cation of *p*-nitrobenzoic acid (346 mg of methyl *p*-nitrobenzoate isolated, 87% yield, based on limiting CH_2N_2).

Two Equivalents of *n*-Butyllithium.—To a sodium of *N*-nitroso-*N*-methylurea (220 mg, ~2.2 mmol) in 10 ml of 1,2-dimethoxyethane under N_2 was added *n*-butyllithium (2 ml, 2.2 *M* in pentane, 4.4 mmol). A precipitate (202 mg) formed and no diazomethane generation was observed. Quenching of the isolated precipitate with H_2O afforded rapid gas liberation and diazomethane, suggesting that the precipitate was a mixture of lithium cyanate and the methyl diazotate. This was supported by the infrared spectrum of the solid, which had bands at 2275 (cyanate) and 2180 cm^{-1} (diazotate).

Decomposition of *N*-Nitroso-*N*-methylurea with Triethylamine in 1,2-Dimethoxyethane.—To a solution of *N*-nitroso-*N*-methylurea (0.50 g, ~5 mmol) in 15 ml of 1,2-dimethoxyethane at 0° was added triethylamine (2.7 ml, 25 mmol). Gas evolution began immediately and the decomposition of the urea was followed spectrophotometrically. The reaction was complete in 45 min. The final solution contained cyanate ion, as judged by infrared spectroscopy. The diazomethane generated by this procedure could be trapped by the addition of *p*-nitrobenzoic acid to the initial reaction mixture.

Decomposition of *N*-Nitroso-*N*-methylurea with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—To a solution of potassium *tert*-butoxide (2.17 g, 19.4 mmol) in 50 ml of *tert*-butyl alcohol at 20° was added *N*-nitroso-*N*-methylurea (1.0 g, 9.7 mmol). The suspension was maintained under nitrogen and stirred for 20 min. Essentially no diazomethane was observed to have been formed. The suspension of potassium cyanate was filtered, yield 0.73 g (96%), identification by infrared spectroscopy. The filtrate was concentrated under diminished pressure to afford potassium methyl diazotate as a yellow solid, yield 0.76 g (~80%, identification by infrared spectroscopy), which rapidly decomposed (gas evolution) upon addition of water. Decomposition of the urea with 1 equiv of potassium *tert*-butoxide resulted in the rapid formation of diazomethane. The diazomethane could be utilized in the conversion of *p*-nitrobenzoic acid to its methyl ester. The yield of diazomethane (based on methyl *p*-nitrobenzoate formed in the presence of excess *p*-nitrobenzoic acid) was about 90%. Work-up of the initial reaction mixture indicated the presence of potassium cyanate (93%) and methyl diazotate (18%).

Rate of Decomposition of *N*-Nitroso-*N*-methylurea by Sodium Phenoxide and Sodium Thiophenoxide.—*N*-Nitroso-*N*-methylurea (67 mg, 0.65 mmol) was dissolved in 20 ml of 1,2-dimethoxyethane. The solution was cooled to 0° and sodium phenoxide (75 mg, 0.65 mmol) was added quickly. At 30-sec intervals, 20 μl of the solution was added to 2 ml of EtOH and acidified with 2 drops of 1 *N* hydrochloric acid solution, which quenched the reaction. The ultraviolet absorbance spectrum (A_{230}) was recorded for each aliquot and then 4 *N* sodium hydroxide solution was added to decompose the unreacted urea. The solution was reacidified and A_{230} was again recorded. The difference in each set of two spectra was employed as a measure of unreacted *N*-nitroso-*N*-methylurea. A control experiment demonstrated that all *N*-nitroso-*N*-methylurea absorbance was eliminated by the acid–base treatment and did not affect the other reactants.

Data for the phenoxide- and thiophenoxide-induced decompositions of *N*-nitroso-*N*-methylurea indicated half-lives of decomposition of ~75 and 210 sec, respectively.

Registry No.—*N*-Nitroso-*N*-methylurea, 684-93-5.

Acknowledgments.—We thank Professors C. G. Swain and F. D. Greene for helpful discussions during the course of this work.

Synthesis of 2-Aminomethylpyrroles and Related Lactams

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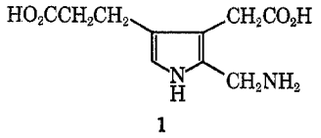
The potassium enolate of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate was C-alkylated and C-acylated with methyl iodide, ethyl iodide, *n*-propyl iodide, ethyl bromoacetate, ethyl chloroformate, and benzyl chloroformate and the corresponding ethyl 2-oxobutyrate, 2-oxocaproate, 2-oxoglutarate, and the oxalacetates were obtained. The same procedure afforded the 2-benzyloxy and 2-anisyloxy oxalacetates. Reductive cyclization of the α-keto monoesters afforded the corresponding ethyl 5-methoxy-6-azaindole-2-carboxylates and in several cases also the 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-ones. The 6-azaindoles were transformed with hydrobromic acid into the corresponding 6-azaindanones, which were reduced to the corresponding 2-carboxy-3-alkylpyrrole lactams. The latter were transformed into the corresponding 4-alkyl-3-carboxymethyl-2-aminomethylpyrroles. The catalytic hydrogenation of the oxalacetates, followed by cyclization of the resulting 5-aminopyridines, afforded 2,3-dicarbethoxy-6-azaindoles and 2,3-dicarbethoxy-6-azaindanone. The latter were transformed by catalytic hydrogenation into diethyl 5-oxo-3a,4,5,6-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2,3-dicarboxylate which could not be saponified to a 2-aminomethylpyrrole.

The synthesis of 2-aminomethyl-3-carboxymethylpyrroles was a task of particular interest in pyrrole chemistry ever since it was conclusively established[1] that the natural metabolite porphobilinogen was a 2-aminomethyl-3-carboxymethyl-4-carboxyethylpyrrole **1**. This unique compound has no other metabolic



1

analogs and, since it is the precursor of all the natural porphyrins, chlorins, and corrin derivatives,[2] it was tempting to develop a synthetic method which should afford not only porphobilinogen but also analogous 2-aminomethylpyrroles to study their chemical and biological behavior. 2-Aminomethylpyrroles proved also to be very suitable intermediates for dipyrrylmethane synthesis,[3] being in many senses more advantageous than the classical 2-bromomethyl or 2-acetoxymethylpyrrole derivatives.

In our previous work[4] we approached the problem of the synthesis of porphobilinogen **1** by considering it to be a derivative of a 5-oxo-4,5,6,7-tetrahydro-6-azaindole (pyrrole lactam) structure. The synthesis of the 6-azaindole ring was then achieved[4] by a sequence modeled on the Reissert-type synthesis of indoles, which was based on the synthesis of the ethyl *o*-nitro-4-pyr-

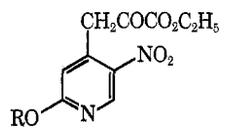
(1) G. H. Cookson and C. Rimington, *Biochem. J.*, **57**, 476 (1954).

(2) J. Lascelles, "Tetrapyrrole Biosynthesis and its Regulation," W. A. Benjamin, New York, N. Y., 1964, p 47.

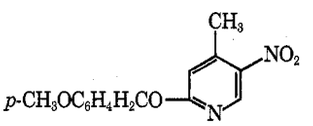
(3) B. Frydman, S. Reil, A. Valasinas, R. B. Frydman, and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 2738 (1971).

(4) B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965); B. Frydman, S. Reil, M. E. Despuy, and H. Rapoport, *ibid.*, **91**, 2338 (1969).

idinepyruvates **2** and **3**, and its catalytic hydrogenation and subsequent cyclization to give the corresponding ethyl 6-azaindole-2-carboxylates. The easily available potassium enolates of **2** and **3** offered the possibility of obtaining different 4-alkyl-2-aminomethyl-3-carboxymethylpyrroles by a C-alkylation of the pyruvate carbon atom followed by subsequent synthetic sequence analogous to that used in our previous porphobilinogen synthesis.[4] The C-alkylation on the same carbon atom could also open the possibility of obtaining 2-aminomethylpyrroles with β-unsaturated residues. An additional ethyl pyridinepyruvate was obtained by preparing 2-anisyloxy-5-nitro-4-methylpyridine **4** and condensing it with ethyl oxalate in the presence of potassium ethoxide. The resulting ethyl 2-anisyloxy-5-nitro-4-pyridinepyruvate **5** had the potential synthetic



2, R = CH_3
3, R = $CH_2C_6H_5$
5, R = $CH_2C_6H_4$-*p*-OCH_3



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advantage of the lability of the anisyloxy group to treatment with mild acids.

