[CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

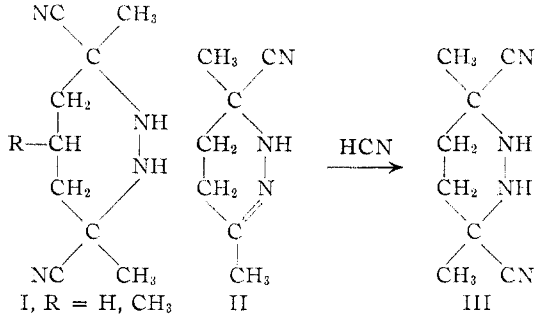
Azo Nitriles. VI.[1] The Preparation of Cyclic Hydrazines from Diketones. A New Type of Seven-Membered Ring

BY C. G. OVERBERGER, THOMAS B. GIBB, JR.,[2] SHELDON CHIBNIK,[2] PAO-TUNG HUANG AND JOHN J. MONAGLE

RECEIVED DECEMBER 14, 1951

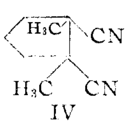
It was the purpose of this research to prepare a cyclic azo nitrile which would decompose to give a biradical at convenient temperatures. As starting materials, two examples of I (R = H, CH_3) which represents a new type of seven-membered ring, have been synthesized. The former on oxidation gives a homopiperidazine which spontaneously eliminates nitrogen to form a biradical. Syntheses of the necessary diketones have been improved. Reaction of acetonylacetone in a similar manner with the dilution technique gave II. Addition of hydrogen cyanide to this product in excess liquid hydrogen cyanide gave III in high yield. 2-Ethyl-5-ketohexanal dioxime has also been prepared and characterized.

A previous paper[3] in this series has described the reaction of monofunctional ketones with cyanide ion and hydrazine to give symmetrically 1,2-disubstituted hydrazines. We have now begun a study of this reaction with diketones in order to prepare cyclic and linear derivatives. This paper describes the preparation of 3,7-dicyano-3,7-dimethylhomopiperidazine (3,7-dicyano-1,2,4,5,6-pentahydro-3,7-dimethyl-1,2-diazepine) (I, R = H) and the corresponding 3,5,7-trimethyl compound (I, R = CH_3) from heptandione-2,6 and 4-methylheptanedione-2,6, respectively, by their reaction with cyanide ion and hydrazine in dilute solution. Also described is the preparation of 3,6-dicyano-3,6-dimethylpiperidazine (III) from acetonylacetone by the scheme



I, R = H, CH_3 II III

Compounds of type I represent a new class of seven-membered ring. Both I and III are precursors for the synthesis of substituted cyclopentanes and cyclobutanes, respectively, and are potential sources of biradicals in vinyl polymerization. The oxidation of the homopiperidazine (diazepine) (I, R = H) is described here. The azo intermediate is unstable and immediately decomposes with a quantitative evolution of nitrogen to give two stereoisomers of IV and a linear product.



IV

The dioximes of the heptanediones were prepared from 2,6-lutidine and 2,4,6-collidine by the general procedure described by Shaw[4] which consists of reduction of the substituted pyridine to give the alleged 1,4-dihydro derivative followed by cleavage with hydroxylamine in acid solution. In most of Shaw's experiments there is inadequate characterization of the products. With heptane-2,6-dione, reference 4c implies that the dioxime can be prepared in this way, but no yield, analysis, or properties are reported. It was convenient to distil the dioximes since *cis–trans* isomers made purification by crystallization impractical. The dioxime derived from aldehyde collidine has also been prepared and characterized. Treatment of the dioximes according to the procedure of Keagle and Hartung[5] with nitrous acid at 0° gave the heptanediones which can be utilized without purification or which can be purified by distillation, provided that all traces of acids or bases are removed (R = H, 47.5% based on dioxime; R = CH_3, 50.2%). This is a far superior procedure for preparing such diketones when compared with procedures previously reported (see Experimental section)..

Treatment of the aqueous solution of the diketones with hydrazine sulfate and sodium cyanide with a higher dilution than that reported by reference 3 gave the homopiperidazines (R = H, 33.8%; R = CH_3, 32.7%, yields based on dioximes). The over-all yield of the homopiperidazines based on the dioximes is about the same whether or not the ketone is isolated.

