

zinc and 40 ml. of water were added 5.0 g. (0.043 mole) of 3-ketothiacyclohexane and 30 ml. of concentrated hydrochloric acid. The mixture was heated to boiling, and 100 ml. of concentrated hydrochloric acid was added over the course of one hour while water and steam-volatile oil were collected by distillation. The distillate was extracted with three 25-ml. portions of ether. The combined extracts were dried and the ether was removed, leaving 1.5 g. of crude product. Fractionation through a Craig still<sup>17</sup> gave 0.9 g. (21%) of a colorless liquid, with physical properties identical with those of authentic 2-methylthiacyclohexane (IVa); b.p. 132° (750 mm.);  $n_{20}^D$  1.4920;  $d_{20}^{25}$  0.962. The infrared absorption spectrum of the Clemmensen product was superposable on that of the authentic sulfide (Fig. 1, curve A). Of special significance is the strong absorption due to the  $\text{CH}_3$ -group (1375  $\text{cm}^{-1}$ ) which was created by the reduction-rearrangement and the absence of absorption bands characteristic of thiacyclohexane (curve B).

**Clemmensen Reduction of 3-Ketothiacycloheptane (IIIb).**—The reduction was carried out in the manner described for IIIa, using 5.5 g. (0.042 mole) of 3-ketothiacycloheptane, with the exception that the ketone was allowed to react with the amalgamated zinc and hydrochloric acid (80 ml. of concentrated acid, 20 ml. of water) at the reflux tempera-

ture for one-half hour before distillation was begun. The product from the reaction was fractionally distilled, b.p. 85–87° (94 mm.);  $n_{20}^D$  1.4940; wt. 1.9 g. (34% yield). The higher-boiling residue was distilled twice from sodium in an air-bath at 160–165°;  $n_{20}^D$  1.5046. The infrared absorption spectrum of this portion of the product showed a strong  $\text{CH}_3$  band at 1372  $\text{cm}^{-1}$  and a  $\text{C}=\text{C}$  band at 1647  $\text{cm}^{-1}$ , but the constitution of this unsaturated by-product was not otherwise established. The 1.9-g. distillate fraction mentioned above was distilled twice from sodium at an air-bath temperature of 170–175°; b.p. 153° (750 mm.);  $n_{20}^D$  1.4923. The infrared spectrum of this portion of the product is practically identical (Fig. 1, curve D) with that of an authentic sample of 2-methylthiacyclohexane (curve C), although the Clemmensen product exhibited extraneous weak absorption bands at 950, 850 and 775  $\text{cm}^{-1}$ . Nevertheless, these spectra show that the major constituent of the Clemmensen product is 2-methylthiacyclohexane. The product which would result if the Clemmensen reduction of IIIb were to occur *without* rearrangement, namely, thiacycloheptane, has an infrared absorption spectrum (curve E) which is markedly different from curves C and D.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

## The Friedel-Crafts Alkylation of 2,5-Dimethylthiophene

BY NICHOLAS MESSINA<sup>1</sup> AND ELLIS V. BROWN

The Friedel-Crafts alkylation of 2,5-dimethylthiophene has been accomplished using various alkyl halides with aluminum chloride as the catalyst. In contradistinction to thiophene itself, it was found that this substituted thiophene alkylated readily with only a minor amount of polymerization when an active halide like *t*-butyl chloride was used. With less active halides, such as *n*-butyl chloride, some replacement of alkyl groups in 2,5-dimethylthiophene occurred and polymerization increased. Structures for most of the alkylated thiophenes prepared have been proved by synthesis.

