[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Infrared Spectra of Some 1,4-Thiapyrone Derivatives

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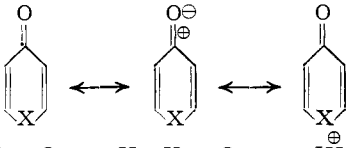
A study of the infrared spectra of 1,4-thiapyrone, its hydrochloride, 3-carboxy-1,4-thiapyrone, the corresponding ester and the amide, shows no evidence for normal carbonyl absorption. The spectrum of 1,4-thiapyrone hydrochloride is shifted toward lower frequencies compared to the thiapyrone itself. These results are in agreement with numerous other lines of evidence in indicating that the thiapyrone nucleus, and the thiapyrylium salts especially, are resonance hybrids with little or no contributions from forms with a carbon–oxygen double bond. The infrared spectrum of 1,4-thiapyrone sulfone, on the other hand, shows the absorption expected from a conjugated carbonyl group and carbon–carbon double bonds. The preparation of 3-carboxy-1,4-thiapyrone and its derivatives from 3-carbomethoxytetrahydro-1,4-thiapyrone is described.

Several lines of evidence indicate that the 4-pyrones (Ia) and the 4-thiapyrones (Ib) exist as resonance hybrids, with important contributions from structures such as II and III.

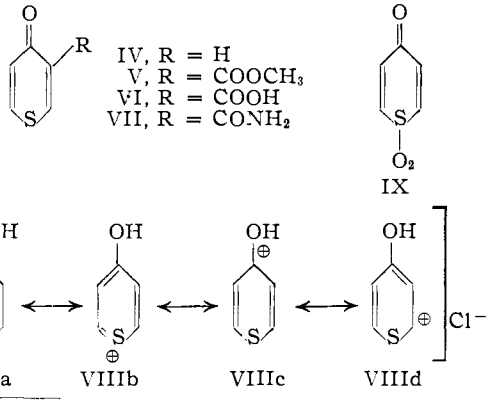


Ia, X = O IIa, X = O III
Ib, X = S IIb, X = S

The evidence includes the lack of normal carbonyl reactivity in the pyrones and thiapyrones,[2] the dipole moments,[3] heats of combustion[3a,4] and the basic properties of the compounds.[2] A recent molecular orbital study of 4-pyrone[5] indicates that IIa is the most important contributing form.

It would be expected that evidence confirming the absence of a normal carbonyl group in these compounds would be obtained by an infrared study. The Raman spectra of 2,6-dimethyl-4-pyrone and its hydrochloride are in agreement with this expectation.[6]

During some synthetic studies in the 1,4-thiapyrone field, we have measured the infrared spectra of 1,4-thiapyrone (IV), some of its 3-carboxy derivatives V–VII, its hydrochloride VIII and the corresponding sulfone IX. The results are indicated in Table I.



IV, R = H
V, R = $COOCH_3$
VI, R = COOH
VII, R = $CONH_2$

IX

VIIIa VIIIb VIIIc VIIId

(1) Abbott Laboratories Fellow, 1952–1953.

(2) B. Eistert, "Tautomerie und Mesomerie," Enke, Stuttgart, 1938, p. 58 ff; J. Fried in "Heterocyclic Compounds," Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 370–376, 396.

(3) (a) F. Arndt, G. T. O. Martin and J. R. Partington, *J. Chem. Soc.*, 602 (1935); (b) C. G. Le Fèvre and R. J. W. Le Fèvre, *ibid.*, 1088 (1937).

(4) L. Lorenz-Oppan and H. Sternitzke, *Z. Elektrochem.*, **40**, 501 (1934).

(5) R. D. Brown, *J. Chem. Soc.*, 2670 (1951).

(6) L. Kahovec and K. W. F. Kohlrausch, *Ber.*, **75**, 627 (1942). Some early observations on the infrared spectra of pyrones are given by A. Ross, (*Proc. Roy. Soc. (London)*, **113A**, 213 (1926)), but nothing seems to have been published on the thiapyrones.

