Reactions of 2H,3H-Thieno[3,2-*b*]pyrrol-3-one.[1,2] VI. Methylene Derivatives

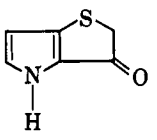
D. E. MACHIELE, J. WITT, JR., AND H. R. SNYDER

William Albert Noyes Laboratory, University of Illinois, Urbana, Illinois

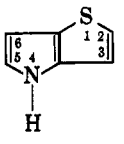
Received July 28, 1964

3-Hydroxythieno[3,2-*b*]pyrrole-2-carboxaldehyde (III) reacts with *n*-butanethiol and N-methylaniline to give the methylene derivatives IVb and IVc, respectively. In the Mannich reaction with formaldehyde and secondary amines, 2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVa) and IVb are attacked in the 6-position. One of the Mannich bases, Va, reacts with acetic anhydride to form 4-acetyl-6-acetoxymethyl-2-benzylidene-2H,-3H-thieno[3,2-b]pyrrol-3-one. Bromination of IVa, IVb, and IVc also occurs in the 6-position.

Reactions of the indole analog II, thieno[3,2-*b*]pyrrole, of most interest for the synthesis of compounds of potential biological activity would be those permitting the introduction of substituents at position 6, the position corresponding to the seat of the side chain in such indole derivatives as tryptophan, tryptamine, and serotonin. Unfortunately, attempts to effect simple substitution on II have not been successful; even so mild a process as the Mannich condensation has given only intractable materials, presumably as the result of the reaction at more than one site.[3] The ketonic precursor I, in which the available positions might be expected to differ in reactivity to a greater degree than those in II, likewise has failed to give a simple Mannich reaction product.[4] However, in some reactions, such as formylation[5] and condensation with benzaldehyde,[5] the ketone I is attacked preferentially at position 2 (yielding III and IVa). Such reactions would be useful in blocking the 2-position, provided that further substitution of products occurs in position 6 and provided that the blocking groups can be removed under conditions mild enough that undesirable changes do not occur.



I



II

IVa, 2-Benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one,[5] would be expected to undergo substitution only in the pyrrole ring and, although difficulties would be anticipated in the subsequent removal of the benzylidene group from products so prepared, the easily available substance IVa nevertheless appeared an attractive model for study of the orientation in unsaturated derivatives of the ketone I. Although IVa was recovered after treatment with aqueous formaldehyde and either piperidine or dimethylamine in ethanol, reaction did occur in acetic acid with formation of Mannich bases Vb and Va in yields of 78 and 51%, respectively; the use of dimethylamine hydrochloride instead of the free base reduced the yield to 20%.

Because of its low solubility in solvents suitable for n.m.r., 6-dimethylaminomethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Va) was treated with refluxing acetic anhydride to convert it to 4-acetyl-6-acetoxymethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (VI). The introduction of the N-acetyl group and replacement of the dimethylamino group by acetoxy also occur when gramine is treated with acetic anhydride.[6] The N-acetyl group of VI was removed upon refluxing in aqueous ethanolic acetic acid, giving Vc.

The location of the acetoxymethyl group in the β-position of the pyrrole ring is indicated by comparison of the n.m.r. spectra of VI and Vc with those of 4-acetyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (VII) and IVa. The spectrum of IVa has doublets at τ 2.20 and 3.50, and that of VII at 2.12 and 3.64, which are assigned to the α- and β-protons, respectively, of the pyrrole ring.[7,8] The spectrum of VI has a peak at τ 2.13 and the spectrum of Vc, one at 2.25. There is no absorption in either the spectrum of VI or Vc in the range where the β-proton would be expected to absorb. These data provide evidence that the acetoxymethyl group is in the 6-position. Therefore, the structure of the Mannich base Va is also known, and that of Vb is assumed by analogy.

In an attempt to remove the benzylidene group and regenerate I by a reverse aldol condensation, the benzylidene derivative, IVa, was treated with varying amounts of sodium hydroxide in aqueous ethyl alcohol. Steam distillation removed 90% of the theoretical amount of benzaldehyde which was isolated as the 2,4-dinitrophenylhydrazone. However, the basic conditions led to decomposition of the thieno[3,2-*b*]pyrrole ring system, as indicated by the evolution of hydrogen sulfide when the reaction solution was acidified.

