

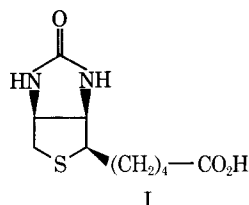
Synthetic Approaches to the Pyrrolo [3,4-*d*] Imidazole Nucleus

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Abstract □ A synthetic scheme for the preparation of compounds containing the pyrrolo [3,4-*d*] imidazole ring system has been developed. *cis*-Hexahydropyrrolo [3,4-*d*] imidazole-2-one has been prepared and its stereochemistry confirmed.

Keyphrases □ *cis*-Hexahydropyrrolo [3,4-*d*] imidazole-2-one—synthesis □ TLC—separation □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ Mass spectroscopy—structure

The pyrrolo [3,4-*d*] imidazole ring system has been the subject of limited study,¹ and since it is closely related to the thieno [3,4-*d*] imidazole nucleus, the ring system of biotin (I), the preparation of certain representatives of this class of compounds was desirable.

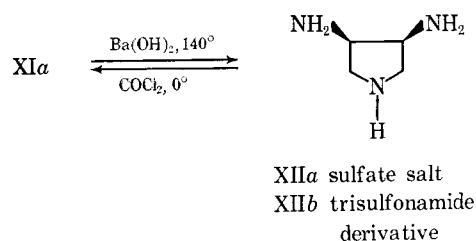


This report describes a convenient procedure for the synthesis of *cis*-hexahydropyrrolo [3,4-*d*] imidazole-2-one (XIa) which should be applicable to the preparation of a variety of 4-substituted derivatives.

1,3-Dicarbethoxy-4-pyrrolidone (V) provided a suitable moiety on which to build the imidazolone system. The pyrrolidone was obtained by a Dieckmann cyclization carried out as described previously (1) and as outlined in Scheme I. From the tracer study of Rapoport and Willson (2) it is now certain that the ring closure affords the desired β -ketoester V rather than the isomeric 1,2-dicarbethoxy-3-pyrrolidone. Pyrrolidone V was then converted to the ureido-3-pyrroline VI in 66% yield, by condensation with urea under acid-catalyzed conditions. The ureidopyrroline, unlike the pyrrolidone, is a relatively stable substance which can be kept for extended periods of time without undergoing decomposition. The reduction of the 3-pyrroline was attempted with platinum oxide in ethanol. The reaction was found to be very slow and incomplete. Work-up afforded two closely related compounds with similar R_f values. These two compounds were characterized as isomeric 1,3,4-trisubstituted pyrrolidines (*cis* VIIa and *trans* VIIb) by elemental analysis and additional reactions as shown in Scheme I. Reduction of Compound VI using freshly prepared W-2 Raney nickel (3) afforded exclusively VIIa in 90% yield, providing additional support for the

assigned stereochemistry. Compound VIIa was converted to the hydrazide VIII which in turn gave an acyl azide upon treatment with nitrous acid. Curtius rearrangement of this intermediate afforded two pyrrolo-imidazolones (IX and X). Barium hydroxide hydrolysis of either IX or X afforded the desired product XIa in 81 and 69% yields, respectively.

The structure of product XIa was established by the following reactions:



Drastic hydrolysis in a sealed tube with barium hydroxide opened the imidazolone ring with the formation of *cis*-3,4-diaminopyrrolidine which was characterized as the crystalline sulfate XIIa and the tris-*p*-toluenesulfonamide XIIb. Treatment of a cold sodium bicarbonate solution of XIIa with phosgene reintroduced the carbonyl group into the molecule and the resulting bicyclic derivative was found to be identical to XIa.

