110° and evacuated as described above.

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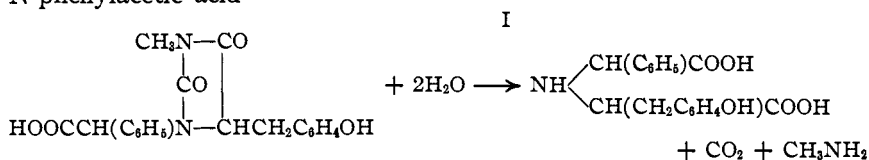
**TYROSINE-N-ACETIC ACID: INTRODUCING A NEW GENERAL METHOD FOR PREPARING SYMMETRICAL AND ASYMMETRICAL IMINO DIBASIC ACIDS**

BY DOROTHY A. HAHN AND ANNE LITZINGER

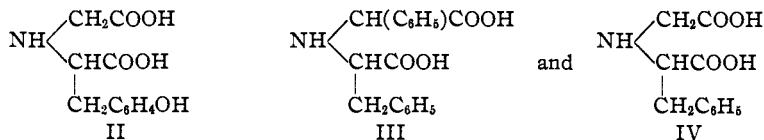
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It has been shown that the *N*-3-methyl-5-tyrosylhydantoin-*N*-1-phenylacetic acid, on hydrolysis with barium hydroxide, breaks down to tyrosine-*N*-phenylacetic acid<sup>1</sup>



This reaction has now been found applicable as a new general method for preparing  $\alpha$ -imino dibasic acids of the diacetic acid type,  $\text{HOOCCH}_2\text{NH}-\text{CH}_2\text{COOH}$ , in which the methylene hydrogen atoms are replaced by different hydrocarbon residues. Previous to this time substances belonging to this class have been prepared almost exclusively by hydrolysis of the corresponding dinitriles.<sup>2</sup> In addition to the acid referred to above (I), three others have now been synthesized in this Laboratory, namely, tyrosine-*N*-acetic acid (II),  $\beta$ -phenylalanine-*N*-phenylacetic acid (III) and  $\beta$ -phenylalanine-*N*-acetic acid (IV)



A detailed study of the intermediate products involved in the synthesis of the hydantoin used in the preparation of III and IV is still in progress. The present report is, therefore, limited to a brief description of these acids at the end of this paper preceded by a detailed consideration of *tyrosine-N-acetic acid* and its salts.

A crystalline diethyl ester and a barium salt of the latter acid (II) have

<sup>1</sup> Hahn and Dyer, *THIS JOURNAL*, **52**, 2495 (1930).

<sup>2</sup> Jongkees, *Rec. trav. chim.*, **27**, 287-326 (1908).

already been prepared<sup>3</sup> by the hydrolysis of N-3-methyl-5-tyrosylhydantoin-N-1-acetic acid, but both of these substances were isolated with difficulty and in very small quantities. A method for the hydrolysis of the hydantoin has now been developed which provides approximately quantitative yields. The acid may be transformed into the corresponding hydrochloride by treatment with aqueous hydrochloric acid; it also furnishes the dimethyl ester hydrochloride by the standard procedure, practically quantitative yields being obtained. On treatment with aqueous alkalis it yields the mono-potassium and mono-sodium salts; these in turn may be converted into the salts of heavy metals by double decomposition. A dipotassium salt separates on treating a solution of the acid in excess of concentrated potassium hydroxide with alcohol.

Table I shows the similarity in the melting points of imino-diacetic acid and the four acids referred to above and also the solubility relationships which exist among these five substances.

TABLE I  
COMPARISON OF PHYSICAL PROPERTIES OF IMINO ACIDS

Imino acid	Imino-diacetic	I	II	III	IV
M. p., °C.	225-226 <sup>4</sup>	222-224	228-230	227-228	220-228
Solubility, <sup>5</sup> g.	0.3975	0.0107	0.0604	0.0024	0.0154

### Experimental

**Tyrosine-N-acetic Acid**,  $\text{NH}(\text{CH}_2\text{COOH})\text{CH}(\text{CH}_2\text{C}_6\text{H}_4\text{OH})\text{COOH}$ .—To a solution of 57.5 g. of N-3-methyl-5-tyrosylhydantoin-N-1-acetic acid in 250 cc. of boiling water was added a hot solution of 225 g. of crystallized barium hydroxide in 500-600 cc. of water. The mixture was heated on a steam-bath under reflux for twenty to twenty-four hours and then distilled with steam (four to five hours) in order to remove the resulting methylamine. The solution was then freed of barium with exactly the necessary amount of sulfuric acid, filtered, and concentrated under reduced pressure to one liter. On standing overnight most of the free  $\alpha$ -imino-dibasic acid separated in the form of rosetts made up of small white hard well-defined prisms, which after extraction with hot alcohol and recrystallization from water melted with decomposition at 228-230°.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_5\text{N}\cdot\text{H}_2\text{O}$ :  $\text{H}_2\text{O}$ , 7.00. Found:  $\text{H}_2\text{O}$ , 5.38, 5.34. Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_5\text{N}$ : N, 5.86. Found: N, 5.88, 5.86.

