recrystallizations from 95% ethanol afforded the analytical sample, m.p. 124.5–126.5° with darkening, ν_{max}^{KBr} 1657 cm.$^{-1}$ (shoulder at 1675).

Anal. Calcd. for $C_{13}H_9Br_2NOS$: C, 40.33; H, 2.35. Found: C, 40.17; H, 2.41.

B. From 4-Benzyl-6-bromo-2H,3H-thieno[3,2-*b*]pyrrol-3-one (II).—A solution of 100 mg. (0.32 mmole) of II and 57 mg. (0.32 mmole) of NBS in 15 ml. of benzene was stirred at room temperature until it gave a negative starch–iodide test (20 hr.). Work-up as above gave 29 mg. (23%) of once-recrystallized yellow needles. Two additional recrystallizations gave the raised m.p. 124.5–126.5°, undepressed upon admixture with the sample prepared by route A. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{13}H_9Br_2NOS$: C, 40.33; H, 2.35; N, 3.62. Found: C, 40.56; H, 2.30; N, 3.42.

Preparation of 2-Benzylidene-4-benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (VIIIb). A. From 4-Benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (Ib) and Benzaldehyde.—To a solution of 343 mg. (1.5 mmoles) of Ib and 164 mg. (1.55 mmoles) of benzaldehyde in 8 ml. of 95% ethanol was added 0.25 ml. of 5% NaOH. The orange solution was refluxed on a steam bath for 4 hr. Cooling produced 350 mg. (73%) of orange needles, m.p. 138–143°. Recrystallization from 95% ethanol (Darco) gave the raised m.p. 141.5–146.5°.

B. From 4-Benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ib) and Benzal-*t*-butylamine.—The benzal-*t*-butylamine was prepared according to the method of Robertson[19] and isolated as a yellow oil. An infrared spectrum obtained from a film of this oil showed a strong band at 1640 cm.$^{-1}$ (C=N absorption) but no N–H stretching absorption band.

To a solution of 229 mg. (1.0 mmole) of Ib in 6 ml. of absolute ethanol was added 374 mg. of the above yellow oil (2.3 mmoles). The red solution was refluxed on a steam bath for 12 hr. A few drops of water were then added to the red solution, and it was allowed to cool. After several hours, 177 mg. (56%) of product had crystallized as orange needles, m.p. 136.5–142°, undepressed upon admixture with the product prepared by route A. The products prepared by routes A and B were combined. Three recrystallizations of this mixture from 95% ethanol afforded an analytical sample, m.p. 144.5–146.5°, ν_{max}^{KBr} 1642 (carbonyl absorption) and 1590 cm.$^{-1}$ (benzylidene C=C absorption).

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.42. Found: C, 75.62; H, 4.92; N, 4.25.

Synthesis of Substituted 2,2′-Bipyrroles[1a]

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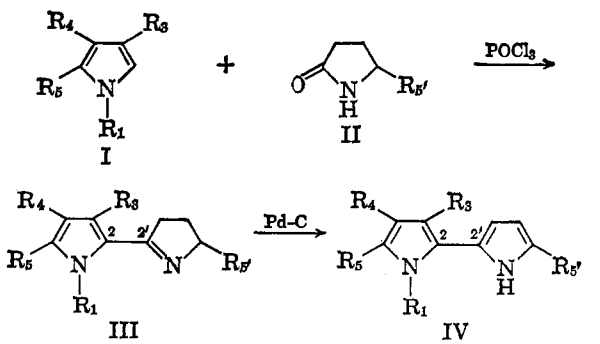
The procedure for preparing 2,2′-bipyrrole, involving condensation of a 2-pyrrolidinone and a pyrrole followed by dehydrogenation of the resulting pyrrolinylpyrrole, has been extended to the synthesis of a number of unsymmetrical bipyrroles. Reaction proceeded equally well with alkyl- and alkoxycarbonyl-substituted 2-pyrrolidinones. However, the presence of an ester group on the pyrrole nucleus prevented condensation except in the case of the β-alkyl β′-ester. Dehydrogenation proceeded much more smoothly and in better yields with pyrrolinylpyrroles prepared from methyl pyroglutamate. The availability of various substituted pyrrolinylpyrroles and bipyrroles has allowed a complete assignment of the n.m.r. absorption in each case.

