of alcohols to chlorotrifluoroethylene resulting in the formation of ethers of the type $ROCF_2CFClH$, which in general are quite stable. The reaction is carried out at room temperature and atmospheric pressure. Some of the physical properties of the ethers, along with their ultraviolet absorption spectra are discussed.

BOULDER, COLORADO RECEIVED NOVEMBER 21, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOUSTON REFINERY, SHELL OIL COMPANY, INCORPORATED]

Alkylation of Thiophene with Olefins[1]

BY W. G. APPLEBY, A. F. SARTOR, S. H. LEE, JR.,[2] AND S. W. KAPRANOS[3]

In connection with other work in these laboratories, it was necessary to prepare several alkyl thiophenes. When the experimental work was started in 1943, no method of preparation of the desired compounds which would meet our needs was found in the literature. It seemed worthwhile, consequently, to investigate the possibility of the direct alkylation of thiophene with appropriate olefins. This paper presents the results of our investigation of the alkylation of thiophene with propylene and isobutylene.

In the intervening time, the direct alkylation of thiophene by olefins and alcohols was reported by Kutz and Corson.[4] These authors reported the results of two experiments on the direct alkylation of thiophene with propylene and isobutylene under conditions considerably removed from those to be presented here. It is remarkable that in these experiments no evidence was presented for the formation of 3-isopropyl- and 3-*t*-butylthiophene, whereas in the experiments described below a considerable reaction to the 3-isomer was observed with each olefin. An explanation of the discrepancy will be presented in following sections of this paper.

Experimental

Purity of Chemicals.—The catalyst was phosphoric acid on kieselguhr (50–60%) manufactured by Universal Oil Products Company. The commercial $^1/_4$-inch pellets were cut into $^1/_8$-inch pellets. A fresh sample of catalyst was used for each experiment.

Synthetic thiophene was obtained from the Eastman Kodak Company. Satisfactory purity of the sample was indicated by a comparison of its properties with those reported in the literature: our sample, n^{20}_D 1.5287, d^{20}_4 1.0646: literature,[5] n^{20}_D 1.5286, d^{20}_4 1.0642.

Technical isobutylene from the Phillips Petroleum Corporation and propylene from the Ohio Chemical Company were used. The propylene had a purity of 98%, and the isobutylene contained a maximum of 4% isobutane as the only impurity.

Apparatus.—The alkylation reactions were carried out under continuous flow conditions in an 18–8 stainless steel reactor with a one-inch diameter. The unit was pressured with nitrogen prior to the introduction of thiophene and the olefin. For experiments in which 1:1 thiophene to olefin mole ratios were used, the liquids were charged from separate cylinders of a dual displacement pump. Higher thiophene to olefin ratios were obtained by dissolving the liquid olefin in the thiophene and maintaining the mixture at a low temperature until it was charged to the pump.

Alkylation of Thiophene with Propylene.—The alkylation of thiophene with propylene was carried out at 288°, 21.5 atmospheres, 1.1 thiophene to propylene mole ratio, and a flow rate of 3.6 g. of liquid charge per gram of catalyst per hour (WHSV). Under these conditions 70% of the thiophene and 50% of the propylene reacted to give an 80% by weight yield of liquid product which contained 40% mono-isopropylthiophene and significant amounts of di-isopropylthiophenes. This was equivalent to 30–35% conversion of propylene to the mono-isopropylthiophene. The amount of mono-isopropylthiophene recovered in in each experiment was too small for analysis. The combined monoalkylate fractions from several experiments were therefore distilled and then hydrogenated over a catalyst of mixed tungsten and nickel sulfides[6] at 288°, 33 atmospheres pressure, 0.1 WHSV and a hydrogen/-alkylate molal ratio of 15. The resulting paraffin hydrocarbons, as determined by physical properties and infrared spectra, consisted by weight of 38% 2,3-dimethylpentane, 54% 2-methylhexane and 8% of lower boiling hydrocarbons (perhaps from the propylene polymerization reaction). These values correspond to a relative distribution by weight of the mono-isopropylthiophenes in the liquid product of 41% 3-isopropylthiophene and 59% 2-isopropylthiophene.

Although the isopropylthiophenes were not purified as efficiently as the *t*-butylthiophenes (see below), the physical properties of selected distillation cuts were as follows: 2-isopropylthiophene,[7] b. p. 152.0°, n^{20}_D 1.5037, d^{20}_4 0.9673; 3-isopropylthiophene,[7] b. p. 155.5°, n^{20}_D 1.5060, d^{20}_4 0.9722.

