The Chemistry of 4-Benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one. I. Reactions with N-Bromosuccinimide and with Aldimines[1]

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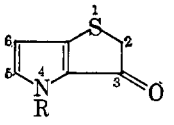
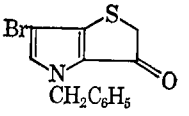
The reaction of the ketone Ib with 1 mole of N-bromosuccinimide affords the 6-bromo ketone II, whereas treatment of Ib with 2 moles of N-bromosuccinimide yields the 2,6-dibromo derivative IV. The action of benzaldehyde and base on II gives rise to 2-benzylidene-4-benzyl-6-bromo-2H,3H-thieno[3,2-*b*]pyrrol-3-one (III). Reaction of Ib with benzal-*t*-butylamine affords the 2-benzylidene compound VIIIb, and treatment of Ib with methylene-*t*-butylamine affords a mixture believed to form *via* the 2-methylene derivative VIIIa.

Reactions of 2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ia) have been studied in a search for useful methods of synthesis of substituted thieno[3,2-*b*]pyrroles.[2] The presence of a benzyl group on the nitrogen atom might be expected to change the course of certain substitution reactions. The synthesis of the N-benzyl ketone, 4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ib), has been reported,[3] but its reactions have not been examined previously. Its behavior toward N-bromosuccinimide (NBS) and toward some aldimines is now described.



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



II

Treatment of the ketone Ib with NBS in benzene at room temperature and in the absence of free-radical initiators gave a good yield of a monobromo derivative, which proved to be 4-benzyl-6-bromo-2H,3H-thieno-[3,2-*b*]pyrrol-3-one (II). Attempts to carry out the reaction under the usual conditions of the Wohl–Ziegler bromination (carbon tetrachloride solution, radical initiators, illumination) surprisingly gave no characterizable product.

The nuclear magnetic resonance (n.m.r.) spectrum[4] of II revealed a singlet at τ 2.66, having an area corresponding to five protons, and a singlet at τ 4.72 (two protons), which were assigned to the benzene ring protons and the benzyl methylene protons, respectively. In addition, there were singlets at τ 2.98 (one proton) and 6.02 (two protons) due to the α-pyrrole proton and the 2-protons, respectively. The positions of these peaks are all in good agreement with those of the corresponding absorptions in the unsubstituted ketone Ib (Table I). That the chemical shift of the α-pyrrole proton is not affected by the presence of the adjacent bromine atom is not surprising, for it has been shown that in the thiophene series the introduction of a bromine atom does not appreciably alter the chemical shifts of the adjacent protons.[5]

TABLE I

N.M.R. DATA

Compound	c,[a] %	τ-Value (peak multiplicity),[b] and coupling constant (J), c.p.s.	Assignment
Ib	20	2.70 (s)	Benzene
		2.97 (d)	α-Pyrrole
		3.93 (d)	β-Pyrrole
		4.72 (s)	Benzyl methylene
		6.06 (s)	C-2
		$J_{5,6}$ = 2.5	
II	20	2.66 (s)	Benzene
		2.98 (s)	α-Pyrrole
		4.72 (s)	Benzyl methylene
		6.02 (s)	C-2
III	12	2.5 (m)	Benzylidene group
		2.75 (s)	Benzene(benzyl group)
		3.14 (s)	α-Pyrrole
		4.72 (s)	Benzyl methylene
IV	15	2.63 (s)	Benzene
		2.87 (s)	α-Pyrrole
		4.28 (s)	C-2
		4.69 (s)	Benzyl methylene
VIIIb	20	2.51 (m)[c]	Benzylidene group
		2.72 (s)	Benzene (benzyl group)
		3.07 (d)	α-Pyrrole
		3.91 (d)	β-Pyrrole
		4.66 (s)	Benzyl methylene
		$J_{5,6}$ = 2.5	

[a] Concentration of compound in $CDCl_3$. [b] s = singlet, d = doublet, m = multiplet. [c] The multiplet due to benzylidene protons occurs at about τ 2.5 in the spectra of various derivatives of the *des*-benzyl compound, 2-benzylidene-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (J. W. Van Dyke, Jr., Thesis, Doctor of Philosophy, University of Illinois, 1962).