EXPERIMENTAL²

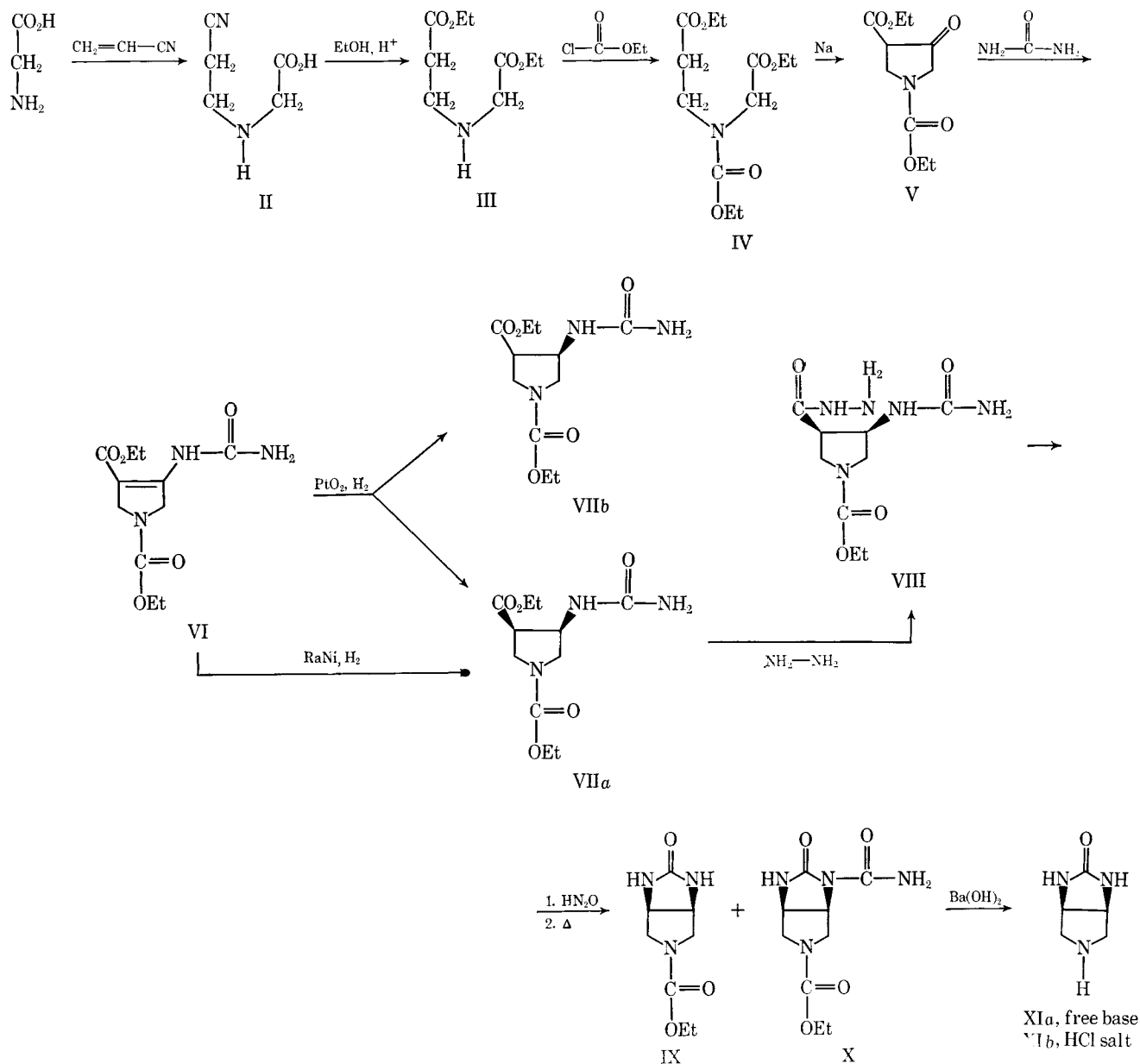
1,3-Dicarbethoxy-4-ureido-3-pyrroline (VI)—A solution of 11.4 g. (50 mmoles) of 1,3-dicarbethoxy-3-pyrrolidone (V) (1), 3.5 g. (57 mmoles) of urea, and 0.5 g. (2.6 mmoles) of *p*-toluenesulfonic acid monohydrate in 400 ml. of absolute ethanol and 200 ml. of benzene was heated under reflux for 56 hr. in a continuous extraction apparatus containing anhydrous sodium sulfate in the thimble. The solution was concentrated, cooled, and the crystalline product collected by filtration to yield 9.1 g., (66%), m.p. 182–187°. Several recrystallizations from 95% ethanol gave colorless crystals of VI, m.p. 208–209°. UV spectrum showed $\lambda_{\text{max}}^{\text{EtOH}}$ 273 m μ (ϵ 22,790). IR spectrum (mineral oil) showed bands at 2.81, 3.00, 3.15, 5.84, 5.97, and 6.15 μ .