TABLE I

INFRARED SPECTRA ($CM.^{-1}$) OF 1,4-THIAPYRONE AND RELATED COMPOUNDS[a,b]

1,4-Thiapyrone (IV)	3-Carboxy-1,4-thiapyrone (VI)	3-Carbomethoxy-1,4-thiapyrone (V)
1609 (s, very broad)	1718 (s)	1682 (s)
1574 (s)	1590 (s)	1607 (s)
1545 (m)	1567 (s)	1569 (m)
1504 (m)	1508 (s)	1508 (s)
1271 (m)	1408 (s)	1335 (m)
1162 (s)	1336 (m)	1266 (s)
1124 (s)	1227 (s)	1255 (s)
967 (w)	1135 (m)	1211 (m)
914 (w)	945 (m)	1182 (m)
846 (s)	912 (m)	1134 (m)
791 (m)	896 (s)	1040 (m)
736 (m)	842 (s)	976 (s)
710 (s)	769 (m)	911 (m)
	766 (m)	876 (m)
	717 (m)	830 (s)
		753 (s)

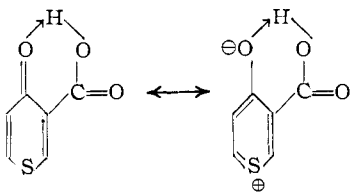
1,4-Thiapyrone sulfone[c] (IX)	3-Carboxamido-1,4-thiapyrone (VII)
1657 (s)	1684 (s)
1617 (s)	1575 (s)
1590 (s)	1392 (s)
1350 (s)	1329 (s)
1339 (s)	1208 (s)
1305 (s)	1144 (s)
1271 (m)	983 (w)
1182 (s)	911 (s)
1126 (s)	896 (s)
1091 (m)	852 (s)
974 (w)	846 (s)
887 (w)	835 (m)
869 (s)	785 (w)
850 (s)	759 (m)
	694 (s)

[a] The spectra were obtained with a Perkin–Elmer Spectrometer, Model 12-A, with a sodium chloride prism, using Nujol mulls and a 0.025 mm. cell. We are indebted to Mr. Carl Whiteman for obtaining the tracings. [b] Intensity of absorption indicated as s (0–25% transmission); m (25–60%), w (over 60%). [c] Prepared by the procedure of Fehnel and Carmack (ref. 7b).

It is clear that the thiapyrone IV does not show an absorption band in the 1660 cm.$^{-1}$ region which would be expected of a conjugated carbonyl group. The corresponding sulfone IX, however, does show normal carbonyl absorption, with sharp bands in the conjugated carbonyl and carbon–carbon double bond regions. These observations are in agreement with the fact that the reactions of the sulfone are those of a normal α,β-unsaturated carbonyl compound[7]; in the sulfone, contributions from resonance forms analogous to II and III are impossible, because the sulfur atom no longer has unshared electrons, as has been pointed out previously by Arndt.[3,7,8]

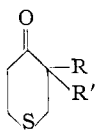
Conversion of the thiapyrone to its hydrochloride VIII shifts the strong absorption still farther toward lower frequencies, indicating that the thiapyrylium cation has no detectable amount of double bond character in the carbon–oxygen bond, and that it is a resonance hybrid in which the positive charge can be written on carbon or sulfur,[9] as indicated in resonance forms VIIIb, c and d.

The 3-carboxy derivatives V, VI and VII show bands in the 1680–1720 cm.$^{-1}$ region, due to the carbonyl group in the 3-position. Contrary to the usual result, the carbonyl frequency in the carboxylic acid VI is higher than that of the ester V, which would indicate that in the solid state, at least, there is not much intermolecular hydrogen bonding in the carboxyl derivative VI, because this would tend to lower the carbonyl frequency. Presumably the carboxylic acid is hydrogen-bonded intramolecularly, with consequent enhancement of the stabilization of the ring by forms such as Xa.