By treating the potassium enolate of **2** with alkyl iodides or ethyl bromoacetate the corresponding α-keto esters **6**, **7**, **8**, and **9** were obtained. The attempted alkylation of the potassium enolate with ethyl β-iodopropionate was unsuccessful and led to the recovery of the ethyl pyridinepyruvate **2** and to formation of ethyl acrylate by a β-elimination reaction. The C-acylation of **2** with ethyl chloroformate and benzyl chloroformate afforded the corresponding oxalacetates: diethyl 3-(2′-methoxy-5′-nitro-4′-pyridyl)oxalacetate (**10**) and the benzyl ethyl oxalacetate **11**.

In a similar manner, treatment with ethyl chloroformate of the potassium enolates of **3** and **5** allowed the synthesis of the oxalacetates **12** and **13** (Scheme I and Table I).

TABLE I

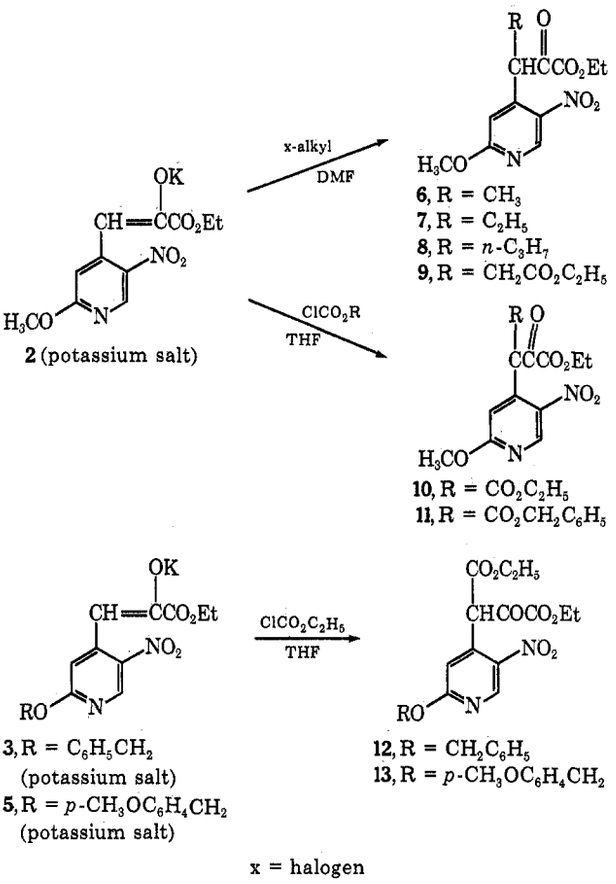
ETHYL 3-(5′-NITRO-4′-PYRIDYL)-2-KETO ESTERS[a]

Compd	Mp, °C	Yield, %
6	83–84	40
7	35–36	32[b]
8	48–50	14[b]
9	...[c]	24[b]
10	64–65	65
11	84–86	50[d]
12	83–84	60[d]
13	64–65	40[d]

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds: Ed. [b] Prepared with the same procedure used for the synthesis of **6**. [c] Bp 188–190° (0.005 mm). [d] Prepared with the same procedure used for the synthesis of **10**.

The catalytic hydrogenation of **6** over palladium afforded exclusively the ethyl 3-methyl-5-methoxy-6-azaindole-2-carboxylate **14**, formed by the spontaneous cyclization of the intermediate 5-aminopyridine. When the same reductive cyclization was applied to the α-ketovalerate **7** two compounds were obtained: the ethyl 3-ethyl-5-methoxy-6-azaindole-2-carboxylate

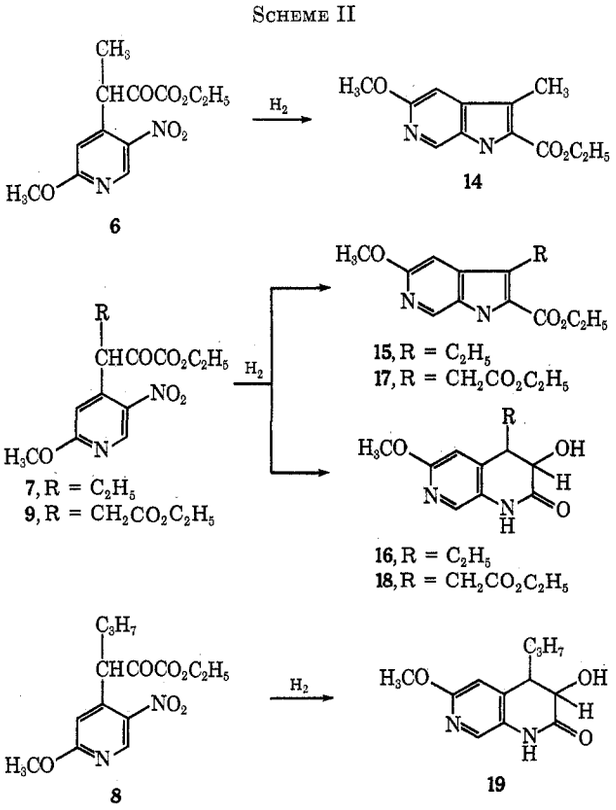
SCHEME I



2 (potassium salt)
6, R = CH_3
7, R = C_2H_5
8, R = *n*-C_3H_7
9, R = $CH_2CO_2C_2H_5$
10, R = $CO_2C_2H_5$
11, R = $CO_2CH_2C_6H_5$
3, R = $C_6H_5CH_2$ (potassium salt)
5, R = *p*-$CH_3OC_6H_4CH_2$ (potassium salt)
12, R = $CH_2C_6H_5$
13, R = *p*-$CH_3OC_6H_4CH_2$

15 (23%) and the 1,2,3,4-tetrahydro-3-oxy-4-ethyl-6-methoxy-1,7-naphthyridin-2-one **16** (47%) (Scheme II). Both substances could be easily separated due to

SCHEME II



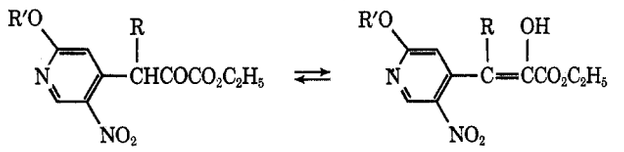
6
14
7, R = C_2H_5
9, R = $CH_2CO_2C_2H_5$
15, R = C_2H_5
17, R = $CH_2CO_2C_2H_5$
16, R = C_2H_5
18, R = $CH_2CO_2C_2H_5$
8
19

their different basicities, since the naphthyridinone **16** gave a water-soluble hydrochloride while the 6-azaindole **15** did not. The catalytic hydrogenation of the α-ketoglutarate **9** afforded the 3-ethoxycarbonylmethyl-6-azaindole **17** (73%), together with some 3-oxynaphthyridinone **18** (11%), and they were also separated by making use of their different basicities. The catalytic hydrogenation of the α-ketocaproate **8**, resulted in the exclusive formation of the 3-oxy-4-propyltetrahydronaphthyridinone **19**.

The formation of both types of ring systems, 6-azaindoles and 1,7-naphthyridinones, can be rationalized on the basis of the keto–enol equilibrium of the α-keto esters. As can be seen in Table II the 4′-

TABLE II

KETO–ENOL EQUILIBRIUM OF ETHYL 3-(5′-NITRO-4′-PYRIDYL)-2-KETO ESTERS[a]

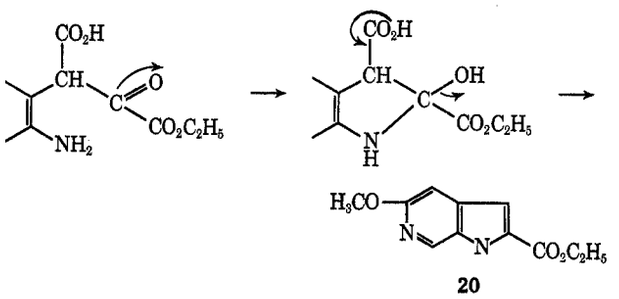


Compd	H_3	C=C(OH)	R
6	5.2, q, 1 (J = 7.0)		1.6, d, 3 (J = 7.0)
7	5.5, t, 0.5 (J = 8.0)	7.32, s, 0.5	1.4, t, 4.5; 4.3, m, 3
8		7.2, s, 1	0.9, t, 3 (J = 6.0) 1.67, q, 2 (J = 6.0) 3.9, t, 2 (J = 6.0)
9	5.5, t, 1 (J = 8.0)		3.05, d, 2 (J = 8.0)
10		7.25, s, 1[b]	
11		7.2, s, 1	
12		7.7, s, 1	
13		7.65, s, 1	

