On cooling, the alkaline decomposition residue gave yellow crystals, probably potassium sinapate. The free sinapic acid, resulting on acidification, was recrystallized from acetone, yielding cream-colored crystals (161 mg.), decomposing at 193.6–195.6° (Gadamer 191–192°) with evolution of carbon dioxide.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40; 2-(OCH_3), 27.69; neut. equiv., 224.21. Found: C, 58.97; H, 5.48; OCH_3, 26.2; neut. equiv., 214; *pK*, 4.5.

Sinapic acid gives a pink precipitate with ferric chloride and forms a monoacetate, m. p. 198–200° (Gadamer, 181–187°).

Methyl Sinapate Monomethyl Ether.—A suspension of 120 mg. of sinapic acid in 1 ml. of ether was treated with excess diazomethane at a temperature below 10°. The gummy residue obtained on concentration of the ethereal solution was washed several times with small volumes of 1% sodium hydroxide solution, and then with water. Recrystallization from aqueous acetone gave the monomethyl ether of methyl sinapate as colorless prisms (51 mg.), m. p. 96.4–98° (Gadamer, 91–91.5°).

Oxidation of Methyl Sinapate Monomethyl Ether.—Fifty milligrams of methyl sinapate monomethyl ether was treated with saturated potassium permanganate solution on a steam-bath, until the purple color persisted. The oxidation mixture was acidified with hydrochloric acid, and the manganese dioxide was destroyed by sulfur dioxide. The resulting solution was extracted with several 1-ml. portions of ether, and the ethereal extract was evaporated to a gummy residue, which when recrystallized from acetone, produced colorless plates (15 mg.), m. p. 166.4–168.4°. A comparison of this compound with gallic acid trimethyl ether in melting point, neutralization equivalent, absorption spectrum showed identity. Demethylation of the oxidation product yielded a crystalline material which was identified as gallic acid by its melting point, color reactions[9] and absorption spectrum.[10]

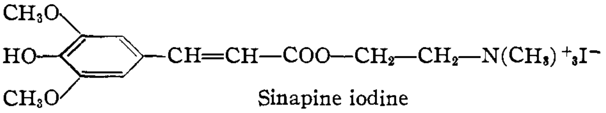
Sinapine Iodide from White Mustard Seed.—Following the same procedure as given above, sinapine iodide was isolated from white mustard seed for comparison with our sample. Identical ultraviolet absorption spectra were obtained from both samples. The melting point of the iodide from mustard seed was 184–186° (Gadamer 178–179°) and on admixture with *Draba* seed iodide gave no depression.

Other components present in the seed of *Draba nemorosa*, L., are being investigated.

We are grateful to the Abbott Laboratories, and to Mr. N. Y. Leung, for grants of equipment in support of this research.

Summary

1. A quaternary ammonium iodide has been isolated from the Chinese drug, *Draba nemorosa*, L., and identified as



Sinapine iodine

2. Ultraviolet absorption spectra of the iodide, of sinapic acid and of gallic acid trimethyl ether are presented.

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[9] Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, New York, N. Y., 1941, p. 174.

[10] Landolt-Börnstein, "Physikalisch Chemische Tabellen," Erg. III, 1935, p. 1383.

CANTON, CHINA RECEIVED JANUARY 13, 1948

[CONTRIBUTION FROM ELECTROCHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO.]

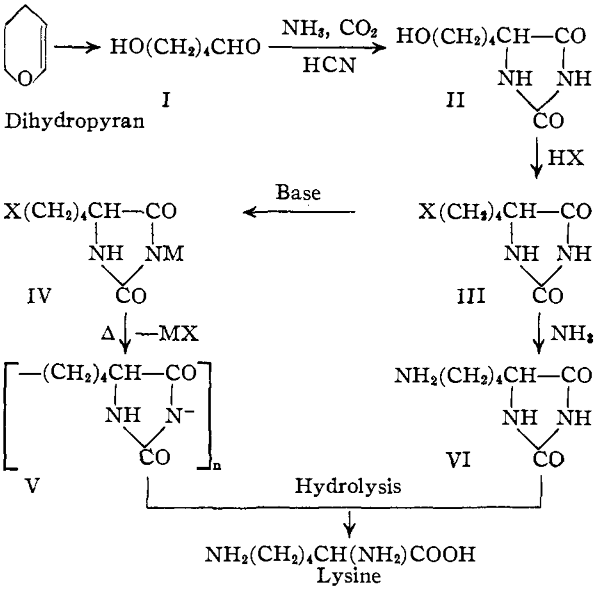
The Synthesis of DL-Lysine from Dihydropyran