The alkylation of thiophene was first reported by Schleicher in 1886, who used isopropyl chloride and aluminum chloride.<sup>2</sup> However, he obtained only traces of an alkylthiophene. This reaction was not investigated further until 1946 when Kutz and Corson reported the alkylation of thiophene employing olefins in the presence of an alumina-silica type catalyst.<sup>3</sup> Later Appleby, Sartor and Lee achieved the alkylation with phosphoric acid catalyst and olefins at elevated temperatures and pressure.<sup>4</sup> They reported that alkylation not only took place in the expected alpha position but considerable alkylation also occurred in the beta position. In recent years many other reports on the alkylation of thiophene have appeared in the literature,<sup>5</sup> however, in all cases these involved olefins as the alkylating agents.

In view of the fact that thiophene has not been alkylated by alkyl halides in the presence of the metallic halide catalysts, it was considered of interest to investigate the reaction with substituted thiophene using these conditions.

It was found that the Friedel-Crafts alkylation of 2,5-dimethylthiophene would take place when alkyl halides in the presence of aluminum chloride were employed. Thus replacement of both  $\alpha$ -hydrogens with methyl groups activated thiophene

to such an extent that alkylation took place before polymerization. Table I shows the results of the alkylation of 2,5-dimethylthiophene with *t*-butyl chloride, isopropyl chloride, *n*-butyl chloride and ethyl bromide in the presence of aluminum chloride. The yield of the expected  $\beta$ -alkylthiophene decreased with decreasing reactivity of the alkyl halide. This becomes quite evident when comparing the yields obtained with *t*-butyl chloride (90–93%) and *n*-butyl chloride (38–43%). In fact, when the more reactive *t*-butyl chloride was the alkylating agent, the only product isolated was the expected 2,5-dimethyl-3-*t*-butylthiophene. If the less reactive alkyl halides were employed, some replacement of one of the  $\alpha$ -methyl groups by the corresponding alkyl group of the alkyl halide occurred. Even when the alkyl halide was slightly less reactive as, for example, isopropyl chloride, the yield of the expected  $\beta$ -alkylthiophene decreased and replacement of one of the  $\alpha$ -methyl groups occurred.

The 2,5-dimethyl-3-ethylthiophene, obtained from the alkylation with ethyl bromide, was characterized by preparing it from the known 2,5-dimethyl-3-acetothienone by a Clemmensen reduction.<sup>6</sup> Both hydrocarbons were acetylated to give 2,5-dimethyl-3-ethyl-4-acetothienone. Since the ketone seemed to be hindered and did not react readily with the usual carbonyl reagents and since it was resistant to oxidation, solid derivatives were prepared by putting both samples through Willgerodt reactions according to the method of Blanch-

(1) A portion of a thesis by Nicholas Messina submitted to Fordham University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) E. Schleicher, *Ber.*, **19**, 672 (1886).

(3) W. Kutz and B. Corson, *This Journal*, **68**, 1477 (1946).

(4) W. Appleby, A. Sartor and H. Lee, *ibid.*, **70**, 1552 (1948).

(5) H. Pines, B. Kvetinakas and J. Vesely, *ibid.*, **72**, 1568 (1950); V. Weinmayr, *ibid.*, **72**, 918 (1950); P. Caesar, *ibid.*, **70**, 3623 (1948).

(6) Buu-Hoi and Nguyen-Hoan, *Rec. trav. chim.*, **67**, 309 (1948).

TABLE I  
 ALKYLATION OF 2,5-DIMETHYLTHIOPHENE

Alkylating Agent	Substituents on Thiophene	B.p.,		Yield, %	Carbon, %		Hydrogen, %	
		°C.	Mm.		Calcd.	Found	Calcd.	Found
<i>t</i> -Butyl chloride	2,5-Dimethyl-3- <i>t</i> -butyl-	99-100	24	90-93	71.43 <sup>a</sup>	71.26	9.53	9.32
<i>i</i> -Propyl chloride	2-Methyl-5- <i>i</i> -propyl-	172-173	760	5-7	15.79	15.66	1.85	1.64 <sup>b</sup>
	2,5-Dimethyl-3- <i>i</i> -propyl-	85-86	21	40-67	70.13	69.92	9.09	8.87
Ethyl bromide	2-Methyl-5-ethyl-	159-160	760	9-10	...	...	..	..
	2,5-Dimethyl-3-ethyl-	75-77	21	40-50	68.57	68.36	8.57	8.65
<i>n</i> -Butyl chloride	2,5-Dimethyl-3- <i>t</i> -butyl-	99-100	24	38-43	...	...	..	..
	2-Methyl-5- <i>t</i> -butyl-	184-185	760	9-10	27.76	27.92	3.35	3.15 <sup>c</sup>

