TABLE III
FIRST ABSORPTION BANDS AND pK_A FOR I AND II

Compd	pK_A	Solvent for spectroscopic measurement	First absorption band P_{max}, nm	Log ϵ
IIIb		95% EtOH	327	4.014
Ib	9.65	95% EtOH	345	4.021
		95% EtOH + excess OH^-	457	4.253
IIb	9.80	95% EtOH	375	3.754
		95% EtOH + excess OH^-	514	3.954
Ia	9.64	95% EtOH	352	3.928
		95% EtOH + excess OH^-	465	4.212
IIa	9.01	95% EtOH	390	3.697
		95% EtOH + excess OH^-	495	3.939

acidic than water.[7] These results show unequivocally that there must be strong π bonding between boron and nitrogen in compounds such as III, corresponding to significant participation by the dipolar resonance structures written above, as otherwise introduction of nitro groups would not have such a large effect on the Lewis acidity of the boron, nor would salt formation by addition to boron have such a large effect on the absorption spectrum. Introduction of a nitro group leads to cross conjugation, with consequent decreases in the π-electron density on boron and in the mesomeric stabilization of the boron-containing ring; both these effects should increase the Lewis acidity of boron. Likewise addition of base to boron removes it from conjugation with the adjacent imino nitrogen, thus greatly increasing the interaction of the latter with an *ortho* or *para* nitro group. It is true that the nitro group should also indirectly increase the acidity of the hydroxylic protons in Ia or IIa by making the boron atom more positive; the change in acidity of the proton should, however, be much less than that of boron, so it is not surprising that Ia and IIa behave as Lewis acids, while IIIa behaves as a protic one.

The conclusion that the B–N π bonds in compounds such as III must be strong is not surprising in view of clear evidence that such compounds are aromatic.[8]

In conclusion, it might be remarked that the color changes shown by these compounds on treatment with base are very marked and that they might therefore prove useful as indicators; the alkaline solutions of Ia and IIa in particular are quite stable, and the color change in the case of Ia is particularly intense.

(7) R. Dietz, Ph.D. Thesis, Queen Mary College, University of London, 1960.

Experimental Section

Compounds I and II were prepared by nitration of III, and of the analogous 10-methyl derivative, as described previously,[4] these in turn being obtained by the procedure of Dewar, Dewar, and Gaibel.[9]

The pK_A measurements were carried out spectrophotometrically by the method of Perkampus and Rossel.[10]

Registry No.—Ia, 15813-11-3; Ib, 15856-52-7; IIa, 15889-55-1; IIb, 15813-12-4; IIIb, 15813-13-5.

(8) See M. J. S. Dewar, *Prog. Boron Chem.*, **1**, 235 (1964).
(9) M. J. S. Dewar, R. B. K. Dewar, and Z. L. F. Gaibel, *Org. Syn.*, **46**, 65 (1966).
(10) H. H. Perkampus and T. Rossel, *Z. Electrochem.*, **60**, 1102 (1956).

The Synthesis of 6-Substituted Thieno[3,2-*b*]pyrroles[1,2]

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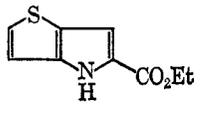
The synthetic pathway to 5-carbethoxythieno[3,2-*b*]pyrrole has been improved and a new product isolated from its reaction with formaldehyde and dimethylamine. Several 6-substituted 5-carbethoxythieno[3,2-*b*]pyrrole compounds have been hydrolyzed and decarboxylated under mild conditions to afford important intermediates for the preparation of thieno[3,2-*b*]pyrrole analogs of natural indole compounds.

In a recent paper, the preparations of 5-carbethoxythieno[3,2-*b*]pyrrole (I) and a number of its 6-substituted derivatives were reported.[4] In a continuing effort to prepare 6-substituted derivatives of thieno[3,2-*b*]pyrrole which would be analogous to naturally occurring 3-substituted indole compounds, a study of the hydrolysis and decarboxylation of several of these disubstituted thieno[3,2-*b*]pyrroles has been undertaken. Moreover, the synthetic pathway to I has been improved and a new product isolated from its reaction with formaldehyde and dimethylamine.



