at 180° in a sealed tube for 24 hr., and then treated as described under (1) above. The chloroform extract, on evaporation, furnished 1.4 g. (23%) of an oil; this was converted into a yellow picrate which was identified as 4-bromo-2,6-lutidine picrate[6] by m.p. and mixed m.p. (183.5–185°).

Reactions of 4-Chloro-2,6-lutidine 1-Oxide. (1) With Sodium Sulfite.—A mixture of 8 g. (0.064 mole) of sodium sulfite, 5 g. (0.032 mole) of chloro compound, 20 ml. of water, and 25 ml. of 95% alcohol was heated at 180° in a sealed tube for 12 hr. The red reaction mixture was evaporated to dryness and the resinous material was extracted four times with boiling methyl alcohol. Evaporation of the extract furnished 6.6 g. (92%) of resinous material which was dissolved in the minimum quantity of water and acidified with three times its volume of concd. hydrochloric acid. After cooling and filtration, the solution was evaporated to dryness and the residue fractionally recrystallized from methyl alcohol to yield a product identified as 2,6-lutidine-4-sulfonic acid (VII) by equiv. wt., and its ultraviolet spectrum in 0.1 N HCl (λ_{max} 278 mμ, ϵ_{max} 9,200). The expected 2,6-lutidine-4-sulfonic acid 1-oxide had a different ultraviolet spectrum in 0.1 N hydrochloric acid (λ_{max} 217 mμ, ϵ_{max} 13,390; λ_{max} 268 mμ, ϵ_{max} 9700).

(2) **With Phosphorus Trichloride.**—A solution of 7 g. (0.044 mole) of 4-chloro-2,6-lutidine 1-oxide in 100 ml. of ice-cold chloroform was slowly treated with 12 ml. (1.12 mole) of phosphorus trichloride. The solution was allowed to warm up to room temperature over 2 hr. and then refluxed on the steam bath for 1 hr. The cold solution was decomposed with ice, made alkaline with aqueous sodium hydroxide, and extracted three times with chloroform. The chloroform extract, after drying over magnesium sulfate, furnished 6.6 g. (100%) of oil on evaporation; this was quantitatively converted into a picrate m.p. 160.5–162° alone or when mixed with authentic 4-chloro-2,6-lutidine picrate.[6]

(3) **With Sodium Borohydride–Aluminum Chloride.**[8]—Three and three-tenths milliliters of 1.0 M aluminum chloride in diglyme was cautiously added to an ice cold mixture of 0.8845 g. (0.0056 mole) of chloro compound and 10 ml. of 1.0 M (0.01 mole) sodium borohydride also in diglyme. After standing at room temperature for 3 hr., the reaction mixture was decomposed with 2 N hydrochloric acid. Five hundred and sixty milliliters of hydrogen was evolved at 33.5° and 735 mm. compared with 1080 ml. for a blank experiment run without chloro compound under similar conditions, indicating that 1 mole of compound had required 0.9 mole of borohydride for reaction. The acidic solution was evaporated to dryness and the residue extracted with hot alcohol. Picric acid precipitated from the alcoholic extract 4-chloro-2,6-lutidine picrate, identified by m.p. and mixed m.p.

(4) **With Iron and Acetic Acid.**—The 4-chloro-2,6-lutidine 1-oxide hydrochloride obtained from a sealed tube reaction of 5 g. (0.03 mole) of 4-nitro-2,6-lutidine 1-oxide with hydrochloric acid was suspended in 25 ml. of hot (100°) glacial acetic acid and 3 g. of iron powder was cautiously added down the reflux condenser. After 2 hr. heating at 100°, the mixture was diluted with water, made alkaline with aqueous sodium hydroxide, and steam distilled. Chloroform extraction of the distillate furnished 0.5 g. (12%) of liquid which was converted by picric acid into 4-chloro-2,6-lutidine picrate again identified by m.p. and mixed m.p.

