tassium ferricyanide and 10 g. of potassium hydroxide were added and reflux continued for two more hours. Iron oxide was removed by filtering the hot mixture. The solution was then evaporated under 15 mm. pressure to one-half its original volume, cooled and filtered, made acidic with hydrochloric acid and extracted with ether. The ether was evaporated and the residue recrystallized from ligroin giving 0.02 g. of a solid; m. p. 130°; mixed m. p. with Eastman Kodak Co. white label furoic acid, 130°.

Oxidation of N-Butyl-(α-ethylthenyl)-amine.—To a solution of 8 g. of sodium hydroxide and 8.8 g. of potassium permanganate in 500 ml. of water was added slowly with stirring 1 g. of N-butyl-(α-ethylthenyl)-amine. After six hours the solution was filtered, evaporated to about 100 ml. and again filtered. The filtrate was washed with ether, made acidic with dilute hydrochloric acid and extracted with ether. Evaporation of the ether gave 0.55 g. of crystals; m. p. 126–126.5° after two recrystallizations from water.

Neutral equivalent: calcd. for 2-thiophenecarboxylic acid, 128.1; found, 128.8.

Summary

1. Five furfurylideneamines, three of which are new, and one new thenylideneamine have been prepared.

2. Six new furfurylamines and one new thenylamine have been synthesized.

3. The structures of the furfurylamines and of the thenylamines have been shown to be most probably those which result from 1,2-addition of the alkylmagnesium halides to the carbon–nitrogen double bond of the Schiff bases.

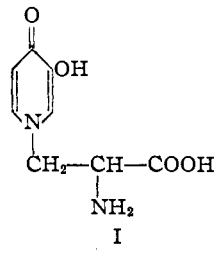
LATROBE, PA. RECEIVED OCTOBER 11, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Leucenol. VI. A Total Synthesis

BY ROGER ADAMS AND J. L. JOHNSON[1]

Leucenol, from *Leucaena glauca Bentham*, has been shown through degradation studies to have formula I.[2] During the investigation of leucenol



I

in this Laboratory, a variation in the melting point and rotation was frequently observed, which appeared to be dependent on the method of extraction and purification. Experiments have now been completed which permit a clarification of this variability. As obtained directly from the extract by the procedure used originally in this Laboratory or by the method of Kostermans,[3] leucenol had a rotation of −21° in water and a melting point of 228–229°. One recrystallization from water does not cause any essential change in these constants. Mascré[4] and Adams, *et al.*,[2a] reported optical inactivity for leucenol, Bickel and Wibaut[2c] reported −9°, while still others[2e,3,5] gave values of −21° or −22°. The rotation in 1% hydrochloric acid was found to be +10° as compared with Bickel and Wibaut's[2c] value of +6.7°. Mascré[4] and Adams, *et al.*,[2a] observed melting point values of 283–287° and 291°, the latter authors specifying a Maquenne block, but in open tubes previous investigators have given values of 226–227°,[2c] 228°,[5] and 231°.[5]

An explanation of these variations is found in the following observations. Samples of leucenol, after two or three crystallizations from water, were found to have rotations of −16 to −18°, although the melting points were about the same as before recrystallization. By boiling in water for forty-eight hours, the optical activity completely disappeared. The product had obviously racemized. When the racemic modification crystallized from a boiling aqueous solution as the water was evaporated to a volume below that of saturation of the compound, the product had a melting point of 235–236°. On the other hand, if a cold aqueous solution was permitted to evaporate, the product which was obtained had a melting point of 227–228°. By analysis, the former was shown to be anhydrous and the latter hydrated with one-half molecule of water. The anhydrous and hydrated forms are interconvertible by the treatment described. The hydrate does not lose its water even at 150°, and at 180° it decomposes. These two products have quite different infrared absorption spectra (Fig. 1). It is noteworthy that 3,4-dihydroxypyridine (3-hydroxy-4-pyridone) and α-amino-β-(N-4-pyridone)-propionic acid, of which leucenol is a derivative, hydrate and the infrared absorption spectra of the anhydrous and hydrated forms differ.[2b] Optically active leucenol does not form a hydrate under the conditions used for preparing the hydrated racemic modification. The facile

(1) From a thesis presented by J. L. Johnson to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1949.

