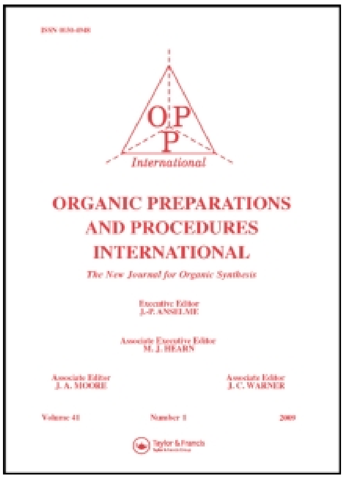

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Thoman, C. J. , Tien, J. M. , Anselme, J. -P. and Hunsberger, I. M.(1969) 'N-(2-PYRIMIDYL) GLYCINE HYDROCHLORIDE', Organic Preparations and Procedures International, 1: 2, 137 — 142
To link to this Article: DOI: 10.1080/00304946909458368
URL: http://dx.doi.org/10.1080/00304946909458368

ORGANIC PREPARATIONS AND PROCEDURES 1(2), 137-142 (1969)

N-(2-PYRIMIDYL)GLYCINE HYDROCHLORIDE

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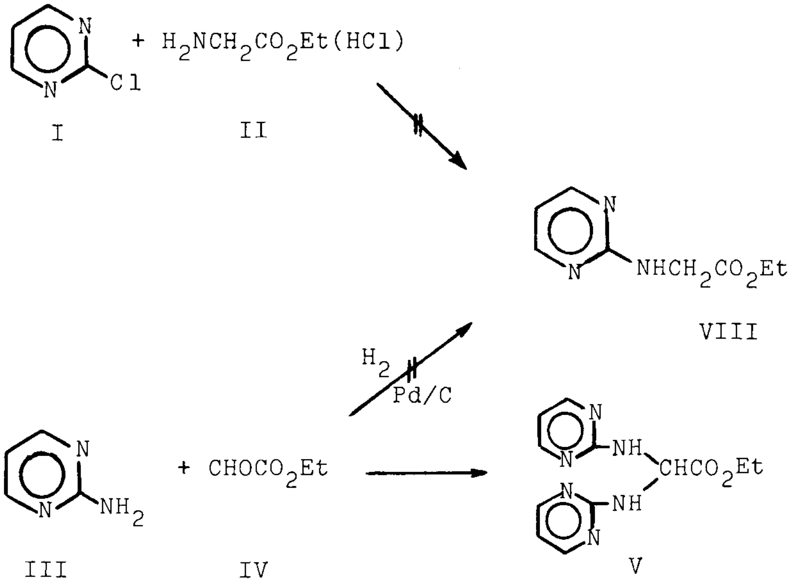
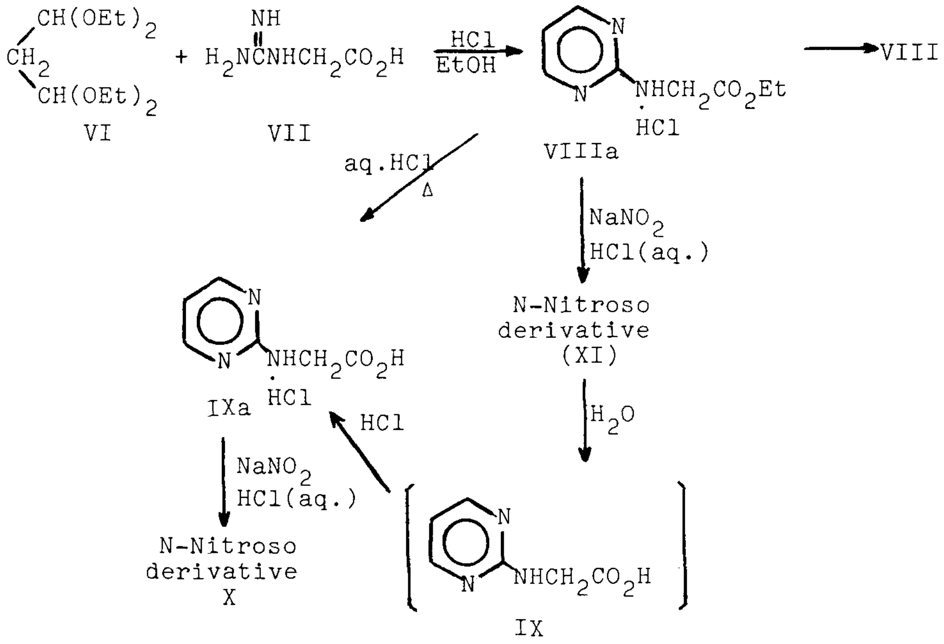
The ethyl ester of N-(2-pyrimidyl)glycine (VIII) was desired as the starting point for the synthesis of the corresponding sydnone. Numerous attempts to prepare VIII by the condensation of 2-chloropyrimidine (I) with the ethyl ester of glycine (and its hydrochloride) were unsuccessful.



