and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* afforded 2.36 g. of a dark tar.

This tar was dissolved in the minimum amount of chloroform and introduced onto a column of neutral alumina. During elution with chloroform a broad yellow band, and above it a broad rust-colored band, developed on the column. The eluate collected before the yellow band reached the bottom of the column was concentrated *in vacuo* to give 0.658 g. of brown oil, which crystallized upon standing in the refrigerator. The yellow and rust-colored bands were eluted, and the eluates were concentrated to give brown oils which did not crystallize upon chilling. They were discarded.

The brown crystals were placed in a sublimator and heated to 110° (0.025 mm.). The product sublimed as oily white crystals, which weighed 0.268 g. (12%). Since a sample of this sublimate darkened when allowed to stand in the air at room temperature, the remainder was kept refrigerated. A portion of this sublimate was rinsed with several drops of ether in an attempt to remove the oily material. Then it was sublimed at 80° (0.025 mm.). As soon as the oily sublimate began to crystallize, the sublimation was interrupted and the cold finger was cleaned. Sublimation then was resumed at 80° (0.025 mm.). This fractional sublimation did not effect removal of the oily material. One additional sublimation at 100° (0.025 mm.) gave slightly oily white crystals, m.p. 107–117° with previous softening, which were submitted for analysis.

An infrared spectrum of the compound in a potassium bromide pellet had a band at 1638 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.35; H, 5.10; N, 5.53.

Preparation and Reactions of 5-Carbethoxythieno[3,2-*b*]pyrrole and Some of Its Derivatives[1,2]

WALTER W. GALE,[3] ALAN N. SCOTT, AND H. R. SNYDER

The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

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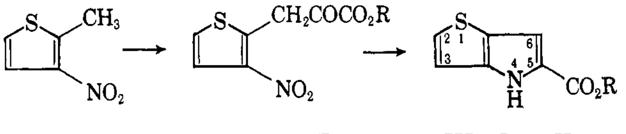
The preparation of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) is accomplished by condensation of 2-methyl-3-nitrothiophene (I) with diethyl oxalate followed by stannous chloride reduction of the product, ethyl 3-nitro-2-thienylpyruvate (IIb), in an over-all yield of 47%. A similar procedure gives rise to 2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIV) from 2-methyl-3-nitro-5-carbethoxythiophene (XII) in an over-all yield of 38%. Some typical electrophilic, aromatic reactions are carried out on these two thieno[3,2-*b*]pyrrole derivatives. Structures of the various substances are proposed on the basis of chemical and spectral data.

Although thieno[3,2-*b*]pyrrole and several of its derivatives have been synthesized,[4-9] there remained a need for additional synthetic pathways, and especially for routes leading to compounds having substituents of unambiguous orientation. In the earliest preparation of the parent heterocycle,[4] the pyruvic acid IIa was prepared *via* an azlactone in several steps from 2-methyl-3-nitrothiophene (I), since the condensation of I with diethyl oxalate was thought to be unsuccessful.[10] Compound IIa was then reduced to yield 5-carboxythieno[3,2-*b*]pyrrole (IIIa), which was decarboxylated thermally.[4]

The preparation of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) now has been accomplished by reaction of 2-methyl-3-nitrothiophene (I) and diethyl oxalate followed by reduction of the product, ethyl 3-nitro-2-thienylpyruvate (IIb), with stannous chloride. The over-all yield of this sequence was 47%. The structure of IIIb was confirmed by its hydrolysis to 5-carboxythieno[3,2-*b*]pyrrole (IIIa), a known compound,[4] with which it was identical in all respects. Nuclear magnetic resonance data for IIIb are shown in Table I. The coupling constant, $J_{2,3}$ = 5.3 c.p.s., is the same as that for N-benzylthieno[3,2-*b*]pyrrole.[11] The spectrum of IIIb exhibits a long-range splitting ($J_{3,6}$ = 0.7 c.p.s.), an effect which also has been observed in N-benzylthieno[3,2-*b*]pyrrole.[11]

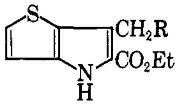


I

IIa, R = H
b, R = Et

IIIa, R = H
b, R = Et

When IIIb was treated with dimethylamine and formaldehyde, 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVa) was isolated in good yield.



IVa, R = $N(CH_3)_2$
b, R = $N(CH_2)_5$
c, R = H
d, R = CN

The structure of IVa was indicated by its n.m.r. spectrum, which contained two equally split doublets, J = 5.7 c.p.s., in the aromatic region. These were assigned to the thiophene protons. The reaction of piperidine, formaldehyde, and IIIb afforded the 6-piperidinomethyl compound IVb, which gave an n.m.r. spectrum similar in the aromatic region to that of IVa.

Chemical proof for the position of the aminomethyl group was obtained through the conversion of IVb in a modified Sommelet reaction[12] to 6-formyl-5-carbethoxythieno[3,2-*b*]pyrrole (V), from which, by treatment with

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[1] Abstracted from portions of the theses submitted by W. W. Gale (June, 1961) and A. N. Scott (June, 1964) to the Graduate College of the University of Illinois in partial fulfillment of the requirements for degrees of Doctor of Philosophy.

[2] This investigation was supported in part by a grant [3969 Bio] from the National Cancer Institute, U. S. Public Health Service.

[3] University Fellow, June–August, 1959; Phillips Petroleum Co. Fellow, 1959–1960.

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[10] L. A. Carpino, Thesis, Doctor of Philosophy, University of Illinois, 1953.