The acid is very soluble in cold aqueous ammonia and alkali and in cold dilute aqueous hydrochloric acid and can be recovered in exceptionally pure condition on hydrolysis of these salts. It is fairly soluble in boiling water, 5 g. dissolving in 135 cc. It is only slightly soluble in cold water, 4.1 g. separating from the above solution on cooling. There seems to be a tendency for the acid to form supersaturated aqueous solutions since it separates very slowly, usually upon standing overnight. It is almost insoluble in hot alcohol and other neutral organic solvents. It is only slightly soluble in boiling acetic acid (2 g. in 225 cc.) except upon prolonged heating, when relatively large quantities dissolve and are recovered with difficulty.

<sup>3</sup> Hahn and Renfrew, *THIS JOURNAL*, **47**, 161, 162 (1925).

<sup>4</sup> Eschweiler, *Ann.*, **278**, 231 (1894).

<sup>5</sup> Solubility is measured by the number of grams present in 10 cc. of a saturated aqueous solution at 25°.

Further quantities of the acid were obtained on concentrating the filtrates, the final yield averaging over 90% of the theoretical. In cases where the product was slightly discolored, the color was removed with only negligible loss by extracting with boiling alcohol. The alcoholic extract was found to contain, in addition to the coloring matter, small quantities of an acid melting at 217–220°, which upon analysis showed the same composition as the main product. This acid crystallized in large hard transparent prisms and differed also in being more soluble in water and in alcohol; it was readily soluble in dilute aqueous hydrochloric acid and ammonia. It has not been investigated in greater detail owing to the difficulty of obtaining it in sufficient quantity.

**Hydrochloride of Tyrosine-N-acetic Acid.**—This separated on cooling a solution of 5 g. of the free acid in 35 cc. of boiling aqueous hydrochloric acid (1:1), the weight of the crop so obtained being 4.2 g. On recrystallization from the same solvent it formed hard glistening plates, m. p. 212.5–213°.

*Anal.* Calcd. for  $C_{11}H_{13}O_5N \cdot HCl$ : N, 5.08; Cl, 12.88. Found: N, 4.98, 5.18; Cl,<sup>6</sup> 12.98, 13.00.

The salt dissolves in about 5 parts of boiling 1:1 hydrochloric acid, but requires about 60 parts of the same solvent in the cold. It dissolves in 2 parts of cold water but within five to ten minutes separation of the free acid takes place.

The hydrochloride of dimethyl tyrosine-N-acetate was obtained by dissolving 12 g. of free acid in 75 cc. of methyl alcohol saturated with dry hydrogen chloride gas, solution being accompanied by the development of a pink color. After refluxing for half an hour the solution was concentrated to 45 cc. and treated with two to three times this volume of ether, when 13.2 g. of ester separated. The product melted at 163–165° and decomposed at 200°. It was analyzed without further purification.

*Anal.* Calcd. for  $C_{13}H_{15}O_5NCl$ : N, 4.61; Cl, 11.69. Found: N, 4.87, 4.92. Cl,<sup>6</sup> 11.67, 11.63.

This salt is fairly soluble in cold methyl alcohol (8 g. in 30 cc.), not quite so soluble in cold water (5 g. in 25 cc.) and insoluble in ether.

**Metallic Salts.**—The mono-alkali salts were prepared in good yield by dissolving the free acid in cold aqueous solutions containing somewhat more than an equivalent weight of the corresponding hydroxide; and a dipotassium salt when two equivalents was used. The salts of the heavy metals (6, 9, 10 and 11) were obtained by treating aqueous solutions of the mono-potassium salt with 2.2 equivalents of the corresponding nitrates. Two different barium salts were obtained with 2 equivalents of the hydroxide<sup>3</sup> and the chloride, respectively, and a silver salt with 1.2 equivalents of nitrate.<sup>7</sup> The salts 1, 4, 6 and 10 were transformed quantitatively into the free acid, m. p. 228–230°, by the action of dilute hydrochloric acid, carbon dioxide and dilute sulfuric acid, respectively.