<sup>a</sup> All analyses were conducted by A. A. Sirotenko of this Laboratory. <sup>b</sup> Analyzed as the dichloromercuri derivative. <sup>c</sup> Analyzed as the chloromercuri derivative.

ette and Brown.<sup>7</sup> A mixed melting point of the two resulting samples of 2,5-dimethyl-3-ethyl-4-thienylacetamide showed no depression.

2-Methyl-5-ethylthiophene, the by-product from the reaction with ethyl bromide, has been known since Steinkopf prepared it in 1920,<sup>8</sup> but no solid derivative of it has been reported. We therefore prepared a solid derivative by first iodinating with mercuric oxide and iodine, then the Grignard reagent prepared from the iodo compound reacted with phthalic anhydride and the resulting substituted thenoylbenzoic acid was cyclized to give the crystalline 2-methyl-7-ethylthiophanthrenequinone. A mixed melting point with a sample obtained from the known 2-methyl-5-ethylthiophene, by the same series of reactions, showed no depression.

2,5-Dimethyl-3-isopropylthiophene, obtained by the alkylation of 2,5-dimethylthiophene with isopropyl chloride, was synthesized by treating the known 2,5-dimethyl-3-acetothienone with methylmagnesium iodide, dehydrating the resulting tertiary alcohol, and subsequently hydrogenating the 3-isopropenyl derivative with palladium-on-charcoal and 30 lb. of hydrogen pressure. The 2,5-dimethyl-3-isopropylthiophene thus obtained and that obtained by alkylation were acetylated to give 2,5-dimethyl-3-isopropyl-4-acetothienone. Since the ketone did not react with the usual carbonyl reagents, a solid derivative was prepared by using the Willgerdt reaction to give 2,5-dimethyl-3-isopropyl-4-thienylacetamide.<sup>7</sup> A mixed melting point determination of the amides obtained by both methods showed no depression.

The by-product, 2-methyl-5-isopropylthiophene, obtained from the reaction with isopropyl chloride was converted to 5-isopropyl-2-thiophenecarboxylic acid by treatment with *N*-bromosuccinimide in the presence of benzoyl peroxide, followed by a Sommelet reaction and oxidation of the resulting aldehyde by alkaline permanganate. The acid was also synthesized by hypochlorite oxidation of the known 5-isopropyl-2-acetothienone.<sup>9</sup> A mixed melting point of these acids showed no depression.

To show that the alkylated 2,5-dimethylthiophenes obtained from *t*-butyl chloride and *n*-butyl chloride were identical, the products were iodinated with mercuric oxide and iodine. The resulting samples of 2,5-dimethyl-3-*t*-butyl-4-iodothiophene

showed no depression by the method of mixed melting points. The absolute structure of 2,5-dimethyl-3-*t*-butylthiophene has not been proved by synthetic methods. The proposed structure seems to be justified by analogy with the beta alkylated products obtained from the reactions with isopropyl chloride and ethyl bromide, whose structures have been proven. It does not seem probable that the main product obtained from the reaction with *t*-butyl chloride would differ in the position of the alkyl group from those obtained with isopropyl chloride or ethyl bromide.

