Synthesis of *dl*-4ξ-(4-Carboxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo-[3,4-*d*]imidazol-2-one (*N*-Carbethoxyazabiotin)

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Abstract □ The total synthesis of *dl*-4ξ-(4-carboxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (*N*-carbethoxyazabiotin) by a 16-step sequence, starting from 2-bromo-6-methoxyhexanoic acid, has been accomplished.

Keyphrases □ *dl*-4ξ-(4-Carboxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one—16-step synthesis from 2-bromo-6-methoxyhexanoic acid □ *N*-Carbethoxyazabiotin—16-step synthesis from 2-bromo-6-methoxyhexanoic acid □ Biotin derivatives—16-step synthesis of *N*-carbethoxyazabiotin □ 2-Bromo-6-methoxyhexanoic acid—starting material for 16-step synthesis of *N*-carbethoxyazabiotin

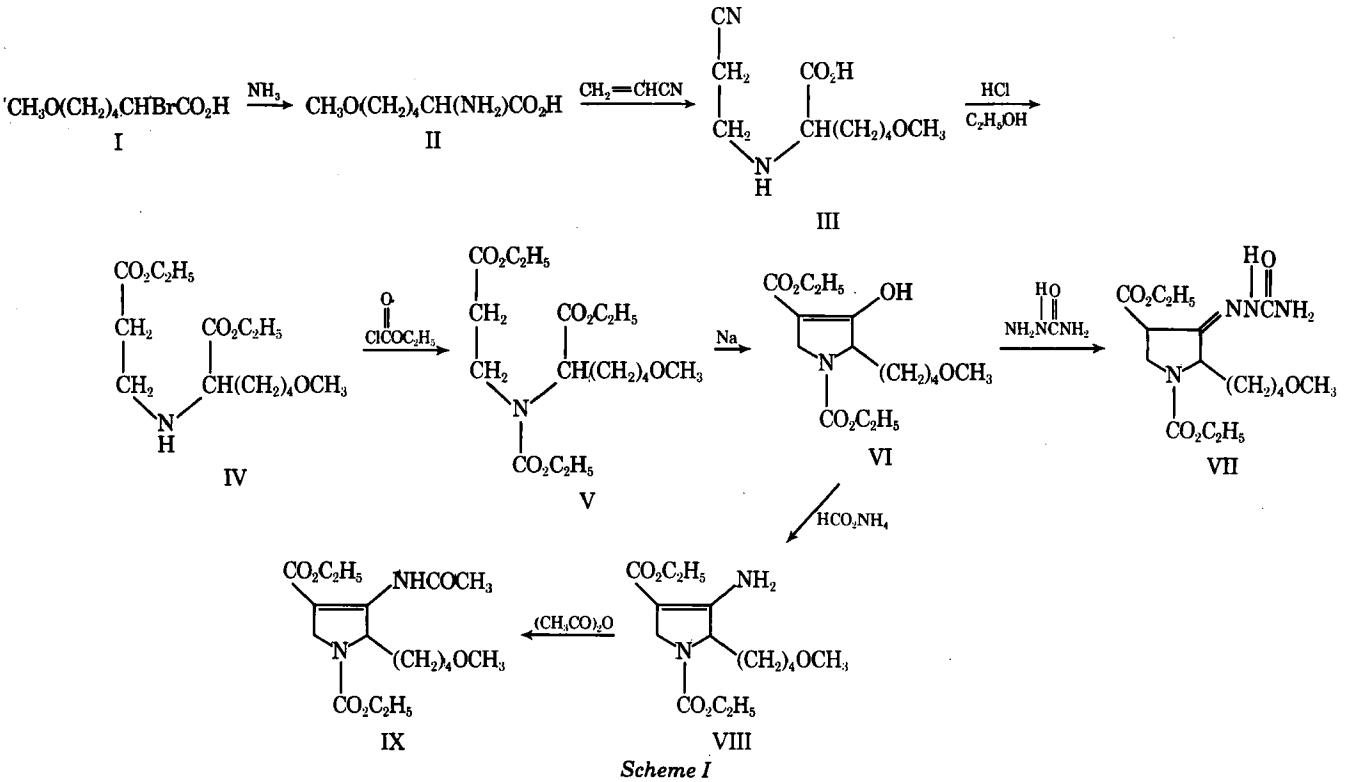
As part of a program for the development of new agonists and antagonists of biotin (1–3), a close analog of the vitamin has been synthesized in which the sulfur atom has been replaced by a nitrogen. It is yet unclear whether the sulfur atom is indeed essential for optimum activity of the cofactor, since compounds such as oxybiotin (4–6), carbobiotin (3), and desthiobiotin (7) exhibit some degree of activity as growth promoters in microorganisms.

