concentrated hydrochloric acid,[9] and 30 ml. of water was refluxed for 20 hr. The hot mixture was treated with charcoal and filtered. The cooled filtrate deposited 0.23 g. of benzoic acid, m.p. 121–122°.

**Treatment of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine with PPA. A. Ambient Temperature.**—A mixture of 3.0 g. of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine and 50 g. of PPA was allowed to stand, with occasional stirring, at room temperature for 24 hr. The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol to give 2.5 g. (83%) of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 97.5–101.5°.

B. At 65°.—The reaction was repeated as above, except that the mixture was heated at 65° for 1 hr. instead of being kept at 25° for 24 hr. There was obtained 0.66 g. (22%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine which melted at 141–142°, and 1.7 g. (57%) of the unchanged *cis* isomer, m.p. 100–101°.

**Acknowledgment.**—The authors express their appreciation to Drs. W. J. Potts and J. Heeschen for recording and interpreting infrared and n.m.r. data, respectively.

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[9] Sulfuric and hydrobromic acids gave benzoic acid as the only identified product.

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# Reactions of N-Benzylthieno[3,2-*b*]pyrrole. I. Metalation and an Electrophilic Substitution[1]

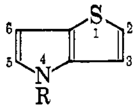
Edmund T. Holmes and H. R. Snyder

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

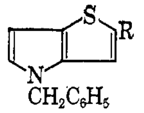
*Received January 20, 1964*

Treatment of N-benzylthieno[3,2-*b*]pyrrole (Ib) with a slight excess of *n*-butyllithium yielded the 2-lithium compound, IIa, which was converted to the 2-carbomethoxy derivative, IIb. The structure of IIb was shown by nuclear magnetic resonance spectroscopy and by unequivocal chemical evidence. The reaction of Ib with *n*-butyllithium in large excess, followed by carbonation and esterification, afforded a tricarbomethoxy derivative believed to be III. The action of acetyl chloride and stannic chloride on Ib in benzene at 0° led to the 5-acetyl derivative, VIII.

A practical synthesis of thieno[3,2-*b*]pyrrole (Ia) was developed by Matteson and Snyder,[2] but investigations of the chemistry of this compound were severely restricted by its instability. The stability of the ring system of Ia can be increased, however, by placing a benzyl group on the nitrogen atom, and the resulting compound, N-benzylthieno[3,2-*b*]pyrrole (Ib), has been prepared.[3] The chemistry of Ib has not been explored previously; its behavior toward *n*-butyllithium and under Friedel–Crafts acetylation conditions is now described.



Ia, R = H
b, R = $CH_2C_6H_5$



IIa, R = Li
b, R = $CO_2Me$

When N-benzylthieno[3,2-*b*]pyrrole (Ib) was allowed to react with *n*-butyllithium, 4-benzylthieno[3,2-*b*]-pyrrole-2-lithium (IIa) evidently was formed. The reaction of this lithium derivative with acetyl chloride at −78° led to uncharacterizable products, but carbonation of IIa followed by treatment with diazomethane afforded 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb) in 70% yield, based on Ib. The lithium compound IIa is the first derivative prepared by direct substitution of N-benzylthieno[3,2-*b*]pyrrole.

The structure of IIb was initially deduced from its nuclear magnetic resonance (n.m.r.) spectrum. The n.m.r. spectrum of N-benzylthieno[3,2-*b*]pyrrole (Ib) has been examined,[4] and the new data obtained in this work are tabulated in Table I.[5] Spin–spin interactions are observed between the α- and β-thiophene protons, and between the α- and β-pyrrole protons. In addition, long-range spin–spin couplings between the α-thiophene and α-pyrrole protons, and between the β-thiophene and β-pyrrole protons, are observed. The former interaction is large enough to be clearly visible, but the latter, being of a magnitude close to the limit of resolution of the instrument, hitherto has been observed only once.[4]

The n.m.r. spectrum of IIb showed a multiplet centered at τ 2.77 (benzene ring protons), a singlet at 4.85 (benzyl methylene protons), and a singlet at 6.19 (carbomethoxy protons). It also had doublets at τ 2.98 and 3.61 ($J$ = 3.0 c.p.s.), and a singlet at 2.47, each having an area corresponding to one proton. Because of the field strengths at which they appeared and the magnitude of their coupling constant, the doublets were assigned to the α- and β-pyrrole protons, respectively. The absence of evidence of interaction between an α-thiophene proton and the α-pyrrole proton indicated that the former proton was missing. The remaining singlet at τ 2.47 was therefore assigned to the β-thiophene proton.

