oxide[32] was added slowly (1 hr.), with stirring, to 30 ml. of distilled pyridine in a three-necked flask fitted with a dropping funnel, an air-tight mechanical stirrer and a water condenser with a drying tube outlet. The solid complex which formed was diluted with 10 ml. of pyridine and cooled in an ice-bath. An amount of 5.0 ml. of freshly distilled 2-aminoethanol was then added dropwise, with stirring, over a period of 4 hr. The reaction mixture was heated to 60° for 30 min. and kept at room temperature overnight. The pyridine supernatant was decanted carefully and the viscous residue was carefully neutralized, under vigorous stirring and cooling, with *N* methanolic sodium methoxide. The voluminous white precipitate which formed was collected by filtration, washed well with diethyl ether and stored over phosphorus pentoxide under reduced pressure; yield 19.1 g. (72%) of a white powder, very soluble in water, slightly soluble in abs. methanol but insoluble in diethyl ether. This product exhibited a negative ninhydrin test. An amount of 1.0 g. of the above powder was dissolved in 20 ml. of distilled water and 9 vol. of methanol was added. The cloudy solution was centrifuged and diethyl ether was added with stirring to incipient turbidity. Crystallization was initiated by storing at 0° for a week. Recrystallization was effected in the same manner; yield 0.9 g. of white crystals, m.p. 220–221° (water of hydration evolved at *ca.* 80°); X-ray powder diffraction data: 11.8[33]s,[34] 9.12vs(1), 6.36m, 5.44s, 4.50s, 4.34w, 4.12w, 3.87vs(1), 3.70w, 3.55s, 3.21m, 3.10w, 3.03m, 2.94vw, 2.77w, 2.68w, 2.53s. Its infrared spectrum showed bands at 1,560 cm.$^{-1}$ and at 1,050 and 993 cm.$^{-1}$.

Anal. Calcd. for $C_2H_5NNa_2O_7S_2\cdot 3H_2O$: C, 7.52; H, 3.47; N, 4.39; S, 20.09; Na, 14.41; H_2O, 16.93. Found: C, 7.57; H, 3.26; N, 4.13; S, 19.78; Na, 14.65; H_2O, 16.78.

Infrared Absorption Spectral Data.—Infrared absorption spectral data of the samples (potassium bromide pellets) were obtained with the Baird Associates infrared recording spectrophotometer (model B). Results are noted in Fig. 1 and under compound descriptions. A sample of sulfamic acid showed the 1,560 cm.$^{-1}$ band, whereas 2-deoxy-2-sulfoamino-D-glucose (sodium salt),[9] previously prepared in this Laboratory, had no bands at 1,560 and 1,000 cm.$^{-1}$.

Acknowledgments.—A commercial sample of heparin and a standardized heparin sample (110 I. U. per mg.) were kindly supplied by The Upjohn Co., Kalamazoo, Mich. The counsel of Dr. T. M. Shen Han on the anticoagulant assays is gratefully acknowledged.

COLUMBUS 10, OHIO

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[32] "Sulfan B," a product of The General Chemical Division, Allied Chemical and Dye Corp., New York, N. Y.

[33] Interplanar spacing, Å., CuKα radiation.

[34] Relative intensity, estimated visually; s, strong; m, medium; w, weak; v, very.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILLINOIS]

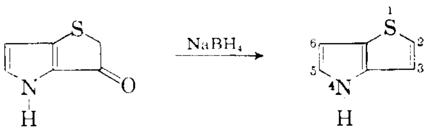
Reactions of 2*H*,3*H*-Thieno[3,2-b]pyrrol-3-one. I.[1]

BY WAYNE CARPENTER[2] AND H. R. SNYDER

RECEIVED JULY 2, 1959

Carbethoxylation of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one(I) by reaction with ethyl carbonate catalyzed by sodium ethoxide occurs not only by attack on the α-methylene group of I but also by attack on the nitrogen atom, yielding a mixture of mono- and dicarbethoxy derivatives. Both the products (V and VI) exist as enolic dimers, and a similar "mixed dimer" forms from one of each of the monomeric units corresponding to V and VI. The reactions of the compounds with diazomethane, methyl iodide and potassium carbonate, and lithium aluminum hydride are studied. Structures of the various substances are proposed on the basis of chemical and spectral data.

The recent synthesis of thieno [3,2-*b*]pyrrole[3,4] from 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one(I) suggests that derivatives of the ketone (I) may be useful intermediates in the synthesis of substituted thieno[3,2-*b*]pyrroles. Perhaps the simplest reaction by means of which I could be converted to a substituted thienopyrrole is acylation, which would be expected to yield 2-acyl-3-hydroxy derivatives. In the present work the carbethoxylation of the ketone I is examined.



I II

The reaction of I with ethyl carbonate was effected in the same manner as the carbethoxylation of ketones and esters,[5] that is, in the presence of excess ethyl carbonate with sodium ethoxide as catalyst. A mixture of the sodium salts III and IV precipitated from the reaction mixture. These salts could be separated by virtue of their different solubilities in tetrahydrofuran, and the N-carbethoxyl group of IV could be removed by the action of boiling water or ethanol, effecting the conversion of IV to III. Acetic acid converted the salts III and IV to the enols V and VI, each of which was found to be dimeric by molecular weight determination in boiling methyl ethyl ketone. A third dimeric enol (IX) was obtained when the mixture of III and IV was acidified or when equimolar amounts of V and VI were mixed in cyclohexane solution.

That the ring structure was not altered in the carbethoxylation was shown by the hydrolysis and decarboxylation of V with the regeneration of I in high yield. The fact that V and VI give colors with ferric chloride, whereas I does not, shows that a carbethoxyl group is located at position 2 in V and VI. In the n.m.r. spectra of compounds V, VI and IX, the peaks due to the hydroxyl proton are observed in the same region as the corre-

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[1] Abstracted from a portion of the Thesis submitted by Wayne Carpenter to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1959.

