[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

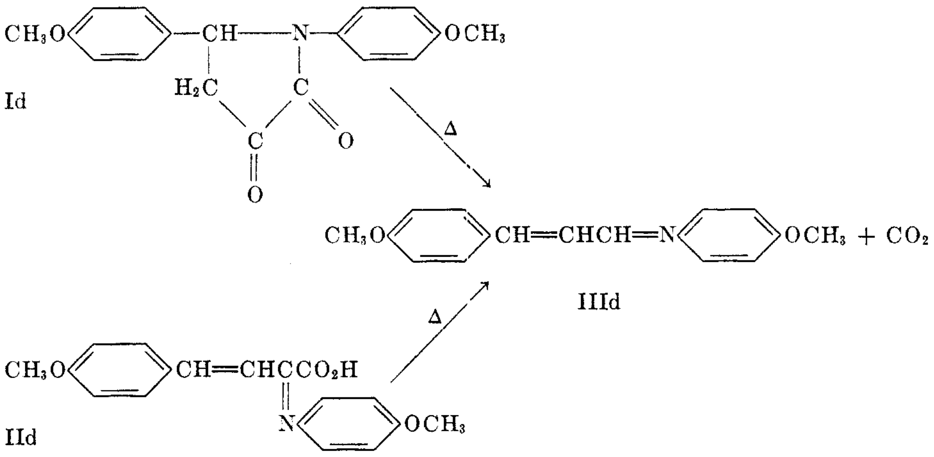
2,3-PYRROLIDINEDIONES. III. TAUTOMERIC REARRANGEMENT

WYMAN R. VAUGHAN AND LYNN R. PETERS[1,2]

Received September 17, 1952

In the preceding paper of this series (1) it was suggested that 1,5-diaryl-2,3-pyrrolidinediones (I) which suffer thermal decomposition with loss of carbon dioxide do so by conversion to α-arylimino-β-benzylidenepropionic acids (II), which subsequently are decarboxylated to cinnamylideneanilines (III). In the present paper we shall present evidence in support of this hypothesis.

Inasmuch as compounds of structure II are readily converted to compounds of isomeric structure (2, 3), this being one of the more important preparative methods for compounds of structure I, the reversibility of the process was investigated: thus 3-benzylidene-2-phenyliminopropionic acid (IIa) decarboxylated smoothly in *o*-dichlorobenzene to give N-cinnamylideneaniline (IIIa), the same product obtained from 1,5-diphenyl-2,3-pyrrolidinedione (4) under the same conditions; and 3-anisylidene-2-anisyliminopropionic acid (IId) afforded N-(4-methoxycinnamylidene)-4′-anisidine, the same anil produced in the thermal decomposition of 1,5-dianisyl-2,3-pyrrolidinedione (Id) under identical conditions (1).



More significant than such qualitative comparison of decomposition products is a comparison of the rates of thermal decomposition of Id and IId into IIId and carbon dioxide: thus the first order constants for the decarboxylation of IId (triangles) fall on the line connecting the constants for the decomposition of Id (1) as shown in Figure 1. These compounds, Id and IId, constitute the only α-imino acid-pyrrolidinedione pair whose decomposition rates were compared

---

[1] Rackham Predoctoral Fellow 1950–1951.

[2] Abstracted from a portion of the Ph.D. dissertation of Lynn R. Peters, University of Michigan, 1952.

quantitatively because IId is the only acid of the series (1, 2) which could be purified without rearrangement to the isomeric 2,3-pyrrolidinedione.

It seems almost certain, however, that acids IIa, IIb, and IIc would appear to decarboxylate at the same rate as the corresponding pyrrolidinediones, because they are transformed rapidly into Ia, Ib, and Ic, respectively, by heating, even in the solid state. This transition is indicated by change of color, by the fact that the melting points of the acids are those of the isomeric pyrrolidinediones, and by the failure of the latter to depress the melting points of the isomeric acids. The temperatures and reaction times necessary for converting the other acids (IId–IIh) to pyrrolidinediones (Table I, ref. 2) indicate that here, too, the rearrangement is rapid, probably more rapid than the decarboxylation.

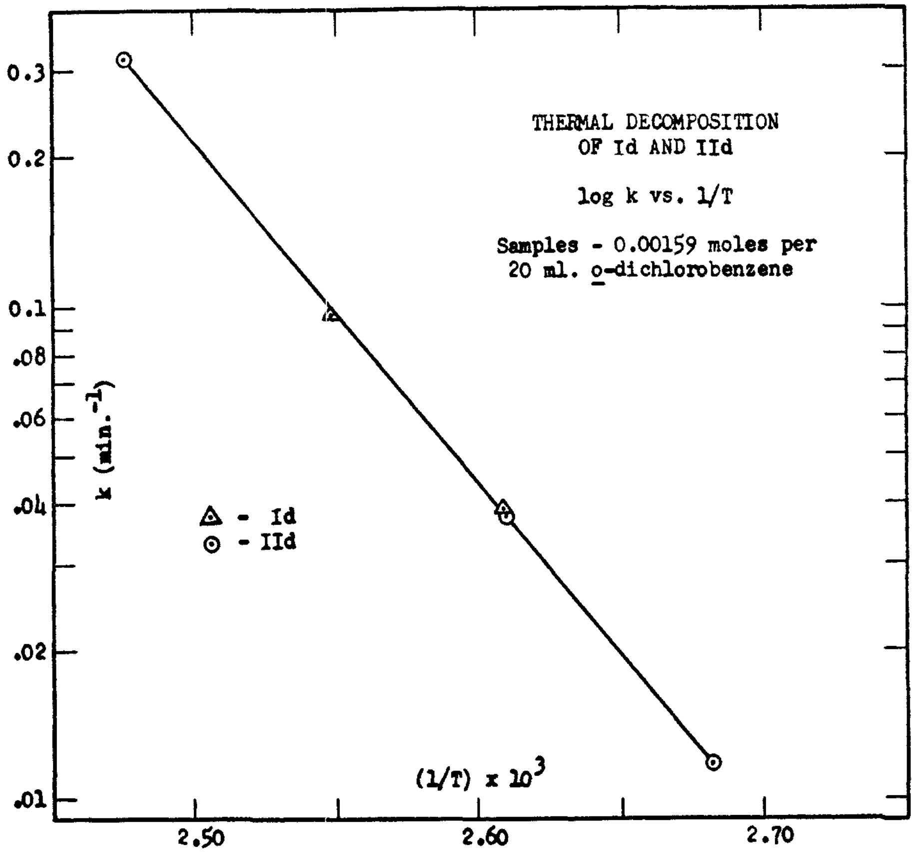


FIG. 1. THERMAL DECOMPOSITION OF Id AND IId

Although examples of the conversion of compounds of structure II into the isomeric form, I, are numerous, the first suggestion of a realizable reverse process is implied by the kinetic data obtained from Id and IId. Further investigation afforded supporting evidence: thus Ib and Id were converted into the isomeric imino acids IIb and IId: for example, acidification of a solution of Ib in aqueous ethanolic sodium carbonate affords yellow acidic IIb which rearranges to the pyrrolidinedione at ordinary temperatures and shows the same melting point as Ib.[3]

Inasmuch as both Id and IId could be obtained in reasonably pure condition, this pair were particularly suitable for study. The conversion of IId into Id is effected by recrystallization from a large volume of acetic acid-ethanol; Id is converted into IId by warming in a small volume of methanol. All other α-imino acids prepared in the course of this study (1, 2) cyclized on attempted recrystallization; all other 2,3-pyrrolidinediones showed no tendency to isomerize on warming in alcoholic solvents.

