Concerning the Position of Thiocyanation in Pyrrole[1]

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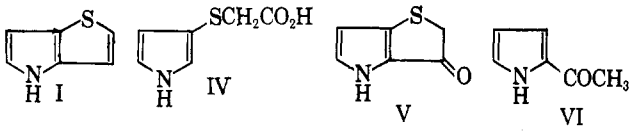
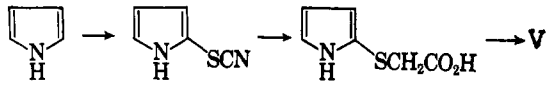
Chemical evidence is presented which confirms the assignment of the structure of 2-thiocyanopyrrole to the product of the thiocyanation of pyrrole. The thiocyanopyrrole obtained from pyrrole is converted to 2-methylsulfonylpyrrole, the structure of which is established by its identity with 2-methylsulfonylpyrrole synthesized from diethyl 3,4-pyrroledicarboxylate by thiocyanation, methylation, oxidation, and decarboxylation.

The position of thiocyanation in pyrrole has been of recent interest.[3,4] In the synthesis of thieno[3,2-*b*]-pyrrole (I), the initial step was thiocyanation of pyrrole (II) with thiocyanogen to give a compound whose structure was assigned as 3-thiocyanopyrrole (III).[5] The evidence for this assignment was that the ketone V, obtained by treating III with bromoacetic acid in basic aqueous methanol and subsequent ring closure of the resulting acid IV with polyphosphoric acid, yielded 2-acetylpyrrole (VI) upon desulfurization with Raney nickel.[5]



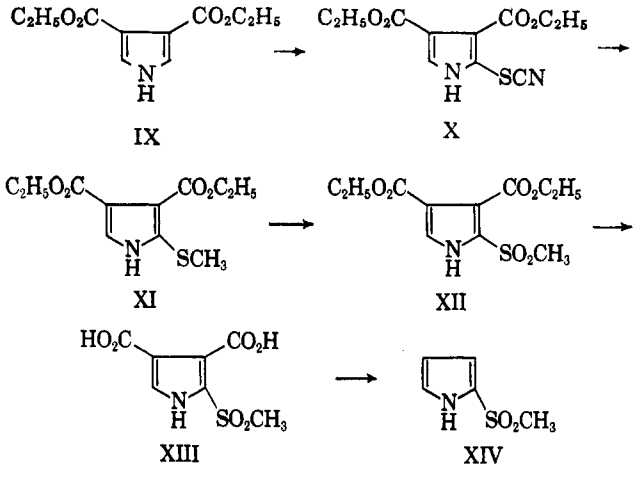
I IV V VI

In studies of the nuclear magnetic resonance spectra of various substituted thiophenes[6] and pyrroles,[7] it developed[3] that the n.m.r. spectra of monothiocyanopyrrole and its simple derivatives are consistent with those of 2-substituted pyrroles and not of the 3-isomers. Gronowitz, Hörnfeldt, Gestblom, and Hoffman, therefore, reassigned the structure of the thiocyanation product as 2-thiocyanopyrrole and recognized the occurrence of rearrangement in the ring closure of 2-pyrrolylthioacetic acid (VIII) in polyphosphoric acid.[3] This paper reports new chemical evidence concerning the position of thiocyanation in pyrrole.



II VII VIII

The initial goal was the thiocyanation of a pyrrole having the 3 and 4 positions blocked by groups that could be removed subsequently. Diethyl 3,4-pyrroledicarboxylate[8] (IX) appeared to be a suitable starting material, provided that the combined effect of the two electron-withdrawing groups would not entirely inhibit the thiocyanation. Although attempts at the thiocyanation with thiocyanogen under a variety of conditions failed, the desired monothiocyano derivative X could be obtained in good yield with the aid of the more reactive reagent thiocyanogen chloride.[9] The infrared spectrum of X has a band at 2155 cm.$^{-1}$ due to the thiocyano group, plus bands for the N–H and ester groups. Compound X was converted to the methylthiopyrrole XI by the reaction with methyl iodide and base in aqueous methanol.[5] Oxidation of XI with hydrogen peroxide in acetic acid[10] occurred to yield the sulfone XII, the infrared spectrum of which has bands at 1300 and 1133 cm.$^{-1}$ due to the sulfonyl group. The sulfone XII underwent basic hydrolysis to the diacid XIII which was decarboxylated upon heating under reflux in 2-aminoethanol[11] to yield 2-methylsulfonylpyrrole (XIV). The reactions all occurred in yields of better than 70% except for the decarboxylation, which occurred in a yield of 53%.



