[CONTRIBUTION FROM THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE RESEARCH LABORATORY OF AMERICAN HOME PRODUCTS CORP., INTERNATIONAL VITAMIN DIVISION]

7-Methoxy-5-aminoquinoxaline and 7-Methoxy-5-diethylaminoalkylamino-quinoxalines

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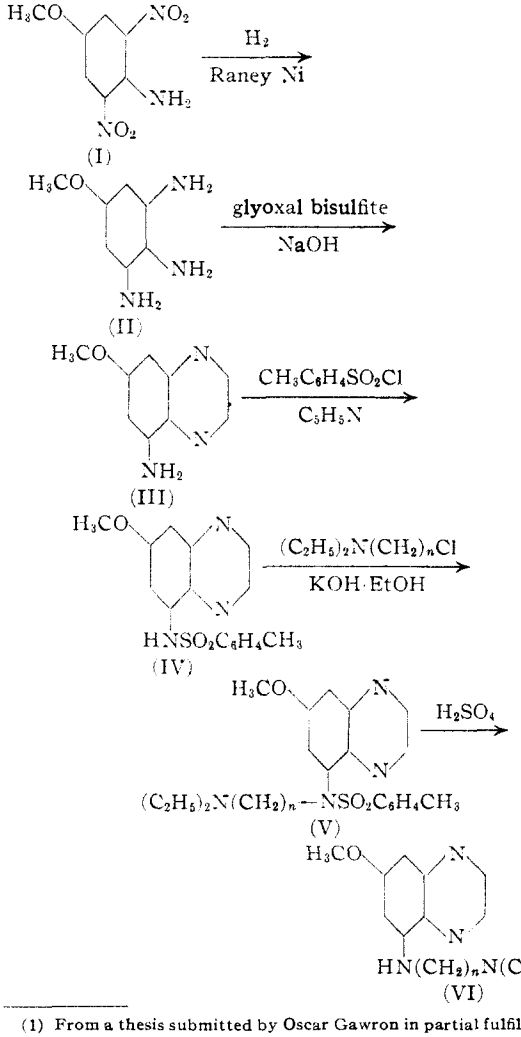
It seemed to us of interest from several points of view to attempt at this time the synthesis of aminoquinoxalines possessing hydroxy or methoxy substituents and also the synthesis of diethylaminoalkyl derivatives of the aforementioned quinoxalines.

In this publication we wish to report the synthesis of 7-methoxy-5-aminoquinoxaline (III), 7-methoxy-5-(β-diethylaminoethyl)-aminoquinoxaline (VI, $n = 2$) and 7-methoxy-5-(γ-diethylaminopropyl)-aminoquinoxaline (VI, $n = 3$).

The accompanying flow chart, starting with 3,5-dinitro-4-aminoanisole (I), illustrates the reactions by which we achieved this synthesis.



(1) From a thesis submitted by Oscar Gawron in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, Polytechnic Institute of Brooklyn, 1944.

The catalytic reduction[1a] of 3,5-dinitro-4-aminoanisole (I) in dioxane proceeded rapidly at an initial pressure of 600 pounds and an initial temperature of 100° using 2 to 3 g. of moist Raney nickel catalyst per gram of starting material. No promoter[2] was found necessary and the product, 3,4,5-triaminoanisole (II), was isolated as the dihydrochloride. The condensation with glyoxal[3] to 7-methoxy-5-aminoquinoxaline (III) was effected in dilute aqueous solution, adjusting the *p*H to 5.5–7.0 before addition of glyoxal bisulfite. Heating the amine (III) with the hydrochloride of β-diethylaminoethyl chloride alone or with alcohol as a solvent resulted in a great deal of tar formation and since no product could be isolated condensation was effected by heating the potassium salt of the *p*-toluenesulfonyl derivative[4] (IV) with the chloro base in alcohol. The 7-methoxy-5-(β-diethylaminoethyl)-5-(*p*-toluenesulfonyl)-aminoquinoxaline (V, $n = 2$) and the corresponding propyl compound (V, $n = 3$) were easily hydrolyzed with concentrated sulfuric acid to the desired compounds.