These deviations of behavior of Id and IId from the other compounds in the series made it desirable to confirm their structures. The infrared spectrum of Id (2) shows the bands at 2.92 μ, 5.72 μ and 6.03 μ due to hydroxyl, carbonyl, and carbon-carbon double bond, which appear in the spectra of all the 1,5-diaryl-2,3-pyrrolidinediones prepared, including Ia whose structure is definitely established (2).

Chemical evidence as to structure is summarized in Chart I:

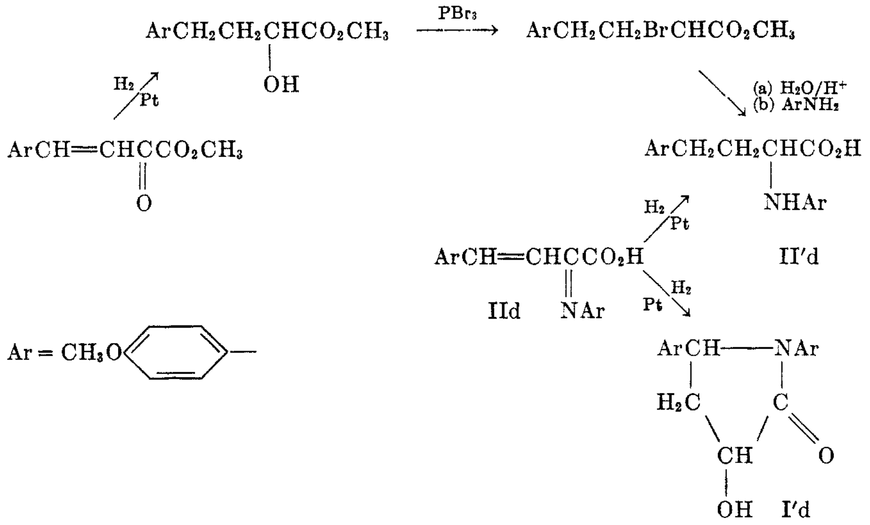


CHART I

IId was converted by catalytic reduction to α-anisylamino-γ-anisylbutyric acid (II'd), which was independently synthesized. The reduction afforded as a byproduct the neutral hydroxylactam I'd, which can be benzoylated. The isolation of the hydroxylactam illustrates the ease with which IId is converted into Id, and helps to confirm further the structure assigned to Id.

---

[3] Base-soluble gums were obtained upon similar treatment of Ia and Ic. This may be due to the recognized instability of benzylidenepyruvic acid toward bases at ordinary temperatures. (5)

It is possible to recrystallize Id from aprotic solvents such as ether, carbon tetrachloride, benzene, chlorobenzene, or acetonitrile. Dissolving Id in alcohol or nitromethane, however, affords yellow solutions from which only IId is recovered upon evaporation of the solvent. On the other hand, IId is practically insoluble in the aprotic solvents, but it can be dissolved in alcohol.

The ultraviolet absorption spectra of dilute alcoholic solutions of both Id and IId rapidly become identical. The spectrum of a freshly prepared solution of IId (concentration 5×10^{-5} molar) changes so rapidly at room temperature that the complete spectrum cannot be measured with the Model DU Beckman spectrophotometer. Band-maxima are located at approximately 324 mμ and 230 mμ, however, with the optical densities decreasing steadily (Table I).

TABLE I

CHANGE OF OPTICAL DENSITY OF A SOLUTION OF IId IN METHANOL

Concentration = 5.0×10^{-5} molar (room temperature)

$\lambda_{max.}$	TIME AFTER SOLUTION	OPTICAL DENSITY
324 mμ	15 min.	1.319
	45 min.	1.260
	19 hr.	1.172
230 mμ	45 min.	0.763
	19 hr.	.760

TABLE II

CHANGE OF OPTICAL DENSITY OF A SOLUTION OF Id IN METHANOL

Concentration = 5.1×10^{-5} molar (room temperature)

$\lambda_{max.}$	TIME AFTER SOLUTION	OPTICAL DENSITY
324 mμ	15 min.	1.08
	60 min.	1.198
	75 min.	1.300
	12 hours	1.180
230 mμ	20 min.	0.815
	12 hours	.801

Freshly prepared methanolic solutions of Id (concentration 5×10^{-5} molar) also have a changing spectrum. The maxima are at 324 mμ and 230 mμ, the same wave lengths as the bands in IId. The intensity of the 324 mμ band increases, however (Table II). The two spectra become identical after several hours at room temperature. Thus, the spectrum of the solution of IId after 19 hours (Figure 2) is nearly superimposable on that of Id after 12 hours (Figure 3). The identity of the two solutions is further demonstrated by the similar manner in which the spectra change on longer standing (Figures 2 and 3).

These observations indicate an equilibrium between Id and IId in methanol, accompanied by a slower secondary reaction. The nature of the secondary reaction is not known, but the new band which appears at 269 mμ is due neither to

