markably small range in all of the experiments and was below about 0.6 only in the experiments involving lower temperature and low yields of mono-alkylate. This suggests that an isomerization equilibrium between the two isomers was established under all of the conditions except those under which the low concentration of mono-alkylate prevented the attainment of equilibrium at the space velocities used.

The possibility that the catalyst influences the "normal" action of the sulfur atom in controlling the point of substitution should not be overlooked, however, since our data show that appreciable thiophene decomposition (evolution of hydrogen sulfide) occurred in all experiments. This suggests that the thiophene molecule, during the heterogeneous reaction, is not in the state corresponding to that of the aforementioned homogeneous reactions and, therefore, is not subject to the orientation rules of the homogeneous reactions. A study of the activity of the phosphoric acid catalyst for isomerization of the 2- to the 3-isomer should show which of the above two hypotheses is correct.

The complicated array of simultaneous and consecutive reactions which appear to be involved in the over-all reaction make it impossible to obtain an adequate theoretical treatment of the reaction kinetics which can be tested by the experimental data herein presented.

Acknowledgments.—We wish to express our thanks to the following people for their contributions to the work: Messrs. M. P. L. Love and L. L. Lovell at whose suggestion the larger project, of which this work was a part, was carried out; Mr. W. K. Meerbott who carried out the hydrogenation of the alkylates; and Dr. R. A. Friedel for his interpretation of the infrared spectra of the decanes.

Summary

Alkylthiophenes were prepared by direct alkylation of thiophene with isobutylene and propylene over a phosphoric acid polymerization catalyst. Alkylation was predominantly in the 2-position, although remarkably high yields of the 3-isomer were obtained. The physical properties and absorption spectra of several of the alkylthiophenes were determined. A study was made of the influence of several reaction variables on the alkylation with isobutylene.

Houston, Texas Received July 7, 1947

[Contribution from the Chemistry Laboratory of Indiana University]

3-Substituted Thiophenes. I

By E. Campaigne and William M. LeSuer[1]

A great deal of work has been reported in the recent literature on the preparation and pharmacological evaluation of thiophene compounds.[2–5] Due to the fact that 3-substituted thiophene derivatives have not been available in the desired quantities, this work has been limited, by necessity, to thiophene compounds substituted in the 2-position.

It has been shown repeatedly that replacement of the 2-thienyl radical for the benzene nucleus in pharmacologically active compounds leads to products of similar activity.[3,4,6] In some cases the thiophene analog has been toxic to a lesser degree.[7] It therefore seemed of interest to prepare some 3-substituted thiophene compounds in order that their pharmacological properties might be compared with those of the 2-substituted derivatives and the benzene analogs. The work described in this paper deals with the synthesis of intermediate compounds required in the preparation of some 3-substituted thiophene derivatives with possible pharmacological activity.

The synthesis of 3-thenaldehyde (V)[8] has been previously carried out in poor yield in a reaction utilizing the difficultly obtainable 3-iodothiophene.[9] 3-Thenoic acid (VII) has been prepared in small amounts by numerous methods: oxidation of 3-methylthiophene (I)[10,11]; chlorination of I followed by hydrolysis, oxidation and finally reduction[12]; treatment of 3-iodothiophene with potassium cyanide and water in a sealed tube[13];

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[1] Taken from part of a thesis to be submitted by William M. LeSuer in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Indiana University.

[2] Blicke and Burckhalter, This Journal, **64**, 477 (1942).

[3] Chen and Abreu, *Fed. Proc.*, **6**, 316 (1947).

[4] Dann and Moller, *Ber.*, **80**, 23 (1947).

[5] Johnson, Green and Pauli, *J. Biol. Chem.*, **153**, 37 (1944).

[6] Blicke and Zienty, This Journal, **63**, 2945 (1941).

[7] Steinkopf and Ohse, *Ann.*, **448**, 205 (1926).