I

A key intermediate in the preparation of I and in the first synthesis of thieno[3,2-*b*]pyrrole[5] was 2-methyl-3-nitrothiophene (V) which was obtained in 16% over-all yield from 2,5-dibromothiophene. This same intermediate has also been prepared in 14% over-all yield from 2-methylthiophene (II) by successive chlorosulfonation, nitration, and dechlorosulfonation reactions.[6] By adapting the method of Siedel and Sturn[7] for the chlorosulfonation reaction and the method of Carpanelli and Leandri[8] for the nitration reaction, the latter process has been improved to give 2-methyl-3-nitrothiophene in

(1) Supported in part by a research grant (CA-8663) from the National Cancer Institute, U. S. Public Health Service.
(2) Abstracted in part from a thesis submitted by R. L. Keener to the Graduate College of the University of Illinois, Urbana, Ill., in partial fulfillment of requirements for the degree of Doctor of Philosophy, 1967.
(3) (a) National Science Foundation Summer Fellow, 1964; (b) Phillips Petroleum Co. Fellow, 1965–1966.
(4) W. W. Gale, A. N. Scott, and H. R. Snyder, *J. Org. Chem.*, **29**, 2160 (1964).
(5) H. R. Snyder, L. A. Carpino, F. Zack, Jr., and J. F. Mills, *J. Amer. Chem. Soc.*, **79**, 2556 (1957).
(6) C. Sone and Y. Matsuki, *Nippon Kagaku Zasshi*, **83**, 496 (1962).
(7) W. Siedel and K. Sturn, German Patent 1,088,509; *Chem. Abstr.*, **56**, 456*f* (1962).
(8) C. Carpanelli and G. Leandri, *Ann. Chim.* (Rome), **51**, 181 (1961).

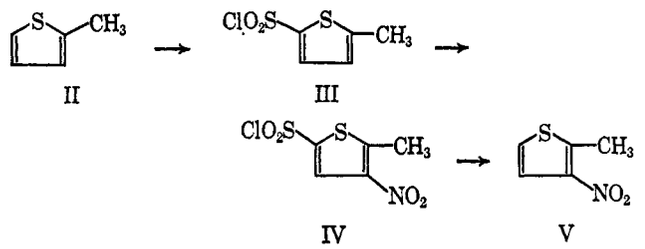
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compd	Aromatic protons[a,b] Chemical shift (δ), ppm	Ring position	Coupling constants, cps	Substituent protons[a,b] Chemical shift (δ), ppm	Assignment
XIII[c]	7.40 (d)	2	$J_{2,3}$ = 5.0	9.80	(—CHO)
	7.10 (d)	3	$J_{2,5}$ = 1.3		
	8.00	5			
XIV[d]	6.98 (d)	2	$J_{2,3}$ = 5.0	3.56	($CH_2N(CH_2)_5$)
	6.75 (d)	3	$J_{2,5}$ = 1.3		
	6.69	5		2.46 (m), 1.52 (m)	($CH_2N(CH_2)_5$)
XV[d]	6.95 (d)	2	$J_{2,3}$ = 5.0	3.48	($CH_2N(CH_3)_2$)
	6.76 (d)	3	$J_{2,5}$ = 1.3	2.26	($CH_2N(CH_3)_2$)
	6.72	5			
IX[d]	7.25 (d)		$J_{2,3}$ = 5.0	4.34 (q)	($CO_2CH_2CH_3$)
	6.80 (d)			1.35 (t)	($CO_2CH_2CH_3$)
				3.83	($CH_2N(CH_3)_2$)
				2.34	($CH_2N(CH_3)_2$)
XVI[d]	6.71	3	$J_{3,6}$ = 0.7	4.34 (q)	($CO_2CH_2CH_3$)
	7.08	6	$J_{4,6}$ = 1.9	1.36 (t)	($CO_2CH_2CH_3$)
				3.65	($CH_2N(CH_3)_2$)
				2.28	($CH_2N(CH_3)_2$)

[a] Spectra were determined on Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal reference. [b] Letters in parentheses refer to peak multiplicity: d, doublet; t, triple; q, quartet; m, unresolved multiplet. [c] 20% in dimethyl sulfoxide-d_6. [d] 10–20% in deuteriochloroform.

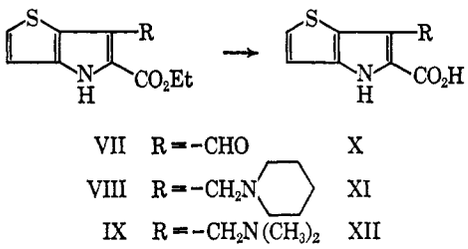
an over-all yield of approximately 50%. The chlorosulfonation and nitration reactions yielded 2-methylthiophene-5-sulfonyl chloride (III) and 2-methyl-3-nitrothiophene-5-sulfonyl chloride (IV) in yields of 63 and 91%, respectively.