Treatment of acetonylacetone by the same procedure at the same dilution gave 3-cyano-3,6-dimethyl-2,4,5-trihydropyridazine (II) in 57.6% yield. The addition of anhydrous hydrogen cyanide with acid catalysis at room temperature gave III in 83.5% yield.

On oxidation of I, R = H, a quantitative volume of nitrogen was evolved and two stereoisomers of IV were isolated and characterized. It seems likely that these coupled products arise from ring closure by coupling of the intermediate biradical $[CH_3\text{-}\dot{C}(CN)(CH_2)_3(CN)\dot{C}\text{-}CH_3]$. Both of these products gave no reaction with bromine and phosphorous tribromide[6] indicating the proposed struc-

---

[1] For the fifth paper in this series, see C. G. Overberger and M. B. Berenbaum, THIS JOURNAL, **73**, 4883 (1951).

[2] A portion of theses submitted by T. B. Gibb, Jr., and S. Chibnik in partial fulfillment of the requirements for the Master of Science degree in the Graduate School of the Polytechnic Institute of Brooklyn.

[3] C. G. Overberger, M. T. O'Shaughnessy and H. Shalit, *ibid.*, **71**, 2661 (1949).

[4] (a) B. D. Shaw, *J. Chem. Soc.*, **125**, 1930 (1924); (b) *ibid.*, **127**, 215 (1925); (c) *ibid.*, **151**, 300 (1937); (d) A. C. Cope, H. L. Dryden, Jr., C. G. Overberger and A. A. D'Addieco, THIS JOURNAL, **73**, 3416 (1951).

[5] L. C. Keagle and W. H. Hartung, *ibid.*, **68**, 1608 (1946).

[6] C. L. Stevens, *ibid.*, **70**, 165 (1948); C. L. Stevens and T. H. Coffield, *ibid.*, **73**, 103 (1951). For a discussion of this reaction see reference 1.

tures. A linear product was also isolated. The structure of this and related products will be discussed in a forthcoming paper dealing with internal disproportionation reactions. Oxidation studies of other cyclic hydrazines is in progress.

Experimental[7]

Preparation of Heptanedione-2,6-dioxime.—The procedure used in the preparation of this diketone was the procedure reported by Shaw as modified,[4d] except the reaction product was isolated in a different way. From 107.2 g. (1.00 mole) of 2,6-dimethylpyridine in 450 ml. of absolute alcohol, 23.0 g. (1.00 mole) of freshly cut sodium, 69.5 g. (1.00 mole) of hydroxylamine hydrochloride in 125 ml. of 50% ethanol and 75.0 g. (0.76 mole) of concentrated hydrochloric acid in 125 ml. of ethanol, there was obtained on distillation under reduced pressure 30.4–35.2 g. of viscous oil, b.p. 165–169° (2–3 mm.). The product was isolated in the following way. After the reaction mixture was heated with reflux 2.5 hours, cooled, and filtered, excess 2,6-dimethylpyridine and alcohol were removed under reduced pressure. The residue was cooled, 70 g. (1.75 moles) of sodium hydroxide in 200 ml. of water was added, and the solution was extracted with ether. The water layer was acidified with 5 *N* hydrochloric acid while the temperature of the solution was held at 0 to 5°, the product was extracted with ether, and the ether solution was dried over anhydrous magnesium sulfate (40% based on hydroxylamine hydrochloride).

Anal.[8] Calcd. for $C_7H_{14}N_2O_2$: N, 17.72. Found: N, 17.72.

When the distilled product was crystallized twice from an ether–petroleum ether (b.p. 60–68°) solution the melting point was 83.4–84.6° (89°, prepared from the diketone prepared from a hydropyran, no yield reported)[9] (87°, prepared from the diketone which was prepared by ozonolysis of rubber hydrochloride, no yield reported).[10]

Preparation of 4-Methylheptanedione-2,6-dioxime.—This dioxime was prepared from 2,4,6-trimethylpyridine, b.p. 167°, by the same procedure used to prepare heptanedione-2,6-dioxime. The alcohol used in this preparation was dried immediately before using and distilled directly into the reaction vessel. Several attempts were made to prepare a sample of this dioxime using commercial absolute alcohol, but no product was obtained until the dry alcohol was used. A 29.2 to 32.8% yield of a viscous liquid product, $n^{55}\mathrm{D}$ 1.4870, b.p. 130–135° (0.5 mm.), was obtained (275° (12 mm.), no yield reported).[4c]

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.70; H, 9.36; N, 16.27. Found: C, 55.57; H, 9.21; N, 16.66.

