of two to three bubbles per second for the times indicated in Table I. The polymers were treated with excess methanol, filtered, and dried in a desiccator.

Anal. Calcd. for $C_{17}H_{26}S_2$: C, 69.33; H, 8.9; S, 21.77. Found (Run 1, Table I): C, 66.12; H, 8.50; S, 21.88. Found (Run 2, Table I): C, 68.61; H, 8.98; S, 21.98. Found (Run 4, Table I): C, 69.09; H, 8.63; S, 21.69.

General Procedure for Polymercaptals and Polymercaptols.—In general the carbonyl compound and an equivalent amount of dithiol were placed in 10 cc. of freshly distilled dry dioxane. The solution was cooled in an ice-bath and dry hydrogen chloride was bubbled into the mixture for varying lengths of time in different experiments. In all cases the reaction developed heat and usually a pink color appeared. The mixture was cooled thoroughly and 20 cc. of cold methanol added to precipitate the polymer. The polymer was filtered and the unreacted dithiol titrated amperometrically. The polymer was dried in a desiccator first under water pump pressure (approximately 20–30 mm.) and finally at about 1 mm.

The results are summarized in Table II.

Amperometric Titrations of –SH Groups.—The method of Kolthoff and Harris[8] was used to determine unused dithiol. The sample solution was diluted with absolute methanol to 100 cc. for the titration.

To determine end-groups in the polymers it was necessary to adapt the method to use in a dioxane solution. A solution of 0.5 g. of polymer in 100 cc. of dioxane (dried and freed of peroxides) was used as the base solution. Aliquots (about 5 cc.) of this solution were added to 100 cc. of pure dioxane, 10 cc. of dilute ammonium hydroxide was added, and then 0.3 g. of ammonium nitrate was introduced. The solution was stirred until the salt was entirely dissolved. This solution was titrated with 0.005 *N* silver nitrate. A blank without polymer was run and the difference was used to calculate the –SH groups in the polymer.

Oxidation of Polymercaptals to Give –S–S Links.—To a solution of 0.1 g. of the benzaldehyde-hexamethylenedithiol polymer (inherent viscosity, 0.86) in 20 cc. of benzene was added 0.01 g. of iodine and small amounts of aqueous sodium hydroxide solution. The mixture was shaken, the water layer removed, and the benzene evaporated. The polymer was precipitated with methanol and purified by solution in benzene and reprecipitation with methanol. The white polymer thus obtained had an inherent viscosity of 1.25.

A sample of butyraldehyde-hexamethylenedithiol polymer (inherent viscosity, 0.05, m. p. 40°) oxidized in the same way gave an oxidation product, m. p. 60–70°, inherent viscosity, 0.055.

A sample of *m*-nitrobenzaldehyde-decamethylenedithiol polymer (inherent viscosity, 0.16, m. p. 75°) on oxidation gave a polymer m. p. 90°, inherent viscosity 0.23.

Oxidation of Benzaldehyde-Decamethylenedithiol Polymer.—To a solution of 1.2 g. of benzaldehyde-decamethylenedithiol polymer (m. p. 93°) in 21 cc. of hot benzene was added 33 cc. of 10% sulfuric acid and then a solution of 4 g. of potassium permanganate in 40 cc. of water was introduced dropwise. The mixture was heated under a reflux condenser for an hour and filtered. The precipitate was suspended in 150 cc. of water and sulfur dioxide added to dissolve the manganese dioxide. The white powder remaining was collected on a filter and dried, m. p. 180° with decomposition.

Anal. Calcd. for $C_{17}H_{26}S_2O_4$: C, 56.95; H, 7.31; S, 17.88. Found: (corrected for ash) C, 54.33; H, 6.97; S, 18.99.

The sample contained 5.73% ash and its high degree of insolubility prevented recrystallization from solvents. The high sulfur content indicates that oxidation was incomplete.