The 2-methyl-5-*t*-butylthiophene obtained as the by-product from the reaction with *n*-butyl chloride was converted to 5-*t*-butyl-2-thiophenecarboxylic acid by bromination with *N*-bromosuccinimide, a Sommelet reaction and oxidation of the resulting aldehyde with alkaline permanganate. This acid was synthesized by condensing  $\omega$ -bromopinacolone with ethyl acetoacetate in the presence of sodium ethylate to give the expected  $\alpha$ -pinacolonylacetate. The hydrolysis of the ethyl  $\alpha$ -pinacolonylacetate was accomplished by treating the ester with 3% potassium hydroxide solution for three days. The 6,6-dimethylheptanedione-2,5 thus obtained, was treated with phosphorus pentasulfide following the known method,<sup>10</sup> to give 2-methyl-5-*t*-butylthiophene. This was brominated with *N*-bromosuccinimide, converted to the aldehyde by a Sommelet reaction and the resulting aldehyde converted to 5-*t*-butyl-2-thiophenecarboxylic acid by alkaline permanganate oxidation. A mixed melting point of the acids showed no depression.

### Experimental

**General Procedure for Alkylation of 2,5-Dimethylthiophene.**—To a well-stirred suspension of 350 ml. of carbon disulfide and 67 g. (0.5 mole) of aluminum chloride, cooled in ice, there was added dropwise, a solution of 56 g. (0.5 mole) of 2,5-dimethylthiophene and 0.5 mole of the appropriate alkyl halide. After standing in the cold for ten hours, the usually dark reaction mixture was decomposed with cracked ice and hydrochloric acid. The carbon disulfide layer was separated and the water layer extracted with several portions of ether. The combined ether extracts and carbon disulfide layer were washed with water, 10% sodium carbonate, water and dried over calcium chloride. The entire distillate was then fractionated in a Todd column of 50 theoretical plates at a reflux ratio of 10:1. The lower boiling 2-methyl-5-alkylthiophene was fractionated at atmospheric pressure. When this fraction was removed the higher boiling 2,5-dimethyl-3-alkylthiophene was distilled at reduced pressure.

**2,5-Dimethyl-3-ethyl-4-thienylacetamide.**—From 12.7 g. (0.09 mole) of 2,5-dimethyl-3-ethylthiophene<sup>8</sup> by acetyla-

(7) J. A. Blanchette and E. V. Brown, *THIS JOURNAL*, **72**, 3414 (1950).

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

(9) H. Scheibler and M. Schmidt, *Ber.*, **54**, 139 (1921).

(10) C. Paal, *ibid.*, **18**, 2251 (1885).

tion in the usual manner<sup>11</sup> there was obtained 14 g. (85%) of 2,5-dimethyl-3-ethyl-4-acetothienone, b.p. 134–136° (20 mm.).

2,5-Dimethyl-3-ethyl-4-acetothienone (3 g.), 16 ml. of yellow ammonium polysulfide, 1.5 g. of sulfur and 20 ml. of dioxane were sealed in a glass combustion tube and heated for 12 hours at 155–160°. The contents were evaporated to dryness and the residue extracted with boiling water. Recrystallization from water gave 1.8 g. (58%) of 2,5-dimethyl-3-ethyl-4-thienylacetamide, m.p. 143–144°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>ONS: N, 7.11. Found: N, 7.22.

**2-Methyl-7-ethylthiophanthrenequinone.**—2-Methyl-5-ethylthiophene (34 g.) (0.26 mole) was iodinated in the usual manner<sup>12</sup> with 67.6 g. (0.26 mole) to give 45 g. (65%) of monoiodo-2-methyl-5-ethylthiophene, b.p. 128–130° (23 mm.).