II III IV V

A new product (VI) was obtained in 25% yield during the preparation of I and was subsequently converted in 70% yield into I by treatment with acid. Mass and nmr spectral data indicated that the new product was a dimer of I. The nmr spectrum of VI in dimethyl sulfoxide-d_6 (15%) exhibited three aromatic proton singlets at δ 6.60, 6.76, and 7.00. Although the last peak was found to be split by 0.8 cps when the aromatic region was expanded, the other two peaks could not be sufficiently resolved to observe fine splitting. Based on previously observed aromatic coupling constants for thieno[3,2-*b*]pyrroles,[9] the above data suggest that the dimer is formed by connection across the two thiophene rings and that the fully aromatized thienopyrrole portion of the dimer is unsubstituted at the 3 position.

Gale, Scott, and Snyder[4] obtained the Mannich bases VIII and IX from the reaction of I with formaldehyde and piperidine or dimethylamine, respectively, and converted the methiodide salt of VIII into the 6-formyl derivative VII in a modified Sommelet reaction.[4] Scott hydrolyzed VII to the carboxylic acid X but was unable to effect the decarboxylation of X or its anil derivative in hot dimethylaniline or 2-aminoethanol.[10]

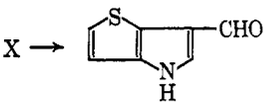


VII R = —CHO X

VIII R = —CH_2N(piperidine) XI

IX R = —$CH_2N(CH_3)_2$ XII

A number of substituted indole-2-carboxylic acids have been decarboxylated in good yield in recent years by heating the appropriate acid with a small amount of its copper salt in quinoline[11] or dimethylacetamide.[12] When X was heated with a small amount of its copper salt in a minimum volume of two parts tetramethylurea and one part dimethylacetamide, decarboxylation occurred smoothly to give thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII) in 60% yield. Less satisfactory yields of XIII were obtained if X was replaced by its *p*-chloroanil derivative, if either solvent was employed alone, or if the same two solvents were used in a 1:1 ratio.



XIII

The nmr spectrum (Table I) of XIII in dimethyl sulfoxide-d_6 was consistent with the structure assigned to XIII. This spectrum showed three proton signals in the aromatic region and the observed coupling constants, $J_{2,3}$ = 5.0 cps and $J_{2,5}$ = 1.3 cps, were similar to those previously reported for N-benzylthieno[3,2-*b*]-pyrrole.[9] The latter compound also exhibits a long-range coupling of approximately 0.7 cps between the 3 and 6 protons.[9]

The conversion of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (VIII) into acid XI was effected

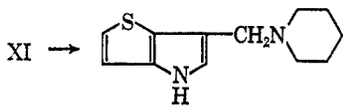
(9) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(10) A. N. Scott, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965.

(11) E. Piers and R. K. Brown, *Can. J. Chem.*, **40**, 561 (1961).

(12) G. Casini and L. Goodman, *ibid.*, **42**, 1235 (1964).

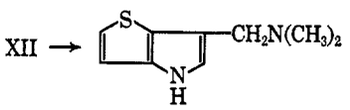
in 81% yield when VIII was heated in refluxing water for 12 hr. This acid (XI) underwent facile decarboxylation in a weakly acidic solution to afford 6-piperidinomethylthieno[3,2-b]pyrrole (XIV) in 77% yield. The



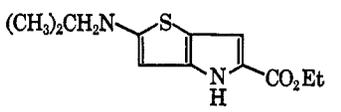
XIV

conversion of VIII into XIV was also accomplished in 58% over-all yield without isolation of the intermediate acid XI by acidifying the aqueous solution after hydrolysis and by heating the acidified solution to reflux until carbon dioxide evolution ceased. The hydrolysis of VIII also could be achieved by saponification with dilute sodium hydroxide in 50% aqueous ethanol. No decarboxylated product was obtained when XI was subjected to the same conditions of decarboxylation which afforded the maximum yield of the 6-formyl compound XIII. The structure of XIV was indicated by its nmr spectrum (Table I) in deuteriochloroform which showed three aromatic proton signals whose observed coupling constants $J_{2,3}$ = 5.0 cps and $J_{2,5}$ = 1.3 cps were also in agreement with those values previously reported for N-benzylthieno[3,2-b]pyrrole.[9]

Similarly, when chromatographically pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX) was heated in refluxing water for 6 hr and the solution subsequently acidified and refluxed until carbon dioxide evolution ceased, 6-diethylaminomethylthieno[3,2-b]-pyrrole (XV) was obtained in an over-all yield of 50%. The structure of XV was also indicated by its nmr spectrum (Table I) in deuteriochloroform which showed aromatic proton resonance and coupling constants almost identical with those found for XIV.