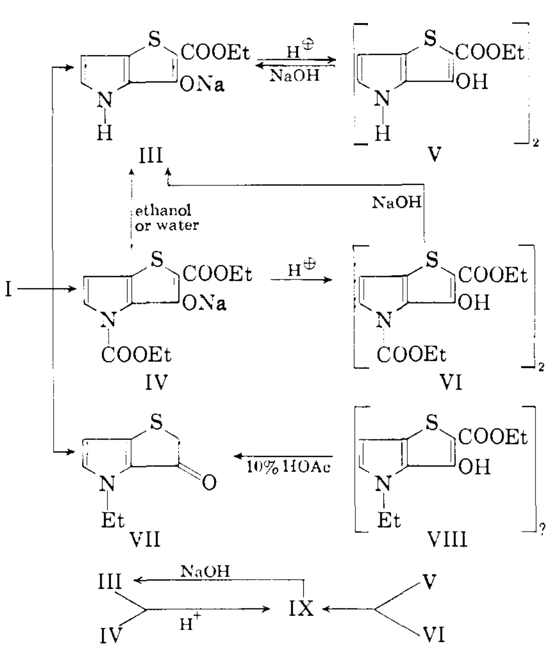
[2] National Science Foundation Fellow, 1956–1959.

[3] H. R. Snyder, L. A. Carpino, J. F. Mills and J. F. Zack, THIS JOURNAL, **79**, 2556 (1957).

[4] D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

[5] V. H. Wallingford, A. H. Homeyer and D. M. Jones, THIS JOURNAL, **63**, 2252 (1941).

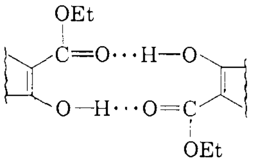
sponding peak in the spectrum of methyl salicylate and other features of the spectra are consistent with the structures shown. The infrared spectra[6] are in general agreement with the monomeric structures corresponding to V and VI but give little information concerning the precise nature of the bonding in the dimers. The infrared spectrum of IX in solution may be duplicated by "adding" the spectra of V and VI in solution. However, the spectrum of IX in Nujol differs significantly, especially in the carbonyl region, from the curve obtained by adding the spectra of V and VI in Nujol. These observations suggest that IX may be stable only in the solid state and that it reverts to a mixture of V and VI in solution.



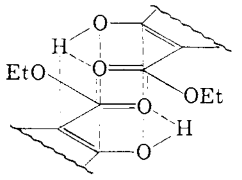
$$\underset{\text{V}}{\text{AA}} + \underset{\text{VI}}{\text{BB}} \rightleftarrows \underset{\text{IX}}{2\text{AB}}$$

The formation of IX from V and VI in cyclohexane solution also suggests that there is a rapid equilibrium among the three dimeric species and the two monomers. The ultraviolet spectra of the compounds do not show any surprising features.

Since the O-methyl derivative of V (see below) is monomeric, it is clear that the enolic hydroxyl group is concerned in the dimerization. Since both V and VI (as well as IX) are dimeric, the substituent on the nitrogen atom, and most probably the nitrogen atom itself, cannot be involved in the formation of the dimers. From the n.m.r. spectra of V and VI, it may be concluded that these dimers are symmetrical, for otherwise the number of different types of protons would be twice the observed value. These factors exclude from consideration such dimeric structures as Diels-Alder adducts, aldol addition products and hemiacetals. Of the possibilities which remain, the twelve-membered cyclic chelate structure X appears at present to be the most probable; a somewhat similar twelve-membered ring has been considered to exist in the trimer of acetic acid.[7] Another possibility which remains is a "layer" structure (XI) similar to one which has been proposed for polymers of fatty acids,[8] but which appears less probable.



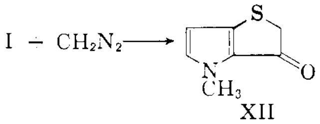
X



XI

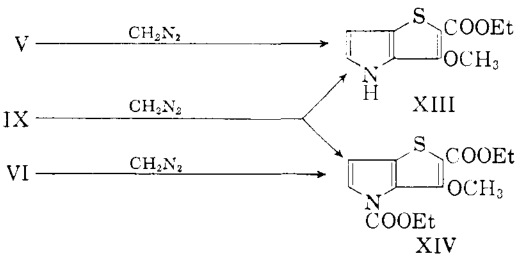
Since the formation of IX from V and VI requires the dissociation of the latter two compounds in solution, it was expected that the infrared spectrum of V, especially in the carbonyl region, would show variation with concentration, resulting from the presence of increasing relative amounts of the monomeric form at higher dilutions. This expectation was not realized; neither the position nor the shape of the carbonyl peak varied in spectra of V measured in Nujol, in 5% solution in chloroform and in 0.5% solution in carbon tetrachloride.

It is of interest that *N-ethylation* occurred to a minor extent in the carbethoxylation of I. Very small amounts of VII, the N-ethyl derivative of I, and of VIII, the N-ethyl derivative of V, were isolated as by-products. The structures of VII and VIII were assigned on the basis of analytical and spectral data, especially the spectral similarity between VII and N-methyl-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (XII), obtained from I and diazomethane. The N-methylation of I attests to the acidity of the NH link in I. The ethylation probably occurs by an SN2 displacement of ethyl carbonate anion ($C_2H_5OCO_2^-$) from ethyl carbonate by the anion of I,



XII

Among the reactions of V, VI and IX which have been studied are methylation and reduction. Methylation with diazomethane occurred in accordance with the following scheme. The ethers XIII and XIV, formed from IX in equimolar amounts, were easily separable. The ethers,



XIII and XIV, were also formed from the methylation of V and VI, respectively, with diazomethane. The methylation of V with methyl iodide and

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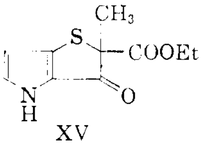
[6] The complete infrared spectra of the compounds described here appear in the Ph.D. Thesis of Wayne R. Carpenter, University of Illinois, 1959.