It has been shown[9] that the benzylidene group can be removed in the cyclohexanone series by adding chlorine or bromine to the exocyclic double bond and then hydrolyzing the dihalo compound, converting it to the original ketone. The possibility of removing the benzylidene group by this method was investigated. When a bromine–acetic acid solution was allowed to react with IVa, the product isolated was found to be a monobromo compound. The ultraviolet spectrum of the compound has peaks at 347 and 263 mμ. The ultraviolet spectrum of IVa has peaks at 341 and 261 mμ, indicating that the double bond remains in the monobromo compound. Evidence that the bromine atom is in the 6-position is obtained from the n.m.r. spectrum, which contains a singlet at τ 2.25, assigned to the 5-proton, but no peak in the region where the 6-proton would be expected to absorb.

(1) For the preceding paper, see G. W. Michel and H. R. Snyder, *J. Org. Chem.*, **27**, 2689 (1962).

(2) This investigation was supported by a grant (3969-Bio) from the National Cancer Institute, U. S. Public Health Service.

(3) J. F. Zack, Jr., Ph.D. Thesis, University of Illinois, 1956.

(4) J. Witt, Jr., Ph.D. Thesis, University of Illinois, 1961.

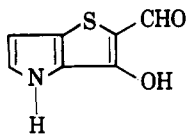
(5) R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 4360 (1960); R. J. Tuite and H. R. Snyder, *ibid.*, **82**, 4364 (1960).

(6) T. A. Geissman and A. Armen, *ibid.*, **74**, 3916 (1952).

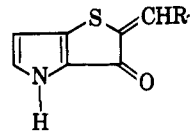
(7) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

(8) L. A. Cohen, J. W. Daly, H. King, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).

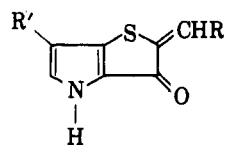
(9) W. S. Johnson, *ibid.*, **65**, 1317 (1943).

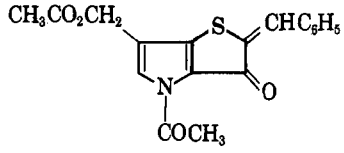


III



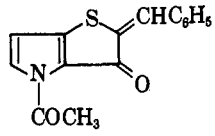
IVa, R = C_6H_5
b, R = S-*n*-C_4H_9
c, R = $NCH_3C_6H_5$
d, R = O—C_2H_5
e, R = O—$CH(CH_3)_2$





VI

Va, R = C_6H_5; R′ = $CH_2N(CH_3)_2$
b, R = C_6H_5; R′ = $CH_2NC_5H_{10}$
c, R = C_6H_5; R′ = CH_2OCOCH_3
d, R = C_6H_5; R′ = Br
e, R = S-*n*-C_4H_9; R′ = Br
f, R = S-*n*-C_4H_9; R′ = $CH_2NC_5H_{10}$
g, R = $NCH_3C_6H_5$; R′ = Br



VII

Hydroxymethylene compounds have been used as intermediates for other blocking groups.[10-12] The reaction of I with ethyl formate in a suspension of sodium methoxide in anhydrous benzene affords a good yield of 3-hydroxythieno[3,2-*b*]pyrrole-2-carboxaldehyde (III).[5] Refluxing of III in 10% hydrochloric acid for 10 min. resulted in the regeneration of I in 80% yield. Thus a relatively mild way of removing the blocking group has been found. When III is recrystallized from ethyl alcohol, the alkoxymethylene derivative IVd is formed.[5] Similarly, the reaction of III with isopropyl alcohol gives IVe. This blocking group was particularly attractive because of the ease with which it can be removed. In the cyclohexane series the isopropoxy and hydroxymethylene groups were removed in yields of 87.5%.[12] However, attempts to form Mannich bases from the thienopyrrole derivatives were unsuccessful. Apparently, the conditions necessary to prepare a Mannich base were sufficient to cause hydrolysis of the isopropoxymethylene group.

The *n*-butylthiomethylene group has also been used as a protecting group for active methylene groups.[11] The reaction of III with *n*-butanethiol in glacial acetic acid with magnesium sulfate gave an excellent yield of 2-*n*-butylthiomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVb). Ireland and Marshall[11] have effected removal of the *n*-butylthiomethylene group by refluxing with base. This treatment on IVb leads to decomposition of the thieno[3,2-*b*]pyrrole system. When refluxed in 15% hydrochloric acid for 20 min. only IVb is recovered.