In previous articles (1, 2), a scheme was devised for the synthesis of substituted pyrrolo[3,4-*d*]imidazole compounds. The method now has been applied in the synthesis of the title compound, *dl*-4ξ-(4-carboxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*] imidazol-2-one, hereafter referred to as *N*-carbethoxyazabiotin (XIX) (Schemes I–III).

DISCUSSION

The synthesis of XIX starts with 2-bromo-6-methoxyhexanoic acid (I), prepared by the method of Schmid (8) from 1,4-dibromobutane. The α-bromo acid was first converted to the corresponding α-amino acid (II) by treatment with concentrated ammonium hydroxide. Monocyanoethylation with acrylonitrile in aqueous base followed by ethanolysis–esterification gave the aminodiester (IV) in good yield. The amino group was protected with a carbethoxy group by treating IV with ethyl chloroformate, and a Dieckmann condensation afforded an oily pyrroline (VI) in 93% yield.

A crystalline semicarbazone (VII) of the β-keto ester (VI) was prepared to secure an analytical sample since attempts to distill the Dieckmann product only led to decomposition. Condensation of VI with ammonium formate in ethanol afforded a 96% yield of the enamine (VIII). Following acetylation with acetic anhydride at 90°, the oily pyrroline was reduced at 1000 psi of hydrogen over freshly prepared W-2 Raney nickel. Reduction at lower pressures (Parr apparatus) was very slow and incomplete, and reduction utilizing platinum as the catalyst failed completely. A crystalline 3,4-*cis*-pyrrolidine (X) was obtained in 40% yield from the Raney nickel reduction.



Scheme I

Hydrazinolysis of X under relatively mild conditions afforded a mixture of two products, consisting primarily of the 3,4-*cis*-hydrazide (XII*a*) and a small amount of the 3,4-*trans*-epimer (XII*b*). This latter product could also be obtained by first epimerizing X in ethanol containing catalytic amounts of ethoxide and subsequent treatment of the 3,4-*trans*-pyrrolidine (XI) with hydrazine hydrate. Because of the relatively small amount of the 3,4-*trans*-epimer by-product in the crude hydrazide product, no attempt was made to purify the mixture for the next step and it was found suitable as such.

Conversion to the azide, followed by Curtius rearrangement, gave the pyrrolo[3,4-*d*]imidazole (XIII) as a dark oil. Cleavage of the side-chain methoxy group without additional damage to the ring system proved somewhat problematic. Attempts with 48% hydrobromic acid in acetic acid, concentrated hydrochloric acid, and the mixed anhydride acetyl *p*-toluenesulfonate (9) failed to afford a suitable product either by giving unresolvable resinous mixtures or by failing to alter the starting material at all. A solution of XIII in acetic anhydride containing boron trifluoride etherate finally afforded the triacetyl compound (XIV) along with small quantities of the *N,N*-diacetyl ether (XIV*a*).

Room temperature hydrolysis of XIV in 48% hydrobromic acid gave the carbinol (XV), which was converted to the homologous nitrile (XVII) *via* the mesylate (XVI). Ethanolysis of the nitrile to the ester (XVIII) followed by base hydrolysis gave the title compound (XIX). Although XIII–XVIII were obtained as noncrystalline, nondistillable oils, spectroscopic data for these compounds were in agreement with the assigned structures.