[7] E. W. Johnson and L. K. Nash, THIS JOURNAL, **72**, 547 (1950).

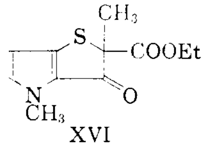
[8] H. L. Ritter and J. H. Simmons, *ibid.*, **67**, 757 (1945).

potassium carbonate in acetone gave only the C-methyl derivative XV when the reaction was conducted for a short time only. When the reaction time was extended, the pyrrole nitrogen atom of XV was attacked, yielding XVI, and a little of the O-methyl derivative XIII was also isolated from the mixture.

The structure assignments of XV and XVI were made on the basis of elemental analyses, ultraviolet, infrared and n.m.r. spectra. The ultraviolet chromophores of both compounds are nearly the same as that of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (I). The infrared spectra of XV and XVI are nearly alike with the exception that the spectrum of XVI shows no N–H band. Each of these spectra also shows two carbonyl bands, one band in each at 1735 cm.$^{-1}$ and the other at 1650 cm.$^{-1}$ with XV or 1670 cm.$^{-1}$ with XVI. In the infrared spectrum of V there is only one carbonyl band, which is at 1640 cm.$^{-1}$. The fact that two carbonyl bands are associated with XV and XVI shows that the 3-keto group and the carbethoxyl group are both present. The 3-keto group would not be present unless a methyl group had been introduced into the 2-position.



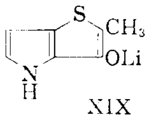
XV



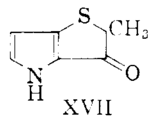
XVI

The sodium salts of V and VI are readily acylated on the oxygen atom by acetic anhydride or tosyl chloride to produce the corresponding esters.

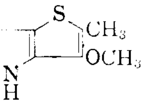
Compound V and its methyl derivative (XIII) were converted smoothly by lithium aluminum hydride to white, crystalline compounds, (XVII and XVIII), the latter in quantitative yield.



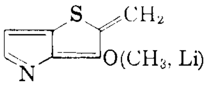
XIX



XVII



XVIII



XX

These compounds were characterized by elemental analyses, ultraviolet, infrared and n.m.r. spectra. The proposed structures are entirely in accord with all the data obtained. Apparently, V is reduced as a lithium salt to XIX, which, upon treatment with water, is hydrolyzed and ketonized to form XVII. The reduction of an ester group to a methyl group with lithium aluminum hydride has its precedent in the reduction of methyl anthranilate to *o*-toluidine.[9] Perhaps the reductions of V and XIII proceed *via* an intermediate such as XX. This could then be further reduced to give the products observed.

Ultraviolet, N,m,r. and Infrared Spectra.[10]—The ultraviolet spectra, with the following exceptions, were determined of solutions of the compounds in 95% ethanol. The spectra of compounds V, VII, XV and XVI were determined of solutions in absolute methanol. The spectra of compounds VI, VIII, XIII, and XIV were determined of solutions in cyclohexane. All spectra were determined on a qualitative basis only. The wave lengths are recorded in mμ; the figures in parentheses are the logarithms of the extinction coefficients.

The n.m.r. spectra are recorded in p.p.m. relative to pure water. The abbreviations used are: s. = singlet(s), d. = doublet(s), t. = triplet(s), q. = quartet; abbreviations for the interpretations, given in parentheses, are a.p. = aromatic protons, m. = methylene group protons, m.g. = methyl group protons, e.g. = ethyl group protons, h.p. = hydroxyl group proton.

The principal bands in the infrared spectra are recorded for the region from 1600 to 3600 cm.$^{-1}$.

For the purposes of comparison, certain of the spectra of I[4], II[4] and methyl salicylate were determined and are listed herewith.

2*H*,3*H*-Thieno[3,2-*b*]pyrrol-3-one[4] **(I)**,—Ultraviolet, $\lambda_{max.}$ 279 (4.2), $\lambda_{min.}$ 236 (2.7); $\lambda_{max.}$ 330 (3.9), $\lambda_{min.}$ 303 (3.6). N.m.r., −2.53, −1.35; t. (a.p.). 0.83; s. (m.) *thieno*[3,2-*b*]*pyrrole*[4] (II). Ultraviolet $\lambda_{max.}$ 260 (4.1), $\lambda_{min.}$ 233 (3.7). *Methyl salicylate*, n.m.r. −5.9; s. (h.p.).

The spectra of other compounds are given at the appropriate points in the Experimental section.

Experimental[11]

Carbethoxylation Procedure.—Sixty ml. of ethyl carbonate and 1.39 g. of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one were heated to boiling under nitrogen atmosphere, and after about 10 ml. of condensate had been collected, a solution made by dissolving 0.34 g. of sodium in 20 ml. of absolute ethanol was added. After another 40 ml. of condensate had been collected by slow distillation over a period of 90 minutes, the heating was discontinued. The flow of nitrogen was not stopped until the reaction mixture had cooled to room temperature. The reaction products consisted of a mixture of the sodium salts III and IV in excess ethyl carbonate.

The Dimer of 2-Carbethoxy-3-hydroxythieno[3,2-*b*]-pyrrole(V).—The mixture of sodium salts (see above procedure) was shaken with a mixture of 100 ml. of water and 100 ml. of cyclohexane before being filtered to remove insoluble materials. The aqueous layer was removed and neutralized with dilute hydrochloric acid. The brown precipitate which formed was collected, washed with water and dried in a vacuum desiccator; wt. 1.16 g. (55%). It melted at 120–122°. An analytical sample was prepared by two recrystallizations from cyclohexane followed by sublimation at 110° (0.2 mm.). The white sublimate melted at 127–128° and gave a positive ferric chloride test.