[a] Nmr spectra: (δ values, multiplicity, integral value (J in Hz). [b] Ir spectra 3500 (OH), 1790, 1750 (CO esters), 1670 cm^{-1} (CO keto).

pyridyl-2-keto esters exist in a keto–enol equilibrium. The shift of the hydroxylic proton in the latter (δ 7.2) suggest that it exists in an intramolecular hydrogen bond, probably bridged with the oxygen of the vicinal ester carbonyl group. When the simultaneous hydrogenation of the enol form and the nitro group took place, the formation of the six-membered ring was the only choice and a 3-oxynaphthyridin-2-one was obtained. In the case of **6**, where the steric effect of the methyl group and the ethoxycarbonyl group repressed entirely the enol formation, only a 6-azaindole was obtained, since the formation of a five-membered ring could be expected to prevail as long as the α-keto group is available. This was also the predominant compound during the reductive cyclization of **9**, while **8** afforded only a naphthyridinone and **7** a mixture of both types of compounds, as could be expected from the equilibrium between the keto and enol forms (Table II).

The catalytic hydrogenation of the oxalacetates **10**–**13** took a different course. The benzyl ethyl oxalacetate **11**, when reduced with hydrogen either over palladium or over platinum under mild conditions, was unexpectedly transformed into the ethyl 5-methoxy-6-azaindole-2-carboxylate **20**. The loss of the benzyloxycarbonyl group could originate in a previous hydrogenolysis of the benzyl group followed by a decarboxylation during the cyclization process.



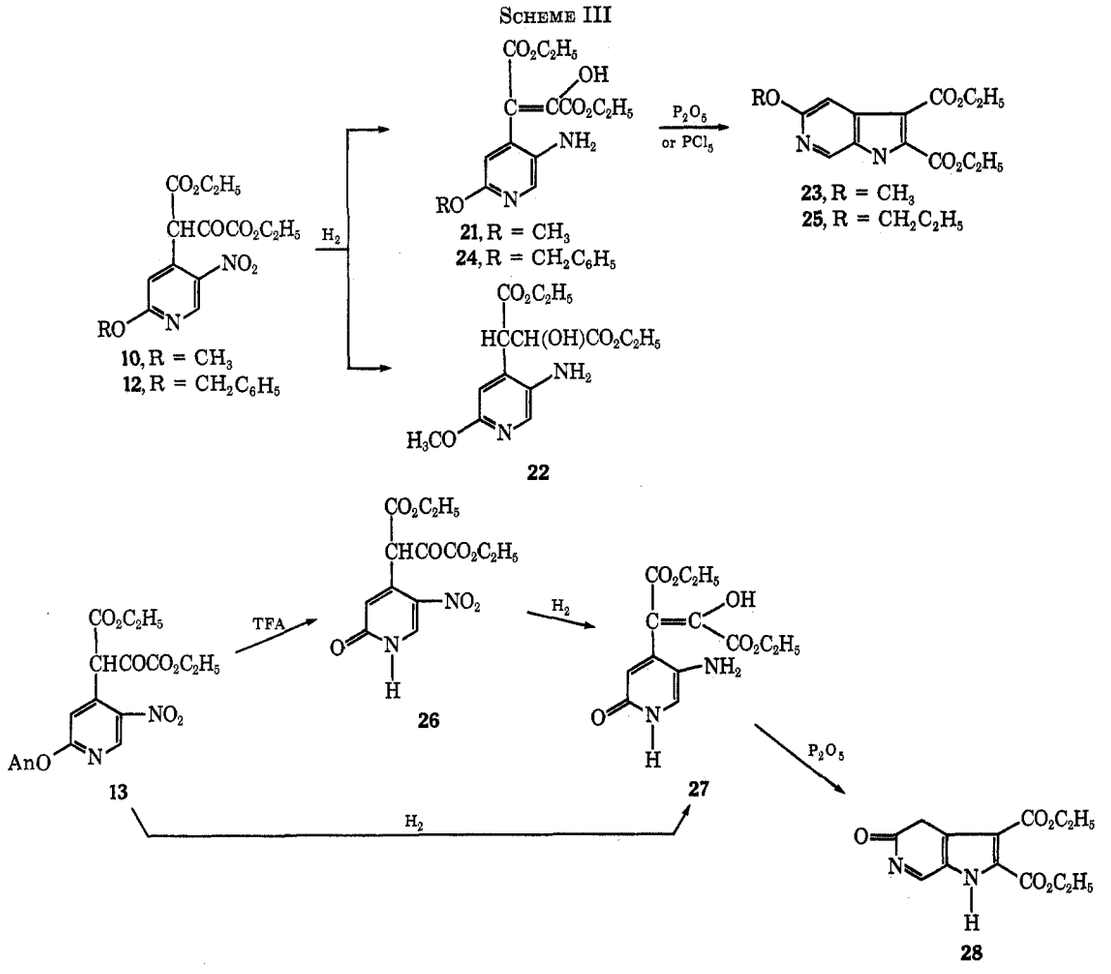
20

The catalytic hydrogenation of the diethyl oxalacetate **10**, however, afforded the 5-aminopyridine derivative **21** together with a small amount of its reduced derivative, the diethyl malate **22** (Scheme III). The 5-aminopyridine **21** existed entirely in its enolic form (see Experimental Section) and the nonformation of a 3-oxynaphthyridinone derivative must be attributed to the steric effect across the double bond, with the ethoxycarbonyl and aminopyridyl groups lying trans to each other. Its cyclization could not be achieved by thermal means (boiling butanol or decaline) or by treatment with p-toluenesulfonyl chloride in pyridine. An efficient cyclization method was achieved by treatment with phosphorus pentoxide in xylene, which resulted in the exclusive formation of the diethyl 6-azaindole-2,3-dicarboxylate **23**. In an analogous manner, the catalytic hydrogenation of the 2′-benzyloxy diethyl oxalacetate **12** afforded the 5-aminopyridine derivative **24**, which was cyclized by treatment with phosphorus pentachloride in dry chloroform to the 5-benzyloxy-6-azaindole derivative **25**.

The catalytic hydrogenation of the 2′-anisyloxy-4′-pyridyloxalacetate **13** took place with a simultaneous hydrogenolysis of the anisyloxy group which could also be cleaved with trifluoroacetic acid first, and the resulting 2′-hydroxy-5′-nitro-4′-pyridyl oxalacetate **26** could then be hydrogenated to the 5-aminopyridine derivative **27**. The ir and nmr data indicated that both **26** and **27** had the α-pyridone structure. The ester **27** could also be obtained directly from **12** by catalytic hydrogenation, as mentioned above, but the overall yields were lower than in the two-step procedure. The diethyl 5-aminopyridone oxalacetate **27**, was then cyclized by means of the phosphorus pentoxide–xylene procedure and the 6-azaindanone **28** was obtained. The structure of **28** was assigned on the basis of its spectral data. The cyclic amide carbonyl adsorbed at 1675 and 1640 cm^{-1}, the nmr spectra indicated the presence of a methylene group and an aromatic proton in the ring, and the fragmentation in the mass spectrum showed the loss of a ring carbonyl group. The 6-azaindoles **14**, **15**, and **17** were then transformed into the corresponding 2-aminomethylpyrroles. The synthesis of **17** by a multistep procedure and its transformation into 3,4-dicarboxymethyl-2-aminomethylpyrrole has already been described.[4] The present simplified synthesis of **17** makes the aforementioned pyrrole easily accessible. The two azaindoles **14** and **15** were treated with hydrobromic acid, the ether group was cleaved and the 6-azaindanones **29** and **30** were obtained (Scheme IV).

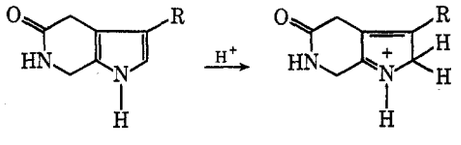
The ir and nmr spectra confirmed the assigned structures, isomeric with the formerly described 6-azainda-

SCHEME III



An = anisyl

none **28**. By catalytic hydrogenation of **29** and **30**, the 2-carboxypyrrole lactams **31** and **32** were obtained. They were decarboxylated by heating at 100° in water. The obtained lactams **33** and **34** were very stable to oxidation by air and to heat (they were easily sublimed), unlike the open-chain alkylpyrroles. In trifluoroacetic acid they existed entirely in the conjugated α-pyrrolenine form (see Experimental Section).