To seek chemical support for the structure II, a reaction which normally occurs in the 2-position of Ia and Ib was carried out. When II was treated with benzaldehyde and sodium hydroxide in refluxing 95% ethanol, 2-benzylidene-4-benzyl-6-bromo-2H,3H-thieno [3,2-*b*]pyrrol-3-one (III) was isolated in 24% yield. (The base-catalyzed condensation of Ib and benzaldehyde will be discussed again below.) The n.m.r. spectrum of III showed a multiplet centered at τ 2.5, upon which was superimposed a singlet at 2.75, due respectively to the protons of the benzylidene moiety and the benzene ring protons of the benzyl group. The only other peaks were singlets at τ 3.14 (α-pyrrole proton) and 4.72 (benzyl methylene protons).

Reaction of Ib with 2 moles of NBS gave 2,6-dibromo-4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IV), which was also prepared from the monobromo derivative II and 1 mole of NBS. The n.m.r. spectrum of IV showed singlets at τ 2.87 and 4.28, which were assigned to the

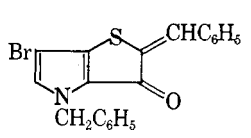
(1) Supported by a grant (C 3969) from the U. S. Public Health Service.

(2) J. W. Van Dyke, Jr., and H. R. Snyder, *J. Org. Chem.*, **27**, 3888 (1962); G. W. Michel and H. R. Snyder, *ibid.*, **27**, 2689 (1962), and references cited therein.

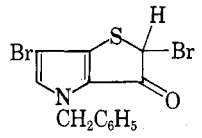
(3) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 1597 (1960).

(4) Proton magnetic resonance spectra were obtained by Mr. D. H. Johnson and his associates on 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, *J. Phys. Chem.*, **62**, 1151 (1958).

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



III



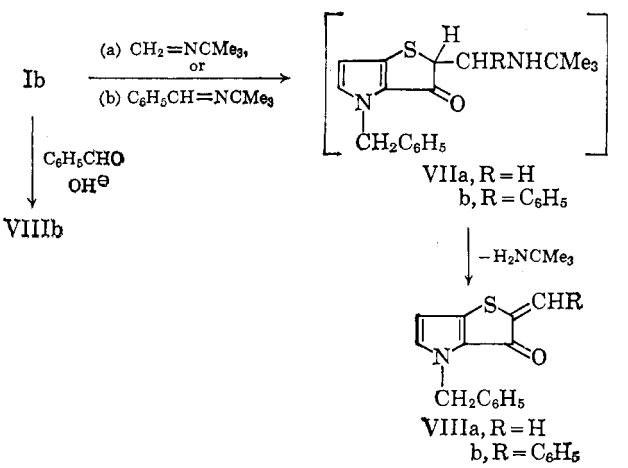
IV

α-pyrrole proton and the 2-proton, respectively. The absorptions due to the benzene ring protons and the benzyl methylene protons appeared in their usual places (Table I). The change in the chemical shift of the 2-proton is expected; the 2-bromine atom should lower the magnetic field strength at which the proton absorption appears.[6]

It is of interest to compare the behavior of Ib toward electrophilic reagents with that of 2-acetylpyrrole (VIa) and 1-methyl-2-acetylpyrrole (VIb), to which Ib bears a formal resemblance. Electrophilic attack generally occurs at the 4-positions in VIa[7-11] and VIb,[12] which correspond to the 6-position of Ib.

Several unsuccessful attempts have been made to prepare Mannich bases of Ia and Ib,[13] using formaldehyde, various amines, and acetic acid. In view of the addition of indole to aldimines such as benzalaniline,[14] Δ^1-piperidine,[15] 3,4-dihydroquinoline,[15] and methylene-*t*-butylamine,[16] it seemed that the reaction of Ib with aldimines might afford thienopyrrole derivatives having N,N-dialkylaminomethyl side chains at the 6-position.