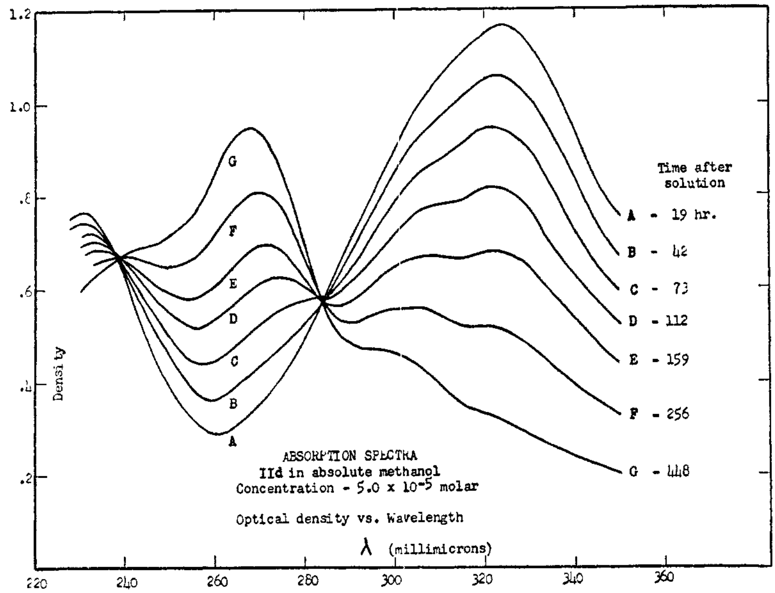


FIG. 2. ABSORPTION SPECTRA: IId in absolute methanol. Conc. 5.0 × 10^{-5} molar

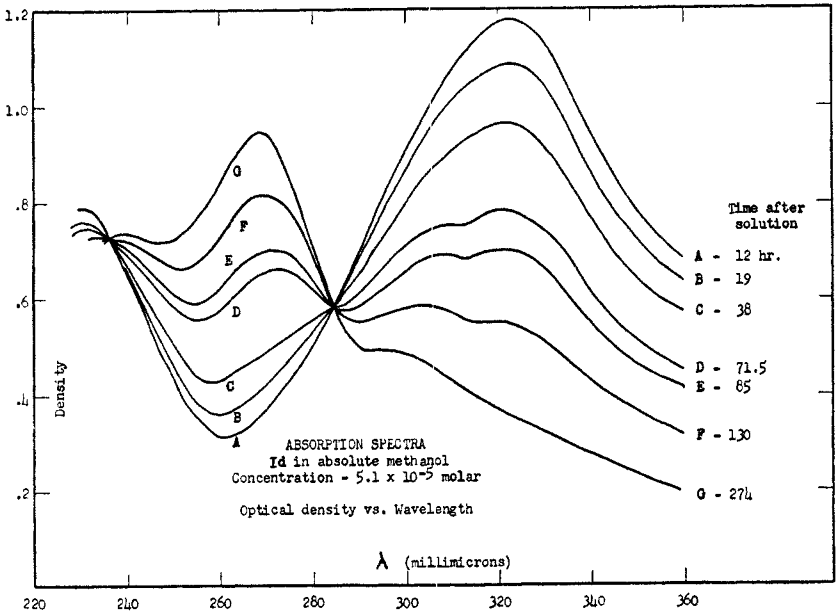


FIG. 3. ABSORPTION SPECTRA: Id in absolute methanol. Conc. 5.1 × 10^{-5} molar

the decarboxylation product IIId, nor to methyl anisylidenepyruvate, whose spectra are recorded in Figure 4.

Ether solutions of Id are stable at room temperature for hours. At elevated temperatures the spectra change in a manner which indicates that "decarboxylation" is occurring. The curves of Figure 5 were obtained from a solution of Id in di-*n*-butyl ether kept at 60–80°. The initial curve (I, Figure 5) is the same

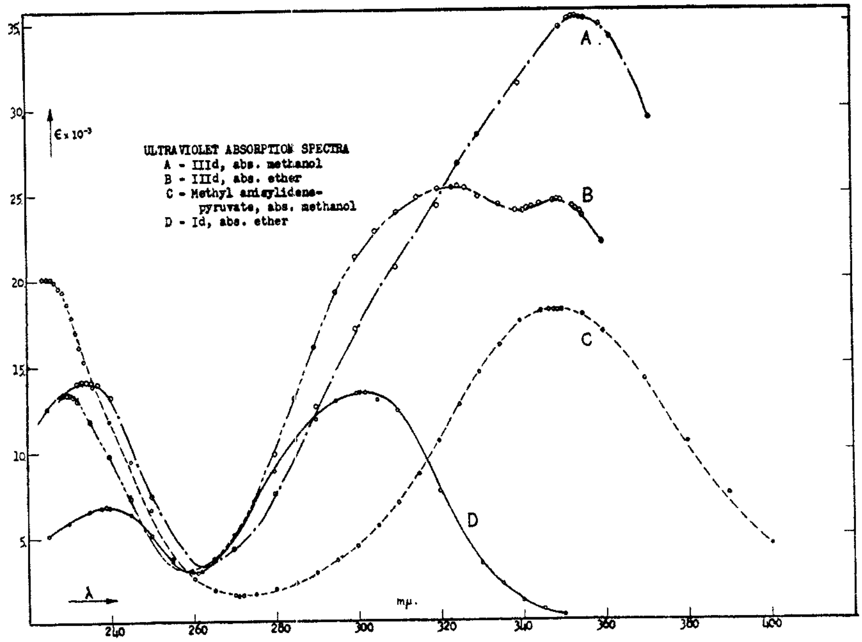


FIG. 4. ULTRAVIOLET ABSORPTION SPECTRA

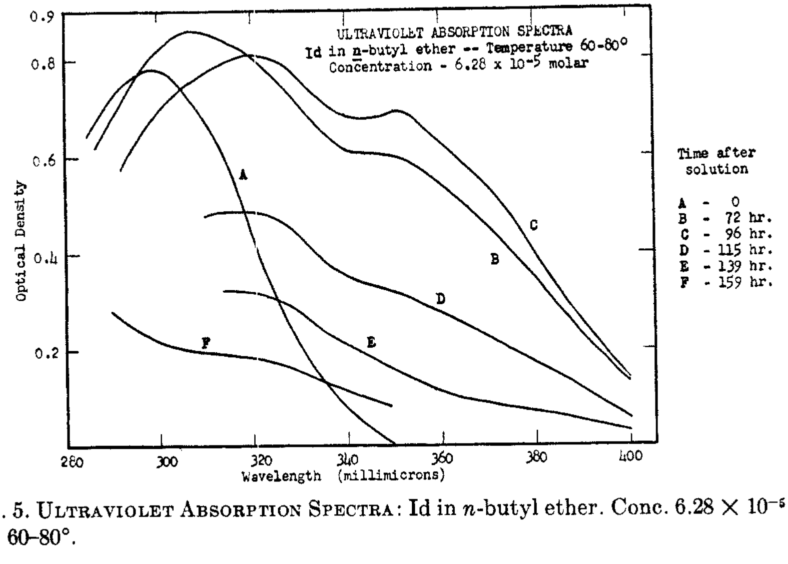


FIG. 5. ULTRAVIOLET ABSORPTION SPECTRA: Id in *n*-butyl ether. Conc. 6.28×10^{-5} molar. Temp. 60–80°.

as that of Id in ethyl ether (Figure 4, D). After 96 hours, the two maxima at 320 mμ and 350 mμ, due to the anil IIId (*cf.* Figure 4, B) are apparent. These bands decrease in intensity on longer standing, indicating decomposition of

IIId. The 159 hour spectrum (F, Figure 5) shows a high point at 290 mμ, which appears to be the base of a new band at a somewhat shorter wavelength, similar to the unidentified 270 mμ bands of Figures 2 and 3. Because the butyl ether was opaque to the spectrophotometer below 285 mμ, the entire band could not be observed.

A suspension of IId in methanol-dioxane, provided it was stirred to achieve equilibrium, gave a normal titration curve with sodium hydroxide using a glass electrode. Solutions of Id in the same medium or in pure methanol gave similar curves. When sodium hydroxide was added to the yellow solutions of Id, the solutions became colorless, and the *p*H indicator needle went off the scale. Then the yellow color slowly reappeared while the *p*H dropped to a steady value, which was plotted for the titration curve. This indicates that sodium hydroxide reacts rapidly with a yellow acidic component (IId) of the solution and that this component is replenished more slowly by isomerization of Id.