Preparation of 2-Ethyl-5-ketohexanal Dioxime.—This dioxime was prepared from 5-ethyl-2-methylpyridine, b.p. 172–174°, $n^{25}\mathrm{D}$ 1.4961 (b.p. 68° (18 mm.), $n^{20}\mathrm{D}$ 1.4971).[11] A yield of 23.8% of the theoretical amount of crystals, m.p. 57–64°, was obtained without distilling the crude product. When this material was recrystallized from benzene seven times, the melting point was 77.5–79.5° (no yield reported, no product described[4c]).

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.70; H, 9.36; N, 16.27. Found: C, 55.66; H, 9.24; N, 16.57.

Preparation of Heptanedione-2,6.—The procedure used is similar to one described by Keagle and Hartung[5] who prepared succindialdehyde from its dioxime by this method. A solution of 25.2 g. (0.156 mole) of purified heptanedione-2,6 dioxime dissolved in 110 ml. of 10% aqueous sulfuric acid was cooled below 0°, while 22.5 g. (0.285 mole) of sodium nitrite was added slowly with vigorous stirring for one hour. The temperature was held below 0° during the addition, then was allowed to rise to 18°. The solution was neutralized by adding barium carbonate with stirring for 15 minutes then filtered through a filter aid, saturated with sodium chloride and extracted with a total of 700 ml. of ether (6 portions). A red oil separates after neutralization with barium carbonate. After the extract was dried, about 600 ml. of ether was removed and the dark red solution cooled at Dry Ice temperatures. The solid which formed was removed by filtration through a cold buchner funnel, 7.93 g. Concentration of the filtrate gave an additional 4.53 g. The total solids were recrystallized using "Norite" from an ether–petroleum ether (b.p. 28–38°) mixture, 9.7 g. (47.5%). This product may be purified by distillation. The distillate boiled at 48–50° (1 mm.), $n^{37}\mathrm{D}$ 1.4256, m.p. 31–33°. When this product was crystallized from petroleum ether (b.p. 35–60°) the melting point was raised to 32.6–33.4° (m.p. 33–34°, b.p. 96.5–97° (10–11 mm.), 221–222° (764 mm.), $n^{37}\mathrm{D}$ 1.42767 prepared from a rubber hydrochloride)[10] (m.p. 31°, b.p. 221–222° (764 mm.), no yield, prepared from a dihydropyran).[9]

Preparation of 4-Methylheptanedione-2,6.—This diketone was prepared from its purified dioxime by the method described above (50.2%), b.p. 49–51° (1 mm.); $n^{25}\mathrm{D}$ 1.4312 (b.p. 95–96° (12 mm.), no yield given, by reduction of 4-methylheptene-3-dione-2,6).[12]

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.60; H, 9.92. Found: C, 67.36; H, 10.00.

The 2,4-dinitrophenylhydrazone was prepared by a conventional procedure, m.p. 204.4–205.6° (199°).[4c]

Anal. Calcd. for $C_{20}H_{22}N_8O_8$: N, 22.31. Found: N, 22.40.

Preparation of 3,7-Dicyano-3,7-dimethylhomopiperidazine (3,7-Dicyano-1,2,4,5,6-pentahydro-3,7-dimethyl-1,2-diazepine).—The procedure is the same as one described by Overberger and co-workers[3] except that the amount of water used was increased fourfold. To a solution of 56.2 g. (0.426 mole) of hydrazine sulfate and 41.7 g. (0.861 mole) of sodium cyanide was added the diketone solution obtained from 61.1 g. (0.387 mole) of the dioxime of heptanedione-2,6. The total volume of solution was 2900 ml. After the solution had been shaken for 50 hours, solid had separated. This solid, 10.2 g., m.p. 101–104°, was removed by filtration; recrystallization from ether gave 8.94 g., m.p. 104.8–105.4°. The residual liquid was extracted 5 times with methylene chloride. After drying and removal of the methylene chloride at reduced pressure, a solid residue was obtained, 25.9 g. Recrystallization of the residue from ether gave 14.34 g., m.p. 104–104.8°; total yield 23.3 g. (33.8%). Shaking for 62 hours gave a 36.3% yield.

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 61.03; H, 7.63; N, 31.22.

The picrate, m.p. 123.1–123.5° (dec.), was prepared by a conventional procedure. It was found necessary to use anhydrous solvents in the preparation and purification of this derivative to avoid hydrolysis.