Infrared analysis of the C_{10} hydrocarbons resulting from the hydrogenation of the di-isopropylthiophenes showed that the principal product was 2,7-dimethyloctane (from 2,5-di-isopropylthiophene). The presence of the other three possible decanes (2,3,4,5-tetramethylhexane, 2,3,6-trimethylheptane, and 2,5-dimethyl. 3-ethylhexane) was also indicated.

Alkylation of Thiophene with Isobutylene.—No physical properties were available in the literature for *t*-butylthiophene. Consequently, in order to have this information for identification of the products in later experiments, it was necessary to prepare pure samples of these compounds for such determinations. The liquid product for this purpose was prepared by alkylating thiophene with isobutylene (1:1 mole ratio) at 21.5 atmospheres, 270°, and a WHSV of 4.3.

The liquid product from this experiment was distilled in a column having nine theoretical plates at total reflux. This distillation separated the product roughly into three fractions: (1) unreacted thiophene, (2) mono-alkylthio-

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(1) Presented before the Organic Division at the September, 1947, meeting of the American Chemical Society at New York City.

(2) Present address: Department of Chemistry, University of Texas, Austin, Texas.

(3) Present address: Corn Products Company, Chicago, Illinois.

(4) Kutz and Corson, THIS JOURNAL, **68**, 1477 (1946).

(5) Haines, Wanger, Helm and Ball, U. S. Bur. Mines, R. I. 4060 (1946).

(6) Appleby, Lovell and Love, U. S. Patent 2,429,575 (1947).

(7) Haines, *et al.*, ref. 5, reported for the 2-isomer, b. p. 153°, n^{20}_D 1.503, d^{20}_4 0.967; for the 3-isomer, b. p. 157°, n^{20}_D 1.505, d^{20}_4 0.973.

TABLE I

PROPERTIES AND ANALYSES OF ALKYLATION PRODUCTS

Compound	Density d^{20}_4	Refractive index $n^{20}D$	$n^{20}C$	$n^{20}F$	B. p., °C.	M. p., °C.	Sulfur, % Calcd.	Found	Mol. weight Calcd.	Found
2-*t*-Butylthiophene	0.9514	1.49788	1.49395	1.50755	163.9	−59.2	22.8	22.4	140	141
3-*t*-Butylthiophene	.9574	1.50149	1.49755	1.51113	168.9	−54.8	22.8	22.5	140	141
Di-*t*-butylthiophene[a]	.9192	1.49312	1.48951	1.50205	223.5	....	16.3	16.3	196	196
Di-*t*-butyl-isomer A[b]	.9192	1.4923	1.4885	1.5008	221	....	..	..	...	...
Di-*t*-butyl-isomer B[b]	.9230	1.4935	1.4897	1.5022	224	....	..	..	...	...
Residue	....	....	....	....	...	....	..	21.7	...	253

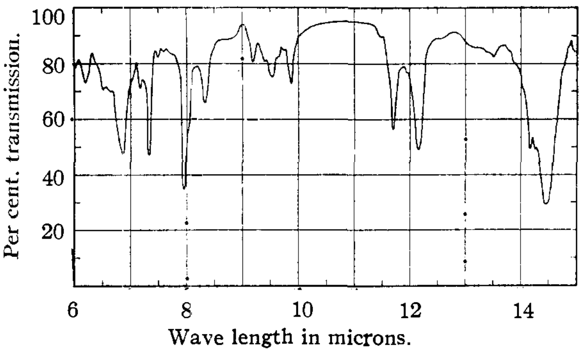
[a] Mixture of di-*t*-butylthiophenes. [b] Partially separated di-*t*-butylthiophenes.

phene, and (3) di-alkylthiophene and heavier. The last fraction was vacuum distilled to separate the di-alkylthiophene from the heavier residue.

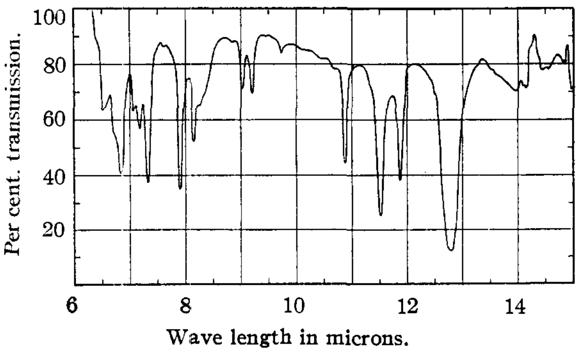
The isomeric mono-*t*-butylthiophenes were separated and purified by a series of precision distillations which were carried out at a 49:1 reflux ratio in a Stedman column having 60 theoretical plates at total reflux.