[11] R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

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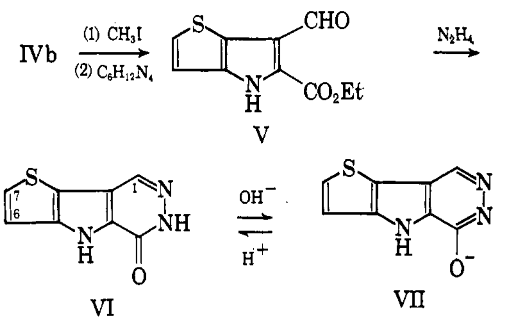
TABLE I

N.M.R. DATA[a]

Compound	Chemical shifts (δ) of aromatic protons, p.p.m.	Assignment of protons, ring position numbers	Couplings, c.p.s.
IIIb[b]	7.4	2	$J_{2,3} = 5.3$
	7.0	3	$J_{3,6} = 0.7$
	7.2	6	$J_{4,6} = 2.0$
IVa[c]	7.3	2	$J_{2,3} = 5.7$
	6.8	3	
IVb[c]	7.3	2	$J_{2,3} = 5.7$
	6.9	3	
IVc[d]	7.4	2	$J_{2,3} = 5.7$
	6.9	3	
IVd[d]	7.5	2	$J_{2,3} = 5.7$
	6.9	3	
V[e]	7.7	2	$J_{2,3} = 5.3$
	7.1	3	
VI[e]	8.6	1	$J_{6,7} = 5.3$
	7.3	6	
	7.8	7	
VIII[d]	7.2	2	. . .
IXa[d]	7.8	3	
	7.2	6	$J_{4,6} = 1.9$
IXb[d]	7.6	3	
	7.1	6	$J_{4,6} = 1.6$
IXc[d]	8.0	3	
	7.2	6	$J_{4,6} = 1.7$
XII[d]	7.7	3	
	7.2	6	$J_{4,6} = 1.6$
XIII[d]	7.8	3	. . .
XIV[d]	7.6	3	. . .

[a] Spectra obtained on Varian Associates spectrometers, Models V-4300-B or A-60, by Mr. O. W. Norton and Mr. D. H. Johnson. [b] 25% solution in acetone. [c] 20% in deuteriochloroform. [d] 20% in dimethyl sulfoxide. [e] 5% in dimethyl sulfoxide.

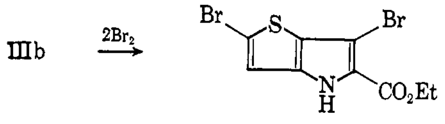
hydrazine under suitable conditions,[13] the pyridazinone VI was prepared. The formation of a new ring which joins positions 5 and 6 of thienopyrrole clearly establishes that aminomethylation of IIIb occurred in the pyrrole ring, in contrast to monoacylations (discussed below) in which the thiophene ring is attacked.



The pyridazinone VI, although ketonic in the solid state, dissolves reversibly in aqueous alkali to form the anion VII, which contains an aromatic pyridazine ring.

The methiodide of IVa could be reduced by sodium borohydride to give 6-methyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVc) in 64% yield. The n.m.r. spectrum of IVc was entirely consistent with the assigned structure. In addition, the methosulfate of IVa was used to alkylate potassium cyanide. The product, 6-cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVd) was isolated in only 17% yield.

When 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) was treated with 1 molar equiv. of bromine, a mixture of IIIb and a dibromo derivative of IIIb was obtained. All attempts to isolate a monobromo compound were unsuccessful even at temperatures below 0°. The dibromo compound, 2,6-dibromo-5-carbethoxythieno[3,2-*b*]pyrrole (VIII), was obtained in 96% yield when IIIb was treated with 2 molar equiv. of bromine. The n.m.r. spectrum of VIII contained one peak, a singlet, in the aromatic region. The absence of splitting in this peak indicated that position 6 had been substituted in VIII. The fact that VIII did not yield a Mannich base even at a temperature of 100° for a period of 2 weeks also furnished evidence that VIII was not the 2,3-disubstituted derivative. The 2,6- rather than the 3,6-dibromo structure was implied by the position of the aromatic singlet in the n.m.r. spectrum (Table I). A bromine atom in the 3-position of thiophene has been found to lower the magnetic field at which the 2-proton resonance appears.[14] The fact that the resonance of the aromatic proton in VIII appeared at a higher field than the resonance of the 2-proton in IIIb gave evidence that VIII was not the 3,6-disubstituted isomer.

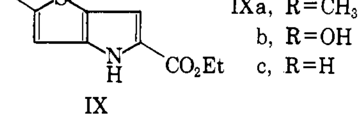


VIII

Under the same mild conditions which led to the dibromo derivative VIII, 3 molar equiv. of bromine afforded, 2,3,6-tribromo-5-carbethoxythieno[3,2-*b*]pyrrole. The n.m.r. spectrum of this compound contained no aromatic peaks.

The behavior of IIIb shows that positions 2 and 6 are similar in reactivity toward bromine, while position 3 is only slightly less reactive. From the Mannich reactions, in which the attacking electrophiles appear to be more selective, only the 6-aminomethyl compounds have been isolated.