(2) (a) Adams, Cristol, Anderson and Albert, THIS JOURNAL, **67**, 89 (1945); Adams and Jones, *ibid.*, **69**, 1803 (1947); Adams and Govindachari, *ibid.*, **69**, 1806 (1947); (b) Adams, Jones and Johnson, *ibid.*, **69**, 1810 (1947); (c) Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946); Wibaut and Kleipool, *ibid.*, **66**, 24 (1947); Wibaut, *Helv. Chim. Acta*, **29**, 1669 (1946); (d) Bickel, THIS JOURNAL, **69**, 1801, 1805 (1947); (e) **70**, 326, 328 (1948).

(3) Kostermans, *Rec. trav. chim.*, **65**, 319 (1946).

(4) Mascré, *Compt. rend.*, **204**, 890 (1937).

(5) Renz, *Z. physiol. Chem.*, **244**, 153 (1936); Nienburg and Tauböck, *ibid.*, **250**, 80 (1937).

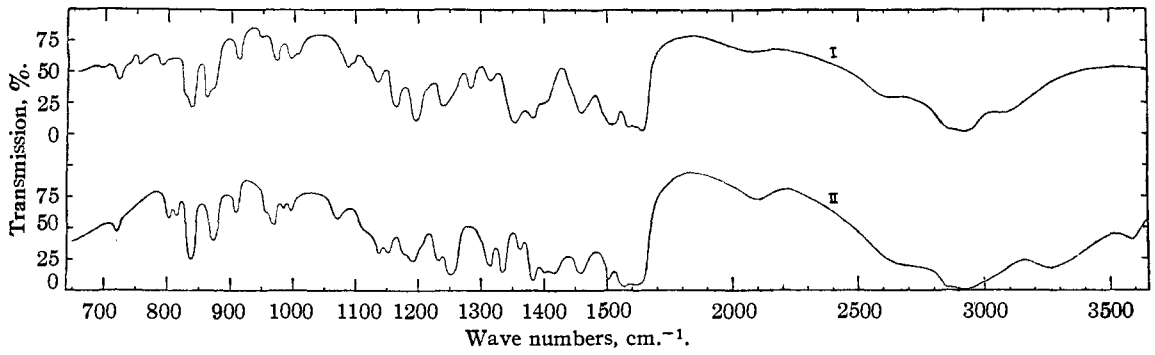
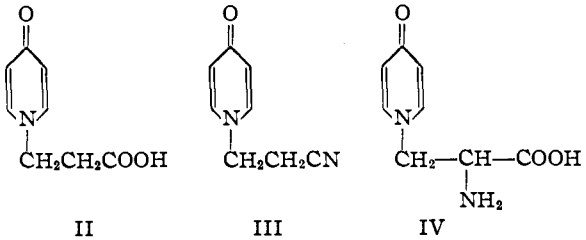


Fig. 1.—I, Anhydrous *dl*-leucenol; II, *dl*-leucenol hemihydrate. [The samples were prepared by grinding the crystalline compounds with paraffin oil to reduce light scattering. Absorptions due to the C–H frequencies of the paraffin oil occur at 2920, 2855, 1459 and 1378 cm.$^{-1}$, and mask the C–H frequencies of the compounds.]

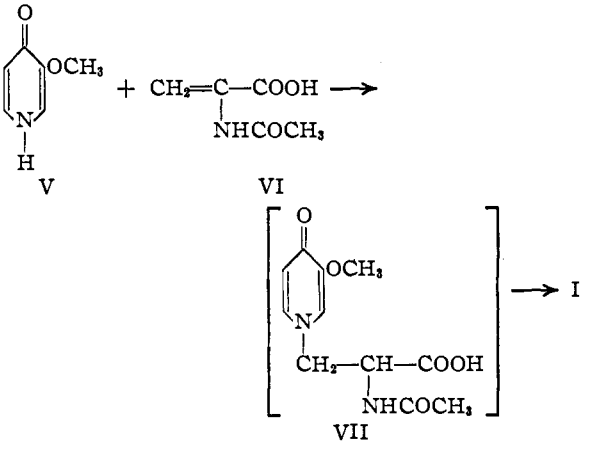
racemization of the natural product is fortunate since it provides a compound with which a *dl* synthetic product may be compared.

