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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

# The 2-Pyridyl Analog of Demerol

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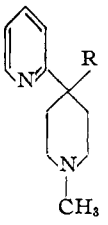
2-Pyridylacetonitrile has been converted by established procedures *via* the intermediate nitrile I and amide II to 1-methyl-4-(2-pyridyl)-4-carbomethoxypiperidine (III), the 2-pyridyl analog of Demerol.

The replacement of a benzene ring of a physiologically active compound by an isosteric system such as the pyridine nucleus is a process which has led to many interesting compounds and some useful drugs.[2] We have made use of this principle in the preparation of the 2-pyridyl analog of the known analgesic Demerol (Meperidine).[3] No previous report of the preparation of this compound or its 3- or 4-pyridyl isomers could be found in the literature.



I, R = CN
II, R = $CONH_2$
III, R = $COOCH_3$
IV, R = H

2-Pyridylacetonitrile was condensed with di-(2-chloroethyl)-methylamine in the presence of sodium amide according to the procedure of Eisleb[3] to give 1-methyl-4-(2-pyridyl)-4-cyanopiperidine (I) (48% yield). This was converted with concentrated sulfuric acid to the amide II (94% yield) which was treated with methanol and hydrogen chloride to give the ester III (34% yield), the desired analog.

Considerable difficulty was encountered in converting the nitrile I to the ester III. A series of attempts to prepare the ester III directly from the nitrile I in hydrogen chloride saturated methanol gave poor results, due in part at least to the insolubility of the nitrile hydrochloride in the reaction medium. Attempts to prepare the ethyl ester directly from the nitrile using ethanol and concentrated sulfuric acid gave 1-methyl-4-(2-pyridyl)-piperidine (IV), the product to be expected from hydrolysis and decarboxylation. Compounds I, II and III were submitted to Parke, Davis and Co. for pharmacological evaluation.

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## Experimental

**Methyl 2-Pyridylacetate.**—This compound was prepared, with slight modification, according to the procedure of Woodward and Kornfeld[4] for the corresponding ethyl ester. 2-Picolyllithium prepared from 30 g. (4.3 gram-atoms) of lithium, 314 g. (2.00 moles) of bromobenzene and 186 g. (2.00 moles) of 2-picoline, under an atmosphere of dry natural gas, was added to an ether slurry of Dry Ice which had been powdered in a polyethylene bag. The resulting paste was dissolved in dry methanol, and saturated below 10° with hydrogen chloride gas. On standing, a crystalline precipitate formed. If this precipitate did not redissolve completely on standing at room temperature, more hydrogen chloride gas was introduced. After the solid had redissolved and the mixture had separated into two layers, the reaction mixture was evaporated under reduced pressure. The residue was treated with sodium carbonate-water paste, and extracted with dichloromethane. The extract was evaporated and distilled, b.p. 74–78° (2 mm.), $n^{24}D$ 1.5070–1.5092, 151 g. (1.00 mole), 50% yield. The picrate was prepared from ethanol; m.p. 141–142.5°.[5,6]

**2-Pyridylacetamide. A.**—Methyl 2-pyridylacetate (80.3 g., 0.531 mole) was dissolved in 125 ml. of concentrated ammonium hydroxide (28%, 2.28 moles). The solution was allowed to stand at room temperature for two days. After treatment with Norit and Celite, evaporation of the solution to near dryness at reduced pressure, and recrystallization of the residue from acetone, the amide, 59.2 g. (81.7% yield), was obtained, m.p. 120–122°.[7]

**2-Pyridylacetamide. B.**—This compound was also prepared by the Willgerodt reaction, according to the procedure of Carmack and DeTar.[7] Some modifications in details of this procedure were worked out. In each Pyrex combustion tube there was placed 15 g. (0.143 mole) of freshly distilled 2-vinylpyridine (Reilly Tar and Chemical Co.), 23 g. (0.719 gram-atom) of sifted sulfur, 28 ml. of concd. ammonium hydroxide (0.511 mole) and 25 ml. of purified dioxane. Each tube was sealed and heated for two hours at 150°. After cooling, the contents of several tubes were combined and evaporated under reduced pressure at 40–60°. Acetone was added to the tarry residue to precipitate solid sulfur. The evaporation was continued to near dryness, and the residue extracted with three portions of boiling methyl ethyl ketone. The extract was treated with Norit and Celite, and evaporated to a mass of yellow or brown crystals containing some sulfur. Recrystallization from acetone gave white needles, m.p. 120–122°.[7] The combined yield of fifteen tubes initially containing 225 g. (2.14 moles) of 2-vinylpyridine, was 119 g. (0.875 mole), 40.8% yield. The picrate was prepared from ethanol, m.p. 155–157°, and the hydrochloride, m.p. 185–186°.

