tion of bromine color was allowed during the addition. Distillation yielded 16.5 g. (30%) of 2-bromo-1-chloro-1-phenylethane, b.p. 111–115° (7 mm.), $n^{20}D$ 1.5660. The reaction mixture also yielded 11% of the dibromide. The analysis of the bromochloride for total halogen was quite low. This result as well as the lowered index of refraction points to the chlorohydrin, b.p. 110–111° (6 mm.), $n^{20}D$ 1.5400[16] as a possible contaminant. The product when dehydrohalogenated as described below gave a 56% yield of α-chlorostyrene.

Dehydrohalogenation of 2-Bromo-1-chloro-1-phenylethane.—A solution of 7.3 g. (0.19 mole) of sodium hydroxide in 38 ml. of 70% ethanol was treated with 31 g. (0.14 mole) of the bromochloride according to the directions of Emerson and Agnew[17] for the dehydrochlorination of styrene dichloride. A 15.0 g. (78%) yield of α-chlorostyrene, b.p. 80–83° (20–22 mm.), $n^{20}D$ 1.5578, was obtained. No bromine could be detected in the product. The α-chlorostyrene gave a precipitate with hot alcoholic silver nitrate whereas β-bromostyrene did not. The α-position of the chlorine was also checked by conversion of the compound to acetophenone by the action of 80% sulfuric acid.[17]

Addition of Bromine Chloride to *trans*-Cinnamic Acid.—To a solution of 20 g. (0.135 mole) of cinnamic acid and 59 ml. of 37% hydrochloric acid in 200 ml. of dimethylcellosolve 28.3 g. (0.205 mole) of N-bromoacetamide was added portionwise so that the temperature remained between 25 and 30°. Dilution with water led to two liquid phases. Both were separated and cooled to give samples of the product. Crystallization twice from aqueous ethanol yielded 19.8 g. (56%) of α-bromo-β-chlorohydrocinnamic acid, m.p. 180–181° (dec.). Pfeiffer and Praetorius[14] report m.p. 183–184° for a sample whose analysis indicated dibromide as a contaminant. It has been our experience that such mixtures melt higher than the pure bromochloride. These authors did not dehydrohalogenate their product.

(16) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 1319.

(17) W. S. Emerson and E. P. Agnew, THIS JOURNAL, **67**, 518 (1945).

Anal. Calcd. for $C_9H_8O_2ClBr$: C, 41.0; H, 3.04. Found: C, 40.9; H, 3.02.

Dehydrohalogenation of α-Bromo-β-chlorohydrocinnamic Acid.—A 6.0 g. (0.023 mole) sample of the bromochloride was treated with 2.1 g. (0.050 mole) of sodium hydroxide in 28 ml. of 60% ethanol in the same way as styrene bromochloride was. The reaction mixture was diluted with 500 ml. of water and neutralized to congo red with hydrochloric acid to form 2.8 g. (54%) of α-bromocinnamic acid, m.p. 130–133°. Crystallization from water gave a sample of m.p. 131–132° which checked with an authentic sample.

Addition of Bromine Chloride to the Stilbenes.—A solution of 1.0 g. (0.0055 mole) of the stilbene and 1 ml. of 37% hydrochloric acid in 30 ml. of dimethylcellosolve was treated with 0.83 g. (0.0060 mole) of N-bromoacetamide as described for cinnamic acid. The product from *trans*-stilbene separated on cooling. Crystallization from ligroin (b.p. 85–100°) yielded 1.09 g. (67%) of *erythro*-α-bromo-α′-chlorobibenzyl[9] (III), m.p. 222–224° (dec.). The product from *cis*-stilbene was obtained after the reaction mixture was concentrated to about 5 ml. Crystallizations from 95% ethanol and then from ligroin (b.p. 85–100°) yielded 0.22 g. (14%) of the *erythro* isomer, m.p. 222–224° (dec.) and 0.76 g. (47%) of *threo*-α-bromo-α′-chlorobibenzyl (IV), m.p. 99–101°.

Anal. Calcd. for $C_{14}H_{12}BrCl$: C, 56.8; H, 4.06. Found: C, 56.7; H, 4.09.

