4-Acetamido-1,2-isopropylidenedioxybenzene was prepared as described for the corresponding methylene- and ethylenedioxy- compounds. A small portion of the product was purified for analysis, m. p. 107–108°, after recrystallization from a mixture of ethyl acetate and hexane.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.73; H, 6.28; N, 6.76. Found: C, 63.60; H, 5.99; N, 6.67.

5-Nitro-4-acetamido-1,2-isopropylidenedioxybenzene was obtained in the manner described for the corresponding methylene- and ethylenedioxy- compounds, m. p. 162–163° after recrystallization from 95% ethanol. The yield, based on the 4-nitro-1,2-isopropylidenedioxybenzene, was 85%.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.35; H, 4.77; N, 11.12. Found: C, 52.28; H, 4.87; N, 11.32.

5-Nitro-4-amino-1,2-isopropylidenedioxybenzene was prepared by the hydrolysis of the corresponding acetamido compound in the same manner as described for the methylene- and ethylenedioxy- compounds. Employing 45 g. (0.18 mole) of 5-nitro-4-acetamido-1,2-isopropylidenedioxybenzene and 350 ml. of 1.3 N ethanolic hydrochloric acid there was obtained 30 g. (80% yield) of product, m. p. 123.5–124.5°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.79; N, 13.33. Found: C, 51.35; H, 5.07; N, 13.38.

Attempted preparation of 5,6-isopropylidenedioxy-8-nitroquinoline: (a) Method A, with acrolein.—Carried out in the usual manner there was obtained no acid-soluble material. The principal product was a black acid insoluble gum, which was somewhat soluble in boiling ethanol, giving a red solid which did not melt up to 250°.

(b) Method B, with phosphoric acid at 25° and 40°; none of the desired quinoline compound was obtained.

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Summary

The preparation of several prototype alkylene bridged 5,6-dihydroxyquinoline compounds is described. The compounds have shown fairly high activity against *Plasmodium lophurae* and *Plasmodium cathemerium* in the duckling.

Alkylation of Thiophene with Olefins

BY PHILIP D. CAESAR[1]

The direct alkylation of thiophene with olefins and alcohols in the presence of alumina–silica type catalysts and of 100% phosphoric acid was reported by Kutz and Corson.[2] In contrast to their observations, it has been found in this Laboratory that thiophene can be alkylated with olefins under suitable conditions in the presence of sulfuric acid, aluminum chloride, or boron trifluoride–diethyl ether complex without excessive decomposition or resinification of the thiophene. Other suitable alkylation catalysts were found to be fluoacids of boron trifluoride with water, ethyl acetate, ethyl alcohol and acetic acid. The olefinic alkylating agents employed were isobutylene, trimethylethylene, 1-pentene, diisobutylene, 1-octene and 1-hexadecene.

There are two primary factors which determine the selection of the catalyst. One is the reactivity of the olefinic alkylating agent and the other is the relative proportion of mono- and dialkylthiophene desired. If a reactive olefin such as isobutylene, trimethylethylene or diisobutylene is used, any of the catalysts described above, with the possible exception of aluminum chloride and concentrated sulfuric acid, will give satisfactory yields of the corresponding alkylthiophenes at moderate temperatures and atmospheric pressure (see Table I). The alkylation of thiophene with the relatively unreactive, straight chain olefins such as 1-pen-

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

tene, 1-octene or 1-hexadecene, takes place most satisfactorily in the presence of strong catalysts such as 90–96% sulfuric acid or boron trifluoride-water complex.

