JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

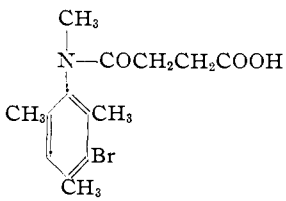
VOLUME 63 NOVEMBER 7, 1941 NUMBER 11

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

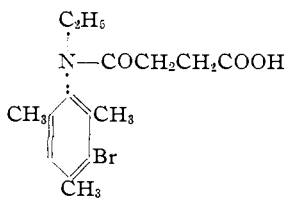
Restricted Rotation in Arylamines. II. Preparation and Resolution of N-Succinyl-N-ethyl-3-bromomesidine and 5-Alkoxy-4-N-succinyl-4-alkylamino-1,3-dimethylbenzenes[1]

BY ROGER ADAMS AND H. W. STEWART[2]

The preparation and resolution of N-succinyl-N-methyl-3-bromomesidine (I) has been described previously.[1] Since the optically active forms exhibited remarkable stability to racemization, a study of analogous compounds has been undertaken. The N-ethyl isomer (II) was synthesized by a series of reactions similar to that used for the N-methyl compound and was resolved through the cinchonidine salt. The half-life of the active



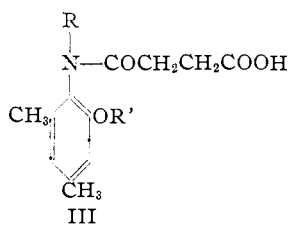
I



II

amine in boiling *n*-butanol was twenty-eight hours as compared with nine hours for the N-methyl derivative. Thus, it is obvious that the ethyl group increases the restricted rotation. This verifies the conclusion from experiments in the biphenyl series[3] that additional atoms attached to the ones which appear to be directly involved in the restriction induce additional hindrance.

Analogous molecules in which a methyl group *ortho* to the nitrogen is replaced by an alkoxyl group are illustrated by formula III



III

where R and R′ = CH_3 or C_2H_5

The alkoxyl group has been shown in numerous instances to be smaller than the methyl group so that such compounds, if resolvable, should yield much more easily racemized enantiomorphs. Of the four different compounds shown in III, all were synthesized, but only the one in which the R and R′ groups were methyls was resolved. The other three acids gave salts which in most instances were non-crystalline. In a few cases the salts appeared crystalline but their physical characteristics made separation of the diastereoisomers impossible. It was, therefore, impossible to obtain data which would have allowed a comparison of the effectiveness of the methyl and ethyl groups in two different positions in the molecule.

The 5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene was obtained in optically active form and the *l*-modification had a half-life in boiling anhydrous methyl acetate (b. p. 56°) of two and seven-tenths hours. This value is in marked contrast to that for compound I whose half-life is nine hours in boiling *n*-butanol (b. p. 118°). It did not racemize at room temperature and the racemization rate was very rapid in boiling *n*-

(1) For previous paper see Adams and Dankert, THIS JOURNAL, **62**, 2191 (1940).

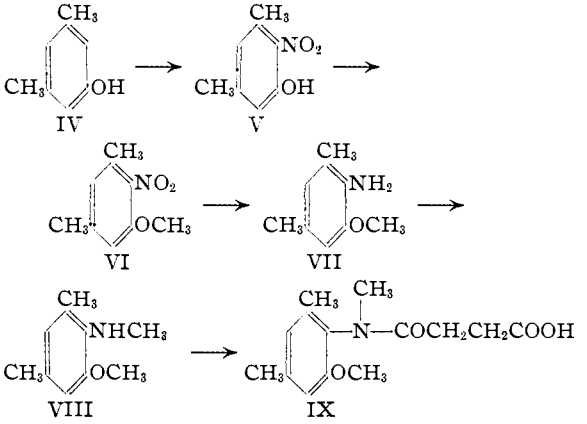
(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(3) Li and Adams, THIS JOURNAL, **57**, 1565 (1935).

butanol. It is recognized that no quantitative comparison can be made of half-life periods determined in different solvents and at different temperatures. It is also true that the presence of the bromine in the mesitylene derivative and absence of it in the xylenol derivative undoubtedly influences, probably in a minor way, the rates of racemization of the respective compounds.

Qualitatively the difference in the restricted rotation between I and III is large, which confirms the predicted results.