Anal.—Calcd. for C₁₁H₁₇N₃O₅: C, 48.70; H, 6.32; N, 15.49. Found: C, 48.71; H, 6.32; N, 15.39.

1,3-Dicarbethoxy-4-ureido-pyrrolidine (VIIa and VIIb)—*Method A*—A solution of VI (1.0 g., 3.7 mmoles) in 100 ml. of absolute ethanol was hydrogenated in a Parr shaker over 0.2 g. (84.7%) of platinum oxide at 3 atm. for 5 days. Evaporation of the filtered solution *in vacuo* gave a thick, colorless, oily residue which showed three spots on TLC. The mixture was separated by preparative TLC on Silica Gel HF₂₅₄₊₃₆₆ (12% methanol in chloroform). The

¹ The only additional work thus far recorded in the literature on compounds having this ring system concerns a derivative of hexahydropyrrolo [3,4-*d*] imidazole mentioned in a communication by J. Sicher, M. Rajsner, J. Rudinger, M. Eckstein, and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 3719(1959). This compound is 3-benzoyl-hexahydropyrrolo [3,4-*d*] imidazole-2,4-dione.

² Melting points were determined on a Fisher-Johns melting point stage and a Thomas-Hoover melting point apparatus which had been calibrated with standard samples. UV absorption spectra were determined in 95% ethanol on a Beckman (model DK2A) recording spectrophotometer. IR absorption spectra were recorded in chloroform (unless otherwise specified) on a Beckman (model 8) recording spectrophotometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectra were determined on an Atlas CH-4 mass spectrometer with TO-4 ion source. TLC was carried out with Silica Gel G and Silica Gel HF₂₅₄₊₃₆₆ (Brinkmann Instruments),



higher R_f band gave 0.35 g. of starting material VI, m.p. 208–209°; mixed m.p. 208–209°. The intermediate R_f band gave 0.24 g. of product VIIa which after recrystallization from chloroform-diethyl ether had m.p. 137–139°. IR spectrum (mineral oil) showed bands at 2.94, 2.98, 3.16, 5.81, 6.00, and 6.16 μ .

Anal.—Calcd. for $C_{11}H_{19}N_3O_5$: C, 48.34; H, 7.01; N, 15.37. Found: C, 48.39; H, 6.95; N, 15.42.

The lower R_f band gave 0.17 g. of product VIIb which crystallized from chloroform-diethyl ether as colorless plates having m.p. 152–154°. IR spectrum (mineral oil) showed bands at 2.92, 2.99, 3.05, 5.80 and 6.01 μ .

Anal.—Calcd. for $C_{11}H_{19}N_3O_5$: C, 48.34; H, 7.01; N, 15.37. Found: C, 48.40; H, 6.95; N, 15.42.

Method B—A solution of 2.0 g. (7.4 mmoles) of VI in 150 ml. of absolute ethanol was hydrogenated over freshly prepared W-2 Raney nickel. The reaction was run under 3 atm. for 24 hr. Evaporation of the filtered solution gave a thick, colorless oil which showed a single spot on TLC. Crystallization from chloroform-diethyl ether afforded 1.82 g. (90%) of colorless microcrystals, m.p. 137–139°. The IR spectrum (mineral oil) and TLC mobility were

identical with those of VIIa (Method A), mixed m.p. 137–138°. The *cis* configuration was assigned to this product.