Methylene-*t*-butylamine was prepared according to the method of Hurwitz[17] and refluxed with Ib in absolute ethanol. The product was a tan, amorphous solid which resisted attempted purification by recrystallization or sublimation. The infrared spectrum of this solid is devoid of N–H stretching absorption, and its n.m.r. spectrum has no peaks at higher field than τ 5 (the methyl protons in *t*-butylamine absorb at τ 8.85[18]). The spectra strongly suggest that the *t*-butylamino group has been lost from the reaction product, perhaps as a result of the elimination of the amine from the expected addition product (VIIa) to give 2-methylene-4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (VIIIa), most of which may have undergone further reaction. If the process does proceed through VIIIa, it would seem possible that reaction with an aldimine prepared from an aromatic aldehyde might lead to a characteriz-



able product such as VIIIb. Benzal-*t*-butylamine was therefore prepared according to the method of Robertson,[19] and was allowed to reflux with Ib in absolute ethanol. The product, isolated in 56% yield, was 2-benzylidene-4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (VIIIb), which can also be prepared by treating Ib with benzaldehyde and base.[20] The melting point of the sample of VIIIb prepared by the former method was not depressed by admixture with a sample prepared by condensation with benzaldehyde.

Experimental[21]

Preparation of 4-Benzyl-6-bromo-2H,3H-thieno[3,2-*b*]pyrrol-3-one (II).—A solution of 1.146 g. (0.0050 mole) of 4-benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ib)[3] and 0.805 g. (0.0050 mole) of NBS in 100 ml. of benzene was stirred at 25° until it gave a negative starch–iodide test (about 5 hr.), by which time succinimide had precipitated from the solution. Filtration, washing with 2% NaOH and with water, drying ($MgSO_4$), and evaporation *in vacuo* afforded 1.36 g. (88%) of a gray-brown crystalline solid. Recrystallization from 95% ethanol gave nearly colorless crystals of II, m.p. 108–109°, ν_{max}^{KBr} 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{10}BrNOS$: C, 50.66; H, 3.27; N, 4.55. Found: C, 50.56; H, 3.21; N, 4.53.

Preparation of 2-Benzylidene-4-benzyl-6-bromo-2H,3H-thieno-[3,2-*b*]pyrrol-3-one (III).—A mixture of 710 mg. (2.3 mmoles) of crude II, 265 mg. (2.5 mmoles) of benzaldehyde, and 0.4 ml. of 10% sodium hydroxide in 20 ml. of 95% ethanol was refluxed for 9 hr. The dark mother liquor was decanted from a solid residue, reheated to the boiling point, treated with Darco, filtered, and chilled. The first crop of orange needles (211 mg., 24%), m.p. 155–162°, was recrystallized from 95% ethanol four times to give beautiful orange crystals, m.p. 163–165.5°, ν_{max}^{KBr} 1640 (carbonyl absorption) and 1590 cm.$^{-1}$ (conjugated benzylidene C=C absorption).

Anal. Calcd. for $C_{20}H_{14}BrNOS$: C, 60.61; H, 3.56; N, 3.54. Found: C, 60.65; H, 3.56; N, 3.43.

Preparation of 2,6-Dibromo-4-benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (IV). A. From 4-Benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (Ib).—A solution of 343 mg. (1.5 mmoles) of Ib and 534 mg. (3.0 mmoles) of NBS in 20 ml. of benzene was stirred at room temperature until it gave a negative starch–iodide test (19–20 hr.). The filtered solution was washed with 5% NaOH and, after drying ($MgSO_4$), concentrated *in vacuo* to give 463 mg. (81%) of crude brown solid. Recrystallization from 95% ethanol (Darco) yielded 174.5 mg. (30%) of yellow needles, m.p. 120–122°, with darkening, and two additional

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 59.

(7) G. Ciamician and P. Silber, *Chem. Ber.*, **18**, 1456 (1885); **20**, 2605 (1887).

(8) I. J. Rinkes, *Rec. trav. chim.*, **53**, 1167 (1934); **56**, 1142 (1937).

(9) A. P. Terentyev and L. A. Yanovskaya, *J. Gen. Chem. USSR*, **19**, a591 (1949).

(10) I. J. Rinkes, *Rec. trav. chim.*, **60**, 303 (1941).

(11) G. Ciamician and M. Dennstedt, *Chem. Ber.*, **16**, 2348 (1883); A. P. Terentyev, L. I. Belenky, and L. A. Yanovskaya, *J. Gen. Chem. USSR*, **24**, 1251 (1954). The structure of the monobromination product was proved by R. J. Tuite, Ph D. Thesis, University of Illinois, 1960.