Recent interest in the 2,2′-bipyrrole system, generated by its occurrence in vitamin B_{12}[2] and prodigiosin,[3] has stimulated activity in the synthesis of this ring system. Symmetrical, highly substituted bipyrroles have been known for some time and are readily prepared by an Ullmann-type condensation.[4] This reaction recently has been improved and extended.[4c] However, other routes have been needed for the synthesis of less substituted, unsymmetrical 2,2′-bipyrroles. These routes have been found in the catalytic dehydrogenation of (a) 2,2′-pyrrolidinylpyrroles, prepared from 1-pyrroline and pyrroles,[3a,5a] and (b) 2,2′-(1′-pyrrolinyl)pyrroles, prepared from 2-pyrrolidinones and pyrrole.[5] Of these two methods, the second seemed to offer the greater promise of wide applicability and better yields. Its further development for the synthesis of a variety of 2,2′-bipyrroles is the subject of this report.

The procedure consists of two steps: a Vilsmeier-type condensation between a pyrrole (I) and a 2-pyrrolidinone (II) in the presence of phosphorus oxychloride, and catalytic dehydrogenation of the resulting pyrrolinylpyrrole (III) to give the bipyrrole (IV). The activating effect of a methyl substituent and the deactivating and stabilizing influence of a carboxylic ester group were examined. The various combinations prepared are shown below, with the subscript referring to the substituent's position in the 2,2′-(1′-pyrrolinyl)pyrrole and 2,2′-bipyrrole.



III, IV	R_1	R_3	R_4	R_5	R_5'
a	H	H	H	CH_3	H
b	H	H	H	H	CH_3
c	H	H	H	CH_3	CH_3
d	H	H	CH_3	H	H
e	H	CH_3	H	H	H
f		CH_3	$CO_2C_2H_5$	H	H
g	H	H	H	H	CO_2CH_3
h	CH_3	H	H	H	CO_2CH_3

(1) (a) Sponsored in part by grant AI-04888 from the National Institutes of Health, U. S. Public Health Service; (b) Public Health Service Predoctoral Research Fellow of the National Institute of General Medical Sciences.

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TABLE I

2,2′-(1′-PYRROLINYL)PYRROLES (III)

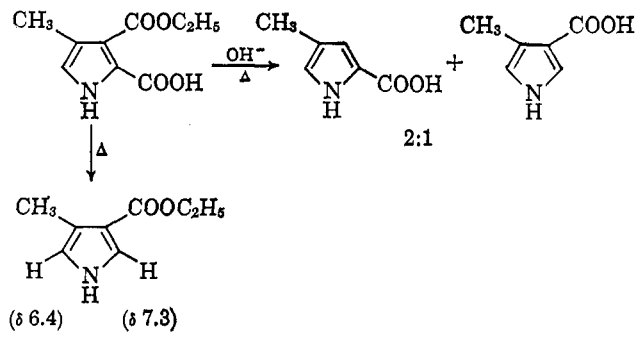
III	M.p., °C.	Yield, %	Ultraviolet Absorption[a] $\lambda_{max}^{H^+}$ (ϵ)	$\lambda_{max}^{OH^-}$ (ϵ)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
a	151–152	78	330 (28,100)	290 (15,300)	$C_9H_{12}N_2$	72.9	72.8	8.2	8.0	18.9	19.1
b	109–110	84	318 (22,600)	279 (19,100)	$C_9H_{12}N_2$	72.9	72.8	8.2	8.1	18.9	19.1
c	58–59	78	317 (26,200)	281 (20,300)	$C_{10}H_{14}N_2$	74.0	73.8	8.7	8.7	17.3	17.1
d	139–140	40	323 (23,100)	285 (15,500)	$C_9H_{12}N_2$	72.9	72.7	8.2	8.2	18.9	19.4
e	173–174	40	318 (26,200)	281 (21,400)	$C_9H_{12}N_2$	72.9	73.0	8.2	7.9	18.9	19.0
f	186–188	37	313 (28,200)	281 (13,600)	$C_{12}H_{16}N_2O_2$	65.4	65.2	7.3	7.0	12.7	13.0
g	101–102	51	324 (29,800)	279 (16,900)	$C_{10}H_{12}N_2O_2$	62.5	62.6	6.3	6.4	14.6	14.6
h	42–43	69	324 (27,000)	279 (18,900)	$C_{11}H_{14}N_2O_2$	64.1	64.3	6.8	6.7	13.6	13.6

[a] Ultraviolet spectra were measured in 0.1 *M* ethanolic hydrochloric acid ($\lambda_{max}^{H^+}$) and 0.1 *M* ethanolic sodium hydroxide ($\lambda_{max}^{OH^-}$).

