was extracted with ether. Distillation of the dried ether extracts yielded 4 g. of forerun (b.p. up to 165° at 3 mm.) and 15.5 g. of a dark green viscous oil boiling at 165–170° (3 mm.).

The product was transferred to a small distilling flask, mixed with 2 g. of 10% palladium–charcoal and slowly distilled over an open flame. The violet distillate was redistilled using a modified Claisen flask. Fraction 1, wt. 2.8 g., b.p. up to 105° (1.5 mm.), was fairly mobile; fraction 2, wt. 3.1 g., deeply colored and more viscous, boiled in the range 105–140° (1.5 mm.). The higher-boiling material could be used for a second dehydrogenation.

Fraction 2 was dissolved in 20 ml. of ethanol and treated with 4 g. of trinitrobenzene in 125 ml. of warm ethanol. The purple trinitrobenzolate separated immediately and weighed 4.1 g. The derivative was dissolved in a minimum of hexane–benzene (2:1) and decomposed by chromatography over alumina. The violet eluate was concentrated and distilled, the fraction boiling at 110–115° (1.5 mm.) being collected. This material, wt. 1.55 g., was used for absorption spectra and for the preparation of the derivatives described below. On prolonged chilling, it crystallized and remelted at 29°.

The trinitrobenzolate, purplish-black needles from absolute ethanol, melted at 177–178°.

Anal. Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.48; H, 4.43; N, 10.87.

The picrate, reddish-black needles from absolute ethanol, melted at 156.5°.

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.15; H, 4.29; N, 10.52. Found: C, 56.75; H, 4.36; N, 10.31.

The ultraviolet spectrum of the redistilled azulene in *n*-pentane solution was determined on a Beckman model DU spectrophotometer and is reproduced in Fig. 1.

TALLAHASSEE, FLORIDA RECEIVED APRIL 14, 1951

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORIES, STANFORD UNIVERSITY]

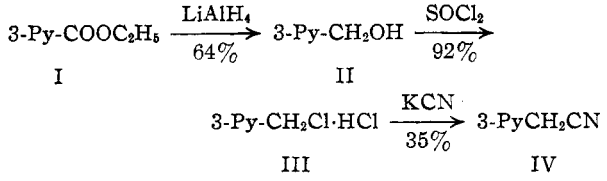
Heterocyclic Basic Compounds. XIV. 4-Phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone[1]

BY HARRY S. MOSHER AND JOHN E. TESSIERI[2]

Panizzon[3,4] has condensed 2- and 4-halopyridines with phenylacetonitrile in the presence of sodium amide but did not extend the reaction to the 3-isomer, presumably because of the well-recognized aromatic nature of the 3-position in the pyridine ring. It has been found, however, that 3-bromopyridine is readily converted into α-phenyl-α-(3-pyridyl)-acetonitrile by this reaction. This was converted to 4-phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone which is related to the analgesic of the amidone type. In these studies the lithium aluminum hydride reduction of various pyridine esters to the corresponding carbinols was also studied as well as the conversion of 3-pyridylcarbinol to 3-chloromethylpyridine and 3-cyanomethylpyridine.

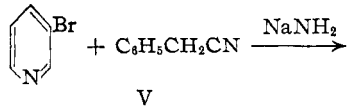
The original plan of this investigation was to prepare pyridine analogs of the analgesic methadone by reactions analogous to those used in its well-known synthesis[5] with the substitution of a cyanomethylpyridine for phenylacetonitrile. None of the three isomeric pyridylacetonitriles has been previously reported.

The 3-isomer was made *via* 3-pyridylcarbinol according to the equations

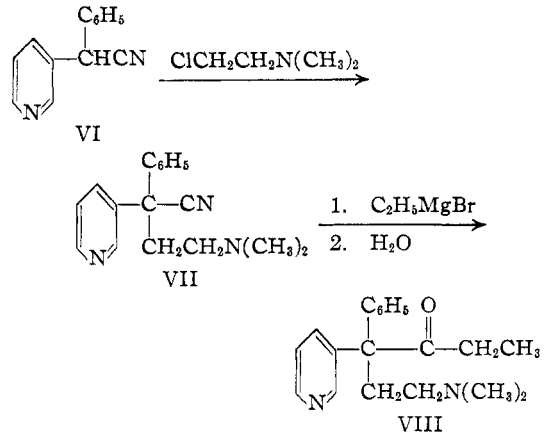


Although the 3-cyanomethyl-pyridine could be brominated successfully, attempted Friedel–Crafts reactions with benzene were uniformly unsuccessful and it was necessary to abandon this approach.