XV



XVI

When the crude product obtained from the reaction of I with formaldehyde and dimethylamine was recrystallized once from methylcyclohexane and then subjected to the same conditions of hydrolysis employed for the Mannich bases VIII and IX, a new product (XVI) was isolated in 70% yield. The nmr spectrum (Table I) of XVI in deuteriochloroform was similar to that reported[4] for IX except that the thiophene AB system of protons was replaced by singlets at δ 6.71 (β-thiophene proton) and at 7.08 (β-pyrrole proton). Moreover, the peak at δ 7.08 showed a primary coupling of 1.9 cps attributed to interaction between the 4 and 6 protons,[4,9] and a secondary coupling of 0.7 cps with the peak at 6.71; since the magnitude of the latter coupling has been shown to be characteristic of interaction between the 3- and 6-protons of thieno[3,2-b]-pyrroles,[9] XVI has been tentatively identified as 2-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole.

Both XVI and I were recovered in good yields when they were heated in refluxing water for 12–24 hr. Moreover, the fact that pure IX was converted into the acid XII rather than into XVI when it was heated in refluxing water indicates that XVI is not an artifact of IX. Indeed, both nmr spectral data and thin layer chromatography indicated that the once-recrystallized product from the preparation of IX was a mixture of IX and XVI. The former compound could be readily eluted from an acid-washed alumina column with an ethanolic benzene solution, but the latter compound could not be eluted from the column in a pure form. The above data suggest that the major product of the reaction of I with formaldehyde and dimethylamine is XVI rather than IX and that the major product of the reaction when piperidine is used in place of dimethylamine is VIII, as originally reported.[4]

The preceding hydrolysis studies also suggest, but do not establish, that the hydrolysis of the Mannich bases VIII and IX in water may be intramolecularly catalyzed, possibly by involvement of the tertiary nitrogen atom of these compounds. It has recently been reported, for example, that a tertiary nitrogen atom intramolecularly catalyzes the solvolysis of some ceveratrum alkaloid esters.[13]

Experimental Section[14]

2-Methylthiophene-5-sulfonyl Chloride (III).—To 88 ml of chlorosulfonic acid at 0–5° was added with stirring and in small portions 112 g of phosphorus pentachloride. The solution was warmed to 10° and maintained at 10–15° while 40 g of 2-methylthiophene was added dropwise to the stirred solution. After the addition was completed, the deep red solution was rapidly, but cautiously, poured onto 1 kg of ice with vigorous stirring.

This mixture was then extracted with two cold 500-ml portions of chloroform. The chloroform extracts were washed with 300 ml of water and dried over anhydrous sodium sulfate. The wash water was reextracted with 200 ml of chloroform and the organic layer combined with the original chloroform extracts. The chloroform was removed from the dried, filtered solution on a rotary evaporator to afford 72 g of a black tarry residue which was distilled *in vacuo*. There was obtained 50.4 g (63%) of 2-methylthiophene-5-sulfonyl chloride, bp 94–97° (0.6–0.7 mm) [lit.[6] bp 96–98° (0.5 mm)].

2-Methyl-3-nitrothiophene-5-sulfonyl Chloride (IV).—A solution of 15 ml of acetic anhydride and 20 ml of fuming nitric acid (sp gr, 1.5) was cooled to 0° and was maintained below 5° while a solution of 6 g of 2-methylthiophene-5-sulfonyl chloride in 15 ml of acetic anhydride was added dropwise with stirring. The solution was poured onto 50 g of crushed ice 45 min after the addition had been completed. The white crystalline solid was collected on a Büchner funnel and dried *in vacuo* over phosphorus pentoxide to yield 6.64 g (91%) of 2-methyl-3-nitrothiophene-5-sulfonyl chloride, mp 75–76° (lit.[6] mp 75.5–76°).