The starting material for this synthesis, 3,5-dinitro-4-aminoanisole (I), was prepared by nitrating *p*-diacetylaminophenol to 3,5-dinitro-*p*-diacetylaminophenol,[5] saponifying with aqueous sodium carbonate to 3,5-dinitro-4-acetylaminophenol,[6] methylating[7] with methyl iodide and silver oxide, and hydrolyzing with concentrated sulfuric acid to the required 3,5-dinitro-4-aminoanisole (I).

The literature procedures for these reactions were followed except in the case of the nitration. For the nitration of *p*-diacetylaminophenol, Reverdin and his co-workers[5,6] employed nitric acid, density 1.52 and 1.525, the more concentrated giving the better yield. Using nitric acid of this density and also red fuming nitric acid, density 1.59 to 1.60, we obtained under varying conditions of temperature and concentration only the 3-mononitro derivative of *p*-diacetylaminophenol. The 3,5-dinitro-*p*-diacetylaminophenol was finally obtained by nitrating either *p*-diacetylaminophenol or the 3-nitro derivative with a 2 to 1 molar mixture of fuming nitric acid and acetic anhydride.

β-Diethylaminoethyl chloride and γ-diethyl-

(1a) Voris and Spoerri, THIS JOURNAL, **60**, 935 (1938).
(2) Lieber and Smith, *ibid.*, **58**, 1417 (1936).
(3) Autenrieth and Hinsberg, *Ber.*, **25**, 492 (1892).
(4) Simonov, *J. Gen. Chem.* (U. S. S. R.), **10**, 1588 (1940); *C. A.*, **35**, 2870 (1941).
(5) Reverdin and Dresel, *Ber.*, **38**, 1593 (1905).
(6) Reverdin and Bucky, *ibid.*, **39**, 2679 (1906).
(7) Meldola and Stephens, *J. Chem. Soc.*, **87**, 1199 (1905).

aminopropyl chloride were prepared by known methods[8,9] from the corresponding alcohols. The β-diethylaminoethyl alcohol was purchased and used without further purification. γ-Diethylaminopropyl alcohol was synthesized from allyl alcohol and diethylamine by a slight modification of the procedure of Hromatka.[10]

All melting points recorded are corrected. The microanalyses were performed by Mr. Wm. Saschek of the College of Physicians and Surgeons of Columbia University.

Experimental

3,5-Dinitro-*p*-diacetylaminophenol.—To 345 g. (5.0 moles) of fuming nitric acid, cooled to —10° in an ice-salt mixture, 60 g. (0.31 mole) of *p*-diacetylaminophenol m. p.[11] 154°, prepared by acetylating *p*-aminophenol hydrochloride with acetic anhydride in pyridine, was added slowly followed by the dropwise addition of 245 g. (2.4 moles) of acetic anhydride. Stirring was vigorous and the temperature was kept below 0° at all times. The dinitro compound separated as the addition of acetic anhydride neared completion. The reaction was completed by stirring for an additional hour and the product isolated by pouring the reaction mixture into water, filtering, washing with water, drying at the suction pump and recrystallizing from 95% alcohol; yield, 66 g. (75%), white, felt-like needles, m. p. 226–227°, literature[5,6] 223–224°.

γ-Diethylaminopropyl Alcohol.—To 57.0 g. (1.0 mole) of allyl alcohol 8.2 g. (0.36 g. atom) of sodium was added in small portions under reflux. Before this solution cooled to room temperature 26.2 ml. (0.24 mole) of diethylamine was added, the mixture then heated in a glass-lined pressure vessel at 115° for three hours, instead of the one hour recommended by Hromatka,[10] cooled (solution sets to a gel) and water added cautiously, decomposing the allylate. The solution was then extracted with ether and the ether extract washed with dilute potassium carbonate solution, dried over anhydrous potassium carbonate, and evaporated on the steam-bath. The residue was fractionated *in vacuo;* yield 20 g. (43%, based on diethylamine used) b. p. (60 mm.) 100–105°.

