[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE TRANSAMINATION REACTION. THE EFFECT OF VARIOUS NUCLEAR SUBSTITUTED PHENYLAMINOACETIC ACIDS ON THE COURSE OF THE REACTION ¹

EDWARD K. HARVILL² AND ROBERT M. HERBST²

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The results of previous transamination studies in chemical systems were explained by the assumption of the formation of a Schiff base-like intermediate as the initial stage of the interaction of *alpha*-amino acids with *alpha*-keto acids (1, 2). This was followed by the elimination of carbon dioxide, generally accompanied by the shift of the carbon-nitrogen double bond from the ketonic side of the Schiff base to the amino acid side. Hydrolysis then produced a new amino acid and an aldehyde. In certain reactions two aldehydes were formed, necessitating the assumption that the intermediate Schiff base could be decarboxylated to a lesser extent and hydrolyzed without shift of the carbon-nitrogen double bond, thus regenerating the original amino acid and forming the aldehyde derived from the keto acid.

In the reaction between pyruvic acid and α -aminophenylacetic acid, carbon dioxide, alanine, and only one aldehyde, benzaldehyde were formed. On the other hand, pyruvic acid and α -amino-*p*-methoxyphenylacetic acid produced, in addition to carbon dioxide and alanine, two aldehydes, anisaldehyde and acetaldehyde. In general, it has been observed that carbon dioxide evolution is much more rapid in transaminations with arylaminoacetic acids than with aliphatic amino acids.

$$\begin{array}{c} p\text{-}\mathrm{CH}_{3}\mathrm{OC}_{6}\mathrm{H}_{4}\mathrm{CH}(\mathrm{NH}_{2})\mathrm{COOH} \\ + \\ \mathrm{CH}_{3}\mathrm{COCOOH} \end{array} \xrightarrow{p\text{-}\mathrm{CH}_{3}\mathrm{OC}_{6}\mathrm{H}_{4}\mathrm{CHO} + \mathrm{CO}_{2} + \\ (\mathrm{II}) & \mathrm{CH}_{3}\mathrm{CHO} + \mathrm{CO}_{2} + \\ (\mathrm{III}) & \mathrm{CH}_{3}\mathrm{CHO} + \mathrm{CO}_{2} + \\ p\text{-}\mathrm{CH}_{3}\mathrm{OC}_{6}\mathrm{H}_{4}\mathrm{CH}(\mathrm{NH}_{2})\mathrm{COOH} \end{array}$$

It was of interest to determine the effect of nuclear substituents in the arylaminoacetic acids on the speed and course of the reaction. For this purpose the reactions between pyruvic acid and o-chloro-,o-methoxy-,o-hydroxy-, p-chloro-, p-methoxy-, and p-hydroxy-phenylaminoacetic acids as well as furylaminoacetic acid were studied. Phenylaminoacetic acid was included in the series for comparison purposes.

In Figures 1 and 2 the rates of carbon dioxide evolution in the various systems are represented graphically. It will be observed that carbon dioxide was evolved more rapidly in transaminations with the *ortho* substituted arylamino-acetic acids than with the *para* substituted compounds. In the *para* substituted series, as in the *ortho* series, the rate of carbon dioxide formation fell in the well defined sequence: $Cl > CH_3O > OH$

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² Present address E. Bilhuber, Inc., Orange, N. J.

A similar sequence was found by Shoppee (3, 4, 5) in determining the mobility of methyleneazomethine systems which involved a reversible prototropic change of various substituted Schiff bases. These results were interpreted in accordance with the ideas of Ingold and his collaborators (6, 7) by assuming that an electron recession from the side chain caused the ionization of a proton from the *alpha* carbon atom with the formation of an electromeric ion in which the anionic charge was distributed between the *alpha* and *gamma* carbon atoms. The position taken up by the proton on recombination with the electromeric ion is deter-



Figure 1. Carbon dioxide evolution from 30 mM pyruvic acid and 10 mM of (1) phenylaminoacetic acid, (2) o-chlorophenylaminoacetic acid, (3) o-methoxyphenylaminoacetic acid, (4) o-hydroxyphenylaminoacetic acid, (5) pyruvic acid alone, and (6) furylaminoacetic acid.

mined by the electron distribution, which in turn depends in part upon the nature of the group Y.