Spectra. Ultraviolet, λ_{max} 297 (4.3), λ_{min} 248 (3.0). N.m.r., 5.59; s. (h.p.). −2.50, −2.22; t. (a.p.) +0.30; q. +3.28 (e.g.). Infrared, ($CHCl_3$) 3480, 3290, 1642 cm.$^{-1}$.

Anal. Calcd. for $(C_9H_9NO_3S)_2$: C, 51.17; H, 4.30; N, 6.63; mol. wt., 422.5. Found: C, 51.29; H, 4.37; N, 6.37; mol. wt. (ebullioscopic in methyl ethyl ketone), 404.

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(9) L. H. Conover and D. S. Tarbell, THIS JOURNAL, **72**, 3586 (1950).

(10) The infrared spectra were determined by Mr. James Brader, Mr. Paul E. McMahon, Miss Mary DeMott and Miss Charlene Luebke. The nuclear magnetic resonance spectra were determined by Mr. B. E. Shoulders, who also assisted in their interpretation. The instrument employed was a Varian Associates V-4300-B high resolution n.m.r. spectrophotometer using a hydrogen precession frequency of 40 mc. The ultraviolet spectra were determined by Mr. J. Chiu with a Cary recording spectrophotometer, Model 14.

(11) All melting points are uncorrected. The microanalyses were performed by Mr. Joseph Nemeth, Mrs. Maria Stingl, Miss Claire Higham, Miss Jane Liu and by the Clark Microanalytical Laboratory, Urbana, Illinois.

The Dimer of 2,N-Dicarbethoxy-3-hydroxythieno[3,2-*b*]-pyrrole(VI).—(See Carbethoxylation Procedure.) Fifty ml. of cyclohexane was added to the cooled mixture of sodium salts in excess ethyl carbonate and the resulting mixture was allowed to stand at room temperature overnight. The gray precipitate which had formed was collected, washed with tetrahydrofuran and then dried in a vacuum desiccator, The dry, gray sodium salt of VI weighed 2.00 g. and melted at 238–242° with decomposition. It gave a positive sodium flame test and left an alkaline residue upon combustion.

The dried sodium salt of VI (0.310 g.) was shaken with 15 ml. of dry tetrahydrofuran containing a few drops of acetic acid. After a few minutes of shaking, most of the gray solid had dissolved. The solution was filtered into 200 ml. of water. The resulting mixture was extracted with two 100-ml. portions of ether. The ether extracts were dried over magnesium sulfate, filtered and concentrated under vacuum on the steam-bath to a dark brown oil, which, upon cooling, crystallized to a brown solid, m.p. 70–75°. The yield was 0.177 g. or 62% of the theoretical amount. An analytical sample, m.p. 84.5–85°, was prepared by one recrystallization from cyclohexane followed by two recrystallizations from ethanol–water; it gave a positive ferric chloride test. The white needles thus obtained were dried at 0.2 mm. over phosphorus pentoxide for 20 hr.

Spectra. Ultraviolet, $\lambda_{\text{max.}}$ 291 (4.4), $\lambda_{\text{min.}}$ 250 (3.1); $\lambda_{\text{max.}}$ 318 (4.17), $\lambda_{\text{min.}}$ 305 (4.10). N.m.r., −5.96, s. (h.p.). −2.75, −1.72; d. (a.p.). +0.15; q. +3.12; t. (*e.g.*). +0.38; q. +3.43; t. (*e.g.*). Infrared, ($CHCl_3$) 3200, 1740, 1705, 1640 cm.$^{-1}$.

Anal. Calcd. for $(C_{12}H_{13}NO_5S)_2$: C, 50.87; H, 4.63; N, 4.95; mol. wt., 566.6. Found: C, 50.94; H, 4.79; N, 4.98; (ebullioscopic in methyl ethyl ketone), 596.

The Mixed Dimer of 2-Carbethoxy-3-hydroxyethieno-[3,2-*b*]-pyrrole and 2,N-Dicarbethoxy-3-hydroxythieno[3,-2-*b*]pyrrole (IX).—(See Carbethoxylation Procedure.)—The cooled mixture of sodium salts in excess diethyl carbonate was stirred into 300 ml. of cyclohexane containing 1.5 ml. of acetic acid. The thick emulsion which formed was broken up by the addition of 100 ml. of water. The organic layer was removed, filtered, washed with 100 ml. of water, dried over magnesium sulfate and again filtered. The yellow filtrate was evaporated under vacuum on the steam-bath to remove volatile solvents. The residue, a yellow oil which completely solidified upon cooling, was recrystallized from cyclohexane to give 1.12 g. of light tan crystals, m.p. 101–104°. A second crop of tan crystals was obtained by concentrating the mother liquor. The total yield was 1.74 g. (71.5%). An analytical sample was prepared by three sublimations at 110° (0.2 mm.). The white sublimate melted at 110.5–111° and gave a positive ferric chloride test.

Spectra. Ultraviolet, λ_{max} 293 (4.58), λ_{min} 250 (3.3); λ_{max} 316 (4.58), λ_{min} 3.08 (4.56). N.m.r., −5.74; s. (h.p.). −5.43; s. (h.p.). −2.80, −1.72; d. (a.p.). −2.50, −1.67; t. (a.p.). +0.22; q. +3.38; t. (*e.g.*) +0.35; q. +3.40; t. (*e.g.*). Infrared, ($CHCl_3$) 3480, 3240, 1745, 1712, 1645 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{22}N_2O_8S_2$: C, 51.00; H, 4.48; N, 5.67; mol. wt., 494.5. Found: C, 50.75; H, 4.35; N, 5.72; mol. wt. (ebullioscopic in methyl ethyl ketone), 473.

The mixed dimer was also prepared by dissolving 26.7 mg. of V, m.p. 124–125°, and 35.6 mg. of VI, m.p. 83–84°, in 20 ml. of hot cyclohexane and collecting the crystals which were deposited upon cooling. A sample of these crystals melted at 109–110° and did not depress the melting point of an authentic sample of IX. However, the mixtures of IX with either V or VI exhibited marked melting point depressions. A mixture of V and IX melted at 100–124°. A mixture of VI and IX melted at 77–105°.

