[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORIES OF BRYN MAWR COLLEGE AND THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

Isomerism and Adduct Stability in the Diels–Alder Reaction.[1a] I. The Adducts of Furan and Maleimide

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The synthesis and characterization of the isomeric *endo-* and *exo*-adducts resulting from the Diels–Alder condensation of furan and maleimide is reported here. The relationship of these adducts to the one stable furan–maleimic anhydride adduct previously characterized is set forth.

Because of our interest in the kinetic and thermodynamic aspects of the Diels–Alder reaction, we have sought a typical system in which the various forms of the adduct could be studied and recognized. We report in this paper the preparation and behavior of the *exo-* and *endo*-adducts secured from the reaction of maleimide with furan.

When maleimide and furan are dissolved in ether or water, and heated together for 10 hours at 90° in a closed vessel from which the atmosphere has been exhausted, long needles of an almost pure product melting at 162° are obtained. When the temperature of reaction is lowered to about 25° and the period of reaction increased to four to seven days, the product obtained melts at 131°.

Evidently the solvent, whether water or ether, has no influence on the course of the reaction[2] but the temperature does determine which of the possible isomers will form. It was demonstrated that strong illumination as well as heating the isomer melting at 131° in a variety of solvents for a short period of time converted it largely into the high melting material.

During the characterization of the isomers we were fortunate in being able to take advantage of the known structure of a related furan–maleic anhydride adduct, *exo*, *cis*-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (VI) whose structure had been brilliantly delineated earlier by Woodward and Baer.[2] The flow sheet (Fig. 1) outlines our approach to this problem.

It is seen that the higher melting isomer II in keeping with many similar observations[3] on the relationship of the melting points of *exo–endo* isomers, has the *exo* configuration. Other differences in the properties of the isomers besides melting point are immediately obvious. Upon saponification with strong aqueous potassium hydroxide (both I and II are soluble in water as well as in a variety of solvents) the higher melting isomer gave off NH_3 much less readily but in both cases it proved impossible to isolate the expected products of the saponification, the corresponding Δ^4-dibasic acids. Reduction of I and II in ethyl acetate solution with hydrogen and Adams catalyst gave smoothly the saturated imides: III, m.p. 135°, and IV, m.p. 181°. However, on saponification in strong aqueous base the same nitrogen-free dibasic acid, V, could be recovered from each of the reduced imides. V melted at 177° alone or mixed with an authentic specimen secured by the aqueous alkaline treatment of the dihydro derivative of VI. Adduct VI and its dihydro derivative VII were prepared according to directions reported by Alder and Backendorf.[4]

The hydrolysis of VII gave the acid hydrate VIII, the dehydration of which led to the anhydrous acid IX. Acid hydrate VIII was reported without configurational assignment by Diels and Alder.[5]

It seems evident that the isomerization of the *exo–cis*-acids VIII and IX to V in hot alkali can be regarded as an epimerization involving base-catalyzed enolization of carboxylic acids.[6] The interrelation of these compounds is made even clearer by the easy transformation of the anhydride VII to the imide IV by a procedure similar to that used by Kao and Shao-Yuan Ma[7] employing $(NH_4)_2CO_3$ and HOAc to convert benzoic acids to benzamides. That the dibasic acids VIII and IX have the *exo–cis* configuration was demonstrated by their facile conversion to the *exo–cis*-imide IV by this method. Strong support for the *trans* configuration of V was obtained by the failure of all attempts to convert this substance to an imide by the procedure by which VII, VIII and IX were smoothly transformed. The dibasic acid of the *endo–cis* configuration representing the third possible isomer would have been expected to yield the *endo–cis*-imide.

The structure of VII established by Woodward and Baer[4] is seen to be the key to the identities and interrelationships of all the compounds depicted on the flow sheet. Thus the interconversion of compounds IV, VII and IX by the mild procedures indicated is best understood in terms of their assigned structures. The structures assigned to compounds VIII and IX are thus also substantiated by the related cycle of easy transformations going from VIII to IX to V and by the fact that V is obtainable directly from VIII on hot alkali treatment. Accepting the *trans* configuration (*vide supra*) for V which did not form a stable hydrate confirms the conclusion that VIII which was readily

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[1] (a) Work done under the sponsorship of the Office of Naval Research, Contract N-onr-01800 and Contract N-onr-567(00). (b) Department of Chemistry, University of Delaware.

