infrared spectrogram[2] gave the following estimated composition of the product: 51% of 2′,5-dibromosalicylanilide and 44% of 2′,3,5-tribromosalicylanilide.

From the sensitivity of the infrared method it is concluded that the ratio of 3- to 4′-substitution is at least four to one. From this evidence the order of reactivity to bromination in acetic acid of the sites in salicylanilide can be postulated to be 5- (highest), 3-, 4′-, 2′-.

EXPERIMENTAL

2′,5-Dibromosalicylanilide. A mixture of 11 g. of 5-bromosalicylic acid, 9 g. of 2-bromoaniline, and 2 ml. of phosphorus trichloride was allowed to react in 100 ml. of refluxing chlorobenzene for 2.5 hr. The solution was filtered hot and the crude product obtained on cooling. Recrystallization from chlorobenzene gave 11 g. (59%) of product m.p. 189–191°.

Anal. Calcd. for $C_{13}H_9Br_2NO_2$: Br, 43.08. Found, 43.04.

In a similar manner the following compounds were prepared as standards for infrared analysis:

2′,3,5-Tribromosalicylanilide, m.p. 178–179°.

Anal. Calcd. for $C_{13}H_8Br_3NO_2$: Br, 53.28. Found, 53.16.

2′,4′,5-Tribromosalicylanilide, m.p. 233–236°.

Anal. Calcd. for $C_{13}H_8Br_3NO_2$: Br, 53.28. Found, 52.95.

2′,3,4′,5-Tetrabromosalicylanilide, m.p. 206–208°.

Anal. Calcd. for $C_{13}H_7Br_4NO_2$: Br, 60.44. Found, 60.46.

Bromination of 2′,5-dibromosalicylanilide. A solution of 3.72 g. (0.0100 mole) of 2′,5-dibromosalicylanilide was prepared in 1.2 l. of warm glacial acetic acid and 1.60 g. of bromine in 100 ml. of acetic acid was added. The solution was held at 60° in an open flask for a total of 68 hr. over a period of a week. Most of the solvent was then removed at reduced pressure. The moist crystals were dissolved in acetone which was then filtered to remove boiling chips. The solution was dried, first in air at 50° and finally in a vacuum over potassium hydroxide at 60°. The dry product weighed 4.13 g. Analysis showed 47.30% bromine, indicating a mixture of about 60% dibromosalicylanilide (2.48 g., 0.0067 mole), and 40% tribromosalicylanilide (1.65 g., 0.0037 mole).

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RESEARCH AND DEVELOPMENT DIVISION
LEVER BROTHERS CO.
EDGEWATER, N. J.

(2) Details of infrared analysis to be published by S. Goldwasser and A. A. Rapisarda of these laboratories.

Preparation of 3-(3-Quinolyl)alanine[1,2]

ELIZABETH DYER AND WAKO YOKOYAMA

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Since it is known[3] that increased amounts of dietary tryptophan increase the number of certain induced cancers in rats, an inhibitor for tryptophan might be a useful chemical. Hence, 3-(3-quinolyl)-alanine was synthesized as a possible antimetabolite of tryptophan. The 2- and 4-quinolylalanines are known,[4,5] but the 3-isomer has not been reported, possibly because of the difficulty of placing substituents on the 3-position of quinoline.

The 3-(3-quinolyl)alanine was prepared from quinoline-3-aldehyde[6] by the azlactone synthesis and was characterized through hydantoic acid and hydantoin derivatives.

Pharmacological tests[7] showed that the 3-(3-quinolyl)alanine was nontoxic and inactive toward Sarcoma 180, Ehrlich Ascites, and Leukemia 1210.

EXPERIMENTAL

Quinoline-3-aldehyde. This compound was prepared in an overall yield of about 1% from quinoline through the following intermediates: 3-bromoquinoline,[8] 3-cyanoquinoline[9] quinoline-3-carboxylic acid,[9] ethyl-3-quinolinecarboxylate,[9] 3-quinolinecarboxyhydrazide,[10] and its *p*-toluenesulfonyl derivative.[10] Yields in the various steps were satisfactory except in the first (20–34%) and the last (10–18%).

3-Bromoquinoline.[8] Because of the difficulty of preparing this compound, procedural details are given. Into a solution of 400 ml. (3.1 moles) of quinoline in 1 l. of chloroform, cooled in an ice bath, was slowly passed dry hydrogen bromide (to a 40% excess). Bromine (3.4 moles) was added dropwise during stirring and continued cooling. After standing overnight, the chloroform was decanted and the solid quinoline hydrobromide dibromide was heated at 175–180° for about 3.5 hr., until a new solid, 3-bromoquinoline hydrobromide, appeared on the sides of the container. After 10 min. the heating was stopped, and while the mixture was still warm, 400 ml. of chloroform was added with stirring to dissolve a tarry material. The cooled product was filtered and washed thoroughly with chloroform. The gray solid hydrobromide was treated with cold 10% sodium carbonate, the oily 3-bromoquinoline separated, and the aqueous layers extracted with ether. Distillation of the combined dried extracts and oil gave 220 g., b.p. 104–106° at 1 mm. (34% yield).

