Synthesis of 2-Aminomethyldipyrrylmethanes

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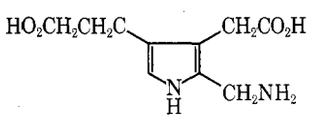
The synthesis of 2-aminomethyl-3,4′-(β-carboxyethyl)-4,3′-carboxymethyldipyrrylmethane and of 2-aminomethyl-3,3′-(β-carboxyethyl)-4,4′-carboxymethyldipyrrylmethane is outlined. The condensation of ethyl 2-methyl-3-formyl-5-ethoxycarbonyl-4-pyrroleacetate with benzyl hydrogen malonate afforded a benzyl acrylate which was reduced and esterified to a benzyl 2-methyl-3-pyrrolepropionate. The latter was transformed by oxidation with sulfuryl chloride into its 2-formyl derivative, whose oxime was reduced to afford the 2-aminomethyl-3-pyrrolepropionic acid. Cyclization of the amino acid followed by sodium benzylate transesterification allowed the synthesis of benzyl 3-(benzyloxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate, which was then converted into methyl pyrrolohexahydroazepin-6-one-3-acetate. The 2-bromomethyl- or 2-chloromethylpyrroles derived from the 2-methyl-3- (or 4-) methoxycarbonylmethyl-4- (or 3-) β-methoxycarbonylethyl-5-benzyloxycarbonylpyrroles were prepared. Condensation of the halomethylpyrroles with the pyrrolohexahydroazepinone afforded the corresponding 5′-benzyloxycarbonyldipyrrylmethane lactams. Hydrogenolysis, decarboxylation, and saponification of the ester groups and the seven-membered lactam ring afforded the 2-aminomethyldipyrrylmethanes.

The chemical mechanism underlying the enzymatic polymerization of porphobilinogen (1) to uroporphyrinogen III is a fertile field for biosynthetic speculations.[1] As yet, no open-chain polypyrrolic intermediates have been isolated and identified from the enzymatic reaction that could help clarify the nature of this metabolic process. The synthesis of the four possible dipyrrylmethanes **2–5** formally derived from the self-condensation of two units of porphobilinogen was hence undertaken. Once the synthetic dipyrrylmethanes are obtained they will be used to study their enzymatic and chemical behavior in the process of uroporphyrinogen biosynthesis.



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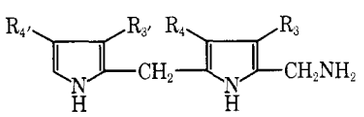


2, $R_3 = R_{3'} = CH_2CO_2H$; $R_4 = R_{4'} = CH_2CH_2CO_2H$

3, $R_3 = R_{4'} = CH_2CO_2H$; $R_4 = R_{3'} = CH_2CH_2CO_2H$

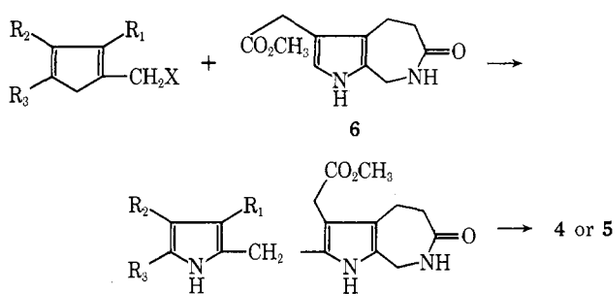
4, $R_3 = R_{4'} = CH_2CH_2CO_2H$; $R_4 = R_{3'} = CH_2CO_2H$

5, $R_3 = R_{3'} = CH_2CH_2CO_2H$; $R_4 = R_{4'} = CH_2CO_2H$

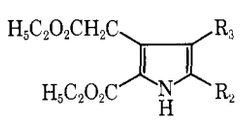
The synthesis of the dipyrrylmethanes **2** and **3** and several of its enzymatic and chemical properties obtained during the course of studies on uroporphyrinogen biosynthesis were already reported.[1-6] The enzymatic incorporation of dipyrrylmethane **4** into uroporphyrinogen III, as well as some of its chemical properties of relevance for the study of uroporphyrinogen III biosynthesis, was discussed elsewhere.[4,7] In this paper we will discuss the synthetic method used to obtain the dipyrrylmethanes **4** and **5**. The sequence was based on the condensation of properly activated and protected 2-halomethylpyrroles with a seven-membered pyrrole lactam **6** to obtain the corresponding dipyrrylmethane lactams (Scheme I). It was then expected that the cleavage of the protecting groups and the saponification of the lactam ring would afford the dipyrrylmethanes **4** and **5**.

The seven-membered pyrrole lactam **6** was prepared according to the following sequence. The diethyl ester aldehyde **7**, prepared by a Vilsmaier–Haak formylation of ethyl 5-ethoxycarbonyl-4-pyrroleacetate, was condensed with

Scheme I



benzyl hydrogen malonate, affording the benzyl 3-pyrroleacrylate **8**. The benzyl hydrogen malonate was obtained by partial saponification of dibenzyl malonate. Reduction with hydrogen of the acrylate resulted in the simultaneous cleavage of the benzyl ester group and reduction of the acrylic side chain. No specific hydrogenation conditions of the double bond could be found which should avoid the hydrogenolysis of the benzyl ester. The resulting 3-pyrrolepropionic acid **9** was transformed into its benzyl ester **10** by treatment with distilled diazotoluene, and the latter was oxidized to the corresponding aldehyde **11** by reaction with sulfuryl chloride. The transformation of the aldehyde **11** into its oxime **12** and the catalytic hydrogenation of the latter allowed the synthesis of the 2-aminomethyl-3-pyrrolepropionic acid **13**.