2,N-Dicarbethoxythieno[3,2-*b*]pyrrolyl-3-acetate.—The sodium salt of VI was prepared according to the method indicated in the synthesis of VI. Two g. of the sodium salt was stirred for three days in a solution of 0.7 ml. of acetic anhydride in 50 ml. of dry tetrahydrofuran. Diatomaceous earth and Darco were added before the reaction mixture was filtered. The filtrate was concentrated under vacuum on the steam-bath to 1.47 g. of red oil, which slowly solidified. After two recrystallizations from ethanol–water, 1.14 g. of white crystals, m.p. 95–99°, were obtained. This amount corresponds to a 40.3% yield based on the amount of I used. An analytical sample was prepared by two more recrystallizations from ethanol–water. The white needles thus obtained were dried 24 hr. in an evacuated desiccator containing phosphorus pentoxide. The pure material melts at 102° and does not give a ferric chloride test.

Anal. Calcd. for $C_{14}H_{15}NO_6S$: C, 51.70; H, 4.65; N, 4.31. Found: C, 51.82; H, 4.65; N, 4.43.

2-Carbethoxythieno[3,2-*b*]pyrrolyl-3-acetate.—A solution of 0.468 g. of sodium hydroxide in 50 ml. of absolute ethanol was added to 2.43 g. of V. The solution thus formed was concentrated to dryness under vacuum by heating on the steam-bath. The sodium salt of V was then dissolved in 50 ml. of dry tetrahydrofuran. Acetic anhydride (1.2 ml.) was then added. The reaction mixture was allowed to stand at room temperature overnight before being concentrated to dryness under vacuum. The residue was dissolved in a mixture of 50 ml. of ether and 50 ml. of water. The ether layer was removed from the mixture and combined with a subsequent 50-ml. ether extract of the aqueous layer. The ether extracts were washed with 50 ml. of 0.05*N* sodium hydroxide, dried over magnesium sulfate, treated with Darco, filtered and then concentrated to dryness under vacuum. The yield of 2-carbethoxythieno[3,2-*b*]pyrrolyl-3-acetate, m.p. 119–126°, was 2.86 g. or 98% of the theoretical amount. The material was recrystallized three times from ethanol–water and dried 24 hr. at room temperature (0.2 mm.) over phosphorus pentoxide; m.p. 123–125.5°.

Anal. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.05; H, 3.45; N, 5.35.

2-Carbethoxythieno[3,2-*b*]pyrrolyl-3-tosylate.—The sodium salt of V was prepared by dissolving 0.523 g. of V and 0.100 g. of sodium hydroxide in 25 ml. of absolute ethanol and then removing the solvent under vacuum at 100°. The tan sodium salt and 0.475 g. of tosyl chloride were dissolved in 25 ml. of tetrahydrofuran. The reaction flask was stoppered and left overnight at 25°. The reaction mixture was concentrated to dryness under vacuum at 100°. The residue which remained was dissolved in 50 ml. of ethanol and the solution was treated with Darco before being filtered. Thirty ml. of water was added to the filtrate and the resulting solution, after standing overnight in the refrigerator, deposited 0.797 g. of tan needles. The yield was 88% of the theoretical amount. After having been recrystallized twice from ethanol–water and dried 24 hr. at 25° over phosphorus pentoxide (0.2 mm.), the material melted at 153–154°.

Anal. Calcd. for $C_{16}H_{15}NO_5S_2$: C, 52.59; H, 4.14; N, 3.83. Found: C, 52.93; H, 4.36; N, 4.03.

The sodium salt of V may also be prepared by treatment of the sodium salt of VI with boiling ethanol until complete solution results. The residue obtained by removal of the ethanol is the sodium salt of V.

Hydrolysis of the Dimer of 2-Carbethoxy-3-hydroxythieno-[3,2-*b*]-pyrrole.—Four tenths of a gram of V, 5.0 ml. of glacial acetic acid and 45 ml. of water were heated under reflux for 24 hr. The reaction mixture was concentrated to dryness under vacuum on the steam-bath. The solid residue was washed with a dilute solution of sodium hydroxide and then with water and then dried in a vacuum desiccator. The yield of crude 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (I), m.p. 185–186°, was 0.20 g. or 76% of the theoretical amount.

Hydrolysis of the Mixed Dimer of 2-Carbethoxy-3-hydroxy-thieno[3,2-*b*]pyrrole and 2,N-Dicarbethoxy-3-hydroxythieno[3,2-*b*]-pyrrole.—Two hundred ml. of water, 0.5 g. of sodium hydroxide and 1.42 g. of IX were heated under reflux for 1 hr. The solution was cooled and neutralized with dilute hydrochloric acid. The brown precipitate thus formed was collected and dried. The yield of crude 2-carbethoxy-3-hydroxythieno[3,2-*b*]pyrrole dimer (V) was 0.78 g. or 64% of the theoretical amount.

Methylations of I, V, VI and IX with Diazomethane.—The preparation of an ether solution of diazomethane, which was required in the methylation of I, V, VI and IX, was carried out as follows. Two g. of N-nitrosomethylurea was stirred with 10 ml. of 50% potassium hydroxide and 25 ml. of ether at 0° for 30 minutes. The ether layer was carefully decanted and combined with three subsequent 10-ml. ether washings of the aqueous layer. The diazomethane solution was used without distillation.

2-Carbethoxy-3-methoxythieno[3,2-*b*]pyrrole (XIII).—An ether solution of diazomethane, prepared from 2.0 g. of

N-nitrosomethylurea was shaken with 0.5 g. of V until solution was complete. The reaction vessel was lightly stoppered and allowed to stand at 25° for two days. The ether was then removed under reduced pressure, The residue was sublimed twice at 140° (0.2 mm.); m.p, 132–134°. The yield was 0.44 g. or 83% of the theoretical amount. An analytical sample, m.p. 134°, was prepared by two more sublimations of the compound.