As the pyrrolidinone components, the commercially available 2-pyrrolidinone and 5-methyl-2-pyrrolidinone were used. Another pyrrolidinone, 5-methoxycarbonyl-2-pyrrolidinone was prepared by esterification[5b] of pyroglutamic acid. The pyrroles used were substituted either with alkyl or alkoxycarbonyl groups, or both.

The pyrroles were prepared by existing literature procedures, with a few modifications. In the case of 2-methylpyrrole, we found that the very simple and convenient preparation[6] from pyrrole-2-carboxaldehyde semicarbazone and alkali led to a product containing pyrrole as an impurity (10%).[7] A probable explanation lies in side reaction to the nitrile, as is found with oximes,[8] and hydrolysis and decarboxylation of the latter. Although the pyrrole may be removed by fractional distillation, a more convenient procedure is the lithium aluminum hydride reduction of the aldehyde. This hydride reduction also applies to ketones and esters[9] and was the method of choice for preparing the alkylpyrroles.

The readily prepared 3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid[10] was a most versatile intermediate for the preparation of a number of alkyl and alkoxycarbonyl pyrroles. However, some confusion exists in the literature as to the nature of the product resulting from the action of strong alkali. The product has been assigned the structure 4-methylpyrrole-3-carboxylic acid on two occasions.[10,11] This assignment was shown to be incorrect by preparation of authentic 4-methylpyrrole-3-carboxylic acid[12] which differed considerably in properties from the material resulting from the alkali treatment. Therefore, the latter was formulated as 4-methylpyrrole-2-carboxylic acid.[12] We have found[7,13] that the product actually is a mixture of both acids, the ratio of 2-acid to 3-acid being 2:1. This was established by quantitative conversion of the acidic reaction product to methyl ester with diazomethane and vapor phase chromatography. The pure 4-methylpyrrole-2-carboxylic acid may be obtained by repeated crystallization or preparative v.p.c. of the methyl ester mixture, followed by hydrolysis. The pure 4-methylpyrrole-3-carboxylic acid is best prepared by thermal decarboxylation of the ester acid, followed by hydrolysis.



Methyl 3,4-dimethylpyrrole-2-carboxylate was conveniently prepared by silver oxide oxidation[14] of the aldehyde, itself readily available by formylation of 3,4-dimethylpyrrole. The acid then was esterified with diazomethane.

Having obtained the necessary pyrroles, their coupling reactions with the three pyrrolidinones were studied. As expected, pyrrole and the alkyl pyrroles, including N-methyl, readily underwent reaction to give good yields of the 2,2′-(1′-pyrrolinyl)-pyrroles (III) listed in Table I. An open α-position is necessary for reaction to occur, since attempts to obtain a pyrrolenine product from 2,3,4,5-tetramethylpyrrole or a β-coupled product from 2,5-dimethylpyrrole both failed.

3-Methylpyrrole can give two isomers in this reaction, and it did, as indicated by the n.m.r. spectrum of the crude product which showed four equal pyrrole proton signals in the region δ 6.9–6.1 and two equal C-CH_3 singlets at δ 2.2 and 2.1. Separation of the two isomers was extremely troublesome until use was made of a continuous chromatographic procedure which allowed reuse of solvent. Thus, a poor eluting solvent, such as benzene in this case, could be used over a period of 10 days, being continuously redistilled to the head of the column. When material ceased to be removed from the column, the solvent was changed to benzene–chloroform (1:1), and the second fraction was rapidly removed. This principle, of using a very poor eluting solvent over a long period of time by continuous redistillation to the column head, has proved useful on numerous occasions. A convenient apparatus for this purpose is described in the Experimental section.