[8] The recent literature contains various names for the same thiophene compound. For instance, thiophenecarboxylic acid, 2-thienoic acid, 2-thiophenoic acid, and thenoic acid are all used to designate the same compound. We have used the system which seems simplest, based on the analogy between thiophene and benzene compounds. In this system the prefix "then" corresponds to the prefix "benz"; *i. e.*, "benzyl chloride," "2-thenyl chloride," "benzaldehyde," "3-thenaldehyde," "benzoic acid," "3-thenoic acid," "2-thenoyl chloride," etc. The prefix "thienyl" corresponds to "phenyl" and we have "2-thienylacetic acid," "3-acetothienone," etc. This system fits into the framework of the large group of useful trivial names which has been established in the benzene series, and saves much space. Thus 1-hydroxy-2-keto-1,2-di-(3-thienyl)-ethane becomes 3,3′-thenoin, and thiophene-3-aldehyde becomes 3-thenaldehyde.

[9] Steinkopf and Schmitt, *Ann.*, **533**, 264 (1938).

[10] Muhlert, *Ber.*, **18**, 3003 (1885).

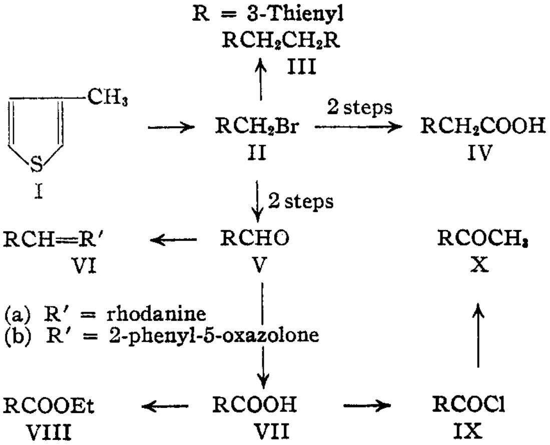
[11] Damsky, *ibid.*, **19**, 3282 (1886).

[12] Voerman, *Rec. trav. chim.*, **26**, 293 (1907).

[13] Rinkes, *ibid.*, **55**, 991 (1936).

and by the Grignard reaction with carbon dioxide on 3-iodothiophene.[9]

We have used N-bromosuccinimide as a bromination agent in the preparation of 3-thenyl bromide (II) from 3-methylthiophene. Buu-Hoi and Lecocq[14] described the preparation of α-bromomethylnaphthalene by the action of N-bromosuccinimide on α-methylnaphthalene, but Buu-Hoi[15] was unable to prepare benzyl bromide from toluene by the same procedure. Schmid and Karrer[16] reported that the latter reaction yielded benzyl bromide in 64% yield in the presence of small amounts of benzoyl peroxide. In the absence of the peroxide catalyst we have obtained only nuclear substitution in the reaction of N-bromosuccinimide with 3-methylthiophene, but when benzoyl peroxide was added to the reaction mixture side chain bromination predominates, yielding mainly II along with a small amount of nuclear substituted material. The latter material is probably 2-bromo-3-methylthiophene. Some difficulty has been experienced in the separation of the side chain and nuclear substituted products. 3-Thenyl bromide decomposes on distillation at atmospheric pressure and a sharp separation of the two isomers could not be effected by distillation under reduced pressure. The presence of the nuclear substituted material caused no trouble as it was removed in the next step in the sequence of reactions leading to the aldehyde. The aldehyde was prepared from II by the method of Sommelet.[17] The mixture of bromides was treated with hexamethylenetetramine in chloroform and the salt formed with II separated from solution while the nuclear substituted material remained in solution. Steam-distillation of a water solution of the salt yields V in 30–40% yield.



The aldehyde was converted to 3-thenoic acid (VII) in nearly quantitative yield by silver oxide oxidation, but only to the extent of 40–60% by alkaline permanganate. The aldehyde undergoes the usual aromatic aldehyde reactions. Treatment with sodium cyanide in alcoholic solution yielded the benzoin analog, 3,3'-thenoin. Normal condensation products were obtained with hippuric acid and rhodanine, namely, 2-phenyl-4-(3-thenal)-5-oxazolone and 3-thenalrhodanine, respectively.