Shoppee found that the effect of nuclear substitutions in either the meta or para position varied with the electron attracting power of the substituted phenyl group and could be correlated with the dipole moment. The effect of the substituents fell into the order

$$NO_2 > Cl > I > OMe > Me > NMe_2$$
.

Transamination reactions appear to involve methyleneazomethine systems similar to those studied by Ingold. Knoop and Martius' (8) synthesis of an imino dicarboxylic acid by the catalytic hydrogenation of a solution of arginine and pyruvic acid favors the assumption of a Schiff base-like intermediate.



Figure 2. Carbon dioxide evolution from 30 mM pyruvic acid and 10 mM of (1) phenylaminoacetic acid, (2) *p*-chlorophenylaminoacetic acid, (3) *p*-methoxyphenylaminoacetic acid, (4) *p*-hydroxyphenylaminoacetic acid, and (5) pyruvic acid alone.

Brewer and Herbst (9) have shown that the reaction between ethyl pyruvate and ethyl aminophenylacetate is catalyzed by sodium ethoxide and that mineral acids cause a marked decrease in the speed of the reaction. Their reaction appears to be closely analogous to the true prototropic systems of Ingold and Shoppee in that it depends upon the dissociation of a proton from the intermediate Schiff base.

However, transamination reactions in which the carboxyl groups of both the *alpha*-amino acid and the *alpha*-keto acid are free differ from the true methylene-

azomethine systems. The reactions are unidirectional and proceed with the evolution of carbon dioxide. The presence of mineral acids has little effect on the reactions, whereas the addition of alkali inhibits them almost completely (1). These systems appear to involve an electrotropic change as shown by Herbst and Rittenberg (10), rather than a prototropic change in which proton transfer is necessary. They suggested that the reaction involved the decarboxylation of the intermediate Schiff base-like compound with a simultaneous shift of the double bond to form an electrotropic carbonium ion. The process was completed by the addition of a proton from the medium to the carbonium ion and hydrolysis of the resulting Schiff base.

$$\begin{array}{cccc} \text{RCH-N=CR'} & \xrightarrow{\text{H}^{+} + \text{CO}_2} + & \overrightarrow{\text{RCH-N=CR'}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{RCH=N-CR'}} & \xrightarrow{\text{H}^{+}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{RCH=N-CR'}} & \xrightarrow{\text{H}^{+}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{RCH=N-CR'}} & \xrightarrow{\text{H}^{+}} & \xrightarrow{\text{COOH}} & \xrightarrow{\text{RCH=N-CR'}} & \xrightarrow$$

Since decarboxylation is presumed to occur simultaneously with a shift of the double bond from the *beta*, *gamma* to the *alpha*, *beta* position, the rate of evolution of carbon dioxide may be considered a measure of the electrotropic change.

Although the mechanism of transamination differs from that of the methyleneazomethine systems studied by Shoppee, our results show that similar factors will influence the rates of reaction in both cases. In both systems reaction is facilitated by the withdrawal of electrons from the side chain, the greater the electron attracting effect of the group $Y-C_6H_4$ - the more rapid is the conversion. The effects of the various substituents in the benzene ring upon the rate of decarboxylation fall into the sequence determined by Shoppee.

Relatively little work has been done with regard to the effect of *ortho* substituents in the benzene ring on the rate of side-chain reactions of this type. In the cases here reported all the *ortho* substituents were more effective than the *para* substituents in promoting decarboxylation. This was not surprising since the *ortho* substituents are closer to the seat of the reaction than the *para* substituents which transmit their electronic effects through a system of conjugated double bonds. For the entire series studied carbon dioxide evolution was facilitated by the groups in the following order:

$$o-\mathrm{Cl} > o-\mathrm{CH}_{3}\mathrm{O} > o-\mathrm{OH} > p-\mathrm{Cl} > p-\mathrm{CH}_{3}\mathrm{O} > p-\mathrm{OH}$$

The simplicity of the method recommends it for further use in studying the electronic effects of various groups and allows a direct comparison not only of aryl but also alkyl groups, a possibility not realized in the reversible methylene-azomethine systems.