Summary

The reactions of hexamethylenedithiol and decamethylenedithiol with a variety of aldehydes and ketones have given a variety of new polymeric mercaptals and mercaptols. The polymers seem to have at least one and sometimes two terminal –SH groups. They have fair stability toward hydrolytic agents and heat.

URBANA, ILLINOIS RECEIVED OCTOBER 11, 1949

[CONTRIBUTION FROM THE ANTIBIOTICS RESEARCH DEPARTMENT, THE UPJOHN COMPANY]

5-Substituted 2-Thiopheneacetic Acids and Amides as Penicillin Precursors

BY JARED H. FORD, GEORGE C. PRESCOTT AND DONALD R. COLINGSWORTH

A series of 5-substituted 2-thiopheneacetic acids was desired for evaluation as penicillin precursors[1] since it had been demonstrated that the parent compound, 2-thiopheneacetic acid, was readily utilized by penicillin-producing molds.[2] Furthermore, the resulting 2-thiophenemethylpenicillin[3] was found to be one of the most promising of a large number of new biosynthetic penicillins from the standpoint of blood level duration as tested in animals.[4]

2-Thiopheneacetic acid was prepared by the method of Blicke and Zienty[5] which involved chloromethylation of thiophene, conversion of the 2-thiophenemethyl chloride to the nitrile and alkaline hydrolysis of the nitrile. When this method was applied to 2-chlorothiophene, the first two steps gave better yields than with thiophene, but attempts to hydrolyze the 5-chloro-2-thiopheneacetonitrile to the acid were unsuccessful. The nitrile was treated with dry hydrogen chloride in methanol and the resulting imino ether hydrochloride was converted to the methyl ester when it was refluxed with slightly more than the calculated amount of water.

An attempted chloromethylation of 2-methylthiophene yielded the corresponding diarylmethane as the principal product.

An effort to prepare 2-thiopheneacetic acid from 2-acetylthiophene by the Willgerodt–Kindler reaction[6] was unsuccessful, but this method was used

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[1] Behrens, Corse, Huff, Jones, Soper and Whitehead, *J. Biol. Chem.*, **175**, 771 (1948).

[2] Jones, Soper, Behrens and Corse, THIS JOURNAL, **70**, 2843 (1948).

[3] Behrens, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 672.

[4] Personal communication, Anderson, Behrens and Chen, The Lilly Research Laboratories.

[5] Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941).

[6] Carmack and Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 97.

in the case of 5-*t*-butyl-2-thiopheneacetamide. Apparently the reactive hydrogen in the 5-position must be replaced before this reaction can be used.

Methyl 5-bromo-2-thiopheneacetate was obtained in low yield by direct bromination of methyl 2-thiopheneacetate in carbon tetrachloride, but the attempted replacement of the bromine by the cyano group was unsuccessful.

Methyl 2-thiopheneacetate and 2-*t*-butylthiophene were acetylated easily and in good yields by heating them with acetic anhydride in the presence of Super-Filtrol. This excellent method has been described by Hartough, Kosak and Sardella for the acetylation of thiophene.[7] Iodine[8] was also used to catalyze these reactions but the yields are somewhat lower.

A hypochlorite oxidation of methyl 5-acetyl-2-thiopheneacetate gave 2,5-thiophenedicarboxylic acid instead of the desired 5-carboxy-2-thiopheneacetic acid.

The oximes of 5-acetyl-2-thiopheneacetic acid and its methyl ester did not undergo the Beckmann rearrangement when heated with 96% sulfuric acid. The sulfuric acid treatment made it possible to separate the *syn* and *anti* forms of the methyl ester oxime and to purify one form of the acid oxime.

