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Quinoxaline Studies. IV. The Preparation of *dl*-2,6-Dimethyl-1,2,3,4-tetrahydroquinoxaline and *dl*-2,7-Dimethyl-1,2,3,4-tetrahydroquinoxaline

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Hinsberg[2] condensed 3,4-diaminotoluene with chloroacetone to give a substance which was either a mixture of 2,6- and 2,7-dimethylquinoxaline, or one of the pure compounds. The purpose of this investigation was to determine whether the Hinsberg condensation of chloroacetone with 3,4-diaminotoluene gave both of the above isomers, or only one.

All attempts in this Laboratory to synthesize either 2,6- or 2,7-dimethylquinoxaline failed; hence, an indirect proof of the identity of Hinsberg's compound was achieved in the following manner. Both 2-hydroxy-3,6- and -3,7-dimethylquinoxaline had been previously prepared unequivocally by Marks and Schultz[3]; replacement of the 2-hydroxy group in these two known compounds with a hydrogen atom should have given the desired 2,6- and 2,7-dimethylquinoxalines. This attempt, produced instead the tetrahydro derivatives of 2,6- and 2,7-dimethylquinoxaline.

Since the preparations of 2-hydroxy-3,6- and -3,7-dimethylquinoxaline were tedious, initial experimental work was carried out on 2-hydroxy-3-methylquinoxaline. Treatment of this compound with phosphorus oxychloride gave 2-chloro-3-methylquinoxaline. Catalytic reduction of the chloro derivative over palladium-on-charcoal gave *dl*-2-methyl-1,2,3,4-tetrahydroquinoxaline, previously prepared by Ris[4] by a different method.

In an analogous fashion 2-hydroxy-3,6- and -3,7-dimethylquinoxaline were transformed into *dl*-2,7- and -2,6-dimethyltetrahydroquinoxaline, respectively. In the course of this portion of the work a new synthesis of 2-hydroxy-3,6-dimethylquinoxaline, superior to that of Marks and Schultz,[3] was developed. This was achieved by condensation of 3-amino-4-nitrotoluene with α-bromopropionic acid to give N-(2-nitro-5-methylphenyl)-*dl*-α-alanine; reductive cyclization and subsequent oxidation gave the known 2-hydroxy-3,6-dimethylquinoxaline.

A mixed melting point curve (Fig. 1) of the two pure isomers, *dl*-2,6- and -2,7-dimethyl-1,2,3,4-tetrahydroquinoxaline, indicated a eutectic, m.p. 88–89° at a 1:1 composition of isomers. The ultraviolet absorption spectra of these two compounds were very similar; these data are summarized in Table I.

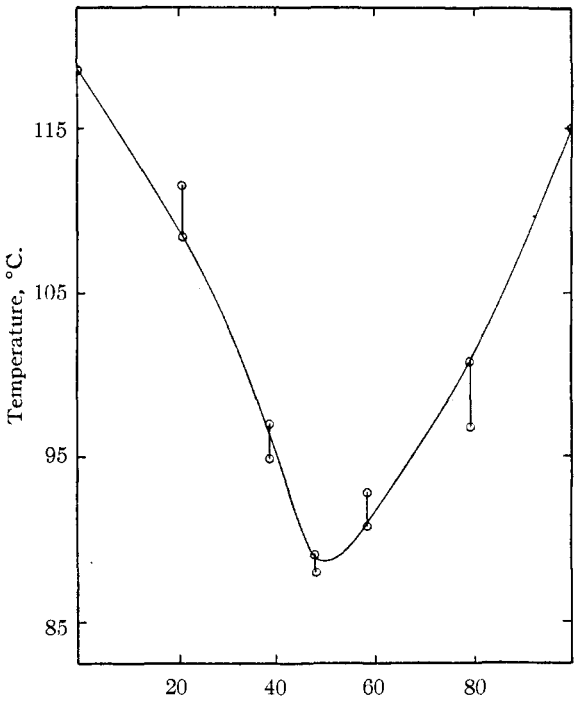

Fig. 1.—Melting point–composition curve of *dl*-2,6- and 2,7-dimethyl-1,2,3,4-tetrahydroquinoxaline; melting point range of each mixture indicated by O–O.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF *dl*-2,6-DIMETHYL-1,2,3,4-TETRAHYDROQUINOXALINE AND *dl*-2,7-DIMETHYL-1,2,3,4-TETRAHYDROQUINOXALINE

1,2,3,4-Tetrahydroquinoxaline	Solvent	Maxima mμ	Maxima ε × 10⁻³
dl-2,6-Dimethyl-	Ethanol, 95%	256	4.95
		314	3.83
	HCl, 0.1 *N*	243	5.16
		294	1.31
dl-2,7-Dimethyl-	Ethanol, 95%	256	5.19
		314	4.27
	HCl, 0.1 *N*	244	4.26
		295	0.92