An alternate route, the first step of which has been studied by Panizzon[3,4] for the 2- and 4-isomers, is illustrated by



V



Apparently this first reaction was not considered feasible for the β-isomer. In spite of the well-recognized aromatic nature of the β-position of the pyridine ring several reactions indicate that 3-bromopyridine is considerably more reactive than bromobenzene.[6] For this reason the reaction of 3-bromopyridine with phenylacetonitrile in the presence of sodium amide was attempted. The reaction was successful and gave the desired product VI in 36% yield. This indicates the activation of the β-position of the pyridine nucleus by the inductive effect of the ring nitrogen atom is greater than generally considered.

The α-phenyl-α-(3-pyridyl)-acetonitrile (VI) was converted to 4-phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone (VIII), which is related structurally to the analgesic amidone, by successive

(1) Abstracted from the Ph.D. thesis submitted by J. E. T. to Stanford University in partial fulfillment of the requirements for the Ph.D. degree.

(2) Parke Davis and Co. Research Fellow, 1949.

(3) L. Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944); **29**, 324 (1946); British Patent 589,625 (June 25, 1947).

(4) M. Hartmann and L. Panizzon, U. S. Patent 2,507,631 (May 26, 1950).

(5) Office of the Publication Board, Report 981 (1945), pp. 94–96.

(6) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 517.

treatment with dimethylaminoethyl chloride and ethylmagnesium bromide.

This compound was tested for analgesic activity by Dr. C. V. Winder of Parke, Davis and Company and found to possess approximately 36% of the activity of morphine in the modified Wolff–Hardy technique in guinea pigs.[7] The compound was, however, very toxic, being fatal to a dog in 40 mg./kg. dose and showing depression even at 12.5 mg./kg. dose. The high toxicity of this compound discouraged work on the other possible analogs.

After the present work was completed, several publications on the lithium aluminum hydride reduction of pyridine ester appeared.[8]

In the experimental section is reported still another method for working up the lithium aluminum hydride reduction from ethyl nicotinate as well as reductions of ethyl picolinate, ethyl isonicotinate and ethyl cinchomeronate.

Acknowledgment.—We gratefully acknowledge the support of Parke, Davis and Co. which made this work possible.

Experimental

3-Pyridylcarbinol.[8]—Ethyl nicotinate (20.3 g., 0.13 mole) was dissolved in anhydrous ether (200 ml.) and added to a solution of lithium aluminum hydride (4.0 g., 0.11 mole) in anhydrous ether (500 ml.). After stirring for 15 minutes, absolute ethanol (50 ml.) was added to decompose the excess lithium aluminum hydride. Most of the solid dissolved and glycerol (92 g.) was added. The ether was distilled directly from the reaction mixture and the residue was distilled from a Claisen flask. The distillate, b.p. 160–180° (4 mm.) was a mixture of glycerol and 3-pyridylcarbinol from which the 3-pyridylcarbinol was separated by conversion to the hydrochloride in alcoholic solution. The hydrochloride was extracted in a Soxhlet apparatus with ether to remove the last of the glycerol; 12.5 g. (64% crude yield) m.p. 118–121°, picrate m.p. 158–160°. A comparable yield (61.5%) was obtained by making the reaction mixture strongly basic and continuously extracting the resultant slurry as described in the patent literature[8b,8c]; the extractions were slow and not mechanically satisfactory, however. The method of Jones and Kornfeld[8a] was probably the most convenient and obviated the troublesome distillation necessary in the method described above. It was modified to advantage as indicated in the following preparation for 4-pyridylcarbinol.

4-Pyridylcarbinol.—Ethyl isonicotinate (38 g., 0.25 mole) dissolved in anhydrous ether was added to a solution of lithium aluminum hydride (9.1 g.) in 500 ml. of anhydrous ether over a two-hour period. The reaction mixture was worked up by adding 35 ml. of water, stirring for one hour, and filtering the mixture. The solid was slurried with 200 ml. of methanol containing 2 ml. of water while being saturated with carbon dioxide. The mixture was brought to boiling and filtered. The original ether filtrate and the methanol extract were concentrated to an oil and treated with 50 ml. of 10% sodium hydroxide. This was continuously extracted with ether and the ether extracts concentrated to an oil and dried by azeotropic distillation with benzene. The residue crystallized and was relatively pure (20.5 g., 75% yield). It was distilled however to give 18.3 g., b.p. 107–110° (1 mm.), m.p. 55–60°. It could be further purified by vacuum sublimation, m.p. 58–60°.