Investigation of the reductive condensation of ethyl glyoxylate with 2-aminopyrimidine in aqueous hydrochloric acid over palladium and charcoal[2] indicated that the expected condensation had indeed occurred but was attended by partial reduction of the heterocyclic ring.

The synthesis of VIII (as its hydrochloride VIIIa) was achieved by the condensation of guanidoacetic acid (VII) and malonaldehyde tetraacetal (VI). The preparation of some derivatives of VIII and of the aminal V derived from ethyl glyoxylate and 2-aminopyrimidine (III) is also described.



Experimental[3]

Ethyl bis(2-pyrimidylamino)acetate(V). To a solution of 1.0 g (5.9 mmoles) of 60% ethyl glyoxylate in acetic acid was added, with thorough mixing, a solution of 2.0 g (21 mmoles) of 2-aminopyrimidine in 16 ml. of water. On standing overnight the solution deposited 1.1 g (69%) of white needles, m.p. 185-186°. Recrystallization from hot dioxane gave an analytical sample, m.p. 188-189°.

Anal.	Calcd. for $C_{12}H_{14}N_6O_2$:	C, 52.50; H, 5.10; N, 30.60.
	Found:	C, 52.76; H, 5.19; N, 30.40.

The compound is soluble in hot ethanol, hot dioxane, hot benzene and hot acetic acid but is insoluble in water, acetone, ether, chloroform and ethyl acetate.

Ethyl Ester of N-(2-Pyrimidyl)glycine hydrochloride (VIIIa). Guanidoacetic acid (glycocyamine) (50 g, 0.43 mole) was covered with 450 ml. of absolute ethanol in a flask equipped with a mechanical stirrer, reflux condenser, addition funnel and gas-inlet tube. Hydrogen chloride was introduced until esterification was complete (clear solution). This hot solution was cooled almost to room temperature and 94 g (0.43 mole) of malonaldehyde diethylacetal was added through the condenser. Passage of hydrogen chloride was continued and the solution was heated under reflux for one hour, during which time the original yellow solution gradually changed through red to green. Most of the excess hydrogen chloride was removed under reduced pressure. Cooling afforded pea-green needles which were filtered and washed with 1:3 ethanol-ether to yield 64 g (68%) of crude glycine ester hydrochloride (VIIIa), m.p. 161-162° (dec.); these crystals turned blue at about 150° and melted to a blue liquid which soon turned black. Recrystallization from more dilute solutions produced needles of the same m.p.

<u>Anal</u>. Calcd for $C_8H_{12}N_3O_2Cl$: C, 44.14; H, 5.56; N, 19.31; Cl, 16.29; neut. equiv. 217.7.

Found: C, 44.43; H, 4.98; N, 19.22; Cl, 16.21; neut. equiv. 216.2.

