Synthesis of 1,3-Disubstituted Octahydropyrido[1,2-*c*]pyrimidines[1]

Richard F. Shuman,[2a] H. Victor Hansen,[2b] and E. D. Amstutz

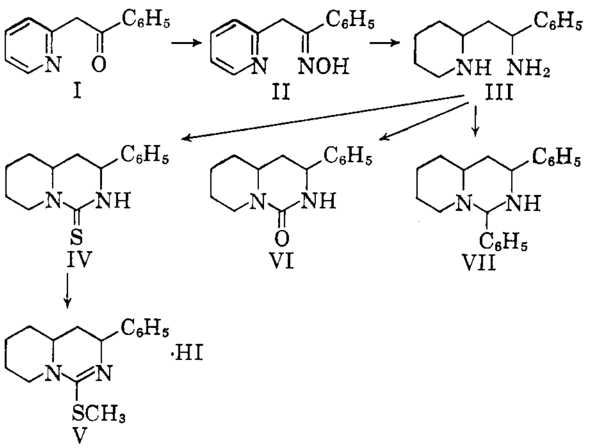
William H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania

Received January 22, 1962

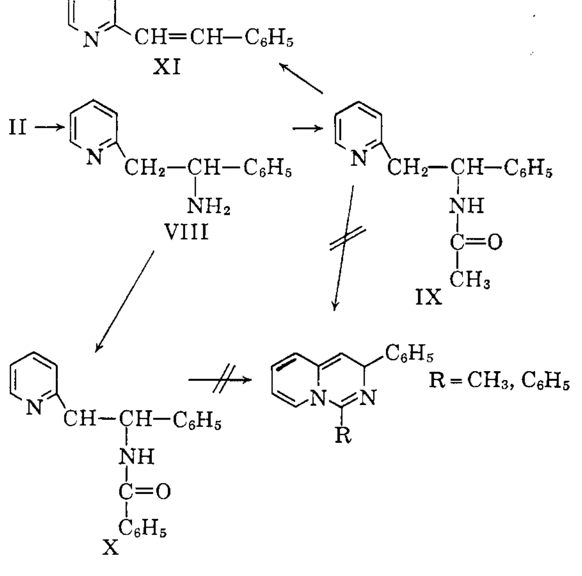
Three 1-substituted 3-phenyloctahydropyrido[1,2-*c*]pyrimidines have been synthesized by condensing 1-phenyl-2-(2-piperidyl)ethylamine with carbon dilsulfide, diethyl carbonate, and benzaldehyde, respectively. The 1-thione obtained was converted to its *S*- methyl homolog by treatment with methyl iodide. Attempts to cyclodehydrate *N*-acetyl- and *N*-benzoyl-1-phenyl-2-(2-pyridyl)ethylamine to 3*H*-1-substituted 3-phenylpyrido[1,2-*c*]pyrimidines with phosphorus oxychloride or phosphorus pentoxide were unsuccessful. The acetamide yielded 2-stilbazole, while the benzamide was recovered unchanged.

Synthesis of 1*H*-pyrido[1,2-*c*]pyrimidines and their completely saturated analogs, octahydropyrido[1,2-*c*]pyrimidines have been published recently.[3,4] We wish to report the synthesis of some new 1,3-disubstituted octahydropyrido[1,2-*c*]pyrimidines as well as unsuccessful attempts to prepare 3*H*-1,3-disubstituted pyrido[1,2-*c*]pyrimidines.