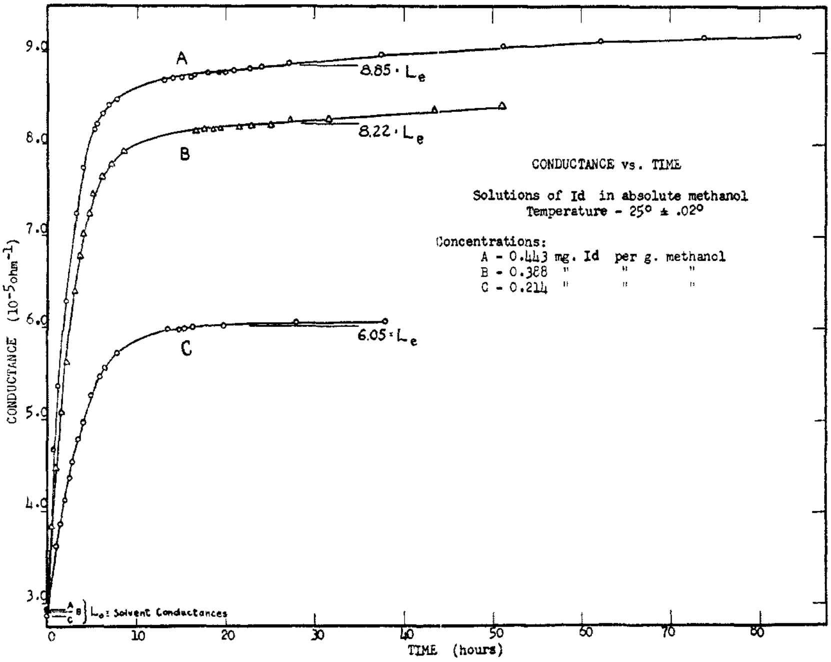


FIG. 6. CONDUCTANCE *vs* TIME: Id in absolute methanol. Temp. 25° ± 0.02°

The electrical conductivity of a freshly prepared methanol solution of Id increases on standing (Figure 6). This is attributable to the formation of IId, which probably exists in the zwitterion form, and which should be more conductive than Id, which is purely non-ionic.

The conductance *vs.* time curves (Figure 6) level off as equilibrium is approached, but the conductance does not become constant within a week at 25°. This slow drift of conductance probably is related to the slow secondary de-

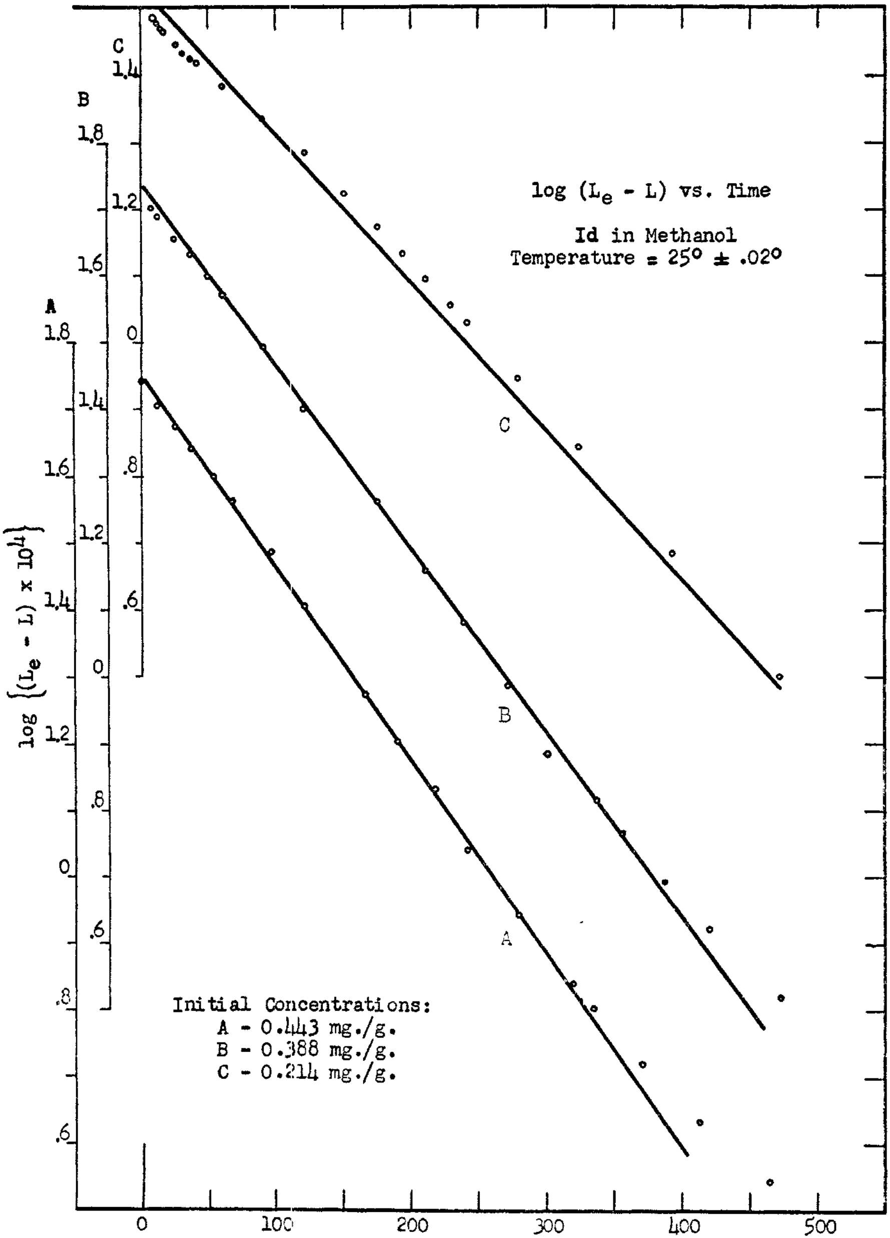


FIG. 7. LOG ($L_e - L$) *vs* TIME: Id in absolute methanol. Temp. 25° ± 0.02°

composition observed as a change in the ultraviolet absorption spectra (Figures 2 and 3).

The conductance data of Figure 6 are consistent with a pair of opposing first-order reactions (Figure 7). By assuming that the conductance of Id is negligible and that the molar conductance of the zwitterion is equal to the molar conductance of the similar α-anisylamino-γ-anisylbutyric acid (II′d), the equilibrium constant and the rate of the Id–IId equilibrium were estimated. The average equilibrium constant is 0.296 (Table III). The average rate constant for the reaction IId → Id was found to be 1.4×10^{-3} min.$^{-1}$ (Table III).

At 25° the rate constant for the conversion of Id to IId in methanol (1.4×10^{-3} min.$^{-1}$) is about one-tenth the rate constant for the decomposition of Id in o-dichlorobenzene at 100° [1.18×10^{-2} min.$^{-1}$ (1)]. For homogenous processes the specific reaction rate is approximately doubled or trebled for each 10° rise of temperature (6). Assuming a doubling of rate for each 10° temperature rise, the conversion of Id into IId would be 18 times as fast as the "decarboxylation" at the same temperature.