Hinsberg's mixture was prepared by condensing 3,4-diaminotoluene with chloroacetone. The product, collected over a wide boiling range, was reduced to give a mixture of *dl*-2,6- and -2,7-dimethyl-1,2,3,4-tetrahydroquinoxaline. The melting point of this purified mixture was 88–89°, about 30° lower than that of either of the pure isomers, comparing exactly with the melting point of the eutectic obtained by mixing the pure isomers together in a 1:1 ratio. Hence, a mixture of 2,6- and 2,7-dimethylquinoxaline was indicated to exist in Hinsberg's mixture. Attempts to achieve separation by fractional crystallization of the two isomers in the reduced Hinsberg mixture failed.

Experimental Procedures

2-Chloro-3-methylquinoxaline.—A solution of 2.0 g. of 2-hydroxy-3-methylquinoxaline[2] in 90 ml. of phosphorus oxychloride was refluxed for one-half hour. The excess phosphorus oxychloride was distilled off, and the residue

(1) Abstracted in part from a thesis by Morton Munk, 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, January, 1952.

(2) O. Hinsberg, *Ann.*, **237**, 368 (1887).

(3) H. B. Marks and H. P. Schultz, THIS JOURNAL, **73**, 1368 (1951).

(4) C. Ris, *Ber.*, **21**, 382 (1888).

poured into ice-water to decompose the remaining phosphorus oxychloride. The water solution was extracted three times with ether; after the ether was dried over magnesium sulfate and evaporated, leaving crude 2-chloro-3-methylquinoxaline, the chloro compound was recrystallized from ethanol–water (1:1) to give 1.1 g. (54% yield) of light pink platelets of 2-chloro-3-methylquinoxaline melting at 90–92°.

Anal. Calcd. for $C_9H_7N_2Cl$: N, 15.7. Found: N, 15.7, 15.5.

***dl*-2-Methyl-1,2,3,4-tetrahydroquinoxaline.**—A solution of 2.0 g. of 2-chloro-3-methylquinoxaline and 0.5 g. of anhydrous sodium acetate in 25 ml. of glacial acetic acid was reduced over 0.2 g. of 5% palladium chloride–charcoal catalyst[5] at 60° and 2 atm. of hydrogen for four hours. After the catalyst was removed, the solution was evaporated to 10 ml. on a steam-bath. Fifty per cent. sodium hydroxide solution was added in excess, and the solid mass was triturated with ether three times; the ether solution was then dried over solid sodium hydroxide, evaporated, and the residue was recrystallized twice from petroleum ether (b.p. 60–90°) to give 1.1 g. (65% yield) of *dl*-2-methyl-1,2,3,4-tetrahydroquinoxaline melting at 70–71°. Ris[4] obtained a melting point of 72° for *dl*-2-methyl-1,2,3,4-tetrahydroquinoxaline prepared by a different method. *dl*-2-Methyl-1,2,3,4-tetrahydroquinoxaline melting at 71–72° was also prepared in this Laboratory by reduction of 2-methylquinoxaline[6] over palladium–charcoal catalyst. There was no depression of the melting point when the *dl*-2-methyl-1,2,3,4-tetrahydroquinoxalines prepared by the two different methods were mixed.

N-(2-Nitro-5-methylphenyl)-*dl*-α-alanine.—Seven and six-tenths grams of α-bromopropionic acid and 15 g. of 3-amino-4-nitrotoluene[7] were heated on a steam-bath for 96 hours in a flask fitted with a cold finger condenser. The reaction mixture was cooled and extracted three times with 40-ml. portions of 15% ammonium hydroxide solution. The red, basic solution was heated with 1.0 g. of charcoal and filtered to clarify the solution. This basic solution was brought to *p*H 4 with 10% hydrochloric acid, giving an orange precipitate which was filtered off. The above process was repeated twice again to give 4.4 g. (39% yield) of N-(2-nitro-5-methylphenyl)-*dl*-α-alanine melting at 127–128°.

Anal. Calcd. for $C_{10}H_{12}O_4N_2$: N, 12.5. Found: N, 12.4, 12.3.

2-Hydroxy-3,6-dimethylquinoxaline.—A solution of 2.5 g. of N-(2-nitro-5-methylphenyl)-*dl*-α-alanine in 40 ml. of ethanol was reduced over a 5% palladium chloride–charcoal catalyst at 30° and 2 atm. of hydrogen for four hours. After the catalyst was removed, the ethanol was evaporated from a steam-bath. The residue was taken up in 25 ml. of 8% hydrogen peroxide and 25 ml. of 8% sodium hydroxide solutions and heated on a steam-bath for two hours. After the basic solution was brought to *p*H 4 with acetic acid, the precipitate was filtered off and recrystallized from ethanol–water (4:1) to give 1.6 g. (82% yield) of 2-hydroxy-3,6-dimethylquinoxaline melting at 248–249°. The product prepared by Marks and Schultz[3] melted at 248–249° after recrystallization; 254° after sublimation. A mixed melting point of these compounds gave no depression.