1-Phenyl-2-(2-piperidyl)ethylamine (III) was the immediate precursor for the octahydropyrido[1,2-*c*]pyrimidines prepared. 2-Phenacylpyridine (I) was obtained from 2-picolyllithium and methyl benzoate according to the method of Goldberg and Levine.[5] Conversion of I to 2-phenacylpyridine oxime (II) was then effected in excellent yield. The pyridine ring and the oximino group were reduced simultaneously in glacial acetic acid with platinum dioxide catalyst at three to four atmospheres of hydrogen to give III. 2-Phenyloctahydropyrido[1,2-*c*]-1-thiopyrimidone (IV) precipitated after heating diamine III with an excess of carbon disulfide in refluxing 95% ethanol. The thiourea IV easily underwent *S*-methylation with an excess of methyl iodide to produce 1-thiomethoxy-3-phenyl-Δ^1-hexahydropyrido[1,2-*c*]pyrimidine hydroiodide (V). 3-Phenyloctahydropyrido-[1,2-*c*)-1-pyrimidone (VI) was realized from heating III with diethyl carbonate in a sealed tube at 200° for fifty hours. Benzaldehyde and III were condensed in refluxing benzene to give 1,3-diphenyloctahydropyrido[1,2-*c*]pyrimidine (VII). This condensation is similar to that of 2-(2-piperidyl)ethylamine with benzaldehyde as carried out by Winterfeld and Göbel[3b] to produce 1-phenyloctahydropyrido[1,2-*c*]pyrimidine.



In an effort to prepare 3*H*-1,3-disubstituted pyrido[1,2-*c*]pyrimidines, oxime II was first reduced with zinc dust in a solution of 95% ethanol and glacial acetic acid producing 1-phenyl-2-(2-pyridyl)ethylamine (VIII). Acetylation and benzoylation were effected to give the acetamide (IX) and benzamide (X). It was hoped that IX and X would undergo cyclodehydration in the presence of phosphorous oxychloride or phosphorous pentoxide to yield 3*H*-1-methyl-3-phenylpyrido[1,2-*c*]-pyrimidine and 3*H*-1,3-diphenylpyrido[1,2-*c*]pyrimidine, respectively. A recently published synthesis[6] of 1-substituted imidazo[1,5-*a*]pyridines



---

[1] Abstracted from Part I of the Ph.D. thesis of R. F. Shuman, Lehigh University, 1961.

[2] (a) The Wm. S. Merrell Research Fellow, February 1959–June 1961; (b) Merrell Fellow, September 1958–January 1959.

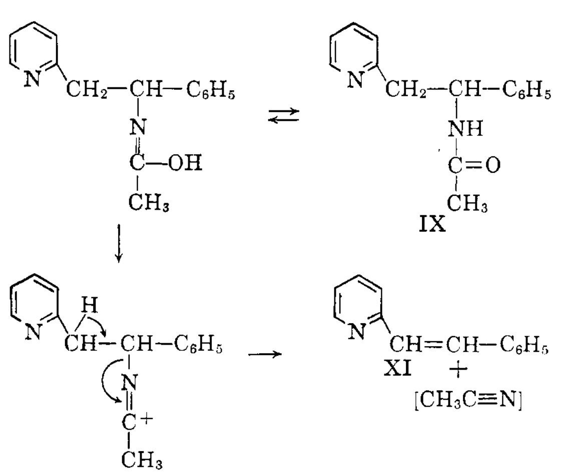
[3] (a) K. Winterfeld and W. Göbel, *Chem. Ber.*, **89**, 1642 (1956); (b) *ibid.*, **92**, 637 (1959).

[4] A. Hunger and K. Hoffman, *Helv. Chim. Acta*, **40**, 1319 (1957).

[5] N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

involves the cyclodehydration of 2-amidomethylpyridines using phosphorus oxychloride.

Reaction of acetamide IX with phosphorus oxychloride or phosphorus pentoxide in refluxing benzene produced 2-stilbazole (XI) in yields of 60% and 21%, respectively. It is possible that 2-stilbazole forms by dehydroxylation of the imidol tautomer of IX to an intermediate iminonium ion followed by the concerted loss of a proton alpha to the pyridyl group, formation of an ethylenic double bond, and elimination of acetonitrile. No attempt was made to isolate acetonitrile from this reaction. Formation of the stable conjugated system represented by 2-stilbazole seems to be the driving force for this reaction, thereby precluding any cyclization.



Benzamide X exhibited an unexpected inertness toward phosphorus oxychloride and phosphorus pentoxide being recovered in amounts of 75% and 100%, respectively.