Anal. Calcd. for $C_{15}H_{17}N_7O_7$: C, 44.22; H, 4.21. Found: C, 44.62; H, 4.23.

In most of the preparations of this homopiperidazine, the diketone was allowed to remain in the water solution obtained from the hydrolysis of the dioxime. The homopiperidazine may also be prepared from the pure diketone in a similar manner.

This substance may be stored at Dry Ice temperature for six weeks without any apparent change, but after six weeks at room temperature the melting point had dropped 15° and a portion of the crystals had turned to an ether insoluble resin.

Preparation of 3,7-Dicyano-3,5,7-trimethylhomopiperidazine (3,7-Dicyano-1,2,4,6-tetrahydro-3,5,7-trimethyl-1,2-diazepine).—This homopiperidazine was prepared by the same procedure that was used above except that the amount of water used was doubled. White crystals, m.p. 130.9–131.4°, were obtained by crystallization of the product from ether–petroleum ether solution; 43.7% when the purified diketone was used as starting material; 32.7% (average of 7 experiments) when the hydrolysis product from the dioxime was used directly.

Anal. Calcd. for $C_{10}H_{16}N_4$: N, 29.15. Found: N, 28.97.

The picrate, m.p. 139.8–141.0° (dec.) was prepared by the method described above.

---

[7] All melting points are corrected.

[8] Analyses by Mr. Harry Biletch and Mr. Pao-tung Huang, Polytechnic Institute of Brooklyn; Dr. F. Schwarzkopf, New York, N. Y.; Dr. K. Ritter, Zurich, Switzerland; Drs. Weiler and Strauss, Oxford, England.

[9] R. G. Fargher and W. H. Perkins, *J. Chem. Soc.*, **105**, 1353 (1914).

[10] C. Harries, *Ber.*, **47**, 784 (1914).

[11] R. L. Frank, J. R. Blegen, R. J. Dearborn, R. L. Myers and F. E. Woodward, THIS JOURNAL, **68**, 1368 (1946).

[12] A. Baeyer and J. Piccard, *Ann.*, **384**, 208 (1911); **407**, 332 (1915).

Anal. Calcd. for $C_{16}H_{19}O_7N_7$: N, 23.2. Found: N, 23.4.

3-Cyano-3,6-dimethyl-2,4,5-trihydropyridazine (3-Cyano-3,6-dimethyl-1,2-diazacyclohexene-6).—The procedure is essentially that employed for the δ-diketones. From 11.3 g. (0.23 mole) of sodium cyanide, 13.0 g. (0.10 mole) of hydrazine sulfate and 11.4 g. (0.10 mole) of acetonylacetone in 1.6 l. of water there was obtained on continual shaking for two days, a homogeneous solution. This solution was extracted with four 250-ml. portions of methylene chloride, and the extracted portion was dried over anhydrous magnesium sulfate. The solvent was removed at room temperature under reduced pressure and an atmosphere of nitrogen to yield 12.4 g. (90%) of yellow oil, b.p. 173°, $n^{25}D$ 1.4854. The compound can be purified by distillation under reduced pressure in a current of nitrogen, b.p. 92.5–94° (2 mm.); it is advisable to distil rapidly from a modified Claisen flask as some decomposition occurs, the rate of which is increased by slow distillation, or by the use of a fractionating column. The crude oil crystallized after standing for several weeks; in later experiments the reaction product could be immediately induced to crystallize by seeding and cooling. The solid product was purified by recrystallization from ether and petroleum ether (b.p. 29–38°) and by sublimation at room temperature under a vacuum of 0.005 mm. to yield 7.9 g. (57.6%), m.p. 57.2–58.4°. On standing in air it liquefies and discolors, but can be kept easily in an atmosphere of nitrogen.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.28; H, 8.08; mol. wt., 137.2. Found: C, 61.49; H, 8.08; mol. wt. (cryoscopic in benzene), 138.9, 136.8.

A hydrochloride was prepared as a derivative by dissolving the compound in ether and saturating the solution with dry hydrogen chloride. The compound was purified by recrystallization from alcohol (some loss occurs due to decomposition) or by dissolving in aqueous sodium hydroxide solution, extraction of the free base with ether, drying the ethereal solution, and reprecipitation by hydrogen chloride. The salt turned brown at 136° and melted at 141–142° (rate of heating 2°/min.).