The lowering of the field strength at which the β-thiophene proton in IIb absorbs is not surprising. Gale[6] noted a shift of 0.80 τ-unit to lower field in the position of absorption of the β-thiophene proton in going from 5-carbethoxythieno[3,2-*b*]pyrrole to 2,5-dicarbethoxy-

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[1] Supported by a grant (C 3969) from the U. S. Public Health Service.

[2] D. S. Matteson and H. R. Snyder, *J. Am. Chem. Soc.*, **79**, 3610 (1957); *J. Org. Chem.*, **22**, 1500 (1957).

[3] A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 1597 (1960).

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

[5] Proton magnetic resonance spectra were obtained by Mr. D. H. Johnson and his associates with a Varian Associates A-60 spectrometer. Tetramethylsilane was employed as an internal standard. Chemical shifts are expressed in τ-units as defined by G. V. D. Tiers [*ibid.*, **62**, 1151 (1958)].

[6] W. W. Gale, Thesis, Doctor of Philosophy, University of Illinois, Urbana, Ill., 1961.

TABLE I

N.M.R. DATA

| Compound | Chemical shift, $\tau$ (peak multiplicity),[a] and couplings, c.p.s. | Assignment |
|---|---|---|
| Ib[b] | 2.77 (m) | Benzene ring protons |
| | 3.01 (q) | $\alpha$-Thiophene proton |
| | 3.15 (q) | $\alpha$-Pyrrole proton |
| | 3.27 (d) | $\beta$-Thiophene proton |
| | 3.58 (d) | $\beta$-Pyrrole proton |
| | 4.87 (s) | Benzyl methylene protons |
| | $J_{2,3} = 5.3$ | |
| | $J_{5,6} = 3.0$ | |
| | $J_{2,5} = 1.0$ | |
| IIb | 2.47 (s) | $\beta$-Thiophene proton |
| | 2.77 (m) | Benzene ring protons |
| | 2.98 (d) | $\alpha$-Pyrrole proton |
| | 3.61 (d) | $\beta$-Pyrrole proton |
| | 4.85 (s) | Benzyl methylene protons |
| | 6.19 (s) | Carbomethoxy protons |
| | $J_{5,6} = 3.0$ | |
| III | 2.46 (s) | $\beta$-Thiophene proton |
| | 2.62 (s) | Benzene ring protons |
| | 2.67 (s) | $\beta$-Pyrrole proton |
| | 3.16 (s) | Benzyl methylene proton |
| | 6.12 (s) | Carbomethoxy protons |
| | 6.16 (s) | Carbomethoxy protons |
| | 6.21 (s) | Carbomethoxy protons |
| VI | 2.75 (m) | Benzene ring protons |
| | 3.29 (m) | 5-Pyrrole proton |
| | 3.80 (m) | 4-Pyrrole proton |
| | 3.97 (m) | 3-Pyrrole proton |
| | 4.89 (s) | Benzyl methylene protons |
| | 6.32 (s) | Carbomethoxy protons |
| | 7.2 (m) | Propionate methylene protons |
| | 7.4 (m) | |
| VIII | 2.79 (d) | $\alpha$-Thiophene proton |
| | 2.92 (m) | Benzene ring protons and $\beta$-pyrrole proton |
| | 3.29 (d) | $\beta$-Thiophene proton |
| | 4.34 (s) | Benzyl methylene protons |
| | 7.58 (s) | Acetyl group protons |
| | $J_{2,3} = 5.5$ | |

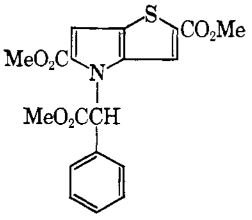
[a] s = singlet, d = doublet, q = quartet, m = multiplet. [b] The $\tau$-values and coupling constants tabulated here differ slightly from those previously reported.[4]

thieno[3,2-*b*]pyrrole. Gronowitz and Hoffman[7] have also noted the deshielding effect of a carbomethoxy group in the 2- or 3-position of thiophene on the adjacent ring proton.

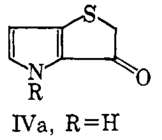
The metalation of Ib in the 2-position parallels the behavior of thiophene,[8] N-substituted pyrroles[9] and indoles,[10] and thianaphthene,[11] all of which undergo metalation $\alpha$ to the hetero atom. This general behavior of heterocycles toward organolithium reagents has been explained by a mechanism involving incipient coordination of the metal atom with an electron pair on the hetero atom, followed by abstraction of a proton from the carbon atom adjacent to the hetero atom by the organic portion of the reagent.[12,13] It is also possible that the $\alpha$-position is attacked merely because the electron-withdrawing effect of the hetero atom renders the $\alpha$-proton more acidic than its neighbors. If any 4-benzylthieno[3,2-*b*]pyrrole-5-lithium was formed, the corresponding carbonation product was apparently lost in the work-up. It appears, however, that metalation at the 2-position is favored, possibly because the anion resulting from abstraction of the 2-proton can be stabilized by p$\pi$–d$\pi$ interaction with the sulfur atom. No such stabilization of a 5-anion is possible.