TABLE I

CATALYTIC ALKYLATION OF THIOPHENE WITH OLEFINS: MOLE RATIO OF REACTANTS = 1.0

Olefin form.	g.	Catalyst form.	g.	Time, hr.	Temp.,[b] °C.	Product,[d] % yield mono.[e]	di.[e]
i-C$_4$H$_8$	116	75% H$_2$SO$_4$	15	3	67	61	30
i-C$_4$H$_8$	116[a]	75% H$_2$SO$_4$	15	4	67	56	41
i-C$_4$H$_8$	26	90% H$_2$SO$_4$	42	1	−10	<20	<20
i-C$_4$H$_8$	24	60% H$_2$SO$_4$	42	1	82	0	0
i-C$_4$H$_8$	117	H$_3$BO$_2$F$_2$	10	3	62	66	31
i-C$_4$H$_8$	110	BF$_3$–ether	10	3	62	25	59
i-C$_4$H$_8$	110[a]	BF$_3$–ether	10	4	62	12	77
i-C$_4$H$_8$	50	AlCl$_3$	3	2	70	<10	..
i-C$_5$H$_{10}$	70	75% H$_2$SO$_4$	15	2	67	62	14
i-C$_5$H$_{10}$	140	H$_3$BO$_2$F$_2$	20	3	62	75	14
i-C$_5$H$_{10}$	140	BF$_3$–ether	20	3	67	16	68
(i-C$_4$H$_8$)$_2$	1120	80% H$_2$SO$_4$	120	4	35	82	7
(i-C$_4$H$_8$)$_2$	1680[a]	BF$_3$–ether	100	4	35	25	54
(i-C$_4$H$_8$)$_2$	55	AlCl$_3$	1	5	47[c]	25	52
1-C$_5$H$_{10}$	76	BF$_3$–ether	25	2	137	16	64
1-C$_8$H$_{16}$	56	96% H$_2$SO$_4$	15	5	100	43	<20
1-C$_8$H$_{16}$	112	BF$_3$·H$_2$O	80	2	75	28	<72
1-C$_{16}$H$_{32}$	224	BF$_3$·H$_2$O	80	2	75	10	< 8

[a] Mole ratio of olefin to thiophene is 2. [b] Range of 5°. [c] Temperature rose from 25–70°. [d] Crude product; see Table II for final distillation. [e] Yield based on total theoretical conversion of thiophene to mono- and dialkylthiophenes, respectively.

If a high ratio of mono- to dialkylthiophene be desired, sulfuric acid (70–80% concentration) or dihydroxyfluoboric acid should be given primary

TABLE II

CONSTANTS AND ANALYTICAL VALUES OF MONO- AND DI-*t*-ALKYLTHIOPHENES

Alkylating agent	Substituents	B. p., °C.	Mm.	$n^{20}D$	d^{25}_4	Sulfur, % Calcd.	Sulfur, % Found	Yield %, of crude fraction, approx.
Isobutylene	2-*t*-Butyl-[a]	165–165.5	760	....	0.9467	..	..	90
	2,5-Di-*t*-butyl-[d]	226–227	760	1.4928	.9103	16.3	17.0	90
Trimethylethylene[b]	2-*t*-Amyl-[a]	188–189	760	1.5007	.9475	20.8	21.1	90
	2,5-Di-*t*-amyl-	256–257	760	1.4954	.9135	14.3	14.7	90
Diisobutylene	2-*t*-Octyl-[c]	81–82	4	1.4980	.9223	16.3	16.4	90
	2,5-Di-*t*-octyl-[e]	146–147	3	1.4890 (35°)	....	10.4	10.6	90

[a] These materials were reported by Kutz and Corson, THIS JOURNAL, **68**, 1477 (1946); reported b. p. 163–164° and d^{20}_4 0.9527 for 2-*t*-butyl- and b. p. 188–189.5, d^{20}_4 0.9484 for 2-*t*-amylthiophene. [b] The impurity, 2-methyl-1-butene, would give the same alkylthiophenes. [c] The structure is probably 2-(1,1,3,3-tetramethylbutyl)-thiophene; for analogy see Niederl, U. S. Patent No. 2,088,032, 1935. [d] Melting point 21–22°. [e] Melting point 36–37°.

consideration as catalysts. Weight ratios of mono-
to dialkylthiophenes up to 14 to 1 have been ob-
tained. These weight ratios usually are reversed,
as low as 1 to 10 has been realized, when boron
trifluoride–diethyl ether complex is used to cata-
lyze the alkylation. This is probably due to its
solubility in the reactants and reaction products.