$\beta$ -Phenylalanine-N-phenylacetic acid, III, m. p. 224–226° with decomposition and  $\beta$ -phenylalanine-N-acetic acid, IV, m. p. 220–228° with decomposition, were obtained by hydrolyzing N-3-methyl-5-benzylhydantoin-N-1-phenylacetic acid and N-3-methyl-5-benzylhydantoin-N-1-acetic acid, respectively, under the action of barium hydroxide in the same manner as has been described in the preparation of tyrosine-N-acetic acid. The crude products obtained in each case were purified both by extraction with alcohol and subsequent recrystallization from water and also by conversion into their respective hydrochlorides and subsequent hydrolysis of the latter in boiling water.

*Anal.* III. Calcd. for  $C_{17}H_{17}O_4N \cdot H_2O$ :  $H_2O$ , 5.68. Found:  $H_2O$ , 5.68. Calcd. for  $C_{17}H_{17}O_4N$ : N, 4.68. Found: N, 4.90, 4.99.

<sup>6</sup> The halogen was determined by direct precipitation with aqueous silver nitrate.

<sup>7</sup> Salts 2 and 6 separated in crystalline condition when the oil obtained from evaporating their aqueous solutions was warmed with alcohol.

TABLE II  
 ANALYSES<sup>8</sup> OF METALLIC SALTS

Salt	Formula	H <sub>2</sub> O, % <sup>9</sup>		N, %		Met., %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
1 K	C <sub>11</sub> H <sub>12</sub> O <sub>6</sub> NK·2H <sub>2</sub> O	11.50	11.56	5.05	5.26		
2 K	C <sub>11</sub> H <sub>11</sub> O <sub>6</sub> NK <sub>2</sub> ·1.5H <sub>2</sub> O	7.89	8.30	4.44	4.65		
3 Na	C <sub>11</sub> H <sub>12</sub> O <sub>6</sub> NNa·H <sub>2</sub> O			5.02	4.95		
4 NH <sub>4</sub>	C <sub>11</sub> H <sub>16</sub> O <sub>6</sub> N <sub>2</sub>			10.94	10.84		
5 Ag <sup>10</sup>	C <sub>11</sub> H <sub>12</sub> O <sub>6</sub> Ag·H <sub>2</sub> O			3.85	4.04	29.65	29.49 <sup>11</sup>
6 Pb	C <sub>11</sub> H <sub>11</sub> O <sub>6</sub> NPb·H <sub>2</sub> O	3.90	3.74	3.15	3.21	46.62	46.62 <sup>12</sup>
7 Ba	(C <sub>11</sub> H <sub>12</sub> O <sub>6</sub> N) <sub>2</sub> Ba·3H <sub>2</sub> O	14.98	14.47	4.57	4.80	22.22	22.21 <sup>12</sup>
8 Ba	2[(C <sub>11</sub> H <sub>11</sub> O <sub>6</sub> N·Ba)]Ba(OH) <sub>2</sub> ·H <sub>2</sub> O	1.92	1.84	3.04	3.24	44.79	44.04 <sup>12</sup>
9 Cu <sup>10</sup>	2(C <sub>11</sub> H <sub>11</sub> O <sub>6</sub> NCu)·H <sub>2</sub> O	2.90	2.21	4.66	4.92	21.15	21.62 <sup>13</sup>
10 Cd	[(C <sub>11</sub> H <sub>12</sub> O <sub>6</sub> N) <sub>2</sub> Cd·5H <sub>2</sub> O]·4H <sub>2</sub> O	9.60	9.52	4.13	3.76	16.52	{ 16.25 <sup>14</sup> 16.66 <sup>12</sup>
11 Cd <sup>10</sup>	C <sub>11</sub> H <sub>11</sub> O <sub>6</sub> NCd·2H <sub>2</sub> O	9.33	9.25	4.01	4.57		