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TABLE II

N.M.R. ABSORPTION[a] OF 2,2′-(1′-PYRROLINYL)PYRROLES (III)

	Structural Element						
III	H_3 [1][b]	$H_{3'}$ [2]	H_4 [1]	$H_{4'}$ [2]	H_5 [1]	$H_{5'}$	CH_3
a	6.5 (d)[c]	2.9 (t)	5.9 (d)	1.9 (m)	...	4.0 (t) [2]	C_5, 2.2 (s)
b	6.2 (d)	2.8 (t)	5.9 (t)	1.5–2.2 (m)	6.6 (m)	4.1 (m) [1]	$C_{5'}$, 1.3 (d)
c	6.2 (d)	2.8 (t)	5.8 (d)	1.5–2.0 (m)	...	4.1 (m) [1]	$C_{5'}$, 1.2 (d); C_5, 2.2 (s)
d	6.4 (s)	2.9 (t)	...	2.4 (m)	6.8 (s)	4.1 (t) [2]	C_4, 2.2 (s)
e	...	3.0 (t)	6.1 (d)	2.4 (m)	6.9 (d)	4.0 (t) [2]	C_3, 2.1 (s)
f	...	3.1 (t)	...	2.2 (m)	7.5 (s)	4.0 (t) [2]	C_3, 2.3 (s)
g	6.6 (d)	3.1 (m)	6.2 (t)	2.3 (m)	6.9 (m)	4.8 (t) [1]	...
h	6.7 (m)	3.1 (m)	6.2 (t)	2.3 (m)	6.9 (m)	5.0 (t) [1]	N_1, 4.1 (s)

[a] Taken in deuteriochloroform and reported as δ-values referred to internal tetramethylsilane (δ 0). [b] Numbers in brackets refer to number of protons obtained by integration. [c] Letters in parentheses refer to singlet (s), doublet (d), triplet (t), and multiplet (m). The splitting patterns reported are the primary ones observed. In many cases, secondary splittings were also observed but are not reported.

TABLE III

N.M.R ABSORPTION[a] OF 2,2′-BIPYRROLES (IV)

	Structural element			
IV	$H_{3,3'}$	$H_{4,4'}$	$H_{5,5'}$	CH_3 (s)
a (= b)	5.5–5.9 (m) [4]		6.3 (m) [1]	C_5, 2.2
c	5.95 (m) [2]	5.85 (m) [2]	.....	$C_{5,5'}$, 2.3
d	6.1 (m) [2]	6.0 (m) [1]	6.4 (m) [1], 6.6 (m) [1]	C_4, 2.1
e	6.0–6.2 (m) [3]		6.6 (m) [2]	C_3, 2.2
f	6.2 (m) [1]	6.2 (m) [1]	7.1 (m) [1], 6.7 (m) [1]	C_3, 2.4
g		6.1–6.8 (m) (5)		
h	6.0–6.6 (m)[4]		6.9 (m) [1]	N_1, 3.8

[a] See footnotes to Table II.

The two isomeric pyrrolinylpyrroles were removed from the column in the order IIIe and IIId, and structures were assigned on the basis of their n.m.r. spectra (Table II). Fraction 1 had its two pyrrole protons split into doublets, indicating adjacent protons on the ring and consistent with structure 3-methyl-2,2′-(1′-pyrrolinyl)pyrrole (IIIe). However, in fraction 2, these proton signals were singlets, allowing assignment of the 4-methyl structure (IIId).

The fact that isomers IIId and IIIe were obtained in equal amount is of interest in regard to steric influences in this reaction. Normally, the α-position adjacent to the alkyl is more activated toward electrophilic attack, and the predominant isomer results from substitution at this position. For example, protonation of 3-methylpyrrole is preferred at the 2-position (over the 5-) by a factor of 15:1.[15] Also, formylation of 3-methylpyrrole gives a 4:1 ratio of 2-formyl-3-methylpyrrole to 2-formyl-4-methylpyrrole.[9b,13] However, with the bulkier pyrrolinyl entering group, steric interaction with the methyl group is sufficient to overcome this preference and leads to an equal mixture of isomers.

Most pyrroles bearing an alkoxycarbonyl group do not undergo reaction with the 2-pyrrolidinones in the presence of phosphorus oxychloride, or phosphorus pentachloride, which was used in some cases. These include methyl pyrrole-2- and -3-carboxylate and the methyl 4-methyl- and 3,4-dimethylpyrrole-2-carboxylates. Presumably, the electron-withdrawing effect of the ester group is sufficient to prevent the electrophilic substitution. The only exception to this generalization was ethyl 4-methylpyrrole-3-carboxylate where the presence of the methyl was enough to overcome the deactivation of a β-alkoxycarbonyl. However, in the case of the α-alkoxycarbonyl, even the presence of two methyl groups was insufficient to confer reactivity.