Experimental[7]

2-Phenacylpyridine (I).—The method used was essentially that of Goldberg and Levine.[5] I was obtained in 72% yield after distillation, b.p. 148–158°/0.6 mm. Recrystallization from petroleum ether (b.p. 30–60°) furnished pure, yellow I, m.p. 56–57.5°, in 92–96% recovery. A deepening of color from yellow to orange was observed upon prolonged exposure to the atmosphere. This was obviated by storing I under nitrogen in a refrigerator. No decomposition was noticed for a period exceeding 1 month.

2-Phenacylpyridine Oxime (II).—In a 100-ml. flask was placed 5.94 g. (0.03 mole) of crude 2-phenacylpyridine (I), b.p. 148–158°/0.6 mm. After dissolving I in 30 ml. of warm 95% ethanol, a solution of 2.30 g. (0.033 mole) of hydroxylamine hydrochloride in 8 ml. of water was added followed by 1.6 g. (0.04 mole) of sodium hydroxide in 10 ml. of water. The resulting solution was refluxed for 1 hr. and then poured into 150 ml. of an ice water mixture containing 0.6 ml. of acetic acid. Upon scratching, the resulting oily precipitate solidified to give 6.24 g. (98%) of impure oxime. Recrystallization from ethanol furnished 5.75 g. (90%) of slightly pink oxime, m.p. 116.5–118°. It also was possible to precipitate pure oxime directly from the reaction mixture by allowing the flask to stand at room temperature overnight. Hauser and Weiss[8] report a 46% yield of 2-phenacylpyridine oxime, m.p. 114–116°.

1-Phenyl-2-(2-piperidyl)ethylamine (III).—A solution of 8 g. (0.038 mole) of 2-phenacylpyridine oxime (II) in 100 ml. of glacial acetic acid and containing 0.50 g. of platinum dioxide was hydrogenated at room temperature and an initial pressure of 55.5 p.s.i. The hydrogenation was interrupted when the pressure had dropped to 41.7 p.s.i. (corresponding to 100% reaction). After filtration to remove the catalyst, the acetic acid was evaporated *in vacuo* and the greenish, very viscous residue swirled with 25 ml. of 25% sodium hydroxide solution. The alkaline mixture was extracted with three 25-ml. portions of ether and the combined extracts were dried over anhydrous sodium sulfate. Evaporation of the ether and distillation of the residue resulted in 5.77 g. (75%) of colorless oil, b.p. 125–135°/0.3 mm. The product forms a monopicrate, m.p. 166–167°, which was used for analysis.

Anal. Calcd. for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.75; H, 5.48; N, 15.90.

3-Phenyloctahydropyrido[1,2-*c*]-1-thiopyrimidone (VI).—In a test tube were placed 0.70 g. (0.0034 mole) of III and 6 ml. of 95% ethanol. Carbon disulfide was added until the solution was no longer basic. A white solid precipitated with evolution of heat. The white solid was collected and refluxed overnight in 6 ml. of fresh 95% ethanol accompanied by the evolution of hydrogen sulfide. Upon cooling, white crystals separated from the clear solution. Filtration gave 0.65 g. (77%) of pure product, m.p. 148.5–149.5°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.15; H, 7.52; N, 11.23.

1-Thiomethoxy-3-phenyl-Δ^1-hexahydropyrido[1,2-*c*]pyrimidine(V).—Eleven-hundredths of a gram (0.00044 mole) of IV was warmed with enough methyl iodide to effect solution. Evaporation of excess methyl iodide gave a yellowish residue. Recrystallization from absolute ethanol resulted in 0.15 g. (85%) of white, powdery product, m.p. 167–168°.

Anal. Calcd. for $C_{15}H_{22}N_2IS$: I, 32.6. Found: I, 32.5.

3-Phenyloctahydropyrido[1,2-*c*]pyrimidone (VI).—One gram (0.005 mole) of III and 0.58 g. (0.010 mole) of diethyl carbonate were placed in a sealed glass tube having a volume of approximately 13 cc. The lower half of the tube was heated in an oil bath at 200° for 50 hr. On cooling overnight in a refrigerator, a light brown solid precipitated. The tube was carefully opened and found to contain some pressure. The solid was filtered and washed with a small amount of ether to give 0.75 g. (66%) of white product, m.p. 152–155°. Recrystallization from a minimum of benzene–ligroin raised the m.p. to 157–158°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.17. Found: C, 73.27; H, 8.00; N, 11.86.