 TABLE III  
 PHYSICAL PROPERTIES<sup>15</sup> OF METALLIC SALTS

Salt	M. p., °C.	Solubility
1 K	250–255 decomp.	1 g. in 2 cc. cold water, insol. alcohol
2 K	174–200 decomp.	V. s. water, insol. alcohol
3 Na	180–186 decomp.	1 g. in 3 cc. cold water, insol. alcohol
4 NH <sub>4</sub>	218.5–220 decomp.	V. s. water, insol. alcohol
5 Ag	148.5–149.5 decomp.	Insol. cold water, decomp. boiling water
6 Pb	260–262 decomp.	5.3 g. in 50 cc. boiling water, 0.4 g. in 50 cc. cold water, insol. alcohol
7 Ba <sup>17</sup>	223–227 decomp.	2.0 g. in 6 cc. boiling water, insol. cold water <sup>16</sup>
8 Ba <sup>17</sup>	Not melted up to 315	1.5 g. in 40 cc. boiling water, insol. cold water
9 Cu	241–242.5 decomp.	1 g. in 50 cc. boiling water, insol. alcohol
10 Cd	Not melted up to 315	1.5 g. in 25 cc. boiling water, 0.01 g. in 20 cc. cold water, <sup>16</sup> insol. alcohol
11 Cd <sup>18</sup>	205–208 decomp.	0.3 g. in 30 cc. boiling water, fairly sol. cold water, insol. alcohol

<sup>8</sup> The figures given are the average of duplicate determinations.

<sup>9</sup> Salts 3 and 5 were analyzed in the hydrated form, all others were heated to constant weight at 110°. In the case of 10 only four molecules of water was lost at 110°.

<sup>10</sup> Salt was not recrystallized for analysis.

<sup>11</sup> Determined by direct precipitation as silver chloride.

<sup>12</sup> Determined by ignition as the sulfate.

<sup>13</sup> Determined by ignition as copper oxide.

<sup>14</sup> Determined electrolytically.

<sup>15</sup> Salts crystallized as follows: 1, 2 and 3 from alcohol–water as fine needles in the form of rosetts; 4 and 11 from alcohol–water as crystalline powders; 5, 6, 8 and 9 from water as crystalline powders; 7 from water in the form of clumps suggesting the cauliflower; 10 from water as needles.

<sup>16</sup> A marked tendency to form supersaturated solutions is exhibited.

<sup>17</sup> The behavior of the two barium salts when heated on platinum serves to distinguish them since 7 forms a snake and 8 merely chars.

<sup>18</sup> Alcohol was used to precipitate this salt, while 10 separated from water.

The free acid is only slightly soluble in boiling water, 0.1 g. dissolving in 300 cc., and almost insoluble in cold water and alcohol. It separates from its aqueous solutions in the form of soft white needles appearing in the form of rosetts.

*Anal.* IV. Calcd. for  $C_{11}H_{13}O_4N$ : N, 6.28. Found: N, 6.03, 6.04.

The free acid is soluble in about 50 parts of boiling water from which it separates in hard elongated white plates which grow in rosetts. It shows no tendency to form super-saturated aqueous solutions and is insoluble in alcohol.

### Summary

Free tyrosine-N-acetic acid, its hydrochloride, the hydrochloride of its dimethyl ester and certain of its metallic derivatives have been prepared and described.

A new general method for the synthesis of  $\alpha$ -imino dibasic acids has been outlined. Investigations will be continued on the derivatives of the four acids referred to in this paper and on the intermediate hydantoin involved in their synthesis.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

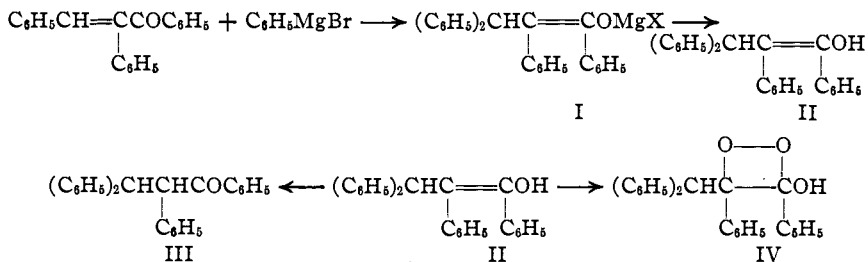
## THE REACTION BETWEEN ALPHA, BETA-UNSATURATED KETONES AND ORGANIC MAGNESIUM COMPOUNDS. THE STRUCTURE OF THE ADDITION PRODUCTS

BY E. P. KOHLER AND W. E. MYDANS

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Many  $\alpha,\beta$ -unsaturated ketones combine with Grignard reagents and other metallic compounds to form metallic derivatives which on hydrolysis yield saturated ketones. In some cases, notably those in which there are substituents in the alpha position, it is known that the saturated ketones are secondary products, and that the primary products of hydrolysis are enols which are capable of combining with oxygen to form peroxides. In these cases it is reasonable to infer that the metallic derivatives are enolates which are formed by 1,4-addition to the conjugated system



Owing to the rapidity with which most enols of mono ketones undergo rearrangement, this method of arriving at the structure of the metallic