NOTES

Synthesis of 1,5-Di-(aminomethyl)-decalin-1,5-diol Diacetate[1,2]

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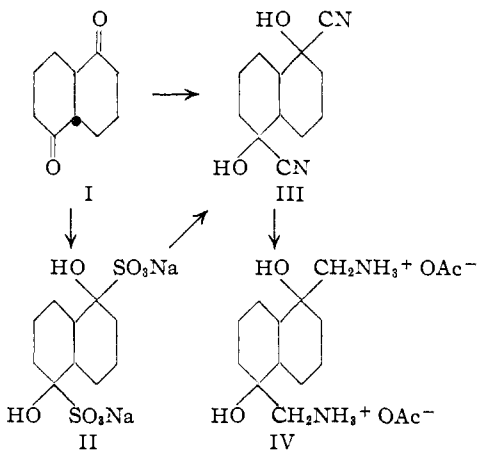
In the course of an attempted synthesis of compounds related to heptalene *via* intermediates having a functional group in each ring, *trans*-decalin-1,5-dione (I) has been converted by two routes to decalin-1,5-dione dicyanohydrin (III) and the latter compound reduced to 1,5-di-(aminomethyl)-decalin-1,5-diol diacetate (IV).



Direct addition of hydrogen cyanide to I gave a 62% yield of III. A superior method (84% yield) involved the formation of the bisulfite addition compound II followed by treatment with aqueous potassium cyanide. Reduction of III with lithium aluminum hydride gave a heavy gum from which no di-(aminomethyl) diol could be isolated.[3] Hydrogenation of III in acetic acid with a platinum catalyst went smoothly to give IV in 90% yield. An attempt to prepare IV *via* the corresponding di-(nitromethyl) diol was halted by the failure of the condensation reaction of I with nitromethane.

The Demjanov ring enlargement of IV could give three isomeric decahydroheptalenediones. Treatment of IV with nitrous acid gave a mixture of ketones which was somewhat unstable and could not be separated[4] but gave a di-2,4-dinitrophenylhydrazone and a disemicarbazone which gave the calculated analyses. Attempts to convert the ketone mixture to a derivative of heptalene (by enol acetate formation and then reaction with N-bromosuccinimide) or to structures related to tropone (by a bromination–dehydrobromination sequence) or tropolone (by oxidation with selenium dioxide and subsequent treatment with N-bromosuccinimide or bromine in acetic acid) having ten π-electrons in the bicyclo[5.5.0]dodecane ring system were unsuccessful.

Experimental[5]

trans-**Decalin-1,5-dione (I).**—Decalin-1,5-diol was prepared from 1,5-dihydroxynaphthalene and converted to *trans*-decalin-1,5-dione, m.p. 165°, as described by Johnson, *et al.*[6]

trans-**Decalin-1,5-dione Dicyanohydrin (III). Method A.**—A suspension of 10 g. (0.06 mole) of the dione I in 150 ml. of ether was shaken with 80 ml. of a saturated solution of sodium bisulfite for 3.5 hours. The crude addition product was separated, washed with ether and shaken for 2 hours with a solution of 24 g. (3.7 moles) of potassium cyanide in 100 ml. of water. The product was collected, washed with water and dried (desiccator). Crystallization from nitromethane and recrystallization from ether gave 11.1 g. (84%) of tiny colorless needles, m.p. 221–222° with evolution of gas.

Anal. Calcd. for $C_{12}H_{16}O_2N_2$: C, 65.42; H, 7.27. Found: C, 65.25; H, 7.39.

Method B.—To a suspension of 3 g. (0.018 mole) of I and 150 ml. of ether was added a solution of 8.1 g. (0.124 mole) of potassium cyanide in 10 ml. of water. The mixture was cooled to 5° and 11 ml. of concentrated hydrochloric acid was added dropwise with stirring. The mixture was allowed to warm to room temperature overnight, water was added to dissolve the precipitated potassium chloride and the separated aqueous layer extracted with ether. The ether extracts combined with the original organic layer were washed with 5% sulfuric acid and then dried over calcium sulfate. One drop of sulfuric acid was added to the solution and the solvent then removed. The product (2.45 g., 62%) was identical (m.p. and m.m.p. 221–222°) with that obtained above (A) and was purified in the same manner.