The stimulation tests (see Table I) indicated that the 5-chloro and 5-bromo compounds were well utilized by the mold and were very effective penicillin precursors. The 5-*t*-butyl derivative had a marked inhibitory effect on the formation of penicillin, presumably because it was toxic to the mold. The 5-acetyl derivatives and their oximes gave penicillin activities which were only slightly greater than those of the control cultures. Other methods such as partition chromatography or counter-current distribution would be required to determine whether or not new penicillins were produced.[1]

TABLE I

EVALUATION OF THE COMPOUNDS AS PRECURSORS OF NEW PENICILLINS

Compound added[a]	Stimulation[b]
2-Thiopheneacetamide	2.0
5-Chloro-2-thiopheneacetic acid	3.1
5-Chloro-2-thiopheneacetamide	2.7
5-Bromo-2-thiopheneacetamide	3.2
5-Acetyl-2-thiopheneacetamide	1.2
5-Acetyl-2-thiopheneacetic acid	1.1
Oxime of above compound	0.9
5-*t*-Butyl-2-thiopheneacetamide	0.1

[a] A concentration of 500 mg. per liter of culture medium was used in all cases. [b] The penicillin activity (*S. aureus* plate assays) of the experimental flasks divided by the penicillin activity of the control flasks. The control flasks varied from 137 to 175 Oxford units per ml.

Acknowledgments.—The authors wish to express thanks to Agatha R. Johnson of our Physics Department for the infrared studies on the oximes and to our Analytical Group for the elementary analyses.

Experimental[8a]

Stimulation Tests.—*Penicillium chrysogenum* Q-176 was used in a chemically defined medium similar to that described by Stone and Farrell[9] except that the lactose concentration was 2.0%, and 0.002% of manganous sulfate was added. The 100-ml. portions of the medium in 500-ml. Erlenmeyer flasks were inoculated with 5 ml. of three day vegetative seed and the flasks were shaken at 24° for five to seven days.

2-Thiopheneacetic Acid.—2-Thiopheneacetonitrile was prepared by a modification of the literature method.[10] The chloromethylation of thiophene was carried out at −5 to 0° and the product was extracted with chloroform instead of ether. The chloroform was removed *in vacuo* and the residue was used directly for the preparation of the nitrile.

The acid was prepared from the nitrile by alkaline hydrolysis, and was found to melt at 59.5–60.5° after several crystallizations from carbon tetrachloride. An analytical sample was obtained by conversion to the potassium salt, which was dissolved in 94% acetone and recrystallized by the addition of two volumes of dry acetone. The acid which was obtained by acidification of the recrystallized potassium salt melted at 62–63°. Recrystallization from methylcyclohexane did not change the melting point.[11]

Anal. Calcd. for $C_6H_6SO_2$: C, 50.69; H, 4.26; neut. eq., 142.2. Found: C, 50.57; H, 4.36; neut. eq., 142.

Esters of 2-Thiopheneacetic Acid.—The methyl ester was prepared from the above-described acid, using methanol and *p*-toluenesulfonic acid; b. p. 100–104° (14 mm.).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 54.06; H, 5.10.

The *n*-butyl ester was prepared by the same method; b. p. 80–82° (0.3 mm.).

Anal. Calcd. for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12. Found: C, 60.77; H, 6.99.

5-Substituted 2-Thiopheneacetamides.—The methyl esters were shaken overnight at 25° with 28% aqueous ammonia (5 ml. per g.). The crude amides were filtered, washed with water and recrystallized from water or benzene. If the product was not white it was recrystallized again, using water and decolorizing carbon. The analyses, melting points and recrystallization solvents are listed in Table II.

TABLE II

5-SUBSTITUTED 2-THIOPHENEACETAMIDES

5-Substituent	M. p., °C.	Molecular formula	Carbon, %		Hydrogen, %	
			Calcd.	Found	Calcd.	Found
None	146–147	C_6H_7NOS	51.04	51.21	5.00	4.80
Chloro[a]	121.5–122.5	C_6H_6NOSCl	41.03	40.97	3.44	3.41
Bromo[15]	125.5–126.5	C_6H_6NOSBr	32.74	32.85	2.75	2.75
t-Butyl[a]	134–136	$C_{10}H_{15}NOS$	60.87	60.73	7.66	7.14
Acetyl	149–150	$C_8H_9NO_2S$	52.44	52.46	4.95	4.80

[a] Recrystallized from benzene. Remaining compounds recrystallized from water.