X Xa

3-Carbomethoxy-1,4-thiapyrone (V) was prepared from 3-carbomethoxytetrahydro-1,4-thiapyrone (XI) by treatment with phosphorus pentachloride, following the procedure of Arndt and Bekir[7a] for the conversion of tetrahydro-1,4-thiapyrone (XII) to 1,4-thiapyrone. The 3-carboxy-1,4-thiapyrone (VI) was best prepared by the same procedure followed by hydrolysis in the reaction mixture of the intermediate 3-carbomethoxy-1,4-thiapyrone, without isolation of the ester. Decarboxylation of 3-carboxy-1,4-thiapyrone gave 1,4-thiapyrone, identical with a sample prepared directly from tetrahydrothiapyrone (XII) by dehydrogenation with phosphorus pentachloride.[7a]



XI, R = $COOCH_3$, R′ = H
XII, R = R′ = H
XIII, R = $COOCH_3$, R′ = NO

Nitrosation of XI yielded the nitroso compound XIII, which was a colorless crystalline solid and was probably dimeric. Basic hydrolysis appeared to give ring cleavage, as has been observed in analogous cases.[10]

Experimental[11]

3-Carbomethoxy-1,4-thiapyrone (V).—To a well-cooled solution of 13.77 g. of 3-carbomethoxytetrahydro-1,4-thiapyrone (XI)[7b] in 50 ml. of dry benzene, in a flask fitted with a reflux condenser and a calcium chloride drying tube, was added 50 g. of phosphorus pentachloride. (In runs of this size it is desirable, and in larger runs it is necessary, to add a solution of XI in dry benzene dropwise to a stirred suspension of phosphorus pentachloride in dry benzene.) After the initial vigorous reaction had subsided, the mixture was refluxed on the steam-bath until the evolution of hydrogen chloride ceased (about 1 hr.). The cooled mixture was rapidly filtered, washed with dry benzene, and the solid complex was added immediately to 250 g. of crushed ice. Excess calcium carbonate was added in small portions with stirring, the mixture was filtered and the filtrate was saturated with sodium chloride. (Alternatively disodium hydrogen phosphate was added to approximate neutrality.) The aqueous solution was extracted extensively with chloroform, the chloroform extracts were dried and evaporated, yielding 2.72 g. of a solid, m.p. 75–82°. The crude product was recrystallized from benzene–hexane (decolorizing charcoal) and 2.48 g. of a colorless solid was obtained, m.p. 82–83°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_7H_6O_3S$: C, 49.41; H, 3.56. Found: C, 49.27; H, 3.50.

3-Carboxy-1,4-thiapyrone (VI). A. From 3-Carbomethoxytetrahydro-1,4-thiapyrone (XI).—Phosphorus pentachloride (11 g.) was added to a well-cooled solution of 3.0 g. of XI in 8 ml. of dry benzene. (In large runs, XI in dry benzene was added dropwise with stirring to a suspension of phosphorus pentachloride in dry benzene.) After the initial vigorous reaction had subsided, the mixture was refluxed on the steam-bath (calcium chloride drying tube) until the evolution of hydrogen chloride ceased (about 1 hr.). The cooled mixture was rapidly filtered, washed with dry benzene and the solid complex was added immediately to 50 g. of crushed ice. The aqueous solution was heated on the steam-bath under reflux for 2 hours, cooled and extracted with chloroform. The dried chloroform extracts (anhydrous magnesium sulfate) were evaporated, yielding 0.77 g. of a discolored solid, m.p. 162–179°. The solid was recrystallized from 95% ethanol to a constant melting point of 185.5–186°. In some runs where an oily impurity was present, the acid was dissolved in sodium bicarbonate solution, shaken with Nuchar, filtered and reprecipitated by the addition of hydrochloric acid.

Anal. Calcd. for $C_6H_4O_3S$: C, 46.15; H, 2.58. Found: C, 46.03; H, 2.44.

