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## On the Cleavage of Benzene, Thiophene and Furan Rings by Means of Ultrasonic Waves<sup>1</sup>

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Bromobenzene, iodobenzene,  $\alpha$ -bromothiophene,  $\alpha$ -iodothiophene,  $\alpha$ -bromofuran and some other similar compounds were suspended in aqueous silver nitrate solution and exposed to ultrasonic waves at ordinary temperature. Thick precipitates of silver halide (and sulfide) appeared that contained some silver acetylide and diacetylide, corresponding, respectively, to about 10 and 1% of the theoretically possible amounts. Methods for the separation, identification and quantitative estimation of these ring cleavage products are described. The behavior of an aqueous benzene solution is discussed.

Although aliphatically bound chlorine is liberated easily in the presence of water by ultrasonic waves,<sup>2</sup> aromatic halides are, as expected, more resistant. In that series the results of pertinent experiments seem to be highly dependent on the conditions, especially on the effectiveness of the ultrasonic equipment. Thus, Kling and Kling<sup>3</sup> have reported positive results when using chlorobenzene while a similar treatment carried out by Feuill<sup>4</sup> and (in an unpublished study) by the present authors did not lead to the elimination of chlorine. However, some liberation of halogen from chloro-, bromo- and iodobenzene was observed by Weissler,<sup>5</sup> who compared quantitatively the ultrasonic behavior of certain aliphatic and aromatic halides.

Recently, we have observed, first in the case of bromobenzene, that under the influence of ultrasonic treatment the aromatic halogen can be removed easily from the ring in the presence of aqueous silver nitrate. While such two-phase systems remain essentially clear when shaken or refluxed, a thick precipitate soon appears upon exposure to ultrasonic waves, at or near room temperature. Similar observations also have been made with iodobenzene,  $\alpha$ -iodothiophene,  $\alpha$ -bromothiophene,  $\alpha$ -bromofuran and some other halogen substituted compounds. In the case of the thiophene derivatives or of thiophene itself the sulfur also is removed from the ring.

The nature of the seemingly complicated mixture remaining in the filtrate and forming the main bulk of the organic products has not yet been clarified; however, two typical cleavage products consistently present in the silver halide (and/or sulfide) precipitate<sup>6</sup> could be identified. When such precipitates are dried and heated at 120–160°, a deflagration takes place, sometimes accompanied by an orange or yellow flash.

This phenomenon was observed with the silver salt precipitates resulting from the ultrasonic treatment of iodobenzene, bromobenzene,  $\alpha$ -iodothiophene,  $\alpha$ -bromothiophene, *p*-bromoanisole, *o*-bro-

motoluene,  $\alpha$ -bromofuran, and others; it was very weak in the case of chlorobenzene, thiophene or  $\alpha$ -chlorothiophene, and was absent when *n*-butyl bromide was the starting material.

We find that the deflagration is caused by the presence in the precipitate of some silver acetylide and, to a much lesser extent, silver diacetylide (both possibly in the form of a complex). A mixture of acetylene and diacetylene can be liberated by means of dilute hydrochloric acid and reprecipitated as explosive salts by absorption in an ammoniacal silver or cuprous solution. These yellowish and dark red precipitates could not be differentiated from corresponding salts obtained from acetylene *ex carbide*.

The amount of acetylene plus diacetylene, calculated as "acetylene," was estimated according to the method of Willstätter and Maschmann<sup>7</sup> by preparing first a cuprous acetylide precipitate; after filtration and washing, the latter is dissolved in a strongly acid ferric sulfate solution ( $\text{Cu}_2\text{C}_2 + 2\text{Fe}^{+++} + 2\text{H}^+ \rightarrow 2\text{Cu}^{++} + 2\text{Fe}^{++} + \text{C}_2\text{H}_2$ ), and the ferrous ion thus formed is titrated with permanganate.

The "acetylene" values thus obtained in independent experiments, after a six-hour ultrasonic treatment, were as follows (the figures indicate percentage of the theoretically possible amount): bromobenzene, 6, 6 and 11; iodobenzene, 16 and 15;  $\alpha$ -bromothiophene, 9 and 10;  $\alpha$ -iodothiophene, 7, 9 and 16;  $\alpha$ -bromofuran, 8 and 9.

Since this method cannot be used for the estimation of the ratio acetylene:diacetylene in the reaction product, another pertinent analytical method was developed, based on the following principle.

As is known, when acetylene is absorbed at room temperature in a chloroform solution of bromine, it quantitatively forms the tetrabromide, while diacetylene is not saturated entirely under these conditions and yields a hexabromide,<sup>8</sup>  $\text{Br}_2\text{CH}\cdot\text{CBr}_2\cdot\text{CBr}=\text{CHBr}$  or  $\text{Br}_2\text{CH}\cdot\text{CBr}=\text{CBr}\cdot\text{CHBr}_2$ .

We find that a mixture of the two bromo compounds mentioned can be resolved by fractional semi-micro steam distillation of a weighed sample, whereby the less volatile, crystalline hexabromide remains behind; it is weighed, and the amount of acetylene tetrabromide is estimated by difference.

This method can be employed either directly,

(1) This research was supported by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command.

(2) A. Weissler, H. W. Cooper and S. Snyder, *THIS JOURNAL*, **72**, 1769 (1950).

(3) A. Kling and R. Kling, *Compt. rend. acad. sci.*, **223**, 1131 (1946).