(12) H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957).

(13) J. Witt, Jr., Thesis, Doctor of Philsophy, University of Illinois, 1961.

(14) M. Passerini and T. Bonciani, *Gazz. chim. ital.*, **63**, 138 (1933).

(15) J. Thesing, S. Klussendorf, P. Ballach, and H. Mayer, *Chem. Ber.*, **88**, 1299 (1955).

(16) H. R. Snyder and D. S. Matteson, *J. Am. Chem. Soc.*, **79**, 2217 (1957).

(17) M. D. Hurwitz, U. S. Patent 2,582,128 (Jan. 8, 1952); *Chem. Abstr.*, **46**, 8146^f (1952); see also K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

(18) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 90.

(19) D. N. Robertson, *J. Org. Chem.*, **25**, 47 (1960).

(20) G. W. Michel and H. R. Snyder, unpublished results.

(21) 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 in a rotary evaporator under water-pump pressure.

recrystallizations from 95% ethanol afforded the analytical sample, m.p. 124.5–126.5° with darkening, ν_{max}^{KBr} 1657 cm.$^{-1}$ (shoulder at 1675).

Anal. Calcd. for $C_{13}H_9Br_2NOS$: C, 40.33; H, 2.35. Found: C, 40.17; H, 2.41.

B. From 4-Benzyl-6-bromo-2H,3H-thieno[3,2-*b*]pyrrol-3-one (II).—A solution of 100 mg. (0.32 mmole) of II and 57 mg. (0.32 mmole) of NBS in 15 ml. of benzene was stirred at room temperature until it gave a negative starch–iodide test (20 hr.). Work-up as above gave 29 mg. (23%) of once-recrystallized yellow needles. Two additional recrystallizations gave the raised m.p. 124.5–126.5°, undepressed upon admixture with the sample prepared by route A. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{13}H_9Br_2NOS$: C, 40.33; H, 2.35; N, 3.62. Found: C, 40.56; H, 2.30; N, 3.42.

Preparation of 2-Benzylidene-4-benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (VIIIb). A. From 4-Benzyl-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (Ib) and Benzaldehyde.—To a solution of 343 mg. (1.5 mmoles) of Ib and 164 mg. (1.55 mmoles) of benzaldehyde in 8 ml. of 95% ethanol was added 0.25 ml. of 5% NaOH. The orange solution was refluxed on a steam bath for 4 hr. Cooling produced 350 mg. (73%) of orange needles, m.p. 138–143°. Recrystallization from 95% ethanol (Darco) gave the raised m.p. 141.5–146.5°.

B. From 4-Benzyl-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ib) and Benzal-*t*-butylamine.—The benzal-*t*-butylamine was prepared according to the method of Robertson[19] and isolated as a yellow oil. An infrared spectrum obtained from a film of this oil showed a strong band at 1640 cm.$^{-1}$ (C=N absorption) but no N–H stretching absorption band.

To a solution of 229 mg. (1.0 mmole) of Ib in 6 ml. of absolute ethanol was added 374 mg. of the above yellow oil (2.3 mmoles). The red solution was refluxed on a steam bath for 12 hr. A few drops of water were then added to the red solution, and it was allowed to cool. After several hours, 177 mg. (56%) of product had crystallized as orange needles, m.p. 136.5–142°, undepressed upon admixture with the product prepared by route A. The products prepared by routes A and B were combined. Three recrystallizations of this mixture from 95% ethanol afforded an analytical sample, m.p. 144.5–146.5°, ν_{max}^{KBr} 1642 (carbonyl absorption) and 1590 cm.$^{-1}$ (benzylidene C=C absorption).

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.42. Found: C, 75.62; H, 4.92; N, 4.25.