The Grignard reagent, prepared from 4.1 g. (0.17 gram atom) of magnesium and 45 g. (0.17 mole) of monoiodo-2-methyl-5-ethylthiophene in 300 ml. of dry ether, was added dropwise to a well-stirred cold solution of 25.1 g. (0.17 mole) of phthalic anhydride in 300 ml. of dry anisole. After an additional six hours stirring the mixture was hydrolyzed, extracted with ether three times and the combined ether solution was washed twice with 100 ml. of cold 10% sodium carbonate. The sodium carbonate solution was then extracted once with 100 ml. of ether and the mixture of 2-(2-methyl-5-ethyl-3-thenoyl)- and 2-(2-methyl-5-ethyl-4-thenoyl)-benzoic acids was precipitated from the well-stirred cold sodium carbonate solution by the slow addition of dilute hydrochloric acid. The oily isomeric acids were then taken up in ether and the ether evaporated under reduced pressure. There resulted 30 g. (64%) of sirupy 2-(2-methyl-5-ethyl-3- and 4-thenoyl)-benzoic acids which was pure enough for the next step.

In a 200-ml. round-bottomed flask, fitted with a reflux condenser, were placed 12 g. (0.04 mole) of the isomeric thenoylbenzoic acids, 33.5 g. (0.25 mole) of aluminum chloride and 18 g. of potassium chloride. After mixing and heating for ten minutes in an oil-bath at 140°, the dark mass was cooled and decomposed by ice-water and hydrochloric acid. The mixture was then extracted with ether, the combined ether extracts were washed with water, 10% sodium carbonate and water. The dark-brown crystals that remain after removal of the ether were recrystallized from dilute acetic acid. Final purification by vacuum sublimation yielded 1.6 g. (15%) of 2-methyl-7-ethylthiophanthrenequinone, m.p. 121°. A mixed melting point with a sample obtained from 2-methyl-5-ethylthiophene produced by the Friedel-Crafts reaction showed no depression.

*Anal.* Calcd. for C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>S: C, 70.31; N, 4.68. Found: C, 70.51; H, 4.57.

**5-Isopropyl-2-thiophenecarboxylic Acid.**—Potassium hypochlorite from 10 g. of commercial calcium hypochlorite<sup>13</sup> was placed in a flask warmed to 60–65° and 3.3 g. (0.02 mole) of 5-isopropyl-2-acetothienone<sup>14</sup> was added. From this oxidation in the usual manner there was obtained 2.8 g. (82%) of 5-isopropyl-2-thiophenecarboxylic acid, m.p. 81°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>S: C, 56.47; H, 5.88. Found: C, 56.70; H, 5.87.

**5-Isopropyl-2-thiophenecarboxylic Acid from 2-Methyl-5-isopropylthiophene.**—To a solution of 2.8 g. (0.02 mole) of 2-methyl-5-isopropylthiophene in 25 ml. of carbon tetrachloride was added 3.5 g. (0.02 mole) of N-bromosuccinimide and 0.05 g. of benzoyl peroxide. The mixture was shaken vigorously and then heated for two hours. After cooling in an ice-bath, the succinimide was removed by filtration and the carbon tetrachloride evaporated at reduced pressure. The remaining lachrymatory oil was dissolved in 25 ml. of chloroform to which was added 7.8 g. of hexamethylenetetramine. The mixture was refluxed for one hour, cooled and the salt filtered. The salt was dissolved in 10 ml. of hot water and rapidly steam distilled. The distillate was acidified with hydrochloric acid, extracted with ether and, after removal of ether at reduced pressure,

the residual oil was oxidized by the addition of an alkaline potassium permanganate solution at room temperature. The crude acid was isolated in the usual manner and recrystallized from water to give 0.5 g. (15%) of 5-isopropyl-2-thiophenecarboxylic acid, m.p. 81–82°. A mixed melting point of the acid with the synthetic acid showed no depression.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>S: C, 56.47; H, 5.88. Found: C, 56.42; H, 5.65.

**2,5-Dimethyl-3-isopropylthiophene.**—One hundred and ten grams (0.72 mole) of 2,5-dimethyl-3-acetothienone was treated with a solution of methylmagnesium iodide prepared from 166 g. (1.0 mole) of methyl iodide and 24 g. (1 gram-atom) of magnesium. The mixture was decomposed in the usual manner, the combined ether extracts were evaporated and the product was dehydrated by steam distillation from a 5% sulfuric acid solution. Rectification yielded 70 g. (63%) of 2,5-dimethyl-3-isopropenylthiophene, b.p. 88–90° (16 mm.).

