The Synthesis of *cis*- and *trans*-1,4-Bis(2-aminoethyl)cyclohexanes[1]

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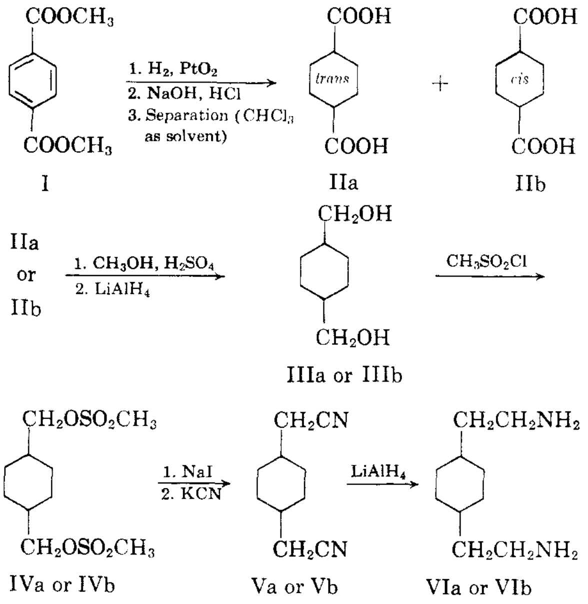
2-Aminoethylbenzenes and 2-aminoethylcyclohexanes have long been noted for their physiological activity, adrenaline, ephedrine, and chloromycetin being familiar examples. Recently, there was reported from this laboratory, the synthesis of several bis(2-aminoethyl)benzenes.[2,3] The compounds, assayed by the Lilly Research Laboratories, were found to possess some sympathomimetic activity (as well as other types of activity) when the two groups were unsymmetrically placed in the benzene nucleus. The work has now been extended to cover some of the bis(2-aminoethyl)-cyclohexanes.

cis- and *trans*-1,4-Bis(2-aminoethyl)cyclohexanes have been synthesized by the procedures outlined in Chart I. Activity assays by The Lilly Research Laboratory revealed that the *cis* isomer was too toxic to be of interest pharmacologically. The *trans* isomer exhibited depressant activity very similar to that of 1,8-diaminooctane.

Chart I



EXPERIMENTAL[4,5]

Intermediate compounds. IIa and IIb were prepared by the catalytic[6] hydrogenation of I. Separation[7] of the isomers yielded mainly the *cis* isomer. Reduction[8] to the diols followed by methanesulfonation gave IVa or IVb. Methane sulfonation of a commercial mixture (Eastman Yellow Label) of the diols (IIIa and IIIb) with subsequent recrystallizations of the product afforded a second method of separating the *cis* and *trans* isomers and resulted in a larger yield of the *trans* compound. *cis*- and *trans*-1,4-Diiodomethylcyclohexane were prepared separately according to the procedure described by Haggis and Owens.[8]

trans-1,4-Cyclohexane diacetonitrile (Va). The procedure described was adapted from that employed in the preparation of pentamethylenedicarbonitrile.[9]

A mixture of 15.4 g. (0.042 mole) of *trans*-1,4-diiodomethylcyclohexane in 110 ml. of 95% ethanol and 11.3 g. (0.174 mole) of potassium cyanide in 30 ml. of water was refluxed over a period of 12 hr. The mixture was distilled until most of the ethanol had been removed. After adding 70 ml. of water, it was extracted thrice with benzene, first with a 40-ml. portion and then with two 35-ml. portions. The first benzene extract was washed with 25 ml. of 1*N* sodium hydroxide and then with 25 ml. of water. The water and sodium hydroxide solutions were used to wash the combined second and third benzene extracts. The combined benzene extracts were dried over magnesium sulfate, and then distilled until most of the benzene was removed. A yellowish white, crystalline solid formed. Two recrystallizations of this solid from 12-ml. portions of ethanol gave 5.8 g. (85%) of white, crystalline, needle-like *trans*-1,4-cyclohexanediacetonitrile, m.p. 65–66°.

Anal. Calcd. for $C_{10}H_{14}N_2$: N, 17.26. Found: N, 17.21.