IX X XI XII XIII XIV

The infrared spectrum of 2-methylsulfonylpyrrole (XIV) shows absorption due to the N–H group at 3420 and the sulfonyl group at 1300 and 1135 cm.$^{-1}$, and has no bands due to carbonyl absorption. The n.m.r. spectrum consists of three multiplets assigned to the three ring protons as follows: $\tau_5 = 2.95$, $\tau_3 = 3.06$, and $\tau_4 = 3.67$ p.p.m., and a singlet at $\tau = 6.86$ p.p.m. due to the side-chain methyl hydrogens. The coupling constants, calculated from a spectrum in which coupling with the proton on nitrogen has been eliminated by addition of a few per cent of pyrrolidine,[3] are $J_{34} = 3.6$, $J_{45} = 2.5$, and $J_{35} = 1.4$ c.p.s. These values are in the range expected for a pyrrole substituted in the α-position, the reported values being $J_{34} = 3.40$–3.80, $J_{45} = 2.40$–3.10, and $J_{35} = 1.35$–1.50 c.p.s.[7]

The second objective was to transform the monothiocyanopyrrole obtained from pyrrole to the corresponding sulfone and to compare this with 2-methylsulfonylpyrrole (XIV). Pyrrole was treated with thio-

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(2) National Science Foundation Fellow, 1962–1963.

(3) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv. Kemi*, **18**, 151 (1961); see also S. Gronowitz, U. Rudén, and B. Gestblom, *ibid.*, **20**, 297 (1963).

(4) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *J. Org. Chem.*, **26**, 2615 (1961).

(5) D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(6) S. Gronowitz and R. A. Hoffman, *Arkiv. Kemi*, **16**, 563 (1960).

(7) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *ibid.*, **18**, 133 (1961).

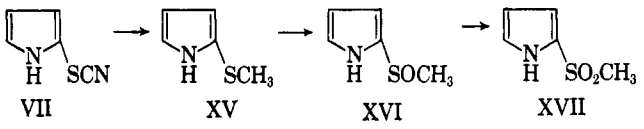
(8) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(9) R. G. R. Bacon and R. G. Guy, *J. Chem. Soc.*, 318 (1960).

(10) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 801.

(11) E. J. Chu and T. O. Chu, *J. Org. Chem.*, **19**, 266 (1954).

cyanogen at −70° in methanol[5] and the thiocyano compound VII was converted to the methylthiopyrrole XV by treatment with methyl iodide and alkali in aqueous methanol.[5] The infrared spectrum of the methylthiopyrrole XV was superimposable on a previously published spectrum[3] of a sample prepared in the same way.



VII XV XVI XVII

The oxidation of the methylthiopyrrole XV to the sulfone proved to be the critical step. The best results were obtained in a stepwise conversion, first to the sulfoxide and then to the sulfone. Attempts to prepare the sulfone directly from XV gave, in poor yields, a mixture of the sulfoxide and sulfone which proved to be difficult to separate. The sulfoxide XVI was prepared either by oxidation with hydrogen peroxide in acetone (73% yield) or with hydrogen peroxide in aqueous acetic acid (81% yield).[10] The infrared spectrum of the sulfoxide XVI shows strong absorption at 1015–1040 cm.$^{-1}$ in the region for sulfoxide absorption. The decoupled n.m.r. spectrum shows the ring protons as three quartets assigned as follows: τ_5 = 3.05, τ_3 = 3.33, and τ_4 = 3.83 p.p.m., and a singlet due to the methyl protons at τ = 7.05 p.p.m. The coupling constants calculated are J_{34} = 3.60, J_{45} = 2.55, and J_{35} = 1.40 c.p.s., in good agreement with those expected for the 2-isomer but not for the 3-isomer.[7] The sulfoxide XVI was reduced to XV with lithium aluminum hydride,[12] thus establishing that no rearrangement had occurred in the oxidation to the sulfoxide.

The sulfone XVII was formed in a 52% yield from the sulfoxide by oxidation with hydrogen peroxide in acetic acid. The sulfone XVII obtained from thiocyanopyrrole proved to be identical with 2-methylsulfonylpyrrole (XIV) (melting point, mixture melting point, infrared, and n.m.r. spectra).

These results provide chemical evidence that thiocyanation of pyrrole does occur in the α-position and that the previously reported monothiocyanopyrrole[3,5] is, indeed, 2-thiocyanopyrrole (VII).