The acid was converted to several esters for characterization. From the acid chloride[9] we have prepared 3-acetothienone (X) employing cadmium methyl, by the method of Gilman and Nelson.[18]

An attempt was made to prepare 3-thienylacetic acid (IV) from II through the Grignard reaction with carbon dioxide. In this preparation the same difficulty reported by Blicke and Burckhalter[2] in a Grignard reaction on 2-thenyl chloride was encountered. Coupling occurred giving rise to the formation of a dithienylethane, in our case *sym*-di-3-thienylethane (III). 3-Methyl-2-thenoic acid[19] was also isolated from this reaction. This may have been formed from a small amount of 2-bromo-3-methylthiophene which contaminated the starting material. The yield of 3-methyl-2-thenoic acid was somewhat higher than expected, considering the purity of the starting material as calculated from the yield of hexamethylenetetramine salt. It is not impossible that some rearrangement has occurred giving rise to the formation of 3-methyl-2-thenoic acid. Such a rearrangement does not occur in the benzene series when benzylmagnesium bromide is treated with carbon dioxide,[20] but the high activity of the alpha position in the thiophene nucleus must be considered in dealing with thiophene compounds substituted in the beta position such as II. Further work is being carried out on the possibility of rearrangement in this reaction.[21]

3-Thienylacetic acid was prepared by conversion of II to the nitrile and hydrolysis of the latter product.

Experimental[22]

N-Bromosuccinimide.—This compound was prepared by the method of Ziegler, *et al.*[23] A good grade of succinimide should be employed in this preparation; that described by Clarke and Behr[24] being satisfactory. Some commercial materials give a poor product which reacts unsatisfactorily in brominations. The product should be thoroughly washed with water to remove any excess bromine. It was found that storing the material open to the air, allowing traces of bromine to escape, gives the most active brominating agent.

3-Thenyl Bromide (II).—To a solution of 55 g. (0.56 mole) of 3-methylthiophene in 150 ml. of carbon tetra-

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(14) Buu-Hoi and Lecocq, *J. Chem. Soc.*, 830 (1946).

(15) Buu-Hoi, *Ann.*, **556**, 1 (1944).

(16) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(17) Sommelet, *Compt. rend.*, **157**, 852 (1913).

(18) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(19) Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).

(20) Gilman and Kirby, This Journal, **54**, 345 (1932).

(21) Since this paper was submitted, Lecocq and Buu-Hoi [*Compt. rend.*, **224**, 658 (1947)] have shown that allylic rearrangement of this type does occur in 5-methyl-2-bromomethylthiophene, yielding 3-substituted-2,5-dimethylthiophenes.

(22) All melting points are uncorrected.

(23) Ziegler, Spath, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(24) Clarke and Behr, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 562.

chloride was added 88.5 g. (0.50 mole) of N-bromosuccinimide and 0.2 g. of benzoyl peroxide. The mixture was shaken vigorously and then heated. During the first ten minutes an additional 0.2 g. of benzoyl peroxide was added. The flask and contents were shaken vigorously at frequent intervals during the first hour, then refluxed for five additional hours. After cooling in an ice-bath the succinimide was removed by filtration and washed with 50 ml. of carbon tetrachloride. The solutions from two identical experiments were combined at this point and the carbon tetrachloride removed at reduced pressure. The remaining highly lachrymatory oil was distilled in vacuum and 114 g. of faintly tan material was collected at 70–100° (2 mm.). This material was unstable and darkened slowly. The best sample contaminated by a small amount of 2-bromo-3-methylthiophene was collected at 75–78° (1 mm.); d^{20}_{4} 1.635, n^{20}D 1.604.