They were saponified at room temperature to the corresponding 2-aminomethylpyrroles **35** and **36** (Scheme IV). These pyrroles were very unstable and started to polymerize at 37° forming porphyrins, as was discussed in detail elsewhere.[5]

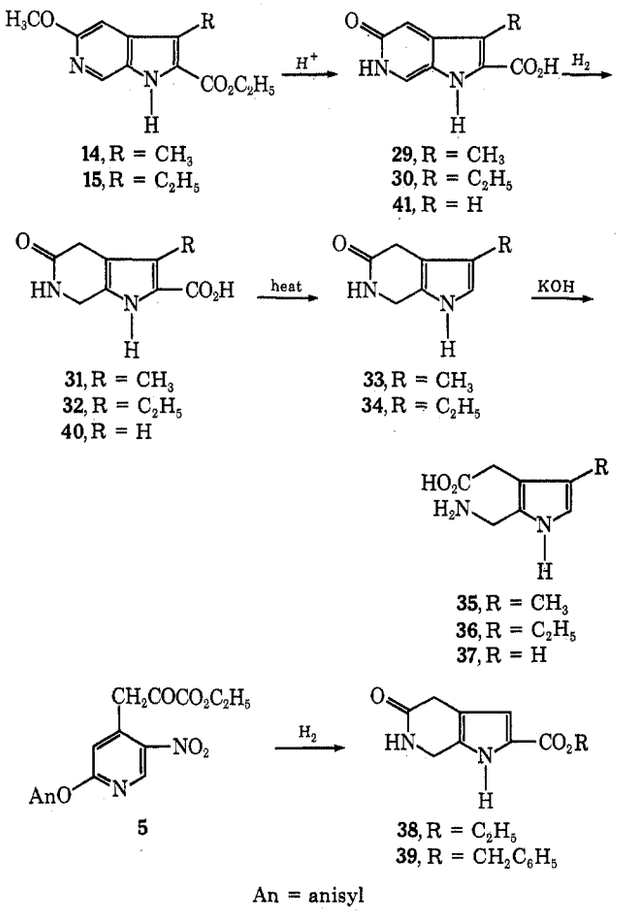
The available intermediates also allowed a simple synthesis of the interesting 2-aminomethyl-3-carboxymethylpyrrole **37**. The catalytic hydrogenation of the anisyloxy pyridinepyruvate **5** afforded directly the 2-ethoxycarbonylpyrrole lactam **38** in good yield. (Scheme IV). The intermediate 6-azaindanone derivative was not isolated and must be reduced "*in situ*" during the hydrogenation. The lactam **38** was transesterified to the benzyl ester **39** and the latter was transformed by hydrogenolysis into the 2-carboxypyrrole **40**. The transformation of **40** into **37** has already been described elsewhere.[4]

The sequence of reactions depicted in Scheme IV was now applied to the 2,3-dicarbethoxy-6-azaindoles in the hope of obtaining the lactam **42**. When the azaindole **23** was treated with hydrobromic acid, the carboxy group at C-3 was unexpectedly cleaved and the 2-carboxy-6-azaindanone **41** was obtained. Hydrogenolysis of the diethyl 5-benzyloxy-6-azaindole-2,3-carboxylate **25** afforded the 3a,4,5,6-tetrahydro-6-azaindole **43**, instead of the expected pyrrole lactam **42** (Scheme V).

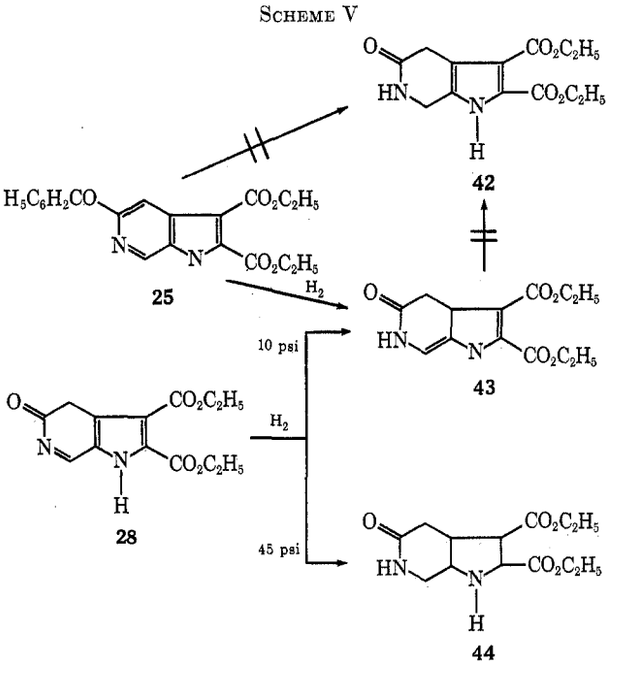
This was also an unexpected result since the ethyl 5-benzyloxy-6-azaindole-2-carboxylate was transformed directly by hydrogenolysis into the 2-ethoxycarbonylpyrrole lactam **38**.[4] Catalytic hydrogenation of **28** under the usual conditions (45 psi) afforded a fully reduced compound whose mass spectrum (M^+ 284) and nmr spectrum were consistent with structure **44**. Catalytic hydrogenation of **28** at low pressure stopped at the tetrahydro stage and the lactam **43** was obtained. Treatment of **43** with base or acids did not isomerize it to the desired pyrrole lactam **42**. Saponification attempts of **43** failed to give definite products, probably due to secondary transformations in the open-ring enamine structure.

(5) R. B. Frydman, S. Reil, and B. Frydman, *Biochemistry*, **10**, 1154 (1971).

SCHEME IV



SCHEME V



The synthesis of pyrrole lactam **42** was thus frustrated. The existence of the 4,5-dihydro structure in **28**, instead of the 5,6-dihydro structure present in **29**, **30**, and **41** must be due to the presence of an electronegative substituent at C-3. It lead to the formation of the pyrrole lactam **43**, which could not be transformed any more in a 2-aminomethylpyrrole. The usefulness of 6-azaindoles as starting materials for 2-aminomethylpyrrole synthesis seems thus limited to the preparation of pyrroles with β-alkyl residues.

Experimental Section[6]

2-Anisyloxy-4-methyl-5-nitropyridine (4).—2-Chloro-4-methyl-5-nitropyridine[4] (25 g, 0.14 mol) was added to a solution of 3.5 g (0.15 g-atom) of sodium in 925 ml of anisyl alcohol. The mixture was kept at 37° for 18 hr, and the reaction was completed by heating at 100° for 2 hr. The excess of anisyl alcohol was distilled off *in vacuo* [130° (0.25 mm)], and the crystalline residue washed with water (2 × 200 ml) and recrystallized from ethanol: 62 g (80%); mp 110–111°; uv_{max} 282 nm (ε 9800).

Anal. Calcd for $C_{14}H_{14}O_4N_2$: C, 61.3; H, 5.1; N, 10.2. Found: C, 61.1; H, 5.2; N, 10.1.

Ethyl 2-Anisyloxy-5-nitro-4-pyridinepyruvate (5).—To a solution of 300 ml of ether and 25 ml of absolute ethanol was added 4.3 g (0.11 g-atom) of potassium, and the mixture was stirred under anhydrous conditions until all the potassium dissolved. Diethyl oxalate (16 ml, 0.12 mol) was then added, followed after 5 min by 30.2 g (0.11 mol) of 2-anisyloxy-5-nitro-4-methylpyridine **4**, and the red mixture was stirred for 36 hr. The precipitated potassium enolate was removed by filtration, washed with ether, dried, suspended in 500 ml of water, and decomposed by adjusting the solution to pH 5 with acetic acid. After cooling at 5° during 30 min, the formed precipitate was filtered, dried, and recrystallized from ethanol when 37.9 g (92%) of pyruvate were obtained: mp 115–116°; uv_{max} 224 nm (ε 24,300), 282 (9700); nmr ($CDCl_3$) δ 1.5 (t, CH_3), 3.8 (s, OCH_3), 4.4 (q, CH_2), 4.5 (s, CH_2CO), 5.4 (s, 2, $C_6H_5CH_2O$), 6.9 (d, 2, $H_{2'}$ and $H_{6'}$), 7.4 (d, 2, $H_{3'}$ and $H_{5'}$), 7.2 [s, 1, CH=C(OH)], 7.6 (s, 1, H_3), 9.1 (s, 1, H_6).