Two isomers are possible from the reaction of ethyl 4-methylpyrrole-3-carboxylate with 2-pyrrolidinone, and the product was assigned structure IIIf by analogy with other pyrrole systems where substitution invariably takes place *ortho* to the alkyl group. This assignment was confirmed by its n.m.r. spectrum which showed a one-proton singlet at δ 7.5. This can be assigned only to an α-pyrrole proton adjacent to an alkoxycarbonyl group, as seen from the example of ethyl 4-methylpyrrole-3-carboxylate above. Additional evidence is supplied by the corresponding bipyrrole (IVf) which has absorption for two protons at δ 6.2 (β-protons), one proton at 6.7 (normal α-proton), and one proton at 7.1 (α-proton adjacent to alkoxycarbonyl, Table III).

Conversion of the 2,2′-(1′-pyrrolinyl)pyrroles (III) to the corresponding 2,2′-bipyrroles (IV) was effected by catalytic dehydrogenation with palladium on carbon. Although this is a relatively easy reaction to carry out, the yields are not good except when an ester group is present on the nucleus, as can be seen in Table IV. Improvement in the presence of an ester presumably arises both from activation of the α-(to the ester) hydrogen and stabilization of the resulting bipyrrole. Since methyl pyroglutamate is available and couples readily with pyrroles, this is an attractive alternative when it can be applied.

The identical bipyrrole (IVa) was obtained on dehydrogenation of the 2-methylpyrrole–2-pyrrolidinone condensation product IIIa and the pyrrole–5-methyl-2-pyrrolidinone condensation product IIIb. Also, lithium aluminum hydride reduction of the bipyrrole ester (IVg) gave IVa. This is further confirmation of the 2,2′-linkage in all these compounds.

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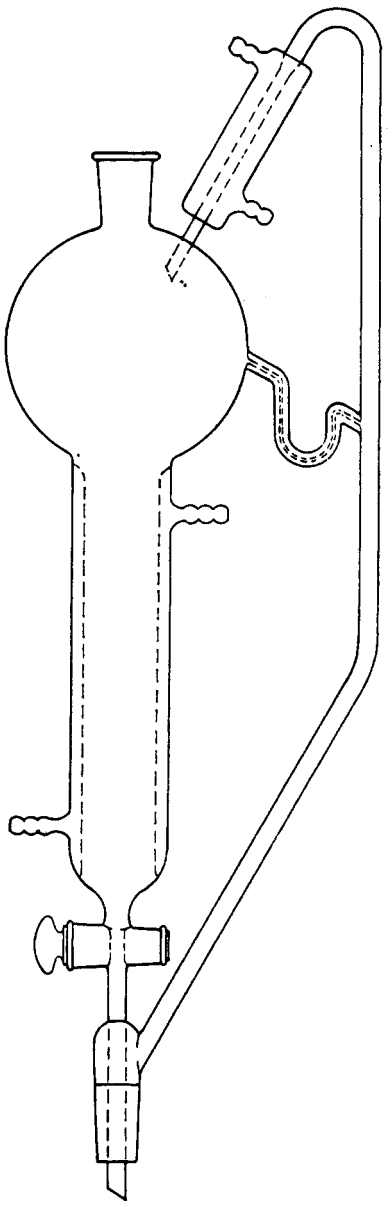

Fig. 1.—Apparatus for continuous chromatography.

There are two points of interest in the ultraviolet absorptions of the 2,2′-bipyrroles listed in Table IV. The first is the practically identical absorption of IVd and IVe, indicating that a single methyl group *ortho* to the 2,2′-bond is not sufficient to cause any steric effect, although four β-methyl groups are.[4c] The second is the significant hypsochromic shift displayed by IVf in relation to IVe. Apparently, addition of the 4-ethoxycarbonyl group is sufficient to cause crowding and some departure from planarity between the two rings.

The n.m.r. spectra of the pyrrolinylpyrroles and bipyrroles are collected in Tables II and III. The presence of the various substituents allows the assignments to be made with certainty.[16]

Experimental[17]

2-Pyrrolidinones.—2-Pyrrolidinone and 5-methyl-2-pyrrolidinone were commercial samples; 5-methoxycarbonyl-2-pyrrolidinone was prepared[5b] from pyroglutamic acid.