The initial approach to the synthesis involved a study of the conversion of γ-pyrone to the appropriate 4-pyridones by a reaction with primary amines. Ammonia and methylamine condense to give 4-pyridone and 1-methyl-4-pyridone, respectively.[6] β-Alanine was found to react similarly to give an 80% yield of 1-β-carboxyethyl-4-pyridone (II). β-Alanine ester did not react as smoothly and the primary condensation product could not be isolated in a pure state; however, on acid hydrolysis, an acid was obtained identical with that formed from β-alanine. The condensation of γ-pyrone with α,β-diaminopropionic acid or α-hydroxy-β-aminopropionic acid failed to give products from which pure compounds could be isolated.

Attention was next directed to reactions of 4-pyridone. Its condensation with β-bromopropionic acid was unsuccessful. On the other hand, it added to acrylonitrile with formation of 1-β-cyanoethyl-4-pyridone (III). Upon hydrolysis of this product, 1-β-carboxyethyl-4-pyridone (II) resulted which is the same compound as that derived from γ-pyrone and β-alanine. α-Acetamidoacrylic acid (VI) and 4-pyridone reacted in a similar manner, using dioxane as solvent. The product could not be isolated, but after hydrolysis with hydrochloric acid, the α-aminopropionic acid derivative (IV) resulted in low yield.



The last reaction provided a possible route to the synthesis of the leucenol molecule through the use of 3-methoxy-4-pyridone (V) and α-acetamidoacrylic acid (VI). The condensation was effected merely by heating the two reactants together without catalyst at 90–100° in presence of dioxane. The reaction product (VII) did not crystallize and was therefore hydrolyzed directly with aqueous hydriodic acid in order to cleave the methoxyl group to hydroxyl and the acetamido group to the amine. After this was completed, the hydriodic acid was neutralized and the water removed. The by-products were extracted with



hot methanol and the residue crystallized by evaporating a water solution at room temperature. A 25.5% yield of *dl*-leucenol hemihydrate resulted. The *dl*-leucenol, anhydrous, was prepared by distilling off water from a saturated boiling solution and filtering the crystals from the hot solvent.

These products showed identical properties with those of racemized natural leucenol. The comparison was made of the melting points, infrared absorption spectra, and analyses of the hydrated and anhydrous forms. Melting points of mixtures of the synthetic and the racemic form from the natural product were not depressed. The color reactions with ferric chloride, ninhydrin, and Folin reagent were the same with synthetic *dl*-leucenol, racemized natural leucenol, and natural leucenol.

(6) Haitinger and Lieben, *Monatsh.*, **5**, 339 (1884); Meyer, *ibid.*, **26** 1311 (1905).

These experiments establish unequivocally the structure of leucenol as I.

The authors are indebted to Mrs. J. L. Johnson for the infrared analyses and their interpretation.

Experimental

Natural Leucenol.—Crude leucenol obtained by the extraction procedure of Kostermans[3] was purified according to the method of Bickel and Wibaut.[2c] The product was obtained as white needles, m. p. 228–229° (cor.) with decomposition. The method of isolation previously used in this laboratory[2a] gives lower yields of leucenol having the same melting point and rotation.

Anal. Calcd. for $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.57; H, 4.98; N, 14.42.

Rotation. 0.049 g. made up to 25 ml. with water at 22° gave α_D −0.084°; *l*, 2; $[\alpha]^{22}D$ −21°. 0.096 g. made up to 10 ml. with 1% hydrochloric acid at 23° gave α_D 0.098; *l*, 1; $[\alpha]^{23}D$ +10°.

An attempt to form a hydrate in the same manner used for preparing *dl*-leucenol hemihydrate from *dl*-leucenol failed.

Racemization of Natural Leucenol.—A solution of 2.5 g. of natural leucenol, ($[\alpha]^{23}D$ −20°) in 250 ml. of water was heated under reflux for forty-eight hours. The volume of the solution was reduced to approximately 50 ml. by distilling off water at atmospheric pressure. The crystals, which separate during this procedure, were filtered while the mixture of crystals and solution was hot. Brownish needles of anhydrous *dl*-leucenol weighing 1.0 g. were thus obtained. Two recrystallizations, in which a saturated boiling aqueous solution was evaporated to a smaller volume and filtered while still hot, resulted in white needles, m. p. 235–236° (cor.) with decomposition. No rotation could be observed.

