precipitate developed. The mixture was heated to boiling for 10 min. and centrifuged. The precipitate was suspended twice in 100-ml. portions of hot 80% aqueous methanol and centrifuged to remove traces of D-glucose. The polysaccharide was washed with methanol and dried over calcium chloride to yield 0.7 g.

The amount of D-glucose combined with the polymer was determined by periodate oxidation. An 18.3-mg. portion was mixed with 80 ml. of 5% potassium chloride solution and 20 ml. of 0.3 M sodium metaperiodate. The mixture was shaken in the dark at 18°. Aliquots were taken every 12 hr., and the formic acid present was titrated by 0.01 N sodium hydroxide solution using methyl red-methylene blue as indicator. 6-Deoxy-6-hydrazinocellulose was used in a blank determination. The oxidation was complete in about 2 days. The amount of formic acid obtained indicated that the number of D-glucose units which had become attached were equivalent to the number of hydrazino groups present.

The product formed by treating D-glucose with the 6-deoxy-6-hydrazinocellulose of D.S. 0.5, when freshly prepared, was readily soluble in water. When 100 mg. of the polymer was shaken in 10 ml. of water for 48 hr., no free D-glucose was evident on paper chromatography of solution aliquots.

Reaction with D-Glucono-1,4-lactone.—6-Deoxy-6-hydrazinocellulose of D. S. 0.50, freshly prepared from 1.0 g. of 6-*O*-tosylcellulose, was placed in a 2.3 × 20 cm. test tube which contained 4 g. of D-glucono-1,4-lactone dissolved in 15 ml. of water. The mixture was shaken thoroughly and heated at 45° for 30 min. After centrifugal removal of a small amount of insoluble material, the centrifugate was mixed with 30 ml. of 1 N sodium hydroxide solution. The mixture, when poured into 200 ml. of methanol and stirred in a Waring Blendor, produced a fine white precipitate. The methanol suspension was heated, centrifuged, and the precipitate was washed twice with 100-ml. portions of 60% aqueous methanol. It then was washed with methanol and dried over calcium chloride to yield 0.7 g. The amount of combined D-gluconic acid was estimated by periodate oxidation of the product and measurement of the amount of formaldehyde released. The amount found corresponded to the attachment of one D-gluconic acid unit to each hydrazino group.

The product was alkaline hydrolyzed by suspending 200 mg. in 15 ml. of hot ethanol, adding 5 ml. of 0.1 N sodium hydroxide solution, and heating at 100° for 5 min. The mixture was filtered while hot, and the filtrate was neutralized with diluted acid and chromatographed using irrigants A, B, and C. On spraying with silver nitrate solution a single strong spot appeared, corresponding to D-gluconate.

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2,2′:5′,2″-Terpyrrole[1a]

HENRY RAPOPORT, NEAL CASTAGNOLI, JR.,[1b] AND KENNETH G. HOLDEN[1c]

Department of Chemistry, University of California, Berkeley, California

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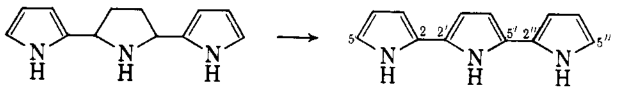
The synthesis of 2,2′:5′,2″-terpyrrole has been accomplished by dehydrogenation of pyrrole trimer and decarboxylation of a terpyrrole dicarboxylic acid. The properties found for this compound differ appreciably from those reported previously for material assigned the terpyrrole structure. A general procedure has been developed for the synthesis of terpyrroles from the condensation of a 2,2′-bipyrrole and a 2-pyrrolidinone to give a pyrrolinylbipyrrole, and dehydrogenation of the latter.