EXPERIMENTAL[1]

2-Amino-6-methoxyhexanoic Acid (II)—2-Bromo-6-methoxyhexanoic acid (I) (8) (225 g, 1.0 mole) was treated with 3 liters of concentrated ammonium hydroxide and allowed to stand at room temperature for 24 hr. The solution was concentrated to about one-quarter volume, and the precipitated crystals were collected by suction filtration and gave 125.0 g, mp 269–271°. An additional 21.0 g, mp 269–271°, was obtained from the mother liquor. Recrystallization from ethanol gave 129.5 g (80%), mp 272–274°. IR: λ_{max} (mineral oil) 3.75, 3.87, and 6.05 μm.

Anal.—Calc. for $C_7H_{15}NO_3$: C, 52.17; H, 9.38; N, 8.69. Found: C, 52.29; H, 9.25; N, 8.78.

2-(2-Cyanoethylamino)-6-methoxyhexanoic Acid (III)—Compound II (129.0 g, 0.80 mole) was dissolved in 600 ml of water and treated with a solution of 32.0 g (0.80 mole) of sodium hydroxide in 200 ml of water, followed by 42.5 g (0.80 mole) of acrylonitrile, while stirring magnetically in an ice bath. Dropwise treatment with 46 ml (0.80 mole) of acetic acid gave a white precipitate. The product was filtered and washed with ether–ethanol followed by ether. The mother liquor was concentrated, filtered, and similarly washed. The total yield amounted to 140.0 g (82% yield), mp 218–224°. Two recrystallizations from ethanol–water gave an analytical sample, mp 220–222°; the melt resolidified at 222–223° and remelted at 249–252° dec.; IR: λ_{max} (mineral oil) 4.44 μm.

Anal.—Calc. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.11; H, 8.41; N, 13.13.

Ethyl 2-(2-Carbethoxyethylamino)-6-methoxyhexanoate (IV)—A solution of 140.0 g (0.65 mole) of III in 500 ml of absolute ethanol was treated with dry hydrogen chloride gas for 8 hr while stirring in an ice bath. After refluxing the reaction mixture for 1 hr, the ethanol was removed *in vacuo*. The residue was dissolved in water and cooled in an ice bath. The cold solution was treated with 10% ammonium hydroxide to pH 9. The oil was extracted into ether. The ether extract was washed with saturated sodium chloride, dried (sodium sulfate), and concentrated to give 149.0 g (79%) of colorless liquid; IR: λ_{max} (neat) 2.91, 3.00, 5.82, and 8.50 μm. The product was considered suitable for conversion to the carbamate (V).

Ethyl 2-[*N*-(2-Carbethoxyethyl)-*N*-carbethoxy]amino-6-methoxyhexanoate (V)—To a solution of 149.0 g (0.52 mole) of IV in 400 ml of chloroform, cooled in an ice bath, was added dropwise 66.5 g (0.62 mole) of ethyl chloroformate followed by a solution of 28.0 g (0.26 mole) of sodium carbonate in 100 ml of water. After stirring in the cold for 2 hr, the reaction mixture was heated at 60° for 1 hr. The chloroform layer was separated, washed with water, dried (magnesium sulfate), and concentrated. Distillation gave 159.0 g (85%) of a colorless liquid, bp 147–150° (0.12 mm); IR: λ_{max} (neat) 5.81 and 5.92 μm; NMR: δ 1.26 (9H, t, $-OCH_2CH_3$, J = 7 Hz), 2.67 (1H, t, $-CH_2CHN(C{=}O)-$, J = 7 Hz), 3.36 (3H, s, OCH_3), 3.46 (2H, t, $-OCH_2CH_2-$, J = 6 Hz), and 4.20 (9H, q, $-COOCH_2CH_3$, J = 7 Hz).

Anal.—Calc. for $C_{17}H_{31}NO_7$: C, 56.50; H, 8.65; N, 3.88. Found: C, 56.36; H, 8.74; N, 3.96.