Spectra. Ultraviolet, λ_{max} 302 (4.5), λ_{min} 249 (3.1). Infrared, (Nujol) 3360, 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.31; H, 4.88; N, 6.22; mol. wt., 225. Found: C, 53.40; H, 4.85; N, 6.36; mol. wt. (ebullioscopic in methyl ethyl ketone), 211.

2,N-Dicarbethoxy-3-methoxythieno[3,2-*b*]pyrrole (XIV).—An ether solution of diazomethane, prepared from 2.0 g. of N-nitrosomethylurea, was shaken with 0.37 g. of VI until solution was complete. The solution was allowed to stand at 25° for four days and was then evaporated under vacuum on the steam-bath to an oil, which was dissolved in 40 ml. of *n*-pentane. The pentane solution was filtered and evaporated under vacuum on the steam-bath to a clear oil, which crystallized slowly upon cooling; m.p, 40–47°. The yield was 0.39 g. or 98% of the theoretical amount. An analytical sample, m.p. 52–53°, prepared by two recrystallizations from ethanol–water, was dried 24 hr. at 25° (0.2 mm.) over phosphorus pentoxide.

Spectra. Ultraviolet, λ_{max} 298 (4.4), λ_{min} 247 (3.2). N. m. r., −2.78, −1.65; d. (a.p.). + 0.80; s. (m.g.). +0.33; q. + 3.36; t. (*e.g.*). +0.48; q. +3.43; t. (*e.g.*) Infrared, (CCl_4) 1738, 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}NO_5S$: C, 52.51; H, 5.08; N, 4.71; OCH_3, 31.3; NCH_3, 0.00. Found: C, 52.58; H, 5.13; N, 4.48; OCH_3, 29.1; NCH_3, 1.35.

Reaction of Diazomethane with the Mixed Dimer of 2-Carbethoxy-3-hydroxythieno[3,2-*b*]pyrrole and 2,N-Dicarbethoxy-3-hydroxythieno-[3,2-*b*]pyrrole.—An ether solution of diazomethane, prepared from 1.0 g. of N-nitrosmethylurea, was shaken with 0.20 g. of IX until solution was complete. The solution was allowed to stand at 25° for 6 days and was then removed from the solvent by heating under reduced pressure. The oily solid which remained was triturated with two 15-ml. portions of *n*-pentane. The combined pentane extracts were concentrated to dryness under reduced pressure to give 0.118 g. of white solid, m.p. 40–48°. The residue which did not dissolve in pentane weighed 0.091 g. and melted at 114–121°. Recrystallization of the low-melting fraction from ethanol–water yielded white, fibrous needles, m.p. 51–52°. The infrared spectrum was identical to that of compound XIV. A mixture of XIV with the material obtained from this reaction showed no melting point depression.

The high-melting fraction from above was sublimed at 140° (0.2 mm.) to give white crystals, m.p. 133–134°. This substance was shown to be identical to XIII by mixture melting point determination and by the identity of the infrared spectra.

N-Methyl-2*H*,3*H*-thieno[3,2-*b*] pyrrol-3-one (XII).—An ether solution of diazomethane, prepared from 2.0 g. of N-nitrosomethylurea, was added to 0.70 g. of 2*H*,3*H*-thieno-[3,2-b]pyrrol-3-one. Fifty ml. of dry tetrahydrofuran was added to effect complete solution. The flask containing the solution was lightly stoppered and left at 25° for 6 days. The solvents were then removed under vacuum by heating on the steam-bath. The residue (0.73 g.) was sublimed at 0.2 mm. At 60°, 0.24 g. of white, oily crystals sublimed. At 100°, 0.11 g. of a yellow, crystalline solid sublimed, m.p. 183–185° (compound I). The material subliming at 60°, (XII), was difficult to purify. It required five consecutive sublimations to free it from the oily impurity. The pure material melts at 99–100°.

Spectra. Ultraviolet, λ_{max} 282 (4.0) λ_{min} 238 (2.2); λ_{max} 333 (3.6); λ_{min} 305 (3.3). N. m. r., −2.27, −1.35; d. (a.p.) +0.75; s. (m.) +0.90; s (m.g.). Infrared ($CHCl_3$) 1640 cm.$^{-1}$.

Anal. Calcd. for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14. Found: C, 55.29; H, 4.46; N, 9.25.

N-Ethyl-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (VII).—A solution of 2.69 g. of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (I) in 110 ml. of ethyl carbonate was put into a 3-necked, 300-ml. flask equipped with dropping funnel, nitrogen inlet tube and distilling head. The contents were heated under nitrogen atmosphere and after the first 10 ml. of distillate had been collected, a solution of 0.45 g. of sodium in 20 ml. of absolute ethanol was added. The ethanol was rapidly distilled and after 10 minutes the reaction mixture was cooled and filtered. The filtrate was diluted with 100 ml. of petroleum ether, washed with 100 ml. of 6 *N* sodium hydroxide, dried over magnesium sulfate and then filtered. The filtrate was concentrated to dryness under vacuum. The 1.07 g. of orange solid obtained (mostly I) was sublimed at 80° (0.2 mm.). A white, crystalline sublimate was obtained which melted at 80°. This material was resublimed to obtain an analytical sample. The yield of VII was 0.050 g. or 1.6% of the theoretical amount.

Anal. Calcd. for C_8H_9NOS: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.61; H, 5.34; N, 8.07.

Compound VII was also prepared by heating crude N-ethyl-2-carbethoxy-3-hydroxythieno[3,2-*b*]pyrrole (VIII) in 10% acetic acid under reflux for 24 hr. The aqueous acetic acid was removed by vacuum evaporation. The residue was sublimed at 80° (0.2 mm.) to furnish white crystals of VII.