2-Methyl-3-nitrothiophene (V).—This compound was prepared from IV in 92% yield by the method of Sone and Matsuki.[6] The observed melting point was 44–45.5° (lit.[6] mp 75–76°).

$C_{18}H_{18}N_2O_4S_2$ (VI).—This substance was isolated as a major by-product in the preparation of 5-carbethoxythieno[3,2-b]pyrrole. A solution of 546 g of stannous chloride dihydrate in 922 ml of concentrated hydrochloric acid was added to a stirred solution of 74 g of ethyl 3-nitro-2-thienylpyruvate[4] in 800 ml of absolute ethanol. The addition took 4 hr and the reaction temperature

(13) S. M. Kupchan, S. P. Eriksen, and Y.-T. S. Liang, *J. Amer. Chem. Soc.*, **88**, 347 (1966).

(14) Melting points were determined on a Kofler heating stage apparatus and are uncorrected. Microanalyses were performed by Mr. J. Nemeth and his associates. Mass spectral determinations were made by Mr. J. Wrona on an Atlas Model CH 4 mass spectrometer. Infrared spectra were determined on a Perkin-Elmer Model 512 infrared spectrophotometer, and nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates Model A-60 nuclear magnetic resonance spectrometer by members of the Spectroscopy Laboratory of the University of Illinois.

was maintained below 30° during this time. After the addition was completed, the heterogeneous reaction mixture was stirred at room temperature for 12 hr. A tan precipitate was filtered from the reaction solution and dried over phosphorus pentoxide to yield 10.0 g of crude VI. The filtrate was extracted with a total of 2.5 l. of methylene chloride and the latter washed successively with 1.5 l. of 6 *N* HCl, 1.2 l. of water, and 1.2 l. of saturated sodium chloride solution. The methylene chloride extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to yield 41 g of a black residue. This residue and the original 10 g of precipitate were purified by chromatography on columns of acid-washed alumina. Initial elution of the columns with benzene afforded 23.9 g (50%) of pure 5-carbethoxythieno[3,2-*b*]pyrrole, mp 131–133° (lit.[4] mp 132–133°). Subsequent elution of the columns with chloroform yielded 11.8 g (25%) of the dimeric product VI. Recrystallization of this solid from 95% ethanol yielded VI as white needles, mp 191–192°. A mass spectrum of this solid run at low ionization voltage gave a parent ion peak at *m/e* 390. An infrared spectrum of the product in a potassium bromide disk showed broad carbonyl absorption centered at 1670 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.43; H, 4.65. Found: C, 55.27; H, 4.61.

Conversion of VI into 5-Carbethoxythieno[3,2-*b*]pyrrole (I).—A solution of 7.0 g of VI and 2.0 g of *p*-toluenesulfonic acid in 300 ml of toluene was refluxed for 3 hr under a nitrogen atmosphere. The dark red solution was cooled to room temperature, washed once with 10% sodium bicarbonate solution and twice with deionized water. The toluene layer was dried over anhydrous sodium sulfate, filtered onto a column of acid-washed alumina and the column eluted with benzene to afford 4.7 g (67%) of 5-carbethoxythieno[3,2-*b*]pyrrole, identified by the mixture melting point method and by thin layer chromatography.

The dimer (VI) was also converted into I in 64% yield by stirring a mixture of 5 g of the former, 750 ml of concentrated hydrochloric acid and 3 l. of absolute ethanol for 96 hr at room temperature. The product was obtained by extraction with methylene chloride and purified by chromatography on a column of acid-washed alumina using benzene as the eluting solvent.

6-Formyl-5-carboxythieno[3,2-*b*]pyrrole (X).—A heterogeneous solution containing 3.03 g of 6-formyl-5-carbethoxythieno[3,2-*b*]-pyrrole[4] in 61 ml of 10% aqueous sodium hydroxide was refluxed for 2 hr. The basic solution was cooled, filtered, and acidified with 3 *N* HCl to precipitate the product which was collected and washed with water. The yield of crude acid after drying *in vacuo* over phosphorus pentoxide was 2.11 g (80%). An analytical sample was prepared by one recrystallization from absolute ethanol, mp 218° dec (lit.[10] mp 220° dec).

Anal. Calcd for $C_8H_5NO_3S$: C, 49.22; H, 2.58; N, 7.18. Found: C, 49.27; H, 2.47; N, 6.86.