The reaction of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) with acetyl chloride and aluminum chloride produced 2-acetyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXa) in 71% yield. The structure of IXa was indicated by its n.m.r. spectrum which contained a singlet at δ = 7.8 and a doublet at 7.2 p.p.m. The doublet had a coupling constant of 1.9 c.p.s. and was assigned to the 6-proton resonance. It is known that an acetyl group in the 2-position of thiophene greatly lowers the magnetic field at which resonance of the 3-proton appears.[14] Chemical proof for the position of the acetyl group was furnished by the oxidation of IXa to 2-carboxy-5-carbethoxythieno[3,2-*b*]pyrrole (Xb) with alkaline permanganate. The oxidation product was identical in all respects with an authentic sample of Xb prepared by the condensation of 2-methyl-3-nitro-5-thenoic acid followed by reductive cyclization.



IX

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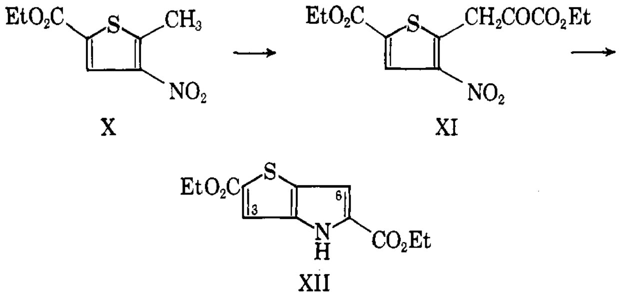
Direct formylation of IIIb also occurred at the 2-position; reaction of IIIb with phosphorus oxychloride and dimethylformamide furnished 2-formyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXc) in 66% yield. The 2-formyl compound gave infrared and n.m.r. spectra distinctly different from those of its 6-formyl isomer V. Through oxidation, the 2-formyl derivative was converted to the 2-carboxy compound IXb.

2,5-Dicarbethoxythieno[3,2-*b*]pyrrole (XII) was synthesized in essentially the same way as was IIIb. Condensation of 2-methyl-3-nitro-5-carbethoxythiophene (X) with diethyl oxalate afforded ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate (XI), which, when reduced with stannous chloride, gave XII. A doublet at $\delta = 7.2$ ($J = 1.6$ c.p.s.) and a singlet at 7.7 p.p.m. were assigned to the resonances of the 6- and 3-protons, respectively. The fact that XII could be synthesized in a manner similar to that of IIIb indicates the general utility of the method for the synthesis of substituted thieno[3,2-*b*]pyrrole derivatives.



Bromination of XII yielded a monobromo derivative even in the presence of excess bromine. The structure of the product was 6-bromo-2,5-dicarbethoxythieno-[3,2-*b*]pyrrole (XIII) on the basis of its n.m.r. spectrum, which showed one singlet in the aromatic region at $\delta =$ 7.8 p.p.m. This peak could only be due to the resonance of the 3-proton because of its position and lack of splitting.

When XII was treated with dimethylamine and formaldehyde, 6-dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIV) was isolated in 79% yield. The structure of XIV was indicated by its n.m.r. spectrum, which revealed a singlet at $\delta = 7.6$ p.p.m., too low in field for a 6-proton.

The formation of a 6-substituted product in the bromination of XII demonstrated the deactivating influence of a 2-carbethoxyl group on the 3-position. The fact that the Mannich reaction and the bromination of XII were carried out under identical conditions with those employed in the same reactions of 5-carbethoxythieno[3,2-*b*]pyrrole indicated that an electron-withdrawing group in the 2-position did not reduce the reactivity of the 6-position.

Experimental[15]

Ethyl 3-Nitro-2-thienylpyruvate (IIb).—This preparation was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 180 ml. of absolute ethanol, while 8.30 g. (0.36 g.-atom) of sodium metal was added. After the addition of the sodium was completed, the mixture was stirred and the ethanol was brought to gentle reflux. A solution of 22.8 g. (0.16 mole) of 2-methyl-3-nitrothiophene,[4] 72.0 g. (0.49 mole) of diethyl oxalate, and 180 ml. of absolute ethanol was added all at once to the gently refluxing solution of sodium ethoxide. Almost immediately there appeared a deep purple precipitate in the reaction mixture. The mixture was kept at reflux for 15 min. The reaction was quenched by the addition of the mixture to 2 l. of water which contained 75 ml. of concentrated hydrochloric acid, and a tan solid was precipitated. The tan solid was collected and dried in the air. The dried product was dissolved in boiling benzene, and the solution was treated with Darco and filtered while still hot. The filtrate was placed in the refrigerator overnight. The yellow crystals which had formed were collected and dried. The yield of ethyl 3-nitro-2-thienylpyruvate was 35.9 g. (93%), m.p. 101–102°. Two additional recrystallizations from methylcyclohexane afforded the analytical sample, m.p. 101.5–102°.

An infrared spectrum of a 10% chloroform solution of the compound indicated peaks at 3430 (enol hydroxyl), 1700 and a shoulder at 1730 (carbonyl absorptions), and 1350 and 1530 cm.$^{-1}$ (nitro group).

Anal. Calcd. for $C_9H_9NO_5S$: C, 44.44; H, 3.73; N, 5.76. Found: C, 44.61; H, 3.70; N, 5.59.

