ommended by Pressman and Lardy.[30] Suspensions prepared according to these methods were inactive.

Liver and kidney slices and frozen sections were incubated for varying periods of time up to 24 hours in the media described above with negative results.

Attempts were made to grow bacteria under conditions where the synthetic substrates constituted a large portion of the carbon source. *E. coli* was tested in a synthetic salt medium[31] containing only 0.01% glucose and 0.1 and 0.01 mg. of substrate per cc. of medium in order to force utilization of the substrate as a source of carbon. Neither phenol nor β-naphthol could be detected even though adequate growth occurred. Similarly, negative results were obtained with *B. subtilis* and *S. aureus*, using extract broth.

Experiments to Demonstrate Inhibitory Effects of the Substrates.—The procedure described by Kennedy and Lehninger[32] was followed exactly in studying the oxygen uptake of the synthetic substrates in the Warburg respirometer except that cytochrome C was omitted and a total volume of 3 cc. was used.

A typical experiment consisted of octanoate in one cup, the naphthoxy or phenoxy[16] substrate in another cup and equimolar combinations of both octanoate and either the naphthoxy or phenoxy substrate in a third cup, and finally a control without substrate. In a typical experiment octanoate consumed 68 μl. of oxygen, the naphthoxy substrate 0 μl., naphthoxy plus octanoate 0 μl. and the endogenous control 12 μl. A similar demonstration of inhibition of oxidation of octanoate was obtained with the phenoxy derivative.

Feeding Experiments.—Aqueous suspensions of 100 mg. of 2-(2-naphthoxy)-propionic acid, the 6-bromo derivative, or naphthoxyacetic acid were given to two rats by stomach tube. Urine from the rats fed with the propionic acid derivatives gave a very strong qualitative reaction for β-naphthol on coupling with tetrazotized diorthoanisidine, while the urine from the rats fed the acetic acid derivative was negative. Similar results were obtained with rabbits.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Friedel–Crafts Alkylation of Methyl 2-Furoate

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RECEIVED JULY 27, 1953

The products of the alkylation of methyl 2-furoate with *s*-butyl bromide and aluminum chloride in carbon disulfide were found by infrared analysis to contain about 43% of the rearranged tertiary and 57% of the secondary butyl groups. The principal absorption peaks of pure *s*- and *t*-butylfurans and 2-methylfuran are reported.

In the investigation of the Friedel–Crafts reaction in the furan series of compounds, Gilman and Calloway[2] reported that alkylation of methyl 2-furoate with the isomeric butyl halides in the presence of aluminum chloride yielded methyl 5-*t*-butyl-2-furoate with all four isomers. Specifically, these percentage yields of methyl *t*-butylfuroate were reported from these halides: *n*-butyl chloride, 45; isobutyl bromide, 66; *s*-butyl bromide, 1.6; and *t*-butyl bromide, 46. The yields were based on isolation of 5-*t*-butyl-2-furoic acid. No other isomeric butylfuroic acid was isolated.

Because alkylation in the benzene series with *s*-butyl halides under various conditions almost without exception has produced the corresponding *s*-butylarene in preponderant amounts,[3] reinvestigation of this irregular alkylation in the furan series was undertaken.

Methyl 2-furoate[2] also has been alkylated with *n*-propyl bromide and isopropyl bromide to give the expected methyl 5-isopropyl-2-furoate. Methyl chloride and ethyl chloride and bromide (with aluminum chloride and carbon disulfide) yielded compounds which were considered to be dithio esters. The products from alkylation with *n*-pentyl and *n*-hexyl halides were identified as branched alkyl substitution products by analogy with the results in the butyl series. Other alkylations in the α-position in the furan series have been performed. 2-Furyl phenyl ketone was alkylated with *t*-butyl chloride to produce 5-*t*-butyl-2-furyl phenyl ketone.[2] Although furfural was found anomalously to yield 4-isopropylfurfural with isopropyl chloride and aluminum chloride,[4] the *n*-butyl, *t*-butyl and isobutyl chlorides gave yields of the order of 10% of product which was identified as 5-*t*-butylfurfural. When the α-position was blocked, profound cleavage of alkyl groups occurred during the alkylation on the β-position[5,6] as witnessed by the formation of ethyl 4-*t*-butyl-5-bromo-2-furoate from ethyl 5-bromo-2-furoate, aluminum chloride and either *t*-butyl, *n*-hexyl or octadecyl bromide.[5]