The *p*-chloroanil derivative of 6-formyl-5-carboxythieno[3,2-*b*]pyrrole (X) was prepared by adding a solution of 65 mg of *p*-chloroaniline in 5 ml of ethanol to a warm solution of 100 mg of X in 10 ml of absolute ethanol. The resulting solution was refluxed for 30 min, cooled in an ice bath and filtered, and the precipitate was collected and air dried. Recrystallization of this precipitate from absolute ethanol afforded 131 mg (84%) of the *p*-chloroanil derivative of X as yellow prisms, mp 220° dec.

Anal. Calcd for $C_{14}H_9N_2O_2SCl$: C, 55.18; H, 2.95; N, 9.20. Found: C. 55.21; H, 3.03; N, 8.90.

Thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII).—Dry nitrogen gas was passed through a solution of 5.2 ml of N,N-dimethylacetamide (DMA) and 10.4 ml of N,N,N′,N′-tetramethylurea (TMU) for 2 hr. Lines for admitting and exiting the nitrogen gas were attached to the top of the reflux condenser and the exit line was led to a saturated barium hydroxide solution. To the DMA and TMU in the reaction flask were added 2.1 g (13.9 mmol) of 6-formyl-5-carboxythieno[3,2-*b*]pyrrole (X) and 0.21 g of the copper salt of X, prepared in 89% yield by the method of Piers and Brown.[11]

The reaction mixture was heated at 190–200° until carbon dioxide evolution was complete (*ca.* 4 hr) and then cooled to room temperature. This mixture was poured onto 100 ml of crushed ice, heated to 70° on a steam bath, and filtered. The precipitate was saved, while the filtrate was cooled in an ice bath, acidified to pH 5 with 1 *N* HCl, and extracted with five volumes of diethyl ether. The ether was removed *in vacuo* and the residue triturated with a small amount of very dilute HCl solution. The solid which formed was collected, washed with cold water, and dried over phosphorus pentoxide *in vacuo* to afford 1.258 g (69%) of slightly impure thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII), mp 146–149°. Recrystallization of part of this material from water afforded 0.434 g of XIII as white prisms, mp 149–150°. Sublimation of the remainder of this material and of the original precipitate at 100° (0.05 mm) yielded an additional 0.545 g of XIII, mp 148–149°. The total yield of XIII was 0.924 g (60%). A sample of the product recrystallized from water showed aldehydic carbonyl absorption at 6135 cm^{-1} in its infrared spectrum (KBr disk) and was submitted for microanalysis.

Anal. Calcd for C_7H_5NOS: C, 55.61; H, 3.33. Found: C, 55.41; H, 3.25.

XIII was similarly prepared and isolated from a number of smaller scale reactions in which the amount of reactants and the amount and ratio of solvents were varied. In one series of experiments, in which all reaction conditions were identical except that the ratio of DMA/TMU employed was 1:0, 0:1, and 1:2 gave XIII in yields of 23, 22, and 37% respectively. The time required for complete decarboxylation in DMA was found to be approximately twice that required in pure TMU. Moreover, over the ranges of concentration examined, the yield of product was found to increase consistently as the total volume of solvent in these reactions was decreased.

An analogous series of studies on the *p*-chloroanil derivative of X consistently gave lower yields of XIII than those obtained from X, apparently because of greater difficulty in isolating the decarboxylated product in these experiments and converting it into XIII.

6-Piperidinomethyl-5-carboxythieno[3,2-*b*]pyrrole (XI).—A mixture of 5 g of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]-pyrrole (VIII)[4] and 1.8 l. of water was refluxed for 12 hr. The solution was cooled, filtered to remove a trace of solid, and evaporated to dryness *in vacuo*. Recrystallization of the residue from absolute ethanol afforded 3.6 g (81%) of 6-piperidinomethyl-5-carboxythieno[3,2-b]pyrrole as a tan granular solid, mp 218–220° dec. Carbonyl absorption appeared at 1600 cm^{-1} in the infrared spectrum of this product in a potassium bromide disk.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.59. Found: C, 58.58; H, 6.10; N, 10.16.

6-Piperidinomethylthieno[3,2-*b*]pyrrole (XIV). A. From 6-piperidinomethyl-5-carboxythieno[3,2-*b*]pyrrole (XI).—A solution of 2.00 g of XI in 50 ml of water was acidified to pH 5 with dilute HCl solution and refluxed under a nitrogen atmosphere until carbon dioxide evolution ceased (*ca.* 24 hr). During this period, dilute HCl solution was periodically added to the refluxing solution in order to maintain the pH at 4–5. Carbon dioxide evolution was followed by passing the exit gases through a saturated barium hydroxide solution.