Preparation of Bromochlorides from Dibromides.—The method followed was that described by Pfeiffer and Eistert[9] for *meso*-stilbene dibromide. A solution of 30 g. (0.113 mole) of styrene dibromide in 400 ml. of benzene was treated with 400 ml. of anhydrous stannic chloride to yield 20.0 g. (80%) of 2-bromo-1-chloro-1-phenylethane, b.p. 106–107° (6 mm.), $n^{20}D$ 1.5770, d^{20}_4 1.500. This product was converted to α-chlorostyrene in 63% yield as described above. In a similar fashion 0.55 g. (0.0016 mole) of either *meso*- or *dl*-stilbene dibromide was treated with excess stannic chloride to yield 0.38 g. (80%) of *erythro*-α-bromo-α′-chlorobibenzyl (III), m.p. 222–224° (dec.).

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORY, TRACERLAB, INC.]

The Synthesis of Ethyl Acetamidocyanoacetate, DL-Lysine, DL-Ornithine and DL-Tyrosine Labeled with Isotopic Carbon[1]

BY MELVIN FIELDS, DORIS E. WALZ AND SEYMOUR ROTHCHILD

The reductive acetylation of ethyl isonitrosocyanoacetate has been achieved in excellent yield by selective catalytic hydrogenation. New syntheses of *dl*-lysine, *dl*-ornithine and *dl*-tyrosine have been devised which have been utilized for the preparation of these compounds labeled with isotopic carbon.

The preparation of ethyl acetamidocyanoacetate (I) labeled with carbon-14 assumes special significance because of the versatility of this reagent in the synthesis of amino acids.[2] In our investigation of this route to a number of labeled amino acids, we have effected an improved preparation of I suitable for small scale work, and have devised satisfactory syntheses of *dl*-lysine, *dl*-ornithine and *dl*-tyrosine labeled at C-2 with carbon-14.

The preparation of ethyl isonitrosocyanoacetate (II) was accomplished in 90% yield by the nitrosation of ethyl cyanoacetate as described by Snyder and Smith for the preparation of ethyl isonitrosomalonate.[3] Previously published methods for the reductive acetylation of II have employed a variety of reagents such as aluminum amalgam,[4] zinc dust[5] and sodium hydrosulfite.[6] We investigated the selective catalytic hydrogenation of II at room temperature and atmospheric pressure in acetic anhydride solution with the results summarized in Table I. With 5% platinum–charcoal, as well as with Adams catalyst, hydrogenation practically ceased after two moles of gas had been absorbed, although the supported catalyst is obviously the more satisfactory under the conditions employed. Under similar conditions with 5% palladium–charcoal catalyst or with Raney nickel, four moles of gas were rapidly consumed with no apparent diminution of rate after two moles had been absorbed; interruption of the reaction after consumption of two moles of gas afforded I in variable yield with the palladium

(1) This research was carried out under Contract AT-(40-1)-279 with the U. S. Atomic Energy Commission.

(2) N. F. Albertson and B. F. Tullar, THIS JOURNAL, **67**, 502 (1945); N. F. Albertson, *ibid.*, **68**, 450 (1946).

(3) H. L. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944).

(4) V. Cerchez and C. Colesiu, *Compt. rend.*, **194**, 1954 (1932).

(5) L. Light and Company, Ltd., British Patent 583,307; *C. A.*, **41**, 2747 (1947).

(6) B. F. Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465 (1946).

catalyst but only intractable oils with the nickel catalyst. The nickel catalyst gave similar results in absolute ethanol solution.

TABLE I

REDUCTION ACETYLATION OF ETHYL ISONITROSOCYANOACETATE IN THE PRESENCE OF VARIOUS CATALYSTS[a]

	Catalyst	Yield, %
1.	Platinum–charcoal (5%)	85–88
2.	Palladium–charcoal (5%)	45–75
3.	Platinum–asbestos	No reduction
4.	Palladium–asbestos	No reduction
5.	Platinum oxide	60–75
6.	Raney nickel	[b]

[a] All runs were interrupted after consumption of two moles of hydrogen. [b] Only non-crystallizable oils were obtained.

It is interesting to note that while II can be hydrogenated under quite mild conditions the reduction of diethyl isonitrosomalonate with 5% palladium–charcoal in acetic anhydride solution is slow and incomplete at room temperature and 40 lb./sq. in., and does not occur at all at atmospheric pressure. The hydrogenation of diethyl isonitrosomalonate, however, is reported[3] to occur at room temperature in absolute ethanol over 10% palladium–charcoal at 1500 lb./sq. in.