Anal. Calcd. for C_6H_7NO: C, 66.01; H, 6.40. Found: C, 65.65; H, 6.24.

The hydrochloride melted at 176–180°, the picrate at 157–161° and the chloroplatinate at 210–211°.[9]

Isonicotinic acid was reduced with lithium aluminum hydride using a Soxhlet apparatus as recommended by Nystrom and Brown[10] for substances difficultly soluble in ether. Although a 46% crude yield was obtained, only 4.2 g. of isonicotinic acid was dissolved in 77 hours and this method was therefore of little practical value.

2-Pyridylcarbinol.—By a method analogous to that used for 4-pyridylcarbinol, 17.4 g. (0.12 mole) of ethyl picolinate was reduced with lithium aluminum hydride (3.07 g., 0.08 mole) to give 3.3 g. (26%) of 2-pyridylcarbinol, b.p. 122–125° (23 mm.), picrate, m.p. 153–156°. Graf[9] reports b.p. 105° (12 mm.), picrate m.p. 158°. The low yield appears to be inherent in the preparation and is not a result of mechanical difficulties in purification. An equal amount of a high boiling material (about 210° at 2 mm.) was also obtained.

3,4-Di-(hydroxymethyl)-pyridine.—Ethyl cinchomeronate[11] (21.3 g., 0.1 mole) was treated with lithium aluminum hydride (0.26 mole), the mixture hydrolyzed with base and continuously ether extracted. A mixture of solid and oil was obtained from which the solid was separated by filtration and recrystallized from alcohol (3.0 g., 22.5%), m.p. 129.5–130.5°, picrate m.p. 144°–145°.[12] An attempt to distil the oil resulted in decomposition.

3-Chloromethylpyridine.—3-Pyridylcarbinol hydrochloride (37.1 g.) was dissolved in 150 ml. of thionyl chloride with cooling and then warmed gently on the steam-bath. After the initial vigorous reaction had subsided, the reaction mixture was refluxed for two hours, cooled, and 250 ml. of benzene added. The white solid which precipitated was washed several times with benzene, filtered, and dried in a vacuum desiccator, 38.3 g., 91.5%, m.p. 126–128°. Recrystallization from ethanol raised the melting point to 142–145°,[13] picrate, m.p. 130.5–132.0°.

Anal. Calcd. for $C_6H_6NCl \cdot C_6H_3O_7$: C, 40.39; H, 2.54; N, 15.71. Found: C, 40.98; H, 2.64; N, 15.96.

4-Chloromethylpyridine.—4-Pyridylcarbinol hydrochloride was converted to 4-chloromethylpyridine in 64% yield by the same procedure. The hydrochloride after recrystallizing from absolute ethanol melted at 170–175° to a clear melt but resolidified at 190° and turned from red to black around 230° but did not remelt.

Anal. Calcd. for $C_6H_6NCl \cdot HCl$: C, 43.93; H, 4.30. Found: C, 44.07; H, 4.25.

A picrate melted at 146–147°.

Anal. Calcd. for $C_6H_6NCl \cdot C_6H_3N_3O_7$: C, 40.45; H, 2.57. Found: C, 40.65; H, 2.63.

3-Cyanomethylpyridine.—Several attempts to bring about reaction between 3-chloromethylpyridine hydrochloride and mercuric cyanide or cuprous cyanide in aqueous or alcoholic medium were unsuccessful and starting material was recovered in each case. Ten experiments using potassium cyanide were conducted under varying conditions including the addition of sodium bisulfite, acetic acid and hydrochloric acid, but none gave more than the 34% yield obtained in the experiment described below. The difficulty seemed to be polymerization of the 3-chloromethylpyridine liberated in the basic medium since it was possible to recover only about 30% of 3-chloromethylpyridine when its hydrochloride was dissolved in a saturated sodium carbonate solution and immediately extracted with ether.

A solution of potassium cyanide (10 g., 0.15 mole) and 3-chloromethylpyridine hydrochloride (10 g., 0.061 mole) in a mixture of methanol (105 ml.) and water (40 ml.) was refluxed for one hour during which time it turned deep red. The reaction mixture was diluted with 100 ml. of water, saturated with sodium carbonate, and ether extracted. There was formed a heavy oil which was neither soluble in water nor ether and presumably was a polymer from 3-chloromethylpyridine. The ether extracts were dried over potassium carbonate and distilled to give 2.44 g. of pale yellow liquid, b.p. 91° (2 mm.), $n^{20}D$ 1.5278, 34% yield. This base in ether solution gave the hydrochloride on treatment with dry hydrogen chloride, yield 3.1 g., m.p. 160–162°.

