

in absolute ethanol according to the general directions of Hantzsch.⁷ After twenty-four hours, the solvent was distilled. The residue after extraction with dilute alkali and acid solidified and was crystallized from methanol to give 29 g. (75%) of yellow needles, m. p. 86–87°.

Anal. Calcd. for C₁₉H₁₃ONBr₂: N, 3.25. Found: N, 3.27.

Rearrangement of (II).—Five grams of (II) in a Pyrex test-tube was heated to 270–280° for one hour and fifty-five minutes and then for five minutes at 285–290° according to general directions of Chapman.⁶ The crude material melted at 140–142°. Crystallization from ethanol gave 4.2 g. (84%) of long white plates (III), m. p. 141.5–142°.

Anal. Calcd. for C₁₉H₁₃ONBr₂: N, 3.25. Found: N, 2.99.

Hydrolysis of N,N-4,4'-Dibromodiphenylbenzamide (III).—Four grams of (III) was hydrolyzed by refluxing for one-half hour with 3 g. of potassium hydroxide in 30 ml. of ethanol. After cooling, the mixture was filtered from a solid which was identified as potassium benzoate by mixed melting point after acidification. The filtrate was poured into water to yield 3 g. of tan solid, m. p. 104–106°. Crystallization from ligroin (65–70°) gave 2 g. (68%) of glistening needles, m. p. 106.5–107°. A mixed melting point with 4,4'-dibromodiphenylamine prepared above showed no depression.

Anal. Calcd. for C₁₉H₉NBr₂: N, 4.28. Found: N, 3.96.

Benzoylation of 4,4'-Dibromodiphenylamine.—Three grams of benzoyl chloride was added to a solution of 3.4 g. of 4,4'-dibromodiphenylamine⁸ in 7 ml. of pyridine. After two hours, the resulting mixture was heated on the steam-bath for five minutes, then poured into dilute hydrochloric acid to give 4.5 g. of tan solid, m. p. 136–138°. Crystallization from ethanol gave 3.5 g. (85%) of colorless plates, m. p. 141–141.5°. A mixed melting point with (II) showed no depression.

Anal. Calcd. for C₁₉H₁₃ONBr₂: N, 3.25. Found: N, 2.92.

(7) Hantzsch, *Ber.*, **26**, 927 (1893).

CHEMISTRY DEPARTMENT
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

RECEIVED FEBRUARY 7, 1945

The Alkaline Hydrolysis of β -Aminopropionitrile

BY JARED H. FORD

The preparation of β -alanine by the hydrolysis of β -aminopropionitrile with hydrochloric acid and subsequent removal of the acid by means of anion exchange resins has been described recently.¹ The present communication describes a more convenient method which employs alkaline hydrolysis.

β -Alanine was obtained in yields of 88–92% by boiling β -aminopropionitrile with 25–50% barium hydroxide solution for twenty to thirty minutes. Although alkaline hydrolysis was found to be less sensitive than acid hydrolysis to changes in experimental conditions, 8% barium hydroxide gave only 68% yield. Since β -aminopropionitrile² and bis-(cyanoethyl)-amine³ have been reported to give β -alanine in approximately the same yields (20%) on hydrolysis with ammonium

hydroxide at 180–225°, it appears that the following equilibrium is established under these conditions⁴



This equilibrium is not established rapidly at the temperatures employed in the present investigation and prolonging the heating to two hours did not decrease the yield of β -alanine perceptibly.⁵ Under the same conditions, bis-(cyanoethyl)-amine gave the monobarium salt of β, β' -iminobispropionic acid in 86% yield.

The free acid and its monoammonium salt, which are probable by-products in several of the previously reported syntheses of β -alanine, have now been characterized for the first time.⁶ Although the monoammonium salt has the same elementary composition as β -alanine, its presence can be easily detected by the usual tests for ammonium salts. The addition of 10% of this compound was found to lower the melting point of β -alanine from 195–196° (dec.) to 175–180° (dec.). The free acid can be determined quantitatively in the presence of β -alanine by titration with alkali using phenol red indicator.

