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

BY MARSHALL KULKA

RECEIVED MARCH 18, 1953

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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[1] von P. Fritsch, *Ann.*, **286**, 1 (1895).

[2] R. H. F. Manske and M. Kulka, *Can. J. Research*, **B27**, 161 (1949).

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

BY GEORGE KYRYACOS[1] AND HARRY P. SCHULTZ

RECEIVED SEPTEMBER 3, 1952

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-

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

[2] C. Bacharach, THIS JOURNAL, **49**, 1522 (1927).

[3] S. Hoogewerff and W. van Dorp, *Rec. trav. chim.*, **8**, 1921 (1889).

tained when α-bromopropionic acid was condensed with 2-nitro-3-aminotoluene than were obtained with the hindered 2-amino-3-nitrotoluene.

The melting point curve for mixtures of 2-hydroxy-3,5- and -3,8-dimethylquinoxalines showed an eutectic at 214–217° for a 1:1 mixture of the two substances. Data from the ultraviolet absorption spectra of the two compounds are recorded in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA FOR 2-HYDROXY-3,5- AND -3,8-DIMETHYLQUINOXALINES

Compound	Solvent	Absorption maxima	
		Mμ	$\epsilon \times 10^{-3}$
2-Hydroxy-3,5-dimethylquinoxaline	95% ethanol	250.0	7.47
		255.5	7.47
		292.0	7.02
	0.1 *N* HCl	230.0	15.7
		256.0	10.2
	0.1 *N* NaOH	241.0	20.7
		300.0 (infl.)	3.55
2-Hydroxy-3,8-dimethylquinoxaline	95% ethanol	256.5	8.00
		291.0	5.91
	0.1 *N* HCl	230.0	16.4
		257.0	11.0
	0.1 *N* NaOH	242.0	21.2

Experimental Procedures

2-Amino-3-nitrotoluene.—This material was prepared in 39% yield by the nitration, hydrolysis and steam distillation of *o*-acetotoluidide according to the procedure used by Bacharach[2] for the nitration of *p*-acetotoluidide.

N-(2-Nitro-6-methylphenyl)-*dl*-α-alanine.—Into an 8-inch test-tube were placed 5.8 g. of 2-amino-3-nitrotoluene and 2.9 g. of α-bromopropionic acid. The reaction mixture was heated in a bath of water and sulfuric acid at 110° for 96 hours, then cooled and extracted with three 40-ml. portions of 15% ammonium hydroxide solution. The combined basic extracts were treated with 1 g. of activated charcoal, filtered through a bed of filter-aid, then slowly brought to *p*H 4 with 10% hydrochloric acid solution. A yellow-orange, powdery precipitate formed and was filtered. This purification process was repeated to give 0.7 g. (16.5%) of yellow N-(2-nitro-6-methylphenyl)-*dl*-α-alanine melting at 122–123°.

Anal. Calcd. for $C_{10}H_{12}O_4N_2$: N, 12.5. Found: N, 12.4, 12.4.

2-Hydroxy-3,5-dimethylquinoxaline.—A solution of 1.0 g. of N-(2-nitro-6-methylphenyl)-*dl*-α-alanine in 16 ml. of 95% ethanol was reduced over 0.1 g. of 5% palladium-charcoal catalyst[4] and 2 atmospheres of hydrogen for four hours at room temperature. The catalyst was removed and the solvent evaporated. The residue was dissolved in 10 ml. of 8% hydrogen peroxide and 10 ml. of 8% sodium hydroxide solution and heated on a steam-bath for two hours. A white precipitate of 2-hydroxy-3,5-dimethylquinoxaline was obtained when the oxidation mixture was cooled and brought to *p*H 4 with acetic acid. This precipitate was filtered and recrystallized from ethanol–water (2:1) to give 0.41 g. (52.5%) of white 2-hydroxy-3,5-dimethylquinoxaline melting at 256.5–257.5°. The product was sublimed with no loss at 180° (1 mm.) to give white, powdery crystals melting at the same temperature.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.97; H, 5.74; N, 16.1. Found: C, 69.37; H, 5.56; N, 16.0, 15.8.

2-Nitro-3-aminotoluene.—This material was prepared in 74% yield from 2-nitro-3-toluamide[5] according to the procedure of Hoogewerff and van Dorp.[3]

N-(2-Nitro-3-methylphenyl)-*dl*-α-alanine.—This material was prepared by heating together α-bromopropionic acid and 2-nitro-3-aminotoluene at 110° for 36 hours in a manner similar to that described for the preparation of N-(2-nitro-6-methylphenyl)-*dl*-α-alanine. A 36.5% yield of yellow N-(2-nitro-3-methylphenyl)-*dl*-α-alanine melting at 164–165° was obtained.

Anal. Calcd. for $C_{10}H_{12}O_4N_2$: N, 12.5. Found: N, 12.6, 12.4.

2-Hydroxy-3,8-dimethylquinoxaline.—The preparation and purification of this compound were executed in the same manner as that described for 2-hydroxy-3,5-dimethylquinoxaline. A 34% yield of white 2-hydroxy-3,5-dimethylquinoxaline melting at 256.5–257.5° was obtained.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.97; H, 5.74; N, 16.1. Found: C, 69.20; H, 5.60; N, 16.1, 16.3.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra data in Table I were obtained on a Beckman Model DU quartz spectrophotometer.

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Some Reactions of Tris-(*p*-nitrophenyl)-methyl Bromide

BY JOHN E. LEFFLER

RECEIVED JANUARY 26, 1953

In an attempt to prepare tris-(*p*-nitrophenyl)-methyl *p*-nitrobenzoate from the bromide by displacement with sodium *p*-nitrobenzoate in acetone it was found that the tris-(*p*-nitrophenyl)-methyl free radical was produced instead. It was then found that the radical is also produced by reaction in acetone with iodide ion, thiosulfate ion, bisulfite ion, thiocyanate ion, bicarbonate ion, pyridine and dimethylaniline. The radical is also formed by phenol in wet pyridine–dioxane and in benzene with phenol plus pyridine. The color produced by these reagents is due to radical rather than to methide ion, since it is not discharged by strong acids but is discharged by oxygen with the formation of the expected peroxide. The reaction with sodium iodide gives iodine in nearly quantitative yield. Radical formation by sodium iodide is not prevented by the carbanion traps alcohol, acetic acid and *p*-nitrobenzaldehyde. Neither the carbinol, the *p*-nitrobenzoate, nor the anisate dissociates appreciably into radicals.

In contrast to its reactivity with negative ions and bases in acetone, tris-(*p*-nitrophenyl)-methyl bromide does not give any radical on treatment at room temperature with hydrazine sulfate, hydroxylamine hydrochloride, anisic hydrazide, sodium nitrite, or weak acids in acetone (acetone enol).

Kinetics of the Reaction with Sodium Iodide in Acetone.—The reaction is markedly slowed down by alcohol, does not take place with mercuric iodide, and is much slower with a mixture of mercuric and sodium iodides than with the latter alone. The reaction with sodium iodide in the presence of air can be followed by the light absorption due to the iodine for about one half-life. It is somewhat greater than first order with respect to sodium iodide and the deviation from first-order kinetics is not a general salt effect since it is only partially corrected by adding sodium perchlorate. The reaction is somewhat *less* than first order with respect to the bromide as is shown by the trend in second-order rate constants of Figs. 1–3. This effect is similar to that observed by Nixon and