Synthesis of 2-(1-Thiaalkyl)thiophenes. I[1]

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A number of 2-(1-thiaalkyl)thiophenes have been prepared for use as reference standards in the possible identification of such compounds in petroleum. Several different methods were employed in the synthesis, but the alkylation of 2-thiophenethiol was the most effective. The purity of the thiophenes was determined by gas chromatographic analysis.

At present the identification of the sulfur compounds in petroleum is greatly hampered by the lack of samples of pure sulfur compounds of known structure which may be used as reference standards. Thus, in connection with a series of studies involving the identification of type sulfur compounds present in petroleum, it was desired to prepare several compounds of the thiaalkylthiophene type. The first in a series of communications is concerned with the preparation of several 2-(1-thiaalkyl)thiophenes. A secondary objective of the work was to test each compound for its biological activity.

Adams[2] and co-workers reported the preparation of 2-(1-thiapropyl)thiophene *via* alkylation of cuprous thiolides with 2-bromothiophene. Profft[3] prepared a series of these compounds *via* alkylation of sodium 2-thiophenethiolide with alkyl halides. The initial approach involved the alkylation of sodium *n*-butylthiolide with 2-bromo- and 2-iodothiophene. The product obtained from the reaction of 2-iodothiophene proved to be 5,6-dithiadecane rather than the expected 2-(1-thiapentyl)thiophene. The 2-bromothiophene failed to react.

The seventeen 2-(1-thiaalkyl)thiophenes prepared were synthesized by general procedure reported by Profft.[3,4] Several methods for the preparation of 2-thiophenethiol were employed, the most successful being the Grignard synthesis reported by Houff and Schuetz[5] and Profft.[3] Alkylation of the thiol proceeded without difficulty except in the attempted alkylation with *t*-butyl halide. The 2-(1-thiaalkyl)thiophenes prepared are listed in Table I.

These compounds have been investigated further by research personnel at the U. S. Bureau of Mines, Bartlesville, Okla. The purity of each sample was ascertained by gas chromatography and is indicated in Table I. A plot of emergence time against carbon number of the normal alkyl chain is shown in Figure 1 at two temperatures. Since no irregularities in this relationship are evident, it is strong evidence that the molecular structure expected is present. Several of the compounds synthesized were desulfurized by the method of Thompson[6] and were found to yield the expected hydrocarbons. Mass spectra and infrared analysis have also been obtained.

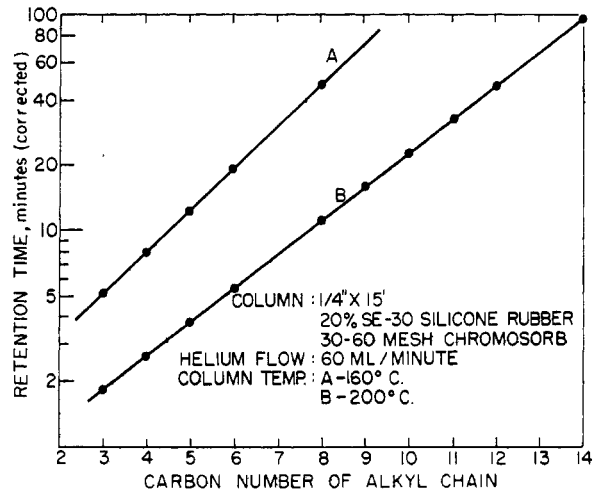

Fig. 1.—Relationship between retention time and carbon number of the normal alkyl chain in 2(1-thiaalkyl)-thiophenes.

From the data so far it appears that 2-(1-thiaalkyl)thiophenes are not present in the particular samples of the petroleum examined. Search is being continued on concentrates and samples from other fields.

The biological activity of the various sulfur compounds being prepared is under investigation by the Microbiological Research Group at Texas Woman's University. The first in a series of papers on the results of those tests has been published.[7] The specific activity of these 2-(1-thiaalkyl)thiophenes will be published at a later date.

Experimental

Alkylation of 2-Thiophenethiol.—The preparation of 2-(1-thiapentyl)thiophene is illustrative of a typical alkylation.

(1) Presented in part before the Division of Organic Chemistry at the Southwestern Regional Meeting of the American Chemical Society, Oklahoma City, Okla., December, 1960.

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TABLE I

2-(1-THIAALKYL)THIOPHENES PREPARED

2(1-Thiaalkyl)thiophenes		B.P. at Press. Indicated °/mm.	Size run, Moles	Yield, %	% Sulfur Obs.[a]	% Sulfur Theor.	Purity[b]	Retention Time[c] at (min.) 160°	Retention Time[c] at (min.) 200°
1-Thiabutyl	—S—C_3	68–70°/3.5	0.35	69	39.6	40.2	99	5.05	1.82
2-Methyl-1-thiapropyl	—S—C(C)—C	45–46°/3.0	.38	67	39.9	40.2	99+	4.08	...
1-Thiapentyl	—S—C_4	93–94°/5.0	.30	75	36.6	37.2	99	7.78	2.60
2-Methyl-1-thiabutyl	—S—C(C)—C_2	64–65°/1.0	.36	76	36.4	37.2	99+	6.35	...
3-Methyl-1-thiabutyl	—S—C(C)—C—C	84–85°/5.0	.49	75	36.9	37.2	98+	6.34	...
1-Thiahexyl	—S—C_5	122–123°/9.0	.17	81	33.8	34.4	96	12.10	3.72
4-Methyl-1-thiapentyl	—S—C_2—C(C)—C	116–118°/3.5	.30	75	33.3	34.4	99	9.95	...
1-Cyclopentyl-1-thiamethyl	—S— 	122–124°/3.0	.36	69	34.2	34.8	100−	15.3	...
1-Thiaheptyl	—S—C_6	122–123°/6.0	.33	78	31.0	32.0	99	18.9	5.37
1-Thiaoctyl	—S—C_7	134–136°/6.0	.30	41	29.2	29.5	100−	...	...
1-Thianonyl	—S—C_8	116–117°/1.5	.33	66	27.3	28.0	100−	46.2	11.0
1-Thiadecyl	—S—C_9	144–145°/12.0	.42	82	26.8	26.4	98	72.7	16.0
1-Thiaundecyl	—S—C_{10}	171–173°/6.0	.47	67	25.5	24.9	99	...	22.6
1-Thiadodecyl	—S—C_{11}	141–143°/1.5	.18	79	23.5	23.6	98+	...	32.8
1-Thiatridecyl	—S—C_{12}	184–186°/3.0	.375	67	21.6	22.5	98	...	46.8
1-Thiatetradecyl	—S—C_{13}	178–180°/2.0	.27	40	21.4	21.4	88	...	...
1-Thiapentadecyl	—S—C_{14}	198–200°/3.0	.17	64	19.9	20.4	83	...	95.6

