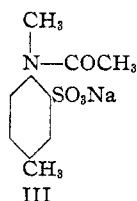
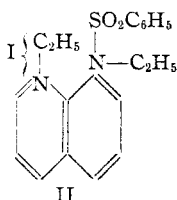
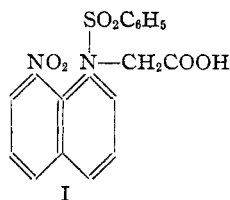


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Arylamines. I. Preparation and Resolution of N-Succinyl-N-methylbromomesidine

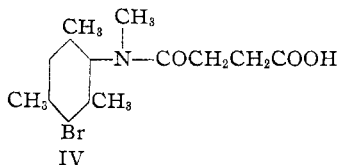
BY ROGER ADAMS AND L. J. DANKERT¹

Optical activity in certain arylamines has been reported by Mills² in which molecules the asymmetry is introduced as a consequence of restricted rotation between a carbon of the ring and the nitrogen atom attached to it. Thus, compound I was reported to have a half-life in chloroform at 14.9° of seventeen minutes; compound



II, a half-life in chloroform at 18° of fourteen minutes; and compound III, a half-life in water at 16.6° of five and one-quarter hours. The statement is also made that various N-acyl-N-alkyl 1-amino-8-naphthalene sulfonic acids are resolvable but a description of these compounds has not yet been published.

A study is now under way of a series of relatively simple arylamines which should exhibit similar restricted rotation. The first of these, now to be reported, is N-succinyl-N-methylbromomesidine (IV). This compound was pre-



pared readily by the action of succinic anhydride in the presence of a drop of sulfuric acid as a catalyst upon N-methylbromomesidine which was synthesized most satisfactorily by the following

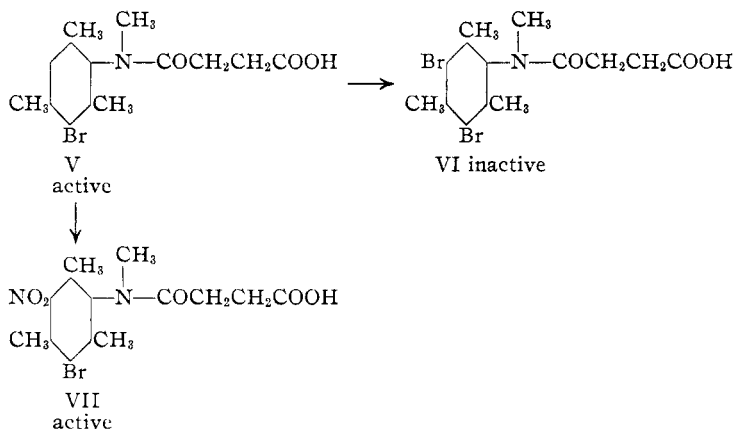
series of reactions: mesitylene \rightarrow nitromesitylene \rightarrow mesidine \rightarrow bromomesidine \rightarrow N-methylbromomesidine. This course proved superior to the N-methylation of mesidine followed by bromination since bromomesidine is a solid which is readily purified. The N-methylbromomesidine was purified through the nitroso compound which was separated thus from bromomesidine or N-dimethylbromomesidine obtained as by-products when one molecule of dimethyl sulfate reacted with bromomesidine.

The N-succinyl-N-methylbromomesidine (IV) was resolved readily through its brucine salt. The less soluble diastereoisomer had in ethanol $[\alpha]^{27D} -37.5^\circ$ and showed no mutarotation. By hydrolysis of the salt with hydrochloric acid, the active acid resulted $[\alpha]^{27D} -29^\circ$. It proved to be an extraordinarily stable active form for it did not racemize at room temperature in aqueous alkali or in ethanol nor, indeed, after boiling in these solvents for twelve hours. In boiling *n*-butanol it racemized very slowly with a half-life period of nine hours. The more soluble diastereoisomeric brucine salt was not obtained crystalline, but a dextrorotatory acid was isolated therefrom $[\alpha]^{27D} +27^\circ$, obviously nearly optically pure. The interference of groups in this molecule is much greater than in the compounds I, II, III, described by Mills.