7, $R_2 = CH_3$; $R_3 = CHO$

8, $R_2 = CH_3$; $R_3 = CH{=}CHCO_2CH_2C_6H_5$

9, $R_2 = CH_3$; $R_3 = CH_2CH_2CO_2H$

10, $R_2 = CH_3$; $R_3 = CH_2CH_2CO_2C_6H_5$

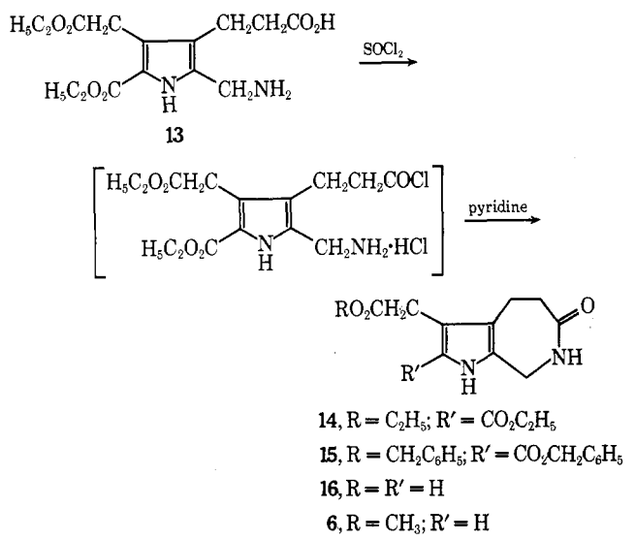
11, $R_2 = CHO$; $R_3 = CH_2CH_2CO_2CH_2C_6H_5$

12, $R_2 = CH{=}NOH$; $R_3 = CH_2CH_2CO_2CH_2C_6H_5$

The cyclization of a 2-aminomethyl-3-pyrrolepropionic derivative to yield a seven-membered pyrrole lactam is not a spontaneous process as is the case with a 2-aminomethyl-3-pyrroleacetic acid derivative. While in the latter case a six-membered pyrrole lactam was spontaneously obtained after esterification of the acetic acid residue,[1] a 2-amino-

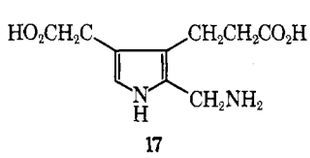
methyl-3-pyrrolepropionate remained mainly in the open form even after heating at 100°. By heating the amino acid 13 above its melting point only a small amount of the desired lactam was obtained. Efficient cyclization could, however, be obtained after transformation of the propionic acid residue into its chloride with thionyl chloride. By dissolving the crude chloride hydrochloride in pyridine the cyclization reaction takes place spontaneously and the diethyl pyrrolehexahydroazepinone 14 was obtained in 50% yield (Scheme II).

Scheme II



14, R = C_2H_5; R′ = $CO_2C_2H_5$
15, R = $CH_2C_6H_5$; R′ = $CO_2CH_2C_6H_5$
16, R = R′ = H
6, R = CH_3; R′ = H

Transesterification of 14 with sodium benzylate afforded the dibenzyl ester 15. The benzyl ester groups were cleaved by hydrogenolysis and the 5-carboxypyrrole lactam was decarboxylated by heating in water at 100° for a short time. The decarboxylation was best carried out in a vacuum-sealed vessel, since the pyrrole lactam 16 was sensitive to heating in air. By treating the lactam 16 with diazomethane, the methyl pyrrolehexahydroazepinone-3-acetate 6 was obtained. The lactam could be kept at 5° during several months without decomposition. It was saponified to isoporphobilinogen (17) when dissolved in a 2 *N* potassium hydroxide solution and kept at room temperature during 72 hr.



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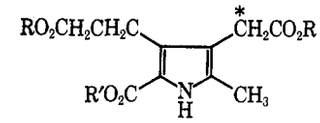
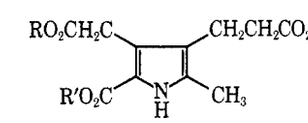
The synthesis of the conveniently substituted 2-halomethylpyrroles necessary for the synthesis of the dipyrrylmethane lactams (Scheme I) made use of selective transesterification reactions based on Kenner's experience with simple pyrroles[8] and on our results with complex pyrroles.[1] The triethyl esters 18 and 19 were used as convenient starting materials for this purpose. They could be prepared by simple and reproducible reaction sequences.[9,10] Treibs' approach[10] was particularly suited, since it allowed the synthesis of the triethyl ester 18 labeled with ^{14}C at the position (*), using [^{14}C]-formaldehyde. The triethyl ester 18 was transformed into the tribenzyl ester 21 by treatment of the triacid 20 obtained by saponification of 18 with distilled diazotoluene, or by transesterification of the triethyl ester 18 with benzyl alcohol in the presence of a small amount of sodium benzylate. The tribenzyl ester 21 was transesterified back with sodium methylate in methyl alcohol to the dimethyl benzyl ester 22 which was thus obtained in 80% yield.



18, R = R′ = C_2H_5
20, R = R′ = H
21, R = R′ = $CH_2C_6H_5$
22, R = CH_3; R′ = $CH_2C_6H_5$

The transesterification of the isomeric triethyl ester 19 with sodium benzylate in benzyl alcohol only afforded an inseparable mixture of esters. However, when the triacid 23 obtained by saponification of 19 was treated with diazotoluene, the tribenzyl ester 24 was easily obtained. The tribenzyl ester 24 could not be transesterified with sodium methylate in methyl alcohol, since under different conditions of reaction time and heating periods it only afforded mixtures of dibenzyl methyl and dimethyl benzyl esters which could not be efficiently separated. A reproducible reaction sequence was then found by the partial saponification of the tribenzyl ester 24 to the monobenzyl ester 25 with potassium hydroxide in benzyl alcohol, followed by treatment of the diacid with ethereal diazomethane. The dimethyl benzyl ester 26 thus obtained in 25% overall yield from the tribenzyl ester was found to be pure by tlc analysis and could be used in the further reaction sequence.