The xylenol derivatives (III) were synthesized by the general procedure illustrated in formulas IV–IX for the methoxyl N-methyl derivative.



The *p*H values of the various amines were essentially identical, all falling into the range 3.97–4.06, so that the relative acidity could not account for the difficulty in the resolution of several of them. The 2,6-dinitro-5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene was synthesized and it proved to be a stronger acid, *p*H 2.92. In spite of this fact, it did not form satisfactory alkaloidal salts for resolution.

Experimental

3-Bromomesidine.[4]—Nitromesitylene was converted to mesidine by reduction at 2–3 atm. with hydrogen and Raney nickel as a catalyst.[5] The mesidine was brominated by the procedure of Adams and Dankert.[1]

N-Ethyl-3-bromomesidine.—A mixture of 21.4 g. (1 mole) of 3-bromomesidine, 15.4 g. (1 mole) of diethyl sulfate and 50 cc. of water was heated with stirring to about 80° on a steam-cone. After one-half hour the homogeneous solution was cooled, acidified with 15 cc. of concentrated hydrochloric acid, cooled to below 10°, and treated with a solution of 6.9 g. (1 mole) of sodium nitrite in 20–25 cc. of water, keeping the temperature between 5 and 10°. After ten minutes the cold solution was extracted with ether, the ethereal layer was washed with 5% aqueous sodium hydroxide, then with water and dried over anhydrous magnesium sulfate. The ethereal solution of the nitrosoamine was reduced by pouring slowly into a solution of 68 g. of stannous chloride ($SnCl_2 + 2H_2O$) in 66 cc. of concentrated hydrochloric acid at 70–75°. Shaking was continued until a solid mass was formed in the flask. After standing for one hour (or longer) the mixture was cooled with an ice-bath and made strongly alkaline by the addition of a solution of 88 g. of sodium hydroxide in 130 cc. of water. The mixture was steam distilled until about two liters of distillate was collected or until no droplets of oil were observed in the condenser. The distillate was saturated with sodium chloride, extracted with ether, the ether layer dried over potassium hydroxide and the ether removed under reduced pressure. The residue distilled at 136–137° (4 mm.); 110–111° (2.5 mm.); yield 12.0 g. (49.5%): d^{20}_4 1.2746; $n^{20}D$ 1.5616; M_D calcd., 61.86; found, 61.55.

Anal. Calcd. for $C_{11}H_{16}NBr$: C, 54.55; H, 6.67. Found: C, 54.76; H, 6.61.

A second experiment was performed, adding the diethyl sulfate to the amine and water at 95°. The yield of N-ethyl-3-bromomesidine was much lower. A by-product was obtained, 3-bromomesitol.

After ether extraction of the N-nitroso-N-ethyl-3-bromomesidine, the aqueous layer was allowed to stand for two days and then extracted again with ether. The diazonium salt from unethylated bromomesidine evidently changed to bromomesitol which was then extracted. It was purified from petroleum ether (b. p. 80–92°); hair-like needles, m. p. 84–84.5° (cor.). Biedermann[6] reports m. p. 81°.

Anal. Calcd. for $C_9H_{11}OBr$: C, 50.25; H, 5.16. Found: C, 50.36; H, 5.35.

N-Succinyl-N-ethyl-3-bromomesidine.—A solution of 17.2 g. of N-ethyl-3-bromomesidine and 14.2 g. of succinic anhydride in 100 cc. of dry benzene with a drop of 85% phosphoric acid as a catalyst was refluxed for four hours, cooled, diluted with 100 cc. of ether, and thoroughly extracted with 5% aqueous potassium hydroxide. The ether–benzene solution on evaporation yielded 2.3 g. of unreacted N-ethyl-3-bromomesidine. The aqueous extracts were washed with ether, acidified with dilute (1:2) hydrochloric acid, filtered, washed with water and the dry residue recrystallized from a solution of three volumes of carbon tetrachloride and one volume of petroleum ether (b. p. 80–92°); white crystals m. p. 111.5° (cor.); yield, 20.1 g. (95.9% based on unrecovered N-ethyl-3-bromomesidine).

Anal. Calcd. for $C_{15}H_{20}O_3NBr$: C, 52.62; H, 5.89. Found: C, 52.88; H, 6.01.