In absolute ethanol I condenses readily as its sodium salt with N-(δ-iodobutyl)-phthalimide to afford ethyl 2-cyano-2-acetamido-6-phthalimidohexanoate (III). After hydrolysis of the latter intermediate with hydrochloric acid, *dl*-lysine was isolated as its monohydrochloride in an over-all yield of 70%. In similar fashion *dl*-ornithine monohydrochloride was prepared from N-(γ-iodopropyl)-phthalimide and acetamidocyanoacetic ester in 59% yield. Preparation of *dl*-tyrosine was achieved in over-all yield of 91% by condensation of the sodium salt of I with *p*-methoxybenzyl bromide followed by hydrolysis of the intermediate with boiling 47% hydrobromic acid solution.

Experimental[7]

Ethyl Cyanoacetate-2-C-14.—Conversion of sodium acetate-2-C-14 to ethyl cyanoacetate-2-C-14 was achieved by bromination of acetic acid[8] followed by reaction of the product with sodium cyanide and esterification under conditions similar to those described in "Organic Syntheses."[9]

The labeled compound had a specific activity of 0.30 mc. per mmole as estimated by combustion of a small aliquot of the product and measurement in a gas counting apparatus of the type described by Janney and Moyer.[10] Calibration of the gas-counting system was achieved by use of a National Bureau of Standards carbon-14 standard. The remaining syntheses were performed using intermediates prepared without isotopic dilution from a sample of labeled ethyl cyanoacetate of this specific activity.

Ethyl Isonitrosocyanoacetate-2-C-14 (II).—The nitrosation of ethyl cyanoacetate was performed by the method of Snyder and Smith.[3] After acidification with dilute hydrochloric acid solution the reaction mixture was extracted with ether. When the ether had been distilled in vacuum, the oxime remained as a crystalline residue, which, after trituration with benzene was obtained in 90% yield as colorless crystals, m.p. 131–133°; reported m.p. 129–130°.[6]

Ethyl Acetamidocyanoacetate-2-C-14 (I).—Reduction of 2.13 g. of II in 50 ml. of acetic anhydride in the presence of 1.0 g. of platinum-on-charcoal (5%) was carried out at room temperature and atmospheric pressure with vigorous shaking. When two moles of gas had been absorbed, the rate of reduction diminished markedly and the reaction was interrupted. The catalyst was filtered by suction through a charcoal pad and washed well with isopropyl alcohol. When the solvent had been removed *in vacuo* at 40° and the residue washed with ether there was obtained 2.17 g. (85%) of I; m.p. 129–130°; reported m.p. 129°.[6]

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.0; H, 5.92. Found: C, 49.3; H, 6.0.

The experiments reported in Table I were run under similar conditions.

N-(δ-Iodobutyl)-phthalimide.—A solution of 13.0 g. of anhydrous sodium iodide and 3.19 g. of N-(δ-bromobutyl)-phthalimide[11] in 85 ml. of acetone was boiled under reflux overnight. After removal of the acetone *in vacuo*, the residue was triturated with 50 ml. of water; 3.68 g. (99%) of the iodo derivative, m.p. 88–90°, was obtained; reported 88–89.5°.[12]

Ethyl 2-Cyano-2-acetamido-6-phthalimidohexanoate-2-C-14 (III).—The ester, I, 851 mg., was dissolved in 5 ml. of anhydrous ethanol in a 100-ml. r.b. 3-necked flask equipped with a mercury-sealed stirrer, a reflux condenser, and a steam-jacketed, pressure equalizing dropping funnel. To the boiling solution was added a solution of 115 mg. of sodium in 7 ml. of ethanol, followed by 1.68 g. of the iodobutylphthalimide dissolved in 10 ml. of boiling ethanol. The reaction mixture was boiled overnight. After cooling and dilution of the mixture with 15 ml. of water, there was obtained 1.86 g. (80%) of III, m.p. 170–171.5°. An analytical sample crystallized from ethanol as colorless needles; m.p. 172.0–172.5°.

Anal. Calcd. for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.70. Found: C, 61.6; H, 5.8.

A similar preparation with N-(δ-bromobutyl)-phthalimide gave III in 73% yield.