After the reaction was complete, the solution was cooled to room temperature and made alkaline with 10% sodium hydroxide solution and the precipitate extracted into 250 ml of ether. The dried (over anhydrous sodium sulfate) extracts were concentrated *in vacuo* to yield a tan solid. This solid was recrystallized from methylcyclohexane and decolorized with Darco to afford 1.3 g (77%) of 6-piperidinomethylthieno[3,2-*b*]pyrrole (XIV) as white needles, mp 136–138°. The infrared spectrum (KBr disk) of this product showed no carbonyl absorption.

Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.90; H, 7.34; N, 12.44.

B. From 6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (VIII).—A mixture of 1.25 g of VIII and 400 ml of water was refluxed under nitrogen for 12 hr. The heterogeneous solution was filtered and the filtrate reduced to 20 ml *in vacuo*. The aqueous solution after another filtration was acidified with 1 *N* HCl to pH 3 and refluxed under a nitrogen atmosphere for 60 hr. The pH was periodically adjusted to a pH of 3–4 during this time by the addition of 1 *N* HCl. By using the isolation procedure described above in paragraph A, 0.548 g (58% based on VIII) of 6-piperidinomethylthieno[3,2-*b*]pyrrole was obtained. The product melted at 135–138° and its infrared spectrum was identical with that of the product obtained in the reaction described in paragraph A.

A 58% yield of XIV was also obtained in a similar run except that the hydrolysis was carried out by refluxing a solution of 0.584 g (2 mmol) of VIII and 0.200 g (5 mmol) of sodium hydroxide in 16 ml of 50% aqueous ethanol for 5 hr. The solution was reduced in volume to remove ethanol, diluted to 100 ml with water, and decarboxylated as described in the previous paragraph. An analytical sample of the product after two recrystallizations from methylcyclohexane melted at 138–140°.

Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.46; H, 7.18; N, 12.53.

6-Dimethylaminomethylthieno[3,2-b]pyrrole (XV).—A suspension of 0.750 g of chromatographically pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX),[4] mp 94–95°, in 500 ml of water was refluxed for 6 hr. Since no significant precipitate formed when this cloudy solution was cooled to 0°, the solution was concentrated to 100 ml, cooled to room temperature, and filtered. The light tan filtrate was acidified to pH 5 with 3 *N* HCl solution and subjected to the same conditions of decarboxylation used for XI. After the ether extracts had been dried over anhydrous sodium sulfate, the ether was removed *in vacuo* to leave 375 mg of crude product which was recrystallized from methylcyclohexane and decolorized with Darco to afford 270 mg (50%) of 6-dimethylaminomethylthieno[3,2-b]pyrrole as buff-colored prisms, mp 117–120°. An infrared spectrum (KBr disk) of this product showed no carbonyl absorption.

Anal. Calcd for $C_9H_{12}N_2S$: C, 59.86; H, 6.71; N, 15.53. Found: C, 60.21; H, 6.89; N, 15.30.

2-Dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (XVI).—The crude product obtained from the reaction of I with formaldehyde and dimethylamine by the method of Gale, Scott, and Snyder[4] was recrystallized once from methylcyclohexane. A 5.0-g sample of this material, mp 90–92°, was suspended in 1.8 l. of water and the aqueous mixture refluxed for 6 hr. When this solution was filtered hot to remove traces of solid and cooled to 0° in an ice bath, a white crystalline precipitate formed which was collected on a Büchner funnel and recrystallized from methylcyclohexane to afford 3.5 g (70%) of XVI as white needles, mp 132–133°. A mass spectrum of this product run at low ionization voltage showed a parent ion peak at *m/e* 252, as expected for an isomer of IX. An infrared spectrum of XVI in chloroform was similar to that of IX, but the two spectra were not superimposable.

Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.45; H, 6.51; N, 10.50.

When 200 mg of XVI was suspended in 100 ml of water and the resulting suspension was refluxed for 6 hr, the solution became homogeneous. Upon cooling of this solution to 0°, 194 mg (97%) of XVI, mp 131–133°, precipitated.

When 3.0 g of the once-recrystallized product from the preparation of IX was placed on a column of acid-washed alumina 28 cm in height and 3.5 cm in diameter and the column was eluted with a 50% ethanolic benzene solution, only 750 mg (25%) of pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX), mp 94–95°, was obtained. Subsequent elution of the column failed to yield any pure material.