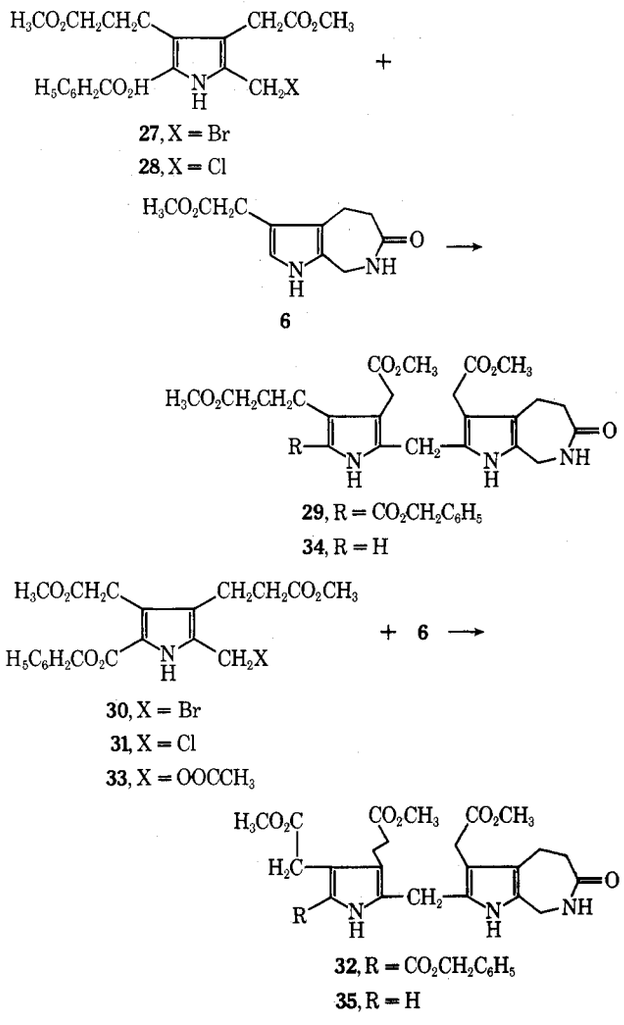
19, R = R′ = C_2H_5
23, R = R′ = H
24, R = R′ = $CH_2C_6H_5$
25, R = H; R′ = $CH_2C_6H_5$
26, R = CH_3; R′ = $CH_2C_6H_5$

Reference should be made here to the procedures described by MacDonald and coworkers[2] and later by Battersby and coworkers,[3] who transesterified the triethyl esters 18 and 19 using large amounts of sodium benzylate in benzyl alcohol, and obtained the 5-benzyloxycarbonylpyrrole diacids as the main reaction products and the tribenzyl esters as the secondary reaction products. In our experience, the monobenzyl diacids obtained by the aforementioned procedures always contained the dibenzyl monoacid derivatives (as judged by tlc analysis), whose complete removal resulted in extremely poor yields of the pure monobenzyl acid.

Dipyrrylmethane lactams have been prepared by condensation of 2-aminomethylpyrroles[1] or of 2-halomethylpyrroles[2,3] and pyrrole lactams. The condensation of 2-aminomethylpyrroles[1] with the lactam 6 failed to give the expected dipyrrylmethanes. The 2-bromomethyl derivative 27 was obtained by bromination of 22 under ultraviolet light and was condensed with the pyrrole lactam 6 in acetic acid containing sodium acetate. The dipyrrylmethane 29 was obtained in 29% yield (Scheme III). The analogous 2-chloromethyl derivative 28, obtained as a solid and stable compound by the action of sulfuryl chloride on 22, reacted in an analogous manner to give the dipyrrylmethane 29 in 41% yield. The reactions were carried out in a sealed vessel under air exclusion and no other definite reaction products

could be identified. By reaction of the 2-bromomethylpyrrole **30** with the pyrrole lactam **6** under the same reaction conditions, the dipyrrylmethane **32** was obtained in 37% yield. When the 2-chloromethylpyrrole **31** was used, the dipyrrylmethane **32** was obtained in 28% yield, along with the 2-acetoxymethylpyrrole **33**, formed in 19% yield. When the condensations of the 2-bromomethylpyrroles with the pyrrole lactam were carried out in pyridine at 90–100°, the dipyrrylmethanes were obtained in much lower yields. The attempted condensation of the 2-acetoxymethylpyrrole **33** with the pyrrole lactam **6** under the usual reaction conditions afforded only traces of the dipyrrylmethane **32** and the major part of **33** was recovered unchanged.

Scheme III



The transformation of the 5′-benzyloxycarbonyldipyrrylmethanes **29** and **32** into the 5′-free derivatives followed the sequence outlined in our former work.[1] Hydrogenolysis of **29** and **32** resulted in formation of the 5′-carboxydipyrrylmethanes, which were decarboxylated by a short heating at 220° under high vacuum. The obtained dipyrrylmethanes **34** and **35** were purified by chromatography and saponified to the 2-aminomethyl derivatives **4** and **5**. The saponification of the dipyrrylmethane lactams **34** and **35** was carried out by dissolving them in a 2 *N* potassium hydroxide solution in 50% ethanol and by keeping the solutions at room temperature during 72 hr. This procedure was previously used to carry out the saponifications of the dipyrrylmethane lactams leading to **2** and **3**, and was later successfully used by other groups.[3,11] The saponification procedure for dipyrrylmethane lactams using a hot ethanolic potassium hydroxide solution[2] led to saponification of the ester groups, but the resulting potassium salt still contained much unsaponified lactam, as evidenced by tlc on cellulose using lutidine–0.7 *N* ammonium hydroxide (10:7 v/v) as a solvent.

The 2-aminomethyldipyrrylmethanes **4** and **5** were very unstable substances, as could be expected from their structures, and were directly used in solution for the ulterior enzymatic and chemical studies. Heating the dipyrrylmethane **4** at 37° and pH 7.4 afforded exclusively uroporphyrin II, while the dipyrrylmethane **5** was transformed under the same reaction conditions into a mixture containing 85% of uroporphyrin I and 15% of uroporphyrin III or IV.

Experimental Section[12]

Benzyl Hydrogen Malonate. A solution of 29 g (0.5 mol) of potassium hydroxide in 300 ml of benzyl alcohol was added to a solution of 142 g (0.5 mol) of dibenzyl malonate in 300 ml of benzyl alcohol and the solution was stirred overnight. The potassium salt which separated was filtered and dissolved in water and the solution was extracted with ether (3 × 100 ml), adjusted to pH 2 with concentrated hydrochloric acid, and repeatedly extracted with ether (3 × 100 ml). The ethereal extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness, and the residue was crystallized from benzene–cyclohexane: 39 g (94%); mp 38–40°; nmr ($CDCl_3$) 2.88 (s, 2, CH_2CO_2H), 3.99 (s, 2, $CH_2C_6H_5$), 6.72 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.8; H, 5.2. Found: C, 61.8; H, 5.3.

