perature. A purified sample, stored for about eleven months on the desk top in a glass-stoppered bottle, decomposed violently, rupturing the bottle and evolving heat.[11]

Acknowledgment.—We express our thanks to Dr. A. Pechukas, who suggested the refluxing solvent technique, and to Dr. F. Strain for helpful discussions.

Summary

1. The thermal stability of phenyl chlorosulfinate, although poor, was about equal to that of *n*-propyl chlorosulfinate and much greater than that of isopropyl chlorosulfinate.

2. Diphenyl sulfite reacted with hydrogen chloride producing phenol and a tarry residue; the other expected cleavage product, chlorobenzene, was not found. Phenyl chlorosulfinate, unlike the unreactive alkyl chlorosulfinates, underwent a disproportionation reaction in the presence of hydrogen chloride to form thionyl chloride and diphenyl sulfite.

3. The refluxing solvent technique afforded an excellent means of preparing phenyl chlorosulfinate and diphenyl sulfite in yields of 83% and 87%, respectively. This was the first successful preparation of the latter by the direct reaction of phenol with thionyl chloride without hydrogen chloride acceptors.

4. The variables of temperature and ratio of reactants have been studied in the reaction of phenol with thionyl chloride in a refluxing solvent. *Under the conditions used,* the lower reaction temperatures seemed to favor undesirable side-reactions; at a 2:1 molar ratio of phenol to thionyl chloride the best yield of diphenyl sulfite occurred at 130°, whereas with excess thionyl chloride the best yield of phenyl chlorosulfinate was obtained in refluxing thionyl chloride at 78°.

5. The reaction of phenol with thionyl chloride in a refluxing solvent is apparently very sensitive to relatively minor changes in the reaction conditions, such as stirring for example, and with such modifications quite different results from those reported here may be obtained. Such sensitivity was not apparent in the aliphatic series.

BARBERTON, OHIO RECEIVED MARCH 15, 1948

[11] Carré and Libermann, *Compt. rend.*, **195**, 799 (1932), reported that the decomposition of phenyl chlorosulfinate was instantaneous at room temperature. The presence of impurities in their material may have been responsible for this reduced stability.

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation of Spermine Tetrahydrochloride[1] (1,12-Diamino-4,9-diazadodecane Tetrahydrochloride)

BY HARRY P. SCHULTZ[2]

The reported synthesis of spermine[3,4] appeared impractical for the preparation of the quantity of material required in the antimalarial program. Therefore, a synthesis of spermine tetrahydrochloride was developed, which consisted of the hydrogenation of succinonitrile to putrescine (I); the dicyanoethylation of putrescine to N,N'-bis-(2-cyanoethyl)-putrescine (II); followed by hydrogenation of II to spermine (III). The tetramine was then converted to the tetrahydrochloride.

$H_2N(CH_2)_4NH_2$ I
$NC(CH_2)_2NH(CH_2)_4NH(CH_2)_2CN$ II
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ III

The hydrogenation of succinonitrile was carried out at 140° in liquid ammonia over Raney nickel. Even under these conditions, which are usually quite unfavorable to formation of secondary amines, the yield of pyrrolidine was more than twice as large as that of the desired primary amine. The dicyanoethylation reaction proceeded well in water, alcohol, or ether. The yield of II was almost quantitative, judged by the amount of the dihydrochloride that was isolated in some experiments. The preferred procedure was to carry out the cyanoethylation in ether solution and, without isolating II, add liquid ammonia and hydrogenate over Raney nickel at 140° to III. The tetramine (III) was then distilled and isolated and purified as the tetrahydrochloride. The over-all yield of the tetrahydrochloride, starting with putrescine, was 51% of the theoretical.

Experimental

Putrescine.—A steel reaction vessel having a void of 1300 ml. was charged with 200 g. (2.5 moles) of succinonitrile,[5] 9 g. of W-2 Raney nickel,[6] and 350 ml. of liquid ammonia. The contents of the bomb was reduced for two and one-half hours at 140° under a hydrogen pressure of 1700 p. s. i. The catalyst-free reaction mixture was distilled to give 79.7 g. (45% yield) of crude pyrrolidine that boiled at 87–88° (740 mm.), and 43 g. (20% yield) of putrescine, b. p. 60–65° (16 mm.); m. p. 27–28°. Ladenburg[7] reported a m. p. of 23–24° for putrescine, while Ciamician and Zanetti[8] gave m. p. 27–28°.

N,N'-bis-(2-Cyanoethyl)-putrescine.—Acrylonitrile from the Rohm and Haas Company (35.0 g., 0.66 mole)

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[1] The work described in this paper was done under Contract OEMcmr-567, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Wisconsin

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[3] Rosenheim, *Biochem. J.*, **18**, 1253 (1924).

[4] Dudley, Rosenheim and Starling, *ibid.*, **20**, 1082 (1926).

[5] Succinonitrile from du Pont Electrochemical Division was used without further purification.

[6] Mozingo, "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

[7] Ladenburg, *Ber.*, **19**, 781 (1886).

[8] Ciamician and Zanetti, *ibid.*, **22**, 1970 (1889).

was added dropwise for eight hours to a stirred solution of 29.0 g. (0.33 mole) of putrescine in 10 ml. of ether. After all acrylonitrile was added, the solution was stirred at room temperature for fifteen hours, on a steam-bath for one hour, and again at room temperature for one hour. During the time of heating, all the ether distilled out, and the weight of the final reaction product was 64 g. All attempts to distil the dinitrile, even at a pressure of 0.01 mm., resulted in decomposition. When the reaction mixture was allowed to stand for a longer period (forty to fifty hours), the yield of spermine tetrahydrochloride was decreased from 50 to 30%.