BY A. O. ROGERS, R. D. EMMICK, L. W. TYRAN, LILLIAN B. PHILLIPS, A. A. LEVINE AND N. D. SCOTT

During the past three years, a process for the synthesis of *dl*-lysine using dihydropyran as starting material was developed in this Laboratory. A similar synthesis, developed independently, has recently been reported by Gaudry.[1] Since our study differs in several important respects from that of Gaudry, publication of our results appears desirable.

Dihydropyran was prepared and converted to δ-hydroxyvaleraldehyde as described by Paul.[2]

In preparing 5-(4-hydroxybutyl)-hydantoin (II), we omitted any intermediate isolation of δ-hydroxyvaleraldehyde (I) or its cyanhydrin and proceeded directly from the crude aqueous solution of the hydroxyaldehyde (I) to the hydantoin. The conversion of 5-(4-hydroxybutyl)-hydantoin (II) to the corresponding chloro- or bromobutylhydantoin (III) was effected by treatment in the fused state with gaseous hydrogen halide. To avoid thermal decomposition, the melting point of the hydroxybutylhydantoin (II) was depressed by mixing with preformed halobutylhydantoin or by adding a small quantity of water. When hydrogen chloride was used in this step, the use of



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[1] Gaudry, *Can. J. Research*, **26B**, 387 (1948).

[2] Paul, *Bull. Soc. Chim. France*, [4] **53**, 1489 (1933); [5] **1**, 971 (1934).

pyridine hydrochloride as solvent and catalyst was convenient for small-scale preparations; however, almost quantitative yields were obtained either with or without catalyst. The two halobutylhydantoins present an unusual case in that their melting points, which are almost the same, show no depression on mixing.

The ammonolysis of 5-(4-chlorobutyl)-hydantoin to 5-(4-aminobutyl)-hydantoin (VI) was carried out in both aqueous and anhydrous ammonia. The conditions found to be most favorable for high yields of the primary amino compound involved the use of a large excess of aqueous ammonia, operation at a relatively low temperature and the addition of a considerable quantity of carbon dioxide to the system. As in Gaudry's work, 5-(4-aminobutyl)-hydantoin (VI) was ordinarily not isolated in pure form before hydrolysis. Hydrochloric acid and sodium hydroxide gave equivalent results as hydrolytic agents; with hydrochloric acid, the conversion was completed in six to eight hours at 150°; with aqueous sodium hydroxide, about ten hours at 125° was sufficient.

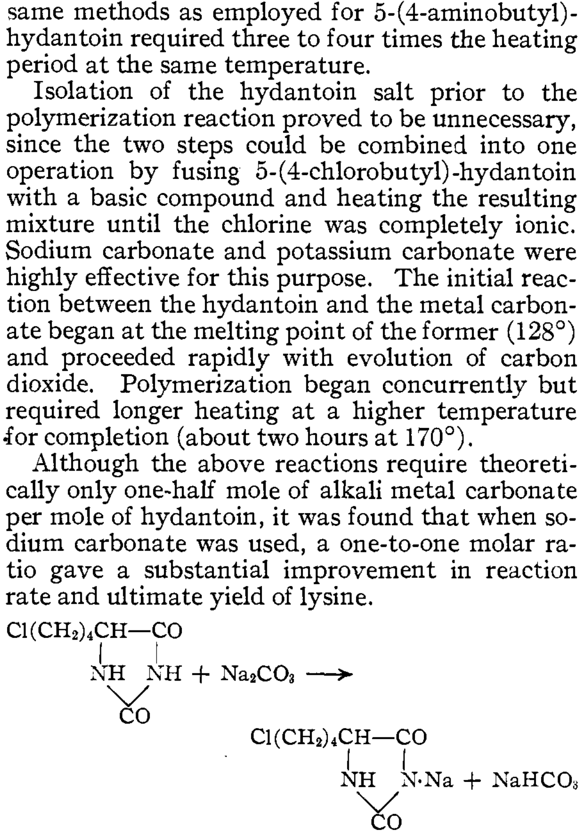
The principal difficulty encountered in the foregoing process is in the formation of more highly substituted amino compounds as by-products in the preparation of the aminobutylhydantoin (VI). These materials decrease the yield of lysine and also interfere with its isolation as the mono- or dihydrochloride. The use of phthalimide, as described by Gaudry, is a possible answer to the difficulty. In considering this type of approach, it occurred to us that the imido group occupying the 3-position in 5-(4-chlorobutyl)-hydantoin (III) might perform the same function as that of phthalimide in the Gabriel reaction. In practice, this method proved highly satisfactory, giving a marked improvement in both yield and simplicity over the route *via* aminobutylhydantoin.