1-Carbomethoxy-3-hydrazino-4-ureido-pyrrolidine (VIII)—A solution of 1.0 g. (3.7 mmoles) of VIIa in 10 ml. of absolute ethanol was treated with 1.5 ml. of hydrazine hydrate and the mixture gently refluxed for 4 hr. Evaporation of the solvent afforded 0.98 g. of crystalline product, m.p. 181–185°. Recrystallization from ethanol gave 0.74 g. (78%) of colorless crystals. The analytical sample had m.p. 190–191°.

Anal.—Calcd. for $C_9H_{17}N_5O_4$: C, 41.70; H, 6.61; N, 27.01. Found: C, 41.79; H, 6.56; N, 27.07.

3-Carbomoyl-5-carbomethoxy-hexahydropyrrolo [3,4-d] imidazole-2-one (IX) and 5-carbomethoxy-hexahydropyrrolo [3,4-d] imidazole-2-one (X)—Three grams (11.6 mmoles) of hydrazide VIII dissolved in 15 ml. of 2 *N* hydrochloric acid and cooled to -2° , was treated dropwise with a cold solution of 1.5 g. (21.7 mmoles) of sodium nitrite in 9 ml. of water. The oily, yellow azide was extracted with several portions of cold ethyl acetate and the combined extracts dried over anhydrous sodium sulfate. The filtrate was refluxed over a steam bath for 3 hr. and the solvent evaporated *in vacuo*. Upon

standing, the yellow oil afforded 0.33 g. of colorless crystals, m.p. 217–220°. Recrystallization from absolute ethanol gave IX, m.p. 221–222°. IR spectrum (mineral oil) showed bands at 3.01, 3.10, 5.89, and 6.00 μ . Mass spectrum (70eV) gave a molecular ion at m/e 199.

Anal.—Calcd. for $C_8H_{13}N_3O_3$: C, 48.20; H, 6.43; N, 21.10. Found: C, 48.08; H, 6.56; N, 20.93.

Upon treatment with an equal volume of anhydrous ether, the original mother liquor afforded a second crystalline product (X): 0.28 g.; m.p. 182–187°. This substance was recrystallized several times from absolute ethanol, m.p. 195–197°. IR spectrum (mineral oil) showed bands at 2.96, 3.10, 5.79, and 5.99 μ . Mass spectrum (70eV) gave a molecular ion at m/e 242.

Anal.—Calcd. for $C_9H_{14}N_4O_4$: C, 44.63; H, 5.83; N, 23.13. Found: C, 44.43; H, 5.98; N, 23.06.

Preparative TLC of the remaining mother liquor on Silica Gel HF₂₅₄₊₃₆₆ gave additional quantities of IX (lower R_f band, 0.39 g., m.p. 219–221°) and X (higher R_f band, 0.44 g., m.p. 195–196°) for an overall yield of 36.4 and 25.6%, respectively.

cis-Hexahydropyrrolo [3,4-d] imidazole-2-one (XIa)—*Method A*—A mixture of 0.53 g. (2.63 mmoles) of IX and 3.0 g. (9.51 mmoles) of barium hydroxide octahydrate in 50% aqueous methanol was refluxed for 15 hr. The white suspension was dried *in vacuo* and the powdered mixture chromatographed over 25 g. of basic alumina eluting successively with chloroform, 5, 10, 20, 30, 40, and 50% methanol in chloroform. Evaporation of the eluate (800 ml.) gave 0.21 g. (81%) of a colorless crystalline product, m.p. 211–214°. Recrystallization from ethanol afforded an analytical sample, m.p. 213–215°. IR spectrum (mineral oil) showed bands at 3.04, 3.12, and 5.92 μ . Mass spectrum (70eV) gave a molecular ion at m/e 127.