In an attempt to prepare the dilithium derivative of N-benzylthieno[3,2-*b*]pyrrole, the latter substance was allowed to react with a severalfold excess of *n*-butyllithium. Upon carbonation of the resulting lithium derivative an acidic compound was obtained, which had a melting range higher than that of the acid derived from IIa. The new acid was treated with an excess of diazomethane to esterify all carboxyl groups present.

The n.m.r. spectrum of the esterified compound showed singlets, each having an area equivalent to one proton, at $\tau$ 2.46. 2.67, and 3.16. Other singlets were observed at $\tau$ 2.62 (five protons) and 6.12, 6.16, and 6.21 (each three protons). These last three peaks, of equal area and in almost the same position, indicate the presence of three carbomethoxy groups. By analogy with IIb, the peak at $\tau$ 2.46 is assigned to the $\beta$-thiophene proton. It was expected that the second lithium atom should enter the thienopyrrole nucleus in the 5-position, and that a carbomethoxy group in this position should deshield the $\beta$-pyrrole proton. The position of absorption of the $\beta$-thiophene proton was 0.80 $\tau$-unit lower in the spectrum of IIb than in that of Ib. If the peak at $\tau$ 2.67 is assigned to the $\beta$-pyrrole proton, it denotes a downfield shift of 0.91 $\tau$-unit from the corresponding position in the spectrum of Ib. The area of the peak at $\tau$ 2.62 indicates that the third carbomethoxy group is not located in the benzene ring. This conclusion is also suggested by the observation that *n*-butyllithium metalates benzene in only 5% yield.[14] The absence of a peak between $\tau$ 4 and 5 indicates that the benzyl methylene group has been attacked, and the peak at $\tau$ 3.16 is assigned to the remaining benzyl methylene proton. This interpretation is in accord with the observation that toluene is metalated (in very low yield, however) at the methyl group,[15] and with the postulated[12,13] initial coordination of the organometallic reagent at the hetero atom. The product is therefore designated as 4-($\alpha$-carbomethoxybenzyl)-2,5-dicarbomethoxythieno[3,2-*b*]pyrrole (III).



III



IVa, R=H

b, R=CH$_2$C$_6$H$_5$

The infrared spectrum of III revealed carbonyl absorption bands centered at 1750 cm.$^{-1}$ and 1700 cm.$^{-1}$,

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(7) S. Gronowitz and R. A. Hoffman, *Arkiv. Kemi*, **16**, 539 (1960), and references cited therein.

(8) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **71**, 1870 (1949).

(9) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

(10) D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).

(11) D. A. Shirley and M. D. Cameron, *ibid.*, **72**, 2788 (1950).

(12) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 261 (1954).

(13) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, p. 14.

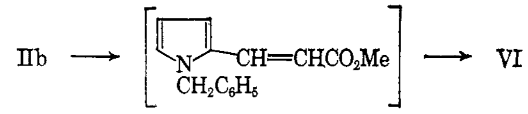
(14) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 265 (1954).

(15) H. Gilman, H. A. Pacevitz, and O. Baine, *J. Am. Chem. Soc.*, **62**, 1514 (1940).

indicating that there are carbomethoxy groups in more than one type of environment. The band at 1700 cm.$^{-1}$ is assigned to the groups in the 2- and 5-positions, by analogy with the corresponding absorptions in IIb (1695 cm.$^{-1}$) and in 2-carbethoxy- and 2,5-dicarbethoxythieno[3,2-*b*]pyrrole (each about 1690 cm.$^{-1}$).[6] The band at 1750 cm.$^{-1}$ is several wave numbers higher than the carbonyl absorption in methyl benzoate (1724 cm.$^{-1}$).[16]

In order to verify the interpretation of the n.m.r. spectrum of the 2-carbomethoxy derivative IIb, the structure of this compound was proved chemically. 2H,3H-Thieno[3,2-*b*]pyrrol-3-one (IVa) and its N-benzyl analog IVb have been desulfurized to give 2-acetylpyrrole[2] and 1-benzyl-2-acetylpyrrole,[3] respectively. The 2-carbomethoxy derivative IIb was desulfurized similarly to convert it to a suitable derivative of the known[17] compound, 1-benzyl-2-pyrrolepropionic acid (V). This derivative then was synthesized from N-benzylpyrrole by a route analogous to that employed by Kutcher and Klamerth[18] in the synthesis of 2-pyrrolepropionic acid.