5-(4-Chlorobutyl)-hydantoin was found to form salts (IV) on treatment with basic compounds. The sodium salt was obtained readily in crystalline form by a reaction of the chlorobutylhydantoin with sodium isobutoxide in isobutyl alcohol. When the salt (IV) was fused at 150–155°, a rapid, exothermic reaction occurred in which the chlorine became ionic and a resinous organic product was formed. The same reaction occurred, but at a much lower rate, in the solid state at temperatures below 150° and was accelerated at such temperatures by the addition of solvents such as tetrahydrofurfuryl alcohol, dimethylformamide and acetamide. However, the use of such solvents was found to decrease the over-all yield of lysine, apparently because of side reactions involving the solvent. When the resinification was carried to completion, the product was insoluble in water but soluble in strong acids and alkalies.

From the mode of formation of the resin, its chemical structure would be assumed to be that of poly-3,5-tetramethylenehydantoin (V). This assumption was confirmed by the fact that on hydrolysis it produced lysine in high yield with carbon dioxide as by-product. Hydrolysis by the same methods as employed for 5-(4-aminobutyl)-hydantoin required three to four times the heating period at the same temperature.

Isolation of the hydantoin salt prior to the polymerization reaction proved to be unnecessary, since the two steps could be combined into one operation by fusing 5-(4-chlorobutyl)-hydantoin with a basic compound and heating the resulting mixture until the chlorine was completely ionic. Sodium carbonate and potassium carbonate were highly effective for this purpose. The initial reaction between the hydantoin and the metal carbonate began at the melting point of the former (128°) and proceeded rapidly with evolution of carbon dioxide. Polymerization began concurrently but required longer heating at a higher temperature for completion (about two hours at 170°).

Although the above reactions require theoretically only one-half mole of alkali metal carbonate per mole of hydantoin, it was found that when sodium carbonate was used, a one-to-one molar ratio gave a substantial improvement in reaction rate and ultimate yield of lysine.



With potassium carbonate as reagent no such large excess was required since the potassium bicarbonate formed at first was rapidly converted to the normal carbonate under the conditions of the reaction.

Calcium, magnesium and tetramethylammonium salts of chlorobutylhydantoin also undergo auto-condensation to polymers which yield lysine on hydrolysis.

Experimental

Preparation of 5-(4-Hydroxybutyl)-hydantoin.—Dihydropyran (4.56 moles, 383.5 g.) was stirred with 1 liter of water and 20 cc. of 1 *N* hydrochloric acid in a water-bath at 40° until a clear solution was obtained. The mixture was cooled and the flask swept with carbon dioxide. Liquid hydrogen cyanide (4.15 moles, 167 cc. tech. grade) was added, then 28% aqueous ammonia (4.5 moles, 304 cc.) was added dropwise over a two-hour period while stirring vigorously under a carbon dioxide atmosphere. The temperature rose to 48°, maximum, during the addition of ammonia, and was afterward held at 50–60° for about twelve hours; stirring under carbon dioxide was continued throughout the reaction period. On cooling to 5–10°, a crop of 5-(4-hydroxybutyl)-hydantoin weighing 324 g. (45.2%) and melting at 149–151° was obtained. By evaporating the mother liquor, an additional 184 g. of less pure product was recovered (total yield 71%). When purified by recrystallization from alcohol, the product melted at 151–152°.[3] (Gaudry[1] reports 152–155°.)