Anal. Calcd. for $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.57; H, 5.21; N, 14.32.

The procedure for forming the anhydrous *dl*-leucenol in a pure state is more reliable than merely cooling a boiling saturated solution which may result in anhydrous *dl*-leucenol contaminated with a small amount of the hydrate.

***dl*-Leucenol Hemihydrate.**—A solution of 0.25 g. of *dl*-leucenol, prepared from natural leucenol, in 30 ml. of water was evaporated to 15 ml. in a vacuum desiccator over phosphorus pentoxide. The hemihydrate separated in the form of white needles in a yield of 0.18 g. The product darkens at 215–226°, and melts at 227–228° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{10}O_4N_2 \cdot {}^1/_2H_2O$: C, 46.46; H, 5.33; N, 13.55. Found: C, 46.42; H, 5.35; N, 13.44.

1-β-Carboxyethyl-4-pyridone

A. From β-Alanine.—A solution of 0.5 g. of γ-pyrone[7] and 0.5 g. of β-alanine in 3 ml. of water was sealed in a 14-mm. Pyrex glass tube, and the tube immersed in an oil-bath at 105° for four hours. The tube was cooled, opened, and the reaction mixture poured into 75 ml. of acetone. The yellow solid which separated was partially purified by dissolving it in 20 ml. of 90% methanol and adding acetone slowly to precipitate the product. Crystallization from water yielded white needles, m. p. 182.5–183.5° (cor.). The yield was 0.68 g. (81%).

Anal. Calcd. for $C_8H_9O_3N$: C, 57.47; H, 5.39. Found: C, 57.20; H, 5.49.

B. From β-Alanine Methyl Ester.—A solution of 1.1 g. of β-alanine methyl ester hydrochloride, in 30 ml. of ethanol was boiled with 2.2 g. of freshly prepared silver oxide for twenty minutes. The precipitated silver chloride and excess silver oxide were separated by filtration. The volume of the filtrate was increased to 50 ml., and 0.8 g. of γ-pyrone was added. The solution was evaporated to 10 ml., but no crystals separated from the yellow solution on standing overnight in a refrigerator. On evaporating the solution to dryness over phosphorus pentoxide in a vacuum desiccator a yellow oil was obtained.

This oil was dissolved in 10 ml. of 20% aqueous sulfuric acid, and the solution was heated under reflux for two hours. The hot solution was made basic by addition of barium hydroxide, and then acidic (*p*H 4) by addition of dilute sulfuric acid. The precipitated barium sulfate was separated by filtration, and the clear filtrate was evaporated to dryness yielding a glassy residue. The residue was extracted with four 10-ml. portions of warm 90% methanol. The methanol insoluble material was recrystallized from water to yield 0.3 g. of β-alanine; its identity was established by means of its infrared absorption spectrum. The methanol was evaporated to 10 ml., and acetone was added to precipitate 0.135 g. (10%) of 1-β-carboxyethyl-4-pyridone.

Hydrolysis of 1-β-Cyanoethyl-4-pyridone to 1-β-Carboxyethyl-4-pyridone.—The substituted propionitrile may be hydrolyzed to give an 80% yield of 1-β-carboxyethyl-4-pyridone; it is more convenient, however, to hydrolyze the cyanoethylation mixture directly.

The crude nitrile obtained from 2 g. of 4-pyridone was dissolved in 20 ml. of 30% aqueous sulfuric acid. The solution was heated under reflux for five hours. While still hot, it was made basic by addition of barium hydroxide, then acidic (*p*H 4) by addition of dilute sulfuric acid. The slurry was filtered to remove the precipitated barium sulfate. The filtrate was evaporated to dryness yielding a glassy yellow residue. The residue was dissolved in 100 ml. of 90% methanol, and the methanol allowed to evaporate off at room temperature. A powdery yellow product separated. After recrystallization from water 1.7 g. (50%) of white needles resulted, identical with the product obtained from the reaction of γ-pyrone with β-alanine.