Treatment of IIb with T-1 Raney nickel[19] gave an oil, which proved to be 1-benzyl-2-pyrrolepropionic acid methyl ester (VI), in 86% yield. The n.m.r. spectrum of VI showed a multiplet at $\tau$ 2.75 due to the benzene ring protons, a singlet at 4.89 due to the benzyl methylene protons, and a singlet at 6.32 due to the carbomethoxy protons. In addition, multiplets were observed at $\tau$ 3.29, 3.80, and 3.97; these were assigned to the 5-, 4-, and 3-protons, respectively, of the pyrrole ring. These absorptions were closely analogous in position and general shape to those of the corresponding protons in 2-methyl-[20,21] and 2-ethylpyrrole.[22] The spectrum also showed complex multiplets centered at $\tau$ 7.2 and 7.4, of the type which can arise from an $A_2B_2$ system in which the chemical shift ($\delta$) between the A and B protons is comparable to their coupling constant ($J_{AB}$).[23] The presence of these multiplets, which were assigned to the propionate methylene protons, indicated that the $\alpha,\beta$-unsaturated ester intermediate VII was smoothly hydrogenated by hydrogen present in the nickel catalyst. The infrared spectrum of the desulfurization product showed no N–H absorption, indicating that no catalytic hydrogenolysis of the benzyl group occurred, and no C=C absorption in the vicinity of 1600 cm.$^{-1}$, indicating that none of the intermediate VII survived.

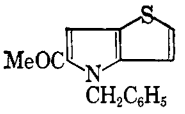


VII

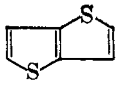
The procedure of Kutcher and Klamerth[18] was readily adapted to the synthesis of 1-benzyl-2-pyrrolepropionic acid methyl ester. N-Benzylpyrrole, prepared according to the method of Josey, Tuite, and Snyder,[3] was converted to 1-benzyl-2-formylpyrrole in 66% yield *via* the Vilsmeier formylation reaction. Treatment of the formyl compound with diethyl malonate and piperidine in refluxing absolute ethanol gave the condensation product, 2-(1-benzylpyrrolyl)methylenemalonic ester, which was subsequently hydrogenated at atmospheric pressure over Raney nickel. The hydrogenation product, 2-(1-benzylpyrrolylmethyl)-malonic ester, was saponified in methanolic potassium hydroxide. It was found that the diacid could be decarboxylated by heating above 140° under reduced pressure. The addition of copper–bronze powder did not appear to facilitate the decarboxylation. Much resinification occurred, and sublimation of the mixture proved to be the best method of isolating the 1-benzyl-2-pyrrolepropionic acid (V). The pure acid, obtained by resublimation, was converted to its methyl ester (VI) by treatment with diazomethane. The n.m.r. and infrared spectra of this ester were identical with those of the desulfurization product of 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb).

N-Benzylthieno[3,2-*b*]pyrrole (Ib) was exposed to several reagents in attempts to discover the position of attack by electrophiles. Treatment of Ib with bromine at temperatures as low as −60° produced a complex mixture of resinous substances. Several attempts to form the mono- and dinitro derivatives of Ib by treating it with cupric nitrate in acetic anhydride[24] met a similar fate. The reaction of ethyl diazoacetate and Ib led only to mixtures of Ib and one or more substitution products which could not be isolated or characterized.

The action of stannic chloride on a solution of Ib and acetyl chloride in benzene at 0° afforded an oily white crystalline material, which corresponded to a 12% yield of a monoacetyl derivative. The infrared spectrum of this material had a carbonyl absorption band at 1638 cm.$^{-1}$. Upon examination of its n.m.r. spectrum, the compound was designated as 4-benzyl-5-acetylthieno[3,2-*b*]pyrrole (VIII). The oil present in the product could not be removed, and it may represent a trace amount of a position isomer of VIII.



VIII



IX

The n.m.r. spectrum of VIII has a multiplet, centered at $\tau$ 2.92, having an area equivalent to at least six protons. Part of this absorption is undoubtedly due to the benzene ring protons. Singlets at $\tau$ 4.34 (two protons) and 7.58 (three protons) are assigned to the benzyl methylene protons and the acetyl group protons, respectively. The spectrum also shows doublets at $\tau$

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(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 179, 182.

(17) O. Cervinka, K. Pelz, and I. Jirkovsky, *Collection Czech. Chem. Commun.*, **26**, 3116 (1961).

(18) W. Kutcher and O. Klamerth, *Z. Physiol. Chem.*, **289**, 229 (1952).

(19) X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

(20) R. Abraham and H. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

(21) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv. Kemi*, **18**, 133 (1961).