1,4-Dicarbethoxy-2-(4-methoxybutyl)-3-hydroxy-3-pyrroline (VI)—A suspension of 12.2 g (0.53 mole) of sodium in 500 ml of toluene was heated at reflux and treated with a solution of 159.0 g (0.44 mole) of V in 600 ml of toluene. When the addition was complete, the reaction mixture was refluxed overnight. While cooling in an ice bath, the mixture was treated dropwise with a solution of 65 ml of acetic acid and 250 ml of water. The mixture was extracted with chloroform. The organic layer was washed with water, dried, and concentrated to yield 129.0 g (93%) of a brown oil; IR: λ_{max} (chloroform) 5.73, 5.85 (sh), 5.90 (sh), 6.00, and 6.15 (sh) μm; UV: λ_{max} (ethanol) 250 and 280 nm; addition of base gave λ_{max} 278 nm. The copper chelate had a melting point of 61–65° after recrystallization from ether.

The pyrroline (VI) was converted to its semicarbazone (VII), mp (analytical sample) 158–161° (from ethanol–water).

Anal.—Calc. for $C_{16}H_{28}N_4O_6$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.79; H, 7.54; N, 15.01.

1,4-Dicarbethoxy-2-(4-methoxybutyl)-3-amino-3-pyrroline (VIII)—A solution of 125.0 g (0.40 mole) of VI and 50.5 g (0.80 mole) of ammonium formate in 2 liters of absolute ethanol was refluxed for 4 hr. The solvent was removed *in vacuo*, and the residue was partitioned between water and chloroform. The organic layer was washed with water, dried (magnesium sulfate), and concentrated to yield 120.0 g (96%) of an oil; IR: λ_{max} (chloroform) 2.88, 3.00, 5.91, and 6.09 μm; UV: λ_{max} (ethanol) 275.5 nm; NMR: δ 1.30 (6H, t, $-OCH_2CH_3$, J = 7 Hz), 3.32 (1H, s, $-OCH_3$), 3.32 (2H, t, $-OCH_2CH_2$, J = 6 Hz), 4.21 (4H, q, $-OCH_2CH_3$, J = 7 Hz), and 5.78 (2H, s, $-NH_2$).