Hexamethylenetetramine Salt of 3-Thenyl Bromide.—Hexamethylenetetramine (90 g.) was added to a solution of 114 g. of 3-thenyl bromide in 200 ml. of chloroform. The mixture was refluxed for one hour, cooled, and the salt filtered. Distillation of the chloroform filtrate yielded a small amount of 2-bromo-3-methylthiophene, b. p. 173–175° (745 mm.). The salt was washed with 100 ml. of ether; yield, 150 g. This material may be purified by crystallization from absolute ethanol, yielding white needles. It softens at 120°, becomes brown and melts completely at 150°. *Anal.* Calcd. for $C_{11}H_{17}N_4SBr$: S, 10.10. Found: S, 9.80.

3-Thenaldehyde (V).—The hexamethylenetetramine salt (150 g.) was dissolved in 500 ml. of hot water and rapidly steam-distilled, one liter of distillate being collected. The distillate was acidified with hydrochloric acid and extracted with three 100-ml. portions of ether. The ether solution was dried over drierite and the ether removed on a steam-bath. Distillation of the residue at atmospheric pressure yielded 35.8 g. (32%, based on N-bromosuccinimide) of 3-thenaldehyde, b. p. 195–199° (744 mm.); d^{24}_{4} 1.2800, n^{20}D 1.5860.

The phenylhydrazone,[25] previously reported,[7] melted at 136–137° after recrystallization from dilute alcohol.

The **2,4-dinitrophenylhydrazone** crystallized as deep orange needles from nitromethane, m. p. 236–237°.

Anal. Calcd. for $C_{11}H_8O_4N_4S$: S, 10.97. Found: S, 11.09.

The **semicarbazone** crystallized from a water–ethanol solution as white leaflets, m. p. 233–234°.

Anal. Calcd. for $C_6H_7N_3OS$: S, 18.95. Found: S, 19.25.

3-Thenoic Acid (VII).—To the brown silver oxide, formed from 150 g. of silver nitrate and 70 g. of sodium hydroxide in 600 ml. of water, was added 47.5 g. (0.424 mole) of 3-thenaldehyde in small portions with cooling. The addition was completed in twenty minutes and the oxidation was completed in thirty minutes as evidenced by the disappearance of the characteristic aldehyde odor. The silver was removed and washed with 200 ml. of water. The solution was acidified with concentrated hydrochloric acid and cooled for twelve hours; yield 49.3 g.; m. p. 136–137°. Concentration of the mother liquors to 50 ml. yielded an additional 3.2 g. of acid; total yield, 52.5 g. (97%); m. p. 137–138° after recrystallization from water.

The ***p*-bromophenacyl ester** was crystallized from ethanol; m. p. 129–130°.

Anal. Calcd. for $C_{13}H_9O_3SBr$: S, 9.86. Found: S, 9.99.

The **amide**[9] was recrystallized from water; m. p. 179–180°.

3-Thenoyl Chloride (IX).[9]—This material was prepared from VII, employing thionyl chloride, in 88% yield; b. p. 203–204° (748 mm.), 110–111° (36 mm.); m. p. 51–52°.

Ethyl-3-thenoate (VIII).—The ester was prepared from IX in 76.7 yield; b. p. 207–208° (736 mm.); d^{27}_{4} 1.1799, n^{20}D 1.5230.

Anal. Calcd. for $C_7H_8O_2S$: S, 20.53. Found: S, 20.77.

3-Acetothienone (X).—The procedure of Gilman and Nelson,[18] used in the preparation of *p*-methoxyacetophenone, was employed in this preparation; yield 81%; b. p. 208–210° (748 mm.). After recrystallization from petroleum ether (30–60°) this material melted at 57°.

Anal. Calcd. for C_6H_6OS: S, 25.41. Found: S, 26.08.

The **2,4-dinitrophenylhydrazone** crystallized as red needles from chloroform, m. p. 265°.

Anal. Calcd. for $C_{12}H_{10}O_4N_4S$: S, 10.47. Found: S, 10.80.

The **semicarbazone** crystallized from water as white leaflets, m. p. 174–175°.

Anal. Calcd. for $C_7H_9N_3OS$: S, 17.50. Found: S, 17.27.