It has been suggested that pyrrole is an intermediate in the formation of naturally occurring melanins and that pyrrole black, generated when pyrrole is oxidized in acetic acid, is structurally similar to melanins.[2] Because of the polymeric character of pyrrole black, Chierici and co-workers attempted to synthesize 2,2′:5′,2″-terpyrrole (I) to determine if this compound is an intermediate in the formation of pyrrole black and of possible significance in relation to melanin.[3] From the reaction of 1,4-di-2′-pyrrylbutane-1,4-dione and ammonia, they reported the isolation of a compound assigned structure I, m.p. 100° dec., too unstable for further characterization. These properties were quite unexpected in view of our experience with 2,2′-bipyrroles.[4] Therefore, we have investigated the synthesis of terpyrroles and describe here several representatives of this system.

Pyrrole, treated with acid, undergoes trimerization[5] to form pyrrole trimer, 2,5-di-2′-pyrrylpyrrolidine (II).[6] When II was subjected to catalytic dehydrogenation, the product obtained had the molecular formula of the desired terpyrrole but was clearly not the same material as previously reported[3b] since it melted at 242°. The following spectral evidence established the structure of this compound as terpyrrole (I). (a) The n.m.r. spectrum showed six β-protons (δ 6.2) and two α-protons (δ 6.7) as complex signals, while integration established the approximate location of the three protons attached to nitrogen (δ $\sim$10). (b) The ultraviolet spectrum retained the same fine structure as found in 2,2′-bipyrrole (III)[4] and exhibited the anticipated bathochromic shift ($\sim$45 mμ) relative to bipyrrole. A methanolic solution of terpyrrole exposed to air and light slowly turns green and, after 24 hr., a black precipitate forms. These changes occur instantaneously when hydrogen peroxide is added to a solution of I in acetic acid. However, crystalline material is stable for long periods when stored in the cold in the absence of air and light. From a comparison of these properties with those reported by Chierici and Serventi,[3b] it is clear that the material they had isolated was not terpyrrole.



II I

A more general synthesis of terpyrroles was effected by condensation of a 2,2′-bipyrrole with a 2-pyrroli-

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(2) (a) A. Angeli and A. Pieroni, *Atti accad. Lincei*, **30**, 241 (1921); (b) A. Pieroni and A. Maggi, *Gazz. chim. ital.*, **53**, 120 (1923).

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TABLE I

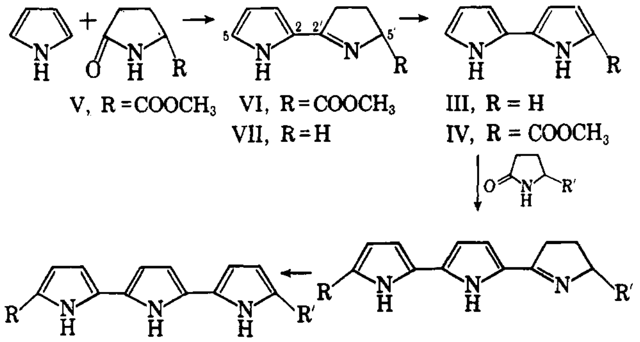
NUCLEAR MAGNETIC RESONANCE ABSORPTION[a] OF TERPYRROLE AND RELATED COMPOUNDS

Compound	Structural element $H_{5',5''}$	$H_{4',4''}$	$H_{3',3''}$	OCH_3	$H\alpha$[h]	$H\beta$[h]
VI[b]	4.8(t)[f][1][g]	2.3(m)[2]	3.1(m)[2]	3.7(s)[3]	6.9(m)[1]	6.2(m)[1] 6.6(m)[1]
IV[c]				3.8(s)[3]		6.8(m)[2] 6.6(m)[1] 6.4(m)[1] 6.1(m)[1]
VIII[d]	3.9(m)[2]	2.2(m)[2]	3.2(t)[2]	3.8(s)[3]		6.7–7.1(m)[4]
IX[d]	4.9(t)[1]	2.4(m)[2]	3.3–3.8(m)[8]			6.7–7.2(m)[4]
XI[c]				3.8(s)[6]		6.4–7.1(m)[6]
I[e]					6.7(m)[2]	6.2(m)[6]