Ethyl 5-Methyl-4-formyl-3-(ethoxycarbonylmethyl)-2-pyrrolecarboxylate (7). A solution of 3.37 g of ethyl 5-ethoxycarbonyl-4-pyrroleacetate[9] dissolved in 23 ml of dry dimethylformamide was added under moisture exclution conditions to a mixture of 15 ml of dimethylformamide and 8.1 ml of phosphorus oxychloride kept at 0–5°. The resulting solution was heated at 75° during 1 hr with continuous stirring and then cooled, adjusted to pH 8 with concentrated sodium hydroxide, and further heated at 75° during 15 min. The mixture was then poured into ice–water (100 ml), and the reaction product was extracted with chloroform. The dried (Na_2SO_4) extracts were evaporated to dryness *in vacuo* and the residue was crystallized from methanol–water: 3.4 g (91%); mp 152° (lit.[9] mp 151–152°); nmr ($CDCl_3$) 1.3, 1.4 (t, J = 8 Hz, CH_2CH_3), 2.5 (s, 3, CH_3), 4.25 (m, 6, CH_2CH_3, CH_2CO), 10 ppm (s, 1, CHO).

Benzyl 2-Methyl-4-(ethoxycarbonylmethyl)-5-ethoxycarbonyl-3-pyrroleacrylate (8). A solution of 12 g of the aldehyde **7**, 35 g of benzyl acid malonate, and 0.5 ml of piperidine in 40 ml of pyridine was heated at 90° during 15 hr, followed by heating under reflux during 2 hr. The mixture was poured over ice (300 ml), adjusted to pH 2 with concentrated hydrochloric acid, and extracted repeatedly with chloroform (5 × 100 ml). The dried (Na_2SO_4) chloroform extracts were evaporated to dryness, the residue was dissolved in 60 ml of methanol, and 20 ml of water was added in small portions with continuous cooling while crystallization was achieved. The solid **8** was filtered and dried (6 g), the filtrates were evaporated to dryness, and the residue, dissolved in 2% methanol in benzene, was filtered through a silica gel column prewashed and later eluted with the same solvent. The acrylate **8** was eluted first (R_f, 0.40, benzene–2% methanol) and collected after evaporation of the elution solvent to dryness. An additional 6 g of **8** was thus obtained: total yield 67%; mp 78–80°; uv max 259 nm (ε 17,200), 321 (19,900); nmr ($CDCl_3$) 1.3 (m, 6, CH_3CH_2), 2.35 (s, 3, CH_3), 3.95 (s, 2, CH_2CO), 4.2 (m, 4, CH_2CH_3), 5.2 (s, 2, $CH_2C_6H_5$), 6.0 (d, 1, J = 15 Hz, =CHCO), 7.3 (br, 5, C_6H_5), 7.65 ppm (d, 1, J = 15 Hz, pyrr–CH=).

Anal. Calc. for $C_{22}H_{25}NO_6$; C, 66.1; H, 6.3; N, 3.5. Found: C, 66.3; H, 6.1; N, 3.6.

2-Methyl-5-(ethoxycarbonyl)-4-(ethoxycarbonylmethyl)-3-pyrrolepropionic Acid (9). A solution of 3.4 g of the benzylacrylate **8** was dissolved in 100 ml of ethanol and reduced with hydrogen at 50 psi during 2 hr over an equal weight of 10% palladium on charcoal. The catalyst was filtered, the solvent was evaporated *in vacuo*, and the residue was crystallized from ethanol–water: 2.4 g (90%); mp 123–125°; nmr (TFA) 1.4, 1.45 (t, 6, J = 7 Hz, CH_3CH_2), 2.3 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 4.0 (s, 2, CH_2CO), 4.4 ppm (m, 4, CH_2CH_3).

Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.8; H, 6.7; N, 4.5. Found: C, 58.0; H, 6.8; N, 4.4.

Benzyl 2-Methyl-5-(ethoxycarbonyl)-4-(ethoxycarbonylmethyl)-3-pyrrolepropionate (10). The pyrrolepropionic acid **9** (4 g) was dissolved in 50 ml of methanol and an excess of freshly distilled diazotoluene was added in small portions until persistence of a pink color. The excess of reagent was destroyed with acetic acid, the solution was evaporated to dryness *in vacuo*, and the residue was crystallized from cyclohexane: 4 g (78%); mp 66–68°; nmr ($CDCl_3$) 1.2, 1.3 (t, 6, CH_3CH_2), 2.1 (s, 3, CH_3), 2.55 (m, 4, CH_2CH_2), 3.7 (s, 2, CH_2CO), 4.15 (m, 4, CH_2CH_3), 5.0 (s, 2, $CH_2C_6H_5$), 7.2 (br, 5, C_6H_5).

Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.7; N, 3.5. Found: C, 65.7; H, 6.6; N, 3.6.

Benzyl 2-(Ethoxycarbonyl)-3-(ethoxycarbonylmethyl)-5-formyl-4-pyrrolepropionate (11). A solution of 2.4 g (6 nmol) of the benzyl ester **10** in 30 ml of anhydrous methylene chloride was cooled at 2–3° under moisture exclusion, and 0.96 ml (12 nmol) of sulfuryl chloride was added in small portions. The mixture was kept with continuous stirring at room temperature during 30 min. The solvent was evaporated to dryness *in vacuo*, 4 g of sodium acetate dissolved in 100 ml of water was added, and the mixture was heated at reflux during 5 min. It was then cooled, the supernatant aqueous solution was discarded, and the oily residue was dissolved in 120 ml of hot ethanol and reprecipitated by addition of 150 ml of water: 2.1 g (83%); mp 70–73°; nmr ($CDCl_3$) 1.2, 1.4 (t, J = 7 Hz, 6, CH_2CH_3), 2.8 (m, 4, CH_2CH_2), 3.75 (s, 2, CH_2CO), 4.2 (m, 4, CH_2CH_3), 5.0 (s, 2, CH_2Bz), 7.2 (br, 5, C_6H_5), 10 ppm (s, 1, CHO).

Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.6; H, 6.0; N, 3.4. Found: C, 63.5; H, 6.0; N, 3.5.