1,3-Diphenyloctahydropyrido[1,2-*c*]pyrimidine (VII).—One gram (0.0049 mole) of III and 0.55 g. (0.0052 mole) of benzaldehyde were heated in 25 ml. of refluxing benzene for 30 min. A small amount of water collected in a water trap. The benzene was evaporated *in vacuo* and the residue distilled to give 0.95 g. (65%) of a light yellow, extremely viscous oil, b.p. 186°/1.5 mm. The oil was triturated with a small amount of petroleum ether (b.p. 60–70°) and the resulting sticky, white solid filtered. The crude solid was dissolved in hot petroleum ether, the solution decanted from an insoluble oil, and the solution cooled to yield 0.40 g. (27%) of white product, m.p. 116–117°.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.14; H, 8.60; N, 9.28.

1-Phenyl-2-(2-pyridyl)ethylamine (VIII).—Three grams (0.014 mole) of 2-phenacylpyridine oxime (II) was dissolved in 45 ml. of 95% ethanol and the solution treated with small portions of zinc dust and glacial acetic acid over a

---

(6) J. Bower and G. Ramage, *J. Chem. Soc.*, 2834 (1955).

(7) All melting points are uncorrected.

(8) M. J. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

period of 8 hr. with occasional swirling until 24 g. (0.367 mole) of zinc and 24 g. (22.8 ml., 0.40 mole) of acetic acid had been added. The reaction mixture was then filtered and the residue of zinc and zinc acetate washed with a small portion of acetic acid. The combined filtrates were evaporated *in vacuo* on a hot water bath. The greenish residue (the reaction mixture itself exhibited a green fluorescence) was stirred with 20% sodium hydroxide and then extracted with ether. After drying over sodium sulfate, the ether was evaporated. The residual oil was distilled to give 1.78 g. (64%) of colorless liquid product, b.p. 131–132°/0.4 mm. The product formed a dipicrate, m.p. 210–211°, which was used for analysis.

Anal. Calcd. for $C_{25}H_{20}N_8O_{14}$: C, 45.74; H, 3.07; N, 17.07. Found: C, 45.94; H, 3.06; N, 16.88.

N-Acetyl-1-phenyl-2-(2-pyridyl)ethylamine (IX).—A solution of 3.5 ml. (0.037 mole) of acetic anhydride, 7.5 ml. of glacial acetic acid, and 1.78 g. (0.009 mole) of VIII were heated on a steam bath for 30 min. The acetic acid and excess acetic anhydride were removed by evaporation *in vacuo*. Upon cooling, the residue solidified to a yellow solid. Recrystallization from 1:1 benzene–ligroin gave 1.41 g. (65%) of white product, m.p. 114–117°. Two more recrystallizations raised the m.p. to 123.5–124.5°.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.02; H, 6.77; N, 11.42.

Attempted Synthesis of 3*H*-1-Methyl-3-phenylpyrido-[1,2-*c*]pyrimidine. Method A.—One gram (0.004 mole) of IX, 2 ml. (3.35 g., 0.02 mole) of phosphorus oxychloride, and 6 ml. of anhydrous benzene were refluxed for 4 hr. The reaction mixture was extracted with chloroform, the extract dried over anhydrous sodium sulfate, and then evaporated to dryness on a steam bath to give a sticky, yellow solid. This solid was eluted from an alumina column with benzene to give a white solid contaminated with yellow oil. The oil was removed by vacuum filtration giving 0.67 g. of product, m.p. 74–84°. Recrystallization of this crude product from dioxane gave an amount of white material, m.p. 140–143°, too small for analysis. The filtrate was evaporated to dryness and the residue (0.63 g.) recrystallized from a minimum of 1:1 benzene–ligroin to give a good recovery of solid, m.p. 91–92°, which did not have the correct analysis for the desired pyridopyrimidine. This material, 0.55 g. (60%), did not show a mixed melting point depression with an authentic sample of 2-stilbazole (XI), and the elemental analysis is in good agreement with that expected for XI.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.14; H, 6.12; N, 7.73. Found: C, 86.29; H, 6.37; N, 7.53.