Experimental⁷

Hydrolysis of β -Aminopropionitrile.—Barium hydroxide octahydrate (185 g.) was fused on the steam-bath and 70 g. of β -aminopropionitrile¹ was added dropwise to the mechanically stirred solution at 90–95°. After thirty minutes, 1 liter of hot water was added and the solution was saturated with carbon dioxide. The precipitate was filtered and washed with hot water and the combined filtrates were evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution, after treatment with decolorizing carbon and evaporation to a 60% concentration, was diluted with 8 volumes of methanol. After standing overnight at 5°, the β -alanine was filtered off and washed with methanol. The yield was 80.6 g. (90%); m. p. 197–8° (dec.).

Hydrolysis of Bis-(cyanoethyl)-amine.—The nitrile (44.9 g.) was added dropwise to a solution of 148 g. of barium hydroxide octahydrate in 100 ml. of water and boiled for thirty minutes. The barium was removed as before and the sirup that was obtained on concentration of the filtrates was triturated with 95% ethanol. The resulting white powder (75.2 g., 86% yield) appeared as needles under a microscope. For analysis a sample was precipitated from 20% aqueous solution with 95% ethanol and dried to constant weight *in vacuo* at 60°; m. p. 175–177°.

Anal. Calcd. for C₁₂H₂₀N₂O₈Ba·H₂O: C, 30.30; H, 4.66; Ba, 28.88; H₂O, 3.79. Found: C, 30.10; H, 4.81; Ba, 28.82, 28.70; H₂O, 3.53.⁸

β, β' -Iminobispropionic Acid.—An aqueous solution of the crude monobarium salt was treated with an equivalent

(4) Experimental evidence for this equilibrium has been obtained by Dr. S. R. Buc of these Laboratories and the author. Similar equilibria may also exist for the corresponding acids and amides.

(5) This is in marked contrast with the observations reported by Aberhalden and Fodor (*Z. physiol. Chem.*, **85**, 119 (1913)), who stated that pure β -alanine evolved ammonia when warmed with dilute alkali.

(6) Heintz (*Ann.*, **156**, 40 (1870)) prepared the monolead salt and obtained the free acid as a sirup which crystallized slowly. Neither physical nor analytical data were reported.

(7) All melting points are uncorrected.

(8) Obtained by drying to constant weight at 100° in a high vacuum. The anhydrous salt reverted rapidly to the monohydrate when exposed to air.

(1) Buc, Ford and Wise, *This Journal*, **67**, 92 (1945).

(2) Carlson, U. S. Patent 2,336,067.

(3) Kirk, U. S. Patent 2,334,163.

amount of dilute sulfuric acid, the mixture filtered and the filtrate evaporated to dryness *in vacuo*. The resulting sirup crystallized when triturated with alcohol; m. p. 148–150° after drying *in vacuo* at 75°. The pH of a 1% solution was 3.5 and the pK'_2 value (calcd. from the titration curve) was 4.2.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; neut. eq., 161.2. Found: C, 44.58; H, 6.83; neut. eq., 161.5 (potentiometric titration).

Recrystallization from methanol raised the melting point to 151–151.5°.

Monoammonium Salt of β,β' -Iminobispropionic Acid.—This compound was prepared from the crude monobarium salt and ammonium sulfate as previously indicated. It crystallized readily from concentrated aqueous solutions when diluted with methanol, but less satisfactorily when ethanol was used; m. p. 172–176°, after two recrystallizations from aqueous methanol.

Anal. Calcd. for $C_6H_{14}N_2O_4$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.22; H, 8.12; N, 15.45.

Acknowledgment.—The author wishes to thank Mr. Anthony Bucci for technical assistance and Messrs. Harold Emerson and William A. Struck for the microanalyses.

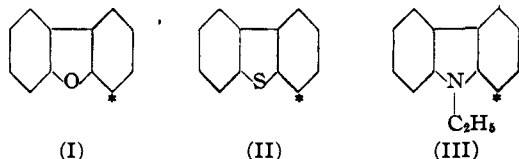
RESEARCH LABORATORIES
THE UPJOHN COMPANY

KALAMAZOO 99, MICHIGAN RECEIVED FEBRUARY 10, 1945

Competitive Metalations of Some Related Heterocycles¹

BY HENRY GILMAN AND C. G. STUCKWISCH

In connection with the metalation of polynuclear systems having more than one hetero element it was desirable to have information on the rates of metalation of related heterocycles containing oxygen, sulfur and nitrogen, respectively. For this purpose, comparisons are best made with dibenzofuran (I), dibenzothiophene (II) and N-ethylcarbazole (III) inasmuch as each of these related heterocycles is known to undergo metalation by *n*-butyllithium in the 4-position (indicated by an asterisk).