[2] Compare R. B. Woodward and H. Baer, THIS JOURNAL, **70**, 1161 (1948).

[3] (a) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937); (b) O. Diels, K. Alder and P. Pries, *Ber.*, **62**, 2081 (1929); (c) R. B. Woodward and H. Baer, THIS JOURNAL, **66**, 645 (1944).

[4] K. Alder and K. H. Backendorf, *Ann.*, **535**, 113 (1938).

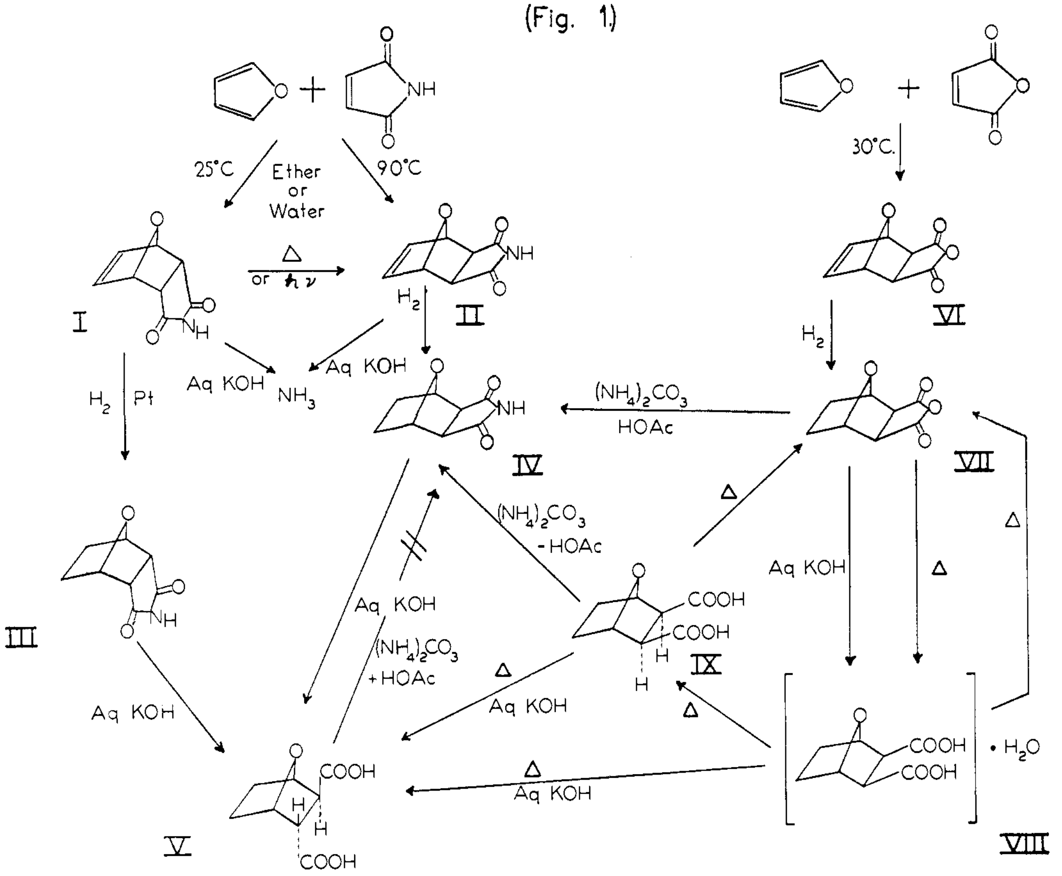
[5] O. Diels and K. Alder, *Ber.*, **62**, 558 (1929).

[6] The mechanism of this process is entirely analogous to those written for the interconversion of the β,γ- and α,β-isomerides of unsaturated acids (*cf.* A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928)) and the racemization of aliphatic nitro compound (*cf.* C. K. Ingold, *Ann. Reports*, **24**, 107 (1927)) by means of strong bases

[7] C. H. Kao and Shao-Yuan Ma, *J. Chem. Soc.*, 2788 (1930); *ibid.*, 443 (1931)

FLOW SHEET

(Fig. 1)



formed as the stable hydrate on treatment of the *exo–cis*-acid IX with water is also of the *exo–cis* configuration. The fact that both VIII and IX easily reformed (on loss of water in sublimation) the *exo*-anhydride VII reinforces the *exo* configuration assigned to both these compounds.