(22) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum no. 130.

(23) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 89–95.

(24) For examples of the use of these reagents as a nitrating medium, see A. G. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953); H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **29**, 97 (1964).

2.79 and 3.29 ($J$ = 5.5 c.p.s.). Because of their position and the magnitude of their coupling constant, these doublets are assigned, respectively, to the $\alpha$- and $\beta$-thiophene protons. The doublet at $\tau$ 2.79 shows no further splitting, denoting no interaction between the $\alpha$-thiophene proton and an $\alpha$-pyrrole proton, and indicating that the acetyl group occupies the $\alpha$-pyrrole position. It is expected[7] that such an acetyl group would deshield the $\beta$-pyrrole proton. The absorption due to this proton, which appears at $\tau$ 3.58 in Ib, is probably obscured beneath the benzene ring multiplet. It is also noteworthy that the $\alpha$-thiophene proton of VIII absorbs at slightly lower field than that in Ib. In view of the interaction between the $\alpha$-thiophene and $\alpha$-pyrrole protons in Ib, it is not surprising that the deshielding effects of an electron-withdrawing group in the 5-position should manifest itself in the 2-position. Gronowitz and Hoffman[7] have observed that the 5-position in 2-acetylthiophene experiences this type of deshielding. The shifts of the absorption bands of the benzene ring protons and the benzyl methylene protons away from their usual values may also be a manifestation of the diamagnetic anisotropy of a carbonyl group in the 5-position. Comparison of the benzyl methylene proton bands of N-benzylpyrrole and N-benzyl-2-formylpyrrole, obtained during the synthesis of V, shows a downfield shift of 0.58 $\tau$-unit between the former compound and the latter.

When the portion of the spectrum of VIII between $\tau$ 2.0 and 3.5 was recorded at a sweep width of 100 c.p.s., the fine structure of the doublet centered $\tau$ 3.29 was observed. Each peak of this doublet was resolved into a doublet whose coupling constant was 0.6 c.p.s. Since these peaks are assigned to the $\beta$-thiophene proton, this fine structure is probably due to spin–spin coupling between the $\beta$-thiophene and $\beta$-pyrrole protons. Although this interaction is not normally visible in routine spectra of thienopyrrole derivatives, it has been shown to exist.[4]

The position of the carbonyl absorption band in the infrared spectrum of VIII cannot be used as supporting evidence for its structure. Although its frequency coincides exactly with that of 2-acetylpyrrole (1638 cm.$^{-1}$),[25] it is also very close to the value reported for the 2-acetyl carbonyl absorption in 3-acetoxy-2,4-diacetylthieno[3,2-*b*]pyrrole (1637 cm.$^{-1}$).[25]

In attempts to increase the yield of VIII, N-benzylthieno[3,2-*b*]pyrrole was treated with acetyl chloride and stannic chloride in carbon disulfide at −78°, with acetic anhydride and orthophosphoric acid at 60°, and with acetyl chloride and the nitromethane–aluminum chloride adduct in nitromethane at −30°. None of these experiments gave a crystalline product.

In view of the poor yield of VIII, no definitive statement on the relative reactivities of the various ring positions in Ib can be made. If any electrophilic substitution occurred at the 2-, 3-, or 6-positions of Ib, the products evidently were lost. Since the thieno[3,2-*b*] pyrrole nucleus is isosteric with indole, some substitution in the 6-position of IIb, which corresponds to the reactive 3-position of indole,[26] might be expected. However, the formation of VIII indicates that the behavior of Ib resembles that of thieno[3,2-*b*]thiophene (IX), which is known to undergo electrophilic substitution $\alpha$ to the hetero atom.[27]

## Experimental[28]

**Preparation of N-Benzylthieno[3,2-*b*]pyrrole (Ib).**—This compound was prepared by the method of Josey, Tuite, and Snyder.[3] When Ib was prepared in this way, its infrared spectrum revealed a weak band at 1650 cm.$^{-1}$, due to carbonyl absorption of unchanged 4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one. Even when the ketone, IVb, was swamped with nearly four times the amount of sodium borohydride previously used,[3] the carbonyl absorption was still visible. The N-benzylthieno[3,2-*b*]pyrrole was isolated as a brown oil which crystallized upon refrigeration and was used without further purification.

**Reaction of N-Benzylthieno[3,2-*b*]pyrrole (Ib) with *n*-Butyllithium.**—A pentane–heptane solution of *n*-butyllithium, obtained from the Foote Mineral Company, was employed. Its concentration was determined by titration according to the method of Gilman and Haubein.[29]

The N-benzylthieno[3,2-*b*]pyrrole was prepared and isolated as an oil in the usual manner.[3] This oil was dried over phosphorus pentoxide at room temperature (0.1 mm.) for 24 hr. The apparatus used was oven-dried, assembled while hot, and flushed with a stream of dry nitrogen as it cooled. The nitrogen atmosphere was maintained throughout the reaction.