The chloride was prepared in 79% yield. It forms a very hygroscopic hydrochloride[9] on passing dry hydrogen chloride into its ether solution.

Anal. Calcd. for $C_7H_{16}NCl\cdot HCl$: Cl^-, 19.1. Found: Cl^-, 19.2.

3,4,5-Triaminoanisole.—Fifty grams (0.24 mole) of 3,5-dinitro-4-aminoanisole, m. p. 161°, recrystallized from a hot mixture of dioxane and water, was suspended with 125 g. of Raney nickel catalyst in 1500 ml. of dioxane and reduced at an initial hydrogen pressure of 600 pounds and at a temperature of 100°. The reaction is exothermic, a temperature rise of 10° being noted, and the theoretical amount of hydrogen is absorbed in thirty minutes. After cooling, anhydrous sodium sulfate is added to remove the water formed by the reduction and the dioxane solution of the tri-amine is freed from catalyst by filtering. Dry hydrogen chloride is bubbled through the clear solution and the salt is isolated by filtering, washing with dioxane and dry ether; yield, 50 g. (95%) after drying *in vacuo*, m. p. 215–216°.

Anal. Calcd. for $C_7H_{11}ON_3\cdot 2HCl$: Cl, 31.4. Found: Cl, 30.6, 31.1.

7-Methoxy-5-aminoquinoxaline.—To a solution of 20 g. (0.088 mole) of the dihydrochloride of 3,4,5-triaminoanisole in 2000 ml. of water, 15% sodium hydroxide was added to a *p*H of 6.5 (glass electrode). To this solution 24 g. (0.09 mole) of glyoxal bisulfite was added in small portions with stirring, which was continued for thirty minutes thereafter. One hundred ml. of 15% sodium hydroxide was then added and the solution extracted 3 times with 1-liter portions of ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and the ether removed on the steam-bath. The residue was recrystallized twice from water yielding 11 g. (71%), m. p. 95°, of 7-methoxy-5-aminoquinoxaline, bright yellow plates.

Anal. Calcd. for $C_9H_9ON_3$: C, 61.7; H, 5.19; N, 24.0. Found: C, 60.71; H, 5.36; N, 24.2.

The acetyl derivative was formed by heating gently in acetic anhydride for ten minutes and isolated by pouring into water; it was recrystallized 3 times from water to give fine white needles, m. p. 175–176°.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.6; H, 5.10; N, 19.3. Found: C, 60.60; H, 4.91; N, 19.0.

7-Methoxy-5-(*p*-toluenesulfonyl)-aminoquinoxaline.—To 10 g. (0.057 mole) of 7-methoxy-5-aminoquinoxaline dissolved in 50 ml. of pyridine, 11 g. (0.058 mole) of *p*-toluenesulfonyl chloride was added with stirring. After the initial evolution of heat the mixture was allowed to stand at room temperature for two hours, then heated on the steam-bath for ten minutes, cooled and poured into water; yield, 15 g. (80%); recrystallized twice from chloroform and petroleum ether to give white plates, m. p. 140°.

Anal. Calcd. for $C_{16}H_{15}O_3N_3S$: N, 12.8. Found: N, 13.1.

7-Methoxy-5-(β-diethylaminoethyl)-5-(*p*-toluenesulfonyl)-aminoquinoxaline.—To 15 g. (0.041 mole) of the potassium salt of 7-methoxy-5-(*p*-toluenesulfonyl)-aminoquinoxaline suspended in 100 ml. of 95% alcohol a solution of 8.0 g. (0.046 mole) of the hydrochloride of β-diethylaminoethyl chloride in 25 ml. of 95% alcohol neutralized to phenolphthalein with alcoholic potassium hydroxide and freed from potassium chloride by centrifuging was added. The reaction mixture was then heated under reflux on the steam-bath. After ten minutes the potassium salt dissolves and potassium chloride precipitates. Refluxing was continued for an additional twenty minutes, followed by cooling and evaporation of the alcohol *in vacuo*. Fifty ml. of 5% potassium hydroxide was added to the residue and the mixture extracted with two 100-ml. portions of ether. The combined ether extracts were washed successively with water, dilute potassium carbonate solution and water, and then dried over anhydrous sodium sulfate. The ether was then evaporated on the steam-bath, leaving a thick dark oil which on dissolving in a hot alcohol–water mixture crystallized on cooling, yielding 9 g. (47%) of the desired product, m. p. 86°, which was recrystallized from an ether–petroleum ether mixture to give white plates, m. p. 87°.