The preference for electrophilic substitution at the 6-position in the *n*-butylthiomethylene derivative was demonstrated by formation of the piperidine Mannich base Vf and the monobromo derivative Ve. The structures are based as before on the n.m.r. data (Table I).

(10) A. J. Buck and R. Robinson, *J. Chem. Soc.*, 501 (1944).
(11) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).
(12) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

TABLE I
N.M.R. DATA[a]

Compd.	Solvent	Concn., %	Chemical shifts 5-H	6-H	Methylene or aromatic H
IVa	TFA[b]	20	2.20(d)	3.50(d)	1.76(s)
					2.43
VII	$CDCl_3$	15	2.12(d)	3.64(d)	2.54
VI	$CDCl_3$	15	2.13(s)		2.50
Vc	DMSO[c]	10	2.25(s)		2.47
Vd	DMSO	10	2.25(s)		2.44
IVb	$CDCl_3$	13	2.72(d)	3.78(d)	2.20(s)
Vf	$CDCl_3$	20	2.85(s)		2.19(s)
Ve	DMSO	20	2.50(s)		2.10(s)
IVc	DMSO	13	2.72(d)	3.81(d)	2.07(s)
					2.35, 2.62
Vg	DMSO	10	2.60(s)		2.04(s)
					2.60

[a] The n.m.r. spectra were determined by Mr. O. Norton, Mr. D. Johnson, and associates with a Varian V-4300-B high resolution spectrophotometer and a Varian A-60 spectrophotometer operating at 60 Mc. Chemical shifts are expressed in units of τ. Tetramethylsilane was used as an internal standard. [b] TFA = trifluoroacetic acid. [c] DMSO = dimethyl sulfoxide.

Buck and Robinson[10] showed that a methylene group adjacent to a carbonyl group can be protected by forming the methylanilinomethylene derivative. The use of this blocking group was attractive because its conversion to the hydroxymethylene derivative can be accomplished by mild acid hydrolysis. Since I was regenerated from III by acid hydrolysis a one-step removal of the blocking group was envisioned. 2-Methylanilinomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVc) was obtained from the reaction of III with N-methylaniline. Refluxing a solution of IVc in 10% hydrochloric acid for 10 min. resulted in the formation of I. Bromination of IVc gave the 6-bromo derivative Vg.

Experimental[13]

6-Dimethylaminomethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (Va).—A solution of 3.00 g. of IVa, 0.59 g. of formaldehyde as a 37% aqueous solution, 0.59 g. of dimethylamine as a 40% aqueous solution, and 150 ml. of glacial acetic acid was heated on a steam bath for 45 hr. The solvent was removed under reduced pressure on a steam bath. To the resulting oil were added 150 ml. of diethyl ether and 150 ml. of water. The insoluble material was removed by filtration and the layers were separated. The aqueous layer was neutralized with 10 *N* sodium hydroxide. The Mannich base which formed was filtered and dried in a vacuum desiccator. The crude material was recrystallized from ethyl alcohol. The yield of the product was 1.91 g. (51%), m.p. 173–174°. An analytical sample was prepared by two additional recrystallizations from ethyl alcohol: m.p. 175°; ultraviolet λ_{max} 347 mμ (log ϵ 4.35) and 268 mμ (log ϵ 3.89); infrared λ_{max} [Nujol and hexachlorobutadiene (HCBD)] 3200 (NH) and 1655 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 67.61; H, 5.64; N, 9.85. Found: C, 67.90; H, 5.90; N, 9.62.

The picrate, prepared by a conventional method,[14] precipitated from 95% aqueous ethyl alcohol. An analytical sample

(13) All melting points are uncorrected. The microanalyses were determined by Mr. Josef Nemeth and his associates, University of Illinois. The infrared spectra were determined by Mr. P. McMahon, Mr. D. Johnson, and their associates with a Perkin-Elmer Model 21 double-beam spectrophotometer equipped with sodium chloride optics. The ultraviolet spectra were determined as solutions of the compounds in absolute alcohol.
(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 228.

was prepared by two recrystallizations from ethyl alcohol, m.p. 229°.

Anal. Calcd. for $C_{22}H_{19}N_5O_5S$: C, 56.77; H, 4.09; N, 15.05. Found: C, 57.06; H, 4.13; N, 15.33.