2,5-Dimethyl-3-isopropenylthiophene (15.2 g.) (0.1 mole) was dissolved in 150 ml. of absolute alcohol and the solution was hydrogenated using 2 g. of 5% palladium-on-charcoal and two atmospheres of hydrogen pressure. The catalyst was filtered from the solution, the alcohol was removed under reduced pressure and the product was fractionated. This gave 11 g. (80%) of 2,5-dimethyl-3-isopropylthiophene, b.p. 80–81° (18 mm.), *n*<sub>D</sub><sup>20</sup> 1.5100.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>S: C, 70.13; H, 9.09. Found: C, 70.10; H, 8.90.

**2,5-Dimethyl-3-isopropyl-4-thienylacetamide.**—The procedure employed for the preparation of 2,5-dimethyl-3-isopropyl-4-acetothienone was the same as that described for the preparation of 2,5-dimethyl-3-ethyl-4-acetothienone. In this manner 15.4 g. (0.1 mole) of 2,5-dimethyl-3-isopropylthiophene gave 10.1 g. (52%) of 2,5-dimethyl-2-isopropyl-4-acetothienone, b.p. 135–137° (18 mm.).

Four grams (0.02 mole) of 2,5-dimethyl-3-isopropyl-4-acetothienone was converted according to the procedure previously described for the preparation of 2,5-dimethyl-3-ethyl-4-thienylacetamide. Recrystallization from benzene-petrol ether resulted in 0.8 g. (19%) of 2,5-dimethyl-3-isopropyl-4-thienylacetamide, m.p. 149°. A mixed melting point with a sample prepared from 2,5-dimethyl-3-isopropylthiophene obtained from the Friedel-Crafts reaction showed no depression.

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>ONS: N, 6.63. Found: N, 6.79.

**2,5-Dimethyl-3-*t*-butyl-4-iodothiophene.**—When 33.6 g. (0.02 mole) of 2,5-dimethyl-3-*t*-butylthiophene was treated in the manner described for the preparation of monoiodo-2-methyl-5-ethylthiophene, there resulted 21 g. of unreacted material and 13 g. (59%) of 2,5-dimethyl-3-*t*-butyl-4-iodothiophene, b.p. 116–117° (3 mm.). Recrystallization from alcohol gave white plates melting at 68–69°. A mixed melting point of samples obtained from the reactions with *n*-butyl chloride and *t*-butyl chloride showed no depression.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>SI: C, 40.81; H, 5.10. Found: C, 41.01; H, 4.87.

**Ethyl  $\alpha$ -Pinacolonylacetate.**—From 179 g. (1.0 mole) of  $\omega$ -bromopinacolone and the sodio derivative of acetoacetic ester in the usual manner there was obtained 153 g. (67%) of ethyl  $\alpha$ -pinacolonylacetate, b.p. 123–124° (5 mm.).

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>: C, 63.15; H, 8.77. Found: C, 63.4; H, 8.76.

**6,6-Dimethylheptanedione-2,5.**—One-hundred and fifty-three grams (0.67 mole) of ethyl  $\alpha$ -pinacolonylacetate was stirred with 1.1 moles of 3% potassium hydroxide solution at room temperature for four days. At the end of this time the solution was acidified with sulfuric acid and the aqueous layer was extracted with ether. The combined extracts were washed with water, 10% sodium carbonate, water and dried over anhydrous sodium sulfate. Fractionation yielded 80 g. (74%) of 6,6-dimethylheptanedione-2,5, b.p. 105–106° (24 mm.).

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>: C, 69.29; H, 10.25. Found: C, 69.44; H, 10.15.

**2-Methyl-5-*t*-butylthiophene.**—Seventy-eight grams (0.5 mole) of 6,6-dimethylheptanedione-2,5 was gently refluxed with 72 g. (0.33 mole) of phosphorus pentasulfide. Another

(11) Steinkopf, "Chemie des Thiophene," Edwards Bros., Ann Arbor, Mich., 1944, p. 70.