As a final check of the purity of the two isomers, time *versus* temperature freezing curves were obtained by a method similar to that of the Bureau of Standards.[8] These curves indicated a minimum purity for each isomer of 97%.

Hydrogenation of the higher boiling *t*-butylthiophene yielded principally 2,2,3-trimethylpentane, thus establishing the identity of that isomer as 3-*t*-butylthiophene. The lower boiling isomer was shown to be 2-*t*-butylthiophene by the formation of 2,2-dimethylhexane upon hydrogenation. These designations are analogous to those of other substituted thiophenes and the picolines; *i. e.*, the 3-isomers have the higher boiling points and densities. The paraffins resulting from the hydrogenation of the pure *t*-butylthiophenes were identified by determination of their infrared spectra.



2-*t*-Butylthiophene.



3-*t*-Butylthiophene.

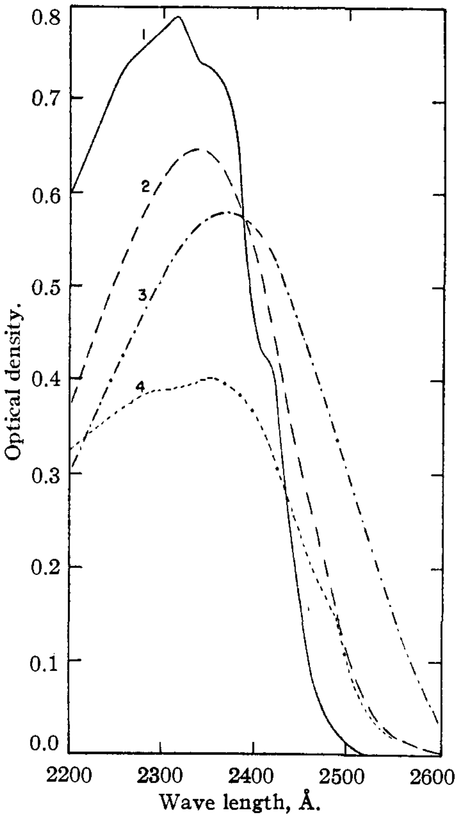
Fig. 1.—Infrared absorption spectra.

The di-*t*-butylthiophene, which was separated from the heavy residue, was pure only as regards the removal of the residue and mono-*t*-butylthiophene. Actually, at least two isomers were present. These were partially separated by precision distillation, but not enough of either of the isomers was available for further identification.

A summary of the physical properties and analytical values which were determined on the pure compounds and fractions discussed above is presented in Table I.

The residue left after removal of the di-*t*-butylthiophene showed, in addition to the analytical data of Table I, values of % C and % H of 70.3 and 7.6, respectively. These values correspond closely to the calculated values for a mixture containing about 70% di-*t*-butyldithienyl and 30% di-*t*-butylthiophene.

A very small amount of material boiling below thio-



1—Eastman thiophene
2—2-*t*-Butylthiophene
3—Mixed di-*t*-butylthiophenes
4—3-*t*-Butylthiophene

Fig. 2.—Ultraviolet absorption spectra—dilution 1:100,000 in cyclohexane.

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[8] Glasgow, Streiff and Rossini, *J. Research Nat. Bur. Standards*, **35**, 355 (1945).

phene and a small amount boiling between thiophene and the monoalkylate and possessing lower refractive indexes were indicated in the distillation of the liquid product. This material could have been formed in the course of a small amount of isobutylene polymerization followed by polymer disproportionation.

There was also noted a small amount of material with a high refractive index boiling between the monoalkylate and dialkylate. A substituted thiophene with a double bond in the side chain could have these properties, but it is not clear how a compound of that type could be formed under the conditions investigated here.

From the foregoing distillation and analytical data, the following approximate liquid product composition by weight can be written—37% 2-*t*-butylthiophene, 23% 3-*t*-butylthiophene, 33% di-*t*-butylthiophenes, 5% di-*t*-butyl-dithienyl and 2% unidentified.

Infrared and ultraviolet absorption spectra of several of the compounds of Table I are shown in Figs. 1 and 2. The marked differences between the spectra of the 2- and 3-*t*-butylthiophenes support the freezing point purity data mentioned above.

Thermal Alkylation.—Thiophene and isobutylene (1.2/1 mole ratio) were passed over glass beads at 267°, 21.5 atmospheres, and 4.4 WHSV. Distillation of the product from this experiment gave an overhead material which was thiophene. Since the sulfur content of the distillation residue was lower than that of thiophene, the residue may have contained two or more of the following products: thiophene, alkythiophenes, isobutylene polymer and polythienyls. If it is assumed that only thiophene and monoalkyl thiophenes were present, the maximum amount of thermal alkylation possible at these conditions is approximately 5%. A small amount of thiophene thermal decomposition was indicated by the presence of hydrogen sulfide in the product.