Benzyl 2-(Ethoxycarbonyl)-3-(ethoxycarbonylmethyl)-5-formyl-4-pyrrolepropionate Oxime (12). A solution of 330 mg of hydroxylamine hydrochloride in 3 ml of ethanol was added to a second solution of 106 mg of sodium in 40 ml of ethanol. The formed precipitate was centrifuged, 1.36 g of aldehyde **11** was added, and the solution was heated under reflux for 45 min. The solution was cooled, poured over 300 ml of ice water, and kept during 15 hr at 5°. The solid was filtered and crystallized from methanol–water, 1.25 g (89%), mp 97–99°.

Anal. Calcd for $C_{22}H_{26}N_2O_7$: C, 61.4; H, 6.05; N, 6.5. Found: C, 61.2; H, 6.15; N, 6.7.

Ethyl 2-Aminomethyl-3-(carboxyethyl)-4-(ethoxycarbonylmethyl)-5-pyrrolecarboxylate (13). A solution of 1.25 g of the oxime **12** in 100 ml of glacial acetic acid was reduced with hydrogen over 1 g of 10% palladium on charcoal at 50 psi. The catalyst was filtered, the solvent was evaporated to dryness *in vacuo*, and the oily residue was crystallized from anhydrous ethanol: 0.61 g (50%); mp 177–179°; nmr (TFA) 1.4 (6, m, CH_3CH_2), 2.9 (br, 4, CH_2CH_2), 4.1 (br, 2, CH_2CO), 4.6 (m, 6, CH_2CH_3, $CH_2NH_3^+$), 7.4 ppm (br, 3, NH_3^+).

Anal. Calcd for $C_{15}H_{22}N_2O_6$: C, 55.2; H, 6.7; N, 8.6. Found: C, 55.1; H, 6.8; N, 8.8.

Ethyl 3-(Ethoxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate (14). The amino acid **13** (0.45 g) was dissolved in 9 ml of freshly distilled thionyl chloride and the mixture was stirred overnight under moisture exclusion conditions. The solvent was completely evaporated to dryness, and the solid residue was dissolved in 9 ml of cold anhydrous pyridine. The solution was kept during 1 hr at 3–5° followed by 30 min at room temperature, 50 ml of water was added, the solution was extracted with chloroform (3 × 10 ml), and the chloroform extracts were evaporated *in vacuo*. The residue was filtered through a silica gel column (10 × 1 cm) prewashed with 10% methanol in chloroform and eluted with the same solvent. The lactam **14** was the only product eluted and was crystallized from methanol: 0.21 g (50%); mp 191–193°; uv max 280 nm (ϵ 21,700); ir 3350 (NH), 1745 (CO ester), 1690 (CO ring ester), 1665 cm^{-1} (CO amide); nmr (TFA) 1.0, 1.2 (t, J = 6 Hz, 6, CH_3CH_2), 3.0 (br, 4, CH_2CH_2), 3.8 (s, 2, CH_2CO), 4.25 (m, 4, CH_2CH_3), 4.5 (br, 2, CH_2NH).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.4; H, 6.3; N, 9.0.

Benzyl 3-(Benzyloxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate (15). Diethyl lactam **14** (1.7 g) was added to a solution of 42 mg of sodium in 100 ml of benzyl alcohol, the mixture was heated under anhydrous conditions and 100° during 2 hr, 20 ml of benzyl alcohol was distilled off *in vacuo* and replaced with fresh benzyl alcohol, and the mixture was heated for an additional 4 hr at 100°. The solvent was then evaporated to dryness *in vacuo*, and the residue was redissolved in 50 ml of chloroform, which was washed with 5 ml of water and evaporated to dryness. The residue was crystallized from ethanol: 1.2 g (50%); mp 169–171°; nmr ($CDCl_3$), 2.75 (br, 4, CH_2CH_2CO), 3.8 (s, 2, CH_2CO), 4.2 (br, 2, CH_2NH), 5.1 (s, 2, $CH_2C_6H_5$), 5.3 (s, 2, ring $CH_2C_6H_5$), 7.35 (br, 10, C_6H_5).

Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.4, H, 5.5; N, 6.5. Found: C, 69.4; H, 5.6; N, 6.4.

Methyl Pyrrolohexahydroazepin-6-one-3-acetate (6). A solution of 0.3 g of benzyl lactam **15** in 50 ml of glacial acetic acid was reduced with hydrogen over 300 mg of 10% palladium on charcoal at 50 psi during 2 hr. The catalyst was filtered and the solution was freeze-dried. The residue was suspended in 60 ml of deaerated water in a vacuum-sealed vessel, and the mixture was heated at 100° during 45 min. The solution was freeze-dried. The residue was shown to be pure lactam **16** (R_f 0.66) when examined by paper chromatography [Whatman No. 1, 1-butanol–acetic acid–water (4:1:5)]. Too unstable to be crystallized, it was dissolved in methanol and treated with an excess of ethereal diazomethane at 5°. The solvent was evaporated *in vacuo*, and the residue was filtered through a short column of silica gel prewashed with 10% methanol in chloroform which eluted the lactam **6** as the only product: 0.108 g (70%); mp 135–138°; ir 1750 ($COOCH_3$), 1653 cm^{-1} (CO amide); nmr (pyridine-d_5) 2.75 (s, 4, CH_2CH_2), 3.35 (s, 2, CH_2CO), 3.45 (s, 3, OCH_3), 4.25 (d, J = 6 Hz, 2, CH_2NH), 6.6 ppm (br, 1, H_5).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.3; N, 12.6. Found: C, 59.4; H, 6.3; N, 12.5.

Ehrlich's reaction was positive in the cold.

Isoporphobilinogen (17). A solution of 41 mg of lactam **6** in 0.5 ml of 2 *N* potassium hydroxide was kept at room temperature during 72 hr. The solution was acidified to pH 4 with glacial acetic acid, cooled at 5°, and filtered. Isoporphobilinogen was collected and dried: 35.7 mg (80%); mp 190° (capillary tube) (lit.[13] mp 192–195°); R_f 0.49 [Whatman No. 1, butanol–acetic acid–water (4:1:5)]; nmr (D_2O, pH 7 with Na_2CO_3) 2.6 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 4.2 (s, 2, CH_2NH_2), 6.7 ppm (s, 1, H_5).