(12) Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 357.

(13) See Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 428.

(14) H. Schreiber and M. Schmidt, *Ber.*, **54**, 139 (1921).

10 g. of phosphorus pentasulfide was added after heating for an hour. After four hours of refluxing, the mixture was cooled, extracted with ether and the ether extracts dried over calcium chloride. Distillation gave the crude hydrocarbon, which was purified by refluxing over sodium. Rectification yielded 40.8 g. (53%) of 2-methyl-5-*t*-butylthiophene, b.p. 74–75° (19 mm.).

The chloromercuri derivative melted at 195°.

*Anal.* Calcd. for  $C_9H_{13}HgClS$ : C, 27.76; H, 3.35. Found: C, 28.01; H, 3.59.

**5-*t*-Butyl-2-thiophenecarboxylic Acid.**—5-*t*-Butyl-2-methylthiophene (24 g.) (0.15 mole) reacted with *N*-bromosuccinimide followed by hexamethylenetetramine in the manner indicated above under 5-isopropyl-2-thiophenecarboxylic acid to give the aldehyde, a small portion of which

was converted to a semicarbazone melting at 215–216° (recrystallized from alcohol).

*Anal.* Calcd. for  $C_{10}H_{15}N_3OS$ : C, 53.33; H, 6.66; N, 18.66. Found: C, 53.14; H, 6.47; N, 18.56.

The crude aldehyde was then oxidized with alkaline potassium permanganate to give the crude acid. Recrystallization from alcohol–water yielded 8.4 g. (31%) of 5-*t*-butyl-2-thiophenecarboxylic acid, m.p. 127–128°. A mixed melting point with a sample obtained in an analogous manner from the 2-methyl-5-*t*-butylthiophene resulting from Friedel–Crafts reaction showed no depression.

*Anal.* Calcd. for  $C_9H_{13}O_2S$ : C, 58.69; H, 6.52. Found: C, 58.70; H, 6.33.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

## The Mechanism of Halide Reductions with Lithium Aluminum Hydride. II. Reduction of 2-Chloro-2-phenylpropionic Acid<sup>1,2</sup>

BY ERNEST L. ELIEL AND JEREMIAH P. FREEMAN

Optically active 2-chloro-2-phenylpropionic acid and its methyl ester are readily reduced to active 2-phenyl-1-propanol by lithium aluminum hydride in either tetrahydrofuran or ether solution with 37–67% racemization.  $\alpha$ -Methylstyrene oxide is not an intermediate, as it is reduced to 2-phenyl-2-propanol. 2-Phenyl-1,2-propanediol is a by-product of the reduction of 2-chloro-2-phenylpropionic acid and is formed with complete inversion of configuration. Formation of the glycol probably proceeds through an  $\alpha$ -lactone intermediate. The alcohol may be formed by way of the primary reduction product, 2-chloro-2-phenyl-1-propanol, assumed to undergo a hydride shift with loss of hydrogen chloride to form 2-phenylpropanal which in turn is reduced to 2-phenyl-1-propanol.

The amazing versatility of lithium aluminum hydride<sup>3</sup> as a reducing agent in organic chemistry has stimulated considerable interest in the manner in which this reagent acts. Shortly after it became known that halides,<sup>4,5</sup> epoxides<sup>5–7</sup> and certain *p*-toluenesulfonates<sup>8–10</sup> can be reduced with lithium aluminum hydride in such a way as to replace a carbon–halogen or carbon–oxygen bond by carbon–hydrogen, Trevo and Brown<sup>6</sup> demonstrated an inversion mechanism in the reduction of cyclic epoxides. They suggested the  $AlH_4^-$  anion to be the active species in the reduction which appears to be of the classical  $S_N2$  type. Cram<sup>10</sup> showed that the reduction of the *p*-toluenesulfonates of the stereoisomeric 3-phenyl-2-butanols, 3-phenyl-2-pentanols and 2-phenyl-3-pentanols involves double inversion of configuration and postulated a "phenonium ion" intermediate. Alexander<sup>9</sup> obtained optically active 3-deutero-*trans*-*p*-menthane by the reduction of 1-menthyl *p*-toluenesulfonate with lithium aluminum deuteride. However, no work