***sym*-Di-3-thienylethane** (III).—To a mixture of 200 ml. of anhydrous ether and 12.2 g. (0.5 mole) of magnesium was added dropwise with stirring 30 g. of the bromide mixture (3-thenyl bromide and 2-bromo-3-methylthiophene) in 75 ml. of ether. After the addition was complete and refluxing had subsided the mixture was stirred at room temperature for one-half hour and was then poured into a beaker containing 200 g. of crushed Dry Ice. The mixture was stirred vigorously and a stiff mass resulted which finally solidified. Water, followed by concentrated hydrochloric acid, was added with stirring. When all the solid material had dissolved the ether solution was removed, washed with water, and extracted twice with sodium bicarbonate solution. Acidification of the bicarbonate solution yielded 3 g. (12.5%) of 3-methyl-2-thenoic acid[19]; m. p. 144–145° after recrystallization from water.

Anal. Calcd. for $C_6H_6O_2S$: neut. equiv., 142.17. Found: neut. equiv., 142.20.

The ether solution was dried and the ether removed on a steam-bath. Vacuum distillation of the oil yielded 8 g. (48%) of *sym*-3,3′-dithienylethane; b. p. 120–130° (2 mm.); m. p. 64–65° after recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{10}S_2$: S, 33.00. Found: S, 33.31.

3-Thienylacetic Acid (IV).—A mixture of 100 ml. of water, 100 ml. of ethanol and 15 g. (0.3 mole) of sodium cyanide was stirred and refluxed while a solution of 54 g. of the mixture of bromides dissolved in 50 ml. of ethanol was added dropwise. After refluxing for three hours, the sodium bromide was removed by filtration. To the alcoholic filtrate was added 30 g. of potassium hydroxide and the solution was refluxed for fifteen hours. The alcohol was then removed by distillation. The basic solution was extracted with ether and the aqueous layer acidified with concentrated hydrochloric acid. The acid separated as an oil which was extracted with ether, dried and the ether removed on a steam-bath. The crystalline acid was recrystallized from petroleum ether (90–130°); m. p. 79–80°; yield 9.7 g. (25%).

Anal. Calcd. for $C_6H_6O_2S$: S, 22.54; neut. equiv., 142.17. Found: S, 23.10; neut. equiv., 142.00.

3,3′-Thenoin.—A solution of 50 ml. of ethanol containing 2 g. of sodium cyanide and 3 g. of 3-thenaldehyde was refluxed for one hour. The reaction mixture was poured into 150 ml. of water, the mixture thoroughly shaken, and cooled overnight; yield 1 g. (33%) after recrystallization from water; m. p. 116–117°.

Anal. Calcd. for $C_{10}H_8O_2S$: S, 28.59. Found: S, 28.59.

3-Thenalrhodanine (VIa).—This compound was prepared following the procedure of Julian and Sturgis[26]

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[25] All derivatives were prepared by the methods described by Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940.

[26] Julian and Sturgis, THIS JOURNAL, 57, 1126 (1935).

for veratralrhodanine, in a yield of 98%. Yellow needles were obtained from a water–acetone mixture, m. p. 212–213°.

Anal. Calcd. for $C_8H_5ONS_3$: S, 42.31. Found: S, 42.27.

2-Phenyl-4-(3-thenal)-5-oxazolone (VIb).—This material was prepared, following the procedure described by Gillespie and Snyder[27] for the preparation of 2-phenyl-4-benzal-5-oxazolone, in a yield of 63.5%. Yellow needles were obtained on crystallization from benzene, m. p. 188–190°.

Anal. Calcd. for $C_{14}H_9O_2NS$: S, 12.56. Found: S, 12.62.

Acknowledgment.—The authors wish to thank Dr. George A. Harrington of the Socony Vacuum Oil Company for the generous gift of 3-methylthiophene used in this investigation.

Summary

A synthesis, based on the side-chain bromination of 3-methylthiophene with N-bromosuccinimide, has been described for a number of 3-substituted thiophenes.