The possibility that optical activity in this compound may be due to asymmetric nitrogen was excluded on the basis of the numerous failures to resolve nitrogen compounds of a similar type. Confirmation of the soundness of this conclusion was obtained by bromination of the active form which resulted in formation of an optically inactive N-succinyl-N-methyldibromomesidine (VI). Such a molecule as VI prepared from optically active V should be optically active, if the activity in V were due to an asymmetric nitrogen; on the other hand, if the activity in V were due to restricted rotation, activity in VI should disappear as was actually found, due to the symmetrical substitution in the benzene ring. Moreover, nitration of the active forms of V gave active N-succinyl-N-methylnitrobromomesidine (VII) which

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

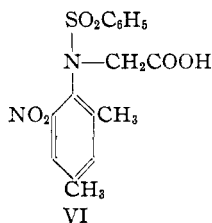
(2) Mills and Elliott, *J. Chem. Soc.*, 1291 (1928); Mills, *Trans. Faraday Soc.*, 26, 431 (1930); Mills and Breckenridge, *J. Chem. Soc.*, 2209 (1932); Mills and Kelham, *ibid.*, 274 (1937).



was optically active since in these molecules unsymmetrical substitution in the benzene ring still persists.

Construction to scale of molecules IV and V using accepted atomic radii indicates clearly the restricted rotation caused by the interference of the ring methyls, N-methyl and acyl group.

It is a bit surprising in view of the results described in this communication that of the compounds prepared by Yuan³ the one having structure VI could not be resolved.



Experimental

Mesidine.—This was prepared from nitromesitylene⁴ by means of iron powder and a little hydrochloric acid as catalyst, b. p. 225–226°, yield 88%; previous b. p. 229–230°; 227°.⁵

N-Methylmesidine.—This was prepared by the method of Ullmann.⁷ For the purification, the method described for N-ethyl-m-toluidine was used.⁸

Bromomesidine.—A suspension of mesidine hydrochloride was prepared by pouring slowly, with vigorous stirring, 13.5 g. of mesidine into 80 cc. of concentrated hydrochloric acid, cooled with ice and water. A solution of 16.8 g. (5.5 cc.) of bromine in 80 cc. of concentrated hydrochloric acid was now added dropwise, keeping the mixture below 15°. After the addition, the reaction mixture was warmed

on a steam cone for thirty minutes, then cooled to 0° and filtered. The precipitate was dissolved in 600–800 cc. of hot water, made alkaline with aqueous ammonia, cooled and the precipitate filtered. Additional material was obtained by extraction of the aqueous layer with ether. The amine was dried over potassium hydroxide and distilled, b. p. 153–155° (17 mm.). The distillate solidified and was recrystallized from petroleum ether (b. p. 30–60°): white crystals, m. p. 40° (cor.); yield 17.5 g. (82%). Fischer and Windaus⁹ report m. p. 39°.

N - Methylbromomesidine.—A. N-Methylmesidine was brominated following the same procedure described for bromina-

tion of mesidine: yield from 14.9 g. of N-methylmesidine, 19 g. (83%); b. p. 145° (15 mm.); d_{20}^{20} 1.3127; n_D^{20} 1.5745.

B. Using the same procedure described for preparing N-methylmesidine, bromomesidine was converted to the N-methyl derivative in 90% yields.

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{NBr}$: C, 52.64; H, 6.14. Found: C, 52.84; H, 6.10.

N-Acetyl-N-methylbromomesidine.—A mixture of 1 g. of N-methylbromomesidine, 5.3 g. of acetic anhydride and a trace of sulfuric acid was refluxed for three hours and then poured onto ice. The product was purified by recrystallization from petroleum ether (b. p. 30–60°) using Norit: white needles, m. p. 71° (cor.); yield 1.1 g. (93%).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{ONBr}$: C, 53.33; H, 5.97. Found: C, 53.56; H, 5.85.