Experimental[8]

Preparation of Maleimide.—This compound was prepared by oxidation of pyrrole by a method similar to that of Plancher and Cottadari.[9] A solution of 1177 g. of potassium dichromate in 1200 cc. of water and 512 cc. of concentrated sulfuric acid was warmed to 35° in a three-necked flask equipped with devices for stirring, refluxing and temperature measurement and control. In later experiments sodium dichromate was found to be superior because of its greater solubility in the medium. Fifty-four grams of pyrrole (du Pont) was slowly run in at a rate such that the temperature did not exceed 50°. The solution turned very dark and small amounts of tar separated continuously as the addition proceeded. After the pyrrole was added stirring was continued while the temperature was maintained at 40–50° until the distinctive odor of pyrrole could no longer be detected. The cooled solution was filtered free of the tars through glass wool, the filter cake slurried with hot water twice and then discarded and the combined filtrate and slurry washings extracted with 200-cc. portions of ethyl ether in a continuous extractor shown and described in Fig. 2. Each 200-cc. portion of ether was permitted to extract the water solution over a period of 10 to 15 hours, then dried over sodium sulfate and evaporated. The crude crystalline product was recrystallized from benzene and decolorized with charcoal. Vacuum sublimation of this slightly yellow material gave a pure white product melting sharply at 93° (uncor.). After five ether extractions a total of 7 g. of pure product was recovered.

Preparation of the *exo* and *endo* Isomers of 3,6-Endoxo-Δ^4-tetrahydrophthalimide.—Early attempts to prepare the pure isomers led to mixtures which could be separated by a chromatographic procedure. A typical chromatographic separation is discussed later in this section.

The *endo* Isomer I.—Using either water or ether as solvent with maleimide and 50% excess furan, the solution of these reagents was permitted to stand for four to seven days at room temperature with complete exclusion of light. The product was caused to separate from the ether solution by blowing off a portion of the solvent with a stream of dry nitrogen. The water solution preparation required repeated extraction with chloroform to separate the product. The chloroform was removed from the extract by blowing it off in a stream of dry nitrogen. The yield in the ether method was somewhat greater than in the water method running as high as 95%. Product purification was accomplished by the following procedure, intended to avoid isomerization to the *exo* isomer which occurs very readily on recrystallization from hot solvents. A saturated solution of crude I was made by shaking at room temperature with a deficiency of analytical reagent chloroform. The saturated solution was carefully decanted from the excess solid and low boiling (30–60°) petroleum ether added dropwise until a faint cloudiness appeared. After several hours of standing the fine crystals which separated were collected at the pump, washed with a small portion of petroleum ether and dried over calcium chloride in a vacuum desiccator. Two such crystallizations resulted in a product melting sharply at 131°.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.2; H, 4.27; N, 8.48. Found: C, 58.3; H, 4.20; N, 8.41.

The *exo* Isomer II–Water Method.—To a saturated furan (du Pont) water solution was added maleimide in an amount such that a 50% excess of furan was present. This reaction solution was heated in a sealed glass tube for 10 hours at 90°. The crystalline product separated on cooling and when re-

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[8] All melting points given are uncorrected.

[9] G. Plancher and V. Cottadari, *Atti della Reale Acad. dei Lincei*, **13**, 1, 490 (1904).