Although the effects of various substituents in the benzene ring on the rate of the reaction were significant, their influence on the course of the reaction was inconsistent. When R was o-methoxyphenyl, p-methoxyphenyl, p-hydroxyphenyl, and furyl, two aldehydes were formed in addition to alanine and carbon dioxide. When R was o-chlorophenyl, p-chlorophenyl, and o-hydroxyphenyl, only the aromatic aldehyde was formed in addition to alanine and carbon dioxide. Acetaldehyde is not formed in an aqueous solution of pyruvic acid under the experimental conditions. Furthermore, the fact that acetaldehyde is formed only in a few of our systems shows that the reaction between alanine and pyruvic acid is too slow to account for its formation in these reactions. In all the reactions scheme I was followed predominantly. The aromatic aldehydes were isolated in yields of 46–80% whereas the maximum yield (15%) of acetaldehyde was obtained in the reaction with furylaminoacetic acid. When R was a substituted phenyl group the highest yield of acetaldehyde was 6.5%.

The formation of acetaldehyde can be explained by decarboxylation and hydrolysis of the Schiff base without shift of the double bond and unaccompanied by an electron shift. Benzoylformic acid and alanine have been reported (2) to produce only a trace of benzaldehyde and carbon dioxide. In this case the initial intermediate is stable since the double bond is conjugated with the benzene ring and the formation of benzaldehyde probably is due to the slow decomposition of the postulated intermediate Schiff base.

EXPERIMENTAL

Transamination reactions. The apparatus described in a previous paper (2) was used in all the transamination reactions.

In all the experiments 10 mM of amino acid and 100 cc. of water were placed in the reaction flask and the system was connected. Nitrogen gas washed with 40% potassium hydroxide and concentrated sulfuric acid was passed through a capillary tube and into the reaction flask at a constant rate of 1.78 liters per hour. The amino acid solution was kept at a gentle boil and 30 mM of pyruvic acid was added through the addition tube. The reaction was considered to start with the addition of pyruvic acid and the rate was followed by weighing periodically the absorption tube charged with 40% potassium hydroxide and concentrated sulfuric acid to determine the carbon dioxide formed. The rates of carbon dioxide evolution are shown in Figures 1 and 2.

Upon the completion of the reaction, the volatile aldehydes absorbed by the bisulfite trap were estimated quantitatively by titrating the excess and bound bisulfite with standard iodine solution (11). The titrated solution was then distilled into a solution of dimedon (dimethyldihydroresorcinol). The dimedon derivatives were identified by melting points and by mixed melting points with authentic specimens.

The reaction mixture was extracted with ether to remove aromatic aldehydes. The ether layer was washed first with 5% sodium carbonate to remove pyruvic acid, then with water, dried over anhydrous sodium sulphate and evaporated. The residual aldehyde was characterized as a derivative whose identity was confirmed by its melting point and mixed melting point with an authentic specimen.

The reaction mixture was then extracted continuously with ether for 48-72 hours to remove pyruvic acid. The water solution was evaporated almost to dryness and the alanine was precipitated by the addition of alcohol. It was characterized by conversion into α -phenylureidopropionic acid whose identity was established by its melting point and mixed melting point with an authentic specimen.

The results of these reactions are recorded in Table I.

Hydantoins. The hydantoins were prepared by a method essentially that of Bucherer and Lieb (12) by heating the appropriate aldehyde, potassium cyanide, and ammonium carbonate in aqueous alcoholic solution.