N-Succinyl-N-methylmesidine.—A solution of 1 g. of N-methylmesidine, 0.671 g. of succinic anhydride and a trace of sulfuric acid in 25 cc. of dry benzene was refluxed for four hours. The mixture was cooled, diluted with 25 cc. of ether and extracted with 5% aqueous sodium hydroxide. The aqueous solution was washed once with ether, then acidified with dilute hydrochloric acid. The precipitated product was purified by recrystallization from benzene with the aid of Norit: white crystals, m. p. 136° (cor.); yield 1.5 g. (90%).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{N}$: C, 67.43; H, 7.63. Found: C, 67.33; H, 7.73.

N-Succinyl-N-methylbromomesidine.—A. Using the same procedure described for N-succinyl-N-methylmesidine, 10 g. of N-methylbromomesidine gave 13.6 g. (96%) of N-succinyl-N-methylbromomesidine. Purified from benzene, it formed white crystals, m. p. 136° (cor.).

B. A solution of 0.1 g. of N-succinyl-N-methylmesidine in 5 cc. of carbon tetrachloride was treated with 0.049 g. of bromine and refluxed for thirty minutes. After removal of the solvent, the product was recrystallized from benzene, m. p. 136° (cor.).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{NBr}$: C, 51.26; H, 5.53. Found: C, 51.61; H, 5.65.

Resolution of N-Succinyl-N-methylbromomesidine.—A solution of 5 g. of N-succinyl-N-methylbromomesidine in 15 cc. of chloroform was added to a solution of 7.1 g. of

(3) Yuan, *J. Chinese Chem. Soc.*, **4**, 131 (1936).

(4) "Organic Syntheses," Vol. 14, John Wiley and Sons, Inc., New York, N. Y., 1934, p. 68.

(5) Ladenberg, *Ann.*, **179**, 172 (1875).

(6) Biedermann and Ledoux, *Ber.*, **8**, 58 (1875).

(7) Ullmann, *Ann.*, **327**, 110 (1903).

(8) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 18, 1938, p. 40.

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

brucine tetrahydrate in 20 cc. of chloroform. The mixture was filtered, concentrated to 15 cc. and allowed to stand for two days during which time crystals separated. Fraction A, weighing 5 g., was filtered and recrystallized twice from chloroform. The original material and each successive crystallization gave the same rotation. The salt contains chloroform of crystallization as shown by analysis and by the tendency of the crystals to effloresce if treated with petroleum ether (b. p. 30–60°).

Anal. Calcd. for $C_{14}H_{18}O_3NBr \cdot C_{28}H_{36}O_4N_2 \cdot CHCl_3$: C, 54.6; H, 5.21. Found: C, 54.50; H, 5.21. *Rotation.* 0.05 g. made up to 25 cc. with ethanol at 27° gave $\alpha_D -0.15^\circ$; *l*, 2; $[\alpha]^{27}_D -37.5^\circ$.

The filtrate from fraction A was concentrated to 7 cc. and allowed to stand. Fraction B, weighing 3 g., was thus obtained. Further evaporation of the filtrate from fraction B to 3 cc. was allowed to stand and fraction C (1 g.) separated. These were not used, but the filtrate from fraction C was evaporated to dryness. An amorphous residue (D) weighing 2.5 g. was primarily the diastereoisomeric salt.

Fraction A was decomposed by digesting six times with 12% aqueous hydrochloric acid at 0° or until no test for brucine was obtained in the filtrates. From 1 g. of salt was obtained 0.4 g. of acid. It was purified by crystallization from petroleum ether (b. p. 60–110°); white crystals, m. p. 132° (cor.).

Anal. (*l*-form) Calcd. for $C_{14}H_{18}O_3NBr$: C, 51.26; H, 5.53. Found: C, 51.39; H, 5.62. *Rotation.* 0.050 g. made up to 25 cc. with ethanol at 27° gave $\alpha_D -0.115^\circ$; *l*, 2; $[\alpha]^{27}_D -29^\circ$.

Fraction D was decomposed in a similar manner. The free acid was recrystallized from petroleum ether (b. p. 60–110°); white crystals, m. p. 132° (cor.).