Anal. Calcd. for $C_7H_{12}N_2O_3$: N, 16.3. Found: N, 16.0.

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[3] All melting points reported in this paper are uncorrected.

In the above preparation the reaction time may be decreased by operating at temperatures up to 120° under super-atmospheric pressure. If sodium cyanide is substituted for hydrogen cyanide, the mixture should be acidified with hydrochloric acid before isolating the product or ammonium chloride should be substituted for ammonium hydroxide.

Preparation of 5-(4-Chlorobutyl)-hydantoin, Using Pyridine Hydrochloride as Catalyst.—Pyridine (50 g.) was saturated with hydrogen chloride and mixed with 0.5 mole (86 g.) of 5-(4-hydroxybutyl)-hydantoin. The mixture was heated in an oil-bath and hydrogen chloride fed with stirring for two hours at approximately 125–130°. The product was crystallized from 250 cc. of water to yield 90.3 g. (94.8%) of 5-(4-chlorobutyl)-hydantoin, m. p. 127–128°. Recrystallization failed to raise the melting point appreciably.

Anal. Calcd. for $C_7H_{11}N_2O_2Cl$: Cl, 18.6. Found: Cl, 18.4.

Preparation of 5-(4-Chlorobutyl)-hydantoin without Catalyst.—A mixture of 5-(4-hydroxybutyl)-hydantoin (2 moles, 344 g.) with an equal weight of 5-(4-chlorobutyl)-hydantoin was heated to fusion in an oil-bath and hydrogen chloride fed with rapid stirring at 130–140°. Samples were removed periodically for melting point determinations to follow the course of the reaction. The melting point of the dried mixture was 125–127° after five and one-half hours and did not change during an additional hour's treatment. The product thus obtained in quantitative yield was satisfactory for use without purification.

Lysine from 5-(4-Chlorobutyl)-hydantoin *via* 5-(4-Aminobutyl)-hydantoin.—An 8-gallon stainless steel vessel was charged with ammonium carbonate (27.5 lb., 0.175 lb. mole), 28% aqueous ammonia (36 lb., 0.59 lb. mole), 5-(4-chlorobutyl)-hydantoin (3.4 lb., 0.0178 lb. mole), and potassium iodide (0.1 lb.). The mixture was heated with stirring at 50–53° until titration for chloride ion showed the reaction to be complete (eight hours). The excess ammonia and carbon dioxide were expelled by heating and the solution concentrated to 2.3 gallons. It was then placed in a 5-gallon stainless steel vessel and solid sodium hydroxide (3.52 lb., 0.088 lb. mole) added gradually. The solution was heated with stirring at 122–127° for ten hours. The by-product ammonia was distilled off, the solution acidified with excess hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with hot methanol and the solution filtered to remove solid sodium chloride. Pyridine (1.77 lb.) was added to the filtrate to precipitate lysine monohydrochloride. The yield of crude product was 2.11 lb. (65% based on 5-(4-chlorobutyl)-hydantoin). The crude product melted at 251–253°.

Anal. Calcd. for $C_6H_{14}N_2O_2 \cdot HCl$: Cl^-, 19.4. Found: Cl^-, 19.5.

Preparation of 3-Sodium-5-(4-chlorobutyl)-hydantoin.—Sodium (1 g. atom, 23 g.) was dissolved in 1 liter of dry isobutyl alcohol at the boiling point and mixed with a solution of 5-(4-chlorobutyl)-hydantoin (1.02 mole, 194 g.) in hot (90°) isobutyl alcohol. A vigorous evolution of heat occurred on mixing and precipitation of the sodium derivative began immediately. After cooling to 8°, the product was filtered off, washed with cold isobutyl alcohol and dried under reduced pressure. The yield was 98%.

The product of the above reaction was a crystalline solid which was extremely soluble in water. Its composition was confirmed by reconversion to 5-(4-chlorobutyl)-hydantoin on treatment with acid and by the substantially quantitative recovery of ionic chlorine in the following experiment.