(7) C. V. Winder, *Arch. intern. pharmacodynamie*, **74**, 176, 219 (1947).

(8) (a) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951); (b) British Patent 631,078 (Oct. 26, 1949); (c) Cohen, U. S. Patent 2,520,037 (Aug. 22, 1950).

(9) R. Graf, G. Perathoner and M. Tatzel, *J. prakt. Chem.*, [2] **146**, 88 (1936), reports b.p. 110–142° (12 mm.); m. p. about 40°, hydrochloride 164° dec. and chloroplatinate 220°.

(10) R. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

(11) We wish to thank the Barrett Division of Allied Chemical and Dye Corporation for a generous sample of cinchomeronic acid.

(12) K. Westphal, U. S. Patent 2,349,318 (May 23, 1944), reports m.p. 144° for this picrate.

(13) Swiss Patent 251,026 (Sept. 30, 1947) reports m.p. 142° for this compound.

Anal. Calcd. for $C_7H_6N_2 \cdot HCl$: C, 54.37; H, 4.57; N, 18.12; Cl, 22.94. Found: C, 54.33; H, 4.50; N, 18.28; Cl, 22.89.

A picrate of the 3-cyanomethylpyridine melted at 161.3°.

Anal. Calcd. for $C_7H_6N_2 \cdot C_6H_3N_3O_7$: C, 44.94; H, 2.61; N, 20.18. Found: C, 44.99; H, 2.68; N, 19.98.

Bromination of 3-Cyanomethylpyridine.—The reaction of bromine with 3-cyanomethylpyridine in glacial acetic acid solvent appeared to proceed normally with the evolution of HBr and resulted in the formation of a quantitative yield of light amber oil when the acetic acid was removed under vacuum. The product could not be obtained crystalline and failed to give any identifiable product when treated with aluminum chloride and benzene.

α-Phenyl-α-(3-pyridyl)-acetonitrile.—Phenylacetonitrile (117 g., 1 mole) was heated at 80° with 300 ml. of toluene and one mole of sodium amide for two hours. The resulting mixture was cooled and 3-bromopyridine (159.1 g., 1 mole) was added over a ten-minute period. The mixture was refluxed for one hour, cooled, water added, and the toluene layer extracted with dilute hydrochloric acid. The acid extract was made basic with sodium hydroxide and extracted with benzene. The benzene layer was dried and distilled to give 79.9 g. of recovered 3-bromopyridine and 35.1 (36%) of α-phenyl-α-(3-pyridyl)-acetonitrile, b.p. 152–157° (2 mm.), m.p. 58–62°. Recrystallization gave a product melting at 63–65°.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.37; H, 5.19; N, 14.44. Found: C, 80.46; H, 5.18; N, 14.52.

This formed a picrate melting at 148–150°. An extended reflux period decreased the yield and although excess sodium amide increased the yield slightly (42%) the product could not be purified as readily.

2-Phenyl-2-(3-pyridyl)-4-dimethylaminobutyronitrile.—A mixture of α-phenyl-α-(3-pyridyl)-acetonitrile (78.7 g.), benzene (200 ml.) and sodamide (16.5 g.) was held with stirring at 40–50° for 1.5 hours. Ammonia was evolved and an oil separated. The mixture was cooled to 20° and β-dimethylaminoethyl chloride (42.5 g.) added over a ten-minute period. The temperature rose spontaneously to 30° and after stirring one hour the reaction mixture was refluxed for 1.5 hours. Water was added and the benzene layer extracted with 500 ml. of 2 *N* hydrochloric acid. Neutralization of the acid extract with ammonium hydroxide caused separation of an oil layer which was removed by benzene extraction. Distillation of the dried benzene extracts gave 64.2 g. (59.7% yield) of a clear viscous oil, b.p. 152° (0.15 mm.). A picrate melted at 193.5–196.5°.

Anal. Calcd. for $C_{17}H_{19}N_3 \cdot 2C_6H_3N_3O_7$: C, 48.13; H, 3.46. Found: C, 48.58; H, 3.68.