TABLE III

CONDUCTOMETRIC STUDY OF REACTION Id ⇄ IId CALCULATION OF EQUILIBRIUM CONSTANT AND SPECIFIC REACTION RATE

Methanol Solutions of IId

	A	B	C
Initial concentration, $[\mathrm{Id}]_o$ (mg. Id/g. methanol)	0.443	0.388	0.214
Slope (Figure 7) (log/min.)	−0.00288	−0.00272	−0.00225
$k_1 + k_2$ (min.$^{-1}$)	0.00665	0.00626	0.00511
Equilibrium conductance (L_e) (ohm^{-1})	8.85×10^{-5}	8.22×10^{-5}	6.05×10^{-5}
Solvent conductance (L_o) (ohm^{-1})	2.88×10^{-5}	2.93×10^{-5}	2.93×10^{-5}
$L_e - L_o$ (ohm^{-1})	5.97×10^{-5}	5.29×10^{-5}	3.12×10^{-5}
$[\mathrm{IId}]_e = (L_e - L_o)(0.0167)\frac{311}{315}$ (mg. IId/g. methanol)	0.0983	0.0870	0.0513
$[\mathrm{Id}]_e = [\mathrm{Id}]_o - [\mathrm{IId}]_e$ (mg. Id/g. methanol)	0.345	0.301	0.163
$K_e = \frac{[\mathrm{IId}]_e}{[\mathrm{Id}]_e} = \frac{k_1}{k_2}$	0.28_5	0.28_9	0.31_4
$1 + \frac{1}{K_e}$	4.51	4.46	4.18
$k_1 = \frac{(k_1 + k_2)}{1 + \frac{1}{K_2}}$ (min.$^{-1}$)	0.0014_8	0.0014_0	0.0012_2

Although Ib and Id are the only 2,3-pyrrolidinediones which were successfully converted to the isomeric α-imino acids, the hypothetical pyrrolidinedione-imino acid equilibrium in other members of the series is supported by isolation of α-imino acid derivatives from other 2,3-pyrrolidinediones. Thus, Ia reacts with methanol in the presence of hydrogen chloride to give methyl benzylidenepyruvate and aniline hydrochloride:

$$\mathrm{Ia} + \mathrm{CH_3OH} + \mathrm{HCl} \rightarrow \mathrm{C_6H_5CH{=}CHCOCO_2CH_3} + \mathrm{C_6H_5NH_2{\cdot}HCl}$$

Here hydrolysis destroys IIa as it is formed so that Ia is used up in maintaining the equilibrium. Similarly, butyl benzylidenepyruvate (isolated as the 2,4-

dinitrophenylhydrazone) was formed from Ia with butanol and hydrogen chloride. The reported easy hydrolysis of α-alkylimino acids (7) is observed also with these α-arylimino acids, methanolic hydrogen chloride converting IIc into methyl benzylidenepyruvate and anisidine hydrochloride on standing.

The foregoing observations establish that the reaction by which 1,5-diaryl-2,3-pyrrolidinediones are formed from α-arylimino acids can be reversed. In methanol, Id appears to be in equilibrium with IId, as shown by rapid approach toward identity of the ultraviolet spectra of the two compounds, and by the identity of the sodium hydroxide titration curves of the two compounds. Further, the specific rate of formation of IId from Id is much greater than the observed specific rate of formation of carbon dioxide during thermal decomposition of either substance. Therefore, assuming that the rate of imino acid formation is of the same order of magnitude in o-dichlorobenzene as in methanol, the observed rate of carbon dioxide evolution does not depend on the rate of tautomerization of the 2,3-pyrrolidinedione to α-imino acid, but instead probably measures only the slower rate of decarboxylation of the tautomeric α-imino acid:

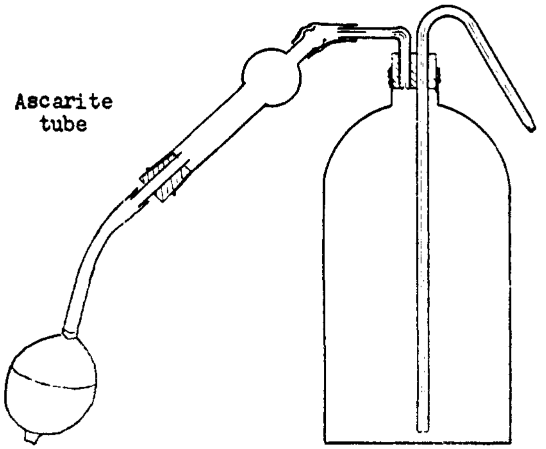


FIG. 8. METHANOL BOTTLE

$$\mathrm{Id} \underset{\text{(fast)}}{\leftrightarrows} \mathrm{IId} \underset{\text{(slow)}}{\rightarrow} \mathrm{IIId} + \mathrm{CO_2}.$$

EXPERIMENTAL[4]

CONDUCTOMETRIC STUDY OF THE REACTION ID $\leftrightarrows$ IID

Solvent. Reagent absolute methanol was dehydrated by refluxing with magnesium according to the procedure of Lund and Bjerrum (8). The distillation was carried out using an eight-inch column packed with glass helices to prevent entrainment of magnesium methoxide, and the distillate was used directly without redistillation.

In order to obtain reproducible conductances it was found necessary to make all transfers of methanol in a dry atmosphere. The methanol bottle, equipped with a capillary

---

[4] Melting points are uncorrected.

delivery tube and rubber bulb as shown (Figure 8), was kept in a dry-box protected with a drying tower of calcium chloride. A dish of fresh phosphorus pentoxide was kept in the box while transfers from the bottle to the cell were being made. Even with these precautions, the conductance of the solvent in the dry-box increased slowly.

Conductivity cell. The cell was constructed as shown (Figure 9). The electrodes were made of smooth platinum with glass bead spacers fused over each corner. Pyrex glass was used in the construction, except for a graded seal (pyrex to uranium glass to Corning #707) where the electrodes were sealed through the glass. The cell was rinsed with methanol and dried over activated silica gel at 20 mm. for one-half hour before each filling. The rinsing was repeated until the resistance of consecutive samples of methanol could be duplicated within about 0.25%. The cell was always filled as exactly as possible to the top of the small diameter portion, and it was sealed shortly after each filling by pouring paraffin into the well around the stopper. It was immersed in the thermostat to the level of the paraffin seal.

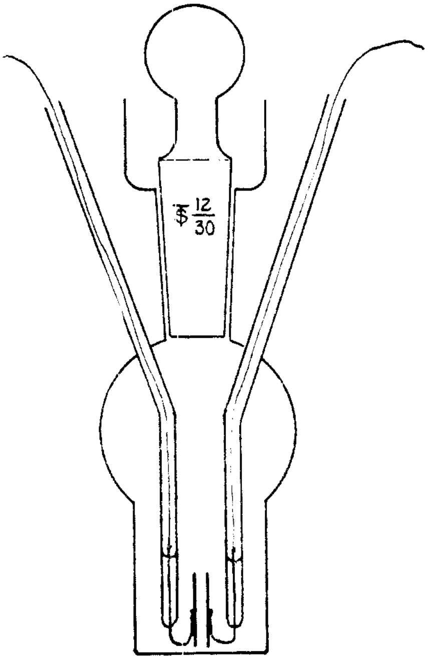


FIG. 9. CONDUCTIVITY CELL

Thermostat. A water-bath maintained at 25° ± 0.02° was used.

