[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

# Quinoxaline Studies. I. The Preparation of 2-Hydroxy-3-methyl-6-methoxyquinoxaline and 2-Hydroxy-3-methyl-7-methoxyquinoxaline

BY SEYMOUR YOLLES[1] AND HARRY P. SCHULTZ

Hinsberg[2] asserted that reaction of 3,4-diaminoanisole with pyruvic acid gave either 2-hydroxy-3-methyl-6-methoxyquinoxaline or 2-hydroxy-3-methyl-7-methoxyquinoxaline. The purpose of this investigation was to prepare each of the above quinoxalines by unequivocal procedures and to compare their properties with those of the material synthesized by Hinsberg.

The synthesis of 2-hydroxy-3-methyl-7-methoxyquinoxaline utilized 3-nitro-4-aminoanisole as the starting material. The condensation of 3-nitro-4-aminoanisole with α-bromopropionic acid to give N-(2-nitro-4-methoxyphenyl)-*dl*-α-alanine necessitated carefully controlled temperature. Reduction of N-(2-nitro-4-methoxyphenyl)-*dl*-α-alanine proceeded equally well with either zinc and acetic acid, or hydrogen over Raney nickel catalyst. The intermediate reduction product, 2 - hydroxy - 3 - methyl - 7 - methoxydihydroquinoxaline, was not isolated, but air-oxidized in basic solution to 2-hydroxy-3-methyl-7-methoxyquinoxaline.

The first synthesis of 2-hydroxy-3-methyl-6-methoxyquinoxaline paralleled the preparation of 2 - hydroxy - 3 - methyl - 7 - methoxyquinoxaline. Reaction of 3-amino-4-nitroanisole with α-bromopropionic acid gave N-(2-nitro-5-methoxyphenyl)-*dl*-α-alanine. After reduction of the N-(2-nitro-5-methoxyphenyl)-*dl*-α-alanine was completed, the intermediate dihydroquinoxaline was air-oxidized to 2-hydroxy-3-methyl-6-methoxyquinoxaline.

An alternate route for the synthesis of 2-hydroxy - 3 - methyl - 6 - methoxyquinoxaline was sought, to avoid using the laboriously prepared 3-amino-4-nitroanisole as a starting material. A second preparation of 2-hydroxy-3-methyl-6-methoxyquinoxaline was achieved, beginning with 3-nitro-4-acetamidoanisole.[3] The known 3-amino-4-acetamidoanisole, prepared from 3-nitro-4-acetamidoanisole, was treated with ethyl α-bromopropionate to give the ethyl ester of N-(2 - acetamido - 4 - methoxyphenyl) - *dl* - α - alanine. Acid hydrolysis of the latter compound removed the protecting acetyl group, permitting cyclization. The probable intermediate, 2-hydroxy-3-methyl-6-methoxydihydroquinoxaline, was oxidized by air to 2-hydroxy-3-methyl-6-methoxyquinoxaline.

Figure 1 is the melting point curve for various mixtures of 2-hydroxy-3-methyl-6-methoxyquinoxaline and 2-hydroxy-3-methyl-7-methoxyquinoxaline; an eutectic point was indicated at 193° for an equimolecular mixture of the two isomers. Figure 2 shows the ultraviolet absorption spectra of the two isomers.

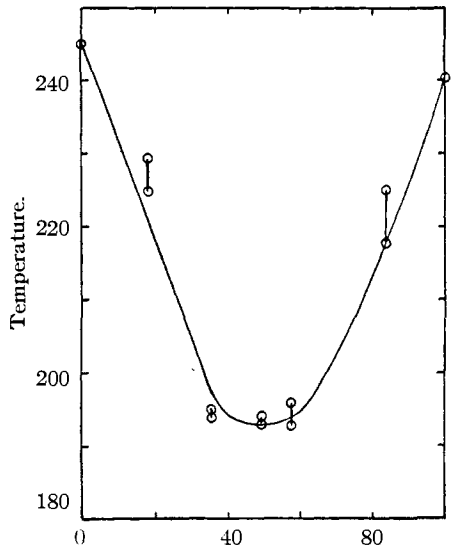


Fig. 1.—Melting point–composition curve of 2-hydroxy-3-methyl-6-methoxyquinoxaline and 2-hydroxy-3-methyl-7-methoxyquinoxaline; melting point range of each mixture indicated by O—O.