4-Phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone.—To the Grignard solution from 0.2 mole of ethyl bromide in 60 ml. of ether was added 2-phenyl-2-(3-pyridyl)-4-dimethylaminobutyronitrile (14 g., 0.053 mole) dissolved in 20 ml. of toluene; a heavy gum formed. The mixture was refluxed for six hours and then hydrolyzed by cold 6 *N* hydrochloric acid. The acid solution was neutralized with ammonium hydroxide until magnesium hydroxide just precipitated. The oil which separated was extracted with benzene and after drying over potassium carbonate was distilled to give 6.1 g. of material, b.p. 115–145° (0.05 mm.) and 3.5 g. b.p. 145–146° (0.05 mm.). The latter material formed a picrate, m.p. 192–194°.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 2C_6H_3N_3O_7$: C, 49.34; H, 3.96. Found: C, 49.01; H, 4.07.

A hydrochloride was formed in absolute isopropyl alcohol–benzene mixture, m.p. 133–136° dec.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 2HCl \cdot 2H_2O$: C, 56.24; H, 7.46; N, 6.91; Cl, 17.49. Found: C, 56.83; H, 7.24; N, 6.96; Cl, 17.60.

STANFORD, CALIFORNIA RECEIVED APRIL 30, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Acid Degradation of Amylopectin to Isomaltose and Maltotriose[1]

BY M. L. WOLFROM, J. T. TYREE,[2] T. T. GALKOWSKI[2] AND A. N. O'NEILL

Mild acetolysis of amylopectin (waxy maize starch) with subsequent conversion of the acetolysate to the β-D-acetate mixture and silicate column chromatography of this led to the isolation in crystalline form of β-D-glucopyranose pentaacetate, β-maltose octaacetate (and heptaacetate) and β-maltotriose hendecaacetate. Since calculation showed that the maximum amount of isomaltose would be expected at 90% hydrolysis, amylopectin was hydrolyzed to this point and the hydrolysate was converted to the β-D-acetate mixture which was chromatographed on silicate columns. There was isolated in crystalline form β-D-glucopyranose pentaacetate, β-maltose octaacetate and β-isomaltose octaacetate (1% yield). Evidence is presented that this amount of the latter is not a reversion (resynthesis) product and therefore offers further definitive evidence, on a crystalline basis, for the 6-α point of branching in amylopectin.

Indirect evidence exists that amylopectin is a two-dimensional polymer branched at C_6. It is desirable to place this evidence upon a definitive basis through the isolation, from an amylopectin hydrolysate, of the disaccharide isomaltose, 6-(α-D-glucopyranosyl)-D-glucose, containing the point of branching together with evidence that the disaccharide is not a product of reversion (resynthesis). It is known that both acids and some enzymes are capable of causing re-synthesis in hydrolysates. Thus an enzyme preparation from *Aspergillus niger* NRRL 337 acts upon maltose to form a trisaccharide[3] containing both maltose and isomaltose disaccharide linkages.[4] It is established that high sugar concentrations and high acidity favor resynthesis by acids.

Action upon amylopectin of the α- and β-amylases of malt does not yield isomaltose,[5] although levoglucosan (1,6-anhydro-D-glucopyranose) is isolable from such an enzymic hydrolysate after subsequent treatment with an amylase preparation from *Aspergillus oryzae*.[6] This same enzyme preparation (containing maltase) acts directly upon amylopectin to give isomaltose,[7] characterizable as its crystalline β-octaacetate. This disaccharide was not isolable from reaction mixtures containing the enzyme and the various substances, other than

(1) A preliminary report, by the same authors, of the acid degradation of amylopectin to isomaltose has appeared in THIS JOURNAL, **72**, 1427 (1950).

(2) Research Associate (J. T. T.) and Research Fellow (T. T. G.) of the Corn Industries Research Foundation (Project 203 of The Ohio State University Research Foundation).

(3) S. C. Pan, A. A. Andreasen and P. Kolachov, *Science*, **112**, 115 (1950); S. C. Pan, L. W. Nicholson and P. Kolachov, THIS JOURNAL, **73**, 2547 (1951).

(4) D. French, *Science*, **113**, 352 (1951); M. L. Wolfrom, A. Thompson and T. T. Galkowski, THIS JOURNAL, **73**, 4093 (1951).

(5) M. L. Wolfrom, L. W. Georges, A. Thompson and I. L. Miller, *ibid.*, **69**, 473 (1947); **71**, 2873 (1949).

(6) Edna M. Montgomery and G. E. Hilbert, *ibid.*, **68**, 916 (1946).

(7) Edna M. Montgomery, F. B. Weakley and G. E. Hilbert, *ibid.*, **69**, 2249 (1947); **71**, 1682 (1949).