[a] As δ-values referred to internal tetramethylsilane (δ = 0). [b] In deuteriochloroform. [c] In acetone. [d] In liquid sulfur dioxide. [e] In methanol. [f] Letters in parentheses refer to singlet (s), triplet (t), multiplet (m). [g] Numbers in brackets refer to number of protons obtained by integration. [h] α- or β-pyrrole hydrogens.

dinone in the presence of phosphorus oxychloride to form a pyrrolinylbipyrrole. Dehydrogenation of the pyrroline then led to the terpyrrole. With the unsubstituted 2,2′-bipyrrole and 2-pyrrolidinone, polymeric material was formed rapidly and neither starting material nor product could be isolated from the reaction mixture. The difficulty appeared to be due to the instability of bipyrrole to acidic conditions and the self-condensation of 2-pyrrolidinone in the presence of phosphorus oxychloride.[7]

To overcome this difficulty, the corresponding reaction was considered with 5-methoxycarbonyl-2,2′-bipyrrole (IV) since the ester group should increase the stability of the bipyrrole significantly. Two methods were examined for the preparation of IV, *viz.*, the condensation of methyl 2-pyrrolecarboxylate with 2-pyrrolidinone, and the condensation of methyl 2-pyrrolidinone-5-carboxylate (methyl pyroglutamate, V) with pyrrole, followed by dehydrogenation in each case. The first procedure failed because of the low reactivity of the carbomethoxypyrrole toward electrophilic attack, over 90% of the starting pyrrole ester being recovered. However, the second method gave the required 2,2′-(5′-methoxycarbonyl-1′-pyrrolinyl)pyrrole (VI) in reasonable yield. As in the case of the unsubstituted pyrrolinylpyrrole (VII) previously reported,[4b] VI shows a reversible acid shift in its ultraviolet absorption, a consequence of the extended resonating system of the protonated form, and a strong band at 1630 cm.$^{-1}$ attributed to C=N stretching. The carbonyl band appeared at 1725 cm.$^{-1}$. The position of the double bond was unambiguously established by n.m.r. (Table I), the low field triplet (δ 4.8) from the methine proton clearly eliminating any other possible isomer. Dehydrogenation of VI proceeded smoothly to yield the desired carbomethoxybipyrrole (IV).



V, R = COOCH₃ VI, R = COOCH₃ III, R = H
VII, R = H IV, R = COOCH₃

I, R = R′ = H
X, R = H, R′ = COOCH₃
XI, R = R′ = COOCH₃
XII, R = R′ = COOH

VIII, R = COOCH₃; R′ = H
IX, R = R′ = COOCH₃

Condensation of IV with 2-pyrrolidinone gave the pyrrolinylbipyrrole (VIII), the structure of which was established by analysis and spectral data similar to that given above. This reaction was complicated by the ease with which 2-pyrrolidinone undergoes self-condensation[4b,7] and the deactivating influence of the ester group on the nucleophilic character of the bipyrrole. The greater stability of methyl pyroglutamate in the presence of phosphorus oxychloride, however, led to an improved yield of the dicarbomethoxy pyrrolinylbipyrrole (IX).

Catalytic dehydrogenation of the two pyrrolinylbipyrroles (VIII and IX) gave the desired terpyrroles (X and XI). It is of interest to note the greater ease with which IX undergoes dehydrogenation (84% of the theoretical volume of hydrogen evolved in 45 min.) compared with VIII under the same conditions (50% of theory in 100 min.). Presumably, this difference is due to the increased lability of the pyrroline α-hydrogen in IX.

The above two routes to terpyrroles were related by saponification of the diester (XI) to the diacid (XII) which, when heated to 200° (20 μ), underwent decarboxylation to give pure terpyrrole, identical with that obtained by the dehydrogenation of pyrrole trimer.