2-Chloro-3,6-dimethylquinoxaline.—2-Hydroxy-3,6-dimethylquinoxaline was transformed into 2-chloro-3,6-dimethylquinoxaline by the method described above under 2-chloro-3-methylquinoxaline in 66% yield, m.p. 76–77°.

Anal. Calcd. for $C_{10}H_9N_2Cl$: N, 14.5. Found: N, 14.4, 14.5.

***dl*-2,7-Dimethyl-1,2,3,4-tetrahydroquinoxaline.**—This was prepared in 72% yield by reduction of 2-chloro-3,6-dimethylquinoxaline, m.p. 118–118.5°.

Anal. Calcd. for $C_{10}H_{14}N_2$: N, 17.3. Found: N, 17.0, 17.1.

2-Chloro-3,7-dimethylquinoxaline.—2-Hydroxy-3,7-dimethylquinoxaline[3] gave 2-chloro-3,7-dimethylquinoxaline in 72% yield, m.p. 86–87°.

Anal. Calcd. for $C_{10}H_9N_2Cl$: N, 14.5. Found: N, 14.4, 14.3.

***dl*-2,6-Dimethyl-1,2,3,4-tetrahydroquinoxaline.**—This was prepared by reduction of 2-chloro-3,7-dimethylquinoxaline in 60% yield, m.p. 115–115.5°.

Anal. Calcd. for $C_{10}H_{14}N_2$: N, 17.3. Found: N, 17.1, 17.1.

A 1:1 mixture of *dl*-2,6- and 2,7-dimethyl-1,2,3,4-tetrahydroquinoxaline was found to melt at 88–89°.

Hinsberg's Mixture of 2,6- and 2,7-Dimethylquinoxaline.—3,4-Diaminotoluene was condensed with chloroacetone according to Hinsberg's procedure,[2] the reaction product fraction boiling between 265–285° finally being collected. Hinsberg collected the fraction boiling 265–270°. The Hinsberg mixture was reduced over 5% palladium chloride–charcoal at 60° and 2 atm. of hydrogen for four hours. The reduction product was worked up in a manner similar to those procedures cited above, giving a 48% yield of a mixture of *dl*-2,6- and -2,7-dimethyl-1,2,3,4-tetrahydroquinoxaline which melted at 88–89°. No change of the melting point was observed when this was mixed with a synthetic 1:1 mixture of the pure isomers. Repeated recrystallizations from petroleum ether (b.p. 60–90°) did not change the melting point.

Anal. Calcd. for $C_{10}H_{14}N_2$: N, 17.3. Found: N, 17.2, 17.2.

Spectrophotometric Data.—The ultraviolet absorption spectra were obtained on a Beckman model DU quartz spectrophotometer. All curves were run on analytical samples at concentrations of 10 mg./l. of solvent.

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Synthesis of Fumaric Acid-2-C^{14} and Maleic Anhydride-2-C^{14} [1]

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In the course of our work on organic and biochemical reaction mechanisms, it was found necessary to develop a useful method for synthesizing fumaric acid-2-C^{14} and maleic anhydride-2-C^{14} on a small scale.

The synthesis of methine-labeled fumaric acid is a six-step process. When the reaction is carried out on a 10-millimole scale the yield of fumaric acid-2-C^{14} is 76% based on $C^{14}O_2$, whereas on a 2-millimole scale the yield of acid is 63%. Briefly outlined the procedure is: (a) conversion of $C^{14}O_2$ to methylene-labeled succinic acid (four steps) in an 89% yield by modification[2] of the method recently described by Kushner and Weinhouse[3]; (b) dibromination of succinic acid-2-C^{14}; and (c) reaction of *meso*-dibromosuccinic acid-2-C^{14} with an acetone solution of sodium iodide to furnish fumaric acid-2-C^{14}.

Maleic anhydride-2-C^{14} is readily obtained from fumaric acid-2-C^{14} and phosphorus pentoxide in 96% yield under carefully controlled conditions. In a forthcoming paper the preparation of ring-labeled benzoic acid from maleic anhydride-2-C^{14} and butadiene will be described.

Fumaric acid-1-C^{14} and maleic anhydride-1-C^{14} can be made from carboxyl-labeled succinic acid[3] by use of the procedure described above.

The *meso*-dibromosuccinic acid-2-C^{14} should also be a useful intermediate in the synthesis of such

(1) This work was performed under Atomic Energy Commission Contract AT-(40-1)-282.
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(3) M. Kushner and S. Weinhouse, THIS JOURNAL, **71**, 3558 (1949).