5-Chloro-2-thiopheneacetic Acid.—A mixture of 40 g. of 2-chlorothiophene,[12] 28 ml. of concentrated hydrochloric acid and 24 ml. of 37% formaldehyde was stirred rapidly and held at 25–30° by means of an ice-bath while a rapid stream of dry hydrogen chloride was added. When the mixture had been saturated with hydrogen chloride, the

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[7] Hartough, Kosak and Sardella, THIS JOURNAL, **69**, 1014 (1947).

[8] Hartough and Kosak, *ibid.*, **68**, 2639 (1946).

[8a] All melting points are corrected. All boiling points are uncorrected.

[9] Stone and Farrell, *Science*, **104**, 445 (1946).

[10] Blicke and Leonard, THIS JOURNAL, **68**, 1934 (1946).

[11] Blicke and Zienty[5] have reported a melting point of 76° for 2-thiopheneacetic acid. Apparently this is a case of dimorphism that has not been previously recorded in the literature.

[12] A sample of this compound was supplied by courtesy of the Socony-Vacuum Oil Company.

product was extracted with chloroform. The extract was dried over magnesium sulfate and then over anhydrous potassium carbonate. The yield of 5-chloro-2-chloromethylthiophene, b. p. 96–98° (17 mm.),[13] was 30.0 g. (54%).

5-Chloro-2-thiopheneacetonitrile was prepared from 5-chloro-2-chloromethylthiophene by the same method that was used for the preparation of 2-thiopheneacetonitrile; b. p. 124–131° (13 mm.); yield, 80%. On redistillation the major portion boiled at 87–88° (0.25 mm.). Analyses indicated that the product was somewhat impure.

Anal. Calcd. for C_6H_4NSCl: C, 45.72; H, 2.56. Found: C, 44.56; H, 2.99.

When the preparation was repeated without distilling the intermediate chloromethyl derivative, the yield of nitrile, based on 2-chlorothiophene, was 62%.

Attempts to hydrolyze the nitrile directly to 5-chloro-2-thiopheneacetic acid were unsuccessful. Both alcoholic potassium hydroxide and 50% sulfuric acid caused extensive decomposition. The nitrile was converted to the methyl ester by dissolving it in an equal volume of dry methanol, saturating the solution with dry hydrogen chloride at 5–10° and allowing it to stand overnight at room temperature. No attempt was made to isolate the intermediate imino ether hydrochloride which precipitated. It was converted to the methyl ester by adding slightly more than the calculated amount of water and boiling under reflux for six hours. The yield of methyl 5-chloro-2-thiopheneacetate, b. p. 71–82° (0.4 mm.), was 67%. On redistillation the main fraction boiled at 77–78° (0.4 mm.).

Anal. Calcd. for $C_7H_9SO_2Cl$: C, 44.10; H, 3.71. Found: C, 44.17; H, 3.82.

5-Chloro-2-thiopheneacetic acid was prepared from the methyl ester by allowing it to stand overnight at room temperature in methanolic potassium hydroxide. The crude product was recrystallized to constant melting point from carbon tetrachloride; m. p. 64.5–65.5°.

Anal. Calcd. for $C_6H_5SO_2Cl$: C, 40.80; H, 2.85; neut. eq., 176.6. Found: C, 40.48; H, 2.78; neut. eq., 176.5.

Bis-(5-methyl-2-thiophene)-methane.—When the procedure that had been used for the chloromethylation of thiophene was applied to 2-methylthiophene,[12] the main product was the corresponding diarylmethane[14]; b. p. 92–94° (0.08 mm.).

Anal. Calcd. for $C_{11}H_{12}S_2$: C, 63.42; H, 5.81; S, 30.78. Found: C, 63.40; H, 5.60; S, 30.94.