Anal. Calcd for $C_{18}H_{18}O_7N_2$: C, 57.7; H, 4.8; N, 7.5. Found: C, 57.8; H, 4.8; N, 7.4.

Ethyl 2-Oxo-3-(2′-methoxy-5′-nitro-4′-pyridyl)butyrate (6).—The potassium enolate of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate **2** (15.3 g, 0.05 mol) was dissolved in 1000 ml of *N,N′*-dimethylformamide, 7 ml of methyl iodide was added, and the mixture was heated at 100° for 90 min with occasional stirring. Two additional portions (7 ml each) of methyl iodide were added every 30 min during the heating period. The solvent was then evaporated to dryness *in vacuo*, the residue dissolved in water (250 ml), and the aqueous layer extracted with chloroform (3 × 150 ml). The pooled extracts were washed with a small volume of water, dried (Na_2SO_4), and evaporated to dryness. The oily residue was dissolved in a small volume of a chloroform–benzene mixture (1:1), adsorbed on a silica gel column (5 cm × 30 cm), and the product was eluted by using the same solvent. The obtained ester was distilled at 129° (0.002 mm): 5.7 g, (40%); mp 83–84°; uv_{max} 282 nm (ε 12,500); nmr ($CDCl_3$) δ 1.35 (t, CH_3), 1.6 (d, 3, J = 7 Hz, $CHCH_3$), 4.05 (s, OCH_3), 4.37 (q, CH_2), 5.2 (q, 1, J = 7 Hz, $CHCH_3$), 6.73 (s, 1, H_3), 9.00 (s, 1, H_6); R_f 0.35 (tlc, chloroform–benzene, 1:1).

Anal. Calcd for $C_{12}H_{14}O_6N_2$: C, 51.5; H, 4.9; N, 9.9. Found: C, 51.2; H, 5.0; N, 9.8.

Diethyl 3-(2′-Methoxy-5′-nitro-4′-pyridyl)oxalactate (10).—The potassium salt of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate **2** (15 g) was suspended 2000 ml of dry tetrahydrofuran, 20 ml of ethyl chloroformate was added, and the mixture was heated under reflux for 30 min. The heating was then discontinued, a second portion of 30 ml of ethyl chloroformate was added, and the heating was resumed for an additional hour. The solvent was evaporated to dryness *in vacuo*, the residue dissolved in 250 ml of chloroform, the chloroform washed with water (2 × 50 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 ml of a mixture of benzene and chloroform (1:1 v/v), adsorbed on a silica gel column (30 × 5 cm) prewashed with the same solvent, and the desired product eluted with 2000

(6) All melting points were taken on the Kofler block; uv absorptions were measured in ethanol; ir spectra were obtained on potassium bromide wafers, and nmr spectra were taken as noted. Microanalyses were performed by the Alfred Bernhardt Mikroanalytisches Laboratorium (Mulheim). Mass spectra were performed by the Morgan and Schaffer Corp. (Montreal). When tlc on cellulose was run, the upper layer of a butanol–acetic acid–water mixture (4:1:5) was used as solvent. The α-keto esters were spotted by spraying the tlc plates with piperidine, which gave red to orange spots with the former. The silica gel used for column chromatography was Kieselgel G (Fluka AG).

ml of the same solvent. Evaporation to dryness of the eluate, followed by crystallization of the residue from benzene–petroleum ether, afforded the diethyl oxalacetate **10**: 11 g (65%); mp 64–64°; R_f 0.35 (tlc, benzene–chloroform, 1:1 v/v); uv_{max} 245 nm (ϵ 33,600), 304 (sh); nmr ($CDCl_3$) δ 1.34. 1.36 (t, 6, CH_3), 4.1 (s, 3, OCH_3), 4.35 (m, 4, CH_2), 6.92 (s, 1, H_3), 7.25 (s, 1, COC=COH), 9.0 (s, 1, H_6).

Anal. Calcd for $C_{14}H_{16}O_5N_2$: C, 49.4; H, 4.7; N, 8.2. Found: C, 49.3; H, 4.8; N, 8.4.

Ethyl 3-Methyl-5-methoxy-6-azaindole-2-carboxylate (14).—The ethyl 2-oxobutyrate **6** (7.2 g of chromatographically pure but nondistilled product were used) was dissolved in 100 ml of ethanol and reduced at 25 psi with hydrogen over 2 g of 10% palladium on charcoal during 45 min. The catalyst was removed and washed with ethanol, the combined filtrates and washings were concentrated *in vacuo* to 5 ml, and the product was precipitated by addition of water. The product was filtered and recrystallized from ethanol–water: 3.5 g (59%); mp 135–136° [sublimed at 130° (0.010)]; uv_{max} 285 nm (ϵ 10,000), 293 (11,600), 346 (6100); nmr (TFA) δ 1.6 (t, 3, CH_3), 2.78 (s, 3, CH_3), 4.3 (s, 3, OCH_3), 4.78 (q, 2, CH_2), 7.6 (s, 1, H_4), 8.6 (b, 1, H_7).

Anal. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.5; H, 6.0; N, 11.9. Found: C, 61.3; H, 6.0; N, 11.9.

Ethyl 3-Ethyl-5-methoxy-6-azaindole-2-carboxylate (15) and 1,2,3,4-Tetrahydro-3-oxy-4-ethyl-6-methoxy-1,7-naphthyridin-2-one (16).—Ethyl 2-oxo-3-(2′-methoxy-5′-nitro-4′-pyridyl)valerate **7** (7.4 g) was reduced with hydrogen with the same procedure used for the ethyl 2-oxobutyrate **16**. The crude product obtained on evaporation of the solvent (4.4 g) was dissolved in 150 ml of water; the solution was adjusted to pH 2 with concentrated hydrochloric acid and kept at 5° for 15 hr. The precipitate was filtered, dried, and crystallized from ethanol–water affording 1.4 g (23%) of 6-azaindole **15**: mp 110–112° [sublimed at 100° (0.1 mm)]; uv_{max} 285 nm (11,300), 294 (13,000), 358 (3500); nmr ($CDCl_3$) δ 1.3 (t, 3, $CO_2CH_2CH_3$), 1.4 (t, J = 7 Hz, 3, CH_2CH_3), 3.1 (q, J = 7 Hz, 2, CH_2CH_3), 4.0 (s, 3, OCH_3), 4.5 (q, 2, $CO_2CH_2CH_3$), 6.97 (s, 1, H_4), 8.5 (s, 1, H_7).

Anal. Calcd for $C_{13}H_{16}O_3N_2$: C, 62.9; H, 6.4; N, 11.3. Found: C, 62.9; H, 6.4; N, 11.2.

The acidic mother liquors were adjusted to pH 10 with solid sodium carbonate and extracted with chloroform (4 × 30 ml). The chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*, the residue was crystallized from ethanol, and 2.6 g (47%) of the naphthyridone was obtained: mp 173° (sublimed); uv_{max} 246 nm (17,800), 298 (6200); nmr ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3, CH_3), 3.05 (s, 1, OH), 3.17 (b, 1, C-4 H), 3.65–4.15 (m, 3, CH_2CH_3 and CHOH), 3.9 (s, 3, OCH_3), 6.6 (s, 1, H_5), 7.7 (b, 1, H_8).

Anal. Calcd for $C_{11}H_{14}O_3N_2$: C, 59.4; H, 6.3; N, 12.6. Found: C, 59.3; H, 6.5; N, 12.7.

1,2,3,4-Tetrahydro-3-oxy-4-*n*-propyl-6-methoxy-1,7-naphthyridin-2-one (19).—The ethyl 2-oxocaproate **8** (1.5 g) was reduced with hydrogen over palladium as described above, and the obtained product was crystallized from ethanol affording 400 mg (34%) of the naphthyridinone **19**: mp 136°; nmr (TFA) δ 1.0 (t, 3, CH_3), 1.8 (q, J = 8 Hz, 2, $CH_2CH_2CH_3$), 3.62 (s, 1, COH), 3.7 (b, 1, C-4 H), 3.8 (m, 2, $RCH_2CH_2CH_3$), 4.15 (s, 3, OCH_3), 4.27 (m, 1, C-3 H).

Anal. Calcd for $C_{12}H_{16}O_3N_2$: C, 61.0; H, 6.8; N, 11.9. Found: C, 61.1; H, 6.7; N, 11.8.