Resolution of N-Succinyl-N-ethyl-3-bromomesidine.—Of the various alkaloids and solvents studied, only cinchonidine in ethyl acetate proved satisfactory. The presence of a small amount of methanol was desirable to prevent separation of alkaloid during crystallization of the salt. Heating a concentrated solution and cooling led to precipitation of some alkaloid which made purification of the salt difficult. Consequently crystallizations were performed by concentration of solutions at room temperature.

(4) Fischer and Windaus, *Ber.*, **33**, 1974 (1900).

(5) Fuson and Corse, private communication.

(6) Biedermann and Ledoux, *Ber.*, **8**, 60 (1875).

A boiling solution of 5 g. of N-succinyl-N-ethyl-3-bromomesidine and 4.3 g. of cinchonidine in 130 cc. of ethyl acetate and 10 cc. of methanol was filtered and allowed to cool to room temperature. The solution was then concentrated to 90 cc. by directing a gentle stream of air at the top of the flask and frequently rinsing the walls of the flask. At 90 cc., 2.83 g. of salt had crystallized; at 75 cc. another 1.56 g. of salt. These two fractions were combined and dissolved in 110 cc. of boiling ethyl acetate and 10 cc. of methanol. After concentration at room temperature to 90 cc., 1.14 g. of salt crystallized, at 70 cc., 1.15 g. and at 40 cc., 0.84 g. The residual fraction was discarded. All three fractions gave a rotation of $[\alpha]^{30}D$ −41°. From another crystallization of the combined three fractions in a similar manner just two fractions were isolated both of which were identical in rotation with each other and with the product from the previous crystallization; white crystals, m. p. 117–118° (cor.).

Rotation. 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.205; *l*, 1; $[\alpha]^{30}D$ −41°.

Upon evaporating further the original solution of the salt, 1.33 g. of product was obtained at 60 cc., 1.0 g. at 40 cc., 0.72 g. at 25 cc. and a residue at dryness of 1.90 g. This residue was dissolved in a mixture of 15 cc. of ethyl acetate and 1.5 cc. of methanol, the solution filtered and evaporated to 10 cc.; 0.47 g. of salt separated. At dryness a residue of 1.37 g. was left. Both gave identical rotations; white crystals, m. p. 112.5–114.5° (cor.).

Rotation. 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.33; *l*, 1; $[\alpha]^{30}D$ −66°.

***d*- and *l*-N-Succinyl-N-ethyl-3-bromomesidine.**—About 1 g. of less-soluble salt, $[\alpha]^{30}D$ −41°, was decomposed by stirring with 100 cc. of 12% aqueous hydrochloric acid at 0° for about three hours or longer. The salt turned to a gum on treatment with the hydrochloric acid and was allowed to remain with the acid until the product again appeared crystalline. The material was filtered and treated four times for one-half hour each in a similar manner. Cinchonidine was shown to be absent from the filtrate by Folin's reagent.[7] It was necessary also to remove a small amount of occluded salt in the crystals. This was done by dissolving in 2% aqueous sodium carbonate, filtering and precipitating with 1:2 hydrochloric acid. This treatment had to be repeated once before the crystals were free of cinchonidine. The acid thus obtained was decolorized in carbon tetrachloride solution with Darco and recrystallized from a mixture of three volumes of carbon tetrachloride and two volumes of petroleum ether (b. p. 80–92°); white crystals, m. p. 104.5° (cor.).

Anal. Calcd. for $C_{15}H_{20}O_3NBr$: C, 52.62; H, 5.89. Found: C, 52.22; H, 5.91.

Rotation. (*d*-Acid) 0.05 g. made up to 5 cc. with absolute ethanol at 30° gave αD +0.25; *l*, 1; $[\alpha]^{30}D$ +25°.

Decomposition of the more-soluble salt, $[\alpha]^{30}D$ −66°, in a similar manner gave white crystals, m. p. 104.5° (cor.).

Anal. Calcd. for $C_{15}H_{20}O_3NBr$: C, 52.62; H, 5.89. Found: C, 52.28; H, 6.02.

Rotation. (*l*-Acid) 0.05 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.25; *l*, 1; $[\alpha]^{30}D$ −25°.

(7) Folin and Denis, *J. Biol. Chem.*, **12**, 239 (1912).