Anal. Calcd. for $C_{22}H_{28}O_3N_4S$: C, 61.6; H, 6.55; N, 13.1. Found: C, 61.65; H, 6.38; N, 12.7.

7-Methoxy-5-(γ-diethylaminopropyl)-5-(*p*-toluenesulfonyl)-aminoquinoxaline.—Fifteen grams (0.041 mole) of the potassium salt of 7-methoxy-5-(*p*-toluenesulfonyl)-aminoquinoxaline was treated with 7.0 g. (0.046 mole) of γ-diethylaminopropyl chloride as described before. It was necessary to reflux for twelve hours before complete solution of the potassium salt took place; yield 9 g. (46%) of a difficultly crystallizable oil which was finally crystallized from acetone–water to give white plates melting at 67°.

Anal. Calcd. for $C_{23}H_{30}O_3N_4S$: C, 62.0; H, 6.84; N, 12.70. Found: C, 61.80; H, 6.94; N, 12.70.

7-Methoxy-5-(β-diethylaminoethyl)-aminoquinoxaline and 7-Methoxy-5-(γ-diethylaminopropyl)-aminoquinoxaline.—To 15.0 ml. of concentrated sulfuric acid was added 15.0 g. of the *p*-toluenesulfonyl derivative of the diethylaminoalkyl aminoquinoxaline. The mixture became hot as solution took place and was allowed to stand overnight at room temperature. It was then heated for ten minutes

(8) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(9) Gilman and Shirley, THIS JOURNAL, **66**, 888 (1944).

(10) Hromatka, *Ber.*, **75B**, 131 (1942).

(11) Ladenburg, *ibid.*, **9**, 1528 (1876), reports the melting point as 150°.

on the steam-bath, cooled and made alkaline with 40% sodium hydroxide and extracted with ether. The ether extract was washed successively with water and dilute potassium carbonate solution and then dried over anhydrous potassium carbonate. The dried extract was evaporated on the steam-bath and the residual oil distilled *in vacuo* yielding 7 g. of product.

7-Methoxy-5-(β-diethylaminoethyl)-aminoquinoxaline was a yellow oil, b. p. (1 mm.) 165–168°, after purification through the picrate.

Anal. Calcd. for $C_{15}H_{22}N_4O$: C, 65.60; H, 8.10; N, 20.40. Found: C, 65.47; H, 8.19; N, 20.32.

Di-picrate from alcohol, recrystallized from acetone–ether; purple-red needles, m. p. 184–185°.

Anal. Calcd. for $C_{27}H_{28}N_{10}O_{15}$: C, 44.3; H, 3.85; N, 19.1. Found: C, 44.79; H, 3.80; N, 18.94.

7-Methoxy-5-(γ-diethylaminopropyl)-aminoquinoxaline, yellow oil, b. p. (5 mm.) 185–186°.

Anal. Calcd. for $C_{16}H_{24}ON_4$: C, 66.60; H, 8.42; N, 19.50. Found: C, 66.25; H, 8.54; N, 19.41.

Di-picrate recrystallized from acetone–ether, deep brownish-red needles, m. p. 174°.

Anal. Calcd. for $C_{28}H_{30}O_{15}N_{10}$: C, 45.00; H, 4.05; N, 18.80. Found: C, 44.87; H, 4.00; N, 18.60.

Summary

1. *p*-Diacetylaminophenol was nitrated with a mixture of nitric acid and acetic anhydride to give 3,5-dinitro-*p*-diacetylaminophenol in good yield.