Ethyl 5-Methoxy-3-ethoxycarbonylmethyl-6-azaindole-2-carboxylate (17) and 1,2,3,4-Tetrahydro-3-oxy-4-ethoxycarbonylmethyl-6-methoxy-1,7-naphthyridin-2-one (18).—The diethyl 2-oxoglutarate **9** (7 g of ester purified by chromatography) was reduced with hydrogen over palladium following the usual procedure. The product was dissolved at 50° in 100 ml of water adjusted to pH 3.5 with hydrochloric acid, the solution was kept for 12 hr at 5° and filtered, and the filtrates were kept for further work-up. The obtained product was recrystallized from ethanol–water affording 2.2 g (73%) of the 6-azaindole **17**: mp 125–126°; uv_{max} 283 nm (ϵ 13,000), 292 (16,000), 348 (4100); nmr (TFA) δ 1.4 (t, 3, $CH_2CO_2CH_3$), 1.6 (t, 3, $CO_2CH_2CH_3$), 4.3 (s, 3, OCH_3), 4.4 (s, 2, CH_2), 4.5 (q, 2, $CH_2CO_2CH_2CH_3$), 4.8 (q, 2, $CO_2CH_2CH_3$), 7.7 (s, 1, H_4), 8.95 (s, 1, H_8).

Anal. Calcd for $C_{15}H_{18}O_5N_2$: C, 58.8; H, 5.9; N, 9.1. Found: C, 58.7; H, 6.0; N, 9.0.

The substance was identical (mp, ir, tlc) with a sample prepared by the action of diazoethane on the 2-carboxy-5-methoxy-6-azaindole-3-acetic acid.[4]

The aqueous acidic filtrates obtained after filtering the 6-azaindole were adjusted to pH 10 with sodium carbonate and extracted with chloroform (4 × 25 ml). The chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol affording 0.5 g (11%) of 1,7-naphthyridinone: mp 136–138°; uv_{max} 248 nm (ϵ 15,000); nmr (TFA) δ 1.4 (t, 3, CH_2CH_3), 3.7 (s, 1, COH), 3.8 (b, 1, C-4 H), 4.35 (s, 3, OCH_3), 4.27 (b, 1, C-3 H), 4.6 (b, 2, CH_2CO_2), 7.6 (s, 1, H_5), 8.2 (s, 1, H_8).

Anal. Calcd for $C_{13}H_{16}O_5N_2$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.6; H, 5.8; N, 10.1.

Diethyl 3-(2′-Methoxy-5′-amino-4′-pyridyl)oxalacetate (21) and Diethyl 3-(2′-Methoxy-5′-amino-4′-pyridyl)malate (22).—Diethyl oxalacetate **10** (2 g) dissolved in 100 ml of ethanol was reduced with hydrogen over 0.5 g of 10% palladium on charcoal at 25 psi during 45 min. The catalyst was removed and the solvent was evaporated to dryness; the residue was dissolved in a small volume of a benzene–methanol (9:1 v/v) solution and adsorbed on a silica gel column (30 cm × 3 cm) prewashed with the same solvent. Elution was carried out with the same solvent. The first 100 ml of eluate were collected and discarded. Fifty fractions of 2 ml each were then collected. Fractions 15–30 were pooled and evaporated to dryness *in vacuo* affording 820 mg (45%) of the diethyl oxalacetate **21**: mp 93–95° (from benzene–cyclohexane); R_f 0.60 (tlc, benzene–methanol, 9:1 v/v); uv_{max} 236 nm (ϵ 17,000), 299 (4300); ir 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.25, 1.35 (t, 6, CH_3); 3.35 (b, 2, NH_2), 3.9 (s, 3, OCH_3), 4.3 (9, 4, CH_2CH_3), 4.8 (b, 1, C=COH), 6.6 (s, 1, H_3), 8.3 (b, 1, H_6); mass spectrum m/e (rel intensity) 310 (M^+, 35) 237 (M − $CO_2C_2H_5$, 90), 209 (M − $COCO_2H_5$, 30), 191 (237 − C_2H_5OH, 80), 163 (209 − HOC_2H_5, base peak), 135 (163 − CO, 22).

Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.8; N, 9.0. Found: C, 54.4; H, 5.8; N, 9.2.

Fractions 41–47 were pooled and evaporated to dryness *in vacuo* affording 51 mg (6%) of the diethyl malate **22**: mp 79–81° (benzene–petroleum ether); R_f 0.48 (tlc, benzene–methanol, 9:1 v/v); uv_{max} 232 nm (ϵ 27,600), 285 (4000); ir 3350 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.25, 1.28 (t, 6, CH_3), 3.0 (m, NH_2), 3.9 (s, 3, OCH_3); 4.0–4.5 (m, 6, CH_2CH_3, CHOH), 6.5 (s, 1, H_3), 7.5 (b, 1, $PyCHCO_2$), 8.3 (s, 1, H_6); mass spectrum m/e (rel intensity) 312 (M^+, 12), 266 (M − HOC_2H_5, base peak), 193 (266 − $CO_2C_2H_5$, 50), 165 (266 − $CO_2C_2H_5CO$, 90).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.8; H, 6.4; N, 8.9. Found: C, 53.7; H, 6.4; N, 9.1.

When the benzyl ethyl oxalacetate **11** was reduced using the same procedure it afforded ethyl 5-methoxy-6-azaindole-2-carboxylate **20**: 440 mg (80%); mp 103–106°; identical with a sample prepared as described[4] (by tlc, ir, and mmp).

Diethyl 5-Methoxy-6-azaindole-2,3-dicarboxylate (23).—The diethyl oxalacetate **21** (300 mg) was dissolved in 200 ml of dry xylene, 400 mg of phosphorus pentoxide were added, and the mixture was heated with continuous stirring at 130° for 3 hr. The solvent was then evaporated to dryness at reduced pressure, the residue was dissolved in 30 ml of water adjusted to pH 10 with sodium carbonate, and the solution was extracted with chloroform (3 × 10 ml). The chloroform extracts were pooled, dried (Na_2SO_4), and evaporated to dryness. The residue was filtered through a silica gel column (20 cm × 2 cm) using a 3% methanol in benzene solution as eluent. The eluates were evaporated to dryness affording 122 mg (42%): mp 55–57° (ethanol–water); R_f 0.80 (tlc, benzene–3% methanol); uv_{max} 242 nm (ϵ 12,800), 263 (11,100), 316 (5600); nmr ($CDCl_3$) δ 1.3 (m, 6, CH_3); 3.9 (s, 3, OCH_3), 4.3 (m, 4, CH_2), 6.8 (b, 1, H_4), 8.9 (b, 1, H_7); mass spectrum m/e (rel intensity) 292 (M^+, 95), 247 (M − OC_2H_5, 30), 219 (M − $CO_2C_2H_5$, 90), 174 (219 − OC_2H_5, base peak), 146 (174 − CO, 90).

Anal. Calcd for $C_{14}H_{16}O_5N_2$: C, 57.5; H, 5.4; N, 9.6. Found: C, 57.3; H, 5.5; N, 9.7.

Diethyl 3-(2′-Benzyloxy-5′-amino-4′-pyridyl)oxalacetate (24).—Diethyl oxalacetate **12** (700 mg) was dissolved in 100 ml of ethanol and reduced with hydrogen over 70 mg of platinum oxide at 15 psi during 45 min. The catalyst was filtered and the solvent was evaporated to dryness; the residue was dissolved in a small volume of benzene containing 7% methanol and adsorbed on a silica gel column (30 cm × 3 cm) prewashed with the same solvent. The substance was eluted with the same solvent affording after evaporation 344 mg (53%): mp 82–84° (benzene–cyclohexane); uv_{max} 240 nm (ϵ 21,600), 296 (5100); nmr ($CDCl_3$) δ 1.3 (m, 6, CH_3), 3.3 (m, 2, NH_2), 4.3 (m, 4, CH_2CH_3), 4.8 (b, 1, OH), 5.3 (s, 2, $CH_2C_6H_5$), 5.65 (s, 1, H_3), 7.4 (b, 5, C_6H_5), 8.4 (b, 1, H_6).

Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.2; H, 5.7; N, 7.2. Found: C, 62.3; H, 5.9; N, 7.4.

Diethyl 5-Benzyloxy-6-azaindole-2,3-dicarboxylate (25).—The diethyl oxalacetate **24** (300 mg) was dissolved in 50 ml of dry chloroform, and 300 mg of finely powdered phosphorus chloride was added in small portions with continuous stirring at 5°. The solution was kept at room temperature for 24 hr and then washed with a 1 *N* sodium hydroxide solution. The excess of alkali was washed out with water and the chloroform layer dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from ethanol–water: 200 mg (70%); mp 54–55°; uv_{max} 235 nm (ϵ 14,700), 263 (10,800), 318 (5500).

Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.2; H, 5.4; N, 7.6. Found: C, 65.0; H, 5.6; N, 7.4.

Diethyl 3-(2′-Hydroxy-5′-nitro-4′-pyridyl)oxalacetate (26).—The anisyl derivative **13** (1 g) was dissolved in 10 ml of trifluoroacetic acid, and the mixture was kept for 24 hr at room temperature. The solution was then poured in a large excess of ice–water and the formed precipitate filtered and crystallized from ethanol: 584 mg (80%); R_f 0.70 (tlc, benzene–10% methanol); uv_{max} 237 nm (ϵ 16,300); ir 1780, 1750 (CO esters), 1675, 1640 cm^{-1} (bands I and II, CO amide); nmr (TFA) δ 1.4, 1.5 (t, 6, CH_3), 4.5 (m, 4, CH_2), 7.1 (s, 1, H_3), 7.8 (s, 1, COC=COH), 8.9 (s, 1, H_6).

Anal. Calcd for $C_{13}H_{14}O_8N_2$: C, 47.8; H, 4.3; N, 8.6. Found: C, 47.8; H, 4.3; N, 8.7.

Diethyl 3-(2′-Hydroxy-5′-amino-4′-pyridyl)oxalacetate (27).—Diethyl oxalacetate **26** (1 g) was dissolved in 100 ml of ethanol and reduced with hydrogen over 500 mg of 10% palladium on charcoal at 15 psi during 45 min. The catalyst was filtered, the solvent evaporated to dryness *in vacuo*, and the residue filtered through a column of silica gel (20 cm × 2 cm) using a 10% methanol in benzene solution as eluent: 568 mg (58%); mp 217–218° (methanol–ether); R_f 0.43 (tlc, benzene–10% methanol); uv_{max} 245 nm (ϵ 14,800), 330 (4200); ir 3200 (broad, OH), 1630, 1600 cm^{-1} (CO amide, bands I and II); nmr (TFA) 1.2 (m, 6, CH_3), 3.8 (m, 2, NH_2), 4.6 (m, 4, CH_2), 7.4 (s, 1, H_3), 8.3 (b, 1, H_6); mass spectrum *m/e* (rel intensity) 296 (M^+, 66), 223 (M − $CO_2C_2H_5$, 90), 195 (223 − CO, 80), 177 (M − CO_2-$C_2H_5HOC_2H_5$, 95), 150 (M − $2CO_2C_2H_5$, base peak).

Anal. Calcd for $C_{13}H_{16}O_6N_2$: C, 52.7; H, 5.4; N, 9.5. Found: C, 52.6; H, 5.4; N, 10.0.

The amino derivative **27** was also obtained by direct hydrogenation at 45 psi (2 hr) of the anisyl derivative **13** in 21% yield.

Diethyl 5-Oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2,3-dicarboxylate (28).—Diethyl oxalacetate **27** (500 mg) was suspended in 50 ml of dry xylene, 500 mg of finely divided phosphorus pentoxide were added, and the mixture was heated under reflux with continuous stirring during 2.5 hr. The mixture was cooled, the solvent decanted, and the residue dissolved in water adjusted to pH 7 with sodium hydroxide. The aqueous solution was evaporated to dryness, and the residue was extracted with boiling absolute ethanol (3 × 100 ml). The ethanolic solution was evaporated to dryness *in vacuo*, and the residue was dissolved in 10 ml of chloroform containing 10% methanol and adsorbed on a silica gel column (20 cm × 2 cm) previously washed with the same solvent. The 6-azaindanone **28** developed on the column as a fluorescent yellow band and was eluted using the same solvent affording 282 mg (60%): mp 144–146° (benzene–cyclohexane); R_f 0.54 (tlc, chloroform–10% methanol); uv_{max} 227 nm (ϵ 25,300), 257 (15,300), 366 (6900); ir, 1780, 1740 (CO ester), 1675, 1640 cm^{-1} (CO lactam, bands I and II); nmr (Cl_3CD) δ 1.35, 1.39 (t, 6 CH_3), 4.35, 4.40 (q, 4, CH_2), 6.7 (s, 2, CH_2CO), 8.3 (s, 1, H_7); mass spectrum *m/e* (rel intensity) 278 (M^+, 25), 233 (M − OC_2H_5, 15), 206 (M − $CO_2C_2H_4$, 80), 160 (206 − HOC_2H_5, base peak), 132 (160 − CO, 85), 104 (132 − CO, 26).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.1; H, 5.0; N, 10.1. Found: C, 56.2; H, 5.0; N, 10.1.

5-Oxo-3-methyl-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (29).—6-Azaindole **14** (3 g) was dissolved in 90 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 4 hr. The dark solution was evaporated to dryness; the residue was dissolved in a small volume of a concentrated ammonium hydroxide solution, adsorbed on a neutral alumina column (25 × 2 cm) prewashed with a normal ammonium hydroxide solution, and eluted with the same solvent collecting fractions of 10 ml. The eluates were acidified to pH 4; the precipitated acid of the pure fractions was collected by filtration, dried, and washed with boiling methanol (5 × 10 ml): 1.2 g (50%); mp dec above 300°; uv_{max} 242 nm (ϵ 22,000), 298 (8600), 302 (7500).

Anal. Calcd for $C_9H_8N_2O_3$: C, 56.2; H, 4.2; N, 14.6. Found: C, 56.1; H, 4.3; N, 14.7.

5-Oxo-3-ethyl-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (30) was obtained following the same procedure used for the 3-methyl derivative **29**. From 2.2 g of the 6-azaindole **15**, 990 mg (55%) of **30** were obtained: mp dec above 300°; uv_{max} 235 nm (ϵ 22,000), 298 (9500), 302 (8700).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.2; H, 4.8; N, 13.6. Found: C, 58.3; H, 4.5; N, 13.5.

5-Oxo-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (31).—6-Azaindanone **29** (1 g) was dissolved in 30 ml of a sodium carbonate solution at pH 8–9 and reduced with hydrogen at 50 psi over 0.5 g of 10% palladium on charcoal for 2 hr. The catalyst was removed and the solution was adjusted to pH 4 with acetic acid, cooled at 5°, and filtered: 720 mg (72%); mp dec above 315°; uv_{max} 272 nm (ϵ 11,700).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.1; N, 14.4. Found: C, 55.6; H, 5.2; N, 14.5.

5-Oxo-3-ethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (32) was prepared following the procedure described for the 3-methyl analog **31**. From 1 g of the 6-azaindanone **30** was obtained 520 mg (52%) of **32**: mp 270° dec; uv_{max} 274 nm (ϵ 16,000).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.6; H, 5.7; N, 13.4.

5-Oxo-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine (33).—The acid **31** (1.8 g) was suspended in 250 ml of water and heated under reflux for 1 hr. The solution was evaporated to dryness and the residue sublimed at 200° (0.010 mm) to afford 700 mg (50%) of lactam **33**: mp dec above 260°; R_f 0.65 (tlc, ethyl acetate–methanol, 2:1 v/v); ir 1655, 1625 cm^{-1} (CO lactam); nmr (TFA) δ 2.5 (s, 3, CH_3), 3.9 (b, 2, CH_2CO), 5.1 (b, 4, CH_2NH, $=N^+HCH_2$); Ehrlich's reaction was positive in the cold.

Anal. Calcd for $C_8H_{10}N_2O$: C, 64.0; H, 6.7; N, 18.7. Found: C, 64.1; H, 6.7; N, 18.6.

5-Oxo-3-ethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine (34) was prepared following the same procedure used for the synthesis of the 3-methyl homolog **33**, except for the heating period which was extended to 90 min. The lactam **34** was obtained in 70% yield: mp dec above 250° [sublimed at 180° (0.010 mm)]; nmr (TFA) δ 0.8 (t, J = 7 Hz, 3, CH_3), 2.3 (q, J = 7 Hz, 2, CH_2CH_3), 3.7 (b, 2, CH_2CO), 4.6 (b, 4, CH_2NH, $=NH^+CH_2$); Ehrlich's reaction positive in the cold.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.9; H, 7.3; N, 17.1. Found: C, 65.9; H, 7.3; N, 17.0.