In the present work it was desired to compare the properties of the alkylation products resulting from the reaction of *s*-butyl bromide and methyl 2-furoate in the presence of aluminum chloride in carbon disulfide solution with the known pure compounds. The most satisfactory procedure for this purpose was decarboxylation of the butylfuroic acids resulting from the alkylation into butylfurans, which then could be compared with pure *s*- or *t*-butylfuran. The last two compounds were prepared by unequivocal methods and their infrared spectra were obtained. The methyl furoate was alkylated according to the directions of Gilman and Calloway.[2] The product was distilled at 10 mm. and the fraction boiling from 107 to 125° was hydrolyzed by potassium hydroxide in methanol. As indicated by Gilman and Calloway, the acid appeared as a viscous oil. This oil was decarboxylated to yield a mixture of butylfurans boiling between 119 and

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[1] Holder of a University Fellowship, 1951-1953.

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[3] C. C. Price, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 31.

[4] H. Gilman, N. O. Calloway and R. R. Burtner, THIS JOURNAL, **57**, 906 (1935).

[5] H. Gilman and R. R. Burtner, *ibid.*, **57**, 909 (1935).

[6] H. Gilman and J. A. V. Turck, Jr., *ibid.*, **61**, 473 (1939).

135°. An infrared spectrum was run on a sample of this distillate.

Results.—The principal absorption peaks of pure 2-*s*-butylfuran, 2-*t*-butylfuran and 2-methylfuran in sodium chloride cells of width 0.03 mm. are shown in Table I. (Absorption = 100 − % transmit.) It can be seen that seven peaks were common with only slight shift and within the same order of magnitude to each of these three compounds. Since the bands of high absorption differ materially from those reported for furan itself,[7] it is apparent that these bands are due to the presence of the 2-alkyl group in these alkylfurans. In the analysis of the mixture of *s*- and *t*-butylfurans these peaks were avoided as being non-critical. For analysis, selection of a band depended on two criteria: (1) a large spread between the two pure compounds, and (2) a slope of zero or nearly zero in all three spectra at the particular wave length. The selected wave lengths and the percentage transmittancies are given in Table II. The extinction coefficients, ϵ, for the pure compounds were calculated from the equation of Beer's law, $\log I_0/I = \epsilon c$, where c is the concentration (or 100%), I_0 = 100% transmittancy, and I = the percentage transmittancy of the pure compound. If the densities of the pure butylfurans are assumed to be approximately equal, the concentrations of the components can be represented as percentage, the pure compounds as 100%. In all measurements the cell width was 0.03 mm. The concentrations of the two components in the mixture were calculated from the equation $\log I_0/I_{\text{mixt}} = \epsilon_s c_s + \epsilon_t c_t$, where s and t represent secondary and tertiary, and $c_s = 100 - c_t$. The results for each band are shown in the last two columns of Table II. The average percentage composition found was 43% *t*-butylfuran and 57% *s*-butylfuran with a standard deviation of 2.8%. The intent of the investigation, however, was to show only semi-quantitatively the presence of the *s*-butyl group in the alkylation product. The results, therefore, do confirm the *t*-butylfuroic acid as Gilman and co-workers claimed, but the results also demonstrate an even larger amount of *s*-butylfuroic acid in the reaction products.

TABLE I

PRINCIPAL ABSORPTION PEAKS OF PURE METHYL- AND BUTYLFURANS IN THE REGION 5.6 TO 11.6 μ

2-*s*-Butylfuran		2-*t*-Butylfuran		2-Methylfuran	
Band, μ	Absorption, %	Band, μ	Absorption, %	Band, μ	Absorption, %
5.91	54	6.28	68	6.20	83
6.27	60	6.62	78	6.60	84
6.64	73	6.82	82	6.88	81
6.85	81	7.33	77	7.20	51
7.25	61	7.80	86	8.06	83
7.48	52	8.28	79	8.18	86
7.78	39	8.57	93	8.66	93
8.12	52	8.93	54	9.18	85
8.40	49	9.22	66	9.82	96
8.63	84	9.69	65	10.23	32
9.21	44	9.92	94	10.87	96
9.90	90	10.83	90	11.24	65
10.40	50	11.25	54		
10.85	84				
11.26	52				