2. 7-Methoxy-5-aminoquinoxaline was synthesized by condensing 3,4,5-triaminoanisole (prepared from 3,5-dinitro-4-aminoanisole by catalytic reduction) with glyoxal bisulfite in aqueous solution.

3. 7-Methoxy-5-(β-diethylaminoethyl)-aminoquinoxaline and 7-methoxy-5-(γ-diethylaminopropyl)-aminoquinoxaline were synthesized from 7 - methoxy - 5 - (*p* - toluenesulfonyl) - aminoquinoxaline by condensing the potassium salt with the appropriate diethylaminoalkyl chloride and subsequent hydrolysis.

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Syntheses with Styrene Oxide

BY WILLIAM S. EMERSON

In contrast to ethylene oxide, styrene oxide has had practically no use as a synthetic intermediate. Tiffeneau[1,2,3,4] examined several of its reactions and recently its behavior with the Grignard reagent has received some attention.[5,6]

The fact that styrene oxide reacts with dimethylamine to give a quantitative yield of β-dimethylamino-α-phenylethyl alcohol[3] suggested that it would be a valuable source of β-amino-α-phenylethyl alcohol derivatives. We have treated styrene oxide with four secondary amines and obtained the expected tertiary amino alcohols in 80–92% yields. The alternative route from styrene chlorohydrin, which was also tested, gave yields of 63–66% in three cases. Each of these amino alcohols was esterified as a check on the presence of the hydroxyl group. When styrene oxide was slowly added to an excess of each of four primary amines, 56–70% yields of the corresponding β-alkylamino-α-phenylethyl alcohols resulted. In the case of *n*-butylamine, a by-product, whose analysis suggested it might be 4-*n*-butyl-2,6-diphenylmorpholine, was also isolated. With ammonia, side reactions predominated, so that only 18% of β-amino-α-phenylethyl alcohol was obtained. Some 2,6-diphenylmorpholine was also isolated in this reaction. After the completion of our experimental work, our results were borne out by the subsequent publication of the reaction of styrene oxide with ethylenediamine to give 60% of β-(β-aminoethyl)-amino-α-phenylethyl alcohol.[7]

In the presence of sulfuric or phosphoric acid, styrene oxide reacted vigorously with ethyl and *n*-butyl alcohols to give 47–57% yields of the corresponding β-alkoxy-α-phenylethyl alcohols. The identity of these compounds was proved by synthesis from styrene chlorohydrin, potassium hydroxide and the alcohol in question, a method which Tiffeneau had previously used with styrene iodohydrin.[8] In the preparation from styrene oxide, a high boiling by-product, probably 2,6-diphenyldioxane contaminated with some of the 2,5-isomer, was always produced. Seven esters of these two alcohols and of β-methoxy-α-phenylethyl alcohol were prepared by standard methods.

When refluxed with an excess of an organic acid in toluene solution in the presence of *p*-toluenesulfonic acid, styrene oxide yielded diesters of styrene glycol. Three of these compounds were prepared and characterized.

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Experimental

Styrene oxide was prepared from styrene through styrene bromohydrin essentially by the method of Read and Reid.[9]

Styrene Chlorohydrin.—In a 5-liter three-necked flask equipped with a mercury-sealed stirrer, reflux condenser, gas inlet and dropping funnel was placed 218 g. (2.1 moles)

(1) Fourneau and Tiffeneau, *Compt. rend.*, **140**, 1595 (1905).
(2) Tiffeneau, *Ann. chim.*, [8] **10**, 345 (1907).
(3) Tiffeneau and Fourneau, *Compt. rend.*, **146**, 697 (1908).
(4) Tiffeneau and Tchoubar, *ibid.*, **207**, 918 (1938).
(5) Kharasch and Clapp, *J. Org. Chem.*, **3**, 355 (1938).
(6) Golumbic and Cottle, THIS JOURNAL, **61**, 996 (1939).
(7) Kitchen and Pollard, *J. Org. Chem.*, **8**, 342 (1943).
(8) Tiffeneau, *Compt. rend.*, **145**, 812 (1907).
(9) Read and Reid, *J. Chem. Soc.*, 1487 (1928).