To a solution of 1.45 g. (6.8 mmoles) of Ib in 80 ml. of anhydrous ether was added 8.4 mmoles of *n*-butyllithium in pentane–heptane solution (6.5 ml. of solution) dropwise with magnetic stirring at room temperature over a 30-min. period. The solution turned brown during this time. The solution was stirred at room temperature for 15 hr. longer, and then was poured onto an excess of Dry Ice under anhydrous ether. When the solid carbon dioxide had disappeared and the dark brown reaction mixture had warmed to room temperature, 70 ml. of water was added. The organic phase was separated and extracted with two 20-ml. portions of 2% aqueous sodium hydroxide. The aqueous solutions were combined, chilled in ice, and acidified with concentrated hydrochloric acid. When pH 4 was reached, a flocculent brown solid appeared. Acidification was continued until precipitation was complete. The crude 2-carboxy-4-benzylthieno[3,2-*b*]pyrrole weighed 1.52 g. (87%). A small portion of this acid was recrystallized twice from methanol–water, and recovered as tan microcrystals, m.p. 192–196° dec. An infrared spectrum of the recrystallized compound (in a potassium bromide pellet) revealed a broad band centered at 1670 cm.$^{-1}$ (carbonyl absorption).

The crude acid was suspended in 50 ml. of ether and treated with an ethereal solution of diazomethane, prepared from 1.5 g. of nitrosomethylurea.[30] Nitrogen evolution occurred as the diazomethane solution was added. The reaction mixture, which contained a finely divided tan solid, was allowed to stand at room temperature for several hours. The ether was then removed *in vacuo* to give 1.28 g. (80%, based on the crude acid) of crude 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIa). Four recrystallizations from cyclohexane afforded an analytical sample, m.p. 95–96°.

An infrared spectrum of the compound in a potassium bromide pellet had a peak at 1695 cm.$^{-1}$ (carbonyl absorption).

*Anal.* Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.38; H, 4.96; N, 4.80.

**Reaction of N-Benzylthieno[3,2-*b*]pyrrole (Ib) with Excess *n*-Butyllithium.**—The antimoisture precautions observed here were identical with those taken in the preparation of Ia. To a solution of 2.29 g. (10.7 mmoles) of Ib in 100 ml. of anhydrous ether under an atmosphere of dry nitrogen was added 42.9 mmoles of *n*-butyl-

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[25] R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Org. Chem.*, **82**, 4360 (1960).

[26] V. Schomaker and L. Pauling, *ibid.*, **61**, 1779 (1939).

[27] H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, p. 10.

[28] All melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his associates. Infrared spectra were determined by Mr. D. H. Johnson and his associates with a Perkin-Elmer Model 21 infrared spectrophotometer equipped with sodium chloride optics. Solvent evaporations carried out *in vacuo* were done with a rotary evaporator under water pump pressure.

[29] H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

[30] F. Arndt, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166.

lithium in a pentane–heptane solution dropwise with stirring over a 30-min. period. After the addition was completed, the dark brown reaction mixture was stirred for 14 hr. under the nitrogen atmosphere, then was poured onto an excess of Dry Ice under anhydrous ether. When the excess Dry Ice had sublimed and the mixture had warmed to room temperature, 20 ml. of water was added. The ether layer was removed and extracted with four 20-ml. portions of 2% aqueous sodium hydroxide. The aqueous extracts were added to the original water layer. The aqueous solution was chilled in an ice bath, and carefully acidified to pH 5 with hydrochloric acid, whereupon a dark tarry mass appeared. The solution was filtered, the tarry residue was discarded, and the filtrate was acidified further. At pH 4 a tan flocculent precipitate appeared. Acidification was continued until no more solid appeared upon addition of acid. The crude triacid weighed 2.51 g. (68%), and melted at 210–225° dec. An infrared spectrum of the crude acid in a potassium bromide pellet had a very broad band centered at 1685 cm.$^{-1}$ (carbonyl absorption).

To a suspension of 2.51 g. (7.27 mmoles) of the crude triacid in 150 ml. of ether was added an ethereal solution of diazomethane prepared from 3 g. of nitrosomethylurea.[30] The reaction mixture was stirred for 90 min., and the solvent was removed *in vacuo* to give 2.39 g. (85%) of 4-($\alpha$-carbomethoxybenzyl)-2,5-dicarbomethoxythieno[3,2-*b*]pyrrole (III). Two successive recrystallizations from 95% ethanol, followed by sublimation at 130° (0.04 mm.), afforded an analytical sample, m.p. 168.5–169.5°.