An N-nitroso derivative (XI) was prepared as follows.[4] To a solution of 2.2 g (10 mmoles) of the ethyl ester of N-(2-pyrimidyl)glycine hydrochloride (VIIIa) in the least amount of water (at room temperature) cooled to 0°, was added 1 ml. of conc. hydrochloric acid. A solution of 0.7 g (10 mmoles) of sodium nitrite in 2 ml. of water was added portionwise with stirring. The contents of the flask was scratched and refrigerated to give 1.0 g (48%) of yellow grains, m.p. 36-38°. On standing, it was slowly converted to IX which with concentrated hydrochloric acid, gave IXa.

<u>Ethyl Ester of N-(2-Pyrimidyl)glycine (VIII)</u>. The <u>ester free base</u> separated as tiny needles or a powdery solid when a solution of 0.5 g (2.3 mmoles) of the hydrochloride in 2 ml. of water was neutralized with saturated sodium bicarbonate solution. Recrystallization from absolute ethanol produced

colorless rods, m.p. 107.5-108°; from dioxane large transparent rectangular plates, m.p. 109-110°, were obtained.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.02; H, 6.12; N, 23.20.

Found: C, 53.57; H, 6.41; N, 23.25.

N-(2-Pyrimidyl)glycine Hydrochloride (IXa).[5] The crude ethyl ester of N-(2-pyrimidyl)glycine hydrochloride (1.10 g, 5.07 mmoles) was heated for 2 minutes in 3 ml. of boiling 4N hydrochloric acid. Another 1 ml. of concentrated acid and Norit were added. After brief boiling, the solution was filtered to yield, after overnight cooling in the refrigerator, 0.575 g (60%) of the glycine hydrochloride as large colorless thick rectangular plates, m.p. 180-182°.

Anal. Calcd. for $C_6H_8ClN_3O_2$: C, 38.00; H, 4.25; N, 22.17; neut. equiv. 94.8.

Found: C, 37.73; H, 4.23; N, 21.99; neut. equiv. 92.5, 96.8.

N-Nitroso derivative of N-(2-Pyrimidyl)glycine (X).[4] To 1.10 g (5 mmoles) of the ethyl ester of N-(2-pyrimidyl)glycine hydrochloride (VIIIa) was added 1 ml. of conc. hydrochloric acid and 3 ml. of water. The mixture was heated until solution occurred, 3 ml. of water was added and the solution heated to boiling for 3 min. The solution was cooled to 0° in an ice-salt bath and 0.43 g (6.2 mmoles) of sodium nitrite was added. The flask was swirled for a few minutes and, after standing, the yellow solution deposited yellow grains. After having been washed with a minimum amount of water the product weighed 0.59 g (65%), m.p. 119-120° (dec.).

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.56; H, 3.29; N, 30.77.

Found: C, 39.31; H, 2.83; N, 31.08.

References

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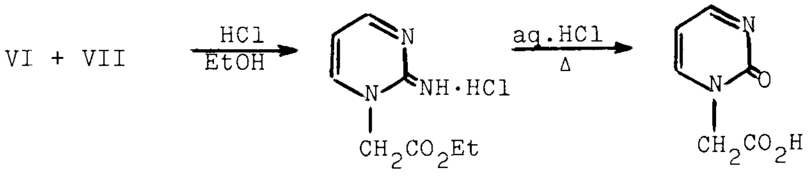
   d) University of Massachusetts, Amherst, Massachusetts 01003.

2. J. M. Tien and I. M. Hunsberger, J. Am. Chem. Soc., 77, 6604 (1955).

3. Elemental analyses were performed by Schwarzkopf Microanalytical Labotatory, Woodside, New York. Both glycocyamine and malonaldehyde diethylacetal are available from Aldrich.

4. The position of the N-nitroso group is unspecified in view of the failure of X to give the corresponding sydnone.

5. The formation of IXa eliminated 2-imino-1,2-dihydropyrimidine-1-acetic acid ethyl ester hydrochloride (VIIIb) as an alternate structure for VIIIa since the hydrolysis of VIIIb would have resulted in the formation of the pyrimidone (VIIIc), a structure clearly incompatible with the results of the elemental analysis and the formation of a hydrochloride.



VIIIb VIIIc

(Received February 20, 1969)