Racemization of *l*-N-Succinyl-N-ethyl-3-bromomesidine.—A solution of 0.30 g. of the *l*-acid made up to 25 cc. with *n*-butanol was prepared. After observing the rotation, it was transferred quantitatively to a 50-cc. round-bottomed flask fitted with a ground glass condenser, the solution concentrated to 15 cc. by boiling without reflux, then refluxed for six hours. The solution was cooled, made up to 25 cc., the rotation observed and this process repeated. The following αD values were obtained; at the start −0.485°, after six hours −0.41°, after fourteen hours −0.34°, after thirty hours −0.265°, after fifty-eight hours −0.115°. The average value of *k* was 2.04×10^{-4} which indicates a half-life of twenty-eight hours.

5-Hydroxy-4-nitro-1,3-dimethylbenzene and 5-Hydroxy-2-nitro-1,3-dimethylbenzene; Nitration of *m*-5-Xylenol.—The procedures previously reported for preparing these nitro compounds resulted in a yield of 22% by one author[8] and 38% by another.[9] The latter yield could not be duplicated. Both methods were unsatisfactory if large amounts of xylenol were nitrated.

To a solution of 122.2 g. (1 mole) of 5-hydroxy-1,3-dimethylbenzene in 122 cc. of ether was added at room temperature with vigorous stirring a few cc. of a mixture of 62.5 cc. (1 mole) of concentrated nitric acid and 250 cc. of water. In a few minutes a light brown color appeared showing that the reaction had begun. The flask was then placed in an ice-bath and the remaining portion of the dilute nitric acid solution was slowly added and stirring was continued for one and a half hours after addition was completed. The ether was removed by distillation and the reaction mixture was steam distilled until about 22 liters was collected or until no solid appeared in the condenser. The distillate was cooled and the bright yellow 5-hydroxy-4-nitro-1,3-dimethylbenzene was filtered. It formed yellow crystals, m. p. 65–66° (cor.); yield 60.1 g. (36%). Rowe, *et al.*,[9] report m. p. 66°.

The hot residual material from the steam distillation was decanted from the tar which had settled. Then the solution was cooled with ice and the product which separated filtered. The filtrate was extracted with chloroform, the chloroform was removed by evaporation and the residue was added to the previously filtered solid. The tar was extracted again in this manner with boiling water or until extraction was complete. The solubility of 5-hydroxy-2-nitro-1,3-dimethylbenzene in cold water is about 2 g. per liter, in boiling water about 7 g. per liter. Crystallized from a mixture of one volume of chloroform and one volume of petroleum ether (b. p. 80–92°) it formed yellow crystals, m. p. 108.5° (cor.); yield 42.6 g. (25%). Auwers and Borsche[8] and Rowe, *et al.*,[9] report m. p. 107–108°.

5-Methoxy-4-nitro-1,3-dimethylbenzene.—To a boiling solution of 44.0 g. (1.1 moles) of sodium hydroxide in 250 cc. of water was added slowly 167.1 g. (1.0 mole) of 5-hydroxy-4-nitro-1,3-dimethylbenzene. Boiling was continued until all had dissolved. The water was removed on a steam-bath under reduced pressure until the red sodium salt was essentially dry. The salt was removed and mashed to a fine powder with a spatula. About 500 cc. of benzene was added and the salt was further dried by azeo-

(8) Auwers and Borsche, *Ber.*, **48**, 1714 (1915).

(9) Rowe, Bannister, Seth and Storey, *J. Soc. Chem. Ind.*, **49**, 469T (1930).

tropic distillation while stirring, adding more benzene when necessary. When all the water had been removed the volume was made up to about 500 cc. by adding dry benzene. To this was introduced 140 cc. (1.5 moles) of neutral dimethyl sulfate and the reaction mixture was refluxed with stirring on a steam-bath for five and one-half hours. The reaction mixture was cooled and 203 cc. (3.0 moles) of concentrated aqueous ammonia was cautiously added with stirring. A solution of 10 g. of sodium hydroxide in about 100 cc. of water also was added, the benzene was removed by distillation without separation from the water layer, the flask was stoppered and shaken vigorously while the reaction mixture was still above 45°. After cooling in an ice-bath the 5-methoxy-4-nitro-1,3-dimethylbenzene was filtered and washed. The filtrate was made acidic with dilute hydrochloric acid and 16.5 g. of unreacted xylenol was recovered. The crude 5-methoxy-4-nitro-1,3-dimethylbenzene was crystallized from methanol using Darco. The filtrate from the crystallization was evaporated to dryness and the residue was steam distilled. The solid from the distillate and crystals obtained by the original methanol were recrystallized from a mixture of ten volumes of methanol and one volume of water; slightly colored crystals, m. p. 44–45° (cor.); yield 152.5 g. (93.5% based on unrecovered xylenol). Rowe, *et al.*,[9] report m. p. 45–46°. The ordinary procedure of alkylation was much inferior to the one described.

