Finally, a solution of 16 g. of bromine in 160 ml. of dioxane was added dropwise with good agitation (stirrer near the bottom of the flask) at 5° to a solution of 9.3 g. of aniline in 30 ml. of dioxane and 5.6 g. of potassium hydroxide in 20 ml. of water. The addition was made over two hours. The organic layer was washed with 15 ml. of 40% potassium hydroxide and distilled under reduced pressure to remove the solvent. The residue was recrystallized from dilute alcohol, yielding 68% of *p*-bromoaniline. This was the highest yield attained.

Dimethylaniline.—When 12.1 g. of dimethylaniline was brominated with 16 g. of bromine according to the technique outlined above (*cf.* aniline), there was obtained 80–85% *p*-bromodimethylaniline, m.p. 55°.

***p*-Nitroaniline.**—When 13.8 g. of *p*-nitroaniline was brominated with 16 g. of bromine according to the above technique, there was obtained, after three crystallizations from ethanol, 40–45% yield of 2-bromo-4-nitroaniline, m.p. 104°.

***p*-Toluidine.**—Reaction of 21.4 g. of *p*-toluidine with 32 g. of bromine, under the conditions described above (350 ml. of dioxane total volume; 11.2 g. of potassium hydroxide in 50 ml. of water; temperature, 5–8°) yielded, upon vacuum distillation of the washed reaction product, a fraction, b.p. 142–145° at 22 mm., weighing 22 g., which after crystallization from dilute alcohol gave 19.8 g. of 2-bromo-4-methylaniline, m.p. 25–26°, which yielded the acetyl derivative, m.p. 117–118°; the yield 53%.

Direct bromination of *p*-toluidine with the powdered complex, as described under aniline, gave considerable amounts of the 2,6-dibromo derivative, which melted at 78–79°, and very small amounts of isolated monobromo compound were obtained. This result is expected owing to the high order of aromatic reactivity of this amine.

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8-Nitro-7-methoxyisoquinoline

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In harmony with theoretical considerations 7-methoxyisoquinoline[1] undergoes nitration in the 8-position. The nitration product, which was obtained in 80% yield, was reduced and the resulting 7-methoxy-8-aminoisoquinoline converted to 7-methoxy-8-chloroisoquinoline. The identity of this was established by comparing with an authentic sample prepared by methylating 7-hydroxy-8-chloroisoquinoline. The latter compound[2] was previously obtained from 2-chloro-3-hydroxybenzaldehyde and aminoacetal.

Experimental

7-Methoxy-8-nitroisoquinoline.—To a stirred solution of 7-methoxyisoquinoline[1] (7.0 g.) in concentrated sulfuric acid (100 cc.) was added portionwise a solution of potassium nitrate (5.0 g.) in concentrated sulfuric acid (35 cc.) while the temperature was maintained at 0–5° by cooling. After stirring for an additional one-half hour at 0–5°, the reaction mixture was poured onto cracked ice. The resulting solution was basified and the yellow precipitate filtered, washed and dried. Crystallization from benzene yielded 7.0 g. (80%) of yellow prisms melting at 164–165°. *Anal.* Calcd. for $C_{10}H_8N_2O_3$: C, 58.83; H, 3.92; N, 13.73. Found: C, 58.66, 58.70; H, 3.97, 3.64; N, 13.53.

7-Methoxy-8-aminoisoquinoline.—To a stirred solution of 7-methoxy-8-nitroisoquinoline (6.0 g.) in concentrated hydrochloric acid (30 cc.) was added portionwise a solution of stannous chloride dihydrate (30 g.) in concentrated hydrochloric acid (50 cc.) while the temperature was maintained at 35–40° by cooling. Then the reaction mixture was allowed to stand at room temperature overnight with occasional cooling during the first hour in order to keep the temperature below 40°. The reaction mixture was diluted with an equal volume of water and then added to a mixture of 30% sodium hydroxide solution (300 cc.) and cracked ice (about 300 g.). The precipitated amine was extracted with three 400-cc. portions of ether and the ether was removed from the extract. Crystallization of the residue from benzene yielded 3.8 g. (74%) of yellow needles melting at 156–157°. *Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.10. Found: C, 69.12, 69.25; H, 5.83, 5.99; N, 15.90.

7-Methoxy-8-chloroisoquinoline.—A solution of 7-methoxy-8-aminoisoquinoline (0.6 g.) in concentrated hydrochloric acid (2 cc.) and water (10 cc.) was diazotized at 0° with sodium nitrite (0.25 g.) in water (5 cc.). The resulting diazonium chloride solution was added to a solution of cuprous chloride (2 g.) in concentrated hydrochloric acid (20 cc.) previously warmed to 70°. After standing overnight the reaction mixture was basified and steam distilled. The steam distillate was filtered and the white solid (0.32 g. or 50%) was crystallized from methanol, white needles, m.p. 124–125°. The methylation of 7-hydroxy-8-chloroisoquinoline[2] with diazomethane yielded a compound melting at 124–125° alone or in admixture with the compound above. *Anal.* Calcd. for $C_{10}H_8NOCl$: C, 62.02; H, 4.14; N, 7.23. Found: C, 62.43, 62.44; H, 4.26, 4.37; N, 7.20.

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Quinoxaline Studies. V. Synthesis of 2-Hydroxy-3,5-dimethylquinoxaline and 2-Hydroxy-3,8-dimethylquinoxaline

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Although a number of papers have discussed the synthesis of unsymmetrically substituted quinoxalines with substituents in the 6- and 7-position of the quinoxaline ring, no work has been reported with substituents in the 5- and 8-positions of the unsymmetrically substituted quinoxaline ring. The purpose of this investigation was to synthesize and determine the physical properties of 2-hydroxy-3,5-dimethylquinoxaline and 2-hydroxy-3,8-dimethylquinoxaline.

The starting material for the synthesis of 2-hydroxy-3,5-dimethylquinoxaline was 2-amino-3-nitrotoluene. *o*-Acetotoluidide was nitrated by the procedure used by Bacharach[2] to nitrate *p*-acetotoluidide. Hydrolysis of the 3-nitro-2-acetotoluidide, followed by steam distillation, gave 2-amino-3-nitrotoluene. Condensation of 2-amino-3-nitrotoluene with α-bromopropionic acid gave N-(2-nitro-6-methylphenyl)-*dl*-α-alanine.

The amino acid, N-(2-nitro-6-methylphenyl)-*dl*-α-alanine, was reduced catalytically to the dihydro derivative of 2-hydroxy-3,5-dimethylquinoxaline. The unisolated 3,4-dihydro-2-hydroxy-3,5-dimethylquinoxaline was oxidized by basic hydrogen peroxide solution to 2-hydroxy-3,5-dimethylquinoxaline.

The preparation of 2-hydroxy-3,8-dimethylquinoxaline utilized similar reactions, starting with 2-nitro-3-aminotoluene, which was prepared by the procedure of Hoogewerff and van Dorp.[3] Higher yields of substituted alanine derivative were ob-

(1) Abstracted from the M.S. thesis of George Kyryacos, The University of Miami, 1952.

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