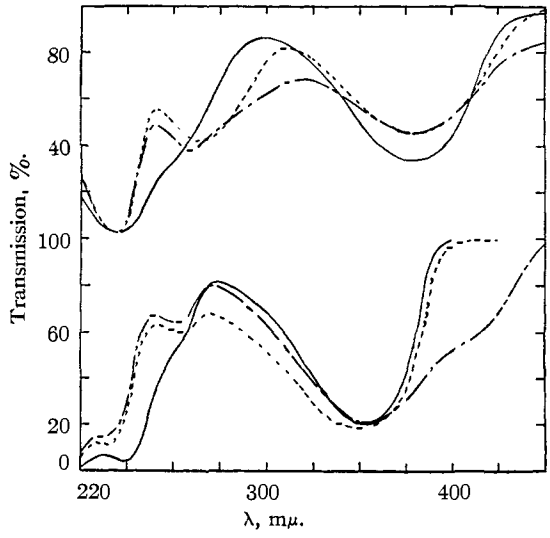


Fig. 2.—Ultraviolet absorption spectra of 2-hydroxy-3-methyl-6-methoxyquinoxaline, above; 2-hydroxy-3-methyl-7-methoxyquinoxaline, below; - - - - -, 95% ethanol; —, 0.1 *N* sodium hydroxide; —·—·—, 0.1 *N* hydrochloric acid.

(1) Abstracted in part from a thesis by Seymour Yolles, presented to the Graduate Faculty of the University of Miami, in partial fulfillment of the requirements for the degree of Master of Science in chemistry, September, 1948.

(2) Hinsberg, *Ann.*, **292**, 249 (1896).

The melting points of neither 2-hydroxy-3-methyl-6-methoxyquinoxaline, nor 2-hydroxy-3-methyl-7-methoxyquinoxaline agreed with that of the compound prepared by Hinsberg[2] (m. p. 197°); hence, a preparation was carried out using Hinsberg's procedure, wherein 3,4-diaminoanisole was treated with pyruvic acid. The Hinsberg product obtained in this Laboratory melted at 193°, indicating that Hinsberg undoubtedly prepared a mixture of the two isomers. Exhaustive fractional crystallization of the product prepared by Hinsberg's procedure resulted in isolation of a small amount of the slightly less alcohol-soluble 2-hydroxy-3-methyl-6-methoxyquinoxaline.

## Experimental Procedures

**N-(2-Nitro-4-methoxyphenyl)-*dl*-α-alanine.**—A mixture of 16.8 g. (0.1 mole) of 3-nitro-4-aminoanisole[3] and 7.65 g. (0.05 mole) of α-bromopropionic acid[4] was heated for twenty-four hours at 100–105°. The cooled melt was extracted alternately with three 5-ml. portions of 1:1 ammonium hydroxide and three 15-ml. portions of water. The deep red extract was first passed through a column of charcoal and Super-cel, then warmed to 60°, and acidified with acetic acid. Dilute (10%) hydrochloric acid was added dropwise until a red oil precipitated. After cooling and scratching, the oil solidified to give 5.4 g. (46% yield) of orange prisms melting at 137–139°. Material for analysis was obtained by repeating the above purification, m. p. 135–135.5°.

*Anal.* Calcd. for $C_{10}H_{12}O_5N_2$: N, 11.7. Found: N, 11.3.