Spectra. Ultraviolet, λ_{max} 283 (4.0), λ_{min} 239 (2.5); λ_{max} 333 (3.7), λ_{min} 306 (3.5). N.m.r., −2.37, −1.35; d. (a.p.). ±0.70; s. (m.) +0.53; q. +3,26; t. (*e.g.*). Infrared, ($CHCl_3$) 1643 cm.$^{-1}$.

N-Ethyl-2-carbethoxy-3-hydroxythieno[3,2-*b*]pyrrole (VIII).—Several carbethoxylation reactions were conducted in which a total of 15 g. of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one was used. The product, the dimer of 2-carbethoxy-3-hydroxythieno[3,2-*b*]pyrrole, was recrystallized from cyclohexane after each reaction. The mother liquors from these recrystallizations were combined. By evaporation of the combined mother liquors an oily, yellow solid was obtained. The solid was extracted with cold *n*-pentane and the extract was concentrated on the steam-bath to 1.24 g. of yellow oil, which partially solidified upon standing. The solid was again extracted with 10 ml. of cold *n*-pentane and the solvent was removed from the filtered extract by heating on the steam-bath. The extraction with cold pentane was repeated on the oil thus obtained. Each time a small amount of solid, (V), was left undissolved. Finally, the oil obtained by concentrating the last pentane extract was distilled in a micro-distillation apparatus at 140° (0.2 mm.). A yellow oil (about 0.1 g.) was obtained which showed no tendency to solidify. All attempts to recrystallize it failed. It gave a strong positive ferric chloride test.

Spectra. Ultraviolet, λ_{max} 293 (4.2), λ_{min} 248 (3.0); λ_{max} 3.20 (4.14), λ_{min} 312 (4.09). N. m. r., −5.68; s. (h.p.). −2.27, −1.52; d. (a.p.). +0.35; q. +3.56; t. (e.g.). +0.50; q. +3.56 (e.g.). Infrared, ($CHCl_3$) 1638 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.71; H, 5.37; N, 5.87.

2-Methyl-2-carbethoxy-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (XV).—Five tenths of a gram of V, 0.5 g. of potassium carbonate, 5 ml. of methyl iodide and 50 ml. of acetone were heated under reflux for 4 hr. and then allowed to cool. The reaction mixture was filtered and the acetone was evaporated from the filtrate under vacuum to furnish an oily residue, which was then extracted with 120 ml. of cyclohexane. The cyclohexane solution was passed through a column containing 10 g. of alumina. Adsorption on the alumina was nearly complete. Two hundred ml. of ether eluted 0.30 g. of oil, which slowly crystallized to a white solid, m.p. 65–80°. After two recrystallizations, which were carried out by dissolving the material in warm *n*-pentane and cooling it in a Dry Ice–acetone bath, the compound melted at 95–97°.

Spectra. Ultraviolet, λ_{max} 283 (4.1), λ_{min} 247 (3.1); λ_{max} 318 (3.94), λ_{min} 3.06 (3.92). Infrared, (CCl_4) 3180, 1735, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.31; H, 4.88; N, 6.22. Found: C, 53.44; H, 4.77; N, 6.18.

2,N-Dimethyl-2-carbethoxy-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (XVI).—A mixture of 0.50 g. of V, 0.50 g. of potassium carbonate, 4.0 ml. of methyl iodide and 50 ml. of acetone was heated under reflux under a nitrogen atmosphere for 7 hr. An additional 5.0 ml. of methyl iodide was then added and refluxing was contained for a total of 23 hr. The solution was then filtered and evaporated to dryness under vacuum. Fifty ml. of hot cyclohexane was added to the residue and the resulting mixture was filtered. The filtrate was passed through a column containing 10 g. of alumina. Evaporation of the cyclohexane revealed but a few mg. of oil. Twenty-five ml. of ether eluted 0.22 g. of an oil, which crystallized slowly; m.p. 40–50°. An additional 75 ml. of ether eluted another fraction, 0.17 g., m.p. 65–70°. This fraction was shown to be identical to compound XV by infrared analysis and a mixture melting point determination.

The low-melting fraction was purified by subliming it three times at 80° (0.2 mm.). The pure material (XVI) melts at 73–74°.

Spectra. Ultraviolet, λ_{max} 284 (4.1), λ_{min} 246 (2.9); λ_{max} 334 (3.7), λ_{min} 312 (3.5). N.m.r., −2.40, −1.37 d. (a.p.). +0.90; s (m.g.). +2.88; s. (m.g.) +0.53; q. +3.45; t. (*e.g.*). Infrared ($CHCl_3$) 1735, 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.16; H, 5.50; N, 5.61.

2-Methyl-3-methoxythieno[3,2-*b*]pyrrole (XVIII).—2-Carbethoxy-3-methoxythieno[3,2-*b*]pyrrole (0.132 g.) was put into 10 ml. of dry ether. Fifty mg. of lithium aluminum hydride was cautiously added while the contents of the flask were swirled. The swirling was continued until all of XIII had dissolved. The flask was loosely stoppered and left in the refrigerator overnight. The solution was then diluted with 50 ml. of dry ether before the excess lithium aluminum hydride was decomposed by the cautious addition of a few drops of water. The solution was then filtered and evaporated under vacuum to give 0.093 g. of clear, colorless oil, which crystallized completely after several minutes; m.p. 54–60°. This material was recrystallized from *n*-pentane and sublimed at 60° (0.2 mm.); m.p. 64°.

Spectra. Ultraviolet, λ_{max} 256 (4.3). N.m.r., −1.80, −1.45; t. (a.p.) +1.07; s. (m.g.) +2.45; s. (m.g.). Infrared, (CCl_4) 3480 cm.$^{-1}$.

Anal. Calcd. for C_8H_9NOS: C, 57.46; H, 5.43; N, 8.38. Found: C, 57.21; H, 5.28; N, 8.43.