has been reported on the mechanism of the reduction of *halides* with lithium aluminum hydride, beyond the qualitative observation that primary halides react more rapidly than secondary, while tertiary halides produce mainly olefins.<sup>4,6</sup> This again points to an  $S_N2$  mechanism which is also supported by the fact that optically active  $\alpha$ -phenethyl chloride yields active  $\alpha$ -deuteroethylbenzene upon reduction with lithium aluminum deuteride.<sup>1,11</sup>

It was the object of the present study to investigate the steric course of the reduction of a tertiary halide with lithium aluminum hydride. To accomplish this objective, a halide had to be chosen which was sufficiently reactive to be reduced, which could be obtained in a state of known optical purity, and which, upon reduction, would give a compound of known maximum rotation. Such a compound is 2-chloro-2-phenylpropionic acid (I).

Preliminary experiments with the racemic chloro-acid (I) indicated that it was readily reduced to 2-phenyl-1-propanol (II) in about 30% yield by means of lithium aluminum hydride in tetrahydrofuran solution. 2-Phenyl-1,2-propanediol (III) (about 25%) was also obtained in the reduction, as well as small amounts of 2-phenylpropanal (IV) and acetophenone.<sup>12</sup> Reduction of the active chloro-acid (I) revealed that the 2-phenyl-1-pro-

(1) First paper in this series: E. L. Eliel, *THIS JOURNAL*, **71**, 3970 (1949).

(2) Presented before the Organic Division of the American Chemical Society at Cleveland, Ohio, April 11, 1951.

(3) W. G. Brown in R. Adams, "Organic Reactions," John Wiley and Sons, Inc., Vol. VI, New York, N. Y., 1951, p. 469.

(4) J. E. Johnson, R. H. Blizzard and H. W. Carhart, *THIS JOURNAL*, **70**, 3664 (1948).

(5) R. F. Nystrom and W. G. Brown *ibid.*, **70**, 3738 (1948).

(6) L. W. Trevo and W. G. Brown, *ibid.*, **71**, 1675 (1949).

(7) D. A. Prins, *ibid.*, **70**, 3955 (1948); P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1885 (1948); **32**, 265 (1949), P. A. Plattner, H. Heusser and M. Feurer, *ibid.*, **31**, 2210 (1948); **32**, 587 (1949).

(8) H. Schmid and P. Karrer, *ibid.*, **32**, 1371 (1949); P. Karrer and G. Widmark, *ibid.*, **34**, 34 (1951); P. Karrer, H. Asmis, K. N. Sareen and R. Schwyzer, *ibid.*, **34**, 1022 (1951).

(9) E. R. Alexander, *THIS JOURNAL*, **72**, 3796 (1950).

(10) D. J. Cram, Meeting of the American Chemical Society, Chicago, Ill., September 6, 1950, Abstracts pp. 49N, 50N.

(11) The estimates of the optical purity of the  $\alpha$ -phenethyl chloride used in our earlier investigation (ref. 1) are in error. Gerrard [*J. Chem. Soc.*, 741 (1946)] obtained  $\alpha$ -phenethyl chloride with  $[\alpha]_D^{25} +93.5^\circ$ ; thus the chloride used in the lithium aluminum deuteride reduction was at most about 52% pure. This does not affect the conclusions of the earlier paper (ref. 1) which were of a qualitative nature only.

(12) Since an excess of lithium aluminum hydride was employed in the reduction, the carbonyl compounds cannot have been present in the reaction mixture but must have originated during the isolation process.