Method B.—One gram (0.004 mole) of IX and 5.7 g. (0.04 mole) of phosphorus pentoxide were heated overnight in 10 ml. of refluxing benzene. The resulting mixture was made basic with 15% ammonium hydroxide and the light tan product, 0.15 g. (21%), proved to be 2-stilbazole as determined by its mixed melting point with an authentic sample.

2-Stilbazole (XI).—2-Stilbazole, for mixed melting point determinations, was prepared according to the directions of Shaw and Wagstaff.[9]

N-Benzoyl-1-phenyl-2-(2-pyridyl)ethylamine (X).—Two grams (0.01 mole) of VIII was placed in 25 ml. of benzene with 1.41 g. (1.16 ml., 0.01 mole) of benzoyl chloride and 1.5 ml. of pyridine. The resulting solution was refluxed overnight and the precipitate filtered and stirred with an excess of 20% sodium hydroxide. The crude light brown solid was filtered and dried to give 2.05 g. (67%) of product, m.p. 147–148°. One recrystallization from 80% methanol raised the m.p. to 148–149°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.39; H 6.01; N, 9.55.

Attempted Synthesis of 3*H*-1,3-Diphenylpyrido[1,2-*c*]-pyrimidine. Method A.—A solution of 0.80 g. (0.00265 mole) of X in 7 ml. of benzene was refluxed with 3.76 g. (0.0265 mole) of phosphorus pentoxide for 2 hr. The benzene was removed and the residue stirred with ice water. The resulting mixture was made basic with 20% sodium hydroxide and the white precipitate filtered and dried. The melting point and mixed melting point were identical to that of the starting material. The recovery was quantitative.

Method B.—A solution of 0.80 g. (0.00265 mole) of X and 2 ml. (3.35 g., 0.0219 mole) of phosphorus oxychloride in 6 ml. of benzene was refluxed for 4 hr. The benzene and excess phosphorus oxychloride were evaporated *in vacuo* and the residue collected as in method A. The recovery was 0.60 g. of solid (75%), m.p. 110–112°. Two recrystallizations from 80% methanol raised the m.p. to 148–149°, that of the starting benzamide.

Acknowledgment.—The authors wish to express their thanks to Dr. C. H. Tilford and the Wm. S. Merrell Co. for their interest and financial assistance during the course of this work. Our thanks go also to Dr. V. B. Fish of Lehigh University who performed the analyses.

---

[9] B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933).

Decomposition of Mixed Carboxylic-Dithiocarbamic Anhydrides

D. S. TARBELL AND ROLAND P. F. SCHARRER[1]

The Department of Chemistry, University of Rochester, Rochester, N. Y.

Received January 15, 1962

A number of mixed carboxylic-dithiocarbamic anhydrides, derived from aromatic carboxylic acids and piperidine—or methyldithiocarbamic acids, have been prepared and characterized. They have been found in each case to decompose on heating to the corresponding amide and carbon disulfide; the reaction takes place at a measurable rate in refluxing cyclohexane, and can be followed spectrophotometrically. It is catalyzed by triethylamine.

The behavior[2] of the mixed carboxylic-carbonic anhydrides (I), particularly the mechanism of their decomposition[3] has been studied. The present paper reports some observations on the decomposition of the mixed carboxylic-dithiocarbamic anhydrides (*S*-acyldithiocarbamates, II).

---

[1] Aided by Grant NSF-G11240 from the National Science Foundation.

[2] (a) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957). (b) D. S. Tarbell and N. A. Leister, *ibid.*, **23**, 1149 (1958). (c) N. A. Leister and D. S. Tarbell, *ibid.*, **23**, 1152 (1958).

[3] (a) D. S. Tarbell and E. J. Longosz, *ibid.*, **24**, 774 (1959). (b) E. J. Longosz and D. S. Tarbell, *ibid.*, **26**, 2161 (1961).