1,5-Di-(aminomethyl)-decalin-1,5-diol Diacetate (IV).—A mixture of 1 g. (0.0045 mole) of the dicyanohydrin III, 45 ml. of acetic acid and 0.1 g. of platinum oxide took up the theoretical quantity of hydrogen in 5 hours. The isolated amorphous solid was washed with ether and dried in a vacuum desiccator. Recrystallization from glacial acetic acid–ether solvent gave material (1.42 g., 90%) which melted at 231–235° dec.

Anal. Calcd. for $C_{16}H_{32}N_2O_6$: C, 55.17; H, 9.19; N, 7.50. Found: C, 54.83; H, 9.03; N, 7.52.

The dibenzenesulfonamide melted at 92.5–94° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{32}N_2O_6S_2$: C, 56.69; H, 6.29; N, 5.51; S, 12.59. Found: C, 56.80; H, 6.59; N, 5.46; S, 12.26.

Demjanov Ring Enlargement of 1,5-Di-(aminomethyl)-decalin-1,5-diol.—To a cooled solution of 8.4 g. (0.024 mole) of the di-(aminomethyl)-decalin diol in 120 ml. of water and 9 ml. of acetic acid was added dropwise with stirring a cold solution of 5.6 g. (0.08 mole) of sodium nitrite in water over a period of 15 minutes such that the temperature of the mixture was between 0 and 5°. After 10 hours (overnight) the mixture was neutralized with solid sodium bicarbonate and extracted with ether in a continuous extractor. Removal of the solvent from the dried ether solution left 1.81 g. (39%) of an oil which had a boiling point of 108–109° at

(1) From the Ph.D. thesis of David O. Barlow.

(2) Support for a part of this work by contract DA-04-200-ORD-235 with the Office of Ordnance Research is gratefully acknowledged.

(3) Apparently regeneration of ketonic material by the basic reagent and subsequent reduction occurred as the infrared spectrum of the gum showed a strong band at 3.05μ and a weak band at 5.85 μ. J. D. Roberts and W. F. Gorham, This Journal, **74**, 2278 (1952), have reported similar observations.

(4) Separation was attempted by distillation, crystallization and chromatography (on alumina) of the mixture both before and after formation of a bisulfite addition compound, formation and chromatography of an enol acetate derivative, and oxime formation.

(5) Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

(6) W. S. Johnson, C. D. Gutsche and D. K. Banerjee, This Journal, **73**, 5464 (1951).

0.2 mm. and was somewhat unstable.[7] The substance was identified as a decahydroheptalene dione (or a mixture of isomers) by formation of two derivatives.

The di-2,4-dinitrophenylhydrazone, for which no solvent for recrystallization was found, was purified by washing with hot methanol, hot water and hot methanol; m.p. 125–126°.

Anal. Calcd. for $C_{24}H_{24}N_8O_8$: C, 52.17; H, 4.35; N, 20.28. Found: C, 52.42; H, 4.84; N, 19.94.

The disemicarbazone, for which no satisfactory solvent could be found, was purified by successive washing with hot methanol, hot water and hot methanol. It had no discernible melting point but decomposed above 250°.

Anal. Calcd. for $C_{14}H_{24}N_6O_2$: C, 54.54; H, 7.79; N, 27.27. Found: C, 54.76; H, 7.79; N, 26.93.

(7) Other ketonic compounds in this series have been observed to be unstable. See G. Buchi and O. Jeger, *Helv. Chim. Acta*, **32**, 538 (1949).

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The Hydantoin Derivative of 4-Thiazolidinecarboxylic Acid

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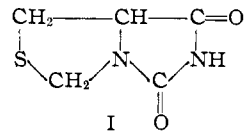
The hydantoin derivative of 4-thiazolidinecarboxylic acid (I) is of interest as a new derivative of cysteine and as an example of a fused ring system analogous to that of some hydantoins and thiohydantoins prepared during the studies of the chemistry of penicillin.[2] Both the D- and L-forms of the hydantoin have been prepared by causing the corresponding thiazolidinecarboxylic acids to react with potassium cyanate and then treating the reaction mixture with acid. Neither isomer showed penicillin activity when assayed with *B. subtilis*, nor biotin activity for *S. cerevisiae*.