5-Methoxy-4-amino-1,3-dimethylbenzene.—A solution of 160.5 g. of 5-methoxy-4-nitro-1,3-dimethylbenzene in 500 cc. of 95% ethanol was reduced with hydrogen at 100° and 135 atm. with Raney nickel as a catalyst. The catalyst was removed by filtration, the solvent was evaporated and the residue was distilled, b. p. 120–121° (10 mm.), m. p. 35.5–36.5° (cor.); yield 132.0 g. (98.5%). Rowe, *et al.*,[9] report m. p. 36–37°.

5-Methoxy-4-methylamino-1,3-dimethylbenzene.—To 30.2 g. of powdered 5-methoxy-4-amino-1,3-dimethylbenzene suspended in 100 cc. of water kept at 25–30° with an ice-bath was added slowly with vigorous stirring 25.2 g. of neutral dimethyl sulfate. When the reaction mixture was homogeneous (about twenty minutes) it was treated with nitrous acid and the secondary amine purified according to the procedure given for the preparation of N-ethyl-3-bromomesidine. The reduction with stannous chloride was carried out at 40–45°. The 5-methoxy-4-methylamino-1,3-dimethylbenzene had a b. p. of 61–62° (1.5 mm.); yield, 20.1 g. (60.8%); d^{20}_4 1.0044; $n^{20}D$ 1.5383; $n^{25}D$ 1.5360.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.68; H, 9.16. Found: C, 72.57; H, 9.15.

5-Methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.—A solution of 19.2 g. of 5-methoxy-4-methylamino-1,3-dimethylbenzene and 12.8 g. of succinic anhydride in 100 cc. of dry benzene with a drop of 85% phosphoric acid as a catalyst was refluxed for four hours, cooled, diluted with 100 cc. of ether and thoroughly extracted with 5% aqueous potassium hydroxide. The aqueous extracts were washed with ether, acidified with dilute (1:2) hydrochloric acid, filtered, washed with water and the dry residue recrystallized from ethyl acetate or benzene; white crystals, m. p. 153.5° (cor.); yield 30 g. (97.2%).

Anal. Calcd. for $C_{14}H_{19}O_4N$: C, 63.37; H, 7.22. Found: C, 63.20; H, 7.10.

Resolution of 5-Methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.—The same precautions in this resolution were observed as were described for the resolution of N-succinyl-N-ethyl-3-bromomesidine.

A boiling solution of 5 g. of 5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene and 5.55 g. of cinchonidine in 200 cc. of ethyl acetate and 10 cc. of ethanol was filtered and allowed to cool to room temperature. Concentration at room temperature to 120 cc. resulted in the crystallization of 2.62 g. of salt; at 60 cc., 0.54 g.; at 35 cc., 1.77 g.; at 20 cc., 0.64 g. These all gave the same rotation so they were combined (5.47 g.) and dissolved at room temperature in 300 cc. of ethyl acetate and 5 cc. of ethanol. Upon concentration at room temperature, four fractions were isolated at various concentrations. All gave the same rotation; white crystals, m. p. 133–136° (cor.).

Rotation. (Less-soluble salt) 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.28; *l*, 1; $[\alpha]^{30}D$ −56°.

From the original solution of the salt, after separation of the four fractions just described, 2 cc. of petroleum ether (b. p. 80–92°) was added and the crystals which separated were filtered. Evaporation to 15 cc. and addition of 7 cc. of petroleum ether gave another salt fraction. Both of these were discarded. The remaining solution was evaporated to dryness. No method was found for purifying this amorphous material (2.88 g.).