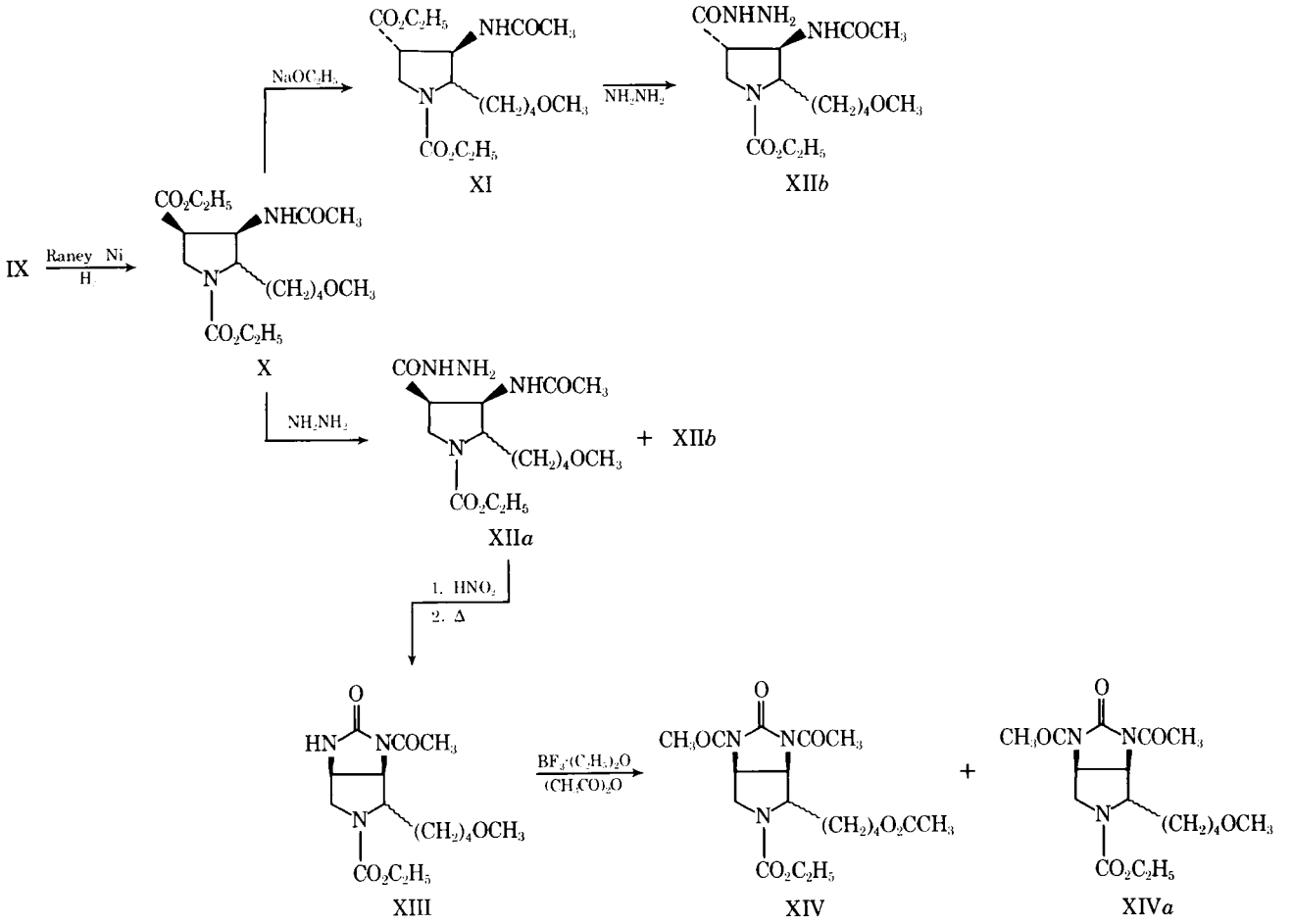
1,4-Dicarbethoxy-2-(4-methoxybutyl)-3-acetamido-3-pyrroline (IX)—A solution of 120.0 g (0.38 mole) of VIII in 300 ml of acetic anhydride was heated on an oil bath at 90–100° for 36 hr. The excess acetic anhydride was removed under high vacuum to give 135.0 g (100%) of a dark-red oil; IR: λ_{max} (chloroform) 3.10, 6.03, and 6.20 μm; UV: λ_{max} (ethanol) 275 nm; NMR: δ 1.30 (6H, t, $-OCH_2CH_3$, J = 7 Hz), 2.17 (3H, s, $-NCOCH_3$), 3.32 (3H, s, $-OCH_3$), 3.32 (2H, t, $-CH_2CH_2O$, J = 6 Hz), 4.24 (4H, q, $-OCH_2CH_3$, J = 7 Hz), and 5.67 (1H, s, —NH).

1,4-Dicarbethoxy- 2ξ- (4-methoxybutyl)-3-acetamido-3,4-*cis*-pyrrolidine (X)—A solution of 45.0 g (0.126 mole) of IX in 150 ml of absolute ethanol was treated with 25 teaspoonsful of W-2 Raney nickel catalyst and hydrogenated at 1000 psi and room temperature for 15 hr. The catalyst was filtered off, and the ethanol was evaporated *in vacuo*. The oily residue was scratched with isopropyl ether. The crystals that appeared were removed by filtration and washed with cold isopropyl ether to yield 18.5 g of 1,4-dicarbethoxy-2ξ-(4-methoxybutyl)-3-acetamido-3,4-*cis*-pyrrolidine (X), mp 95–98°. Two recrystallizations from isopropyl ether gave an analytical sample, mp 98–99°; IR: λ_{max} (chloroform) 2.91, 5.82 (sh), and 5.99 μm; NMR: δ 1.25 (6H, t, $-OCH_2CH_3$, J = 7 Hz), 2.02 (3H, s, $-NCOCH_3$), 3.36 (3H, s, $-OCH_3$), 3.36 (2H, t, OCH_2CH_2-, J = 6 Hz), 4.27 (4H, q, $-OCH_2CH_3$, J = 7 Hz), and 6.90 (1H, d, —NH, J = 5 Hz).

Anal.—Calc. for $C_{17}H_{30}N_2O_6$: C, 56.96; H, 8.44; N, 7.82. Found: C, 56.93; H, 8.40; N, 7.48.