New compounds which have been prepared in this investigation are 3-thenyl bromide, 3-thienylacetic acid, 3-acetothienone, *sym*-di-3-thienylethane, 3-thenalrhodanine, 2-phenyl-4-(3-thenal)-5-oxazolone, 3,3′-thenoin, and some esters of 3-thenoic acid.

BLOOMINGTON, INDIANA RECEIVED AUGUST 21, 1947

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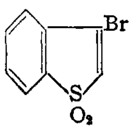
[27] Gillespie and Snyder, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 490.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Studies in the Thianaphthene Series. I. Reactivity of the Bromine Atom in 3-Bromothianaphthene-1-dioxide

BY F. G. BORDWELL AND C. J. ALBISETTI, JR.[1]

Komppa[2] found that the bromine atom in 3-bromothianaphthene was inert to boiling alcoholic alkali and 30% aqueous alkali. In contrast, 3-bromothianaphthene-1-dioxide (I) liberates bromide ion rapidly when treated with hot alkaline solutions, and several reactions in which the bromine atom of I was replaced with other groups were found to occur readily. By oxidation of 3-bromothianaphthene[2] with 30% hydrogen peroxide in acetic acid–acetic anhydride solution I was obtained in good yields.



I

The reaction of I with piperidine in refluxing alcoholic solution was rapid, a 96% yield of 3-(1-piperidino)-thianaphthene-1-dioxide being obtained within thirty minutes. In a similar manner excellent yields of 3-butylaminothianaphthene-1-dioxide and 3-diethylaminothianaphthene-1-dioxide were obtained. When I was dissolved in liquid ammonia no reaction occurred at −38°, but heating the reaction mixture at 110° for one and one-half hours in a pressure vessel gave 3-aminothianaphthene-1-dioxide. Aqueous ammonia at 110° gave only highly colored non-crystalline material. Less basic amines including aniline, 2-aminopyridine and 2-aminopyrimidine did not react with I in refluxing alcoholic solution.[3] Refluxing I with 2-aminopyridine in phenol also failed to effect the desired replacement; instead a small quantity of 3-phenoxythianaphthene-1-dioxide was obtained.

The hydrolytic behavior of 3-diethylaminothianaphthene-1-dioxide was tested in a few experiments. In refluxing solution hydrolysis to 3-hydroxythianaphthene-1-dioxide occurred within ten minutes in the presence of 10% sulfuric acid. 3-Aminothianaphthene-1-dioxide was also hydrolyzed rapidly in acidic solutions. In neutral or basic solutions 3-diethylaminothianaphthene-1-dioxide was more stable to hydrolysis.

It seems probable that the bromine atom in I can be replaced by reaction with nucleophilic reagents other than aliphatic amines. Thus far, the reaction with only one other class of reagents has been investigated. By refluxing I in methanol solution in the presence of an equimolar quantity of potassium hydroxide an excellent yield of 3-methoxythianaphthene-1-dioxide was obtained. When phenol was included in the reaction mixture 3-phenoxythianaphthene-1-dioxide was isolated. Refluxing a methanol solution of I for thirty minutes with an equimolar portion of sodium cyanide also gave 3-methoxythianaphthene-1-dioxide.

To test quantitatively the activity of the bromine atom, I was refluxed in benzene solution with excess piperidine as described by Spitzer and Wheland[4] for the determination of the activity of the bromine atoms in *p*- and *o*-nitrobromobenzenes

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[1] Du Pont Fellow, 1946–1947. Present address: Du Pont Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Abstracted from the Ph.D. dissertation of C. J. Albisetti, Jr.

[2] Komppa, *J. prakt. Chem.*, **122**, 319 (1929).

[3] The bromine atom in I is less active than that in 3-bromoindone, since Schlossberg, *Ber.*, **33**, 2426 (1900), found that the latter reacts readily in alcoholic solution with aniline to give 3-anilinoindone.

[4] Spitzer and Wheland, THIS JOURNAL, **62**, 2995 (1940).