Experimental[13]

Diethyl 2-Thiocyanopyrrole-3,4-dicarboxylate (X).—A solution of thiocyanogen chloride[9] was prepared by adding potassium thiocyanate (2.95 g., 30.4 mmoles) in one portion to a solution of chlorine (2.13 g., 30.0 mmoles) in 170 ml. of acetic acid which had previously been dried by refluxing with a few milliliters of acetic anhydride. The resulting solution was stirred for 0.5 hr. at room temperature. Diethyl 3,4-pyrroledicarboxylate, prepared according to Kornfeld and Jones,[8] was added in one portion to the solution of thiocyanogen chloride and the reaction mixture was stirred at room temperature for 16 hr.

The yellow solution containing dispersed potassium chloride was poured into 600 ml. of cold water, whereupon a yellow solid formed. The mixture was allowed to stand in the refrigerator for 45 min., after which it was filtered, washed with cold water, and the yellow solid allowed to air dry. The crude product weighed 6.1 g. (82%), m.p. 140.5–142.5°. An analytical sample was prepared by three recrystallizations from 95% ethanol, m.p. 144–145°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44. Found: C, 49.25; H, 4.34; N, 10.53.

Diethyl 2-Methylthiopyrrole-3,4-dicarboxylate (XI).—A solution of diethyl 2-thiocyanopyrrole-3,4-dicarboxylate (X) (3.0 g., 11.2 mmoles) and methyl iodide (2.0 g., 14.0 mmoles) in 35 ml. of methanol was cooled in an ice bath. To the stirred solution was added in one portion a solution of potassium hydroxide (0.7 g., 12.5 mmoles) in 20 ml. of water and 10 ml. of methanol. The reaction mixture was stirred for 4 hr. during which time it was allowed to warm to room temperature. Most of the methanol was removed under vacuum on the steam bath. The yellow oil, which formed in the aqueous phase, was extracted with four portions of methylene chloride and the combined extracts were dried over magnesium sulfate. After filtration, the solvent was evaporated on the steam bath to yield a yellow oil. This oil solidified upon cooling 1 hr. in the refrigerator; 2.6 g. (90%), m.p. 86–92°. Recrystallization from benzene–low boiling petroleum ether (b.p. 30–60°) yielded crystals melting at 94–96°.

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.23; H, 5.80; N, 5.27.

Diethyl 2-Methylsulfonylpyrrole-3,4-dicarboxylate (XII).—Diethyl 2-methylthiopyrrole-3,4-dicarboxylate (XI) (1.2 g., 4.67 mmoles) was dissolved in 8 ml. of glacial acetic acid. To this solution was added 6 ml. of 30% hydrogen peroxide. The resulting solution was refluxed for 1 hr. and then allowed to cool and stand at room temperature for 16 hr. The reaction mixture was partially neutralized with 7 *N* ammonium hydroxide until crystals formed, after which it was cooled for 1 hr. in an ice bath. The crystals were filtered, washed with water, and dried overnight in a vacuum desiccator over phosphorus pentoxide to yield 1.0 g. of white needles (74%), m.p. 122–125°. An analytical sample was prepared by recrystallizing three times from ethanol–water, m.p. 125–127°.

Anal. Calcd. for $C_{11}H_{15}NO_6S$: C, 45.65; H, 5.22; N, 4.84. Found: C, 45.71; H, 5.24; N, 4.73.

2-Methylsulfonylpyrrole-3,4-dicarboxylic Acid (XIII).—A solution of diethyl 2-methylsulfonylpyrrole-3,4-dicarboxylate (0.8 g., 2.8 mmoles) and potassium hydroxide (0.6 g., 15 mmoles) in 9 ml. of water and 9 ml. of ethanol was refluxed for 2 hr. The reaction mixture was cooled to room temperature and concentrated to about half under vacuum. The reaction mixture was made slightly acidic with concentrated hydrochloric acid, and a white solid formed. The reaction mixture was cooled in an ice bath, filtered, washed with water, and the solid air-dried. The crude product (0.5 g., 78%) was recrystallized from water, m.p. 282–284° dec.

Anal. Calcd. for $C_7H_7NO_6S$: C, 36.04; H, 3.03; N, 6.01. Found: C, 36.29; H, 3.08; N, 5.94.