1,4-Dicarbethoxy- 2ξ- (4-methoxybutyl)-3-acetamido-3,4-*trans*-pyrrolidine (XI)—A sample of 358 mg (1.0 mmole) of X was refluxed with 5 ml of a freshly prepared 1% sodium ethoxide

[1] Melting points were taken on a Fisher-Johns melting-point stage and a Thomas-Hoover melting-point apparatus and are uncorrected. UV absorption spectra were determined in 95% ethanol on a Beckman (model DK2A) recording spectrophotometer. IR absorption spectra were recorded on Beckman (models 8 and 33) recording spectrophotometers. NMR spectra were determined in deuterochloroform, using tetramethylsilane as reference standard, on Varian T-60 and Varian EM 360 spectrometers. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. TLC was carried out with silica gel G, silica gel $HF_{254+366}$, and silica gel $PF_{254+366}$.



Scheme II

solution for 30 min. The solvent was evaporated, and the residue was partitioned between chloroform and water. The organic layer was washed with water, dried (magnesium sulfate), and concentrated to give 325 mg (91%) of crystals of XI (the 4-epimer of X), mp 75–79°. Recrystallization from ether gave the analytical sample, mp 78–80°; IR: λ_{max} (chloroform) 2.90, 3.00 (sh), 5.82 (sh), and 5.99 μm; NMR: δ 1.26 (6H, t, $-OCH_2CH_3$, J = 7 Hz), 2.03 (3H, s, $-NCOCH_3$), 3.36 (3H, s, $-OCH_3$), 4.24 (4H, q, $-OCH_2CH_3$, J = 7 Hz), and 6.5 (1 H, broad s, NH).

Anal.—Calc. for $C_{17}H_{30}N_2O_6$: C, 56.96; H, 8.44; N, 7.82. Found: C, 56.88; H, 8.36; N, 7.76.

1-Carbethoxy-2ξ-(4-methoxybutyl)-3-acetamidopyrrolidine-4-carboxylic Acid Hydrazide (XII)—A solution of 25.0 g (0.07 mole) of X in 250 ml of absolute ethanol was treated with 50 ml of hydrazine hydrate. The mixture was heated at 45–50° for 4 hr, when TLC analysis showed the absence of starting material. The alcohol and excess hydrazine hydrate were removed *in vacuo*. The resulting product (actually a mixture of epimers consisting primarily of XII*a* with small amounts of XII*b*) weighed 24.0 g and was used directly in the preparation of XIII.

A 430-mg sample of XII was subjected to preparative TLC, utilizing 25% methanol in chloroform as the eluent. The higher R_f band gave 250 mg of a crystalline substance, mp 137–138°. Three recrystallizations from methanol–ether gave an analytical sample, mp 142–144°; IR: λ_{max} (mineral oil) 2.98, 3.02, 6.00, and 6.14 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.00 (3H, s, $-NCOCH_3$), 3.33 (3H, s, $-OCH_3$), 3.33 (2H, t, OCH_2CH_2-, J = 6 Hz), 4.15 (2H, q, $-OCH_2CH_3$, J = 7 Hz), and 7.01 (3H, m, —NH). This compound was designated as the *cis*-isomer (XII*a*).

Anal.—Calc. for $C_{15}H_{28}N_4O_5$: C, 52.31; H, 8.19; N, 16.27. Found: C, 52.23; H, 8.07; N, 16.09.

The lower R_f band yielded 72 mg of an oil, which solidified on long standing in a desiccator. The solid was recrystallized from methanol–ether, mp 125–127°; IR: λ_{max} (chloroform) 3.01 and 6.01 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.01 (3H, s, $-NCOCH_3$), 3.33 (3H, s, $-OCH_3$), 3.33 (2H, t, $-OCH_2CH_2$, J = 6 Hz), and 4.15 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