The methiodide was prepared by a conventional method[14] and was recrystallized twice from ethyl alcohol, m.p. 233°.

Anal. Calcd. for $C_{17}H_{19}IN_2OS$: C, 47.89; H, 4.46; N, 6.53. Found: C, 47.96; H, 4.52; N, 6.28.

6-Piperidinomethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Vb).—The Mannich base was prepared by the same method as Va. The crude product was formed in a yield of 78%. An analytical sample was prepared by two recrystallizations from ethyl alcohol: m.p. 216°; ultraviolet λ_{max} 348 mμ (log ε 4.40), 265 (3.62), and 227 (3.88); infrared λ_{max} (Nujol and HCBD) 3150 (NH) and 1645 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{19}H_{20}N_2OS$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.33; H, 6.23; N, 8.52.

4-Acetyl-6-acetoxymethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]-pyrrol-3-one (VI).—A solution of 0.20 g. of Va and 15 ml. of acetic anhydride was heated at reflux for 6 hr. Ten milliliters of solvent was distilled and the residual solution was allowed to stand at room temperature. The yellow crystals which deposited from the solution were filtered, washed well with water to remove any trace of acid, and dried. The yield of the product was 0.16 g. (66%). An analytical sample was prepared by two recrystallizations from acetic anhydride: m.p. 132°; ultraviolet λ_{max} 345 mμ (log ε 4.40) and 272 mμ (log ε 3.90); infrared $\lambda_{max}^{CHCl_3}$ 1735–1725 (acetyl and acetoxy C=O) and 1650 cm.$^{-1}$ (ring C=O).

Anal. Calcd. for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.40; N, 4.11. Found: C, 63.37; H, 4.68; N, 4.11.

6-Acetoxymethyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Vc).—A solution of 239 mg. of VI, 20 ml. of 10% aqueous acetic acid, and 25 ml. of ethyl alcohol was heated at reflux for 5 hr. The solution was allowed to stand for 12 hr. in a refrigerator at 5°. The yellow product crystallized from the solution. An analytical sample was prepared by two recrystallizations from ethyl alcohol: m.p. 199°; ultraviolet λ_{max} 345 mμ (log ε 4.41) and 268 mμ (log ε 3.89); infrared λ_{max} (Nujol and HCBD) 3225 (NH), 1750 (acetoxy C=O), 1670 (C=O), and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.21; H, 4.34; N, 4.68. Found: C, 64.44; H, 4.32; N, 4.84.

4-Acetyl-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (VII).—The procedure employed was essentially that used by Tuite.[5] The yellow product was formed in a yield of 86%.

6-Bromo-2-benzylidene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Vd).—To a solution of 0.50 g. of IVa and 25 ml. of glacial acetic acid was added 0.35 g. of bromine in glacial acetic acid (0.031 g./ml. The reaction solution was allowed to stand at room temperature for 24 hr. Brown crystals formed when 200 ml. of water was added to the solution. The product was filtered, washed well with water, and dried in a vacuum desiccator. The yield of the crude material was 0.62 g., m.p. 215–220° dec. The material was purified by two recrystallizations from ethyl alcohol. The yield of the yellow compound was 0.41 g. (63%), m.p. 248° dec. An analytical sample was prepared by two additional recrystallizations from ethyl alcohol: ultraviolet λ_{max} 347 mμ (log ε 4.32) and 263 mμ (log ε 3.88); infrared λ_{max} (Nujol and HCBD) 3230, 1670, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_8BrNOS$: C, 50.98; H, 2.61; N, 4.57. Found: C, 51.25; H, 2.84; N, 4.27.

2-*n*-Butylthiomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVb).—A mixture of 4.82 g. of III, 20.8 g. of *n*-butanethiol, and 20 g. of magnesium sulfate in 100 ml. of glacial acetic acid was stirred at room temperature for 24 hr. and then filtered to remove the magnesium sulfate. The filtrate was poured into 500 ml. of chloroform and 600 ml. of 4 *N* sodium hydroxide. The chloroform layer was separated and the aqueous layer was extracted with two 100-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and filtered; the solvent was removed yielding 5.40 g. (79%) of IVb. An analytical sample was prepared by two recrystallizations from ethyl alcohol: m.p. 171–172°; infrared λ_{max}^{KBr} 1620 (C=O) and 1540 cm.$^{-1}$ (conjugated C=C).