5-(o-Hydroxyphenyl)hydantoin could not be prepared by the above general procedure. With salicylaldehyde only a red gummy substance was secured from which no definite product could be isolated. Hydrolysis of 10 g. of 5-(o-methoxyphenyl)hydantoin with 30 cc. of hydriodic acid (sp. gr. 1.5) by boiling under reflux for 3 to 5 hours gave on cooling 5.2 g. (56% yield) of the 5-(o-hydroxyphenyl)hydantoin. Recrystallization from water gave a product melting at 240-244° with decomposition.

5-Furylhydantoin melting at 101° was invariably obtained from furfural. A sample of the hydantoin stored for about one month in a clear glass bottle at room temperature was found to melt at 147° . The two forms are interconvertible. Several recrystallizations of

30 mM Pyruvic acid; 10 mM Amino acid; 100 cc. of Water								
	R	ACETAL- DEHYDE,	ALA- NINE,	<u> </u>				
		mM6	mMe'	MM mM	ISOLATED AS	м.р., °С	REI	
R1	p-Methoxyphenyl	0.19°	8.9	6.5	<i>p</i> -Nitrophenylhydra- zone	160 dec.	14	

7.3

4.6

7.6

5.2

8.0

1

2,4-Dinitrophenyl-

Phenylhydrazone

Phenvlhydrazone

Phenylhydrazone

hydrazone

2,4-Dinitrophenyl-

hydrazone

249 - 250

126 - 127

84

178 dec.

248-252 dec.

14b

15b

15a

15b

14c

TABLE I PRODUCTS OF THE REACTION BETWEEN PYRUVIC ACID AND *a*-Arylaminoacetic Acids^a

^a See Figures 1 and 2 for carbon dioxide evolution.

None

None

0.354

None

1.51°

o-Methoxyphenyl 0.65°

p-Chlorophenyl

o-Chlorophenyl

p-Hydroxyphenyl

o-Hydroxyphenyl

^b Acetaldehyde determined quantitatively by titration of the bisulfite trap.

^o Identified as the dimedon derivative m.p. 138-140°.

^d Identified as acetaldehyde p-nitrophenylhydrazone m.p. 126-127°.

5.7

9.6

8.6

6.9

9.2

1

• Identified as α -phenylureidopropionic acid, m.p. 168-169° with decomposition.

' Only a resinous brown product could be isolated from the reaction mixture.

one form from water inoculating each time with the other form effected conversion to the seeding form. The furylhydantoins turn pink in the presence of light, the lower-melting form changing more rapidly than the higher. The higher-melting form is stable on storage. When kept at 30° for five days the melting point of the lower-melting form had changed from 101° to 142-144°. The higher-melting form showed no change of melting point under the same conditions. Only the form melting at 147° has been previously reported (13).

The melting points, yields, and analyses of the hydantoins are recorded in Table II.

Amino acids. The amino acids were prepared by the hydrolysis of the hydantoins with barium hydroxide.

The para substituted phenylaminoacetic acids were more insoluble in water than the corresponding ortho substituted compounds. Recrystallization of the p-methoxy- and p-hydroxy-phenylaminoacetic acids from water gave compounds that melted with decomposition. Recrystallization of the same compounds from dilute alcohol gave products that sublimed. The sublimation point was much lower than the melting point.

 \mathbf{R}_2

 $\mathbf{R}_{\mathbf{3}}$

R4

 \mathbf{R}_{5}

 \mathbf{R}_{6}

 R_7

Furyl



R ⁱ	FORMULA	WP °Ca	VIETD 07	NITROGEN, %	
		ши, с	110.00, 70	Calc'd	Found
R ₁	C10H10N2O3	195ª	70	13.59	13.74
\mathbf{R}_2	$C_{10}H_{10}N_2O_3$	189*	99	13.59	13.67
-				58.25	58.460
				4.86°	4.82°
R3	$C_{9}H_{7}ClN_{2}O_{2}$	191	69	13.33	13.24
R4	C ₉ H ₇ ClN ₂ O ₂	175-176/	63	13.33	13.38
R_5	C ₉ H ₈ N ₂ O ₃	269-270 dec. ^o	75	14.58	14.43
R ₆	C ₉ H ₈ N ₂ O ₃	240-244 dec.		14.58	14.43
				56.25°	56.28
				4.17°	4.31
R ₇	C ₇ H ₆ N ₂ O ₃	101*	65	16.85	16.79
		147			16.76

^a All melting points corrected.