Acknowledgment.—We wish to thank Dr. B. C. Subba Rao for his aid with the hydride experiments, Mrs. C. S. Tang Yeh and Mrs. S. L. Margerum for the analyses, and Mrs. B. Polister for the infrared measurements.

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(8) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

The Alkylation and Arylation of 2-Thienyllithium and the Reactions of 3-Methylthiophene with Organometallic Compounds(1)

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2-Thienyllithium has been alkylated and arylated to give 2-substituted thiophene derivatives in 45–65% yield. 3-Methylthiophene on metalation with n-butyllithium or phenyllithium and carbonation gave 4-methylthiophene-2-carboxylic acid (61–68%) and 3-methylthiophene-2-carboxylic acid (19%), while phenylsodium led to 4-methylthiophene-2-carboxylic acid (58%) and 3-methylthiophene-2,5-dicarboxylic acid (11%).

The methods which are used for preparing alkylthiophenes can be divided into two types. The first involves the ring closure of either a hydrocarbon with sulfur or of a γ-dicarbonyl compound with phosphorus sulfides. The second starts with the thiophene nucleus and proceeds through the preparation of carbonyl derivatives and their reduction by any of the standard procedures.(2) The direct introduction of alkyl substituents into the thiophene ring by means of metal halides or other acidic catalysts has been studied by some workers.(2)

Both 2-thienylmagnesium iodide(3) and 2-thienylsodium(2) react with allyl bromide to give 2-allylthiophene. 2-Thienylsodium, obtained by the action of sodium amide in liquid ammonia on thiophene, can be alkylated with alkyl bromides to give monoalkyl compounds in 50–70% yields.(4) However, side reactions such as the dialkylation of the thiophene ring—*i.e.*, the formation of 2,5-dialkylthiophene—also take place.

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(1) This study was supported by a grant from the Lithium Corporation of America.

(2) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, 1952.

(3) Grischewitsch-Trochimovski, *J. Russ. Phys. Chem. Soc.*, **43**, 201 (1911).

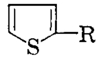
(4) I. J. Spilners and R. Levine, unpublished observations

It was of interest to study the reactivity of 2-thienyllithium for these reactions. In this connection, it should be pointed out that 2-thienyllithium condenses with esters[5,6] and ketones[7] to give carbinols.

Thiophene was metalated in high yield when it was treated with *n*-butyllithium (one equivalent) in ether solution. The alkylations were effected by using equivalent quantities of alkyl halides, generally bromides, except for dimethyl sulfate and benzyl chloride (Table I). The over-all reactions are shown in the following equations. The decrease in yields of the products as the chain length of the alkyl group in the primary halides increases is in accord with the decrease in the reactivity of these halides. *sec*-Butyl bromide did not give any alkylated product probably because of the competing reaction of dehydrohalogenation. From the interaction of two equivalents of 2-thienyllithium with one equivalent of 1,2-dibromoethane, none of the expected 1,2-bis(2-thienyl)ethane was obtained and only 1-bromo-2(2-thienyl)ethane (5.6%) was isolated. Here, also, the dehydrohalogenation of the 1,2-dibromoethane was probably the main side reaction.

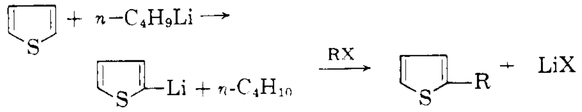
TABLE I

2-ALKYL- AND 2-ARYLTHIOPHENES



Alkylating or Arylating Agent	R	Yield, %	M.P. or B.P.,	Mm.
Dimethyl sulfate	CH_3	65	111[a]	747
Ethyl bromide	C_2H_5	61	132–134[b]	750
n-Butyl bromide	*n*-C_4H_9	47	181–182[b]	750
n-Octyl bromide	*n*-C_8H_{17}	45.6	120	8
			257	750[c]
Benzyl bromide	$C_6H_5CH_2$	62	132–134	12[d]
1,2-Dibromoethane	CH_2CH_2Br[f]	5.6	88	8[e]
	C_6H_5	11.9[g]	42[h]	
Bromobenzene	C_6H_5	30.6[i]	42[h]	
	2,5-Diphenylthiophene	21.6	152–153[j]	