The choice of alkylation conditions is governed
by the reactivity of the olefinic alkylating agent
and the catalyst. In general, temperatures of
25–85° are preferred for the alkylation of thio-
phene with reactive olefins, regardless of catalyst,
while temperatures of 75–150° are required for al-
kylation with unreactive olefins. The use of tem-
peratures of the order of 0° for thiophene alkyla-
tion reactions catalyzed by strong catalysts does
not bring about the expected reduction in rate of
undesirable side reactions with a resultant increase
in alkylthiophene formation. This was shown by
Kutz and Corson.[2] Providing there is any reac-
tion at all under these conditions, the primary re-
actions are decomposition and polymerization of
the thiophene, if the alkylating agent is unreactive,
or polymerization of the olefin if it is reactive. It
is possible to get alkylation of thiophene with tri-
methylethylene at low temperatures by slowly
warming an agitated mixture of these reactants
with 96% sulfuric acid from 0° to about 10°.
However, the reaction when it starts is usually
violent and uncontrollable, and the temperature
rises in several seconds to above 150° in spite of
the prompt application of a Dry Ice–acetone-bath.
The product consists chiefly of amylthiophenes.

Of particular importance is the method of addi-
tion to the charge of catalysts capable of rapidly
polymerizing or decomposing the thiophene.
For example, the addition of concentrated sulfuric
acid (85–96%) to thiophene or a mixture of thio-
phene and 1-octene caused excessive resinification
of the thiophene with a weight yield of octylthio-
phenes of less than 30% of the theoretical value.
However, careful combination of the acid with
the 1-octene prior to the addition of the thiophene
gave a 55–60% yield of octylthiophenes with
much less resin formation. Similarly, the admix-
ture of aluminum chloride with thiophene prior
to the addition of diisobutylene gave a 30% yield

TABLE III

CONSTANTS AND ANALYTICAL VALUES OF OTHER ALKYL-
THIOPHENES

Alkylating agent	Substituents	Boiling range,[a] °C.	$n^{20}D$	Sulfur, % Calcd.	Sulfur, % Found
C_5H_{10}	Pentyl-	195–197	1.4972	20.8	19.5
C_5H_{10}	Dipentyl-	265–270	1.4950	14.3	14.8
C_8H_{16}	Octyl-	245–246	1.4916	16.3	16.6
C_8H_{16}	Dioctyl-	>300	1.4902	10.4	12.8
$C_{16}H_{32}$	Hexadecyl-	150–160[b]	....	10.4	9.9

[a] These cuts were not subjected to high fractionation; pressure, 760 mm. [b] Pressure, 2.0 mm.

of octylthiophenes. When it was added to the
thiophene–diisobutylene charge, a 67% yield of
octylthiophenes was obtained with practically no
decomposition or polymerization of the thiophene
or diisobutylene. Apparently, when the aluminum
chloride particles were added directly to the thio-
phene they became coated with a layer of thio-
phene resin due to local polymerization. In spite
of the resultant decrease in effective catalyst ac-
tivity, it remained sufficient to catalyze the alkyla-
tion of the unpolymerized thiophene with reactive
liquid olefins. This resin formation did not occur
when the fresh catalyst was added to the thio-
phene–olefin mixture because the rate of alkyla-
tion of thiophene with the olefin was considerably
greater than the rate of polymerization of the thio-
phene.

The structures of the alkylthiophenes shown in
Tables II and III were not determined. Those
described in Table II are the products of the alkyl-
ation of thiophene with reactive olefins in the
presence of mild catalysts under mild alkylation
conditions. They represent, in every case, the
lowest boiling and predominant isomer isolated in
their respective fractions. Since Kutz and Corson[2]
proved the structure of the primary product of the
propylation of thiophene to be 2-propylthiophene,
it seems reasonable to assume that these products,
produced under relatively mild conditions, are
likewise the α(2- and 2,5-)-isomers.

Particular care was taken with the alkylation
products of thiophene with diisobutylene to iso-
late any mono- and dibutylthiophenes present,
which would be formed were the diisobutylene to

depolymerize prior to the alkylation reaction. Although butylbenzenes are the primary products of the alkylation of benzene with diisobutylene, no butylthiophenes were isolated. These factors, combined with the differences in physical properties between the products of octylation and butylation of thiophene are the basis for the assumption that octyl- and dioctylthiophenes are formed and not polybutylthiophenes.

Rasmussen[3] reports that the alkylation of thiophene with isobutylene catalyzed by 70% sulfuric acid under conditions of moderate severity gives substantial yields of a butylthiophene having a 4° higher boiling point than the isomer previously described. It is probably the 3-isomer. This indicates that the β-(3,4) positions on the thiophene ring are far more reactive toward alkylation than would be predicted from consideration of thiophene literature.

For this reason it can be assumed that the alkylthiophenes shown in Table III, which are the products of the alkylation of thiophene with unreactive olefins in the presence of strong catalyst under severe alkylation conditions, contain substantial amounts of the beta-substituted alkylthiophenes.