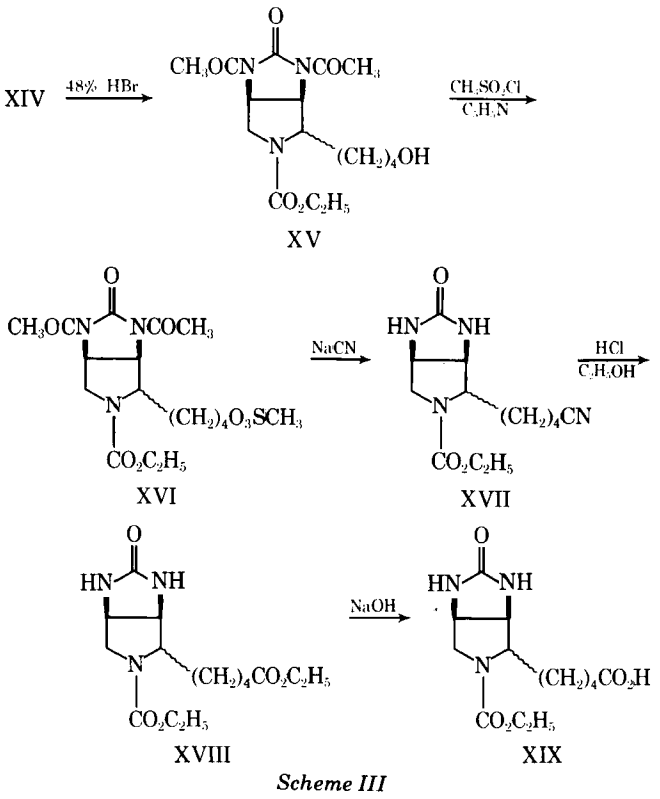
This compound was designated as the *trans*-isomer (XII*b*), since it could be readily prepared by treatment of XI with hydrazine hydrate in ethanol at room temperature.

Anal.—Calc. for $C_{15}H_{28}N_4O_5$: C, 52.31; H, 8.19; N, 16.27. Found: C, 52.13; H, 8.16; N, 16.09.

3-Acetyl-4ξ-(4-methoxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XIII)—A solution of 24.0 g (0.07 mole) of a mixture of XII*a* and XII*b* in 300 ml of 1 *N* hydrochloric acid was cooled in an ice–salt bath and treated with a solution of 20 g of sodium nitrite in 100 ml of water. Near the end of the addition, a flocculent white precipitate formed in the reaction flask. The product was extracted with ethyl acetate several times. The extract was washed with water, dried (magnesium sulfate), and concentrated to give 20.2 g of solid acyl azide; IR: λ_{max} (chloroform) 4.65 μm. This solid was redissolved in 150 ml of ethyl acetate and refluxed on a steam bath for 3 hr. The solvent was evaporated to give 18.0 g of a dark oil; IR: λ_{max} (chloroform) 2.90, 3.05, and 6.05 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.57 (3H, s, $-NCOCH_3$), 3.34 (3H, s, $-OCH_3$), 3.34 (2H, t, $-OCH_2CH_2$, J = 6 Hz), 4.18 (2H, q, $-OCH_2CH_3$, J = 7 Hz), and 6.57 (1H, s, NH).

1,3-Diacetyl-4ξ-(4-acetoxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XIV)—A solution of 29.0 g (0.09 mole) of XIII in 100 ml of acetic anhydride was treated with 15 ml of freshly distilled boron trifluoride etherate. The mixture was heated at 50° for 3.5 hr and then concentrated under high vacuum. The residue was chromatographed on a silica gel column, using increasing concentrations of chloroform in benzene. Elution with chloroform–benzene (3:2) gave 9.4 g of XIV as an uncrystallizable oil; IR: λ_{max} (chloroform) 5.70–5.95 μm (strong, broad); NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.04 (3H, s, $-OCOCH_3$), 2.58 (6H, s, $-NCOCH_3$), and 4.18 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

Further elution of the column with chloroform–benzene (3:2)



Scheme III

gave 1,3-diacetyl-4ξ-(4-methoxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XIV*a*) as an uncrystallizable oil; IR: λ_{max} (chloroform) 5.70–5.95 μm (strong, broad); NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.58 (6H, s, $-NCOCH_3$), 3.34 (3H, s, $-OCH_3$), and 4.18 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