B. From 3-Carbomethoxy-1,4-thiapyrone (V).—3-Carbomethoxy-1,4-thiapyrone (15.2 mg.) was refluxed with 0.5 ml. of 10% sulfuric acid for 2 hr., which gave 7.4 mg. of the carboxylic acid VI, m.p. 182–183.5°.

1,4-Thiapyrone (IV) from 3-Carboxy-1,4-thiapyrone (VI).—The 3-carboxy compound VI (100 mg.) was refluxed with copper bronze in 1 ml. of purified quinoline until the evolution of carbon dioxide ceased. (At lower temperatures the decarboxylation was slow and incomplete.) The cooled mixture was filtered, 10 ml. of water was added, and the solution was acidified with hydrochloric acid. The resulting solution was extracted with chloroform, 50 mg. of an oily solid being obtained from the chloroform extracts. The solid was pressed between filter paper and was then recrystallized from carbon tetrachloride, yielding a colorless solid, m.p. 110–111.5°. A mixed melting point with authentic 1,4-thiapyrone,[7a] m.p. 109.5–111.5°, showed no depression.

(7) (a) F. Arndt and N. Bekir, *Ber.*, **63**, 2393 (1930); (b) E. A. Fehnel and M. Carmack, THIS JOURNAL, **70**, 1813 (1948).

(8) F. Arndt, P. Nachtwey and J. Pusch, *Ber.*, **58**, 1633 (1925).

(9) Similar results were obtained in the Raman spectra of 2,6-dimethylpyrone and its hydrochloride.[6] There does not seem to be any close resemblance between the Raman spectra of the pyrones[6] and the infrared spectra of the thiapyrones reported in the present paper.

(10) O. Touster, in "Organic Reactions," Vol. III, edited by Roger Adams, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 338–339.

(11) All m.p.'s are corrected; microanalyses by Miss Claire King.

1,4-Thiapyrone Hydrochloride (VIII).—This compound, as prepared by the addition of dry hydrogen chloride to the thiapyrone in dry benzene, melted at 125–135°. Arndt and Bekir[7a] reported that the salt melted indefinitely around 135°, and gave no analysis. Sublimation of our sample at 80° (1 mm.) did not improve the m.p., but the analysis was reasonably satisfactory.

Anal. Calcd. for C_6H_5ClOS: C, 40.40; H, 3.39. Found: C, 40.85; H, 3.52.

3-Carboxamido-1,4-thiapyrone (VII).—The 3-carbomethoxy compound V (0.30 g.) was shaken with 3 ml. of concentrated aqueous ammonia. Precipitation of the amide occurred practically simultaneously with the disappearance of the ester. A white solid (0.22 g.) was obtained, m.p. 195.5–197°. Recrystallization from 95% ethanol–ethyl acetate yielded 0.20 g., m.p. 198–198.5°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_6H_5NO_2S$: C, 46.44; H, 3.25. Found: C, 46.59; H, 3.29.

3-Nitroso-3-carbomethoxytetrahydro-1,4-thiapyrone (XIII).—A solution of 1.38 g. of sodium nitrite in 3 ml. of cold water was added dropwise with swirling to a solution of 3.0 g. of the tetrahydro ester XI in 5 ml. of acetic acid in an ice-bath. An immediate dark blue color developed. Toward the end of the addition an oily solid separated and the color of the solution changed to pale orange. After an additional hr. in the ice-bath, the mixture was filtered and washed with water, yielding 1.60 g. of a white solid, m.p. 96.5–97.5° dec. The solid was insoluble in organic solvents in the cold, but dissolved in warm solvents with the development of a transient, pale blue color. No solid could be recovered on cooling. The nitroso compound became oily and discolored on standing for several weeks, and an odor was apparent resembling that of the starting material XI.

The preparation was repeated, and the solid, after washing copiously with water and 95% ethanol, was dried *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_7H_9NO_4S$: C, 41.37; H, 4.47. Found: C, 41.51; H, 4.63.

