Syntheses and Reactions of Some 2,6-Disubstituted Piperidines

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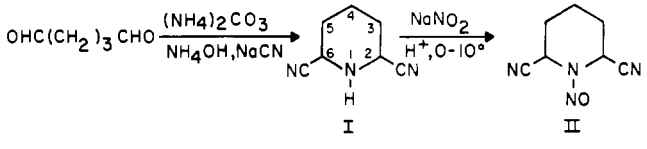
The separation of two isomers of 2,6-dicyanopiperidine and the preparation of the nitroso derivative of one isomer are reported. The synthesis of 1-nitroso-*cis*-2,6-dicarbomethoxypiperidine is also described.

THE ABNORMAL OXIDATION of 1,1-disubstituted hydrazines has been a subject of continuing interest (*3*). With regard to 1-amino-2,6-dicyanopiperidine, only a low yield of one isomer of this compound has been obtained by a Strecker-type reaction (*4–6*). The oxidation of this isomer was found to proceed by the "abnormal" route. Formation of coupled and linear products was suggested to occur via a free radical mechanism.

The following reaction sequence was investigated as an alternate procedure for the preparation of the cis- and trans-isomers of 1-amino-2,6-dicyanopiperidine. By this route, a mixture of the two isomeric 2,6-dicyanopiperidines (I) was obtained. A higher melting isomer (melting point, 113–14° C.) was separated from this mixture. Extraction of the lower melting mixture yielded a fraction enriched in the lower melting isomer. From this, a small quantity of the purified lower melting isomer (melting point 69.5–70.5° C.) was isolated by fractional crystallization. Stereochemical assignments (cis or trans structures) could not be adequately derived from infrared or nuclear magnetic resonance spectra.



I II

From the higher melting isomer of I, nitrosoamine (II) was obtained in high yield and purity. The nuclear magnetic resonance spectrum of this compound is indicative of a rigid ring system rather than a rapidly interconverting one. Reduction of II to 1-amino-2,6-dicyanopiperidine by a variety of catalyst systems could not be effected. The nitrosoamine of the lower melting isomer of I was not prepared because of the limited amount of the purified starting material.

Since many nitrosoamines can undergo the abnormal elimination reaction with sodium hydrosulfite (*4–6*), the reduction of II and of 1-nitroso-*cis*-2,6-dicarbomethoxypiperidine (*1*) was investigated. A partial and variable nitrogen elimination occurred for II, whereas the dicarbomethoxyisomer gave no nitrogen elimination.

EXPERIMENTAL

Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Mühlheim (Ruhr), Germany, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nuclear magnetic resonance spectra were obtained on a Varian HR-60 instrument operating at 60 megacycles per second at 25° C., infrared spectra on a Perkin-Elmer Model 21, and ultraviolet spectra on a Beckman Model DK-2 spectrophotometer.

Preparation of 2,6-Dicyanopiperidines. The preparative procedure was initiated by Cameron (*2*). Product separation, identification, and characterization were not previously reported. A solution of 40 grams (0.40 mole) of glutaraldehyde in 280 ml. of ether was added in a period of 90 minutes to a solution of 228 grams (2 moles) of ammonium carbonate, 43 grams (0.88 mole) of sodium cyanide, and 8 ml. of concentrated ammonium hydroxide in 650 ml. of water. After stirring overnight, the two clear layers were separated and worked up individually. The ether layer, after drying over sodium sulfate, gave 13.8 grams of an off-white solid melting at 55° to 70° C. A quantity of 8.9 grams of 2,6-dicyanopiperidine melting at 112–13° C. was recovered from the sodium sulfate used for drying the ether solution by extraction with boiling toluene. The water layer was extracted with 1 liter of ether after saturation with sodium chloride to give 12 grams of yellow solid. Extraction of the solid with 300 ml. of boiling toluene and crystallization in the freezer gave 2.3 grams of off-white solid melting at 113–14° C. Evaporation of the solvent from the mother liquor yielded 5.0 grams of a yellow solid, the lower melting isomer mixture, melting at 56° to 80° C.

The low melting solids were combined and extracted in a Soxhlet apparatus with pentane for five 24-hour periods. Evaporation of the pentane yielded a mixture of isomers containing 70 to 90% of the low melting isomer (determined by infrared analysis). The extraction residue weighed 4.6 grams and melted at 108°–11° C. and was the higher melting isomer of I. The total yield of the high melting isomer obtained from the ether and water layers was 14.1 grams (26.1%). The yield of mixed isomers recovered from the pentane extract was 12.8 grams (23.7%).

A pure sample of the lower melting isomer was obtained by fractional crystallization. Crystallization from toluene at 25° and −20° C. yielded isomer mixtures. Concentration of the mother liquor followed by crystallization at −20° C. yielded a third crop of mixed isomers. Crystallization from the resulting mother liquor in a dry ice chest formed a small quantity of white crystals melting at 68–70° C. Recrystallization from toluene at −80° C. gave 40 mg. (from ca. 20 grams of mixed isomers) of the purified, lower melting isomer of I, melting at 69.5–70.5° C.

Infrared analysis of both isomers in chloroform showed typical amine and nitrile absorption. An absorption at 11.60 microns was characteristic of the higher melting isomer, and a medium absorption at 11.60 microns and a strong absorption at 11.93 microns were characteristic of the lower melting isomer. The nuclear magnetic resonance spectra of both isomers of I in pyridine solutions are given in Table I.