Anal. Calcd. for $C_{11}H_{13}NOS_2$: C, 55.19; H, 5.47; N, 5.85. Found: C, 55.16; H, 5.51; N, 5.72.

6-Piperidinomethyl-2-*n*-butylthiomethylene-2H,3H-thieno-[3,2-*b*]pyrrol-3-one (Vf).—A solution of 2.0 g. of IVb, 0.71 g. of piperidine, 0.38 g. of formaldehyde as a 37% solution, and 50 ml. of glacial acetic acid was heated at 100° for 48 hr. The solvent was removed under reduced pressure on a steam bath. To the resulting oil were added 100 ml. of water and 100 ml. of diethyl ether. The aqueous layer was separated and neutralized with a cold saturated potassium carbonate solution. The free Mannich base, which separated as an oil, was extracted with three 100-ml. portions of diethyl ether. The combined extracts were dried over magnesium sulfate and filtered. The solvent was removed yielding 2.74 g. (98%) of crude Vf, m.p. 153–156°. An analytical sample was prepared by two recrystallizations from ethyl alcohol, m.p. 158–159°.

Anal. Calcd. for $C_{17}H_{24}N_2OS_2$: C, 60.67; H, 7.19; N, 8.33. Found: C, 60.41; H, 7.26; N, 8.27.

6-Bromo-2-*n*-butylthiomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Ve).—A solution of 0.14 g. of bromine in 10 ml. of glacial acetic acid was added dropwise to a stirred solution of 0.20 g. of IVb in 10 ml. of glacial acetic acid. After stirring at room temperature for 18 hr., 60 ml. of water was added and the precipitate was removed by filtration. The crude material was recrystallized from ethyl alcohol yielding 0.16 g. (60%) of Ve, m.p. 164–167°. An analytical sample was prepared by recrystallization from chloroform: m.p. 168–170°; infrared λ_{max}^{KBr} 1630 (C=O) and 1535 cm.$^{-1}$ (conjugated C=C).

Anal. Calcd. for $C_{11}H_{12}BrNOS_2$: C, 41.50; H, 3.79; N, 4.40. Found: C, 41.55; H, 3.88; N, 4.30.

2-Methylanilinomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVc).—A solution of 0.17 g. of III, 0.21 g. of N-methylaniline, and 10 ml. of toluene was heated at reflux for 90 min., cooled, and filtered to remove 0.05 g. of III. The solvent of the filtrate was removed giving an oil which was allowed to stand overnight at room temperature. The crystals which formed were removed by filtration and air dried. The yield of IVc was 0.113 g. (62%, based on unrecovered III), m.p. 205–215°. An analytical sample was prepared by two crystallizations from ethyl acetate–ethyl alcohol: m.p. 214–234°; infrared λ_{max}^{KBr} 1625 (C=O) and 1540 cm.$^{-1}$ (conjugated C=C).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.59; H, 4.72; N, 10.93. Found: C, 65.53; H, 4.67; N, 10.74.

2-Isopropoxymethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (IVe).—A solution of 0.46 g. of III and the minimum amount of isopropyl alcohol required for solution was heated to boiling. Crystals formed when the solution was allowed to cool slowly. The yield of IVe was 0.19 g. (33%). An analytical sample was prepared by two recrystallizations from isopropyl alcohol, m.p. 187°.

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.41; H, 5.26; N, 6.69. Found: C, 57.52; H, 5.10; N, 6.45.

6-Bromo-2-methylanilinomethylene-2H,3H-thieno[3,2-*b*]pyrrol-3-one (Vg).—A solution of 0.23 g. of bromine in 5 ml. of glacial acetic acid was added dropwise to a stirred solution of 0.30 g. of IVc in 10 ml. of glacial acetic acid over a period of 2 hr. Stirring was continued for an additional 20 hr. The solution was filtered and air dried giving 0.33 g. (84%) of Vg, m.p. 242–248°. An analytical sample was prepared by two recrystallizations from 1,4-dioxane: m.p. 244°; infrared λ_{max}^{KBr} 1640 and 1540 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{11}BrN_2OS$: C, 50.16; H, 3.31; N, 8.36. Found: C, 50.47; H, 3.42; N, 8.32.