Methyl 5-Bromo-2-thiopheneacetate.—A solution of 15.6 g. of methyl 2-thiopheneacetate in 100 ml. of carbon tetrachloride was cooled in an ice-bath and stirred while a solution of 16.0 g. of bromine in 45 ml. of carbon tetrachloride was added over a period of ninety minutes. The solution was washed with water, then with bicarbonate solution, and the solvent was removed *in vacuo*. The residual liquid was vacuum distilled, giving 16.9 g. of product that boiled at 75–84° (0.06 mm.). The product turned yellow and evolved hydrogen bromide on standing.

In attempting to convert the above product to the 5-cyano compound, 11.9 g. was mixed with 7.0 g. of cuprous cyanide and 25 ml. of dry pyridine. An exothermic reaction took place on shaking the stoppered flask. The temperature rose to about 50°. The resulting product boiled at 68–75° (0.1 mm.). The major portion distilled at 73–74° (0.1 mm.). The recovered product (7.7 g.) did not evolve hydrogen bromide on standing and the elementary analyses were in fair agreement with the calculated values for methyl 5-bromo-2-thiopheneacetate.

Anal. Calcd. for $C_7H_7BrO_2S$: C, 35.76; H, 3.00; Br, 33.99. Found: C, 37.08; H, 3.23; Br, 32.38.

When the purified bromo ester was refluxed overnight with cuprous chloride in pyridine it was converted to an asphalt-like material.

5-*t*-Butyl-2-acetylthiophene.—A mixture of 101.3 g. of 2-*t*-butylthiophene,[12] 175 ml. of acetic anhydride and 35 g. of Super-Filtrol was stirred and heated on the steam-bath for six hours. The catalyst was removed and the filtrate was vacuum distilled. The main fraction (105 g.) boiled at 122–127° (9.5 mm.). Although the analyses were not in good agreement with the theoretical values, a good yield of the semicarbazone was obtained from this product.

Anal. Calcd. for $C_{10}H_{14}OS$: C, 65.89; H, 7.74. Found: C, 66.56; H, 7.52.

The semicarbazone melted at 223–225°, after recrystallization from nitromethane.

Anal. Calcd. for $C_{11}H_{17}N_3OS$: C, 55.20; H, 7.16. Found: C, 55.27; H, 6.68.

Methyl 5-*t*-Butyl-2-thiopheneacetate.—The ketone described above (18.2 g.) was mixed with 18 ml. of morpholine and 4.8 g. of sulfur and refluxed for ten hours. The resulting dark brown liquid was diluted with ether and washed with sodium hydroxide, dilute hydrochloric acid and then water. Removal of the ether left an oil that did not crystallize. It was dissolved in 100 ml. of methanol and 25 ml. of 50% sodium hydroxide was added. After boiling under reflux for 18 hours, the methanol was removed by distillation. The residue was diluted with water, extracted with ether and then acidified. A dark red–brown oil separated. This was dissolved in ether and treated with activated carbon to remove part of the color. Removal of the ether gave an oil which also failed to crystallize. This crude acid was esterified with methanol in presence of *p*-toluenesulfonic acid to give a methyl ester, b. p. 75–76° (0.15 mm.); yield 5.0 g.

Anal. Calcd. for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60. Found: C, 62.45; H, 7.40.

Methyl 5-Acetyl-2-thiopheneacetate.—A mixture of 100 g. of methyl 2-thiopheneacetate, 100 ml. of acetic anhydride and 30 g. of Super-Filtrol was heated on the steam-bath for five hours with mechanical stirring. The catalyst was filtered and washed thoroughly with boiling benzene. The solvents were removed *in vacuo* and the residue distilled at 0.15 mm.; b. p. 114–124° (bath temp. 150–170°). The product solidified in the receiver; m. p. 44–46° (capillary) and 45.5° (time temperature curve). The yield was 120.7 g. (87%).

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.53; H, 5.09. Found: C, 54.28; H, 5.00.

5-Acetyl-2-thiopheneacetic Acid.—A mixture of 14.2 g. of 2-thiopheneacetic acid, 25 ml. of acetic anhydride and 5.0 g. of Super-Filtrol was heated on the steam-bath with stirring for six hours. After filtering off the catalyst and removing the solvents *in vacuo*, the resulting orange–brown solid (15 g.) was recrystallized once from ethylene dichloride. After two recrystallizations from hot water, using 6 g. of activated carbon each time, a colorless product was obtained; yield 8.1 g. (44%); m. p. 130–131°.