Experimental[8]

2,2′:5′,2″-Terpyrrole (I).—A mixture of 561 mg. (2.79 mmoles) of pyrrole trimer II,[6] 575 mg. of 5% palladium on carbon, and 15 ml. of *p*-cymene was boiled under a slow nitrogen sweep with magnetic stirring. After 30 min., the reaction mixture was cooled to about 80° and 20 ml. of benzene (oxygen-free) was introduced. The warm mixture was filtered under a nitrogen atmosphere and the filtrate was reduced to about one-half its original volume *in vacuo*. Cooling of the residual solution caused crystallization of the product (76 mg., 0.39 mmole, 14%). Sublimation at 130° (20 μ) gave pure terpyrrole, m.p. 242°; $\lambda_{max}^{CH_3OH}$ 345 mμ (sh) (ε 13,000), 327 (25,900), 319 (26,000).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.1; H, 5.6; N, 21.3. Found: C, 73.2; H, 5.7; N, 21.1.

Methyl 2-Pyrrolidinone-5-carboxylate (Methyl Pyroglutamate, V).—Sublimed, commercial pyroglutamic acid (m.p. 179–183°, 300 g., 2.32 moles) was added to 3 l. of anhydrous methanol

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(7) H. Bredereck and K. Bredereck, *Ber.*, **94**, 2278 (1961).

(8) Microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley, Calif.. Ultraviolet spectra were determined in methanol.

which previously had been saturated with anhydrous hydrogen chloride. The heterogeneous mixture was stirred for 72 hr. during which time all of the solid had gone into solution. An n.m.r. spectrum taken at this time showed that over 98% of the acid had undergone esterification. The methanol was removed by distillation at room temperature *in vacuo* and the residue was dissolved in chloroform (500 ml.). The chloroform solution was extracted with two 50-ml. portions of aqueous bicarbonate, dried over magnesium sulfate, concentrated on a rotary evaporator, and distilled to give 280 g. (1.96 moles, 85%) of the pure ester, b.p. 101–103° (0.15 mm.), lit.[9] b.p. 160° (8 mm.).

2,2′-(5′-Methoxycarbonyl-1′-pyrrolinyl)pyrrole (VI).—To a mixture of 10 g. (70 mmoles) of methyl pyroglutamate, 5 g. (75 mmoles) of pyrrole, and 50 ml. of anhydrous methylene chloride was added, at a temperature of 0° with stirring and under a nitrogen atmosphere, 10.5 g. (69 mmoles) of phosphorus oxychloride over a 1-hr. period. After stirring at 0° for 19 hr. more, the slightly pink solution was added with vigorous swirling to 100 ml. of 7.5 *N* potassium hydroxide with an adequate amount of ice to maintain the temperature at 0°. The resulting mixture was extracted with three 100-ml. portions of chloroform, each extract being washed with water. The combined organic phase was then dried over potassium carbonate and the solvent was removed *in vacuo* to yield a nearly colorless solid which, on crystallization from benzene–hexane (1:1), gave 6.9 g. (35.5 mmoles, 51%) of 2,2′-(5′-methoxycarbonyl-1′-pyrrolinyl)pyrrole, m.p. 101–102°; $\lambda_{\text{maa}}^{0.1\ N\ \text{KOH-CH}_3\text{OH}}$ 279 mμ (ε 16,900); $\lambda_{\text{max}}^{0.1\ N\ \text{HCl-CH}_3\text{OH}}$ 324 mμ (ε 29,800), 270 sh (3900).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6; OCH_3, 16.1. Found: C, 62.6; H, 6.4; N, 14.6; OCH_3, 16.0.

5-Methoxycarbonyl-2,2′-bipyrrole (IV).—A suspension of carbomethoxypyrrolinylpyrrole VI (1.9 g., 10 mmoles) and 30% palladium on carbon (3.56 g., 100 mole % Pd) in 50 ml. of di-*n*-hexyl ether was stirred vigorously for 45 min. at 200°. The hot reaction mixture was then filtered under an atmosphere of nitrogen and cooling gave 1.5 g. (79%) of 5-methoxycarbonyl-2,2′-bipyrrole. Sublimation at 120° (10 μ) provided an analytical sample, m.p. 231–232°; λ_{max} 325 mμ (ε 26,900), 220 (13,600).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7; OCH_3, 16.3. Found: C, 63.4; H, 5.5; N, 14.5; OCH_3, 15.9.