2-Methylsulfonylpyrrole (XIV).—2-Methylsulfonylpyrrole-3,4-dicarboxylic acid (0.137 g., 0.59 mmole) in 1 ml. of 2-aminoethanol was heated at reflux for 15 min. The yellow reaction mixture was cooled and poured into 10 ml. of water. The clear aqueous solution was acidified with concentrated hydrochloric acid and extracted with four portions of methylene chloride. The combined methylene chloride extracts were washed once with 10% sodium bicarbonate, twice with water, and dried over magnesium sulfate. After filtration, the solvent was removed on a steam bath. There was obtained 45 mg. (53%) of light yellow needles, m.p. 121–123°. An analytical sample was prepared by recrystallizing twice from a methylene chloride–low boiling petroleum ether (b.p. 30–60°) solvent pair, m.p. 122–123°.

Anal. Calcd. for $C_5H_7NO_2S$: C, 41.36; H, 4.86; N, 9.65. Found: C, 41.19; H, 4.80; N, 9.76.

2-Methylsulfinylpyrrole (XVI). Method A.—Freshly distilled 2-methylthiopyrrole (1.5 g., 13.3 mmoles), prepared from pyrrole according to the method of Matteson and Snyder,[5] was dissolved in 3 ml. of acetone. To this solution was added dropwise a solution of 2 ml. of 30% hydrogen peroxide and 3 ml. of acetone. The temperature rose and the reaction mixture turned a rose color within minutes after addition of the hydrogen peroxide solution. The reaction mixture was allowed to stand at room temperature for 72 hr. Most of the acetone was removed under vacuum. The brown liquid that remained was taken up in methylene chloride; water was added and the layers were separated. The aqueous phase was extracted again with methylene

(12) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **73**, 2251 (1951).

(13) Melting points are uncorrected. The spectra were determined by Mr. D. H. Johnson and his associates. The microanalyses were performed by Mr. Josef Nemeth and his associates.

chloride. The combined extracts were dried over magnesium sulfate. After filtration and removal of the solvent on the steam bath, there was obtained 1.26 g. (73%) of an orange liquid which crystallized upon standing in the refrigerator for 2 hr., m.p. 83–88°. Infrared and n.m.r. spectra showed the product to contain less than 5% of the sulfone. An analytical sample was prepared by chromatography on a short column of neutral alumina, eluting with methylene chloride. The clear liquid obtained crystallized upon standing in the refrigerator and the solid was recrystallized three times by dissolving in methylene chloride and adding low boiling petroleum ether (b.p. 30–60°) almost to the cloud point, m.p. 88.5–90°.

Anal. Calcd. for C_5H_7NOS: C, 46.47; H, 5.46; B, 10.84. Found: C, 46.78; H, 5.47; N, 10.67.

Method B.—Freshly distilled 2-methylthiopyrrole[4] (3.0 g., 26.6 mmoles) was dissolved in 3 ml. of acetic acid. Water was added until the solution became cloudy. The mixture was stirred magnetically and cooled in an ice bath, whereupon more solid formed. To this heterogeneous mixture was added 4 ml. of 30% hydrogen peroxide at such a rate as to maintain the temperature between 10–14°. The reaction mixture became homogeneous shortly after addition of the hydrogen peroxide; it was then allowed to warm to room temperature and was stirred for 13 hr. The reaction mixture was made slightly basic with 50% potassium hydroxide, extracted with four portions of methylene chloride, and the combined extracts were dried over magnesium sulfate. After removal of the drying agent and solvent, there was obtained 3.14 g. (81%) of tan colored crystals, m.p. 73–83°. Two recrystallizations as described in method A gave product melting at 87–89°.

Reduction of 2-Methylsulfinylpyrrole (XVI) with Lithium Aluminum Hydride.[11]—To a suspension of lithium aluminum hydride (0.19 g., 5 mmoles) in 12 ml. of dry ether was added in portions a solution of 2-methylsulfinylpyrrole (XVI) (0.488 g., 3.78 mmoles) in 20 ml. of ether. After the addition, the reaction mixture was refluxed for 6 hr. The excess lithium aluminum hydride was destroyed with water and the aluminum salts were dissolved by the addition of 10% hydrochloric acid. The two layers were separated and the aqueous phase was extracted with three more portions of ether. The combined ether extracts were dried over magnesium sulfate. Filtration and evaporation of the solvent yielded a yellow liquid. Distillation of the liquid through a 24-cm. heated column gave a 50% yield of 2-methylthiopyrrole (XV), identified by comparison of the infrared spectrum with that of an authentic sample.