5-Carbethoxythieno[3,2-*b*]pyrrole (IIIb).—To a solution of 10.0 g. (0.04 mole) of ethyl 3-nitro-2-thienylpyruvate in 110 ml. of absolute ethanol was added slowly with stirring a solution containing 74 g. of stannous chloride dihydrate in 125 ml. of concentrated hydrochloric acid. During the addition, the temperature of the mixture was kept below 30° by means of external cooling. Initially much of the pyruvate precipitated. The mixture was stirred for 3 hr., during which time it became homogeneous and its temperature spontaneously rose to 35–40° owing to the heat of reaction, and then fell gradually. If the temperature exceeded 40°, a cooling bath was applied. By the end of the reaction period, the solution was red and usually homogeneous, but occasionally part of the product had crystallized. The acidic reaction mixture was extracted three times with chloroform. The combined chloroform extracts were washed successively with hydrochloric acid, water, and aqueous sodium chloride solution, and were dried over anhydrous sodium sulfate. Evaporation of the chloroform gave the crude thienopyrrole, which was purified by elution with benzene on a chromatographic column of acid washed alumina. The nearly white crystals thus obtained weighed 4.4 g. (55% yield), m.p. 122–130°. One recrystallization from cyclohexane–benzene afforded a product which melted 129–130.5°. An analytical sample was prepared by one recrystallization from methylcyclohexane, m.p. 132.5–133°.

An infrared spectrum (10% in chloroform) contained peaks at 3450 and 3300 (pyrrole NH, free and bonded), and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.26; H, 4.69; N, 7.13.

6-Dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVa).—To 3.5 ml. of glacial acetic acid were added 170 mg. (3.78 mmoles) of dimethylamine (as a 40% aqueous solution), 110 mg. (3.67 mmoles) of formaldehyde (as a 37% aqueous solution), and 700 mg. (3.59 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole. The temperature was kept between 0–5° while the components were added. The reaction mixture was heated on the steam bath for 1 hr. and then allowed to stand at room temperature for 12 hr. The mixture was poured onto 10 g. of ice, and it was brought to pH 10 by the careful addition of 10% sodium hydroxide. The temperature was not allowed to exceed 10° while the base was added. The gummy, white substance which precipitated could not be enticed to solidify; therefore, it was taken up in 50 ml. of ether. The ether solution was extracted with three 10-ml. portions of 10% hydrochloric acid. The hydrochloric acid extracts were combined and brought to pH 10 by the careful addition of 10% sodium hydroxide while the temperature was kept below 10°. The gummy, white substance which precipitated, solidified when stored in the refrigerator overnight. The solid was collected and dried in a vacuum desiccator for 36 hr. over phosphorus pentoxide. It was recrystallized from petroleum ether (30–60°) to yield 840 mg. (93%) of a white solid, m.p. 90–93°. The analytical sample was prepared by three recrystallizations from petroleum ether (30–60°) and was crushed in a mortar and dried in the air, m.p. 95–96°.

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1675 cm.$^{-1}$ (carbonyl absorption).

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(15) Melting points are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his associates, University of Illinois. Infrared spectra were obtained from a Perkin-Elmer Model 21 spectrophotometer by Mr. D. H. Johnson and associates.

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.37; H, 6.55; N, 10.82.

6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVb).—Piperidine (5.1 ml.), 37% aqueous formaldehyde (4.0 ml.), and 5-carbethoxythieno[3,2-*b*]pyrrole (10.0 g., 0.051 mole) were mixed in that order into 20 ml. of glacial acetic acid with cooling in an ice–water bath. The mixture was heated on a steam bath for 0.5 hr. and was allowed to stand at room temperature for 12 hr. After dilution with an equal volume of water, the mixture was extracted with ether to remove unchanged ester. The aqueous solution was brought to pH 8 by slow addition of excess potassium carbonate solution, during which the Mannich base separated as an oil or a white solid. The product was extracted into ether. After the ethereal solution was dried over sodium sulfate, most of the ether was evaporated. The residue was crystallized from hexane.

Another crystallization from cyclohexane afforded a first crop of 7.6 g., m.p. 126–136°, and a second crop of 1.0 g. From the ether extract of the acidic reaction mixture, 1.67 g. of unchanged ester was recovered. The yield of aminomethylated product, corrected for recovered ester, was 69%. Two recrystallizations of the product from petroleum ether (30–60°) afforded analytically pure 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 127.5–136°.

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1675 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{15}H_{20}N_2O_2S$: C, 61.61; H, 6.89; N, 9.58. Found: C, 61.43; H, 6.84; N, 9.57.

6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole Methiodide.—A solution of 540 mg. of 6-piperidinomethyl-5-carbethoxythienopyrrole in about 15 ml. of ether was added dropwise to 10 ml. of methyl iodide with stirring. The mixture was refrigerated for 24 hr. The solid was collected and washed with ether, yielding 803 mg. (96%), m.p. 175–183° dec.

6-Formyl-5-carbethoxythieno[3,2-*b*]pyrrole (V).—The methiodide salt of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (870 mg., 2.0 mmoles) was dissolved with warming in 8 ml. of propionic acid–water (2 to 1 by volume). The solution was cooled and 550 mg. of hexamethylenetetramine was added and dissolved with swirling. This solution was added over a 1-hr. period in an atmosphere of nitrogen to a boiling solution of 116 mg. of hexamethylenetetramine in 0.56 ml. of the same solvent. After the addition was complete, boiling was continued for 1.5 hr. under nitrogen. Then the light yellow solution was cooled and poured into 32 ml. of water. The solid product began to separate immediately. After the mixture had been stored in the refrigerator overnight, the solid was collected and washed with ice–water. The material weighed 270 mg. after drying *in vacuo* over potassium hydroxide. For purification the crude material was sublimed at 110–120° (10 μ), in a cold-finger sublimator and recrystallized from benzene-absolute ethanol. A yield over 50% of theoretical was obtained, m.p. 214–220° dec. An analytical sample was prepared by two recrystallizations from benzene-ethanol, m.p. 217–221° dec. The substance absorbed in the infrared (KBr pellet) at 1705 (ester carbonyl) and 1635 cm.$^{-1}$ (aldehyde carbonyl). The unpurified dinitrophenylhydrazone of the aldehyde ester melted at 306–309°.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.07; N, 6.27. Found: C, 53.54; H, 4.19; N, 6.53.