**2-Hydroxy-3-methyl-7-methoxyquinoxaline.**—A solution of 1.1 g. (0.0046 mole) of N-(2-nitro-4-methoxyphenyl)-*dl*-α-alanine in 20 ml. of ethanol was reduced with hydrogen over W-2 Raney nickel catalyst[5] at 60° and atmospheric pressure until the theoretical quantity of hydrogen had been taken up. Catalyst and solvent were removed, and the brown residue was placed in 10 ml. of 5% sodium hydroxide solution and oxidized by drawing air through the solution for four hours at 70–80°. After four hours, all solid had dissolved, and the dark brown solution was filtered through a column of charcoal and Super-cel, then brought to *p*H 4 with dilute acetic acid to give a white precipitate of 2-hydroxy-3-methyl-7-methoxyquinoxaline that weighed 0.42 g. (48% yield) and melted at 236–238°. The material was recrystallized from ethanol to constant melting point with no appreciable loss of product, m. p. 240–240.5°.

*Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.2; H, 5.32; N, 14.7. Found: C, 63.1; H, 5.41; N, 14.8.

Reduction of N-(2-nitro-4-methoxyphenyl)-*dl*-α-alanine with zinc dust and acetic acid, followed by air oxidation, also gave 2-hydroxy-3-methyl-7-methoxyquinoxaline, m. p. 240–240.5°.

**3-Amino-4-nitroanisole.**—N-Acetyl-*m*-anisidine was prepared in 83% yield by methylating N-acetyl-*m*-aminophenol[6] with dimethyl sulfate. Twenty grams (0.12 mole) of N-acetyl-*m*-anisidine was slowly added to a cooled, stirred solution of 100 ml. of nitric acid (sp. gr. 1.42), holding the temperature below 0°. After all the solid had been added, and the reaction mixture had warmed to room temperature, it was poured onto 200 g. of ice and kept at 10° for twenty-four hours. The dark green mixture was filtered, washed, and dried to give 15.4 g. (66% yield) of mixed nitro-isomers of N-acetyl-*m*-anisidine.

The crude, dry nitro compounds were mixed with 10 g. of Super-cel and the 3-acetamido-4-nitroanisole extracted with petroleum ether (b. p. 30–60°) in a Soxhlet extractor. The average yield of 3-acetamido-4-nitroanisole obtained from several runs was 50% of the weight of crude, mixed nitro compounds.

3-Acetamido-4-nitroanisole was hydrolyzed by boiling in 5% hydrochloric acid for two hours to give a 90% yield of material, m. p. 126–128°. After recrystallization from ethanol, the 3-amino-4-nitroanisole melted at 129–130.5°. The melting point previously reported[6] was 129°.

**N-(2-Nitro-5-methoxyphenyl)-*dl*-α-alanine.**—This material was prepared by treating 3-amino-4-nitroanisole with α-bromopropionic acid according to the procedure used to synthesize N-(2-nitro-4-methoxyphenyl)-*dl*-α-alanine. The yield of yellow powder was 52%, m. p. 140–142°. The compound was purified by solution in 1:1 ammonium hydroxide, twice passed through a column of charcoal and filter-aid, and reprecipitated with dilute hydrochloric acid; m. p. 149–150°.

*Anal.* Calcd. for $C_{10}H_{12}O_5N_2$: N, 11.7. Found: N, 11.2.

**2-Hydroxy-3-methyl-6-methoxyquinoxaline. A. From N-(2-Nitro-5-methoxyphenyl)-*dl*-α-alanine.**—A solution of 2.4 g. (0.01 mole) of N-(2-nitro-5-methoxyphenyl)-*dl*-α-alanine in 40 ml. of ethanol was reduced with hydrogen over W-2 Raney nickel catalyst at 60° and atmospheric pressure until the theoretical quantity of hydrogen had been absorbed. Catalyst and solvent were removed, and the brown residue was placed in 10 ml. of 5% sodium hydroxide and oxidized by drawing air through the solution for twelve hours at 70–80°. The solution was cooled and brought to *p*H 7 with 10% hydrochloric acid, then evaporated completely to dryness. The black, crystalline residue was sublimed at 200° (10 mm.) to give 0.7 g. (37% yield) of light yellow needles, m. p. 245–245.2°. This material was dissolved in 5 ml. of 2.5 *N* sodium hydroxide, passed through a column of filter-aid and charcoal, then reprecipitated with dilute hydrochloric acid. The purification was completed by twice recrystallizing the product from ethanol, with bone-blacking, to give 0.35 g. of light yellow needles, m. p. 245–245.2°. A second crop of 0.2 g. of product was obtained from the mother liquors; m. p. 245–245.2°.

*Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.2; H, 5.32; N, 14.7. Found: C, 63.1; H, 5.26; N, 14.8.

**Ethyl Ester of N-(2-Acetamido-4-methoxyphenyl)-*dl*-α-alanine.**—A solution of 10.8 g. (0.06 mole) of 3-amino-4-acetamidoanisole,[7] 5.43 g. (3.9 ml., 0.03 mole) of ethyl α-bromopropionate,[8] 19.2 ml. of ethanol and 15 ml. of water was heated on a steam-bath for four hours. The brown solution was cooled to 5°, scratched to initiate crystallization, and kept at 10° for twenty-four hours. The white precipitate was filtered to give 4 g. of white, fluffy needles, m. p. 119–120°. Addition of 50 ml. of water to the filtrate, plus cooling, brought down 1.7 g. more of product, m. p. 115–119°. Total yield was 5.7 g. (68% yield). Material for analysis was recrystallized from benzene, m. p. 119–120°.

*Anal.* Calcd. for $C_{14}H_{20}O_4N_2$: N, 10.0. Found: N, 9.89.

**2-Hydroxy-3-methyl-6-methoxyquinoxaline. B. From the Ethyl Ester of N-(2-Acetamido-4-methoxyphenyl)-*dl*-α-alanine.**—Into 10 ml. of 10% hydrochloric acid was placed 2.8 g. (0.01 mole) of the ethyl ester of N-(2-acetamido-4-methoxyphenyl)-*dl*-α-alanine. The solution was boiled for two hours, cooled and neutralized with 3 g. of sodium hydroxide; air was then drawn through the warm solution at 70–80° for twelve hours. After the solution cooled, it was adjusted to *p*H 4 with acetic and hydrochloric acids. The yellow precipitate was filtered, rinsed and dried to give 0.3 g. of 2-hydroxy-3-methyl-6-methoxyquinoxaline, m. p. 240–241°. This product was recrystal-

(3) "Organic Syntheses," Vol. XXV, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 78.

(4) Eastman Kodak Co. White Label material was used without further purification.

(5) "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

(6) Reverdin, *Ber.*, **46**, 4071 (1913).

(7) Izmail'shii and Simonov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1588 (1940); *C. A.*, **35**, 2871 (1941).

(8) Zelinsky, *Ber.*, **20**, 2026 (1887).

lized twice with bone-blacking from ethanol to give 0.25 g. (13% yield) of light yellow, fluffy needles, m. p. 243.5–244.5°. The mixed melting point and ultraviolet absorption spectra proved the product to be identical with the 2-hydroxy-3-methyl-6-methoxyquinoxaline prepared by method A, above.

**Preparation of Hinsberg's Mixture of 2-Hydroxy-3-methyl-6-methoxyquinoxaline and 2-Hydroxy-3-methyl-7-methoxyquinoxaline.**—A solution of 5.05 g. (0.03 mole) of 3-nitro-4-aminoanisole in 20 ml. of ethanol was reduced with hydrogen over W-2 Raney nickel catalyst at room temperature and pressure until the theoretical amount of hydrogen had been taken up. The alcoholic solution of 3,4-diaminoanisole was filtered into a solution of 2.9 g. (0.033 mole) of pyruvic acid[9] in 10 ml. of ethanol. After the brown solution had been refluxed for thirty minutes, the alcohol was concentrated to a small volume, and the product crystallized out to give 5.05 g. of dark brown material. The product was dissolved in 10 ml. of 5% sodium hydroxide solution, passed through a column of charcoal and Super-cel, and reprecipitated with acetic acid. The light brown product was recrystallized from ethanol to give 3.1 g. (54% yield) of light tan crystals, m. p. 192–193°. The melting point reported by Hinsberg[2] was 197°. (Reference to Fig. 1 shows that a 1:1 mixture of analytical samples of 2-hydroxy-3-methyl-6-methoxyquinoxaline and 2-hydroxy-3-methyl-7-methoxyquinoxaline melted at 193–194°.) This material was exhaustively recrystallized from 95% ethanol to give as the least soluble component 0.1 g. of the amphoteric, light-yellow crystals of 2-hydroxy-3-methyl-6-methoxyquinoxaline, m. p. 241–244°.