[a] Shell-Braun method. [b] By gas-liquid chromatography (peak area). [c] Column 1/4 in. by 15 ft.; packing, SE-30 Silicone Rubber; carrier gas, helium at 60 ml./min. Retention times corrected for dead volume in column.

A 1-l. three-necked round bottom flask was equipped with a reflux condenser, stirrer, and dropping funnel. The flask was charged with 200 ml. of methanol, 116 g. (1 mole) of 2-thiophenethiol prepared by the method of Houff and Schuetz,[5] and 138.5 g. (1.01 moles) of *n*-butyl bromide. This reaction mixture was brought to reflux and then 56 g. (1.0 mole) of potassium hydroxide in 200 ml. of methanol was added dropwise. Refluxing and constant stirring was continued for a total of 8 hr.

After cooling, the precipitated potassium bromide was removed. Concentration of the alcoholic filtrate led to two layers and the separation of an additional quantity of potassium bromide. The organic layer was extracted with benzene and distilled. Procedure repeated two or three times until all the salt was separated. Removal of solvent and vacuum distillation gave rise to the desired products.

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Pyrimidines. VI. A Study of the Nuclear Reduction of Certain Pyrimidines[1]

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The nuclear reduction of chloro-, amino-, and methylpyrimidines (and their chloro derivatives) using platinum and supported palladium catalysts under acid conditions was investigated. The theoretical hydrogen consumption for the formation of the corresponding 3,4,5,6-tetrahydropyrimidine was observed whereupon hydrogenation ceased. The tetrahydropyrimidines could not be isolated as the pure hydrochlorides but only as the picrate derivatives in low yields. The preparation of the benzoyl derivatives leads only to degradation products.

Paper chromatography was used to show that the nuclear reduction products are unstable in aqueous media yielding a mixture of degradation products together with the desired tetrahydropyrimidine.

Nuclear reduction of substituted pyrimidines as a practical procedure for the preparation of positional isomers of the tetrahydropyrimidines has received little attention. Isolated reports of catalytic nuclear reduction of certain pyrimidines is to be found in the literature.[2-4] Smith and Christensen[5] initiated a systematic investigation of the nuclear reduction reaction as a practical preparative procedure. According to the report of their results, the acid reduction of substituted pyrimidines is straightforward yielding the expected products in good yield. Recent attempts to use their procedure for the preparation of the tetrahydropyrimidines were unsuccessful. This together with certain discrepancies in their analytical data necessitated reinvestigation of the entire scope of nuclear reduction of substituted pyrimidines in acid media by catalytic hydrogenation.

The catalyst-compound ratio necessary to effect nuclear reduction of all substituted pyrimidines at room temperature, low pressure, and aqueous acid solutions was determined by a series of experiments, the results of which are presented in Table I. 4-Amino-2,6-dichloropyrimidine absorbed only one half the amount of hydrogen required to reduce the compound to 4-amino-3,4,5,6-tetrahydropyrimidine even when more than the suggested catalyst-to-compound ratio was employed.[5] Since one half of the starting material was recovered, it is evident that the reduction does not yield a dihydropyrimidine as reported by Smith and Christensen.[5]

The fact that hydrogenation stops after absorption of the amount of hydrogen required for conversion to the tetrahydropyrimidine, yet requires a high catalyst-to-compound ratio, suggests that products are formed which are toxic to the catalyst. The relative ease of reducing dichloronitropyrimidines to the corresponding aminodichloropyrimidines is demonstrated by the data in Table I. Nitrodichloropyrimidines can be reduced stepwise to aminodichloropyrimidines and these in turn to aminopyrimidines,[5] both products being isolable. Aminodichloropyrimidines and aminopyrimidines will absorb the theoretical amount of hydrogen necessary to form the amino-3,4,5,6-tetrahydropyrimidine derivative. Reduction beyond this state cannot be effected under these conditions.

Both palladized charcoal and palladized barium sulfate[6] were equally effective as catalysts for the nuclear reduction of the substituted pyrimidines. Adams' catalyst, on the other hand, was effective only in the nuclear reduction of the amino- and methyl- substituted pyrimidines; it was inactive in experiments with chloro-substituted derivatives.

(1) Abstracted from a dissertation submitted by Harvey Aft to the faculty of Oregon State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Published with the approval of Monographs Publication Committee, Oregon State University, as Research Paper No. 420, Department of Chemistry, School of Science.

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