Measurement of resistance. Resistance of the filled cell was measured with a slide-wire bridge, using 1000 cycle current.

Conductance (L). L is the reciprocal of the measured resistance.

Conductance of II'd. Three 10-ml. volumetric flasks were thoroughly rinsed with methanol and dried. Into one of them was weighed 0.302 mg. of II'd. All were partly filled with methanol (7.165 g. in the flask containing the acid), sealed with paraffin, and shaken for 24 hours. The conductances were then determined with the results shown in Table IV.

Conductance of Id. Samples of Id were weighed directly into the conductivity cell, the cell was filled with methanol, weighed, sealed, and shaken gently for a minute or two to dissolve the sample. The cell was placed in the thermostat and resistance was measured at intervals thereafter. The measured resistances were converted to conductances by taking reciprocals. These values are plotted against time in Figure 6 for three runs using different initial concentration.

Calculation of rate and equilibrium constants from conductance measurements. The choice of a value of "equilibrium conductance" (L_e) necessary for calculating rate and equilibrium constants is somewhat arbitrary since, probably due to secondary decomposition as observed in spectographic measurements (Figures 2 and 3), the conductance does not remain absolutely constant after equilibrium has been reached. In this work, the conductance just beyond the point where the rate of change of slope of the conductance *vs.* time curve appeared to have become zero was called equilibrium conductance (L_e). The equilibrium points chosen are indicated on the graphs (Figure 6).

TABLE IV

CONDUCTANCE OF II'd IN METHANOL

Concentration* of solution—.302/7.165 = .0421 mg./g.

Conductance of blank #1	2.938×10^{-5} ohm^{-1}
blank #2	2.789
Conductance of solution	5.391
Average conductance of solvent	2.863
Conductance of solute	2.528×10^{-5} ohm^{-1}

Concentration of solution having solute conductance 1×10^{-5} ohm^{-1} = .0421/2.528 = 0.0617 mg./g.

* This solution is nearly saturated.

For a reversible first order reaction,

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$$

k_1 = first order forward rate constant
k_2 = first order reverse rate constant

the well known equation

$$\ln \frac{X_e}{X_e - X} = (k_1 + k_2)t$$

X_e = concentration of B formed from A at equilibrium
X = concentration of B formed from A at time *t*

applies (9). Since, over a limited concentration range, the concentration of a conducting species in solution is linearly proportional to the conductance of the solution minus the conductance of the solvent, the expression becomes

$$\ln \frac{L_e - L_o}{L_e - L} = (k_1 + k_2)t$$

L_e = conductance at equilibrium
L_o = conductance of solvent
L = conductance at time *t*

Thus, the slope of a plot of log ($L_e - L$) against time is -0.4343 ($K_1 + k_2$).

The log ($L_e - L$) *vs. t* plots of the three runs describe reasonably straight lines (Figure 7), whose slopes, determined graphically, are recorded in Table III, together with the values of $k_1 + k_2$ calculated therefrom.

On experimental and theoretical grounds, the conductance of Id may be considered negligible compared with that of the zwitterionized IId. Therefore $L - L_0$ is directly proportional to the concentration of IId ($\equiv$[IId]). By assuming that the molar conductivity of IId is equal to that of the amino acid II'd (Table III), the measured conductances may be converted to (IId). Thus at equilibrium,

$$[\mathrm{IId}]_e = (L_e - L_0)(0.00167^{5}) \frac{\text{Molec. wgt. of IId}}{\text{Molec. wgt. of II'd}}$$

$$= (L_e - L_0)(0.167)\frac{311}{315}\ \text{mg./g. methanol}$$

Since $[\mathrm{Id}]_e = [\mathrm{Id}]_{\text{initial}} - [\mathrm{IId}]_e$, the equilibrium constant,

$$K_e = \frac{[\mathrm{IId}]_e}{[\mathrm{Id}]_e}\ \text{can be evaluated.}$$

But since $K_e = \frac{k_1}{k_2}$, $\quad k_2 = \frac{k_1}{K_e}$

and $k_1 + k_2 = \left(1 + \frac{1}{K_e}\right) k_1$,

whence $k_1 = \dfrac{(k_1 + k_2)}{1 + \frac{1}{K_e}}$

The calculated values of K_e and k_1 are recorded in Table III.

Decarboxylation of 3-benzylidene-2-phenyliminopropionic acid, IIa. IIa, 0.86 g., was heated in 45 ml. of *o*-dichlorobenzene. Carbon dioxide was evolved as shown by precipitation in limewater. The solvent was blown down, leaving a brownish-yellow partially crystalline residue which was extracted with carbon tetrachloride. Cinnamylideneaniline (IIIa) was obtained by partial evaporation of the carbon tetrachloride extract. After two recrystallizations from carbon tetrachloride, it melted at 104–107°. The melting point was undepressed by admixture with IIIa (m.p. 104–106°) prepared by mixing equivalent amounts of cinnamaldehyde and aniline and recrystallizing the resulting product from alcohol. This is the same product obtained by Bachmann and Vaughan (4) from the thermal decomposition of Ia. The reported melting point is 109° (10).

Decarboxylation of 3-anisylidene-2-anisyliminopropionic acid, IId. A 0.5% solution of IId in chlorobenzene was refluxed one hour while carbon dioxide (limewater test) was liberated. The residue from blowing down the solution to dryness was recrystallized from absolute ethanol, affording IIId, yellowish-white plates, liquefying at 166–167.5°, melt clearing at 177–177.5°. This compound is identical (mixed m.p.) with that obtained by decarboxylation of Id. The reported melting point of IIId is: solid, 167°; liquid crystal, 180° (11).

IIb from Ib. A mixture of 0.040 g. of Ib, six drops of 10% sodium carbonate solution, and five ml. of ethanol was warmed on a steam-bath to dissolve the solid and then two minutes longer. The yellow reaction mixture was filtered and treated with two drops of acetic acid and sufficient 5% hydrochloric acid to cause a yellow precipitate. After washing with water and drying between pieces of filter paper, the product melted at 150–152° after turning white about 120°. When freshly precipitated, the yellow solid was soluble in cold aqueous sodium carbonate solution, but on standing it became largely insoluble, presumably due to recyclization to Ib. All observed properties of this product are identical to those of IIb prepared in the usual manner (2).

---

[5] Table IV.

IIb plus methanolic hydrogen chloride. IIb, 0.114 g., was suspended in 5 ml. of absolute methanol cooled in an ice-bath. The reaction mixture was then saturated with dry hydrogen chloride, and the resulting orange solution was allowed to stand overnight. Evaporation of the solvent under an air jet left a yellow residue which after recrystallization from methanol proved to be methyl benzylidenepyruvate by comparison with a sample of the latter compound prepared according to Reimer (5). The melting points and the mixed melting point of the two samples were 72–74°. Reported by Reimer: m.p. 73–74°.