(9) Pyruvic acid obtained from Paragon Chemical Company was used without further purification.

*Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: N, 14.7. Found: N, 14.8.

Mixed melting points proved this material to be identical with the 2-hydroxy-3-methyl-6-methoxyquinoxalines prepared by methods A and B, above.

**Absorption Spectra.**—The ultraviolet absorption spectra in Fig. 2 were obtained on a Beckman Model DU Quartz Spectrophotometer. All curves were run on analytical material at concentrations of 10 mg./l. of solvent; width of quartz sample cell was 1.003 cm.

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## Summary

Starting with 3-amino-4-nitroanisole and also 3-nitro-4-acetamidoanisole, 2-hydroxy-3-methyl-6-methoxyquinoxaline was prepared by two unequivocal procedures.

2-Hydroxy-3-methyl-7-methoxyquinoxaline was prepared by an unequivocal procedure, starting with 3-nitro-4-aminoanisole.

The product of the direct condensation of 3,4-diaminoanisole with pyruvic acid was shown to be an equimolecular mixture of 2-hydroxy-3-methyl-6-methoxyquinoxaline and 2-hydroxy-3-methyl-7-methoxyquinoxaline.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

# Preparation of Some Polymerizable Esters of 10-Hendecenoic (Undecylenic) Acid

BY E. F. JORDAN, JR., AND DANIEL SWERN

As an extension of our work on the relationship between the structure of long-chain unsaturated esters and their polymerizability,[2,3] we have prepared a series of esters of 10-hendecenoic (undecylenic) acid with seven unsaturated alcohols, and have briefly investigated the polymerizability of the more reactive products. A search of the literature revealed that none of the esters we planned to prepare had been described, although the vinyl[4] and allyl[5] esters have been mentioned in patents.

Vinyl 10-hendecenoate was prepared by acidolysis of vinyl acetate with 10-hendecenoic acid in the presence of mercuric acetate and 100% sulfuric acid as catalysts.[2,3,6] The allyl, 2-chloroallyl, crotyl and 3-buten-2-yl esters were prepared by direct esterification of 10-hendecenoic acid with the appropriate alcohol, naphthalene-2-sulfonic acid being employed as the catalyst and benzene as an entraining agent to remove the water formed during the reaction.[2,3,7] The methallyl and furfuryl esters were prepared by the alcoholysis of methyl 10-hendecenoate with the appropriate alcohol, the corresponding sodium alcoholate being employed as catalyst.[2,3,7,8] The yields and characteristics of the esters are summarized in Table I. In general, yields were high. The products were colorless, odorless, water-insoluble, high-boiling liquids, with the exception of furfuryl 10-hendecenoate, which was pale yellow.

To obtain information regarding their polymerizability the vinyl, 2-chloroallyl, allyl and methallyl esters were heated with small quantities of benzoyl peroxide. Vinyl 10-hendecenoate was heated at 100° in the presence of 1% of benzoyl peroxide as initiator. In less than one hour, considerable insoluble material had formed, and within two hours the product appeared to be completely converted to a soft, crumbly, transparent gel. At 80°, approximately sixteen hours was required to obtain complete gelation. Gelation was considered complete when no liquid could be seen in the test tube in which the polymerization was being carried

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Swern, Billen and Knight, THIS JOURNAL, **69**, 2439 (1947).

(3) Swern and Jordan, *ibid.*, **70**, 2334 (1948).

(4) Imperial Chemical Industries, Ltd., British Patent 581,501 (1946).

(5) Renault, French Patent 846,063 (1939).

(6) Toussaint and MacDowell, U. S. Patent 2,299,862 (1942).

(7) Swern and Jordan, THIS JOURNAL, **67**, 902 (1945).

(8) Swern, Jordan and Knight, *ibid.*, **68**, 1673 (1946).