Preparation of Poly-3,5-tetramethylenehydantoin from 3-Sodium-5-(4-chlorobutyl)-hydantoin.—A 1-liter erlenmeyer flask was immersed in an oil-bath at 168° and 3-sodium-5-(4-chlorobutyl)-hydantoin (0.2 mole, 42.5 g.) placed in the hot flask. When the temperature of the charge reached 150–155°, the material fused and a vigorous reaction set in. The flask was immediately removed from the oil-bath. The reaction was apparently complete in about one-half minute, during which time the charge swelled to a spongy mass.

Anal. Calcd. for $C_7H_{10}N_2O_2 + NaCl$: Cl^-, 16.7. Found: Cl^-, 16.85.

Preparation of Poly-3,5-tetramethylenehydantoin from 5-(4-Chlorobutyl)-hydantoin and Sodium Carbonate.—A mixture of 5-(4-chlorobutyl)-hydantoin (1.69 moles, 321 g.) and anhydrous sodium carbonate (1.69 moles, 179 g.) was placed in a 1-liter stainless steel beaker equipped with a paddle stirrer and heated in an oil-bath. When the bath temperature reached 135° (thirty minutes), the mixture became semi-liquid; carbon dioxide was evolved for about twenty minutes, during which the bath temperature was raised to 150°. The bath was heated gradually to 170° and held at that temperature for approximately two hours. The viscosity of the mixture increased gradually and was too high to permit stirring during the last one and one-half hours. The product weighed 452 g. and contained 12.25% chloride ion (93%). It was readily soluble in aqueous sodium hydroxide and in concentrated hydrochloric acid but could be freed of inorganic salts by extracting with water containing sufficient hydrochloric acid to neutralize the excess sodium carbonate.

Hydrolysis of Poly-3,5-tetramethylenehydantoin with Hydrochloric Acid.—A Carius tube was charged with 20% aqueous hydrochloric acid (from 0.30 mole, 25 cc. of concd. hydrochloric acid and 24.5 cc. of water) and poly-3,5-tetramethylenehydantoin. The latter, prepared as described in the preceding experiment, was equivalent in quantity to 0.075 mole of 5-(4-chlorobutyl)-hydantoin and was freed of inorganic material by water extraction prior to use. The tube was heated for three hours at 180–185° and the contents evaporated to dryness under reduced pressure. The residue was dissolved in hot 95% ethyl alcohol (95 cc.) and treated with pyridine (7.5 cc.) to precipitate lysine monohydrochloride. The yield of the latter (10.64 g.) was 78% based on poly-3,5-tetramethylenehydantoin; 76% based on the 5-(4-chlorobutyl)-hydantoin from which the polymer was prepared.

Hydrolysis of Poly-3,5-tetramethylenehydantoin with Sodium Hydroxide.—Poly-3,5-tetramethylenehydantoin was prepared as described in a preceding experiment from 3 moles of 5-(4-chlorobutyl)-hydantoin and 3 moles of sodium carbonate. A portion of the product (746 g.), equivalent to 2.78 moles of 5-(4-chlorobutyl)-hydantoin, was dissolved in a solution of sodium hydroxide (13.9 moles, 556 g.) in water (2.9 liters) and placed in a 5-gallon stainless steel vessel. The mixture was heated at 125–126° with occasional stirring for forty-one hours. The solution was partially evaporated under reduced pressure, acidified with excess hydrochloric acid and evaporated to dryness under reduced pressure, filtering off sodium chloride periodically as the concentration progressed. The residue was extracted with hot 95% ethyl alcohol and the alcoholic solution treated with the usual excess of pyridine to precipitate lysine monohydrochloride. The yield of the latter, based on 5-(4-chlorobutyl)-hydantoin, was 72%. Aliquots withdrawn during the reaction period and worked up in the same way indicated that the hydrolysis was completed in twenty-four hours and that yields of 76–77% could be obtained.

Summary

1. Improved procedures have been developed for the synthesis of lysine from dihydropyran, involving 5-(4-hydroxybutyl)-hydantoin, 5-(4-chlorobutyl)-hydantoin and 5-(4-aminobutyl)-hydantoin as intermediates.

2. A new route from 5-(4-chlorobutyl)-hydantoin to lysine is described, in which the imido group and terminal halogen of the hydantoin are condensed to form poly-3,5-tetramethylenehydantoin. Hydrolysis of the latter compound gives lysine in good yield.

Niagara Falls, N. Y. Received October 30, 1948