An infrared spectrum of a 10% solution of the compound in chloroform had a broad band centered at 1700 cm.$^{-1}$ and a narrower band at 1750 cm.$^{-1}$ (carbonyl absorptions).

*Anal.* Calcd. for $C_{19}H_{17}NO_6S$: C, 58.80; H, 4.43; N, 3.62. Found: C, 58.72; H, 4.40; N, 3.38.

**Desulfurization of 2-Carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb).**—Two hundred milligrams (0.74 mmole) of IIb was mixed with 2.0–2.5 g. of T-1 Raney nickel[19] in 25 ml. of 95% ethanol. The mixture was refluxed for 5 hr., allowed to cool, and the nickel was filtered and was washed with a little 95% ethanol which was added to the clear mother liquor. The ethanol then was removed *in vacuo* to give 154 mg. (86%) of methyl 1-benzyl-2-pyrrolepropionate (VI) as a clear yellow oil, which could not be induced to crystallize.

An infrared spectrum of a 10% solution of this oil in chloroform revealed a peak at 1730 cm.$^{-1}$ (carbonyl absorption).

**Preparation of 1-Benzyl-2-formylpyrrole.**—A 200-ml. three-necked round-bottom flask fitted with a magnetic stirrer, reflux condenser, and dropping funnel was placed in an ice bath and charged with 5.11 g. (0.0699 mole) of dimethylformamide. To this was added, with stirring over a 15-min. period, 10.74 g. (0.0699 mole) of phosphorus oxychloride. The ice bath was removed, and the phosphorus oxychloride–dimethylformamide complex was stirred for 15 min. The ice bath was replaced, and 15 ml. of ethylene dichloride was added to the complex. After the resulting solution had been allowed to chill, a solution of 10.0 g. (0.06 mole) of freshly distilled N-benzylpyrrole in 15 ml. of ethylene dichloride was added dropwise with stirring over a 1-hr. period. The ice bath was replaced with a heating mantle, and the orange solution was refluxed for 25 min. The solution was allowed to cool, and about 50 g. (0.37 mole) of sodium acetate trihydrate in 60 ml. of water was added. The orange mixture was stirred at room temperature for 80 min., then refluxed for 20 min. The cooled mixture was poured into a separatory funnel. The orange organic phase was separated and washed with two 7-ml. portions of a saturated sodium carbonate solution (the washings were alkaline). The ethylene dichloride solution was dried over anhydrous sodium carbonate and, after the filtered solution was concentrated *in vacuo*, 12.6 g. of a red oil was obtained.

The oil was distilled *in vacuo*. Only one fraction was collected, b.p. about 130° (0.9 mm.). The colorless distillate weighed 8.08 g. (69%). It was stored in a brown bottle in the refrigerator. An infrared spectrum of a 10% solution of the compound in chloroform had a peak at 1660 cm.$^{-1}$ (carbonyl absorption).

**Reaction of 1-Benzyl-2-formylpyrrole with Diethyl Malonate.**—A solution of 3.63 g. (0.0196 mole) of 1-benzyl-2-formylpyrrole, 3.2 g. (0.0200 mole) of diethyl malonate, and 0.1 ml. of piperidine in 10 ml. of absolute ethanol was refluxed for 14 hr. Upon cooling, white platelets precipitated from the yellow solution. These crystals were removed by filtration, and the mother liquor was concentrated *in vacuo*. Upon chilling, the concentrated solution yielded a small quantity of white platelets, which were combined with the first crop to give 3.92 g. (61%) of 2-(1-benzylpyrrolyl)methylenemalonic ester, m.p. 92–98°. This product was used without further purification.

An infrared spectrum of the compound in a potassium bromide pellet had a doublet with maxima at 1720 and 1700 cm.$^{-1}$ (carbonyl absorption), and a band at 1610 cm.$^{-1}$ (conjugated C═C absorption).

**Hydrogenation of 2-(1-Benzylpyrrolyl)methylenemalonic Ester.**—A suspension of 4 g. of T-1 Raney nickel[19] in about 20 ml. of 95% ethanol was placed in an atmospheric pressure hydrogenation apparatus, and to it was added 2.00 g. (0.0061 mole) of 2-(1-benzylpyrrolyl)methylenemalonic ester dissolved in the minimum amount of warm 95% ethanol. The resulting mixture was stirred under hydrogen for about 27 hr., or until hydrogen uptake was complete. The nickel then was removed by filtration and washed once with a little 95% ethanol which was added to the mother liquor. Removal of the solvent *in vacuo* afforded 1.76 g. (88%) of 2-(1-benzylpyrrolylmethyl)malonic ester as a clear oil, which was used without further purification.