[a] F. S. Fawcett, *J. Am. Chem. Soc.*, **68,** 1420 (1946). [b] V. Meyer and W. Kreis, *Ber.*, **17,** 1559 (1884). [c] V. Schweinitz, *Ber.* **19,** 644 (1886). [d] See ref. 9. [e] See ref. 8. [f] Two equivalents of 2-thienyllithium and 1 equivalent of 1,2-dibromoethane were used. [g] Tetrahydrofuran was the solvent. The arylation was effected at room temperature overnight. [h] W. Kues and C. Paal, *Ber.*, **19,** 3141 (1886). [i] Tetrahydrofuran was the solvent. The arylation was effected at reflux for 3 hr. [j] S. Kapf and C. Paal, *Ber.*, **21,** 3053 (1888).



The last-named thiophene derivative has been made earlier by the reaction of phosphorus tribromide on 2-hydroxyethylthiophene. Benzyl chloride, being a very reactive halide, gave, as was expected, the highest yield of the alkylated product (2-benzylthiophene, 62%), which had been prepared earlier by Steinkopf and Schubart[8] by the condensation of thiophene with benzyl alcohol in the presence of zinc chloride. Ethyl chloroacetate did not alkylate thiophene and only polymeric material was formed.

Bromobenzene does not ordinarily function as an effective arylating agent and only an 18% yield of diphenyl was formed[9] when a mixture of phenyllithium and bromobenzene in ether was allowed to stand for seven days at 0°. This reaction is believed to proceed through a benzyne intermediate. Recently,[10] tetrahydrofuran has been used as a solvent for a number of reactions involving organometallic reagents. This solvent is particularly valuable for reactions which either do not proceed in diethyl ether or which proceed at a very slow rate and in low yields in this solvent. These earlier observations suggested that the arylation of 2-thienyllithium in tetrahydrofuran be studied. Therefore, *n*-butyllithium was prepared in tetrahydrofuran[10] and thiophene was metalated with this reagent at −15°. An equivalent of bromobenzene was added and, after the reaction was allowed to stand overnight at room temperature, 2-phenylthiophene was isolated in 12.9% yield. In a second experiment, after the bromobenzene had been added and the mixture was allowed to warm up to room temperature it was refluxed for three hours. In this way a mixture of 2-phenylthiophene (30.6%) and 2,5-diphenylthiophene (21.6%) was obtained. It would appear that either some 2,5-dilithiothiophene was formed or that part of the 2-phenylthiophene was metalated and then arylated.

Schick and Hartough[11] have reported that 3-methylthiophene is metalated by reaction with sodium in the presence of alkyl or aryl halides such as ethyl bromide, *n*-butyl bromide, and bromobenzene in diethyl ether. Carbonation apparently gave exclusively 4-methyl-2-thiophenecarboxylic acid, I, in 42% yield. In this connection it should also be noted that the formation of 4-methyl-2-alkylthiophenes through a Wurtz-Fittig coupling of 3-methyl-5-sodiothiophene with alkyl halides has also been observed.[12] Gronowitz[13] and Sice[14] claimed that 3-methylthiophene is

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(5) D. W. Adamson, *J. Chem. Soc.*, 885 (1950).

(6) P. A. Barrett and S. Wilkinson (to Welcome Foundation Ltd.), Brit. Patent 683,978.

(7) L. Berger, A. Ziering, and J. Lee, *J. Org. Chem.*, **12,** 907 (1947).

(8) W. Steinkopf and I. Schubart, *Ann.*, **424,** 1 (1920).