**2-Pyridylacetonitrile.**—This compound was prepared according to procedure B used by Sperber, *et al.*,[8] for the preparation of the 3-isomer. From 75 g. of the amide was obtained 55.1 g. (79%) of the nitrile,[8] b.p. 76–77° (2 mm.), $n^{25}D$ 1.5224, m.p. 23–25.5°; picrate from ethanol, m.p. 155–157°.

(1) Taken in part from the M.S. Thesis of Robert J. Dummel, Stanford University, 1954.

(2) A. Burger, "Medicinal Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 36–50.

(3) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

(4) R. Woodward and E. Kornfeld, *Org. Syntheses*, **29**, 44 (1950).

(5) All melting points were taken on a calibrated Kofler hot-stage, equipped with polarization filters.

(6) Reported m.p. 142–144°; W. Gruber and K. Schlögl, *Monatsh.*, **81**, 473 (1950).

(7) Reported m.p. 120–121°; M. Carmack and D. DeTar, THIS JOURNAL, **68**, 2033 (1946).

(8) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *et al.*, *ibid.*, **73**, 5752 (1951).

**1-Methyl-4-(2-pyridyl)-4-cyanopiperidine.**—To a solution of 2-pyridylacetonitrile (66.8 g., 0.565 mole) and di-(2-chloroethyl)-methylamine[9,10] (47.8 g., 0.565 mole) in 750 ml. of toluene, there was added with stirring a gelatinous suspension of 47.8 g. (1.23 moles) of finely ground sodium amide (Farchan Research Lab.), 100 ml. of toluene and 1 g. of aluminum octanoate. This suspension was injected into the reaction mixture in 20-ml. portions with a syringe. During the addition, which took 20 minutes, the temperature rose spontaneously from 20 to 90°. The mixture was then refluxed one hour, cooled, treated with Norit and Celite, filtered and evaporated to a dark-brown oil under reduced pressure. A light-orange colored, clear oil was obtained by distillation, b.p. 125–165° (1.5 mm.) (55.0 g., 0.273 mole, 48.4%). During the final stages of the distillation, the product was colored intensely red by an unidentified side-product. An additional dark-red oil (22.9 g.) was obtained which did not crystallize on chilling, even after repeated distillation. A sample of the main product was redistilled, b.p. 120–122° (1.5 mm.), and the distillate was recrystallized from hexane to white crystals, m.p. 44–45.5°. The infrared spectrum had a sharp nitrile band at 4.48 $\mu$, compared to a similar band at 4.42 $\mu$ in the spectrum of 2-pyridylacetonitrile. Under ultraviolet light, this nitrile had a yellow fluorescence.

*Anal.* Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.62; H, 7.45; N, 20.98.

The hydrochloride, m.p. 182–183.5° (sublimation), methiodide, m.p. 235–236°, and the picrate, m.p. 203–208°, were prepared from ethanol.

**1-Methyl-4-(2-pyridyl)-4-carboxamidopiperidine.**—1-Methyl-4-(2-pyridyl)-4-cyanopiperidine (25.7 g., 0.128 mole) was dissolved slowly in 100 g. (0.96 mole) of concd. sulfuric acid. After standing two days at room temperature, the solution was poured slowly on powdered ice. The aqueous solution was treated with Norit and Celite, filtered, and ice added to the filtrate to maintain a temperature of 0° while 150 ml. of 28% ammonia was added. The resulting solution, *ca.* 600 ml., was extracted with six 50-ml. portions of chloroform. The extract was dried over sodium sulfate and evaporated to give a solid crystalline residue. After recrystallization from acetone, there was obtained white needles (26.4 g., 0.120 mole, 94.4%), m.p. 159–161°. A sample was recrystallized from toluene, m.p. 160–161.5°. The infrared spectrum had a strong amide carbonyl band at 6.00 $\mu$, compared to a similar band at 5.96 $\mu$ in the spectrum of 2-pyridylacetamide. Under ultraviolet light, the amide II had an intensely white fluorescence.