Anal. Calcd. for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.15; H, 4.28.

Iodine was also used to catalyze the above reaction but the yields were much lower.

The acid was also obtained in good yield by dissolving the methyl ester in warm 1 *N* potassium hydroxide by rapid stirring, and acidifying the clear solution.

Hypochlorite Oxidation of Methyl 5-Acetyl-2-thiopheneacetate.—An attempt to oxidize methyl 5-acetyl-2-thiopheneacetate to 5-carboxy-2-thiopheneacetic acid using sodium hypochlorite in accordance with the procedure described by Newman and Holmes[15] gave a pale yellow solid

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[13] Clapp, Clark, Vaughan, English and Anderson, THIS JOURNAL, **69**, 1549 (1947), reported a b. p. of 67–68° (1 mm.) for this compound.

[14] The chloromethylation of 2-methylthiophene and the conversion of the chloromethyl compound into 2-(cyanomethyl)-5-methylthiophene are described in U. S. Patent 2,425,721 (*C. A.*, **42**, 613h (1948)). However, no physical constants, analyses or yields are given.

[15] Newman and Holmes, "Organic Syntheses," Col. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 428.

that was recrystallized from water. Analytical data indicated that the compound was 2,5-thiophenedicarboxylic acid. The melting point was above 260°.[16]

Anal. Calcd. for $C_6H_4O_4S$: C, 41.86; H, 2.34; neut. eq., 86.07. Found: C, 42.46; H, 2.57; neut. eq., 86.05.

Oximes of 5-Acetyl-2-thiopheneacetic Acid.—Ten grams of methyl 5-acetyl-2-thiopheneacetate was stirred rapidly with a solution of 6.0 g. of sodium hydroxide in 100 ml. of water until a clear solution was obtained. After fifteen minutes, 10.0 g. of hydroxylamine hydrochloride was added (*p*H about 7) and the solution was heated on the steam-bath for thirty minutes, cooled, and acidified to *p*H 2 with concentrated hydrochloric acid. After standing in the refrigerator, the product was filtered and recrystallized from 500 ml. of hot water, using decolorizing carbon; yield 5.5 g., m. p. 159–160° (dec.). An additional 2.1 g., m. p. 156–157°, was obtained by concentration of the filtrate. One gram of the oxime was heated on the steam-bath with 2 ml. of 96% sulfuric acid for fifteen minutes, cooled, and poured into 20 g. of finely chopped ice. The solid which separated was recrystallized four times from hot water; m. p. 172–173° (dec.).

Anal. Calcd. for $C_8H_9NO_3S$: C, 48.23; H, 4.55. Found (m. p. 159–160°): C, 48.42; H, 4.53. Found (m. p. 172–173°): C, 48.10; H, 4.40.

The infrared spectra of the oximes which melted at 159–160° and 172–173° were very similar. The lower melting form contained all the bands of the higher melting form as well as some additional ones in the long wave length region and was probably a mixture of the *syn* and *anti* forms of the oxime. The higher melting form was believed to be predominately a single isomer.

Oximes of Methyl 5-Acetyl-2-thiopheneacetate.—A solution of 10.0 g. of methyl 5-acetyl-2-thiopheneacetate and 10.0 g. of hydroxylamine hydrochloride in 25 ml. of pyridine and 25 ml. of methanol was boiled under reflux for two hours and then concentrated to a sirup under reduced pressure on the steam-bath. About 100 ml. of water was added and the mixture was adjusted to *p*H 2 with hydrochloric acid and then extracted twice with 100-ml. portions of benzene. The benzene extracts were evaporated from the frozen state and recrystallized from 25 ml. of carbon tetrachloride. The resulting white crystals melted at 57–59°; yield, 8.8 g. (82%).