(9) G. Wittig and W. Merkle, *Ber.*, **75,** 1491 (1942).

(10) H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22,** 1165 (1957).

(11) J. W. Schick and H. D. Hartough, *J. Am. Chem. Soc.*, **70,** 1645 (1948).

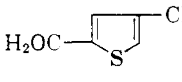
(12) J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.*, **74,** 1849 (1952).

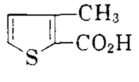
(13) S. Gronowitz, *Arkiv. Kemi.*, **19,** 361 (1954).

(14) J. Sice, *J. Org. Chem.*, **19,** 70 (1954).

metalated exclusively in the 5-position by its reaction with *n*-butyllithium in diethyl ether. Gronowitz[13] claimed that carbonation of this reaction mixture gives 4-methyl-2-thiophenecarboxylic acid, I, in 68% yield while Sice[14] claimed to have obtained exclusively 4-methyl-2-thenaldehyde (61%) by its reaction with dimethylformamide.

However, our observations in this connection have been quite different. 3-Methylthiophene was metalated with both n-butyllithium and phenyllithium in diethyl ether and the mixtures were carbonated by reaction with Dry Ice. From both reactions mixtures of carboxylic acids were isolated. These mixtures were separated into their components: 4-methylthiophene-2-carboxylic acid, I, (61–68%) and 3-methylthiophene-2-carboxylic acid, II, (19%) by chromatography on a Florisil[15] column. The relative proportions of the two acids were nearly the same with these two reagents. *Obviously, metalation did not take place exclusively in the 5-position of 3-methylthiophene.* The use of phenylsodium as the metalating reagent resulted in some dimetalation leading to a mixture of 4-methyl-2-thiophenecarboxylic acid (I) (58%) and 3-methylthiophene-2,5-dicarboxylic acid (III) (11.5%). None of II was detected. It appears that since phenylsodium is probably a stronger base than the lithium reagents, it is able to dimetalate 3-methylthiophene to some extent. An authentic sample of III was prepared by reaction of 2,5-diiodo-3-methylthiophene with phenyllithium followed by carbonation. These results are summarized in Table II.


I


II

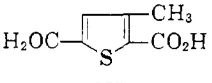
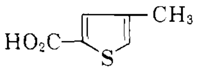
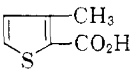

III

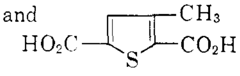
TABLE II

METALATION OF 3-METHYLTHIOPHENE TO GIVE


I

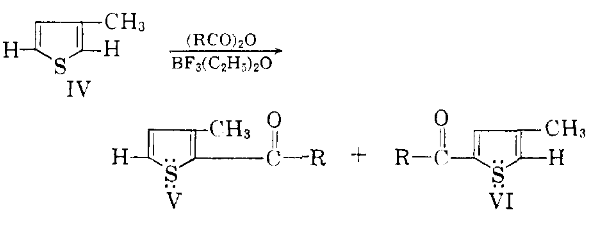

II

and


III

Metalating Reagent	Products % I	% II	% III
Phenyllithium	68	19	0
n-Butyllithium	61	19	0
Phenylsodium	58	0	11

It appears reasonable that the mixture of the lithium derivatives which was formed by the metalation of 3-methylthiophene(IV) is predominantly 2-lithio-3-methylthiophene. Thus, both hyperconjugative and inductive effects would be expected to decrease the acidity of the hydrogen atom on the 2-carbon atom of IV to a greater extent than it would the hydrogen atom of the 5-carbon atom. In this connection earlier work from this laboratory[16] has shown that when IV is acylated with a series of anhydrides under acidic conditions, two isomeric ketones, V and VI, are formed. Since these reactions involve the electrophilic attack of the potentially available carbonium ion from the anhydride on the thiophene ring it is not surprising that in contrast to the metalation reactions, the acylations give ketones VI as the major products.