Various attempts to hydrolyze the nitroso compound with mineral acid yielded no tractable product. However, it slowly dissolved in cold 10% sodium hydroxide to give a pale amber solution. The cooled solution was acidified with concentrated hydrochloric acid, extracted with ether and the dried ether extracts (anhydrous sodium sulfate), were evaporated, leaving an amber oil which solidified on scratching to yield 1.16 g. from 1.71 g. of XIII of a discolored solid, m.p. 118–126° dec. Several recrystallizations from ethyl acetate–benzene (decolorized with Nuchar) raised the melting point to 128–128.5° dec. The analysis was not in accord with that of the expected β-carbomethoxy-β-oximino-β′-carboxydiethyl sulfide but could be accounted for as that of a mixture of the monoester and the dicarboxylic acid. This is not unreasonable in view of the ease of hydrolysis of pyruvic esters.

Anal. Calcd. for $C_7H_{11}O_5NS$: C, 37.99; H, 5.01. Calcd. for $C_6H_9O_5NS$: C, 34.77; H, 4.38. Found: C, 35.50; H, 4.60.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Mercurial Diuretics[1]

BY L. H. WERNER AND C. R. SCHOLZ

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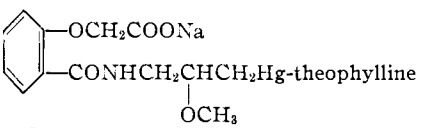
Various mercaptans were combined with 3-hydroxymercuri-2-hydroxypropylcarbamylnicotinic acid sodium salt. A number of mercurated compounds of different structures were prepared and combined with 1-thiosorbitol. The substances were tested for diuretic effect and toxicity.

Organic mercurial diuretics of the type now in general use were introduced in 1924 (Salyrgan) and have since established their place in medicine. More recently, the investigations of Farah[2] and Lehman[3] have shown that replacement of the theophylline moiety of the mercurial diuretic I by a suitable substituted thiol as in II reduces the cardiac toxicity and also the irritation at the site of injection without loss of diuretic potency.

The first part of this investigation was concerned with the structural requirements of the thiol for maximal detoxification. Various thiols were combined with 3-hydroxymercuri-2-hydroxypropyl carbamyl nicotinic acid sodium salt[4] (Table I) and tested for toxicity by our Division of Macrobiology.[5] The compounds were prepared by dissolving the mercurated acid in water containing one equivalent of sodium hydroxide and adding a concentrated aqueous or alcoholic solution of the



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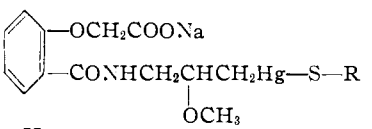

II

thiol. The mercaptomercuri compound was precipitated by the addition of acetone, filtered off and dried. Further purification was difficult as the compounds were only soluble in water and showed no tendency to crystallize. The amorphous compounds, especially the mercaptomercuri derivatives containing thiosorbitol, were in general hygroscopic and retained solvent very tenaciously. This led in some cases (Tables I–IV) to poor agreement of the analytical with the calculated values. Reprecipitation of the mercaptomercuri compounds had little effect or led to decomposition, as did also attempts to remove retained solvent by vigorous drying *in vacuo*. The analytical values of the intermediate acetoxymercuri and hydroxymercuri compounds are given as an indication of their purity.

(1) Presented before the XIIth International Congress of Pure and Applied Chemistry, Section of Medicinal Chemistry, Sept. 10–13, 1951, New York, N. Y.

(2) W. K. Long and A. Farah, *Science*, **104**, 220 (1946); *J. Pharm. Exptl. Therap.*, **88**, 388 (1946).

(3) R. A. Lehman, *Proc. Soc. Expt. Biol. and Med.*, **64**, 428 (1947).

(4) M. Hartmann and L. Panizzon, U. S. Patent 2,136,501; 2,136,503, Nov. 15, 1938.

(5) A. J. Plummer, W. Reitze and F. F. Yonkman, *Federation Proc.*, **11**, Part I, 383 (1952).