Rotation. 0.050 g. made up to 25 cc. with ethanol at 27° gave $\alpha_D +0.11^\circ$; *l*, 2; $[\alpha]^{27}_D +27^\circ$.

Racemization Experiments.—A sample of *l*-acid in ethanol was refluxed for twelve hours with no change in rotation. Similarly, in very dilute aqueous sodium hydroxide containing about two equivalents of alkali per mole of acid, no racemization was observed after boiling for twelve hours.

Rotation. 0.050 g. made up to 25 cc. with water containing 2 mole equivalents of sodium hydroxide at 27° gave $\alpha_D -0.14^\circ$; *l*, 2; $[\alpha]^{27}_D -33^\circ$.

A solution of the *l*-acid in *n*-butanol was refluxed and the rotation determined periodically. By concentrating the solution before each determination, cooling, and transferring quantitatively to the volumetric flask, a series of readings was observed.

Rotation. 0.050 g. made up to 25 cc. with *n*-butanol at 27° gave $\alpha_D -0.115^\circ$; *l*, 2; $[\alpha]^{27}_D -29^\circ$; after 3 hours -23° ; 8.5 hours -15° ; 14 hours -10° ; 17.5 hours -7.5° ; 30 hours -2.5° .

Calculated on the basis of a reversible unimolecular reaction, the half-life period is nine hours.

N-Succinyl-N-methyldibromomesidine.—A mixture of 0.2 g. of *dl*-N-succinyl-N-methylbromomesidine and 0.5 cc. of bromine was allowed to stand at 0° for twenty minutes. The excess bromine was removed under diminished pressure, and the residue treated with 1 cc. of saturated aqueous sodium bisulfite. The product was purified by crystallization from absolute ethanol; white crystals, m. p. 171° (cor.).

Anal. Calcd. for $C_{14}H_{17}O_3N_2Br_2$: C, 41.33; H, 4.17. Found: C, 41.47; H, 4.31.

The *l*-N-succinyl-N-methylbromomesidine was brominated in exactly the same manner. The product had the same melting point as that derived from the *dl*-form and showed no optical rotation.

N-Succinyl-N-methylnitrobromomesidine.—To 1 cc. of fuming nitric acid (sp. gr. 1.5) at room temperature, was added 0.1 g. of N-succinyl-N-methylbromomesidine. After fifteen minutes, the mixture was poured into 50 cc. of water. The product which separated was purified by crystallization from benzene; white flakes, m. p. 165° (cor.).

Anal. Calcd. for $C_{14}H_{17}O_5N_2Br$: C, 45.04; H, 4.60. Found: C, 45.47; H, 4.72.

***d*- and *l*-N-Succinyl-N-methylnitrobromomesidine.**—The active forms were nitrated in a similar manner to the *dl*-modification. Both the *d*- and *l*-forms were crystallized from benzene and both formed white flakes, m. p. 165°.

Anal. (*d*-form) Calcd. for $C_{14}H_{17}O_5N_2Br$: C, 45.04; H, 4.60. Found: C, 45.40; H, 4.55. *Rotation.* (*d*-form) 0.0331 g. made up to 5 cc. with absolute ethanol at 27° gave $\alpha_D +0.08^\circ$; *l*, 2; $[\alpha]^{27}_D +6.0^\circ$. (*l*-form) 0.0316 g. made up to 5 cc. with absolute ethanol at 27° gave $\alpha_D -0.08^\circ$; *l*, 2; $[\alpha]^{27}_D -6.3^\circ$.

Summary

N-Succinyl-N-methylbromomesidine has been prepared by N-methylating bromomesidine followed by treatment with succinic anhydride.

This compound was resolved. The optically active forms were stable in boiling ethanol or aqueous sodium hydroxide but gradually racemized in boiling *n*-butanol with a half-life of nine hours.

The activity in this molecule is due to restricted rotation between the carbon of the ring and the nitrogen atom. That it could not be due to an asymmetric nitrogen atom was demonstrated by bromination of the active forms to the inactive N-succinyl-N-methyldibromomesidine and by nitration of the active forms to active N-succinyl-N-methylnitrobromomesidines.

URBANA, ILLINOIS

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