*Anal.* Calcd. for $C_{12}H_{17}N_3O$: C, 65.72; H, 7.82; N, 19.16. Found: C, 65.77; H, 7.81; N, 19.19.

The hydrochloride, m.p. 240–242.5°, and the methiodide, m.p. 206–209°, were prepared from ethanol-ether. The picrate, m.p. 195–198°, was prepared from ethanol.

(9) W. Hanby and H. Ryder, *J. Chem. Soc.*, 513 (1947).

(10) A. Childs, *et al.*, *ibid.*, 2174 (1948).

**1-Methyl-4-(2-pyridyl)-4-carbomethoxypiperidine.**—1-Methyl-4-(2-pyridyl)-4-carboxamidopiperidine (26.0 g., 0.119 mole) was dissolved in 500 ml. of methanol, and the solution was saturated below 10°, with hydrogen chloride. A crystalline solid precipitated which redissolved on refluxing. The solution was refluxed for eight hours and evaporated to near dryness under reduced pressure. The residue was first treated with 50 ml. of ice-cold saturated sodium carbonate solution and then 10 ml. of 25% sodium hydroxide. This was extracted with five 50-ml. portions of chloroform. The extract was treated with Norit, Celite and anhydrous sodium sulfate, filtered and evaporated to a dark-brown oil under vacuum. By distillation, there was obtained a clear, colorless oil, b.p. 119–129° (1 mm.) (9.5 g., 0.0406 mole, 34.2%), which crystallized on chilling. A sample was redistilled, b.p. 96–97° (0.07 mm.), $n^{23}D$ 1.5248, m.p. 45–47°. The infrared spectrum had a strong carbonyl band at 5.80 $\mu$, compared to a similar band at 5.80 $\mu$ in the spectrum of methyl 2-pyridylacetate. Under ultraviolet light, this ester had an intense blue-white fluorescence.

*Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 66.44; H, 7.74; N, 11.96. Found: C, 66.93, 67.06; H, 7.87, 7.79; N, 11.69, 11.83.

The hydrochloride was prepared from ethanol-ether, and recrystallized from chloroform–hexane, m.p. 193–193.5°.

*Anal.* Calcd. for $C_{13}H_{19}N_2O_2Cl$: C, 57.66; H, 7.07; N, 10.35. Found: C, 57.74; H, 6.88; N, 10.31.

The picrate was prepared from ethanol, m.p. 197–199.5°.

*Anal.* Calcd. for $C_{25}H_{24}N_8O_{16}$: C, 43.36; H, 3.49; N, 16.18. Found: C, 43.80; H, 3.58; N, 15.99.

The methiodide was prepared from ethanol–ether, m.p. 196–198.5°.

**1-Methyl-4-(2-pyridyl)-piperidine.**—During an extended series of attempts to convert the nitrile I directly to an ethyl ester with ethanol and sulfuric acid, there was isolated from the combined crude products by fractionation a colorless, clear oil, b.p. 83–84° (3 mm.), $n^{20}D$ 1.5268. In the infrared spectrum, significant bands in the nitrile and carbonyl region were absent. It is assumed that hydrolysis and decarboxylation took place giving 1-methyl-4-(2-pyridyl)-piperidine.

*Anal.* Calcd. for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.46; H, 9.16; N, 16.09.

The hydrochloride was prepared from ethanol–ether, m.p. 201–205°. *Anal.* Calcd. for $C_{11}H_{18}N_2Cl_2$: C, 53.01; H, 7.28; N, 11.24. Found: C, 52.96; H, 7.27; N, 11.37.

The methiodide was prepared from ethanol-ether, m.p. 187–188°. The picrate was prepared from ethanol. m.p. 212–215°. *Anal.* Calcd. for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.83; H, 3.61; N, 16.88.

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