1,3- Diacetyl- 4ξ- (4-hydroxybutyl) -5 - carbethoxy- *cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XV)—A solution of 9.4 g (0.024 mole) of XIV in 50 ml of 48% hydrobromic acid was stirred at room temperature for 16 hr. The water and hydrobromic acid were removed under high vacuum. The residue was chromatographed on a silica gel column, using increasing concentrations of ether in benzene. Elution with ether–benzene (1:4) gave 3.3 g of XV as an uncrystallizable oil; IR: λ_{max} (chloroform) 2.80, 2.90, 5.70, and 5.90 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.58 (6H, s, $-NCOCH_3$), 3.30 (1H, s, CH_2OH), 3.60 (2H, m, CH_2CH_2OH), and 4.15 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

1,3-Diacetyl- 4ξ- (4-methanesulfonylbutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XVI)—A solution of 1.63 g (0.0046 mole) of XV in 10 ml of pyridine was treated with 3 ml of freshly distilled methanesulfonyl chloride. The solution was allowed to stand in the refrigerator for 16 hr and the pyridine and excess methanesulfonyl chloride were removed under high vacuum. The residue was dissolved in chloroform, washed with water, dried (magnesium sulfate), and concentrated to give 1.90 g (96%) of an uncrystallizable oil; IR: λ_{max} (chloroform) 5.70, 5.92, 7.05, and 8.53 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 2.59 (3H, s, $-NCOCH_3$), 3.02 (3H, s, $-SO_3CH_3$), and 4.16 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

4ξ- (4-Cyanobutyl)-5- carbethoxy-*cis*- hexahydropyrrolo-3,4-*d*]imidazol-2-one (XVII)—Compound XVI (1.68 g, 0.0039 mole) was dissolved in 5 ml of methanol. To this solution was added a solution of 1.62 g of sodium cyanide in 5 ml of water. The reaction mixture was diluted with 5 ml of methanol to remove the cloudiness and was then refluxed for 1 hr. After concentration to dryness *in vacuo*, the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was dried (magnesium sulfate) and concentrated to an uncrystallizable oil (620 mg); IR: λ_{max} (chloroform) 2.83, 3.00, 4.40, and 5.70–6.00 μm; NMR: δ 1.26 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 4.18 (2H, q, $-OCH_2CH_3$, J = 7 Hz), 5.98 (1H, broad s, NH), and 6.50 (1H, broad s, NH).

4ξ-(4-Carbethoxybutyl)-5-carbethoxy-*cis*-hexahydropyrrolo[3,4-*d*]imidazol-2-one (XVIII)—A cold solution of nitrile XVII (0.985 g, 3.51 mmoles) in 20 ml of absolute ethanol was treated with dry hydrogen chloride gas for 2 hr while keeping the reaction flask in a salt–ice bath. The reaction mixture was allowed to reach room temperature and was refluxed for 1 hr. The precipitated ammonium chloride was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in chloroform, and the extract was washed with water, dried (magnesium sulfate), and concentrated under reduced pressure to give a pale-brown oil (0.920 g, 80%); IR: λ_{max} (chloroform) 2.88, 3.08, and 5.88–6.00 μm; NMR: δ 1.27 (6H, t, $-OCH_2CH_3$, J = 7 Hz), 4.17 (4H, q, $-COOCH_2CH_3$, J = 7 Hz), 6.25 (1H, broad s, NH), and 6.40 (1H, broad s, NH).

4ξ- (4-Carboxybutyl)-5- carbethoxy-*cis*- hexahydropyrrolo[3,4-*d*]imidazol-2-one (XIX)—A 1% solution of sodium hydroxide (2 ml) was added to 100 mg (0.31 mmole) of ester XVIII. After 20 min of stirring at room temperature, dissolution of the oily ester was complete. The cooled yellow solution was acidified with concentrated hydrochloric acid, and the mixture was concentrated to dryness. Two successive recrystallizations from 95% ethanol afforded colorless crystals (35 mg, 38%), mp 192–195°; IR: λ_{max} (mineral oil) 3.07, 5.85, and 6.00 μm.

Anal.—Calc. for $C_{13}H_{21}N_3O_5$: C, 52.17; H, 7.07; N, 14.04. Found: C, 52.19; H, 6.93; N, 14.13.

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