***dl*-Lysine-2-C-14 Monohydrochloride.**—The crude ester, III, 1.53 g. in 10 ml. of concd. hydrochloric acid, was boiled under reflux overnight. After dilution of the reaction mixture with 10 ml. of water and filtration of the phthalic acid, the filtrate was brought to dryness *in vacuo*. The residual lysine dihydrochloride was dissolved in 10 ml. of boiling 95% ethanol and centrifuged to remove the ammonium chloride. Treatment of the boiling supernatant solution with 400 mg. of pyridine yielded crude lysine monohydrochloride. On crystallization from 1 ml. of water to which 9 ml. of ethanol was added, there was obtained 563 mg. of analytically pure lysine monohydrochloride, dec. 259–262° (evacuated tube). The filtrate afforded an additional 94 mg. of the pure product, bringing the total yield to 87%.

Anal. Calcd. for $C_6H_{15}N_2O_2Cl$: C, 39.45; H, 8.28. Found: C, 39.5; H, 8.4.

***dl*-Lysine-2-C-14-dipicrate** was prepared from the hydrochloride in aqueous solution, m.p. 186–188°; reported m.p. 188°.[13]

Ethyl 2-Cyano-2-acetamido-5-phthalimidopentanoate-2-C-14 (IV).—N-(γ-Bromopropyl)-phthalimide, m.p. 73–75°, prepared by the procedure of Rumpf,[11] was converted to N-(γ-iodopropyl)-phthalimide, m.p. 84–86°; reported, 88°,[14] by reaction with sodium iodide in acetone. The reaction of I and N-(γ-iodopropyl)-phthalimide under the conditions used for the preparation of III resulted in a 75% yield of IV, m.p. 211–213°. The analytical sample melted at 214.5–215.0°.

Anal. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36. Found: C, 60.4; H, 5.4.

The reaction of I and N-(γ-bromopropyl)-phthalimide gave IV, m.p. 213–215°, in 54% yield.

***dl*-Ornithine-2-C-14 Monohydrochloride.**—Hydrolysis of IV in concd. hydrochloric acid and conversion to the monohydrochloride as described for the preparation of *dl*-lysine monohydrochloride afforded *dl*-ornithine monohydrochloride in 79% yield; dec. 215–216° (evacuated tube).

Anal. Calcd. for $C_5H_{13}N_2O_2Cl$; C, 35.61; H, 7.77. Found: C, 35.8, 35.9; H, 7.9, 8.0.

(7) Analyses by Dr. Carol K. Fitz, Needham, Mass.

(8) M. Fields, S. Rothchild and M. A. Leaffer, in press.

(9) "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 254.

(10) C. D. Janney and B. J. Moyer, *Rev. Sci. Instr.*, **19**, 667 (1948).

(11) P. Rumpf, *Bull. soc. chim.*, [5], **5**, 871 (1938).

(12) S. Gabriel, *Ber.*, **42**, 1253 (1909).

(13) R. Gaudry, *Can. J. Research*, **26B**, 387 (1948).

(14) M. Fränkel, *Ber.*, **30**, 2506 (1897).

Ornithine dipicrate was prepared from the hydrochloride in aqueous solution, m.p. 196–197°; reported, m.p. 195.5–196.5°.[15]

Ethyl *p*-Methoxybenzylacetamidocyanoacetate (V).—The ester, I, 850 mg., was dissolved in 5 ml. of absolute ethanol in a 100-ml. 3-neck flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel. A solution of 119 mg. of sodium in 5 ml. of ethanol was added and the reaction mixture was cooled to room temperature. From a graduated dropping funnel, 0.79 ml. of *p*-methoxybenzyl bromide[16] (density 1.41) was added dropwise, with cooling. After stirring for 2 hours at room temperature, the slurry was diluted with 10 ml. of water. The product, V, weighed 1.39 g. (96%), m.p. 169.5–170.5°. An analytical sample, from dilute alcohol, melted at 170.0–171.0°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25. Found: C, 62.0; H, 6.3.

(15) N. F. Albertson and S. Archer, THIS JOURNAL, **67**, 2043 (1945).

(16) H. Stephen and C. Weizmann, *J. Chem. Soc.*, 1152 (1914).

Substitution of the *p*-methoxybenzyl chloride for the bromide reduced the yield of V to 85%.

***dl*-Tyrosine-2-C-14.**—The ester, V, 1.39 g., was boiled under reflux in 15 ml. of 48% hydrobromic acid for 4 hours. After distillation of the excess acid *in vacuo*, the residue was dissolved in 5 ml. of water and filtered through a charcoal bed. A slight excess of ammonium hydroxide was added and then a slight excess of acetic acid. The tyrosine, washed with water and ethanol, weighed 827 mg. (95%), dec. 303–304° (evacuated tube).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 59.7; H, 6.2.