Acid Hydrolysis of Va. A mixture of 0.5 g. of Va and 10 ml. of hydrochloric acid (specific gravity, 1.19) was refluxed for 3 hr. The reaction mixture was diluted with 5 ml. of water and cooled in a ice-salt bath. The grayish white solid which separated was removed by filtration. One recrystallization of this solid from 150 ml. of boiling water gave 0.4 g. (65%) of white, needle-like *trans*-1,4-cyclohexanediacetic acid, m.p. 226–227°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.93; H, 8.06. Found: C, 60.10; H, 8.00.

cis-1,4-Cyclohexanediacetonitrile (Vb) was prepared from the crude *cis*-1,4-diiodomethylcyclohexane according to the procedure described for Va. Purification of Vb was achieved as follows. Most of the benzene was removed by distillation at atmospheric pressure. The residue was distilled further at reduced pressure (water aspirator) at a bath temperature of 120°. The brown oil which remained was distilled *in vacuo*, employing a semimicro fractionating apparatus. The fraction which distilled at 166–170° (2 mm.) was shown to contain mainly *cis*-1,4-cyclohexanediacetonitrile. The yield was 10.3 g. (50%). The calculation was based on 37.9 g. of IVb as starting material.

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[1] This paper was abstracted from a thesis submitted by Paulina P. Garcia to the Faculty of The Graduate School in partial fulfillment of the requirements of the Master of Science in the Department of Chemistry, The University of Tennessee.

[2] J. H. Wood and R. E. Gibson, *J. Am. Chem. Soc.*, **71**, 393 (1949).

[3] J. H. Wood, M. A. Perry, and C. C. Tung, *J. Am. Chem. Soc.*, **73**, 4689 (1951).

[4] All boiling points and melting points are uncorrected; melting points were determined on a Mel-Temp apparatus.

[5] Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Weiler and Strauss Microanalytical Laboratory, Oxford, England.

[6] T. Fort, Jr., *The Kinetics of the Base-Catalyzed Hydrolysis of the Methyl Esters of Cyclohexanedicarboxylic Acids*, master's thesis, The University of Tennessee, Knoxville, Tenn., 1957.

[7] R. Malachowski and J. Jankiewicsowna, *Ber.*, **67B**, 1783 (1934).

[8] G. A. Haggis and L. N. Owens, *J. Chem. Soc.*, 404 (1953).

[9] J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1950, p. 278.

Acid hydrolysis of Vb was accomplished according to the procedure described for Va. The crude product was purified by two recrystallizations from water. The yield was 0.2 g. (54%) of white, crystalline *cis*-1,4-cyclohexanediacetic acid, m.p. 166–167°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.93; H, 8.06. Found: C, 60.00; H, 8.06.

trans-1,4-Bis(2-aminoethyl)cyclohexane (VIa). *Method A.* To a well-stirred slurry of 21.3 g. (0.56 mole) of lithium aluminum hydride and 554 ml. of tetrahydrofuran was added 27.7 g. (0.17 mole) of Va in 554 ml. of tetrahydrofuran over a period of 4 hr. After addition was complete, the reaction mixture was refluxed for 2 hr. and then cooled in an ice-salt bath. Twenty-four milliliters of water, 15.7 ml. of 20% sodium hydroxide, and 68 ml. of water were added in succession to the cooled reaction mixture. The light brown precipitate which formed was separated by filtration and washed twice with 150-ml. portions of tetrahydrofuran. The combined filtrate and washings were distilled until most of the solvent had been removed. The oily residue was acidified with 200 ml. of 5% hydrochloric acid while the mixture was being cooled. The resulting acidic solution was extracted with two 100-ml. portions of ether to remove the unchanged diacetonitrile. Two hundred milliliters of 10% sodium hydroxide was added to the aqueous acidic layer and the resulting mixture was extracted with ten 80-ml. portions of benzene. After removing the solvent from the combined extracts by distillation, the crude amine (17.0 g.) was distilled *in vacuo* to yield 10.0 g. (34%) of a colorless oil, b.p. 122–126° (1 mm.).

Method B. The procedure followed for this method was adapted from that employed in the preparation of octylamine by Amundsen and Nelson[10] except that the reaction mixture was refluxed for 16 hr. From 9.3 g. (0.057 mole) of Va, there was obtained 8.25 g. (85%) of crude amine. Purification of this crude amine was accomplished in the usual manner. A yield of 5.79 g. (59%) of VIa, b.p. 122–126° (1 mm.) was realized.

cis-1,4-Bis(2-aminoethyl)cyclohexane (VIb). This isomer was prepared according to the procedure described in Method A for the preparation of VIa. Ten grams (0.062 mole) of Vb yielded 3.25 g. (31%) of crude amine. Purification of this crude amine was accomplished in the usual manner. The yield was 2.22 g. (21%) of a colorless oil, b.p. 106–110° (2 mm.).