3H,4H,5H-Thieno[3′,2′:2,3]pyrrolo[4,5-*d*]pyridazin-4-one (VI).—The following procedure was similar to that of Suvorov, *et al.*,[13] for the conversion of 3-formyl-2-carbethoxyindole to the corresponding indolopyridazinone. 6-Formyl-5-carbethoxythieno-[3,2-*b*]pyrrole (68 mg.) was dissolved with warming in 6.5 ml. of redistilled ethyl cellosolve (b.p. 134–135°). A solution containing 0.20 ml. of 100% hydrazine hydrate in 0.68 ml. of ethyl cellosolve was also prepared. While the hydrazine solution was refluxed under nitrogen, the aldehyde solution was added dropwise during a 2-hr. period. The combined solution was boiled for 1 hr. more. About 4 ml. of solvent was removed by distillation. As the remaining solution slowly cooled, the product crystallized. After the mixture had been refrigerated for several hours, the product was collected and washed with ethyl cellosolve and with diethyl ether. The white, needle-like crystals of pyridazinone weighed 42 mg., decomposition above 300°. The material is poorly soluble in common organic solvents, but dissolves readily in alkali.

For purification the product was dissolved in warm 10% sodium hydroxide solution, filtered, and precipitated with excess dilute hydrochloric acid. The precipitate was washed with boiling acetone and with ether. The analytical sample thus prepared was slightly yellow, apparently owing to some decomposition of the compound while in anionic form. An infrared spectrum of a potassium bromide pellet of the compound revealed a carbonyl absorption at 1655 cm.$^{-1}$.

Anal. Calcd. for $C_8H_5N_3OS$: C, 50.25; H, 2.64. Found: C, 49.71; H, 2.60.

6-Methyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVc).—To 700 mg. (2.78 mmoles) of 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole was added 3 ml. of methyl iodide. The mixture was stoppered and allowed to stand at room temperature for 1 hr., and then the methyl iodide was removed. The resulting methiodide salt was dissolved in 10 ml. of absolute methanol. To this solution was carefully added 2.5 g. of sodium borohydride in small portions. After the addition of sodium borohydride was completed, the reaction mixture was diluted to a volume of 50 ml. by the addition of 3 *N* hydrochloric acid. The mixture was stored in the refrigerator overnight, and then the gray-blue precipitate which had formed was collected and dried. The precipitate was dissolved in boiling methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was stored in the refrigerator for several hours. The white crystals which had formed were collected and dried. The yield of 6-methyl-5-carbethoxythieno[3,2-*b*]pyrrole was 372 mg. (64%), m.p. 140–143.5°. Two additional recrystallizations from methylcyclohexane afforded the analytical sample, m.p. 144–145°. An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H), and 1685 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.49; H, 5.23; N, 6.75.

6-Cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (IVd).—The methosulfate salt prepared from 700 mg. (2.78 mmoles) of 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole was dissolved in 30 ml. of water which contained 490 mg. (10.0 mmoles) of potassium cyanide. The reaction mixture was stirred at room temperature for a period of 60 hr. Trimethylamine was evolved during the course of this reaction as indicated by a litmus test. At the end of 60 hr. a brown semisolid had precipitated. The reaction mixture was transferred to a separatory funnel and extracted several times with ethyl acetate. Only a small amount of the brown gum appeared to dissolve in this solvent. The ethyl acetate extracts were combined, dried over sodium sulfate, and filtered to remove the drying agent. The filtrate was concentrated to dryness on a rotary evaporator, and the residue was recrystallized from benzene–methylcyclohexane. Two additional recrystallizations from this solvent afforded 110 mg. (17%, based on 6-dimethylaminomethyl-5-carbethoxythieno[3,2-*b*]pyrrole) of analytically pure 6-cyanomethyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 133.4–133.8°.

An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H), 2245 (nitrile group), and 1670 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.44; H, 4.36; N, 11.60.

2,6-Dibromo-5-carbethoxythieno[3,2-*b*]pyrrole (VIII).—To a solution of 195 mg. (1.0 mmole) of 5-carbethoxythieno[3,2-*b*]-pyrrole in 30 ml. of chloroform was added 160 mg. (2.0 mmoles) of bromine. The solution was stirred for 2 hr. The evolution of hydrogen bromide was shown by a test with a piece of moistened litmus paper. At the end of 2 hr. the reaction mixture was evaporated to dryness on a rotary evaporator. A solid residue was obtained which was recrystallized once from an ethanol-water mixture to yield 339 mg. (96%) of 2,6-dibromo-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 160–162°. An analytical sample was prepared by sublimation of the once recrystallized material at 120° (0.05 mm.). The melting point of the analytical sample was 163.5°.

The infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_7Br_2NO_2S$: C, 30.62; H, 2.00; N, 3.97. Found: C, 30.49; H, 1.89; N, 3.77.