1-β-Cyanoethyl-4-pyridone.—A mixture of 1.0 g. of 4-pyridone,[8] 0.85 g. of acrylonitrile, and approximately 10 mg. of sodium 4-pyridone was heated in an oil-bath at 60–65° for five hours. The solid dissolved slowly during the first three hours of heating. The yellow reaction mixture was warmed with 10 ml. of acetonitrile, the solution filtered to remove a small amount of gelatinous material, and the filtrate evaporated to approximately 3 ml. in a stream of filtered air. A yield of 1.2 g. of slightly yellow product was then obtained. Four recrystallizations from acetonitrile yielded a white product which after drying at 60° and 1 mm. pressure for five hours melted at 109–111° (cor.). The yield of dried product was 0.65 g. (42.5%).

Anal. Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44. Found: C, 64.57; H, 5.59.

α-Amino-β-(N-4-pyridone)-propionic Acid.—A suspension of 1.0 g. of 4-pyridone and 1.45 g. of α-acetamidoacrylic acid[9] in 4 ml. of dioxane was heated in a metal-bath at 90–100° for four hours. The dioxane was evaporated off to yield a brown gum which failed to crystallize from ethanol or methanol. The impure α-acetamidopropionic acid derivative was dissolved in 15 ml. of concentrated hydrochloric acid, and the solution was heated under reflux for six hours. The excess hydrochloric acid and water were evaporated off, and the brown residue was dissolved in 5 ml. of concentrated aqueous ammonia. The ammonia and water were evaporated and the residue dried in a vacuum desiccator. The dry residue was washed with 200 ml. of boiling methanol in four portions. The methanol insoluble material, weighing 0.4 g. was recrystallized from 5 ml. of water to yield 0.25 g. (13%) of white needles, m. p. 178° (cor.) with decomposition. The product was a monohydrate. After heating at 100° and 1 mm. for thirty-six hours, the hydrate lost its water to yield the anhydrous amino acid. Slight decomposition occurred as judged by the sample becoming slightly yellow. The melting point of the anhydrous product was 170–172° (cor.) with decomposition. The anhydrous amino acid is extremely hygroscopic.

(7) Willstätter and Pummerer, *Ber.*, **37**, 3740 (1904); **38**, 1461 (1905).

(8) Arndt, *Ber.*, **63**, 593 (1930).

(9) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

Anal. Calcd. for (monohydrate) $C_8H_{10}O_3N_2 \cdot H_2O$: C, 48.01; H, 6.05; N, 14.02. Found: C, 48.14; H, 6.15; N, 14.12. Calcd. for (anhydrous) $C_8H_{10}O_3N_2$: C, 52.75; H, 5.53. Found: C, 52.43; H, 5.54.

Synthetic *dl*-Leucenol.—A suspension of 0.9 g. of 3-methoxy-4-pyridone[2d] and 0.95 g. of α-acetamidoacrylic acid in 5 ml. of dioxane was heated at 95–100° for five hours. The dioxane was removed in a stream of air during the last hour of heating. A solution of the brown reaction mixture in 20 ml. of aqueous hydriodic acid (sp. gr. 1.50) was heated under reflux for six hours. The water and excess acid were removed under reduced pressure, and the residue was allowed to stand overnight in a vacuum desiccator over solid potassium hydroxide. The dry residue was dissolved in 20 ml. of water, and the solution was filtered to remove a small amount of insoluble brownish material. The filtrate was made just acid to brom cresol green (*p*H range, 3.8–5.4) by addition of dilute potassium hydroxide solution. Most of the water was distilled off under reduced pressure, and the residue was dried in a vacuum desiccator. The dry residue was washed with 200 ml. of hot methanol in 20-ml. portions to remove the potassium iodide and by-products. The insoluble material weighed 425 mg. and was reddish-brown in color. One recrystallization carried out by evaporating a water solution of the product at room temperature gave pinkish needles, m. p. 225–227° (cor.) with decomposition, and having the infrared absorption spectrum of *dl*-leucenol hemihydrate (Fig. 1). The yield was 380 mg. (25.5%). Two more recrystallizations carried out in the same way gave a white product; it darkens at 215–226° and melts at 227–228° (cor.) with decomposition. The melting point of a mixture of this product with racemized natural leucenol hemihydrate showed no depression.