2-Methylsulfonylpyrrole (XVII).—A solution of 2-methylsulfinylpyrrole (0.122 g., 0.94 mmoles) and 30% hydrogen peroxide (0.4 ml., 4.0 mmoles) in 2 ml. of glacial acetic acid was allowed to stand at room temperature for 43 hr. Ten milliliters of water was added and the reaction mixture was extracted with three portions of methylene chloride. The combined methylene chloride extracts were washed once with 10% sodium bicarbonate solution and once with water, followed by drying over magnesium sulfate. The drying agent was filtered off and the solvent removed on a steam bath to yield 71 mg. (52%) of a light yellow solid, m.p. 115–119°. The solid recrystallized from benzene–low boiling petroleum ether (b.p. 30–60°), m.p. 121.5–123°. This compound proved to be identical with 2-methylsulfonylpyrrole (XIV) as shown by melting point, mixture melting point, and comparison of the infrared and n.m.r. spectra.

The Methylpyrroles. Synthesis and Characterization

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Convenient syntheses have been devised for all the C-methylpyrroles with the exception of 3-methylpyrrole. Lithium aluminum hydride reduction of a C-acyl to a C-alkyl group was the key step in most of the syntheses. Attempts to use this method for the preparation of N-methylpyrroles were unsuccessful because reduction of C-acyl-N-methylpyrroles stopped at the hydroxymethyl stage, regardless of whether the acyl group was at the 2- or the 3-position. 1,2-Dimethylpyrrole and 1,2,3,5-tetramethylpyrrole were prepared, however, by methylation of the potassium salts of the required C-methyl derivatives. Infrared, ultraviolet, and proton magnetic resonance spectra are tabulated for pyrrole and fourteen N- and C-methylpyrroles.

In the course of a general study of the behavior of indoles and pyrroles in acidic media,[1] an extensive series of methylpyrroles was required. Although these compounds have been known for many years, most of the reported synthetic routes are tedious to carry out and the compounds themselves have not been well characterized.[2] Exceptions are 2,5-dimethylpyrrole and its N-substituted derivatives which can be prepared with ease from 1,4-diketones and the appropriate amines.[1b]

The pyrroles studied in the course of this work are listed in Table II. Pyrrole, 1-methylpyrrole, 2,4-dimethylpyrrole, and pentamethylpyrrole were purchased. Ring closure of the appropriate 1,4-diketone, the method used to prepare 2,5-dimethyl- and 1,2,5-trimethylpyrrole,[1b] was used for the synthesis of 2,3,-4,5-tetramethylpyrrole. 1,2-Dimethyl- and 1,2,3,5-tetramethylpyrroles were prepared by N-methylation of the appropriate precursor. The other pyrroles were synthesized as described subsequently.

Profiting by the observations that carbonyl groups attached to positions 2 or 3 of the pyrrole ring can be reduced to hydrocarbon residues by lithium aluminum hydride,[3] we have devised relatively simple syntheses of only two or three steps for the remaining C-methylpyrroles, with the exception of 3-methylpyrrole. The methods are summarized in equations 1–6 and yields of products are given in Table I. Starting materials for the hydride reductions were prepared by methods in the literature as shown in the equations and cited in Table I. It should be noted that the conversion of a carbonyl group to an alkyl group is not new in the pyrrole series, Wolff–Kishner reductions having been used for many years for this purpose.[2,4] However, the present methods offer much greater freedom in the choice of starting materials.

(1) For leading references see: (a) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962); (b) E. B. Whippie, Y. Chiang, and R. L. Hinman, *ibid.*, **85**, 26 (1963); (c) Y. Chiang and E. B. Whipple, *ibid.*, **85**, 2763 (1963).

(2) For further discussion of this point and characterization of some of the higher alkylpyrroles, see P. S. Skell and G. P. Bean, *ibid.*, **84**, 4655 (1962).

(3) (a) A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952); (b) A. Treibs and H. Derra-Scherer, *ibid.*, **589**, 188 (1954); (c) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); (d) acyl groups at the 3-position of the indole nucleus also are reduced to the hydrocarbon residue [E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953)], but acyl groups at the 2-position are reduced only to the carbinol [E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959)].

(4) (a) H. Fischer and B. Walach, *Ann.*, **450**, 109 (1926); (b) J. W. Cornforth and M. E. Firth, *J. Chem. Soc.*, 1091 (1958); (c) F. P. Doyle, M. D. Mahta, G. S. Sach, and J. L. Pearson, *ibid.*, 4458 (1958).