Catalytic Decomposition of Thiophene.—The catalytic decomposition of thiophene, as determined by passing thiophene over the phosphoric acid catalyst at 281°, 21.5 atmospheres, and 2.8 WHSV, amounted to 6.7%. In addition to the decomposition reaction, indicated by the amount of hydrogen sulfide formed, there was evidence of a considerable amount of some other reaction to form heavier compounds, possibly dithienyl. Distillation of the liquid product was stopped at 76.3% by volume overhead because of excessive kettle temperature. The overhead product was thiophene, but the remainder of the product solidified upon cooling to room temperature. Since 2,2′-dithienyl and 3,3′-dithienyl melt at 33° and 132°, respectively, it is possible that these materials constituted a major part of the residue.

Discussion

The results of the experiments above indicate that the reactions of major importance in the alkylation of thiophene with isobutylene over phosphoric acid are

(I) Thiophene $\longrightarrow$ H_2S + carbonaceous material
(II) Thiophene $\longrightarrow$ dithienyl
(III) Thiophene + isobutylene $\longrightarrow$ 2- and 3-*t*-butylthiophene
(IV) *t*-Butylthiophene + isobutylene $\longrightarrow$ di-*t*-butylthiophene
(V) *t*-Butylthiophene $\longrightarrow$ di-*t*-butyldithienyl
(VI) Isobutylene $\longrightarrow$ polymer
(VII) Disproportionation of the isobutylene polymer

On the basis of the liquid product compositions and the ratios of moles of isobutylene reacted/moles of thiophene reacted, it was possible to deduce the effects of the reaction variables on the above reactions.

Increase of the pressure in the range 7.8 to 21.5 atmospheres caused increases in the amounts of all reactions, particularly reactions I, II, III and IV. The relative amounts of 2- and 3-*t*-butylthiophenes were not affected appreciably by changes in operating pressure.

In the range of 235 to 302°, increases in the reaction temperature caused increases in the amounts of reactions I, II, IV, V, VI and VII. Although less monoalkylate was produced at the higher temperature, the ratio of the 3-isomer to the 2-isomer was greater than at the lower temperature.

Increase of the thiophene/isobutylene mole ratio in the range 1.2 to 6.1 caused decrease of the amounts of all reactions except I and II, and also a decrease of the ratio of 3-*t*-butylthiophene to the 2-isomer. Reaction I was not markedly affected by the change in mole ratio. The composition of the residue indicated that the amount of reaction II increased, relative to reaction V, at the higher mole ratio.

Increase of the weight space velocity from 2.9 to 9.9 caused decreases in the amounts of all reactions except III. The amount of reaction III increased, but the relative amounts of the 2- and 3-isomers remained approximately constant. Part of the differences in product composition and yields between our results and those of Kutz and Corson can undoubtedly be attributed to the differences in experimental conditions and the physical states of the catalysts used. It does not seem reasonable, however, that no 3-*t*-butylthiophene was formed in their work. An examination of their data on the physical properties of mono-*t*-butylthiophene (assumed by them to be the 2-isomer) reveals that the refractive index and density are intermediate between the values listed in Table I for the 2- and 3-isomers, suggesting that some 3-*t*-butylthiophene was formed in their work. A rough value of the amount may be estimated from these properties to be 21% of the monoalkylate fraction on the basis of the density and 22% on the basis of the refractive index, assuming a linear blending relation in these properties for the isomers. These values are to be compared to a value of 38% from our data reported above.

In the homogeneous reactions of thiophene it has been established[9] that substitution occurs almost entirely in the 2-position. The production of relatively high yields of 3-isopropyl- and 3-*t*-butylthiophenes in the heterogeneous reactions described above must, therefore, be attributed either to (1) some effect of the catalyst on the "normal" orientation influence of the sulfur atom or to (2) isomerization of the 2- to the 3-isomer. If the latter explanation is correct, both the temperature and the space velocity would be expected to have considerable influence on the relative yields of the two isomers. The influence of space velocity was shown to be negligible in the range 3–10 The 3-/2-*t*-butylthiophene ratio varied over a re-

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(9) Steinkopf, "Die Chemie des Thiophenes," Theodor Steinkopf, Dresden and Leipzig, 1941; Edwards Brothers, Inc., Ann Arbor, Michigan, 1944.

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. [illegible] 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).