Attempted Hydrolysis of 5-Carbethoxythieno[3,2-b]pyrrole (I).—A mixture of 0.292 g of 5-carbethoxythieno[3,2-b]pyrrole and 150 ml of water was refluxed for 24 hr. The solution was cooled to room temperature and extracted with an equal volume of diethyl ether. The ether extract was dried over anhydrous sodium sulfate and filtered, and the ether was removed on a rotary evaporator to yield 0.215 g (74%) of 5-carbethoxythieno-[3,2-b]pyrrole, mp 132–133° (lit.[4] mp 132.5–133°). The recovered material had the same R_f value as that of the starting material when compared by tlc.

Registry No.—VI, 15819-12-2; IX, 15811-13-9; X, 15811-14-0; X p-chloroanil derivative, 16315-46-1; XI, 15811-16-2; XIII, 15811-17-3; XIV, 15811-18-4; XV, 15811-19-5; XVI, 15811-20-8.

The Synthesis of Polycyclic Fused [1,2-a]Pyrroles

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The condensation of 2,5-dimethoxytetrahydrofuran with 2-amino-5-chlorobenzophenone and its two oxime forms afforded the 2-(1-pyrrolyl)benzophenone derivatives **4**, **5**, and **6**. These compounds were converted into the corresponding 2-substituted Mannich bases by treatment with formaldehyde and dimethylamine. Subsequent quaternization with methyl iodide followed by heating led to intramolecular condensations to give the pyrrolo[1,2-a]quinoline **8**, the pyrrolo[1,2-a]benzoxadiazocine **13**, and the pyrrolo[1,2-a]benzodiazepine **14**, respectively. Compound **6** with electrophiles in acid gave pyrrolo[1,2-a]quinazolines. Attempted formylation of **6** with dimethylformamide–phosphorus oxychloride yielded the pyrrolo[1,2-a]quinoxaline **21**.

The ready availability of *o*-aminobenzophenones[1] has, in the past few years, led to the synthesis of several heterocyclic systems. Thus, quinazolines,[2] benzodiazepines,[3] quinolones,[4] and indoles[5] have all been prepared from various *o*-aminobenzophenones.

As an extension of this work, and employing 2-amino-5-chlorobenzophenone **1** and its *syn*- and *anti*-oximes (**2** and **3**, respectively[6]) as starting materials, we wish to report a general synthetic approach for the preparation of derivatives of fused [1,2-a]pyrrolo quinolines, quinazolines, benzodiazepines, benzoxadiazocines, and quinoxalines.

Using the method of Clauson-Kaas for the synthesis of 1-substituted pyrroles,[7,8] compounds **1**, **2**, and **3** were treated with 2,5-dimethoxytetrahydrofuran to give the corresponding 2-(1-pyrrolyl)benzophenone derivatives **4**, **5**, and **6**, respectively (Scheme I).

The ketone **4** was then treated with formaldehyde and dimethylamine to give the corresponding Mannich base. This compound was not isolated, but alkylated with methyl iodide to give directly the quaternary salt **7** (Scheme II). When a solution of **7** in aqueous dimethylformamide was then treated with sodium cyanide, trimethylammonium iodide was displaced by cyanide ion and the carbonyl function underwent intramolecular cyclization to give the pyrrolo[1,2-a]-quinoline, compound **8**.

Similar treatment of the oximes **5** and **6** with formaldehyde and dimethylamine gave the Mannich bases **9** and **10**, respectively (Scheme III), which were also alkylated with methyl iodide to afford the corresponding quaternary salts **11** and **12**. When a solution of

(1) (a) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961); (b) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27**, 3781 (1962).

(2) (a) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960); (b) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

(3) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(4) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

(5) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

(6) The *syn* isomer is defined as that isomer in which the hydroxy group is *syn* to the phenyl ring bearing the 2-amino group. See, also, A. Stempel, I. Douvan, E. Reeder, and L. H. Sternbach, *ibid.*, **32**, 2417 (1967), footnote 7.

(7) (a) N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); (b) E. Elming and N. Clauson-Kaas, *ibid.*, **6**, 867 (1952).

(8) A. D. Josey and E. L. Jenner [*J. Org. Chem.*, **27**, 2466 (1962)] recognized the potential of this reaction in the synthesis of a pyrrolo[1,2-a]indole.