TABLE II

ANALYSIS OF *t*- AND *s*-BUTYLFURAN MIXTURE

Analyzed band, μ	Absorption, %			%	%
	Pure *s*	Pure *t*	Mixture	Tertiary	Secondary
10.40	49.5	12.3	37.3	39.2	60.8
9.22	44.4	66.4	55.6	46.7	53.3
8.28	27.5	79.1	59.2	46.1	53.9
7.80	38.0	86.1	67.7	43.6	56.4
7.48	51.8	13.5	38.6	41.4	58.6

Experimental

Infrared spectra were determined by Mr. William Fateley, with a Beckman IR-2T recording spectrophotometer. The three spectra were recorded on the same graph for easy comparison. The 2-methylfuran was a sample from du Pont Electrochemicals Department, which we fractionated in a 50-plate Podbielniak column. The fraction with the highest index of refraction (n^{25}D 1.4283) was used for the infrared spectrum.

Alkylation of Methyl 2-Furoate.—Methyl 2-furoate (0.5 mole) was alkylated with 0.5 mole of *s*-butyl bromide in the presence of 0.75 mole of Baker and Adamson anhydrous sublimed aluminum chloride in carbon disulfide solution, essentially according to the directions of Gilman and Calloway.[2] After the mixture was processed, the products were distilled at 10 mm. yielding (a) 18.2 g. collected between 90–107°, (b) 32.5 g. between 107–125° (mostly at 113–115°) and (c) 15 g. between 127–140°. Fraction b was refluxed with 15 g. of potassium hydroxide in 150 ml. of methanol for 6 hours. After evaporation of some methanol, 200 ml. of water was added and the basic solution neutralized to congo red with 1:2 hydrochloric acid solution. The oil which formed was taken up in ether and the aqueous solution was extracted twice. The solution was dried and the solvent evaporated as much as possible. The oil was then dissolved in 55 ml. of quinoline containing 1 g. of cupric oxide and decarboxylated according to the directions of Wagner and Simons.[8] The liquid boiling up to 140° was collected, dissolved in petroleum pentane, washed with dilute hydrochloric acid and water and distilled. The product, a mixture of *t*- and *s*-butylfurans, was collected at 119–135°. An infrared spectrum was run on a sample of the total distillate.

Preparation of 2-*t*-Butylfuran.—Methyl 2-furoate was alkylated with *t*-butyl bromide in the presence of aluminum chloride as described above. The ester was saponified by refluxing with a slight excess of potassium hydroxide in methanol. Acidification yielded crystalline 5-*t*-butyl-2-furoic acid which, on recrystallization, melted at 103.5–104.5° (lit.[2] 104–105°). Decarboxylation as above yielded 2-*t*-butylfuran boiling at 119–120°.

Preparation of 2-*s*-Butylfuran.—Furan was acetylated by the method of Hartough and Kosak.[9] The 2-furyl methyl ketone, b.p. 51–53° (7 mm.), was treated with ethylmagnesium iodide by the usual Grignard method using ammonium chloride solution to hydrolyze the alkoxide formed. The ether solution was washed with 10% aqueous sodium bicarbonate solution, dried over potassium carbonate and distilled. The products were collected in fractions at 11 mm., consisting of 2-α-furylbutene and 2-α-furyl-2-butanol: < 64°, 64–70°, 70–73° (the latter fraction: 11.6 g., n^{25}D 1.4723). A small amount of the olefin dimer boiled at about 160° (11 mm.). The first two cuts containing the furylbutene were refractionated at 9 mm. in a modified 50-ml. Claisen flask with a 10-inch Vigreux column, yielding (g., b.p. n^{25}D): 1.4, 45–53°, 1.4986; 3.6, 53–61°, 1.4960; 1.0, 61–66°, 1.4854; and 3.2, 66–70°, 1.4729. The 45–61° fractions were hydrogenated in petroleum pentane using 5% palladium-on-charcoal. The *s*-butylfuran obtained boiled at 132–134°.

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