2-Methyl-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (XVIII).—Six tenths of a gram of lithium aluminum hydride was added cautiously to a solution of 0.193 g. of V in 10 ml. of dry ether. The stoppered reaction mixture was allowed to stand overnight in the refrigerator. The excess lithium aluminum hydride was destroyed by the cautious addition of a few drops of water. Fifty ml. of dry ether was added to facilitate filtration. After the mixture was filtered, the filtrate was concentrated under vacuum to an oil (0.119 g.). When the oil was extracted with 30 ml. of boiling cyclohexane, part of it dissolved and a resinous, brown material was left undissolved. The cyclohexane solution was concentrated under vacuum to a red oil, which was then distilled at 100° (0.2 mm.). Crystals appeared in the distillate. These were sublimed at 100° (0.2 mm.) to give a white sublimate, m.p. 119–120°. The yield of analytically pure material was 0.025 g. or 18% of the theoretical amount.

Spectra. Ultraviolet, λ_{max} 278 (4.1), λ_{min} 237 (2.8); λ_{max} 331 (3.8), λ_{min} 305 (3.5). Infrared, ($CHCl_3$) 3180, 1637 cm.$^{-1}$.

Anal. Calcd. for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14. Found: C, 55.11; H, 4.41; N, 9.14.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CAIRO UNIVERSITY]

On the Reactivity of the Exocyclic Double Bond in 5-Arylidene-3-aryl-2,4-thiazolidinediones; Their Reaction with Diazoalkanes, *p*-Thiocresol and Piperidine

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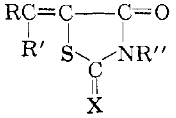
A series of 5-α-aralkylidene-3-aryl-2,4-thiazolidinediones (IV and V) has been prepared by the action of ethereal diazoalkanes on 5-arylidene-3-aryl-2,4-thiazolidinediones (III). Treatment of the appropriate 5-substituted-3-aryl-2,4-thiazolidinedione with *p*-thiocresol in the presence of piperidine give the thiol adducts VI. Under mild conditions piperidine adds to the exocyclic double bond in VIII to give a simple adduct VIII.

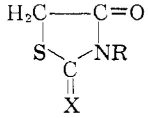
Recently, it has been reported that 5-(1-methylalkylidene)-2,4-thiazolidinedione (Ia) shows antimicrobial activity comparable to that of the most potent of the corresponding rhodanine derivatives (Ib).[1]

The fungicidal action of several organic sulfur compounds may be attributed to the presence of N–C–S linkage in Ia or Ib; or characteristic of thiazole compounds which possess considerable activity.[2]

We now have investigated the preparation of the hitherto unknown 5-α-aralkylidene-3-aryl-2,4-thiazolidinediones[3] (see Table II).

The condensation of the methylene group in 2,4-thiazolidinedione (IIa) and its N-substituted derivatives IIc with aromatic aldehydes, simple aliphatic ketones and cyclic ketones has been tried by different authors under different experimental conditions.[4]





Ia, R = CH_3; R′ = alkyl; R″ = H; X = O
b, R = CH_3; R′ = alkyl; R″ = H; X = S
c, R = H; R′ = R″ = C_6H_5; X = S
d, R = H; R′ = $C_6H_4OCH_3$-*p*; R″ = C_6H_5; X = S
e, R = H; =R′ = $C_6H_3{:}O_2CH_2(3,4)$; R″ = C_6H_5; X = S
f, R = R′ = CH_3; R″ = C_6H_5; X = O
g, R = H; R′ = C_6H_5; R″ = $C_6H_4CH_3$-*p*; X = S

IIa, R = H; X = O
b, R = H; X = S
c, R = C_6H_5; X = O
d, R = C_6H_5; X = S
e, R = $C_6H_4CH_3$-*p*; X = O

Recently, Brown and co-workers[1] have shown that methyl isopropyl ketone, diethyl ketone, acetophenone and *m*-nitroacetophenone failed to

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[1] *Cf.* F. C. Brown, C. K. Bradsher and S. W. Chilton, *J. Org. Chem.*, **21**, 1269 (1956); *cf.* also the pharmacological and toxicological studies on 5-benzylidene-rhodanine (S. A. Tawab, A. Mustafa and A. F. A. Shalaby, *Nature*, **183**, 607 (1959)).

[2] M. K. Rout, B. Padhi and N. K. Das, *ibid.*, **173**, 516 (1954).

[3] In view of the marked interest in many derivatives of thiazolidone which proved to be useful as anesthetics (A. R. Surrey, THIS JOURNAL, **71**, 3354 (1949), anticonvulsants (H. D. Troutman and L. M. Long, *ibid.*, **70**, 3436 (1948)) and amebacidal agents (A. R. Surrey and R. A. Cutler, *ibid.*, **76**, 578 (1954)), the presence of the thiazolidine moiety in penicillin, the fungitoxic or bacteriotoxic activity shown by many derivatives of rhodanines (H. K. Pujari and M. K. Rout, *J. Sci. Indust. Res.*, **14B**, 398 (1955); F. C. Brown and C. K. Bradsher, *Nature*, **168**, 171 (1951); F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum and P. Wilder, THIS JOURNAL, **78**, 384 (1956)), the pharmacological results will be published elsewhere.

[4] For the different experimental conditions *cf.* (a) E. R. H. Jones, F. A. Robinson and M. N. Strachan, *J. Chem. Soc.*, 91 (1946); C. P. Lo, E. Y. Shropshire and W. J. Croxall, THIS JOURNAL, **75**, 4845 (1953), in the case of aromatic aldehydes; (b) D. Libermann, J. Himbert and L. Hengl, *Bull. soc. chim.*, **4**, 1120 (1948), in the case of cyclohexanone; (c) W. J. Croxall, C. P. Lo and E. Y. Shropshire, THIS JOURNAL, **75**, 5419 (1953), in the case of aliphatic ketones; (d) C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson and W. E. Savige, *J. Chem. Soc.*, 2573 (1949), for the indirect preparation of 5-alkylidene-2,4-thiazolidinediones by desulfurization of 5-alkylidene rhodanines.