Three different procedures can be used to establish the relative effects of the hetero elements. First, the rates of metalation can be determined for each heterocycle. Second, competitive reactions can be run with two of the types, using an insufficient quantity of the metalating agent. Third, the preformed RLi compound from one of the heterocycles can be brought into reaction with another heterocycle which is not substituted to determine the extent of interchange. By these procedures, it has been shown² that I is metalated more readily than II. The

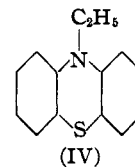
(1) Paper LIX in the series "Relative Reactivities of Organometallic Compounds": the preceding paper is Gilman, Haubein, O'Donnell and Woods, *THIS JOURNAL*, **67**, (June) (1945).

(2) Gilman, Van Ess, Willis and Stuckwisch, *THIS JOURNAL*, **62**, 2606 (1940).

least readily metalated type is III. For example, when a mixture of one equivalent of dibenzothiophene and one equivalent of N-ethylcarbazole was allowed to compete for but one equivalent of *n*-butyllithium, the only compound metalated after a six-hour period of reaction was dibenzothiophene. In support of this finding, other independent experiments showed that II was metalated by 4-N-ethylcarbazolyllithium, and that III was not metalated by 4-dibenzothiopyllithium.

Accordingly, the order of decreasing ease of metalation by *n*-butyllithium of related heterocycles containing oxygen, sulfur, and nitrogen is: oxygen > sulfur > nitrogen. A striking illustration of the relative effects of oxygen and sulfur is found in dibenzo-*p*-dioxin and thianthrene: the di-oxygen heterocycle undergoing more rapid metalation by RLi compounds than its di-sulfur analog.³ Also, phenoxathiin, which has a symmetrically disposed oxygen atom and sulfur atom, is metalated *ortho* to the oxygen.²

It was suggested recently,⁴ in the absence of rigorous experimental evidence, that the metalation of N-ethylphenothiazine (IV) by *n*-butyllithium probably involves the position *ortho* to sulfur, most of the other positions having been eliminated by either synthesis or degradation. The present evidence of the greater influence of sulfur over nitrogen lends a high degree of plausibility to this assumption.



The validity of the generalizations now reported is confined to comparisons of a selected metalating agent which metalates in corresponding positions. For example, N-ethylcarbazole is mercurated more readily than dibenzofuran, but mercuration of N-ethylcarbazole involves the 2-position and mercuration of dibenzofuran involves the 4-position.⁵ Also, N-ethylphenothiazine is mercurated with great ease and metalated by *n*-butyllithium with difficulty; but in the former case the 3-position is involved, and in the latter case the position involved is definitely not 3 and is probably 4.

Experimental

Dibenzothiophene and N-Ethylcarbazole with *n*-Butyllithium.—A mixture of 0.051 mole of *n*-butyllithium in 200 cc. of ether was refluxed for six hours with an equivalent each of dibenzothiophene and N-ethylcarbazole.

The acid isolated subsequent to carbonation was free of nitrogen, and the yield of pure 4-dibenzothiophene-carboxylic acid obtained after crystallization was 40%. Identification was established, as usual, by the method of mixed melting points with authentic acid and methyl ester.

(3) Gilman and Stuckwisch, *ibid.*, **65**, 1461 (1943).

(4) Gilman, Van Ess and Shirley, *ibid.*, **66**, 1214 (1944).

(5) Gilman and Kirby, *J. Org. Chem.*, **1**, 146 (1936). In this paper is a report of the non-metalation of N-ethylcarbazole by 4-dibenzofurylpotassium. This is a reaction that fits in with the generalization that an oxygen-heterocycle is more readily metalated than a related nitrogen-heterocycle. See, also, Gilman and Lister, *THIS JOURNAL*, **67**, (1945), for the different positions involved in the mercuration and metalation by *n*-butyllithium of N-phenylcarbazole.