5-Methoxycarbonyl-5′-(2′′Δ^1′′pyrrolinyl)-2,2′-bipyrrole (VIII).—To a mixture of 2.9 g. (19.2 mmoles) of 5-methoxycarbonyl-2,2′-bipyrrole (IV), 22 g. (260 mmoles) of 2-pyrrolidinone, and 25 ml. of dioxane was added at room temperature, with stirring, under nitrogen, 16.5 g. (110 mmoles) of phosphorus oxychloride over a 20-min. period. The reaction mixture was stirred an additional 100 min. at room temperature. The dark, blue-green contents of the flask were then added to an ice-cold solution of sodium acetate (85 g. of trihydrate, 600 mmoles) with vigorous stirring. While maintaining the temperature at 0° by the addition of ice, the pH of the solution was raised to 9 by the slow addition of 10 *N* sodium hydroxide. Extraction of this heterogeneous mixture with ether gave a dark red ether solution which was washed several times with water, dried over anhydrous potassium carbonate, and evaporated to give 2.7 g. of a glass.

This material was chromatographed on 60 g. of activity IV alumina, using methylene chloride to develop the column. The first 100 ml. gave 400 mg. of the 2-pyrrolidinone self-condensation material[7] followed by 2 g. of a mixture of three compounds (detected by thin layer chromatography) with the next 400 ml. of methylene chloride. This material was crystallized from benzene–acetone to give 1.2 g. (4.7 mmoles, 24.5%) of 5-methoxycarbonyl-5′-(2′′-Δ$^{1′′}$-pyrrolinyl)-2,2′-bipyrrole, m.p. 210–212° dec.; $\lambda_{\text{max}}^{0.1\ N\ \text{KOH-CH}_3\text{OH}}$ 363 mμ (ε 31,000), 350 sh (28,000), 300 sh (11,200); $\lambda_{\text{max}}^{0.1\ N\ \text{HCl-CH}_3\text{OH}}$ 389 mμ (ε 42,300), 384 sh (38,400), 258 (10,500).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.4; H, 5.9; N, 16.3. Found: C, 65.1; H, 6.0; N, 16.1.

5-Methoxycarbonyl-5′-(5′′-methoxycarbonyl-2′′-Δ$^{1′′}$-pyrrolinyl)-2,2′-bipyrrole (IX).—The carbomethoxybipyrrole (IV, 3.35 g., 17.6 mmoles), methyl pyroglutamate (35 g., 244 mmoles), 50 ml. of dioxane, and 50 ml. of methylene chloride were mixed and cooled to 0° under a nitrogen atmosphere. Then, over a 30-min. period, phosphorus oxychloride (5.5 g., 36 mmoles) was added with stirring. The reaction mixture was stirred an additional hour at 0° and poured with rapid stirring into an ice-cold aqueous solution of sodium acetate (31 g. of trihydrate, 216 mmoles). With temperature maintained at 0°, 10 *N* sodium hydroxide was added slowly to pH 9, the heterogeneous, aqueous mixture was extracted several times with ether, and the combined ether extracts were washed with water. Drying over potassium carbonate and removing the solvent gave 5.65 g. of an oil. Upon warming with 25 ml. of benzene, the oil crystallized, and sublimation of the crystalline mass at 150° (10^{-5} mm.) gave 4.2 g. (133 mmoles, 76%) of 5-methoxycarbonyl-5′-(5′′-methoxycarbonyl-2′′-Δ$^{1′′}$-pyrrolinyl)-2,2′-bipyrrole, m.p. 176–178°; $\lambda_{\text{max}}^{0.1\ N\ \text{KOH-CH}_3\text{OH}}$ 360 sh mμ (ε 30,300), 345 (36,000); $\lambda_{\text{max}}^{0.1\ N\ \text{HCl-CH}_3\text{OH}}$ 402 mμ (ε 45,300).

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.9; H, 5.4; N, 13.3. Found: C, 60.8; H, 5.31; N, 13.1.