Pyrroles.—2-Methylpyrrole, b.p. 150–150.5°, was prepared by the action of alkali on pyrrole-2-carboxaldehyde semicarbazone,[6] removing the 10% pyrrole contaminant by fractional distillation, or by reduction of the aldehyde with lithium aluminum hydride.[9]

3-Methylpyrrole,[10] **2,5-dimethylpyrrole,**[18] **3,4-dimethylpyrrole,**[9b] and **2,3,4,5-tetramethylpyrrole**[9b] all were prepared as described.

Methyl pyrrole-2-carboxylate was prepared by silver oxide oxidation[14] of the aldehyde and esterification with diazomethane. **Methyl pyrrole-3-carboxylate** was prepared as directed,[19] except that ether must be used to extract the acid from aqueous solution; chloroform is ineffective.

Ethyl 4-methylpyrrole-3-carboxylate was prepared by thermal decarboxylation[12] of 3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid[10] and melted at 75–76° (lit.[12] m.p. 73–74°). Hydrolysis with ethanolic alkali by refluxing for 3 hr. and sublimation of the acidic product gave pure **4-methylpyrrole-3-carboxylic acid**, m.p. 190–191° dec. (lit.[12] m.p. 191–192°); ultraviolet absorption: λ_{max} 227 mμ (ε 8700), 253 (3500); $\lambda_{max}^{OH^-}$ 225 mμ (ε 6000), 243 (3500). By treatment with diazomethane, this acid was converted quantitatively to its methyl ester, **methyl 4-methylpyrrole-3-carboxylate**, m.p. 55–56° (lit.[12] m.p. 53–54°); ultraviolet absorption: λ_{max} 227 mμ (ε 8900), 253 (3900).

4-Methylpyrrole-2-carboxylic Acid.—The mixture of acids (m.p. 147–148°) resulting from the action of strong alkali on 3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid,[10] dissolved in ether, was treated with 200 mole % of ethereal diazomethane at 0° for 4 hr. After evaporation of the solvent, the residue was distributed between aqueous sodium bicarbonate and ether, and the dried ether phase was evaporated. Vapor phase chromatography of the residue (silicone grease, 60 ml./min. He, 165°) showed it to consist of a mixture of the 2-ester (R_t 3 min. 32 sec.) and 3-ester (R_t 6 min. 12 sec.) in the ratio 2:1. Several crystallizations from ethanol–water and sublimation (50° at 0.1 mm.) yielded 52% of pure **methyl 4-methylpyrrole-2-carboxylate**, m.p. 73–74° (lit.[12] m.p. 74–75°); ultraviolet absorption: λ_{max} 234 mμ (ε 5550), 272 (14,300). This ester was boiled for 3 hr. in 1 *M* 50% aqueous ethanolic potassium hydroxide, the solution was acidified to pH 2 with 1 *M* phosphoric acid, and the acid was extracted into ether. Evaporation of the dried ether solution, crystallization of the residue from ethanol–water, and sublimation (90° at 0.1 mm.) gave pure **4-methylpyrrole-2-carboxylic acid**, m.p. 203–204° dec. (lit.[12] m.p. 149°); ultraviolet absorption: λ_{max} 236 mμ (5600), 270 (12,200); $\lambda_{max}^{OH^-}$ 260 mμ (ε 11,200).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.5; H, 5.6; N, 11.2.

Methyl 3,4-Dimethylpyrrole-2-carboxylate.—Dimethylformamide (4.0 g., 55 mmoles) was slowly added to phosphorus oxychloride (8.5 g., 55 mmoles) at 0° followed by 25 ml. of ethylene dichloride, and then a solution of 3,4-dimethylpyrrole (4.0 g., 42 mmoles) in 25 ml. of ethylene dichloride was added over 1 hr. After being stirred for 1 hr. at room temperature and at reflux for 30 min., the reaction mixture was poured into 38 g. of sodium acetate in 50 ml. of water and boiled for 15 min. Cooling, separation of the organic phase, extraction of the aqueous layer with chloroform, evaporation of the combined, dried organic solutions, and sublimation (80° at 0.1 mm.) of the residue gave 4.4 g. (85% yield) of **3,4-dimethylpyrrole-2-carboxaldehyde**, m.p. 133° (lit.[20] m.p. 133°); ultraviolet absorption: λ_{max} 325 mμ (ε 32000). This aldehyde (0.9 g., 7.3 mmoles), dissolved in 40 ml. of methanol, was added to 1.67 g. (7.7 mmoles) of freshly prepared silver oxide suspended in 100 ml. of water, and the mixture was stirred vigorously in a blender for 2 hr. The filtered solution was washed with ether, acidified to pH 1.5, and extracted thoroughly with ether. Evaporation left 0.9 g. (89% yield) of **3,4-dimethylpyrrole-2-carboxylic acid**, m.p. 233–235° (lit.[20] m.p. 235° dec.); ultraviolet absorption: λ_{max} 265 mμ (ε 26,300). The methyl ester was prepared by treating the acid with excess ethereal diazomethane for 12 hr. at room temperature, washing this solution