2-Aminomethyl-4-methyl-3-pyrroleacetic Acid (35).—The sublimed lactam **33** (600 mg) was suspended in 8 ml of 4 *N* sodium hydroxide, 8 ml of ethanol was added, and the mixture was heated under reflux for 1 hr. The solution was adjusted to pH 5 with acetic acid, and a 15% aqueous mercuric acetate solution was added until no more precipitate formed. The solid was centrifuged, the precipitate suspended in water, and hydrogen sulfide passed through the suspension until all the mercuric salt was decomposed. The mercuric sulfide was centrifuged and washed with water, and the pooled supernatant and wash were evaporated to dryness at 30° *in vacuo*. The crystalline residue was recrystallized by dissolving it in water and adding methanol: 230 mg (30%); mp 150° dec; R_f 0.82 (tlc, on cellulose); nmr (D_2O) δ 2.0 (s, 3, CH_3), 3.25 (b, 2, CH_2CO_2); 3.6 (b, 2, CH_2NH_2), 6.3 (s, 1, H_5).

Anal. Calcd for $C_8H_{12}O_2N_2 \cdot H_2O$: C, 51.6; H, 7.5; N, 15.0. Found: C, 51.6; H, 7.4; N, 15.1.

2-Aminomethyl-4-ethyl-3-pyrroleacetic acid (36) was obtained in 52% yield following the same procedure described for the 4-methyl homolog **35**. The pyrrole was recrystallized by dissolving it in water and adding acetone: mp 142–144° dec; R_f 0.78 (tlc, on cellulose); nmr (D_2O) 1.1 (t, J = 7 Hz, 3, CH_3), 2.4 (q, J = 7 Hz, 2, CH_2CH_3), 3.3 (b, 2, CH_2CO), 3.6 (b, 2, CH_2-NH_2), 6.5 (s, 1, H_5).

Anal. Calcd for $C_9H_{14}O_2N_2 \cdot H_2O$: C, 54.0; H, 8.0; N, 14.0. Found: C, 54.3; H, 8.2; N, 14.0.

Ethyl 5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (38).—Ethyl pyridinepyruvate **5** (2 g) was dissolved in 100 ml of ethanol, and the solution was shaken with hydrogen at 50 psi for 90 min over 600 mg of 10% palladium on charcoal. The catalyst was filtered, the solution evaporated to dryness, and the residue crystallized from ethanol: 770 mg (70%); mp 272–

274° (lit.[4] mp 272–274°); identical by ir, nmr, and tlc with a sample prepared by reduction of ethyl 5-benzyloxy-6-azaindole-2-carboxylate.[4]

Benzyl 5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (39).—The 5-carbethoxylactam **38** (2 g) was dissolved in 20 ml of benzyl alcohol and 50 mg of sodium was added. The mixture was heated at 100° for 2 hr; 5 ml of the solvent was then distilled *in vacuo* at the same temperature. An equal volume of benzyl alcohol was added to the mixture and the heating was continued for an additional 4 hr. The benzyl alcohol was then evaporated to dryness *in vacuo* and the residue crystallized from a large volume of ethanol: 2.2 g (80%); mp 286–287°; ir 1690 (CO ester), 1667 (CO lactam), 695 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{15}H_{14}O_3N_2$: C, 66.7; H, 5.2; N, 10.4. Found: C, 66.6; H, 5.2; N, 10.3.

5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (40).—The benzyl ester lactam **39** (1 g) was dissolved in 50 ml of glacial acetic acid and hydrogenated at 50 psi for 2 hr over 300 mg of 10% palladium on charcoal. The catalyst was filtered, the solution evaporated to dryness *in vacuo* at 50°, and the residue crystallized by dissolving in a 1 *N* sodium hydroxide solution and precipitating with concentrated acetic acid: 530 mg (80%); mp dec above 300°; R_f 0.58 (tlc, on cellulose); uv_{max} 270 nm (ε 15,000).

Anal. Calcd for $C_8H_8O_3N_2$: C, 58.88; H, 4.44; N, 15.55. The product was identical by tlc, ir, and uv with a sample prepared by reduction of 5-oxo-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]-pyridine-2-carboxylic acid.[4]

Diethyl 5-Oxo-3a,4,5,6-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2,3-dicarboxylate (43).—The 6-azaindanone **28** (300 mg) was dissolved in 20 ml of ethanol and was reduced with hydrogen over 100 mg of 10% palladium on charcoal at 10 psi for 90 min. The catalyst was filtered, the solvent was evaporated to dryness *in vacuo*, and the residue was crystallized from ethanol: 130 mg (43%); mp 216–218°; ir 1635, 1610 cm^{-1} (CO lactam); nmr (TFA) δ 1.35 (t, 6, CH_3), 3.6 (m, 2, CH_2CO), 6.4 (q, 4, CH_2CH_3), 5.25 (m, 1, $CHCH_2CO$), 7.1 (s, 1, H_7); mass spectrum *m/e* rel intensity) 280 (M^+, 90), 235 (M − OC_2H_5, 20), 207 (M − $COOC_2H_5$, base peak), 163 (207 − OC_2H_4, 30), 135 (163 − CO, 90), 107 (135 − CO, 80).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.6; H, 5.7; N, 10.2.

The same product was obtained by reducing diethyl 5-benzyloxy-6-azaindole-2,3-dicarboxylate **25** at 50 psi for 2 hr under the described conditions.

Registry No.—2 potassium salt, 38312-68-4; **4**, 38312-69-5; **5**, 38312-70-8; **6**, 38312-71-9; **7**, 38312-72-0; **8**, 38312-73-1; **9**, 38312-74-2; **10**, 38312-75-3; **11**, 38312-76-4; **12**, 38312-77-5; **13**, 38312-78-6; **14**, 38312-79-7; **15**, 38312-80-0; **16**, 38312-81-1; **17**, 38312-82-2; **18**, 38309-19-2; **19**, 38309-20-5; **21**, 38309-21-6; **22**, 38309-22-7; **23**, 38309-23-8; **24**, 38309-24-9; **25**, 38309-25-0; **26**, 38309-26-1; **27**, 38309-27-2; **28**, 38309-28-3; **29**, 38309-29-4; **30**, 38309-30-7; **31**, 33034-45-6; **32**, 38309-32-9; **33**, 32794-21-1; **34**, 38309-34-1; **35**, 32794-17-5; **36**, 38309-36-3; **38**, 22772-51-6; **39**, 38309-38-5; **40**, 32794-19-7; **43**, 38309-40-9; 2-chloro-4-methyl-5-nitropyridine, 23056-33-9.

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Synthesis of Oligosaccharides Containing 2-Acetamido-2-deoxyxylose by Chemical and Enzymic Methods[1a]

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O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-D-xylopyranose (**1**) was prepared from the β(1→4)-linked *N*-acetylglucosamine dimer (**2**) by formation of the diethyl dithioacetal (**3**), glycol cleavage with periodate, reduction with ^3H-$NaBH_4$, and dithioacetal hydrolysis. **1** was isolated by charcoal–Celite column chromatography. A by-product, *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-L-arabinopyranose, was isolated as well. **1** was also isolated from the lysozyme-catalyzed reaction of the *N*-acetylglucosamine tetramer with 5-^3H-2-acetamido-2-deoxy-α-D-xylopyranose (**10**), demonstrating the structure of **1** and supporting a β(1→4) linkage for the higher oligomers containing *N*-acetylxylosamine and two or three *N*-acetylglucosamine residues, which were also produced in the enzymic reaction.

In the past six years, more and more evidence has accumulated for the fascinating, but by no means new,[2] theory that the structure of an enzyme active site is "designed" to fit a conformation of the substrate close to the reaction transition state better than it fits the substrate's ground-state conformation.[3] The synthesis of organic molecules designed to test this theory is a challenging task for the chemist.

In the particular case of lysozyme, Phillips has proposed, on the basis of crystallographic studies of the hen egg white enzyme, that the catalytic region of the active site ("subsite D") can bind an *N*-acetylglucosamine residue in the "half chair" conformation, but cannot bind such a hexopyranose unit in its ground-state "chair" conformation because of steric hindrance to the hydroxymethyl group at C-5 in the latter conformation.[4] The preparation of substrate analogs containing *N*-acetylxylosamine (2-acetamido-2-deoxy-D-xylose), *i.e.*, in which a single C-5 hydroxymethyl group has been removed from an *N*-acetylglucosamine oligomer, would obviously be valuable in the further testing of Phillips' hypothesis. We have briefly reported elsewhere studies of such compounds which support this hypothesis.[5] In this paper we report the

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