2,3,6-Tribromo-5-carbethoxythieno[3,2-*b*]pyrrole.—To a solution of 195 mg. (1.0 mmole) of 5-carbethoxythieno[3,2-*b*]pyrrole in 50 ml. of chloroform was added 240 mg. (3.0 mmoles) of bromine. The reaction mixture was stirred for 2 hr., and then the chloroform was removed on a rotary evaporator to yield an off-white solid. This solid was dissolved in boiling 95% ethanol, and the solution was treated with a small amount of Darco and filtered. The filtrate was allowed to cool in the refrigerator for several hours to yield 375 mg. (87%) of the tribromo compound, m.p. 198–204°. The analytical sample was prepared by sublimation of the once recrystallized material at 145° (0.05 mm.), m.p. 205.2–206.5°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3280 (pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_9H_6Br_3NO_2S$: *C, 25.08; H, 1.40; N, 3.25.* Found: C, 25.35; H, 1.51; N, 3.43.

2-Acetyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXa).—To a suspension of 1.068 g. (8.0 mmoles) of anhydrous aluminum chloride in 25 ml. of carbon disulfide was added slowly 627 mg. (8.0 mmoles) of acetyl chloride. The mixture which resulted was stirred while a solution of 780 mg. (4.0 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole in 60 ml. of carbon disulfide was added rapidly. A green color appeared almost immediately; and, after a short time, a black gum deposited on the bottom of the flask. After the mixture was stirred for 1 hr., the carbon disulfide was poured into 50 ml. of ice-cold 3 *N* hydrochloric acid. The black gum remained in the reaction flask. The carbon disulfide and acid mixture was transferred to a separatory funnel, and the aqueous layer was separated and discarded. The carbon disulfide layer was washed with 25 ml. of 10% sodium bicarbonate and subsequently with 25 ml. of water. The carbon disulfide layer was then collected and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated to dryness. *The residue weighed 43 mg., m.p. 158–162°.*

To the black gum was added 50 ml. of ice-cold 3 *N* hydrochloric acid. After the gum had been scratched for some time, it was completely converted into a yellow solid which was filtered. The yellow solid weighed 680 mg. after drying, m.p. 162–163°, and it was combined with the residue obtained from the carbon disulfide layer. Two recrystallizations of this material from benzene–petroleum ether (60–90°) afforded 670 mg. (71%) of analytically pure 2-acetyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 163–163.5°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H) and 1695 and 1650 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.87; H, 4.71; N, 6.01.

2-Carboxy-5-carbethoxythieno[3,2-*b*]pyrrole (IXb).—This reaction was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 30 ml. of absolute ethanol while 1.38 g. (0.06 mole) of sodium metal was added. *After the addition of the sodium was completed,* the sodium ethoxide solution was brought to reflux. A solution of 8.8 g. (0.06 mole) of diethyl oxalate, 5.00 g. (0.027 mole) of 2-methyl-3-nitro-5-thenoic acid, and 30 ml. of absolute ethanol was added to the sodium ethoxide solution. A deep purple precipitate formed almost immediately. The mixture was heated for 5 min., and 50 ml. of water was added to dissolve the precipitate and quench the reaction. After the solution was cooled, 13.9 g. of sodium hydrosulfite was added in portions of 2 g. while the temperature was kept below 60°. The mixture was stirred for 5 hr., and then the golden yellow solution was acidified to pH 1 by the careful addition of 6 *N* hydrochloric acid. The acidified solution was then extracted with several portions of ether. The ether extracts were combined and extracted several times with 10% sodium bicarbonate. Acidification of the combined bicarbonate extracts to pH 1 yielded a fine, yellow precipitate which was collected and dried. Three recrystallizations of this solid from an acetone–water mixture afforded the analytical sample. The yield of analytically pure 2-carboxy-5-carbethoxythieno[3,2-*b*]pyrrole was 765 mg. (12%), m.p. 278–280° dec.

An infrared spectrum of a potassium bromide pellet of the compound revealed peaks at 3250 (pyrrole N–H) and at 1690 and 1660 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.19; H, 3.79; N, 5.85. Found: C, 50.27; H, 3.95; N, 5.74.

2-Formyl-5-carbethoxythieno[3,2-*b*]pyrrole (IXc).—To 5 ml. of dimethylformamide was added slowly 1.534 g. (10.0 mmoles) of phosphorus oxychloride while the temperature was kept at 0°. To this mixture was added a solution of 975 mg. (5.0 mmoles) of 5-carbethoxythieno[3,2-*b*]pyrrole in 5 ml. of dimethylformamide which had been previously cooled to 0°. The reaction mixture was allowed to warm slowly, and it was stirred for 24 hr. while *the temperature was maintained between 40–50°.* At the end of this time the mixture was cherry red. It was then poured into a mixture of 50 g. of ice and 50 ml. of water. The solution which resulted was neutralized with 10% sodium hydroxide, and a tan precipitate was obtained. This tan solid was collected and dried in the air to a weight of 982 mg. It was then dissolved in approximately 3 ml. of chloroform and chromatographed on 50 g. of alumina with chloroform as the eluent. Two bands appeared after a short time: one, a brown band which did not appear to move; the other, a yellow band which moved quite rapidly. *The first fraction was colorless and yielded upon evaporation to* dryness 142 mg. of white crystals, m.p. 131–132°. A mixture melting point with 5-carbethoxythieno[3,2-*b*]pyrrole yielded no depression. The chromatography was carried out until the yellow band was completely removed. The fractions containing the yellow material were combined and evaporated to dryness to yield 710 mg. of a yellow solid, m.p. 174–178°. Two recrystallizations of this material from benzene afforded 623 mg. (66%, based on the amount of 5-carbethoxythieno[3,2-*b*]pyrrole consumed) of analytically pure 2-formyl-5-carbethoxythieno[3,2-*b*]pyrrole, m.p. 181–181.8°. An infrared spectrum of a potassium bromide pellet of the product revealed peaks at 3250 (pyrrole N–H), 2800 (aldehydic C–H stretch), and 1690 and 1660 cm.$^{-1}$ (carbonyl absorptions).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.07; N, 6.27. Found: C, 53.82; H, 4.16; N, 6.30.