Anal. Calcd. for $C_7H_{12}N_3Cl$: C, 48.41; H, 6.97; N, 24.20; neut. equiv., 174. Found: C, 48.41; H, 7.32; N, 23.95; neut. equiv., 171.

3,6-Dicyano-3,6-dimethylpiperidazine.—This compound was prepared by the method of Alderson and Robertson,[13] except that an acid catalyst was used. From 7.7 g. (0.056 mole) of 3-cyano-3,6-dimethyl-2,4,5-trihydropyridazine, 40 ml. of anhydrous liquid hydrogen cyanide and 3 drops of concentrated hydrochloric acid, at room temperature for 16 hours, there was obtained on recrystallization from a benzene–ether mixture 7.9 g. (83.5%) of dinitrile.

The pure compound melted at 99.0–99.9° with decomposition and gas evolution at 100.3° (heating rate 2°/min.).

Anal. Calcd. for $C_8N_4H_{12}$: C, 58.41; H, 7.37; N, 34.12; mol. wt., 164.2. Found: C, 58.51; H, 7.47; N, 34.09; mol. wt. (cryoscopic in benzene), 162, 163.

Oxidation of 3,7-Dicyano-3,7-dimethylhomopiperidazine (3,7-Dicyano-1,2,4,5,6-pentahydro-3,7-dimethyl-1,2-diazepine).—A solution of 17.8 g. (0.1 mole) of 3,7-dicyano-3,7-dimethylhomopiperidazine in 765 ml. of 95% ethanol was cooled to −5° and 18.6 g. (0.12 mole) of bromine was added dropwise with vigorous agitation while the temperature was held between 0 and −5°. After removal of most of the ethanol under reduced pressure, 65 ml. of water was added and the remainder of the ethanol was removed under reduced pressure. The organic portion of the residue was dissolved in ether, washed with water and dried over magnesium sulfate. After the ether was removed, the product was distilled at 0.5 mm. pressure to give 12.0 g. (81.1%) of mixed liquid and solid.

In order to determine the amount of nitrogen evolved, a solution of 0.1913 g. (0.00108 mole) of the homopiperidazine was oxidized as described above. The reaction vessel, a 25-ml. distilling flask was connected to a gas delivery tube immersed in a water-bath under an inverted, water-filled buret. The volume of water displaced was equivalent to 24.4 ml. of nitrogen (cor. to standard conditions) or 101% of the theoretical amount.

Isolation of Isomeric 1,2-Dimethyl-1,2-dicyanocyclopentanes (A).—The mixed liquid and solid isolated above was placed in a vacuum sublimation apparatus at 35–40° (0.2 mm.) for five hours during which time 0.73 g. of low melting sublimate was collected. The crystals were resublimed under reduced pressure and crystallized from petroleum ether (b.p. 35–60°). Several additional sublimations gave 0.07 g. (0.47%), m.p. 155.7–156.4°.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.9. Found: C, 72.90; H, 7.91; N, 18.9.

(B).—The liquid residue from the first sublimation was cooled to −5° for six hours and filtered to remove 1.99 g. of crystals which had precipitated. On cooling the filtrate for 48 hours, an additional 0.69 g. of crystals was obtained. Distillation of the remaining liquid through a Craig[14] still at 0.1 to 0.3 mm. pressure first gave solid followed by liquid. When this crystalline condensate was crystallized from petroleum ether (b.p. 35–60°), 0.35 g. of crystals were obtained. The total yield of crystals was 1.52 g. (10.3%) m.p. 161.5–162.1°, from petroleum ether (b.p. 35–60°).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.9. Found: C, 73.01; H, 8.11; N, 18.9.

The stereochemistry of these solid isomers and the composition of the liquid fraction will be discussed in a later paper.

Attempted Reaction of Coupled Products with Bromine and Phosphorus Tribromide.—The reactions were carried out according to the directions of Stevens and Coffield.[6] Both isomers gave only starting material, indicating a tertiary nitrile and not a secondary nitrile.

BROOKLYN, N. Y.

---

(13) W. L. Alderson and J. A. Robertson, U. S. Patent 2,469,358, (May 10, 1949); C. G. Overberger and M. B. Berenbaum, THIS JOURNAL, **73**, 2618 (1951).

(14) L. C. Craig, *Ind. Eng. Chem., Anal. Ed.*, **9**, 441 (1937).