4-(3-Quinolylmethylene)-2-phenyl-2-oxazolin-5-one. This azlactone was prepared in 92% yield (crude) from quinoline-3-aldehyde, hippuric acid and acetic anhydride. It melted at 200–201.8° after recrystallization from 2-pentanol.

Anal. Calcd. for $C_{19}H_{12}O_2N_2$: C, 75.98; H, 4.03; N, 9.33. Found: C, 75.66; H, 3.77; N, 9.42.

3-(3-Quinolyl)alanine. Reductive cleavage of the azlactone (0.023 mole) with hydriodic acid and red phosphorus by a standard procedure[11] gave a 34% yield of the amino acid. It melted at 248–253° dec. after recrystallization from water. The solubility in hot water was only 1%. The amino acid gave a reddish-purple spot with ninhydrin.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.67; H, 5.63; N, 12.91.

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5-Phenyl-2-(3-quinolylmethyl)hydantoic acid. The reaction of the 3-(3-quinolyl)alanine with phenyl isocyanate was carried on as described for 4-(3-quinolyl)alanine.[5] The resulting hydantoic acid melted at 219–222° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{17}O_3N_3$: C, 68.04; H, 5.11; N, 12.53. Found: C, 68.02; H, 5.12; N, 12.59.

3-Phenyl-5-(3-quinolylmethyl)hydantoin. The hydantoic acid was cyclized by boiling with dilute hydrochloric acid, and precipitated at *p*H 4 to 5. The hydantoin was recrystallized from ethanol to a melting point of 226–227°.

Anal. Calcd. for $C_{19}H_{15}O_2N_3$: C, 71.89; H, 4.81; N, 13.24. Found: C, 71.39; H, 4.39; N, 13.52.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF DELAWARE
NEWARK, DEL.

A Spectral Study of Some Schiff Base Derivatives of *p*-Aminoazobenzene

JOHN A. RICKETTS AND CHUNG SOOK CHO[1]

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Derivatives of *p*-phenylazoaniline are known carcinogens; *p*-dimethylaminoazobenzenes produce liver tumors in rats.[2,3] In addition as first reported by Kehrman[4] *p*-dimethylaminoazobenzene and its derivatives add protons in acid solutions with a resulting change in their spectra. In the case of the addition of the first proton to these molecules some argument exists in the literature as to its position. Cilento,[5] Badger,[6] Sawicki,[7] and Rogers[8] conclude that addition results in a tautomeric mixture while Klotz[9] and McGuire[10] conclude that the first proton adds exclusively to the amino nitrogen. Prior to the study of their carcinogenic activity a spectral study of the compounds listed in Table I in solutions of varying acid strengths was initiated.

The first and second acid dissociation constants were determined by the method of Rogers[8] with the exception that the buffer solutions used were made up to a constant ionic strength, μ, of 0.1.

$$pK_1 = pH - \log \frac{\epsilon_{BH^+} - \epsilon}{\epsilon - \epsilon_B} - \frac{A\mu^{1/2}}{1 + \mu^{1/2}} \quad (1)$$

Consequently, the equation due to Herington,[11] was used for the addition of the initial proton. Although a color change from light yellow to intense orange was noted in the case of *N,N'*-dibenzal-1,4-diaminobenzene and *N*-(*p*-dimethylaminobenzal)aniline in 50% sulfuric acid solution, it proved impossible to determine the dissociation constants since these Schiff bases hydrolyzed rapidly. This behavior has been previously reported as a general property for Schiff bases.[12] The creditability of the reported measurements can be ascertained by comparison of the results of this work with other investigators in the case of *p*-dimethylaminoazobenzene which has been extensively investigated. The summary appears in Table II.

The results of this study may be summarized by the following statements: (1) The first and second acid dissociation constants for three Schiff base derivatives of *p*-phenylazoaniline have been determined. (2) The visible spectrum of these molecules in mild acid solution displays both the 320 mμ and the 500 mμ absorption peaks which are identical with those observed in the case of the substituted *N,N*-dialkyl-*p*-phenylazoanilines. In the case of these last named molecules spectral evidence strongly indicates that the addition of the first proton results in a tautomeric mixture. The evidence for such a decision is (a) *p,p'*-Dimethoxyazobenzene in acid solution absorbs only at 520 mμ.[6] Presumably this form would exist only in the azonium form. (b) The trimethyl quaternary ammonium salt of *p*-phenylazoaniline has absorption peaks at 315 mμ and 425 mμ which is quite similar to azobenzene itself, 313 mμ and 418 mμ.[13] (c) *N,N*-Dimethyl-2-methyl-4-phenylazoaniline in acid solution has only the absorption peak at 320 mμ. This is reasonable since the methyl group *ortho* to the dimethylamino group prevents this latter group from becoming planar with the ring. The possibility of the quinoid structure is therefore inhibited.[14] The marked spectral similarity between these Schiff bases and the *N,N*-dialkyl-*p*-phenylazoanilines in mild acid allows the conclusion that the addition of the first proton to the Schiff bases results in a tautomeric mixture with the 320 mμ peak due to addition at the azomethine nitrogen and the 500 mμ peak due to addition to the azo nitrogen. (3) Whereas Schiff bases are in general easily hydrolyzed in acid solution, the presence of *p*-phenylazo group stabilizes the molecule even in solutions as concentrated as 96% sulfuric acid. (4) Although the information is admittedly only

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