^b Percentage carbon.

^o Percentage hydrogen.

^{d-h} Henze and Speer, J. Am. Chem. Soc., **64**, 523 (1942) give melting points 191.5°, • 186-187°, / 176°, • 263° dec., * 147°.

See Table I.

TABLE III α-Amino-α-arylacetic Acids RCHCOOH

₽/		¥₽ °C6	umm 07	nitrogen, $\%$	
K.	FORMULA	a .r., C	112,00, 70	Calc'd	Found
Rı	C ₉ H ₁₁ NO ₃	248-285 dec. ^d 230 sub.	51	7.72	7.70 7.67
R1	$C_9H_{11}NO_8 + H_2O$	161-162	74	7.02 54.27 ^b 6.53°	7.02 54.39^{b} 6.48^{c}
R ₃	C ₈ H ₈ CINO ₂	261-262 dec.	47	7.56	7.72
R4	C ₈ H ₈ ClNO ₂	219.5	77	7.56	7.67
\mathbf{R}_{b}	$C_{8}H_{9}NO_{3}$	240-241 dec." 229 sub.	41	8.38	$\begin{array}{r} 8.44 \\ 8.28 \end{array}$
R_6	C 8H 9NO3	194-195 dec.	35	8.38	8.32
R ₇	C ₆ H ₇ NO ₃	212-213 dec.	52	9.93	9.86

• All melting points corrected.

^b Percentage carbon.

^c Percentage hydrogen.

^d Tieman and Kohler, Ber., 14, 1979 (1881) give 225° sub.

* Fromherz, Z. physiol. Chem., 70, 353 (1910) gives 225° sub.

/ See Table I.

TABLE IV α-Phenylureido-α-arylacetic Acids RCHCOOH | NHCONHC6H5

م. ارم	FORMULA	м.р., °С"	NITROGEN, %	
ĸ			Calc'd	Found
R1	C ₁₈ H ₁₆ N ₂ O ₄	196 dec.4	9.33	9.44
\mathbf{R}_2	$C_{16}H_{16}N_2O_4$	186.2	9.33	9.21
			64.00%	64.00
			5.320	4.97
R,	C ₁₅ H ₁₃ ClN ₂ O ₃	185.5	9.21	9.00
R,	C ₁₅ H ₁₃ ClN ₂ O ₃	177-179	9.21	9.19
R_{5}	$C_{15}H_{14}N_{2}O_{4}$	192 dec.	9.79	9.96
R ₇	$C_{13}H_{12}N_2O_4$	147 dec.	10.76	10.75

^a All melting points corrected.

^b Percentage carbon.

^e Percentage hydrogen.

^d Tieman and Kohler, Ber., 14, 1979 (1881), give melting points "about 198°".

• Fromherz, Z. physiol. Chem., 70, 353 (1910), gives m.p. 193°.

/ See Table I.

TABLE V 5-Aryl-3-phenylhydantoins RCH---NH CO CO---NC₆H₅

D۴	DODING 4	N D 909	NITROGEN, %		
K	FURBULA	#. , C	Calc'd	Found	
R1	C16H14N2O3	179	9.92	9.73	
\mathbf{R}_2	$C_{16}H_{14}N_2O_3$	134	9.92	9.79	
			68.08	68.05 ^b	
			4.96°	5.19°	
\mathbf{R}_{3}	$C_{15}H_{11}ClN_2O_2$	167-168	9.79	9.94	
R_4	$C_{15}H_{11}ClN_2O_2$	187.5	9.79	9.88	
R_{5}	$C_{15}H_{12}N_2O_3$	171 and 201 ^d	10.44	10.26	
R ₆	$\mathrm{C_{15}H_{12}N_{2}O_{3}}$	224-225	10.44	10.21	

^a All melting points corrected.