Synthesis of Substituted 2,2′-Bipyrroles[1a]

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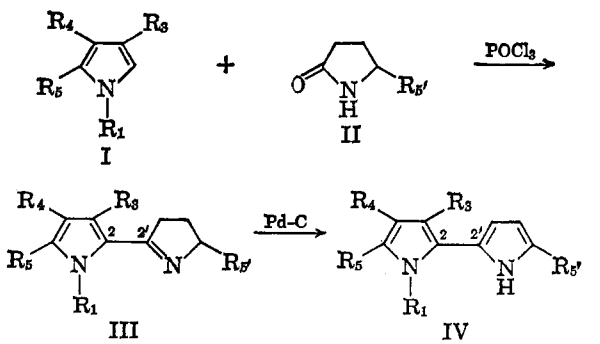
The procedure for preparing 2,2′-bipyrrole, involving condensation of a 2-pyrrolidinone and a pyrrole followed by dehydrogenation of the resulting pyrrolinylpyrrole, has been extended to the synthesis of a number of unsymmetrical bipyrroles. Reaction proceeded equally well with alkyl- and alkoxycarbonyl-substituted 2-pyrrolidinones. However, the presence of an ester group on the pyrrole nucleus prevented condensation except in the case of the β-alkyl β′-ester. Dehydrogenation proceeded much more smoothly and in better yields with pyrrolinylpyrroles prepared from methyl pyroglutamate. The availability of various substituted pyrrolinylpyrroles and bipyrroles has allowed a complete assignment of the n.m.r. absorption in each case.

Recent interest in the 2,2′-bipyrrole system, generated by its occurrence in vitamin B_{12}[2] and prodigiosin,[3] has stimulated activity in the synthesis of this ring system. Symmetrical, highly substituted bipyrroles have been known for some time and are readily prepared by an Ullmann-type condensation.[4] This reaction recently has been improved and extended.[4c] However, other routes have been needed for the synthesis of less substituted, unsymmetrical 2,2′-bipyrroles. These routes have been found in the catalytic dehydrogenation of (a) 2,2′-pyrrolidinylpyrroles, prepared from 1-pyrroline and pyrroles,[3a,5a] and (b) 2,2′-(1′-pyrrolinyl)pyrroles, prepared from 2-pyrrolidinones and pyrrole.[5] Of these two methods, the second seemed to offer the greater promise of wide applicability and better yields. Its further development for the synthesis of a variety of 2,2′-bipyrroles is the subject of this report.

The procedure consists of two steps: a Vilsmeier-type condensation between a pyrrole (I) and a 2-pyrrolidinone (II) in the presence of phosphorus oxychloride, and catalytic dehydrogenation of the resulting pyrrolinylpyrrole (III) to give the bipyrrole (IV). The activating effect of a methyl substituent and the deactivating and stabilizing influence of a carboxylic ester group were examined. The various combinations prepared are shown below, with the subscript referring to the substituent's position in the 2,2′-(1′-pyrrolinyl)pyrrole and 2,2′-bipyrrole.



III, IV	R_1	R_3	R_4	R_5	R_5'
a	H	H	H	CH_3	H
b	H	H	H	H	CH_3
c	H	H	H	CH_3	CH_3
d	H	H	CH_3	H	H
e	H	CH_3	H	H	H
f		CH_3	$CO_2C_2H_5$	H	H
g	H	H	H	H	CO_2CH_3
h	CH_3	H	H	H	CO_2CH_3

(1) (a) Sponsored in part by grant AI-04888 from the National Institutes of Health, U. S. Public Health Service; (b) Public Health Service Predoctoral Research Fellow of the National Institute of General Medical Sciences.

(2) R. Bonnet, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith, and A. Todd, *J. Chem. Soc.*, 1158 (1957).

(3) (a) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962); (b) H. H. Wasserman, J. E. McKeon, L. Smith, and P. Forgione, *ibid.*, **82**, 506 (1960).

(4) (a) H. Fischer and A. Stackel, *Z. physiol. Chem.*, **258**, 121 (1939); (b) J. L. A. Webb and R. R. Threlkeld, *J. Org. Chem.*, **18**, 1406 (1953); J. L. A. Webb, *ibid.*, **18**, 1413 (1953); (c) R. Grigg, A. W. Johnson, and J. W. F. Wasley, *J. Chem. Soc.*, 359 (1963).

(5) (a) H. Rapoport and N. Castagnoli, Jr., *J. Am. Chem. Soc.*, **84**, 2178 (1962); (b) H. Rapoport, N. Castagnoli, Jr., and K. G. Holden, *J. Org. Chem.*, **29**, 833 (1964).