Moreover, some migration of the olefin double bond prior to its alkylation would result in the formation of several isomeric alkylthiophenes. Therefore, since the alkylthiophene cuts shown in Table III were not subject to high fractionation, they cannot be defined more closely than they are.

Experimental

Materials.—Thiophene (99+%), synthesized in this laboratory,[4] was used without further purification.[5] 1-Octane (95%) and 1-hexadecene (95%) were obtained from Connecticut Hard Rubber Co. Isobutylene (95%) was obtained from The Matheson Co., 1-pentene (95%) from Phillips Petroleum Co., and diisobutylene (98%) from Standard Alcohol Co. Trimethylethylene was prepared by dehydration in the presence of 35–40% sulfuric acid of t-amyl alcohol obtained from Sharples Solvent Co. The chief impurity was 2-methyl-1-butene. Boron trifluoride–diethyl ether complex was obtained from Eastman Kodak Co. Dihydroxyfluoboric acid[6] and the other borontrifluoride complexes were prepared in this Laboratory. The latter were made by stirring the liquid component at room temperature with boron trifluoride gas under a pressure of 10 pounds per square inch gage until no further absorption of the gas took place.

General Procedure.—Gaseous isobutylene was passed into a well-stirred mixture of thiophene and a mild catalyst at a rate of about one mole per mole of thiophene per hour, and the temperature was maintained between 50–85° throughout the run. Reactive liquid olefins, such as

(3) Rasmussen, private communication, March 16, 1948.
(4) Rasmussen, Hansford and Sachanen, Ind. Eng. Chem., 38, 376 (1946).
(5) Fawcett and Rasmussen, THIS JOURNAL, 67, 1705 (1945).
(6) Sowa and Nieuwland, ibid., 57, 454 (1935).

trimethylethylene and diisobutylene, were added dropwise to a well-stirred mixture of thiophene and a mild catalyst at 30–70° or mixed with the thiophene prior to the introduction of small portions of a strong catalyst. The rate of addition of strong catalyst is not critical but care should be taken. The less reactive olefins were mixed for about two hours with thiophene and a relatively large amount of boron trifluoride–water or –diethyl ether complex (from 30–100% by weight of thiophene) in an 800-cc. monel stirrer-type autoclave at a temperature of 75–150°. The lower temperatures were used with the water complex as catalyst, the higher temperatures with the weaker ether-complex. The use of such quantities of catalyst is probably unnecessary but gives added assurance of a reaction. Much of the catalyst can be separated from the reaction products and reused. The best alkylation technique using an unreactive olefin such as 1-octene and concentrated sulfuric acid was to add the acid slowly with stirring to the olefin, keeping the temperature below 20°. When no free sulfuric acid remained, the thiophene was added and the mixture heated with stirring to about 100° for three to five hours.

The general procedure for preparing the alkylation product for distillation was to separate it from the sludge and insoluble catalyst by decantation, wash it well with dilute alkali, and dry over calcium chloride. The alkylate was then distilled through a 15-theoretical plate column packed with metal helices or a modified Vigreux column (about 2-theoretical plates) to isolate the mono- and dialkylthiophenes. The alkylthiophenes described in Table II were purified further by redistillation through a 50-theoretical plate column packed with metal helices with a 50:1 reflux ratio.

Summary

Sulfuric acid, dihydroxyfluoboric acid, aluminum chloride, and boron trifluoride complexes with water or organic oxygen-containing compounds were found to promote the alkylation of thiophene with isobutylene, pentenes, diisobutylene, 1-octene and 1-hexadecene. Several new mono- and dialkylthiophenes were prepared.

Yields of 2-t-alkylthiophenes of 80% of theoretical were realized by catalyzing the alkylation of equimolecular amounts of thiophene and the relatively reactive olefins with 70–80% sulfuric acid or dihydroxyfluoboric acid at 30–85°. Similar high yields of 2,5-di-t-alkylthiophenes were obtained using boron trifluoride–diethyl ether complex as catalyst. Combined yields of mono- and dialkylthiophenes of 65–90% of theoretical were obtained using concentrated sulfuric acid or boron trifluoride–water or –diethyl ether complexes at 75–150° to promote the alkylation with the less reactive straight-chain olefins.

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