I

Experimental

L-4-Thiazolidinecarboxylic acid was prepared according to the procedure of Schubert.[3] To a suspension of 0.50 g. of this compound in 25 ml. of water was added 0.61 g. of potassium cyanate; all of the thiazolidinecarboxylic acid went into solution. The solution was heated on a steam-bath for 30 minutes, then acidified by the addition of concd. HCl, an additional 0.5 ml. of concd. HCl was added, and the solution was evaporated to a low volume on a steam-bath. The solid that crystallized when the solution was cooled was collected and recrystallized from a small volume of water; yield 0.41 g. (69%), m.p. 167°. The compound is soluble in dil. alkali, slightly soluble in water and insoluble in acids, alcohol or acetone. It gives a negative test for sulfhydryl when treated with sodium nitroprusside, both before and after treatment with sodium cyanide.

When the rotation is measured immediately upon dissolving in 1 *N* NaOH, $[\alpha]^{20}D$ −115° (*c* 1); the rotation gradually decreases over a period of 12 hours, and then remains constant at $[\alpha]^{20}D$ −23°.

Anal. Calcd. for $C_5H_6O_2N_2S$: C, 37.98; H, 3.80; N, 17.72; S, 20.25. Found: C, 38.06; H, 4.21; N, 17.61; S, 20.53.

The corresponding derivative prepared from D-cysteine hydrochloride was identical with the above compound in all its chemical and physical properties with the exception of the optical rotation; for a 1% solution in 1 *N* NaOH, $[\alpha]^{20}D$ +115°, decreasing to $[\alpha]^{20}D$ +23°.

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(1) Univ. of Utah College of Medicine, Salt Lake City, Utah.

(2) "The Chemistry of Penicillin," Princeton University Press, 1949, pp. 302, 970, 971.

(3) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936).

Experimental Chemotherapy of Tuberculosis. IV. 2-Piperazinecarboxylic Acid and Related Compounds

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In view of the high antituberculous activity of Aldinamide,[1a] pyrazinamide,[1b] it was considered necessary to investigate the effect of various changes in the chemical constitution of this compound. One variation of interest was the reduced form of pyrazinamide, namely, 2-piperazinecarboxamide. Since pyrazine derivatives of this type are not easily reduced, 2-piperazinecarboxylic acid, a new acid, was synthesized as an intermediate.

The disodio derivative of N,N′-di-*p*-tosylethylenediamine was condensed with ethyl α,β-dibromopropionate in a refluxing ethanolic potassium hydroxide solution to yield the ethyl ester of 1,4-di-*p*-tosyl-2-piperazinecarboxylic acid. Hydrolysis of the ester and detosylation occurred when this derivative was refluxed in 48% hydrobromic acid. The free acid released by silver carbonate in an aqueous medium was very soluble in water, insoluble in the ordinary organic solvents and was characterized as a white, crystalline solid which melted with decomposition at 275–277°. The infrared spectrum of this substance shows a typical amino acid carboxylate ion absorption at 6.32 μ.[2] Attempts to esterify 2-piperazinecarboxylic acid by the usual methods such as refluxing with ethanol and hydrogen chloride or by treatment with diazomethane were unsuccessful. However, esterification can be accomplished by a prolonged refluxing of the acid in ethanol, benzene and concentrated sulfuric acid, followed by a periodic distillation from the reaction of an azeotropic mixture consisting of ethanol, benzene and water. The ester prepared in this manner was treated with hydrazine hydrate (100%) to yield 2-piperazinecarboxylic acid hydrazide and an ammonolysis of ethyl 2-piperazinecarboxylate afforded the desired product, 2-piperazinecarboxamide.

The 2-piperazinecarboxylic acid which was purified by sublimation *in vacuo* gave an elemental analysis and neutralization equivalent in accord with the calculated amounts and an electrometric titration of the dihydrochloride of this acid showed end-points at *p*H 3.7, 7.5 and 10.6. One molar equivalent of this cyclic amino acid when condensed with two molar equivalents of ninhydrin in a warm, neutral, aqueous solution gives a deep-red colored solution. A similar reaction between proline and

(1) (a) The trade-mark of American Cyanamid Company for pyrazinamide is Aldinamide; (b) S. Kushner, H. Dalalian, J. L. Sanjurjo, F. L. Bach, Jr., S. R. Safir, V. K. Smith, Jr., and J. H. Williams, THIS JOURNAL, **74**, 3617 (1952).

(2) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 16.