Experimental

The reactions were effected under an atmosphere of dry, oxygen-free nitrogen. The solvents and other chemicals used were commercial products and were dried and distilled. Tetrahydrofuran was freed from peroxides and moisture before use by refluxing over sodium for 2 hr., followed by distillation. Lithium ribbon was supplied through the courtesy of Lithium Corporation of America. The absorbent, Florisil, was supplied through the courtesy of the Floridin Company, Tallahassee, Fla.

Alkylation and Arylation of Thiophene. (a) In Ether.—*n*-Butyllithium (0.3 mole) in ether was prepared according to the method of Gilman.[17] Thiophene (0.3 mole), diluted with an equal volume of dry ether, was added dropwise at 0° and the mixture was then stirred at room temperature for 1 hr. The reactor was cooled to −15 to −20° and the halide (0.3 mole), diluted with an equal volume of dry ether, was added. The reaction mixture was then refluxed for 18 hr. (With a reaction time of 1 hr at room temperature and 1 hr. at reflux benzyl chloride gave only a 10% yield of 2-benzylthiophene and much of the unchanged halide was recovered.) The reaction mixture was cooled to room temperature and was poured over crushed ice. The ether layer was separated, washed with water, dried, and fractionated.

(b) In Tetrahydrofuran.—Tetrahydrofuran (90 ml.) was placed in a three-necked flask fitted with a slip-sealed stirrer, a condenser, and a jacketed addition funnel. The air was swept out of the reactor with dry nitrogen and a steady flow of the gas was maintained throughout the reaction. Lithium ribbon (3.0 g., 0.43 g.-atom) was introduced. The suspension was cooled to −25°. *n*-Butyl chloride (18.5 g., 0.2 mole), diluted with tetrahydrofuran (90 ml.), was placed in the addition funnel. It was cooled and a few milliliters were added to the rapidly stirred suspension of lithium in tetrahydrofuran to initiate the reaction. When the reaction had started as indicated by the appearance of cloudiness, the rest of the halide was added over the course of 1 hr. while the cooling bath was maintained at −30° to −35°. Then the mixture was stirred for 1 hr. with the cooling bath at −25°. Thiophene (16.8 g., 0.2 mole), diluted with an equal volume of tetrahydrofuran, was added at −15° and the mixture was stirred for 2 hr. Bromobenzene (31.4 g., 0.2 mole) was then added. The cooling bath was removed and the mixture was allowed to stand overnight. The contents of the flask was poured over

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(15) Adsorbent marketed by Floridin Company, Tallahassee, Fla.

(16) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **72**, 3695 (1950).

(17) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

crushed ice. The two layers were separated. The aqueous layer was extracted with ether and the extract added to the tetrahydrofuran solution. The combined organic phases were dried and fractionated. The solvents were removed at 20 mm. Unchanged bromobenzene (27 g.) distilled at 60° at 20 mm. 2-Phenylthiophene (3.8 g., 11.9%) distilled at 140° at 20 mm. and soon solidified to colorless crystals, m.p. 42°.[18] Very little residue remained in the distillation flask.

In a second experiment, after the addition of bromobenzene, the reaction mixture was allowed to warm to room temperature and it was then refluxed for three hours. It was then processed as described above. After removing the solvents, 2-phenylthiophene (10.6 g.) distilled at 140° at 20 mm. and soon solidified to colorless crystals (9.8 g., m.p. 42°, 30.6%). The residue in the distillation flask was recrystallized from petroleum ether (b.p. 60–70°) and then from 95% ethanol to give almost colorless plates of 2,5-diphenylthiophene (5.1 g., m.p. 152–153°, 21.6%).[14]

Metalation of 3-Methylthiophene. (a) With Phenyllithium.—Phenyllithium (0.5 mole) was prepared in 200 ml. or anhydrous ethyl ether. 3-Methylthiophene (49 g., 0.5 mole), diluted with an equal volume of ether, was added dropwise and after the addition the mixture was refluxed for 2 hr. It was carbonated by pouring over a slurry of Dry Ice and ether. After the disappearance of the Dry Ice, enough water was added to dissolve the solids. The ether layer was separated and was washed with water. The washings were added to the aqueous layer. The combined aqueous layers were cooled and acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with ice water, and dried to give 67.2 g. of a mixture of crude acids.