Anal. Calcd. for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.13. Found: (higher melting isomer) C, 62.38; H, 6.90; N, 30.91; (lower melting isomer) C, 62.30; H, 6.86; N, 31.00.

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Table I. Nuclear Magnetic Resonance Spectra of Both Isomers of I

Chemical Shifts			
Higher melting I	Lower melting I	Proton Ratio	Assignment
8.34τ	8.36τ	6	Methylene hydrogens
5.95τ	5.93τ	2	Methine 2,6-hydrogens
5.70τ	5.74τ	1	Amino hydrogen

N-Acetyl derivatives were made of both isomers. For the higher melting isomer, this derivative was recrystallized from water, yielding white leaflets melting at 131.2–32.1° C. The lower melting derivative was recrystallized from a toluene-hexane mixture, giving white crystals melting at 62.5–64.1° C.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: (higher melting derivative) C, 61.02; H, 6.48; N, 23.64; (lower melting derivative) C, 60.78; H, 6.18; N, 23.55.

The spectra in Table I were obtained in pyridine solutions using tetramethylsilane as internal standard.

Preparation of 1-Nitroso-2,6-dicyanopiperidine (from Higher Melting Isomer). A solution of 7.2 grams (0.10 mole) of sodium nitrite in 25 ml. of water was added in one-half hour to a solution of 13.5 grams (0.10 mole) of 2,6-dicyanopiperidine (m.p. 113–14° C.) in 300 ml. of 1.25% hydrochloric acid at 25.30° C. After 2 hours, the slurry was cooled in an ice bath, filtered, washed, and dried to yield 14.8 grams (90%) of a pale yellow, fluffy solid melting at 140–41° C. Recrystallization from a chloroform–carbon tetrachloride mixture gave pale yellow needles melting at 142–43° C. The infrared spectrum in chloroform showed strong nitrosoamine absorptions at 6.65, 7.90, 9.15, 10.40, and 10.80 microns. The nuclear magnetic spectrum taken in deuterochloroform solution showed a broad unresolved peak at 7.87τ, corresponding to 6 protons, and two doublets at 4.09τ with $J_{2\text{-}3a}$ = 21.5 c.p.s. and $J_{2\text{-}3e}$ = 12.6 c.p.s. (*a* = axial, *e* = equitorial). This pattern is indicative of an ABX system and to this apparently rigid (noninterconverting) compound can be assigned the cis configuration.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.22; H, 4.91; N, 34.15. Found: C, 51.20; H, 5.05; N, 33.94.

Preparation of *cis*-2,6-Dicarbomethoxypiperidine. 2,6-Dicarbomethoxypyridine (*1*) was reduced by catalytic hydrogenation by the procedure of Rubtsov, Nikitskaya, and Usovskaya (*7*) at 30 to 40 pounds of hydrogen pressure with platinum oxide catalyst, but with one necessary modification. The reported solvent was methanol containing 2% hydrogen chloride. No hydrogen uptake was observed under these conditions. However, in the absence of hydrogen chloride the reaction proceeded readily in 2 hours to form *cis*-2,6-dicarbomethoxypiperidine in 76.5% yield, melting at 90.5–91.2° C. [lit. (*1*) m.p. 92° C.].

Preparation of 1-Nitroso-*cis*-2,6-dicarbomethoxypiperidine. A solution of 5 grams (0.07 mole) of sodium nitrite in 10 ml. of water was added in 10 minutes to a solution of 13.3 grams (0.066 mole) of *cis*-2,6-dicarbomethoxypiperidine in 75 ml. of water containing 5.5 ml. of concentrated hydrochloric acid, while the temperature was kept at 0° to 5° C. A pale yellow, fluffy solid was formed, weighing 13.8 grams and melting at 55.5–57.0° C. An analytical sample, recrystallized from hexane, melted at 56.5–57.7° C.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 46.95; H, 6.13; N, 12.17. Found: C, 47.24; H, 6.37; N, 11.94.

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Methyl-1-(β-D-glucopyranosyl)-3-indoleacetate

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The synthesis of methyl-1-(β-D-glucopyranosyl)-3-indoleacetate, a hydrophilic compound related to the naturally occurring plant hormone, 3-indoleacetic acid, is described.

A NATURALLY occurring plant growth regulator, 3-indoleacetic acid, has been extensively investigated both as the parent acid and in the form of its derivatives in order to learn more about the relationship of structure to biological activity (*8*). Such investigations are important to other areas of research as well, in particular to the area of animal hormone investigations. This synthesis is part of an attempt to relate the effects of solubility, steric requirement, and electronic density to the physiological activity of 3-indoleacetic acid derivatives. These may also serve as models for investigation of animal hormones. The extreme hydrophilic nature of the glucosyl moiety led to its choice as a group for imparting water solubility to 3-indoleacetic acid.

Indoline (I) was converted efficiently (66% yield) to 1-(β-D-tetra-*O*-acetylglucopyranosyl)indoline (II) by treatment with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in ether solution, using Na_2CO_3 to neutralize the HBr evolved (*4*). Pyridine used as an acid in ethanol solution gave only low yields of approximately 20% of product II. Suvorov