^b Percentage carbon.

^c Percentage hydrogen.

^d Melts at 171°. Solidifies immediately and then melts at 201°. After cooling it remelts at 201°.

• See Table I.

 α -Amino-o-methoxyphenylacetic acid was found to crystallize with a molecule of water and melted at 161-162°. Attempts to secure the anhydrous form were unsuccessful. Upon drying at sufficiently high temperature, even under reduced pressure, to remove the water, d ep seated decomposition of the compound took place.

The copper salt of α -amino-o-methoxyphenylacetic acid was obtained in the form of light blue needles.

Anal. Calc'd for $(C_9H_{10}O_8N)_2Cu + 2H_2O$: Cu, 13.83. Found: Cu, 13.74, 13.70.

Decomposition of the salt with hydrogen sulphide led to the original acid as shown by nitrogen analysis and mixed melting point with the original material.

Only the aminohydroxyphenylacetic acids gave a coloration with ferric chloride. α -Amino-p-hydroxyphenylacetic acid gave a pale violet coloration with ferric chloride, while α -amino-o-hydroxyphenylacetic acid gave a deep blue coloration.

The melting points, yields and analyses of the amino acids are recorded in Table III.

 α -Phenylureido acids. The α -phenylureido acids were prepared from the amino acid by the usual treatment with phenyl isocyanate in alkaline solution.

 α -Amino-o-hydroxyphenylacetic acid formed 3-phenyl-5-(o-hydroxyphenyl)hydantoin directly. Acidification of the alkaline reaction mixture produced a gelatinous substance that was extremely difficult to filter. On standing several days in the acid solution, the material became crystalline, m.p. 224-225°. Boiling the gelatinous precipitate with hydrochloric acid caused immediate precipitation of the hydantoin.

The melting points and analyses of the phenylureido acids are recorded in Table IV.

5-Aryl-3-phenylhydantoins. The phenylureides were converted to the hydantoins by boiling with hydrochloric acid.

5-Furyl-3-phenylhydantoin could not be prepared. Phenylureidofurylacetic acid decomposed to a gummy mass when heated with hydrochloric acid.

 $5 \cdot (p-Hydroxyphenyl)$ -3-phenylhydantoin melted at 171°, solidified almost instantaneously, and then melted again at 201°. After solidifying it melted again at 201°.

The melting points and analyses of the 5-aryl-3-phenyl hydantoins are recorded in Table V.

SUMMARY

1. In the reaction between pyruvic acid and α -amino-*p*-hydroxyphenyl-, -*p*-methoxyphenyl-, and -*o*-methoxyphenyl-acetic acids both acetaldehyde and an aromatic aldehyde are formed in addition to alanine and carbon dioxide.

2. In the reaction between pyruvic acid and α -amino-*p*-chlorophenyl-, -*o*-chlorophenyl-, and -*o*-hydroxyphenyl-acetic acids only an aromatic aldehyde is formed together with alanine and carbon dioxide.

3. In the system



the rate of carbon dioxide formation is greater the greater the dipole moment of YC_6H_4 . The effect of the same group is enhanced by shifting it from the *para*to the *ortho* position.

4. In their effect upon the rate of carbon dioxide formation the groups studied fall into the order

 $o-\mathrm{Cl} > o-\mathrm{CH}_{3}\mathrm{O} > o-\mathrm{OH} > p-\mathrm{Cl} > p-\mathrm{CH}_{3}\mathrm{O} > p-\mathrm{OH}.$

5. o-Chlorophenyl, p-chlorophenyl, o-methoxyphenyl, p-methoxyphenyl, o-hydroxyphenyl, p-hydroxyphenyl, and furyl aminoacetic acids have been prepared by the hydrolysis of the corresponding hydantoins. They have been characterized as the substituted *alpha*-phenylureidoacetic acids and substituted 3,5diphenylhydantoins.

NEW YORK, N. Y.

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