5-Carboxythieno[3,2-*b*]pyrrole (IIIa).—A solution of 250 mg. of 5-carbethoxythieno[3,2-*b*]pyrrole, 15 ml. of 5% sodium hydroxide, and 5 ml. of 95% ethanol was refluxed for 12 hr. The light red solution was treated with Darco, filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. A gray solid was precipitated. The mixture was cooled in the refrigerator for several hours, and the solid was collected and dried. The crude material was dissolved in a boiling ethanol–water mixture, and the solution was treated with Darco and then filtered. The filtrate was placed in the refrigerator overnight, and the glistening white crystals which had formed were collected and dried. One additional recrystallization from ethanol–water afforded 129 mg. (60%) of 5-carboxythieno[3,2-*b*]pyrrole, m.p. 204–205° dec.

An infrared spectrum of a Nujol mull of the product revealed peaks at 3290 (pyrrole N–H) and 1690 cm.$^{-1}$ (carbonyl absorption).

2-Methyl-3-nitro-5-carbethoxythiophene (X).—To a solution of 37.4 g. (0.2 mole) of 2-methyl-3-nitro-5-thenoic acid[4] in 600 ml. of absolute ethanol was carefully added 35 ml. of concentrated sulfuric acid. The mixture was then heated at reflux for 18 hr. and allowed to cool. The reaction mixture was concentrated *in vacuo* to a volume of approximately 100 ml. The concentrated solution was brought to pH 8 by the careful addition of 10% sodium bicarbonate. The mixture was then transferred to a separatory funnel and was extracted with four 50-ml. portions of ether. The ether extracts were combined and washed with 100 ml. of 10% sodium bicarbonate. The ether layer was dried over sodium sulfate and then filtered to remove the drying agent. The filtrate was concentrated *in vacuo* to remove the solvent, and the residue was distilled at diminished pressure. The material which boiled between 120–130° (1.6 mm.) was collected. The yield of almost water-white liquid was 34.6 g. (81%). One additional distillation afforded the analytical sample, b.p. 122° (1.6 mm.).

An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 1550 and 1350 (nitro group) and 1710 cm.$^{-1}$ (carbonyl absorption).

Anal. Calcd. for $C_8H_9NO_4S$: C, 44.44; H, 4.20; N, 6.48. Found: C, 44.58; H, 4.06; N, 6.33.

Ethyl 5-Carbethoxy-3-nitro-2-thienylpyruvate (XI).—This preparation was carried out under strictly anhydrous conditions. A slow, steady stream of dry nitrogen was passed over 60 ml. of absolute ethanol while 2.08 g. (0.027 mole) of 2-methyl-3-nitro-5-carbethoxythiophene, 18 g. (0.122 mole) of diethyl oxalate, and 60 ml. of absolute ethanol was added all at once. Immediately, a deep red-brown color appeared. The solution was kept at reflux for 15 min., and then was added to 1 l. of water which contained 30 ml. of concentrated hydrochloric acid. A black, gummy material was deposited. This gum was converted to a red-brown solid when it was scratched. The solid was collected and air-dried. The crude material was then dissolved in 600 ml. of boiling methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was allowed to cool in the refrigerator for several hours. The yield of ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate was 7.44 g. (59%), m.p. 137–142°. Three additional recrystallizations from methylcyclohexane afforded the analytical sample, m.p. 142.8–143.7°. An infrared spectrum of a 10% chloroform solution of the product revealed peaks at 3400 (enolic O–H) and 1700–1725 cm.$^{-1}$ (broad, due to three carbonyl absorptions).

Anal. Calcd. for $C_{12}H_{13}NO_7S$: C, 45.71; H, 4.15; N, 4.44. Found: C, 45.58; H, 4.02; N, 4.23.

2,5-Dicarbethoxythieno[3,2-*b*]pyrrole (XII).—To a solution containing 18 g. of stannous chloride dihydrate, 150 ml. of 95% ethanol, and 50 ml. of concentrated hydrochloric acid was added 3.15 g. (0.01 mole) of ethyl 5-carbethoxy-3-nitro-2-thienylpyruvate. The mixture was stirred for 8 hr. while the temperature was kept between 40–50°. The deep red reaction mixture was placed in a dropping funnel and was slowly added to 150 ml. of 50% potassium hydroxide. The temperature of the strongly alkaline solution was not allowed to exceed 10°. After the addition was completed, the mixture which contained a yellow precipitate was extracted with several portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered to remove the drying agent. The solvent was removed from the filtrate to yield a solid residue. The residue was dissolved in a boiling methylcyclohexane–benzene mixture, and the solution was treated with Darco and filtered. The filtrate was allowed to cool in the refrigerator for several hours. The slightly yellow crystals which had precipitated were collected and dried. The yield of 2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 1.70 g. (64%), m.p. 156–158°. Two additional recrystallizations from benzene-methylcyclohexane afforded the analytical sample, m.p. 158.3–159°. An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3430 and 3280 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1680–1705 cm.$^{-1}$ (broad, carbonyl absorption).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.72; H, 4.81; N, 5.18.