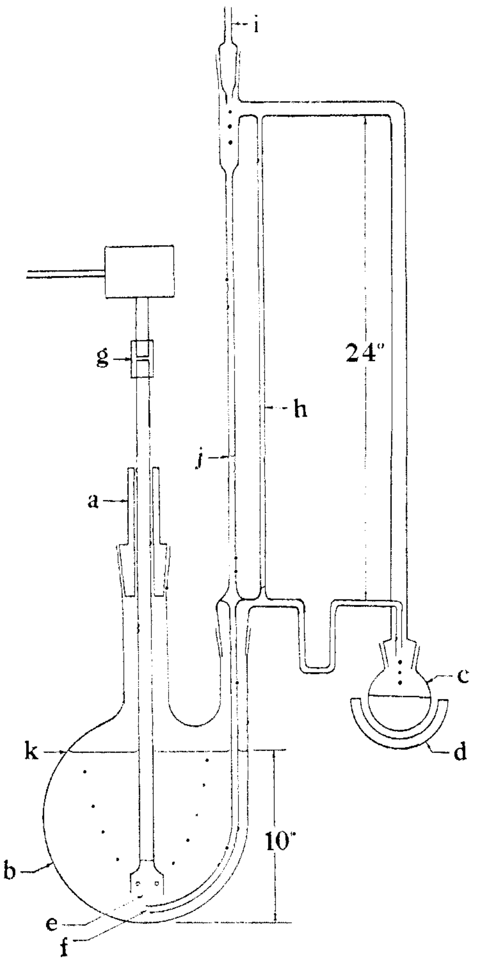

Fig. 2.—a, Trubore stirrer made by Ace Glass Company, Vineland, N. J.; b, 3-l. flask with two long neck ground joints; c, 250-cc. ground joint flask; d, Glas-col heating mantle; e, 1 × 1" glass tubing annulus pierced with 4 equally spaced $^1/_{32}$" holes and sealed to the stirrer. When rotated at 50 r.p.m. the stirring action of this device acts to suck up the small slugs of ether issuing from the orifice (f), whirl them out of the holes and disperse them as fine droplets through the body of aqueous solution; f, fresh solvent entrance fitted to locate exactly under the stirrer; orifice about $^1/_{32}$"; g, motor and flexible coupling to the stirrer; h, pressure balancing tube to prevent siphoning; i, efficient coil condenser; j, ether meniscus; k, water–ether interface.

crystallized from hot water melted sharply at 162°. The yield was approximately 50% over-all.

Ether Method.—Maleimide was dissolved in fifty times its weight of ether and 50% excess furan added. The reaction solution was heated in a sealed tube for 10 hours at 90°. The white crystalline product separated on cooling. The yield of product melting at 162° when purified by recrystallization from absolute ethyl acetate is almost 90%. Sublimation in high vacuum did not change the melting point. Mixed melting point with compound II prepared by the water method gave no depression. Mixed melting point with compound I gave a strong depression.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.2; H, 4.27; N, 8.48. Found: C, 58.1; H, 4.23; N, 8.39.

Conversion of the *endo* (I) to the *exo* (II) Isomer.—The easy isomerization of the *endo* to the *exo* isomer was realized on boiling a solution of I in absolute ethyl acetate or dry benzene for 15 minutes. The product which crystallized out on cooling was identical with II as determined by mixed melting point. A portion of an unheated solution of I in absolute ether when allowed to stand in direct sunlight for three days also yielded pure II on evaporation of the solvent and recrystallization.

Reduction.—All reductions in this series were carried out at room temperature (20–25°). The substance to be reduced was dissolved in roughly one hundred times its weight of absolute ethyl acetate. Adams catalyst (J. Bishop Co., Malvern, Pa.) in the amount of 10 mg. per 0.001 mole of substance to be reduced was used and the hydrogen pressure was kept below two atmospheres in a Hershberg type apparatus.[10] The catalyst was removed by filtration, the last traces with the assistance of a filter-aid. The yields were almost always quantitative. Reductions of the pure substances were always complete in under one hour. ***endo*-3,6-Endoxo-hexahydrophthalimide (III)**, prepared by the reduction of I, after one recrystallization from absolute ethyl acetate showed a m.p. 135° and strongly depressed the melting point of a specimen of I.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.1; H, 5.43; N, 8.38. Found: C, 56.9; H, 5.40; N, 8.31.

***exo*-3,6-Endoxo-hexahydrophthalimide (IV).**—Prepared by the reduction of II melted sharply at 181° and strongly depressed the melting point of II on admixture of the two.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.1; H, 5.43; N, 8.38. Found: C, 56.9; H, 5.44; N, 8.29.

Saponification of Imides and Anhydrides (A).—One-half gram of imide (III or IV) was dissolved in 10 cc. of 30% aqueous potassium hydroxide and the solution refluxed for up to 10 hours. The saponification was considered complete when the effluent gas no longer tested for ammonia with moist litmus. The solution was then acidified to litmus with phosphoric acid and extracted in a continuous extractor of the Palkin[11] type with ether for three to six days. The ether was changed every 12 hours and each extraction batch worked up separately. In this manner up to 60% of the product was recovered.

