acetanilide (I), b.p. 115–120° (0.2 mm.), n_D^{25} 1.531, was obtained. *N*-(2-Anilinoethyl)-*N*-methylacetamide, n_D^{25} 1.560, was isolated from the residue in the flask. Two weeks later the distilled base (I) was reexamined and had rearranged to III, n_D^{25} 1.558.

N-(2-Anilinoethyl)-N-methylacetamide (III). *A. The rearrangement of N-(2-methylaminoethyl)acetanilide* (I). Nine grams of *N*-(2-methylaminoethyl)acetanilide was placed in a distilling flask and warmed in a Woods metal bath held at 135–140°. The index of refraction and infrared absorption curve were measured at intervals. Rearrangement was complete in 3.5 hr. The product was distilled and 7.8 g., n_D^{25} 1.560, was collected at 134–138° (0.1 mm.).

B. Attempted preparation by the reaction of N-methylacetanilide with N-methyl-N'-phenylethylenediamine. *N*-Methyl-*N'*-phenylethylenediamine hydrochloride, m.p. 167–169°, was prepared by the catalytic debenzylation of *N*-benzyl-*N*-methyl-*N'*-phenylethylenediamine hydrochloride.[10]

Anal. Calcd. for $C_9H_{15}ClN_2$: C, 57.9; H, 8.1; Cl, 19.0; N, 15.0. Found: C, 58.0; H, 8.4; Cl, 19.2; N, 15.3.

The base, b.p. 84–90° (0.2 mm.), n_D^{25} 1.559, was obtained when the hydrochloride was treated with aqueous alkali and the oil which separated was extracted into ether and distilled.

A mixture of 3.0 g. of *N*-methyl-*N'*-phenylethylenediamine and 3.0 g. of *N*-methylacetanilide was heated over a Woods metal bath for 6 hr. at 170–200°. On distillation, all material boiled below 100° (0.1 mm.).

N-Ethyl-N-methyl-N'-phenylethylenediamine (IV). *A. By the reduction of N-(2-anilinoethyl)-N-methylacetamide* (III). A solution of 7.7 g. of *N*-(2-anilinoethyl)-*N*-methylacetamide, obtained by the previously described rearrangement, in 50 ml. of tetrahydrofuran was added to a solution of 3.0 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was heated at reflux for 4 hr. and then treated with 3 ml. of water, 3 ml. of 15% sodium hydroxide, and 9 ml. of water. The solid was filtered off and washed with tetrahydrofuran. The filtrate was dried over magnesium sulfate and then distilled. The yield of *N*-ethyl-*N*-methyl-*N'*-phenylethylenediamine, b.p. 86–92° (0.3 mm.), n_D^{25} 1.532, was 85%.

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.1; H, 10.2; N, 15.7. Found: C, 74.4; H, 10.3; N, 15.9.

Hydrochloride, m.p. 117–119°.

Anal. Calcd. for $C_{11}H_{19}ClN_2$: C, 61.5; H, 8.9; Cl, 16.5; N, 13.0. Found: C, 61.9; H, 9.1; Cl, 16.2; N, 12.9.

Picrate, m.p. 125–127°.

Anal. Calcd. for $C_{17}H_{21}N_5O_7$: C, 50.1; H, 5.2; N, 17.2. Found: C, 50.1; H, 5.0; N, 17.2.

B. By the reaction of aniline with 2-chloro-N-methyldiethylamine (V). A solution of 196.5 g. of thionyl chloride in 1200 ml. of chloroform was cooled to −5° and a solution of 103 g. of 2-(ethylmethylamino)ethanol in 200 ml. of chloroform was added over a 1-hr. period at this temperature. The reaction mixture was allowed to come to room temperature and was then concentrated until most of the chloroform was removed. Ethanol (75 ml.) was added and concentration was continued to dryness. This procedure was repeated twice. The crystalline residue was triturated with acetone, filtered, washed with acetone, and dried at 50°. The yield of 2-chloro-*N*-methyldiethylamine hydrochloride, m.p. 171–173°, was quantitative. Recrystallization from ethanol resulted in a 78% yield of m.p. 174–176°.

Anal. Calcd. for $C_5H_{12}ClN$: C, 38.0; H, 8.3; Cl, 44.9; N, 8.9. Found: C, 38.3; H, 8.5; Cl, 44.9; N, 8.8.

A mixture of 63.2 g. (0.4 mole) of 2-chloro-*N*-methyldiethylamine hydrochloride, 54.8 g. (0.6 mole) of aniline, 85 g. of sodium carbonate, and 200 ml. of toluene was heated at reflux for 16 hr. and then cooled. The reaction mixture was shaken with 80 ml. of 5*N* potassium hydroxide, and the organic layer was separated, dried over magnesium sulfate and distilled. The yield of *N*-ethyl-*N*-methyl-*N'*-phenylethylenediamine, b.p. 88–92° (0.3 mm.), n_D^{25} 1.530, was 62%.

The infrared absorption curves of the two samples of *N*-ethyl-*N*-methyl-*N'*-phenylethylenediamine were identical. Mixture melting points of the salts were not depressed.

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Relative Reactivities of Sites in Salicylanilide. The Bromination of 2',5-Dibromosalicylanilide

HENRY LEMAIRE AND ARNO CAHN

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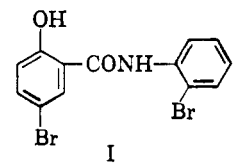
When salicylanilide is treated with one mole of bromine in glacial acetic acid, substitution takes place primarily in the 5-position, *para* to the phenolic group.[1] When two moles of bromine are used, the principal product is 4',5-dibromosalicylanilide.[1] These observations establish the 5-position as the most reactive site under these conditions; they also show that the 4'- position is more reactive than the 2'- position. They do not, however, allow a comparison of the reactivity of the 3- and 4'- positions in unsubstituted salicylanilide because, once the first bromine has entered the 5- position, the 3- position is deactivated.

The relative reactivities of the 3- and 4'- positions of salicylanilide were determined by brominating 2',5-dibromosalicylanilide (I). In this compound both positions are equally deactivated by the two bromine atoms already present in the molecule.



I

Infrared examination of the brominated product was made in dimethylformamide solution between 10.5 μ and 16 μ. All the absorption peaks observed could be ascribed to either 2',5-dibromosalicylanilide (D) or 2',3,5-tribromosalicylanilide (T) as follows: 10.8 μ (T); 11.05 μ (D); 11.5 μ (T); 12.1 μ (D); 12.9 μ (shoulder) (D); 13.1 μ (D,T); 13.55 μ (T); 14.05 μ (D); 14.3 μ (T); 14.9 μ − 15.4 μ (D); 16.0 μ (D). Peaks peculiar to 2',3,4',5-tetrabromosalicylanilide (13.3 μ) and 2',4',5-tribromosalicylanilide (13.8 μ) were not observed. Analysis of the

(1) Schuler, L., German Patent 920,790; U.S. Patent 2,802,029.

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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(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]

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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.

(1) This project was supported by Research Grant CY-3477 from the Public Health Service.

(2) From the M.S. thesis of Wako Yokoyama, 1959.

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