6-Bromo-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIII).—To a solution of 267 mg. (1.0 mmole) of 2,5-dicarbethoxythieno[3,2-*b*]-pyrrole in 30 ml. of chloroform was added 160 mg. (2.0 mmoles) of bromine. At the end of 3 hr. the reaction mixture was concentrated to dryness on a rotary evaporator. A solid residue was obtained which was dissolved in a boiling mixture of methylcyclohexane–benzene, and the solution was treated with Darco and filtered. The filtrate was stored in the refrigerator overnight. The white crystals which had formed were collected and dried. The yield of 6-bromo-2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 306 mg. (88%), m.p. 178.7–179.8°. One additional recrystallization from benzene–methylcyclohexane afforded the analytical sample, m.p. 179.1–179.9°.

An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3450 and 3300 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1690–1705 cm.$^{-1}$ (broad, carbonyl absorption).

Anal. Calcd. for $C_{12}H_{12}NO_4S$: C, 41.63; H, 3.50; N, 4.05. Found: C, 41.32; H, 3.37; N, 3.86.

6-Dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole (XIV).—To 3.0 ml. of glacial acetic acid were added 85 mg. (1.89 mmoles) of dimethylamine (as a 40% aqueous solution) and 470 mg. (1.76 mmoles) of 2,5-dicarbethoxythieno[3,2-*b*]pyrrole. The temperature was kept between 0–5° while the components were added. The reaction mixture was heated on the steam bath for 1 hr. and then allowed to stand at room temperature for 12 hr. The mixture was poured into 25 ml. of ice–water, and the resulting solution was brought to pH 10 by the slow addition of 10% sodium hydroxide. The temperature was not allowed to exceed 10° while the base was added. The white solid which precipitated was filtered and washed freely with ice–water. The solid was dried *in vacuo* over anhydrous calcium sulfate for 24 hr. The yield of the crude Mannich base was 518 mg. (89%), m.p. 120–123°. The material was dissolved in a boiling mixture of benzene–methylcyclohexane, and the solution was treated with Darco and filtered. The filtrate was allowed to cool overnight in the refrigerator. The white crystals which had formed were collected and dried. The yield of 6-dimethylaminomethyl-2,5-dicarbethoxythieno[3,2-*b*]pyrrole was 460 mg. (79%), m.p. 124.3–124.9°. An analytical sample was prepared by one recrystallization from benzene–methylcyclohexane, m.p. 124.3–124.9°. An infrared spectrum of a 5% chloroform solution of the product revealed peaks at 3470 and 3330 (pyrrole N–H and hydrogen-bonded pyrrole N–H) and 1680–1720 cm.$^{-1}$ (broad, carbonyl absorptions).

Anal. Calcd. for $C_{15}H_{20}N_2O_4S$: C, 55.53; H, 6.21; N, 8.64. Found: C, 55.41; H, 6.20; N, 8.69.

Preparation and Reductive Cyclization of Some Carbon-Alkylated Derivatives of Ethyl 3-Nitro-2-thienylpyruvate[1]

ALAN N. SCOTT,[2] BERNARD E. HOOGENBOOM, AND H. R. SNYDER

The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

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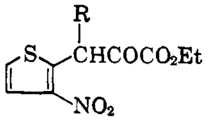
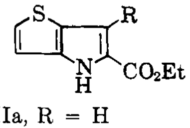
Alkylation reactions of the ambident anion of ethyl 3-nitro-2-thienylpyruvate were studied. The C-allyl and C-benzyl derivatives were prepared and converted in poor yields to the corresponding 6-alkylated 5-carbethoxythieno[3,2-*b*]pyrroles.

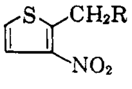
Condensation of 2-methyl-3-nitrothiophene (IIIa) with diethyl oxalate affords ethyl 3-nitro-2-thienylpyruvate (Ia), which can be reduced and cyclized to 5-carbethoxythieno[3,2-*b*]pyrrole (IIa).[3] In this paper we described the behavior of the pyruvic ester Ia toward certain alkylating agents; reductive cyclization of carbon-alkylated derivatives of Ia offers one route to 6-substituted 5-carbethoxythieno[3,2-*b*]pyrroles of type II. These studies were part of a program directed toward synthesis of 6-substituted thieno[3,2-*b*]pyrroles analogous to biologically active indole compounds.



Ia, R = H
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C_6H_5$
d, R = Br



IIa, R = H
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C_6H_5$



IIIa, R = H
b, R = CH_3
c, R = $CH_2C_6H_4NO_2$-*p*
d, R = CH_2CN
e, R = $CH_2CH{=}CH_2$

In the solid state and in fresh solutions the pyruvate Ia exists predominantly as the enol, as indicated by strong infrared peaks at 3400 cm.$^{-1}$ for the enolic hydroxyl absorption, and at 1700 cm.$^{-1}$ for the hydrogen-bonded ester carbonyl absorption. In the nuclear magnetic resonance (n.m.r.) spectrum of Ia in chloroform,

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[2] National Science Foundation Summer Fellow, 1962.

[3] W. W. Gale, A. N. Scott, and H. R. Snyder, *J. Org. Chem.*, **29**, 2160 (1964).