Anal. Calcd. for (hemihydrate) $C_8H_{10}O_4N_2 \cdot {}^1/_2H_2O$: C, 46.46; H, 5.33; N, 13.55. Found: C, 46.21; H, 5.60; N, 13.56.

A portion of the hemihydrate was dissolved in water and the solution boiled down until crystals separated. The hot solution was filtered to give anhydrous *dl*-leucenol, m. p. 235–236° (cor.) with decomposition. The melting point of a mixture of this product with anhydrous racemized natural leucenol showed no depression.

Anal. Calcd. for (anhydrous) $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.47; H, 5.16; N, 14.24.

Condensation of 3-hydroxy-4-pyridone[2b] with α-acetamidoacrylic acid proceeded much less smoothly than the reaction described above. Only a 4% yield of *dl*-leucenol was obtained.

Summary

1. Natural leucenol, which is levorotatory, is racemized when heated in aqueous solution for forty-eight hours.

2. The *dl*-leucenol has been synthesized by condensation of 3-methoxy-4-pyridone with α-acetamidoacrylic acid, and hydrolysis of the primary condensation product.

3. *dl*-Leucenol can be isolated in an anhydrous or a hydrated form.

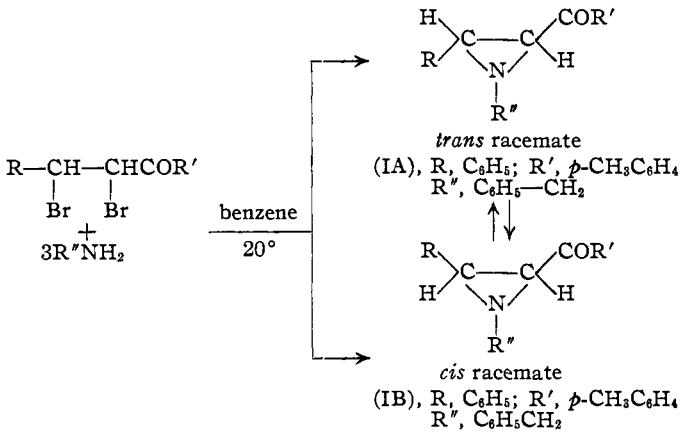
URBANA, ILLINOIS RECEIVED DECEMBER 27, 1948

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Ethylene Imine Ketones. IV.[1] Isomerism and Absorption Spectra[2]

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[3]

In previous investigations[1] of the reaction of primary amines with α,β-dibromoketones, ethylene imine ketones were obtained in yields of about 25%. The fact that diphenylethylenimine exists in *cis* and *trans* forms[4] suggests that these low yields may have been due to the formation of pairs of geometrical isomers, of which only the less soluble was isolated in each instance studied. It is also possible, of course, that products of other types, such as piperazines and α-imino ketones, are formed along with one or more forms of the ethylene imine ketones.



The reaction of benzylamine with α,β-dibromobenzyl-*p*-methylacetophenone[1] has now been found to give the isomeric products (IA) (29%) and (IB) (37%), when carried out in dry benzene solution at temperatures between 20 and 30°. No evidence for the formation of a piperazine was observed in these studies.

The low melting isomer (IB) was the more labile of the two. This compound partially decomposed and rearranged to the higher melting isomer (IA) when saturated petroleum ether solutions of it were exposed to sunlight at room temperature. An inspection of scale models for such ethylene imine ketone structures indicated that the racemate (IB) would be a more highly strained arrangement than (IA). Thus (IB) might be expected to undergo rearrangement, possibly through an enol form, to the less strained structure (IA). Acid and base catalyzed rearrange-

(1) For the previous paper in this series see Cromwell, THIS JOURNAL, **69**, 258 (1947).

(2) Presented before a session of the Division of Organic Chemistry, 113th Meeting of the American Chemical Society, Chicago, Illinois, April 20, 1948.

(3) Abstracted from the Ph.D. thesis (June, 1948); du Pont Fellow, 1946–1947.

(4) Weissberger and Bach, *Ber.*, **64**, 1095 (1931).