Attempts to saponify the adducts I and II failed to yield any crystalline products although complete decomposition of the imide linkage had been accomplished as noted by the negative litmus test on the effluent. Utilizing lower temperatures and lower boiling solvents such as methanol failed to produce a significant amount of reaction as evidenced by the almost total lack of ammonia evolution. Both the reduced imides III and IV were completely reacted under the above conditions, the former apparently at a greater rate. Ammonia evolution on saponification of the reduced *endo*-imide III started vigorously as soon as reflux temperature was attained and ceased completely in under five hours. The *exo*-imide IV required as much as 10 hours. **3,6-Endoxo-hexahydro-*trans*-phthalic acid (V)** was obtained by this procedure from both III and IV, m.p. 177°; neutralization equivalent calculated 93, found 93 ± 1. A mixed melting point with an authentic specimen prepared according to the directions of Alder and Backendorf[3] showed no depression.

(B).—One-half gram of *exo*-3,6-endoxo-hexahydrophthalic anhydride (VII) (prepared by reduction of the adduct VI in the manner described in reference (7)) was dissolved in 10 cc. of hot 30% aqueous potassium hydroxide and the solution permitted to cool to room temperature during half an hour. The product was worked up in the same fashion as described in (A) above. The same product was obtainable by boiling VII in water solution for half an hour. ***exo*-3,6-Endoxo-hexahydrophthalic acid hydrate (VIII)** resulting on recrystallization from hot water melted at 125° and had a neutralization equivalent of 102 ± 1 compared to the calculated value of 102. The properties and analysis of VIII are in agreement with those described for endoxo-3,6-hexahydrophthalic acid by Diels and Alder.[5] Sublimation was accompanied by the loss of water with formation of the pure *exo*-anhydride VII, m.p. 111°. No depression of melting point was observed on admixture with a specimen of the compound prepared by the procedure given in reference 5.

***exo*-3,6-Endoxo-hexahydro-*cis*-phthalic Acid (IX).**—The dibasic acid which had been previously reported as resulting from the hydrolysis of reduced maleic anhydride–furan adduct by Alder and Backendorf[4] and shown later by Woodward and Baer[2] to be of the *exo–cis* configuration was synthesized according to the procedure of the German authors.

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[10] L. Fieser and E. Hershberg, THIS JOURNAL, 60, 940 (1938).

[11] S. Palkin, A. G. Murray and H. R. Watkins, *Ind. Eng. Chem.*, 17, 612 (1925).

The properties of this compound proved to be identical with those of the hydrate VIII above. The product IX was obtained on dehydration of VIII on boiling in 50% benzene-ethyl acetate solution until water was no longer condensed. IX melted at 144° and had a neutralization equivalent of 93 ± 1 compared to the calculated value of 93. Sublimation in vacuum resulted in the loss of a mole of water and formation of VII—identified by no depression in a mixed melting point with an authentic specimen.

Anal. Calcd. for $C_8H_{10}O_5$: C, 51.6; H, 5.42. Found: C, 51.5; H, 5.44.

Preparation of Imides from Acids and Anhydrides.—One-half gram of acid or anhydride was mixed with 0.5 g. of ammonium carbonate and 1 ml. of glacial acetic acid in a small sublimator from which the condenser was removed. The mixture was heated gently and slowly brought to a boil under a good hood. When acetic acid vapors were no longer detected by moist litmus paper the condenser was replaced and the solid residue sublimed in a vacuum of approximately 10 mm. On resublimation in a high vacuum, pure products were obtained. By this procedure compounds VII, VIII and IX were converted to the reduced *exo*-imide IV, the latter being identified by mixed melting point with an authentic specimen. All attempts to convert compound V, the *trans*-dibasic acid, to an imide under the conditions described above resulted in no reaction.