Anal.—Calcd. for $C_5H_7N_3O$: C, 47.24; H, 7.14; N, 33.06. Found: C, 47.23; H, 7.17; N, 32.93.

The hydrochloride salt XIb, prepared in the usual way, was recrystallized three times from absolute ethanol to give colorless needles, m.p. 275–290° dec.

Method B—Compound X (0.50 g., 2.07 mmoles) was treated under identical conditions as Compound IX and the reaction worked up in a similar manner. A colorless crystalline product was obtained (0.23 g., 69%), m.p. 213–215°. The IR and TLC mobility of this product were identical to those obtained for the product of Method A.

cis-3,4-Diaminopyrrolidine Sulfate (XIIa)—Compound XIa (0.31 g., 2.41 mmoles), barium hydroxide octahydrate (2.7 g., 8.56 mmoles), and water (7.5 ml.) were placed in a sealed tube and heated at 130–135° for 16 hr. in an oil bath. The resulting suspension was removed from the tube, brought to a boil, and carbon dioxide was passed into the hot solution for 15 min. The barium carbonate was removed by filtration through diatomaceous earth,³ the clear filtrate was concentrated to a small volume *in vacuo* and acidified to Congo red with 10% sulfuric acid. The barium sulfate was filtered, most of the water removed *in vacuo*, and absolute

ethanol added to precipitate a white crystalline product (0.49 g., 39%, m.p. 275–282° dec.).

Anal.—Calcd. for $C_8H_{28}N_6O_{12}S_3 \cdot H_2O$: C, 18.63; H, 5.87; N, 16.33. Found: C, 18.66; H, 5.85; N, 16.05.

cis-N,N',N''- tris (p-toluenesulfonyl) 3,4-diaminopyrrolidine (XIIb)—A solution of 0.10 g. (0.19 mmole) of the *cis*-diaminopyrrolidine sulfate salt XIIa in 3.0 ml. of 10% sodium hydroxide was treated with 0.2 g. (1.05 mmoles) of *p*-toluenesulfonyl chloride. The mixture was heated on a water bath for 20 min., cooled and acidified to Congo red with concentrated hydrochloric acid. The white precipitate was filtered and dried (0.059 g., m.p. 200–203°). Recrystallization from ethanol afforded a colorless crystalline product, m.p. 205–207°. UV spectrum showed λ_{max}^{EtOH} 229 m μ (ϵ 42,450). IR spectrum (chloroform) showed bands at 3.05, 6.25, 7.41, and 8.6 μ . Mass spectrum (70eV) gave no molecular ion peak at m/e 563, but gave m/e 408 for *M*-155 or *M*-CH₃-C₆H₄-SO₂.

Anal.—Calcd. for $C_{25}H_{29}N_3O_6S_3$: C, 53.27; H, 5.19; N, 7.46. Found: C, 53.38; H, 5.08; N, 7.43.

cis-Hexahydropyrrolo [3,4-d] imidazole-2-one (XIa)—*By Phosgene Treatment of XIIa*.—A solution of 0.10 g. (0.19 mmole) of compound XIIa in 2.0 ml. of 10% sodium bicarbonate was cooled in an ice bath and treated dropwise with 8.0 ml. of a 12.5% solution of phosgene in benzene. The reaction was stirred at 0° for 12 hr. The aqueous layer was found distinctly acid to Congo red. The mixture was evaporated to dryness *in vacuo* and the crystalline residue extracted with hot 95% ethanol. The alcoholic extract following concentration afforded a colorless crystalline material: m.p. 272–288°; mixed m.p. with XIb undepressed. The IR and TLC mobility were identical to those of XIb. The free base XIa was obtained by dissolving the hydrochloride salt in 1.0 ml. of a 5% sodium bicarbonate solution, evaporating to dryness and extracting the residue with hot 95% ethanol. Concentration of the extract afforded colorless needles: m.p. 213–214°; mixed m.p. undepressed by admixture with Compound XIa obtained previously.

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³ Celite, Johns-Manville, New York, N. Y.