An infrared spectrum of a film of this oil had a doublet with maxima at 1720 and 1710 cm.$^{-1}$ (carbonyl absorption). It showed no N–H stretching absorption, and only slight C═C stretch at 1600 cm.$^{-1}$.

**Saponification and Decarboxylation of 2-(1-Benzylpyrrolylmethyl)malonic Ester.**—A solution of 2.14 g. (0.0065 mole) of 2-(1-benzylpyrrolylmethyl)malonic ester in 25 ml. of 50% methanolic potassium hydroxide was refluxed 5 hr. After cooling, the reaction mixture was quenched with 20 ml. of water. The methanol was removed from the mixture *in vacuo* to give an aqueous suspension of fine white platelets. These platelets were collected and dissolved in the minimum amount of water, and the resulting solution was chilled in ice and carefully acidified to pH 4 with hydrochloric acid. At pH 5, the diacid began precipitating from the solution as fine white plates. The dried product weighed 1.14 g. (64%) and had m.p. 136–138° dec.

A mixture of 679 mg. (2.48 mmoles) of the diacid and a pinch of copper–bronze powder was heated under reduced pressure (laboratory vacuum line) at temperatures up to 160° for 90 min. Gas evolution was observed above 135°. The product, a black tarry material, was placed in a microsublimator and heated to 135° (0.11 mm.) for 18 hr. The monoacid sublimed as fine white needles which weighed 107 mg. The residue in the sublimator was heated to 195° (0.11 mm.) for 24 hr., affording an additional 47 mg. of pale yellow sublimate. The total yield of 1-benzyl-2-pyrrolepropionic acid (V) was 154 mg. (27%). A portion of the first crop of sublimed monoacid was placed in the microsublimator and heated to 100° (0.11 mm.) to give the analytical sample of fine white needles, m.p. 139–143°, lit.[17] m.p. 141–142°.

*Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.60; H, 6.77; N, 6.08.

To a suspension of 100 mg. (0.44 mmole) of 1-benzyl-2-pyrrolepropionic acid in 1 ml. of ether was added an ethereal solution of diazomethane until gas evolution ceased and the yellow diazomethane color persisted. Removal of the solvent *in vacuo* afforded 97 mg. (90%) of methyl 1-benzyl-2-pyrrolepropionate (VI) as a tan oil. The infrared and n.m.r. spectra of this oil were identical in every respect with those of the methyl 1-benzyl-2-pyrrolepropionate obtained by desulfurization of IIb.

**Preparation of 4-Benzyl-5-acetylthieno[3,2-*b*]pyrrole (VIII).**—A solution of 2.69 g. (0.0126 mole) of N-benzylthieno[3,2-*b*]pyrrole (Ib) and 0.990 g. (0.0126 mole) of acetyl chloride in 80 ml. of benzene was chilled to 0° in an ice bath. To this solution was added a solution of 3.28 g. (0.0126 mole) of stannic chloride in 20 ml. of benzene dropwise over a 30-min. period with manual swirling. As the first drops of stannic chloride solution were added, the reaction mixture became deep purple, and soon the addition product began to precipitate as a gummy purple solid. After the addition was completed, the reaction mixture was allowed to stand at room temperature for 1 hr. Then it was treated with a solution of 6 ml. of concentrated hydrochloric acid in 80 ml. of water. The resulting mixture was stirred for 18 hr., or until almost all of the purple gum had dissolved. During this period, 80 ml. of benzene was added. At the end of the 18-hr. period, methylene chloride was added to aid the dissolution of the remaining gum and to facilitate the separation of the aqueous and nonaqueous phases. The mixture was filtered to remove interfacial debris, and the dark red organic phase was separated 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.

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# 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

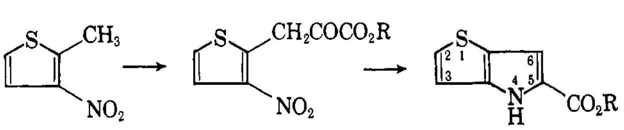
*The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois*

*Received March 10, 1964*

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]

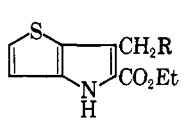
The preparation of 5-carbethoxythieno[3,2-*b*]pyrrole (IIIb) now has been accomplished by reaction of 2-methyl-3-nitrothiophene (I) and diethyl oxalate followed by reduction of the product, ethyl 3-nitro-2-thienylpyruvate (IIb), with stannous chloride. The over-all yield of this sequence was 47%. The 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 IIIa, R = H

b, R = Et 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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