Chromatographic Separation of *endo-exo* Mixtures.—The adsorbent used was activated alumina (Merck grade for chromatographic adsorption). A pressure of 55 mm. of dry (Linde Pre-purified Grade) nitrogen was used. The separation of 0.5 g. of a mixture of *endo*- and *exo*-3,6-endoxotetrahydrophthalimide (compounds I and II) in absolute ether solution is typified by the following table of results using absolute ethyl acetate-ether mixtures in 100-cc. portions for elution.

Elution fractions	Eluting solvent composition, % ethyl acetate	Melting point of product obtained on evaporation of the eluate fractions, °C.
A-C	60	131
D	70	120-139
E-F	70	162
G-I	80	162

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE TOKYO INSTITUTE OF TECHNOLOGY]

On the Thermal Dissociation of Organic Compounds. (1) The Urea Linkage (Diphenylurea in Fatty Acids)

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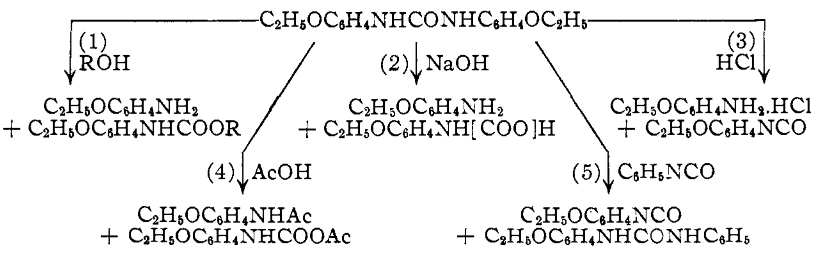
On heating, a urea generally dissociates into an isocyanate and an amine. In the absence of kinetic data on this kind of reaction we have measured the rate constant and activation energy of the dissociation of *sym*-diphenylurea in fatty acids as solvents. When the dissociation is rate-determining, the reaction may be followed by noting the rate of carbon dioxide evolution that results from the reaction of phenyl isocyanate with the solvent acid. A method was devised to measure the quantity of accumulated intermediate (phenyl isocyanate) in cases where the rate of the dissociation and of the subsequent reaction were comparable. The rate of dissociation depends markedly on the nature of the solvent.

Introduction

On heating, disubstituted ureas generally dissociate to isocyanates and amines. As we shall show, this dissociation is a reversal of the formation reaction, and therefore we prefer the term "dissociation" to "decomposition," which has been used by earlier investigators.

Davis and Blanchard[1] obtained *sym*-phenylethyl urea and *sym*-diphenylurea on heating *sym*-diethylurea with aniline, a result attributed to the existence of four equilibria involving both of the possible isocyanates and both of the corresponding amines. Taüfel, Wagner and Dünwald[2] hence assumed that decomposition, in aqueous solution, of *p*-phenetylcarbamide leads mainly to phenetyl isocyanate and ammonia, and, in minor amount, to phenetidine and isocyanic acid; they also measured the velocity constant for the over-all decomposition.

$$C_2H_5OC_6H_4NHCONH_2 \left\{ \begin{array}{l} \rightarrow C_2H_5OC_6H_4NCO + NH_3 \\ \rightarrow C_2H_5OC_6H_4NH_2 + HNCO \end{array} \right.$$



As shown by Iwakura and Nagakubo[3] of this Laboratory, *sym*-di-*p*-phenetylurea yields on heating phenetidine and phenetyl isocyanate. This conclusion is based on the following results: (1) In *n*-butanol phenetidine and *n*-butylphenetylurethan are produced. (2) Alkali in butanol, isoamyl alcohol, anisole, tetralin or decalin causes quantitative conversion to phenetidine. (3) Under the influence of dry hydrogen chloride in anisole, phenetyl isocyanate along with phenetidine hydrochloride is obtained. (4) In acetic acid or anhydride, phenacetine is formed. (5) With phenyl isocyanate in anisole, phenetyl isocyanate and *sym*-phenetylphenylurea are formed.

The thermal dissociation of diphenylurea in acetic acid involves the reactions

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[1] T. L. Davis and K. C. Blanchard, THIS JOURNAL, **45**, 1816 (1923).

[2] K. Täufel, C. Wagner and H. Dünwald, *Z. Elektrochem.*, **34**, 115 (1928).

[3] Y. Iwakura and K. Nagakubo, *Bull. Tokyo Inst. Technol.*, **18**, 25 (1948).