5-Methoxycarbonyl-2,2′:5′,2′′-terpyrrole (X).—A mixture of the pyrroline (VIII, 600 mg., 2.44 mmoles), 30% palladium on carbon (830 mg., 100 mole % Pd), and 35 ml. of hexyl ether was heated at 200° with vigorous stirring for 100 min. The hot reaction mixture was then filtered under a nitrogen atmosphere and the cooled filtrate was diluted with 400 ml. of hexane and kept at −80° for 6 hr. The precipitate that formed was collected and combined with material obtained from acetone digestion (three 25-ml. portions) of the catalyst. Chromatography on 15 g. of activity IV alumina and elution with methylene chloride gave first a complex mixture (100 ml.) that contained none of the desired product followed by 20 mg. (0.08 mmole, 3.2%) of the terpyrrole (X), which was sublimed at 140° (5×10^{-5} mm.), m.p. 191–193° dec., λ_{max} 358 mμ (ε 28,800).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.9; H, 5.1; N, 16.5. Found: C, 65.9; H, 5.3; N, 16.3.

5,5′′-Bismethoxycarbonyl-2,2′:5′,2′′-terpyrrole (XI).—A mixture of the pyrroline (IX, 2.5 g., 7.94 mmoles), 30% palladium on carbon (2.82 g., 100 mole % Pd), and 100 ml. of hexyl ether was heated at 200° for 45 min. with vigorous stirring and a slow nitrogen sweep. The hot reaction mixture was then filtered under a nitrogen atmosphere and hexane (900 ml.) was added to the cooled filtrate causing precipitation. After further cooling, 800 mg. (2.54 mmoles, 32%) of terpyrrole XI was obtained. Material obtained from catalyst digests (three 50-ml. portions of acetone) was chromatographed on 30 g. of activity IV alumina and eluted with methylene chloride to give another 150 mg. (0.47 mmoles, 6.0%) of the desired terpyrrole. Crystallization of the combined 950 mg. from benzene–acetone gave 380 mg. (1.2 mmoles, 15.4%) of pure biscarbomethoxyterpyrrole XI, m.p. 279–280°; λ_{max} 385 sh mμ (ε 34,100), 367 (43,500), 226 (19,400).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.3; H, 4.8; N, 13.4. Found: C, 61.7; H, 5.1; N, 13.0.

2,2′:5′,2′′-Terpyrrole-5,5′′-dicarboxylic Acid (XII).—A solution of 200 mg. (0.64 mmole) of diester XI in 50 ml. of methanol, 25 ml. of water, and 10 ml. of 10 *N* sodium hydroxide was boiled for 1 hr. (the initial red color that formed faded during the course of the reaction). The cooled solution was concentrated to one-half volume *in vacuo* on a rotary evaporator. Then, 100 ml. of water was added, and the solution was washed with three 50-ml. portions of ether. The pH was carefully lowered to 2 with dilute phosphoric acid, the mixture was extracted with three 50-ml. portions of ether, and the combined ether extracts were washed with water and then extracted with two 50-ml. portions of aqueous bicarbonate. Re-extraction into ether after acidifying to pH 2 and evaporation of the dried ether extracts left 156 mg. (0.53 mmole, 82.5%) of the yellowish diacid (XII) which was too unstable for further purification.

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.9; H, 3.9; N, 14.7. Found: C, 58.0; H, 4.5; N, 14.0.

Decarboxylation of Diacid XII to 2,2′:5′,2′′-Terpyrrole (I).—A solution of the diacid (150 mg., 0.52 mmole) in acetone was coated onto the bottom surface of a sublimer. The sublimer was then evacuated to 20 μ and heated in an oil bath maintained at 200°. After about 30 sec., a white solid started to collect on the cold finger and the pressure increased to about 400 μ. After 15 min., the pressure had returned to 20 μ. The sublimate (75 mg., 38 mmoles, 73%) was found by comparison of ultraviolet and n.m.r. absorption and melting point to be identical with the terpyrrole obtained by dehydrogenation of pyrrole trimer.

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(9) T. Weiland and H. Fritz, *Ber.*, **86**, 1186 (1953).