Ia plus butanol and hydrogen chloride. The 2,4-dinitrophenylhydrazone of butyl benzylidenepyruvate. A mixture of about 0.2 g. of Ia and 15 ml. of butanol was placed in an ice-bath and saturated with dry hydrogen chloride. After standing 24 hours at room temperature, the reaction mixture was placed under an air jet until a paste of crystals remained. This paste was extracted with dry ether, leaving white, water-soluble crystals of aniline hydrochloride, m.p. 194–195° with sublimation. The ether extract on evaporation afforded a small volume of liquid which was treated with 2,4-dinitrophenylhydrazine according to the procedure of Shriner and Fuson (12). The immediately-formed orange-red precipitate was recrystallized from ethanol-ethyl acetate; scarlet needles, m.p. 160–160.4° with softening from 156°. This melting point was unchanged by subsequent recrystallizations from ethanol or ethyl acetate. It was not established whether this compound is a true dinitrophenylhydrazone or a pyrazoline.

Anal. Calc'd for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.59.

Found:[6] C, 58.33; H, 4.86; N, 13.66.

Ia plus methanol in the presence of mineral acids. (*A*) *Hydrogen chloride.* A cooled suspension of 0.238 g. of Ia in 15 ml. of commercial absolute methanol was saturated with dry hydrogen chloride. Addition of the HCl gas caused the reaction mixture to become yellow. After standing overnight, most of the Ia dissolved. The mixture was resaturated with HCl and allowed to stand an additional eight hours, whereupon the solvent was evaporated off under an air jet. The yellow residue was washed with water and recrystallized from a small volume of methanol. It was shown to be methyl benzylidene pyruvate by a mixture melting point test with an authentic sample prepared according to Reimer (5). The mother liquors yielded an ether-insoluble white solid decomposing around 190°, which was doubtless aniline hydrochloride.

(*B*) *Sulfuric acid.* To 0.523 g. of Ia suspended in 15 ml. of methanol was added three drops of concentrated sulfuric acid. There was no visible reaction in two days at room temperature. After four hours refluxing, the cooled reaction mixture deposited some of the starting material (Ia) as shown by mixture melting point. One additional drop of sulfuric acid was added and refluxing was continued for ten hours longer. Evaporation of the solvent left a brown gum, from which no crystalline products were obtained.

α-Keto-γ-anisylbutyric acid. A mixture of 5 g. of anisylidenepyruvic acid, 50 ml. of dioxane, and 75 mg. of platinum oxide was shaken with hydrogen (20 p.s.i.g., 27°). One equivalent of hydrogen was taken up rapidly, after which the rate of reaction slowed somewhat. This change of rate was more apparent if the catalyst was slightly deactivated (*i.e.* reused). The reaction was stopped when one equivalent of hydrogen was taken up. The reaction mixture was filtered and the solvent was removed by vacuum distillation. Trituration of the syrupy residue with benzene caused precipitation of some α-hydroxy-γ-anisylbutyric acid, which was filtered off and washed with benzene. The benzene solutions were concentrated to a thick syrup which was sublimed at 120°/0.05 mm. The resulting yellowish solid was recrystallized to constant melting point from benzene; m.p. 82–84°.

Anal. Calc'd for $C_{11}H_{12}O_4$: C, 63.48; H, 5.82.

Found:[7] C, 63.89; H, 6.12.

Semicarbazone. This was prepared according to Shriner and Fuson (12). It was recrystallized from absolute methanol; m.p. 196–196.5° d. (gas).

---

[6] Analysis by Mr. Goji Kodama, Ann Arbor, Michigan.

[7] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

Anal. Calc'd for $C_{12}H_{15}N_3O_4$: N, 15.84. Found:[7] N, 15.68.

α-Hydroxy-γ-anisylbutyric acid. A solution of 20.0 g. (0.0970 mole) of anisylidenepyruvic acid in 180 ml. of dioxane (Eastern Chemical Corp., redistilled after having been previously used as solvent for catalytic hydrogenation) was shaken at room temperature with hydrogen (46.5 p.s.i.g.) in the presence of 0.30 g. of platinum oxide (A.P.W.). The catalyst became deactivated before the theoretical amount of hydrogen had been absorbed, and was reactivated by shaking the reaction mixture for about 30 minutes with air at atmospheric pressure. The total reaction time was 14 hours. After filtration of the reaction mixture, dioxane was distilled off under reduced pressure until a thick paste remained. Recrystallized twice from benzene, the product melted at 113–115.5°; yield, 9.95 g. (48.7%). Repeated recrystallizations from nitromethane and chloroform gave a product melting at 115–117°. The reported melting point is 116–117° (13).

Methyl α-hydroxy-γ-anisylbutyrate. (*A*). This ester was first prepared by treating 11.0 g. (0.0524 mole) of the acid with a slight excess of ethereal diazomethane solution. Distillation of the resulting mixture gave 9.49 g. (80.7%) of a slightly yellow product; b.p. 115–120°/0.15 mm. This was redistilled at 113°/0.05 mm., a colorless hygroscopic liquid; d_4^{32} 1.132 g./ml.; n_D^{25} 1.5161.

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19.
Found:[7] C, 64.07; H, 6.80.

(*B*). The ester was prepared in better over-all yield (based on anisylidenepyruvic acid) by hydrogenation of methyl anisylidenepyruvate, which was obtained in almost quantitative yield by slight modification of the procedure of Reimer (14): absolute methanol containing a small amount of hydrogen chloride was used to esterify anisylidenepyruvic acid instead of the hydrogen chloride-saturated methanol recommended by Reimer. A single recrystallization of the precipitated ester from methanol gave a product melting at 104–107°, of sufficient purity for hydrogenation. Reduction of unrecrystallized ester was unsatisfactory.

A mixture of 8.15 g. (0.0367 mole) of methyl anisylidenepyruvate, 0.20 g. of platinum oxide (A.P.W.), and 100 ml. of commercial absolute methanol was shaken for 2½ hours with hydrogen (49 p.s.i.g., 26°). At the end of this time 0.074 mole of hydrogen had been absorbed and no more hydrogen was being taken up. The catalyst was filtered off, and the methanol was blown off under a dry air stream. Distillation of the residue gave a fraction boiling at 111–112°/0.06 mm.; yield, 5.18 g. (62.9%).

Methyl α-bromo-γ-anisylbutyrate. To a solution of 8.45 g. (0.0377 mole) of the preceding ester and 4.57 g. (0.0377 mole of N,N-dimethylaniline at 0° was added 3.57 ml. (0.0377 mole) of phosphorus tribromide. The mixture was heated at 100° for one hour with occasional shaking. A bright orange solid precipitated from the reaction mixture shortly after the heating was begun. The mixture was extracted with five 20-ml. portions of ether. The ether extract was washed twice with 10% sodium carbonate solution and then with water twice. After drying over sodium sulfate, the ether solution was allowed to evaporate under a dry air stream. Distillation of the residue gave a colorless fraction of 7.16 g.; b.p. 125–133°/0.3 mm. Redistillation of this fraction gave 3 g. of a product boiling at 111–117°/-0.07–.09 mm. and 4 g. of product at 117.5°/0.09 mm. The former product on redistillation seemed to be a mixture, from which pure products were not separated. The latter fraction was the desired product; d_4^{31} 1.347 g./ml.; n_D^{25} 1.5333.