Rotation. (More-soluble salt) 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.23; *l*, 1; $[\alpha]^{30}D$ −46°.

***d*- and *l*-5-Methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.**—About 3 g. of less-soluble salt was stirred at 0° with 25 cc. of 0.5% hydrochloric acid. The salt became gummy at first and gradually crystals formed. After one hour the product was filtered and washed. This procedure was repeated several times until all the cinchonidine was removed; white crystals, m. p. 152–153° (cor.). By decomposition of the crude more-soluble salt, the *l*-form of the acid resulted, m. p. 152–153° (cor.).

Anal. Calcd. for $C_{14}H_{19}O_4N$: C, 63.37; H, 7.22. Found: (*d*-acid) C, 63.37; H, 6.98. (*l*Acid) C, 63.76; H, 7.41.

Rotation. (*d*-Acid) 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD +0.065; *l*, 1; $[\alpha]^{30}D$ +13°. (*l*-Acid) 0.025 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.065; *l*, 1; $[\alpha]^{30}D$ −13°.

Racemization of *d*-5-Methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.—By the same general procedure described under the racemization of *l*-N-succinyl-N-ethyl-3-bromomesidine, 0.40 g. of *d*-acid was made up to 25 cc. with anhydrous methyl acetate (b. p. 56°) and racemized at the boiling point of the solution. The following αD values were obtained: initial +0.445°; after thirty minutes, +0.395°; after ninety minutes, +0.305°; after one hundred eighty minutes, +0.20°; after three hundred ninety minutes +0.085°. The average k is 2.13 $\times 10^{-3}$ which leads to a half-life period of two and seven-tenths hours.

2,6-Dinitro-5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.—To 10 cc. of fuming nitric acid at 0°, 2.65 g. of 5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene was added slowly with stirring. After

standing at room temperature for four hours, the reaction mixture was diluted to several volumes with ice and water. The product was purified from 95% ethanol; white crystals, m. p. 178–178.5° (cor.); yield 3.52 g. (99.2%).

Anal. Calcd. for $C_{14}H_{17}O_8N_3$: C, 47.53; H, 4.83; N, 11.82. Found: C, 47.43; H, 4.93; N, 11.31, 11.42.

5-Methoxy-4-ethylamino-1,3-dimethylbenzene.—A solution of 30.2 g. of 5-methoxy-4-amino-1,3-dimethylbenzene in 20.8 g. of ethyl bromide in a loosely stoppered flask was covered with 150 cc. of water and allowed to stand at room temperature. After two days 4.0 cc. of an additional amount of ethyl bromide was added in 0.5-cc. quantities over a period of three days before all of the reaction mixture was dissolved in the water. Using the same procedure as that described for the preparation of N-ethyl-3-bromomesidine it was treated with nitrous acid and the solid nitrosoamine was isolated by filtration, washed and reduced at about 55°. The product had a b. p. 61–62° (1.5 mm.); yield, 20.1 g. (56.1%); d^{20}_4 0.9808; $n^{20}D$ 1.5267; $n^{25}D$ 1.5242.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56. Found: C, 74.02; H, 9.36.

5-Methoxy-4-N-succinyl-4-ethylamino-1,3-dimethylbenzene.—A solution of 19.9 g. of 5-methoxy-4-ethylamino-1,3-dimethylbenzene and 12.2 g. of succinic anhydride in 100 cc. of dry benzene with a drop of 85% phosphoric acid as a catalyst was refluxed for four hours, cooled, diluted with 100 cc. of ether and thoroughly extracted with 5% aqueous potassium hydroxide. The aqueous extracts were washed with ether, acidified with dilute (1:2) hydrochloric acid, filtered, washed with water and the dry residue recrystallized from ethyl acetate or benzene; white crystals, m. p. 133.5° (cor.); yield 30.6 g. (98.5%).

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.55; H, 7.58. Found: C, 64.60; H, 7.67.