A small exploratory run, made as above, when treated with ethanolic hydrogen chloride, gave a 100% yield of N,N'-bis-(2-cyanoethyl)-putrescine dihydrochloride, m. p. 222–228° (dec.). This salt was recrystallized from ethanol–water (3:1) to give an 84% yield of N,N'-bis-(2-cyanoethyl)-putrescine dihydrochloride, m. p. 232–233° (dec.).

Anal. Calcd. for $C_{10}H_{20}N_4Cl_2$: Cl, 26.6. Found: Cl, 26.6.

Spermine Tetrahydrochloride.—A 270-ml. steel reaction vessel was charged with 18 g. (0.092 mole) of crude N,N'-bis-(2-cyanoethyl)-putrescine, 5 ml. of ether, 60 ml. of liquid ammonia, and 3 g. of W-2 Raney nickel catalyst. The contents of the bomb was reduced for thirty minutes at 140° under a hydrogen pressure of 4900 p. s. i. The catalyst-free reaction mixture was distilled to give 10 g. of viscous distillate that boiled at 100–170° (0.1–0.2 mm.), and 3 g. of a yellow residue.

The crude spermine was dissolved in 130 ml. of absolute ethanol, and to it was added 65 ml. of 20% ethanolic hydrogen chloride. The precipitated amine salt was filtered and air-dried to give 23.5 g. of white, impure spermine tetrahydrochloride that melted at 290–310° (dec.), with darkening at 270°. The crude spermine tetrahydrochloride was dissolved in 130 ml. of 12% hydrochloric acid and added to 1300 ml. of hot, absolute ethanol. After cooling the alcohol solution, the crystals were filtered, washed, and air-dried to give 17 g. of crystals, m. p. 300–310° (dec.). This material was placed in 119 ml. of 12% hydrochloric acid, and added to 357 ml. of hot, absolute ethanol. After six hours at room temperature, the spermine tetrahydrochloride was filtered off, rinsed, and dried to give 16.1 g. (51% yield) of light pink crystals, m. p. 310–311° (dec.), darkening at 300°. The value previously reported[9] was m. p. 310–311° (dec.).

Anal. Calcd. for $C_{10}H_{30}N_4Cl_4$: C, 34.5; H, 8.7; Cl, 40.8. Found: C, 34.2; H, 8.6; Cl, 40.8.

The picrate of spermine melted at 246–247° (dec.), darkened at 240°. The value previously reported[9] was m. p. 248–250° (dec.), with darkening at 242°.

Spermine chloroplatinate was also prepared, and found to melt at 242° (dec.), dark at 235°. The value previously reported[9] was m. p. 242–245° (dec.).

Acknowledgments.—I am grateful to Dr. Carnahan, formerly of this Laboratory, for suggesting this method as a possible synthesis of spermine; and to Drs. Adkins and Wilds, of this Laboratory, for advice which made this synthesis successful.

Summary

Spermine tetrahydrochloride has been prepared from succinonitrile through the formation of putrescine, N,N'-bis-(2-cyanoethyl)-putrescine, spermine, and spermine tetrahydrochloride. The yield of putrescine from succinonitrile was low (20%), but the over-all yield for the three subsequent reactions was 51% of the theoretical.

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[9] Dudley, Rosenheim and Rosenheim, *Biochem. J.*, **18**, 1263 (1924).

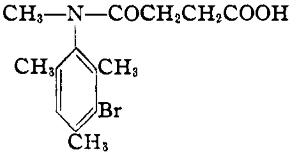
CORAL GABLES, FLORIDA RECEIVED APRIL 28, 1948

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

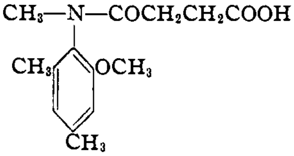
Restricted Rotation in Aryl Amines. IV. Preparation and Resolution of N-Succinyl-1-methylamino-2,4-dimethyl-6-substituted Benzenes

BY ROGER ADAMS AND N. K. SUNDHOLM[1]

A comparison of the relative interference effects of substituent groups, as deduced from the racemization rates of a series of analogous, optically active biphenyls,[2] showed these groups to fall in the following order: Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. Two members of a series of aromatic amines in which restricted rotation exists have been previously described.[3] They are shown in I and II. Compound I, in optically active form, has a half-life of nine hours in boiling *n*-butanol (b.p. 117°) and compound II a half-life of two and seven-tenths hours in boiling methyl acetate (b.p. 57°). Although these values are not directly comparable due to the use of different solvents[4] and to the bromine atom in the former, qualitatively they can be accepted as indicative of the relative interference of the methyl and methoxyl groups in this type of molecule. These relative values coincide with those expected from the study of the biphenyls.



I



II

Several new analogs of I and II, as shown in III and IV, have now been synthesized, resolved and their optically active forms racemized. The half-life periods were as follows: IIIa, three and

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[1] An abstract of a thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry. Allied Chemical and Dye Corporation fellow second semester 1941–942, two semesters 1943–1944; New York Community Trust fellow 1942–1943.

[2] Stoughton and Adams, THIS JOURNAL, **54**, 4426 (1932); Adams and Hale, *ibid.*, **61**, 2825 (1939).

[3] (a) Adams and Dankert, *ibid.*, **62**, 2191 (1940); (b) Adams and Stewart, *ibid.*, **63**, 2859 (1941); (c) Adams and Albert, *ibid.*, **64**, 1475 (1942).

[4] Li and Adams, *ibid.*, **57**, 1565 (1935).