(16) From the data in Table II, it is clear that the previous assignment for 2,2′-(1′-pyrrolinyl)pyrrole (H_5', τ 7.78; H_3', τ 6.5)[5a] is incorrect and should be reversed. It should be H_3, δ 6.5 (s) [1]; H_4, δ 6.3 (s) [1]; H_5, δ 6.9 (s) [1]; H_3', δ 3.0 (t) [2]; H_4', δ 2.1 (p) [2]; H_5', δ 4.1 (t) [2].

(17) All melting points are corrected and were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley, Calif. Ultraviolet spectra were taken in ethanol: λ^{H^+} denotes 0.1 *M* ethanolic hydrochloric acid; λ^{OH^-} denotes 0.1 *M* ethanolic sodium hydroxide.

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 219.

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TABLE IV

2,2′-BIPYRROLES (IV)

IV	M.p., °C.	Yield, %	Ultraviolet absorption[a] λ_{max} (ϵ)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
a (= b)	134–135	29	289 (16,000), 283 (16,400), 278 (15,600)	$C_9H_{10}N_2$	73.9	73.9	6.9	7.0	19.2	19.1
c	190–191	24	295 (14,700), 290 (14,900), 280 (12,800)	$C_{10}H_{12}N_2$	75.0	75.3	7.6	7.7	17.5	17.3
d	200–201	22	288 (16,900), 281 (17,000), 276 (16,200)	$C_9H_{10}N_2$	73.9	74.3	6.9	7.2	19.2	19.2
e	197–198	25	288 (16,600), 281 (16,900), 276 (16,200)	$C_9H_{10}N_2$	73.9	74.1	6.9	7.0	19.2	19.1
f	156–157	46	267 (16,500), 231 (20,600)	$C_{12}H_{14}N_2O_2$	66.0	66.0	6.5	6.4	12.8	13.2
g	231–232	79	325 (26,900), 220 (13,600)	$C_{10}H_{10}N_2O_2$	63.2	63.5	5.3	5.5	14.7	14.5
h	95–96	45	314 (16,800)	$C_{11}H_{12}N_2O_2$	64.7	64.9	5.9	6.0	13.7	14.1

[a] Ultraviolet spectra were measured in ethanol.

with aqueous potassium carbonate, evaporating the ether, and subliming (110° at 0.1 mm.) the residue. **Methyl 3,4-dimethylpyrrole-2-carboxylate** resulted in quantitative yield, m.p. 103–105°; ultraviolet absorption: λ_{max} 285 mμ (ϵ 25,000).

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.2. Found: C, 62.8; H, 7.3; N, 9.0.

2,2′-(1′-Pyrrolinyl)pyrroles.—Condensation between a pyrrole and a 2-pyrrolidinone was carried out in all cases by the following general procedure.

To a solution of 8.0 g. (0.1 mole) of 2-methylpyrrole and 4.0 g. (47 mmoles) of 2-pyrrolidinone in 30 ml. of ethylene dichloride at 0° and in a nitrogen atmosphere, was added 12.0 g. (79 mmoles) of phosphorus oxychloride over a 1-hr. period. The reaction mixture was stirred at room temperature for 2 hr., and the product was isolated as described.[5a] The resulting pyrrolinylpyrrole was recrystallized from hexane–benzene and sublimed at 100° at 0.1 mm.

5,5′-Dimethyl-2,2′-(1′-pyrrolinyl)pyrrole (IIIc) required chromatography on neutral alumina for purification and was eluted with benzene–chloroform, 1:1.

3-Methyl-2,2′-(1′-pyrrolinyl)pyrrole (IIIe) was separated from the 4-methyl isomer (IIId) by continuous chromatography on neutral alumina using the apparatus shown in Fig. 1. After 10 days' continuous elution with benzene, all the 3-methyl isomer (IIIe) had been removed, and the 4-methyl isomer (IIId), present in equal amount, was removed rapidly with benzene–chloroform, 1:1.