Benzyl 2-Methyl-3-(benzyloxycarbonylmethyl)-4-(benzyloxycarbonylethyl)-5-pyrrolecarboxylate (21). Procedure A. A suspension of 1.1 g of the acid **20**[14] in 200 ml of methanol was treated with an excess of freshly distilled diazotoluene[15] at room temperature until esterification was complete. The excess of diazotoluene was destroyed with acetic acid, the solvent was evaporated to dryness *in vacuo*, and the residue was crystallized from cyclohexane: 1.8 g (77%); mp 106–108° (lit.[2] mp 108°); nmr ($CDCl_3$) 2.1 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 4.97, 5.01 (s, 4, $CH_2C_6H_5$), 5.2 (s, 2, ring $CO_2CH_2C_6H_5$), 7.2 (br, 15, C_6H_5).

Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.1; H, 5.9; N, 2.7. Found: C, 73.0; H, 5.8; N, 2.7.

Procedure B. Triethyl ester **18**[10] (3 g) was dissolved in 300 ml of benzyl alcohol and 36 mg of sodium was added. The mixture was heated at 150° during 6 hr *in vacuo* (20 mm), the solvent was then evaporated to dryness under high vacuum, and the residue was crystallized from methanol. The product was recrystallized from the same solvent, affording 1.5 g (33%) of the tribenzyl ester **21**. The product was pure by tlc (chloroform–1% methanol). The same tlc analysis indicated that a dibenzyl monoethyl ester remained in the mother liquors.

Benzyl 2-Methyl-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (22). Tribenzyl ester **21** (3 g) was dissolved in 300 ml of anhydrous methanol, 40 mg of sodium was added, and the mixture was heated under reflux during 90 min. The solution was evaporated to half volume and poured over 1000 ml of ice water. After the solution was kept at 5° during 12 hr, it was filtered and the product was recrystallized from cyclohexane: mp 78° (lit.[3] mp 78.5–79.5°); uv max 286 nm (ϵ 19,000); 1.6 g (80%); nmr ($CDCl_3$) 2.2 (s, 3, CH_3), 2.7 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 3.55, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (s, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2; N, 3.8. Found: C, 64.4; H, 6.2; N, 3.9.

Benzyl 2-methyl-3-(benzyloxycarbonylethyl)-4-(benzyloxycarbonylmethyl)-5-pyrrolecarboxylate (24) was obtained following procedure A used in the synthesis of **21**. From 2 g of the triacid **23**[9] was obtained 2.7 g (70%) of the tribenzyl ester: mp 94–96° (cyclohexane) (lit.[2] mp 92–93°); nmr ($CDCl_3$) 2.1 (s, 3, CH_3), 2.55 (m, 4, CH_2CH_2), 3.8 (s, 2, CH_2CO), 4.98, 5.02 (s, 4, $CH_2C_6H_5$), 5.18 (s, 2, ring $CH_2C_6H_5$), 7.25, 7.27 ppm (br, 15, side chain C_6H_5 and ring C_6H_5).

Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.1; H, 5.9; N, 2.7. Found: C, 73.0; H, 5.8; N, 2.7.

Benzyl 2-Methyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-pyrrolecarboxylate (26). To a solution of

160 mg of potassium hydroxide in 20 ml of benzyl alcohol was added 500 mg of the tribenzyl ester **24**, and the mixture was heated at 100° during 12 hr under moisture exclusion conditions. The solution was cooled and extracted with water (3 × 20 ml), and the aqueous solution was washed with ether and then adjusted to pH 3 with concentrated hydrochloric acid. The precipitated diacid **25** was filtered, dried in vacuo, suspended in methanol, and esterified by addition of an excess of ethereal diazomethane. The ether–methanol solution was evaporated to dryness and the product was crystallized from benzene–cyclohexane: 72 mg (25%); mp 111°; pure by tlc (chloroform–2% methanol) (lit.[3] mp 113–116°); nmr ($CDCl_3$) 3.5, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.2 (s, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2; N, 3.8. Found: C, 64.3; H, 6.2; N, 3.7.

2-Chloromethyl-3-(methoxycarbonylmethyl)-4-(2-methoxycarbonylethyl)-5-benzyloxycarbonylpyrrole (28). To a solution of 420 mg of dimethyl benzyl pyrrole **22** in 5 ml of anhydrous dichloromethane kept at 5° was added 0.088 ml of sulfuryl chloride under moisture exclusion conditions. The mixture was stirred during 45 min at room temperature, the solvent was evaporated *in vacuo* at 30°, and the residue was redissolved in 5 ml of dry methylene chloride and evaporated again *in vacuo*. The residue was crystallized from benzene–hexane: 400 mg (87%); mp 108–111° (in literature[3] described as amorphous and unstable); nmr ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.5, 3.6, 3.65 (s, 8, CH_2CO, OCH_3), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (br, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{22}NO_6Cl$: C, 59.0; H, 5.4; N, 3.4. Found: C, 58.9; H, 5.4; N, 3.5.

Methyl 2-(3′-Methoxycarbonylmethyl-4′-β-methoxycarbonyl-5′-benzyloxycarbonyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (29). Procedure A. A solution of 280 mg of bromine in 6 ml of carbon tetrachloride was added to 447 mg of the benzyl dimethyl ester **22** dissolved in 6 ml of the same solvent contained in a quartz vessel. The mixture was stirred while being irradiated with a Hanovia ultraviolet lamp during 35 min. The solvent was then evaporated *in vacuo* to dryness, the residue was extracted with boiling hexane (3 × 25 ml), and the extracts were pooled and concentrated *in vacuo* to dryness. The residual solid **27** (271 mg, 50%) had nmr ($CDCl_3$) 2.8 (m, 4, CH_2CH_2), 3.55 (s, 2, CH_2CO), 3.65, 3.7 (s, 6, OCH_3), 4.58 (s, 2, CH_2Br), 5.5 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5), and was pure for further work-up. It was dissolved in 6 ml of glacial acetic acid containing 1% of sodium acetate, 135 mg of pyrrole lactam **6** was added, and the mixture was heated during 40 min at 90° in a vessel sealed under vacuum (0.3 mm). After the heating period was completed, the vessel was cooled and opened and the reaction mixture was freeze-dried. The residue was dissolved in a small volume of chloroform containing 3.5% of methanol and filtered through a tlc silica gel column (20 × 2 cm) prewashed and then eluted with the same solvent. The dipyrrylmethane **29** was eluted as the exclusive product and was crystallized from methanol–water: 105 mg (29%); mp 184–186°; uv max (ethanol) 284 nm (ε 39,000); ir 1670 (CO lactam), 1710 (CO benzyl ester), 1740 (CO side-chain esters), 3400 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.9 (br, 4, ring CH_2CH_2), 3.1 (m, 4, side-chain CH_2CH_2CO), 3.4, 3.47, 3.5 (s, 13, CH_2CO, OCH_3), 4.2 (s, 2, pyrr–CH_2–pyrr), 4.3 (d, J = 6 Hz, 2, CH_2NH), 5.3 (s, 2, $CH_2C_6H_5$), 7.3 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{35}N_3O_9$: C, 62.7; H, 5.9; N, 7.1. Found: C, 62.7; H, 5.9; N, 7.0.