Anal. Calc'd for $C_{12}H_{15}BrO_3$: C, 50.18; H, 5.27.
Found:[7] C, 50.30; H, 5.04.

α-Bromo-γ-anisylbutyric acid. This acid was obtained by hydrolysis of the preceding ester with hydrochloric acid. The ester (5.9 g., 0.021 mole) was refluxed 24 hours with 20 ml. of concentrated hydrochloric acid under vigorous stirring. Although the organic layer was still partially insoluble in 5% sodium bicarbonate solution, the reaction mixture was neutralized with solid sodium bicarbonate, enough water being added to dissolve all solids. The resulting solution was washed with ether, and this ether solution was extracted with 5% sodium bicarbonate solution. The bicarbonate solutions were combined and acidified with concentrated hydrochloric acid. The acid separated as a brown oil, which solidified on standing. The aqueous mother liquor was extracted with ether to obtain a small additional amount of the acid. The crude product was sublimed at 140°/0.15 mm.; m.p. 69–77°; yield 4.0 g. After several recrystallizations from petroleum ether (60–75°) and from a 50% mixture of petroleum ether and carbon tetrachloride, the product melted at 75–81°, and this melting point was not improved by further recrystallizations. Because of the long melting range, this acid was not analyzed.

α-Anisylamino-γ-anisylbutyric acid. (*A*). A suspension of 6.0 g. (0.019 mole) of IId in 100 ml. of glacial acetic acid was shaken with hydrogen (50 p.s.i.g.) at 27° in the presence of 0.10 g. of platinum oxide. After nine hours, the mixture had taken up about 80% of the hydrogen calculated for two-mole reduction, and the suspension had changed from yellow to almost white. No more hydrogen was taken up upon continued shaking. The white solid was filtered off and the filtrate was reserved for isolation of 3-hydroxy-1,5-dianisyl-2-pyrrolidone. The solid after filtration turned yellow rapidly on exposure to air. It was washed very thoroughly by decantation with several portions of ether totalling 100 ml. The resulting greenish product, net yield 3.0 g., m.p. 180–185° d. (gas) was recrystallized from nitromethane[8] and washed with ether. The best sample melted at 182–190° d. (gas), after darkening around 165°. The compound is soluble in 5% sodium bicarbonate solution and in concentrated hydrochloric acid.

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71.
Found:[7] C, 68.80; H, 6.62.

(*B*). A solution of 1.358 g. (0.00496 mole) of α-bromo-α-anisylbutyric acid, 1.83 g. (0.0149 mole) of *p*-anisidine, and 10 ml. of absolute methanol was sealed in a combustion tube and heated at 100° for two hours. The resulting snow white precipitate was filtered off and washed thoroughly with methanol; m.p. 183–191° d. (gas); yield, 0.796 g. (51.5%). This product was the same as that from procedure (*A*), as shown by melting points and the formation of a common derivative (below).

Derivative of α-anisylamino-γ-anisylbutyric acid. To a suspension of 0.477 g. of the acid in 50 ml. of commercial absolute methanol at the reflux temperature was added enough methanesulfonic acid to dissolve the amino acid (7 to 8 drops), and then one drop more. After refluxing for 26 hours, the reaction mixture was evaporated to dryness under a dry air stream. The slightly reddish residue was shaken with 20 ml. of 5% sodium bicarbonate solution and 19 ml. of ether. The ether layer was separated and the extraction was repeated six times. The combined ether extracts, dried over sodium sulfate, yielded a brown, semi-crystalline residue upon evaporation. This residue was sublimed (130°/0.3 mm.) and the nearly white, slightly oily crystalline product, which became reddish colored on standing, was recrystallized from petroleum ether (60–75°). After three recrystallizations, the melting point remained unchanged at 69.5–70.5°. The compound is insoluble in hydrochloric acid.

Anal. Calc'd for $C_{35}H_{46}N_2O_5$: C, 73.4; H, 8.01; N, 4.88.
Found:[7] C, 73.59; H, 8.30; N, 5.03.

The substitution of absolute ethanol for the methanol in the above procedure afforded a lower yield of the same derivative, as shown by an undepressed mixed melting point.

3-Hydroxy-1,5-dianisyl-2-pyrrolidone. The filtrate from the preparation of α-anisylamino-γ-anisylbutyric acid was diluted with about twice its volume of water. The crystalline precipitate was filtered off and recrystallized from 95% ethanol. Yield, 0.44 g.; m. p. 163–165.5°. Recrystallization from ethanol (plates) or acetonitrile (spears) raised the melting point to 165–167.5°.

Anal. Calc'd for $C_{18}H_{19}NO_4$: C, 69.01; H, 6.11.
Found:[7] C, 69.20; H, 5.81.

---

[8] Because of the limited solubility of the compound, crystallization was carried out in five 250-ml. batches, the solvent being recovered by vacuum distillation from the mother liquors. Recovery of solid was less than 50% per crystallization, and the red tarry residue from evaporation of the mother liquors did not afford solid products.

Benzoate. The benzoate was prepared by warming over a low flame 0.1 g. of 3-hydroxy-1,5-dianisyl-2-pyrrolidone with four drops of pyridine and 0.1 ml. of benzoyl chloride. Water, 5 ml., was added, and the precipitated product was washed with 5% sodium carbonate solution and recrystallized from 95% ethanol; white needles, m. p. 169.5–170°.

Anal. Calc'd for $C_{25}H_{23}NO_5$: C, 71.95; H, 5.55.

Found:[7] C, 72.30; H, 5.64.

ANN ARBOR, MICHIGAN

REFERENCES

(1) VAUGHAN AND PETERS, *J. Org. Chem.*, **18**, preceding paper (1953).

(2) VAUGHAN AND PETERS, *J. Org. Chem.*, **18**, Paper I this issue (1953).

(3) BODFORSS, *Ann.*, **455**, 41 (1927).

(4) BACHMANN AND VAUGHAN, unpublished research.

(5) REIMER, *J. Am. Chem. Soc.*, **46**, 785 (1924).

(6) GLASSTONE, *Textbook of Physical Chemistry*, 2nd Edition, D. Van Nostrand, New York, 1946, p. 1087.

(7) SKITA AND WULFF, *Ann.*, **455**, 17 (1927).

(8) LUND AND BJERRUM, *Ber*, **64**, 210 (1931).

(9) HAMMETT, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940 p. 102.

(10) DOEBNER AND VON MILLER, *Ber.*, **16**, 1665 (1883).

(11) VORLÄNDER AND GIESELER, *J. prakt. Chem.*, [2] **121**, 239 (1929).

(12) SHRINER AND FUSON, *The Systematic Identification of Organic Compounds*, 2nd Edition, John Wiley and Sons, New York, 1940.

(13) BOUGAULT, *Ann. chim. phys.*, [8] **14**, 131 (1908).

(14) REIMER, *J. Am. Chem. Soc.*, **48**, 2458 (1926).