One gram of the above described oxime of the methyl ester was dissolved in 10 ml. of 96% sulfuric acid and heated on the steam-bath for two minutes, cooled and poured into 80 g. of finely chopped ice. The solid which separated melted at 63–65°. Recrystallization from hot water raised the melting point to 68–69° and a recrystallization from carbon tetrachloride raised the melting point to 72–73°.

A solution of 1.0 g. of the 57–59° oxime in 2 ml. of 96% sulfuric acid was heated on the steam-bath for thirty minutes, cooled and poured into a mixture of ice and water which contained 7 g. of sodium acetate. The resulting solution was dried from the frozen state.' The residual solids were extracted twice with 25-ml. portions of boiling chloroform. A crystalline residue was obtained upon removal of the chloroform; yield, 0.24 g. After two recrystallizations from benzene it melted at 126–127°.

Anal. Calcd. for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20. Found (m. p. 57–59°): C, 50.74; H, 4.93. Found (m. p. 72–73°): C, 50.64; H, 5.04. Found (m. p. 126–127°): C, 50.99; H, 4.89.

Summary

A series of 5-substituted 2-thiopheneacetic acids has been prepared and the compounds tested and evaluated as regards their utilization as penicillin precursors by molds.

KALAMAZOO, MICHIGAN RECEIVED JULY 14, 1949

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[16] Messinger, *Ber.* **18**, 563 (1885), reported the melting point of 2,5-thiophenedicarboxylic acid to be above 350°.

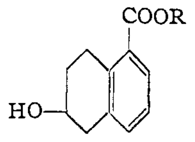
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

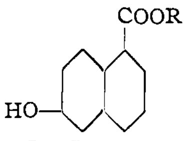
The Hydrogenation of Some Substituted β-Naphthols[1]

BY HERBERT E. UNGNADE[2] AND FRANCIS V. MORRISS[3]

Various reported attempts to prepare hydroxy acids derived from decalin by catalytic hydrogenation of naphthalene derivatives have met with failure due to the tendency of these compounds or perhaps their starting materials to undergo hydrogenolysis of the hydroxyl group.[4,5] Inasmuch as the hydrogenolysis reaction in the hydroxybenzoic acids can be prevented by reducing their esters with Raney nickel in the presence of small amounts of the corresponding sodium salts,[6] it appeared feasible that it could be repressed similarly in the naphthalene series. The reduction method has now been used successfully for the reduction of two hydroxynaphthoic esters and of 6-methoxy-2-naphthol without appreciable hydrogenolysis.[7]

Ethyl 6-hydroxy-1-naphthoate can be reduced partially by this method to give a tetrahydro ester (I) or a mixture (II) with analytical values corresponding to ethyl 6-hydroxyoctahydro-1-naphthoate, or perhydrogenated to give (III) depending on the activity of the catalyst.


I, R = Et
IV, R = H


III, R = Et
V, VI, VIII, R = H

Fresh W-4 Raney nickel catalyst gives an excellent yield (100%) of (III) while aged W-4 catalyst yields (I) or (II) and a little phenolic material which has not been further investigated.

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[1] From the Ph.D. thesis of F. V. Morriss.

[2] Present address: Chemistry Department, New Mexico Highlands University, Las Vegas, New Mexico.

[3] Shell Fellow, 1948–1949.

[4] Price, Enos and Kaplan, THIS JOURNAL, **69**, 2261 (1947).

[5] Long and Burger, *J. Org. Chem.*, **6**, 852 (1941).

[6] Ungnade and Morriss, THIS JOURNAL, **70**, 1898 (1948).

[7] An independent investigation of the hydrogenation of the two hydroxynaphthoic acids came to our attention at the conclusion of this work. Dauben, Hiskey and Markhart (abstract of a paper presented before the Division of Organic Chemistry of the American Chemical Society at San Francisco, March, 1949, page 44L) have disclosed a successful method for the hydrogenation of the free hydroxynaphthoic acids in alkaline solution which enables them to prepare either tetrahydro or perhydro acids.