5-Ethoxy-4-nitro-1,3-dimethylbenzene.—The sodium salt of 89.5 g. of 5-hydroxy-4-nitro-1,3-dimethylbenzene was prepared and dried as described for the preparation of 5-methoxy-4-nitro-1,3-dimethylbenzene. It was isolated from the benzene by filtration and sufficient neutral diethyl sulfate (about 350 cc.) was added to permit stirring. It was heated on a steam-bath with stirring until all of the red color of the sodium salt had disappeared (from two to three hours). A solution of 125 g. of sodium hydroxide in 500 cc. of water was slowly added to the hot solution. The mixture was cooled with vigorous stirring to avoid the formation of a cake. The solid was filtered, washed with water, dissolved in 95% ethanol, decolorized with Darco and recrystallized from the same solvent or petroleum ether (b. p. 80–92°); pale yellow crystals, m. p. 78.5° (cor.); yield 100.5 g. (96.2%).

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.56; H, 6.71. Found: C, 61.91; H, 6.99.

5-Ethoxy-4-amino-1,3-dimethylbenzene.—From 100 g. of the nitro compound, 79 g. (93.3%) of amine was obtained, using the same procedure for reduction as described for the corresponding methoxy compound. The product had a b. p. 73–74° (1 mm.); d^{20}_4 1.0086; $n^{20}D$ 1.5410, $n^{25}D$ 1.5390.

The analytical data on a sample of the amine prepared as described varied one per cent. from the theoretical. When prepared from pure amine hydrochloride, the calculated and found values agree.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.70; H, 9.15; N, 8.47. Found: C, 72.76; H, 9.22; N, 8.87.

The hydrochloride was formed by dissolving the base in dry ether and passing in dry hydrogen chloride. The salt was filtered and crystallized by dissolving in ten volumes of absolute ethanol and adding one volume of petroleum ether (b. p. 80–92°); white crystals which slowly sublime at 190° with decomposition.

Anal. Calcd. for $C_{10}H_{16}ONCl$: C, 59.54; H, 8.00. Found: C, 59.85; H, 8.20.

5-Ethoxy-4-methylamino-1,3-dimethylbenzene.—To 33 g. of 3-ethoxy-4-amino-1,3-dimethylbenzene suspended in 100 cc. of water was added slowly with vigorous stirring 19 cc. of neutral dimethyl sulfate. The temperature was maintained at 25–30°. After the reaction mixture was homogeneous (about twenty minutes) it was treated with nitrous acid as described in the preparation of N-ethyl-3-bromomesidine. The reduction was carried out at 40–45°. The product has a b. p. 65–66° (1 mm.); d^{20}_4 0.9806; $n^{20}D$ 1.5263, $n^{25}D$ 1.5240; yield, 21.5 g. (60%).

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.72; H, 9.56; N, 7.81. Found: C, 74.24; H, 9.81; N, 8.36, 8.45.

5-Ethoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene.—A mixture of 13.1 g. of 5-ethoxy-4-methylamino-1,3-dimethylbenzene and 14.6 g. of succinic anhydride in 100 cc. of dry benzene with a trace of 85% phosphoric acid was refluxed for eight hours, cooled, diluted with 100 cc. of ether and extracted with 5% aqueous potassium hydroxide. The aqueous extracts were acidified with dilute hydrochloric acid, the precipitate filtered and washed. The product was purified from ethyl acetate, white crystals, m. p. 114.5° (cor.); yield 20.0 g. (98%).

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.02; H, 7.66; N, 5.12, 5.23.

5-Ethoxy-4-ethylamino-1,3-dimethylbenzene.—The procedure used was identical with that followed for the preparation of 5-methoxy-4-ethylamino-1,3-dimethylbenzene. From 33 g. of 5-ethoxy-4-amino-1,3-dimethylbenzene 19.74 g. (51%) of pure product resulted, b. p. 69–70° (1 mm.); d^{20}_4 0.9601; $n^{20}D$ 1.5160, $n^{25}D$ 1.5140.

Anal. Calcd. for $C_{12}H_{19}ON$: C, 74.55; H, 9.91; N, 7.24. Found: C, 75.07; H, 10.06; N, 7.54.

5-Ethoxy-4-N-succinyl-4-ethylamino-1,3-dimethylbenzene.—Following the procedure previously described for succinylation 18.5 g. of the ethylamino derivative gave 27.5 g. (98%) of the succinyl derivative; white crystals from a mixture of 1:4 ethyl acetate and petroleum ether (b. p., 80–92°), m. p., 91.5° (cor.).

Anal. Calcd. for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.77. Found: C, 66.12; H, 7.94; N, 4.78.