Procedure B. A mixture of 260 mg of the chloromethyl derivative **28** and 130 mg of the lactam **6** was dissolved in 10 ml of glacial acetic acid containing 1% of sodium acetate and the mixture was heated in a vacuum-sealed vessel at 100° during 30 min. Subsequent work-up was identical with that described under procedure A, and afforded dipyrrylmethane **29** (141 mg, 41%) as the exclusive reaction product. The substance was pure when examined by tlc (chloroform–3.5% methanol). Ehrlich's reaction was negative. It was revealed as an intense orange spot when submitted to bromine vapors.

Methyl 2-(3′-Methoxycarbonylethyl-3′-methoxycarbonylmethyl-5′-benzyloxycarbonyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (32). Procedure A. The 2-bromomethylpyrrole **30** was obtained following the technique described for the isomer **27**. From 373 mg of the dimethyl benzyl pyrrole **26** was obtained 271 mg (60%) of the 2-bromomethylpyrrole **30**: nmr ($CDCl_3$) 2.7 (m, 4, CH_2CH_2CO), 3.6, 3.7 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.5 (s, 2, CH_2Br), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5). Manipulation of the substance led to its gradual decomposition; hence it was used directly for the condensation reaction. The 2-bromomethylpyrrole (271 mg) and the pyrrole lactam **6** (135 mg) were condensed in an acetic acid–sodium acetate solution following the technique described for the synthesis of **29**. The dipyrrylmethane **32** thus obtained was purified by filtration through a tlc silica gel column (20 × 2 cm) using chloroform–4% methanol as a solvent. The dipyrrylmethane was crystallized from methanol–water: 134 mg (37%); mp 111–114°; ir 1680 (CO amide), 1700 (CO ring ester), 1740 (CO side-chain ester), 3450 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.7 (br, 8, CH_2CH_2), 3.35 (s, 2, C_4 CH_2CO), 3.55, 3.6 (s, 9, OCH_3), 3.8 (br, 4, pyrr–CH_2–pyrr, C_4 CH_2CO), 4.1 (d, J = 6 Hz, 2, CH_2NH), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{35}N_3O_9$: C, 62.7; H, 5.9; N, 7.1. Found: C, 62.8; H, 5.9; N, 7.0.

The substance was pure by tlc using various solvents. It was revealed as a bright orange spot when exposed to bromine vapors.

Procedure B. The 2-chloromethylpyrrole **31** was obtained following the technique described for the isomer **28**. From 210 mg of the dimethyl benzyl pyrrole **26** was obtained 207 mg (90%) of **31**: mp 87–89° (chloroform–hexane); nmr ($CDCl_3$) 2.6 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5). It was too unstable to allow the preparation of an analytical sample. It was dissolved (192 mg) in 8 ml of an acetic acid–sodium acetate solution and condensed with 96 mg of lactam **6** as described for the synthesis of **29**. The residue obtained after evaporation of the acetic acid was filtered through a tlc silica gel column (20 cm × 2 cm) using chloroform–4% methanol as eluent. Two substances were eluted. One (tlc, R_f 0.25, chloroform–4% methanol) was dipyrrylmethane **32** (72 mg, 28%); the second (tlc, R_f 0.80, chloroform–4% methanol) was the 2-acetoxymethylpyrrole **33** (40.8 mg, 19%), nmr ($CDCl_3$) 2.1 (s, 3, CH_3CO), 2.6 (m, 4, CH_2CH_2), 3.6, 3.7 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 5.0 (s, 2, CH_2Ac), 5.3 (s, 2, $CH_2C_6H_5$), 7.3 (br, 5, C_6H_5). It was revealed on tlc as a red spot when exposed to bromine vapors.

Methyl 2-(3′-Methoxycarbonylmethyl-4′-β-ethoxycarbonylethyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (34). The monobenzyldipyrrylmethane **29** (210 mg) was dissolved in 20 ml of glacial distilled acetic acid and reduced with hydrogen over 100 mg of 10% palladium on charcoal at 50 psi during 90 min. The catalyst was removed, the solution was freeze-dried, and the residue (160 mg, 90%) was melted at 220° (0.1 mm) under nitrogen and kept as a molten mass during 60 sec. The residue was dissolved in a small volume of chloroform–4% methanol and filtered through a 20 × 2 cm column of tlc silica prewashed with the same solvent. After evaporation of the solvent the dipyrrylmethane **34** was obtained in pure form: 70 mg (47%); mp 134–136° (from methanol); ir 1690 (CO amide), 1720, 1740 (CO esters), 3400 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.9 (br, 8, CH_2CH_2), 3.45, 3.55, 3.57, 3.60 (s, 13, OCH_3, CH_2CO), 4.1 (s, 2, pyrr–CH_2–pyrr), 4.25 (d, J = 6 Hz, 2, CH_2NH), 6.6 ppm (br, 1, C_5H).

Anal. Calcd for $C_{23}H_{29}N_3O_7$: C, 60.1; H, 6.3; N, 9.1. Found: C, 60.0; H, 6.3; N, 8.9.

The substance was homogeneous on tlc analysis. Erhlich's reaction was positive in the cold, (uv max 560 nm, shifting to 490 nm after heating at 60°). It gave an orange spot on tlc when exposed to bromine vapors, R_f 0.70 (tlc, chloroform–4% methanol).