Dibenzenesulfonamide of VIa *and* VIb. The amides were prepared by the usual method.[11] After recrystallizing the reaction product from alcohol, a 54% yield of the white, crystalline *trans*-sulfonamide, m.p. 168–169°, was obtained. Two recrystallizations of the reaction product for the *cis* isomer gave a 60% yield of the *cis*-sulfonamide, m.p. 133–134°.

Anal. Calcd. for $C_{22}H_{30}O_4N_2S_2$: N, 6.22. Found: N, 6.18 (*trans*); N, 6.29 (*cis*).

Dihydrochlorides. The dihydrochlorides were prepared by dissolving crude VIa or VIb in anhydrous ether and passing dry hydrogen chloride into the resulting solution for 10 min. The grayish white, gelatinous solid which formed was removed by filtration and washed with two 15-ml. portions of anhydrous ether. Two or three recrystallizations of this solid from ethanol gave the white crystalline dihydrochloride. The *trans* isomer melted at 319–322° dec.; yield, 34%. The *cis* isomer melted at 300–304° dec.; yield, 37%.

Anal. Calcd. for $C_{10}H_{24}N_2Cl_2$: Cl, 29.16. Found: Cl, 29.05 (*trans*); Cl, 29.72 (*cis*).

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(10) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 103.

Identification of a New, Naturally Occurring, Steam-Volatile Isothiocyanate from *Lesquerella lasiocarpa* Seed[1a]

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As part of a program evaluating the nutritional quality of seed meals from selected Cruciferae, determinations are being made of their contents of enzymatically formed steam-volatile isothiocyanates and thiooxazolidones. These compounds, formed from parent glucosides by action of enzymes normally present in the plant material, are undesirable because of the unpalatability they may confer or the effects they may have on the thyroid glands of animals ingesting them. Volatile isothiocyanates are conventionally isolated from various plant species by steam distillation and identified after conversion to corresponding thioureas by reaction with ammonia. Recent reviews in this field by Challenger[1] and by Kjaer,[2] and the structural work of Ettlinger and Lundeen,[3] provide impetus to further research in this phase of plant biochemistry.

The genus *Lesquerella* has been of special interest in our research on the chemistry of cruciferous oilseeds. Its seed oil glycerides contain major amounts of either 20-carbon or 18-carbon hydroxylated fatty acids, the structure of which will be reported in detail elsewhere. Utilization of seed oil requires profitable outlets for the coproduct protein meal. Seed meal from *Lesquerella* is therefore being investigated, and this note reports a portion of these studies.

Paper chromatography[4] of the thiourea derivatives of the volatile isothiocyanates from *lasiocarpa* seed showed one major and one very minor spot. The major spot gave an R_{ph} value (compared with phenylthiourea) different from that of any known thiourea derivative of an isothiocyanate isolated from a natural product, but was the same as that of *N*-(6-methylthiohexyl)thiourea; CH_3—S—$(CH_2)_6$—NH—CS—NH_2. This compound has been synthesized by Kjaer and Christensen.[5] Our thiourea derivative crystallized readily from alcohol on addition of water. The melting point and elementary analysis agreed with those of the synthetic compound. Infrared spectra and X-ray patterns from

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[1a] This is a contribution from a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(1) F. Challenger, *Aspects of the Organic Chemistry of Sulfur*, Butterworths Scientific Publications, London, 1959, p. 115.

(2) A. Kjaer, *Fortschritte der Chemie Organischer Naturstoffe*, L. Techmeister, ed., Springer Vienna, 1960, p. 122.

(3) M. G. Ettlinger and A. J. Lundeen, *J. Am. Chem. Soc.*, **78**, 4172 (1956).

(4) A. Kjaer and K. Rubinstein, *Acta Chem. Scand.*, **7**, 528 (1953).

(5) A. Kjaer and B. Christensen, *Acta Chem. Scand.*, **11**, 1298 (1957).