Measurements of the *p*H of .N-Succinyl-N-alkyl-3-bromomesidines and of the 5-Alkoxy-4-N-succinyl-4-alkylamino-1,3-dimethylbenzenes.—*p*H values were determined in 0.1 *M* solutions of 70% ethanol. All of the succinyl derivatives gave values varying from 3.97 to 4.06. The only exception was the 2,6-dinitro-5-methoxy-4-N-succinyl-4-methylamino-1,3-dimethylbenzene which has a value of 2.92. This lowering undoubtedly was effected by the presence of the nitro groups.

Summary

1. N-Succinyl-N-ethyl-3-bromomesidine has been prepared and resolved by the method previously described for the N-methyl compound. The half-life of the N-methyl was nine hours, of the N-ethyl twenty-eight hours, in boiling *n*-butanol, thus demonstrating the increased steric effect of the ethyl group.

2. 5-Methoxy-4-N-succinyl-4-methylamino-1,-3-dimethylbenzene was prepared and resolved. Its half-life was two and seven-tenths hours in boiling anhydrous methyl acetate (b. p. 56°) as compared with nine hours in boiling *n*-butanol for the half-life of N-succinyl-N-methyl-3-bromomesidine. The methoxyl has a much smaller steric effect than the methyl.

URBANA, ILLINOIS RECEIVED AUGUST 9, 1941

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Syntheses in the Quinoline Series. II. Some Derivatives of 4-Methylquinoline and a Study of their Structures

BY OSCAR H. JOHNSON[1] AND CLIFF S. HAMILTON

This investigation was undertaken with the object of introducing into the quinoline nucleus chemical groups known to have therapeutic activity. It was felt that if several of these groups could be introduced into one molecule in various combinations, an antimalarial of more general use or greater activity than those now known might be achieved.

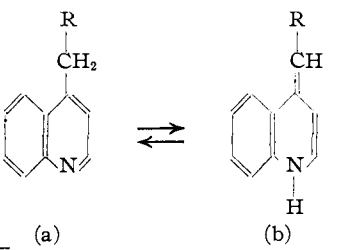
From the readily accessible acetoacetanilide were prepared in turn 2-hydroxy-4-methyl-, 2-chloro-4-methyl- and 4-methylquinoline (lepidine), following the procedures of Mikhailov.[2] Busch and Koenigs[3] nitrated lepidine to give as the major product a compound assumed to be 8-nitrolepidine. In this investigation a similar nitration was performed and the major product was shown to be 8-nitrolepidine by catalytic reduction to the amine followed by conversion to 8-chlorolepidine by a Gattermann diazo reaction. An authentic sample of 8-chlorolepidine was prepared from 2,8-dichlorolepidine.

8-Nitrolepidine was oxidized by selenium dioxide to 8-nitroquinoline-4-aldehyde.[4] This was condensed with nitroethane in a fashion similar to that employed by Kwartler and Lindwall[5] for the reaction of nitromethane with certain quinoline aldehydes. The α-nitroethyl-4-(8-nitroquinolino)-methanol thus obtained was reduced by catalytic means to α-aminoethyl-4-(8-aminoquinolino)-methanol. This compound has a side chain containing a secondary alcohol group and a basic nitrogen atom in the same relative positions as in quinine in addition to the 8-amino group found in the quinoline base from which plasmochin is derived.

The Grignard reaction was also investigated as a means for securing the secondary alcohol group of the quinine type. Quinoline-4-aldehyde was prepared by the Kwartler and Lindwall[5] method. This gave α-methyl-4-quinolinemethanol when treated with methylmagnesium iodide by standard Grignard procedure.

While this alcohol could not be dehydrated with formic acid and was unaffected by 48% aqueous hydrobromic acid, it did react readily with thionyl chloride to give 4-(α-chloroethyl)-quinoline. This compound was very resistant to alkaline hydrolysis and to conversion to 4-vinylquinoline.

The high reactivity of the alpha hydrogen atoms in the alkyl groups of certain homologs (a) of quinoline (RCH_2 group in the 2- or 4-position) has been explained[6] by the assumption of a tautomeric shift of one hydrogen atom to the tertiary nitrogen with a redistribution of double bonds to give a methylene form (b).



(a) (b)

(1) Parke, Davis and Company Fellow.

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