A sample of the mixed crude acids (400 mg.) was dissolved in benzene and chromatographed on a column of Florisil (18 g. of adsorbent in a column 16 in. long and $^7/_8$ in. in diameter). The column was developed with 200 ml. of benzene. The solvent was drained. Nothing was recovered from the percolate. Small portions of the column were removed from the top, treated with dilute hydrochloric acid, and extracted with ether. The first 6 in. gave 4-methylthiophene-2-carboxylic acid (I), m.p. 122°; literature value, m.p. 122°,[19] mixed m.p. with benzoic acid, 85–90°. The next $1^1/_4$ in. contained a mixture of acids. The next $1^1/_2$ in. of the column gave 3-methylthiophene-2-carboxylic acid (II), m.p. 148°.[19] The mixture was refractionated. Finally, 288 mg. of I and 78 mg. of II were obtained representing a total yield of 68% of I and 19% of II.

(b) With *n*-Butyllithium.—The reaction was carried out as above except that *n*-butyllithium was used in place of phenyllithium. By chromatography the yields of the acids I and II were found to be 61% and 19%, respectively.

(c) With Phenylsodium.—Phenylsodium (0.2 mole) was prepared according to the method of Raynolds and Levine.[20] 3-Methylthiophene (19.6 g., 0.2 mole), diluted with an equal volume of dry benzene, was added and the mixture was stirred at room temperature for 2 hr. Subsequent carbonation and processing gave 22 g. of mixed crude acids.

A sample of the crude acid (1.0 g.) was extracted with 10 ml. of benzene. A part (140 mg.) remained undissolved. The extract was chromatographed on a column of Florisil. From the top part of the column 15 mg. of a substance, which was the same as the above undissolved residue, and 750 mg. of 4-methylthiophene-2-carboxylic acid (I) were recovered. None of II was isolated. The material which was sparingly soluble in benzene was allowed to crystallize and was then recrystallized from hot water to give white needles of 3-methylthiophene-2,5-dicarboxylic acid (III), m.p. 278°.

Anal. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.22. Found: C, 44.96; H, 3.50. The yield of I was 58% and that of III was 11.5%.

3-Methylthiophene-2,5-dicarboxylic Acid (III).—2,5-Diiodo-3-methylthiophene[21] was synthesized in 66.7% yield by a modification of the directions of Minnis[22] for preparing 2-iodothiophene, using twice the quantities of yellow mercuric oxide and iodine.

2,5-Diiodo-3-methylthiophene (21 g., 0.06 mole) was diluted with dry ether (20 ml.) and added dropwise over 15 min. to phenyllithium (0.3 mole) in ether. A precipitate was formed immediately. The mixture was refluxed for .5 hr. and was then carbonated with Dry Ice. The reaction was processed as usual and the crude acid was collected. It was washed with benzene to remove any benzoic acid and crystallized from hot water. The needles (8.4 g., 75%) melted at 278° and showed no depression when a mixed melting point was performed with the product from the previous reaction.

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[18] W. Kues and C. Pall, *Ber.*, **19**, 3141 (1886).

[19] H. D. Hartough and L. G. Conley, *J. Am. Chem. Soc.*, **69**, 3096 (1947).

[20] S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

[21] W. Steinkopf and W. Hanske, *Ann.*, **532**, 236 (1937).

[22] W. Minnis, *Org. Syntheses*, **Coll. Vol. II**, 357 (1943).