2,2′-Bipyrroles.—Catalytic dehydrogenation of the 2,2′-(1′-pyrrolinyl)pyrroles to give the corresponding 2,2′-bipyrroles was carried out in all cases by the following general procedure.

A mixture of 2.4 g. (16 mmoles) of 5-methyl-2,2′-(1′-pyrrolinyl) pyrrole, 2.5 g. of 30% palladium on carbon, and 225 ml. of di-*n*-hexyl ether was heated at 200° for 2 hr. using a nitrogen sweep. The hot solution was filtered, 500 ml. of hexane was added to the filtrate, and the solution was now cooled at −70° for 24 hr. The resulting crystals were removed by filtration and sublimed at 120° at 0.1 mm. to give a 29% yield of 5-methyl-2,2′-bipyrrole (IVa), m.p. 134–135°.

Material identical with the 5-methyl-2,2′-bipyrrole (IVa) prepared by catalytic dehydrogenation was obtained when 5-methoxycarbonyl-2,2′-bipyrrole (IIIg, 0.53 g., 2.8 mmoles) in 60 ml. of tetrahydrofuran was added slowly to 5.8 ml. of 1 *M* lithium aluminum hydride in tetrahydrofuran and heated under reflux for 3 hr. Cooling, addition of ice, filtering, extracting with chloroform, evaporating the chloroform, and subliming gave 2.8 g. (67% yield) of IVa.

Steroids. CCLXI.[1] Microbiological Hydroxylation of Estrane Derivatives with *Fusarium moniliforme*

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Incubation of estrone (Ia) with *Fusarium moniliforme* afforded 15α-hydroxyestrone (Ib). Incubation of estradiol (IIa) with the same microorganism provided 15α-hydroxyestradiol (IIc), while 6β-hydroxyestradiol 3-methyl ether (Vb) was obtained by microbial incubation of estradiol 3-methyl ether (IIb). The structure determination of these substances, obtained by enzymatic transformations, results from both chemical and nuclear magnetic resonance evidence.

It has been known for several years that some microorganisms produce enzymes capable of stereospecifically hydroxylating the steroid molecule at a definite position.[2,3] While microbiological hydroxylation of androstane and pregnane molecules has been extensively investigated, little has been reported so far on microbial transformations of estrane derivatives.[3,4]

The present study reports the elucidation of the structure of the compounds obtained by incubation of estrone (Ia), estradiol (IIa), and estradiol 3-methyl ether (IIb) with *Fusarium moniliforme*. This microorganism, corresponding to an imperfect stage of *Gibberella fujikuroi*,[5] is known to hydroxylate the androstane and pregnane molecules at C-6β and/or C-15α.[6] However, no work on the fermentation of estrane derivatives with this microorganism has been reported.

Incubation of estrone (Ia) with *Fusarium moniliforme*[7] provided a crystalline substance (Ib), the elemental analysis of which indicated the introduction of one hydroxyl group into the estrone molecule. While

(1) Part CCLX: A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, in press.

(2) Several review articles on this subject have appeared recently, for example: (a) E. Vischer and A. Wettstein, "Advances in Enzymology," F. F. Nord, Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p. 237; (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 672; (c) L. M. Kogan, *Russ. Chem. Rev.*, **31**, 294 (1962); (d) M. Shirasaka, *Ann. Sankyo Res. Lab.*, **15**, 1 (1963).

(3) C. Tamm, *Angew. Chem.*, **74**, 225 (1962).

(4) A. I. Laskin, J. Fried, P. Grabowich, B. Junta, and C. D. Meyers, *Bact. Proc.* 106 (1963).

(5) See, for example, W. C. Snyder and H. N. Hansen, *Am. J. Botany*, **32**, 657 (1945).

(6) See (a) A. Čapek and O. Hanč, *Folia Microbiol.* (Prague), **5**, 251 (1960); (b) B. Klüger, *et al.*, *Naturwiss.* **44**, 40 (1957); (c) P. D. Meister, *et al.*, unpublished work cited in S. H. Eppstein, *et al.*, *Vitamines and Hormones*, **14**, 359 (1956); (d) see also ref. 2a.

(7) See Experimental. Further microbiological aspects of these incubations as well as other related experiments will be published elsewhere.