Methyl 2-(3′-β-methoxycarbonylethyl-4′-methoxycarbonylmethyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (35) was obtained following the same procedure described for isomer **34**. From 200 mg of **32** was obtained 66 mg (46%) of **35**, homogeneous by tlc (chloroform–4% methanol). The substance could not be recrystallized, although it crystallized after a hexane wash: mass spectrum m/e (rel intensity) 459 (M^+, 100), 400 (M − CO_2CH_3, 30), 386 (M − $CH_2CO_2CH_3$, 50, possible β-cleavage[16]), 372 (M − $CH_2CH_2CO_2CH_3$, 50, β-cleavage[16]), 235 (M − pyrrole lactam **14** ion − 2 H, 50), 222 (pyrrole lactam **14** ion originated in the C_5 H* formation during bridge cleavage from methylene with $C_{3'}$*$CH_2CH_2CO_2CH_3$, 50); nmr (pyridine-d_5) 2.9 (br, 8, CH_2CH_2), 3.5 (s, 2, C_4 CH_2CO), 3.6, 3.65 (s, 12, OCH_3, $C_{4'}$ CH_2CO), 4.1 (s, 2, pyrr–CH_2–pyrr), 4.3 (d, J = 6 Hz, 2, CH_2NH), 6.75 (br, 1, $H_{5'}$); R_f 0.50 (tlc, chloroform–4% methanol).

2-Aminomethyl-3,4′-(β-carboxyethyl)-4,3′-carboxymethyldipyrrylmethane (4).[17] Dipyrrylmethane **34** (30 mg) was dissolved in a mixture of 0.25 ml of perdeuterioethanol and 0.25 ml of 4 *N* potassium deuteroxide. The solution was kept at room temperature for 72 hr and the gradual saponification of **34** was monitored by following the changes in the nmr spectrum as proposed in our former dipyrrylmethane synthesis.[1] The hexadeuterioethanol was eliminated after 48 hr and replaced by deuterium oxide. The $C_{5'}$-H signal at 6.2 ppm (δ 0 for sodium 4,4-dimethyl-4-silapentane-1-sulfonate) exchanged rapidly and faded after 24 hr. This

susceptibility to electrophilic attack of the 5′-free dipyrrylmethanes was already described by us[1] and later confirmed by others.[3] After 72 hr saponification was complete: nmr 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.7 (br, 2, pyrr–CH_2–pyrr), 4.0 (br, 2, CH_2NH_2). The substance was rapidly transformed into porphyrins by manipulation. Addition of an acid resin (IRC-H^+ or IRA 120-H^+) allowed adjustment of the solution to pH 7. This solution could be kept at −10° during 1 week with no decomposition and was used for chemical or enzymatic studies. Ehrlich's reaction was positive in the cold.

2-Aminomethyl-3,3′-(β-carboxyethyl)-4,4′-carboxymethyldipyrrylmethane (5) was obtained as described above for dipyrrylmethane **4**. The dipyrrylmethane **35** (36 mg) was dissolved in 0.4 ml of 2 *N* potassium deuterioxide in 50% perdeuteriomethanol. The saponification was complete after 72 hr. The $C_{5'}$ H (6.0 ppm, 0.20) was not completely exchanged after that period, nmr (δ 0 for DSS) 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.75 (br, 2, pyrr–CH_2–pyrr), 3.9 (br, 2, CH_2NH_2). After the solution was adjusted to pH 7 with IRA 120-H^+ resin, it could be freeze-dried and kept without decomposition at −15° during 1 week. Ehrlich's reaction was positive in the cold.

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Registry No.—**4,** 39649-89-3; **5,** 51911-89-8; **6,** 51911-90-1; **7,** 6122-77-6; **8,** 51911-91-2; **9,** 51911-92-3; **10,** 51911-93-4; **11,** 51911-94-5; **12,** 51911-95-6; **13,** 51911-96-7; **14,** 51911-97-8; **15,** 51911-98-9; **17,** 526-51-2; **18,** 17266-35-2; **20,** 51911-99-0; **21,** 38252-54-9; **22,** 50622-64-5; **23,** 51912-00-6; **24,** 38252-61-8; **26,** 50622-78-1; **27,** 50622-66-7; **28,** 50622-68-9; **29,** 51912-01-7; **30,** 51912-02-8; **31,** 51912-03-9; **32,** 51912-04-0; **33,** 51912-05-1; **34,** 51912-06-2; **35,** 51990-01-3; benzyl hydrogen malonate, 616-75-1.

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Studies on β-Lactams. XXXVI. Monocyclic Cis β-Lactams *via* Penams and Cephams[1]

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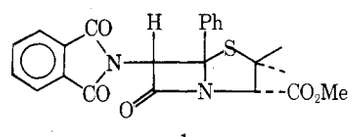
A stereospecific synthesis of monocyclic cis β-lactams has been devised which involves Raney nickel hydrogenolysis of readily accessible penams and cephams. The reaction of various acid chlorides and cyclic imines in presence of a base led to the stereospecific synthesis of a number of 6-substituted penams and 7-substituted cephams with *E* configuration with respect to the β-lactam substituents. These bicyclic β-lactams or their sulfoxides could be desulfurized under mild conditions and in good yields to 1,3,4-trisubstituted cis 2-azetidinones. No convincing rationale is obvious for the exclusive formation of bicyclic β-lactams of *E* configuration by this method.

The synthesis of bicyclic β-lactams became a desirable goal from the time it was first suspected that penicillin had a fused thiazolidine-β-lactam structure.[2] The discovery that cephalosporin C is a fused dihydrothiazine β-lactam made the preparation of bicyclic β-lactams even more attractive. Sheehan and coworkers[3] were the first to synthesize penams (for example **1**) by the action of certain acid chlorides on thiazolines in presence of triethylamine.

We introduced the use of α-azidoacyl chlorides for the synthesis of α-azido-β-lactams[4] and several 6-azidopenams[5,7] and 7-azidocephams[6] (for example **2** and **3**) were synthesized in our laboratory in the course of the total synthesis of a 6-epipenicillin ester.[7] Various other penams and cephams have been prepared in different laboratories[8] and



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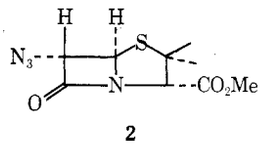

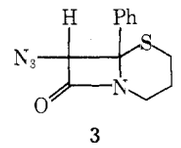

2 **3**

cephalosporins[9] and 4-mercapto-2-azetidinones[10,11] have been synthesized using the "acid chloride method."