A similar hydrolysis of V with concd. hydrochloric acid in a sealed tube at 160° for 3 hours also gave *dl*-tyrosine in 95% yield.

Dibenzoyl *dl*-tyrosine, prepared in dilute sodium hydroxide solution,[17] melted at 208–209° after crystallization from glacial acetic acid; reported m.p. 213–214°.[17]

(17) R. B. Loftfield, THIS JOURNAL, **72**, 2499 (1950).

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF ROCHESTER AND CARNEGIE INSTITUTE OF TECHNOLOGY]

The Benzidine Rearrangement. III. Kinetics of the Rearrangements of Hydrazobenzene

BY ROBERT B. CARLIN, ROBERT G. NELB AND RAYMOND C. ODIOSO

A spectrophotometric method of analysis has been developed by means of which the concurrent rearrangements of hydrazobenzene to benzidine and diphenyline have been followed. Rate constants and energy (20.6 kcal./mole) and entropy (2.9 e.u. at 25°) of activation have been determined for the total process; and the second order dependency of the rate on acid strength, as well as a positive salt effect on the rate, have been confirmed. The benzidine-to-diphenyline product ratio (70:30) has been shown to be independent of temperature, acid concentration and total ionic strength, within the limits investigated. The fallacy of attempting to relate observed activation energy and entropy to the rearrangement step in the reaction sequence without further information is pointed out. Evidence is presented to support the belief that the benzidine rearrangement may occur in the solid state.

Introduction

Although a thorough kinetic study of the benzidine rearrangement has long been recognized as necessary to an understanding of this transformation, experimental difficulties have limited the number and scope of investigations in this field. Van Loon[1] followed the rate of formation of benzidine in several solvent combinations and in the presence of various acids. His results suggested that benzidine formation is first order in hydrazobenzene concentration and second order in oxonium ion concentration. In more recent work, the rate of consumption of hydrazobenzene has been followed. Biilman and Blom[2] used an electrometric method to measure the rates of rearrangements of two *p,p'*-disubstituted hydrazoanilines, but their method was not readily adaptable to studies of simpler aromatic hydrazo compounds. Dewar[3] devised a new analytical scheme which enabled him to determine rates of and Arrhenius activation energies for the rearrangements of hydrazobenzene and of three symmetrically substituted hydrazobenzenes. Recently, Hammond and Shine[4] pointed out that Dewar's interpretations of his results do not take into account the involvement of acid concentration in the rate expression. Using Dewar's analytical method, Hammond and Shine have firmly established the second order dependency of the rate of consumption of hydrazobenzene on acid concentration and have observed a positive salt effect on the rate. They have also perceived that mechanisms for the rearrangement step which have been proposed in recent years[5–8] all are based on the assumption that the rearranging species is the first conjugate acid of hydrazobenzene. It is difficult to adjust any of these formulations to accommodate the indications, derived from kinetic studies,[1,4] that the second conjugate acid undergoes rearrangement.

In no kinetic investigation thus far reported has it been possible to obtain information about both of the concurrent rearrangement reactions which occur when hydrazobenzene is treated with acids. Although it is well known that diphenyline (2,4'-diaminobiphenyl) is formed in appreciable amounts along with benzidine, limitations imposed by the analytical methods used to follow the progress of the reactions restricted all studies either to the sum of the rates of all reactions (consumption of hydrazobenzene) or to the rate of formation of benzidine alone. Thus, even though the over-all reaction is now known to be approximately second

(1) Van Loon, *Rec. trav. chim.*, **23**, 62 (1904).

(2) Biilman and Blom, *J. Chem. Soc.*, **125**, 1719 (1924).

(3) Dewar, *ibid.*, 777 (1946).

(4) Hammond and Shine, THIS JOURNAL, **72**, 220 (1950).

(5) Robinson, *J. Chem. Soc.*, 220 (1941).

(6) Hughes and Ingold, *ibid.*, 606 (1941).

(7) Hammick and Mason, *ibid.*, 638 (1946); 1938 (1949).

(8) Dewar, *Nature*, **176**, 784 (1945); *J. Chem. Soc.*, 406 (1946); "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, pp. 233–240.