(4) A. J. Feuill, *Research*, **2**, 148 (1949).

(5) A. Weissler, *Chem. Eng. Progr. Symp. Ser.*, **47**, 22 (1951); *cf.* especially Fig. 14.

(6) The presence of small amounts of metallic silver is (in part) responsible for the dark color of some sulfur-free precipitates; they become lighter upon treatment with warm, dilute nitric acid.

(7) R. Willstätter and E. Maschmann, *Ber.*, **53**, 939 (1920).

(8) A. A. Noyes and C. W. Tucker, *Am. Chem. J.*, **19**, 123 (1897); F. G. Müller, *Helv. Chim. Acta*, **8**, 826 (1925); F. Straus and L. Kollek, *Ber.*, **59**, 1664 (1926).

*i.e.*, by leading the two gases liberated from the ultrasonically obtained precipitate into bromine solution, or indirectly, by first preparing a mixture of the two copper salts, decomposing it with acid and absorbing the acetylene plus diacetylene in the bromine solution. Although this latter procedure affords somewhat lower yields, Table I shows that, under the conditions applied, roughly 10% of the initially present ring carbons have appeared in the form of acetylene, and about 1% as diacetylene, at the end of the ultrasonic treatment.

TABLE I  
ULTRASONIC CLEAVAGE OF SOME CYCLIC HALIDES TO  
ACETYLENE AND DIACETYLENE

Compound treated	Method	C-atoms recovered, %		Total yield, %
		As acetylene	As diacetylene	
Bromobenzene	Direct	9.0	1.4	10.4
	Via Cu salt	6.5	1.1	7.6
$\alpha$ -Iodobenzene	Direct	7.9	2.4	10.3
	Via Cu salt	7.1	2.1	9.2
$\alpha$ -Bromothiophene	Direct	6.8	1.0	7.8
	Via Cu salt	6.8	1.0	7.8
$\alpha$ -Iodothiophene	Direct	10.4	1.3	11.7
	Via Cu salt	9.9	1.3	11.2
$\alpha$ -Bromofuran	Direct	6.7	0.5	7.2
	Via Cu salt	5.3	0.4	5.7

These results show that by ultrasonic treatment aromatically bound halogen may be activated and the cleavage of some aromatic and heterocyclic ring systems may be effected at ordinary temperature.

It is interesting to note in this connection the recent observation made by Prudhomme and Grabar, and especially by Lapinskaya, Mironova and Khenokh<sup>9</sup> that aqueous benzene solutions when treated ultrasonically become slightly acid and show marked changes in the aromatic spectrum. No reaction products have been identified or isolated by these authors. We were able to confirm the spectroscopic observations made by Lapinskaya, *et al.*, although our curve is somewhat different from that given by the Russian investigators.

The present study is being continued.

### Experimental

The ultrasonic generator used was the Hypersonic Transducer model BU-305A-600 (Brush Electronic Co., Cleveland, Ohio). The cup-shaped barium titanate transducer element (diam., 9 cm.) was operated at about 5 amp. at 25 volts; estimated power input, 125 watts at 550–600 kilocycles. Tap water was circulated through the cooling coil. All treatments were carried out in a 100-ml. round-bottom Pyrex flask with a neck 23 cm. long; the bottom of the flask was placed at 1–4 cm. from the crystal. During treatment, the temperature of the liquid never exceeded 40°.

**Silver Halide (Sulfide) Precipitates.**—A suspension of 0.1 ml. of the liquid halide (about 1 millimole) in 50 ml. of 0.1 *N* silver nitrate showed marked darkening after a few min. of ultrasonic treatment, and soon after a heavy, yellowish-brown to brownish-black precipitate appeared.<sup>10</sup> The

(9) R. O. Prudhomme and P. Grabar, *Bull. soc. chim. biol.*, **29**, 122 (1947); E. M. Lapinskaya, A. N. Mironova and M. A. Khenokh, *Doklady Akad. Nauk, S.S.S.R.*, **94**, 109 (1954); *C. A.*, **48**, 7657 (1954).

(10) Much less or no precipitate appeared in the presence of 50% alcohol in the aqueous phase, while silver acetate or ammoniacal silver solutions did give positive results without offering any special advantages over the method used.

treatment was extended over several hours. (The aqueous phase remained almost colorless and became acid.) Some foamy material was broken up with methanol, and then the precipitate, collected by centrifuging, was used for the estimations as described below.

**Formation of the Cuprous Salts; Estimation of Acetylene plus Diacetylene.**—After a 6-hr. treatment the weight of such precipitates, established after washing with water, methanol, ether and drying *in vacuo*, amounted, for example, to the following percentages of the theoretically possible values (calcd. as silver halide or silver halide plus sulfide): bromobenzene, 84; iodobenzene, 120; bromothiophene, 85; iodothiophene, 104; and bromofuran, 114.

The combined precipitate originating from five 0.1-ml. portions of halide was transferred with water into the flask of an all-glass apparatus connected with three traps, each containing 15–20 ml. of a cuprous solution, prepared, with slight modifications, according to Ilosvay.<sup>11</sup> (To 1.8 g. of cupric nitrate, dissolved in a little water, 10 ml. of concd. ammonia and 7 g. of hydroxylamine hydrochloride were added, the latter in small portions; this solution was diluted to 60 ml.)

After the addition, from a separatory funnel, of 5 ml. of concd. hydrochloric acid, the flask was submerged in a water-bath at 70° for 2 hr. while a slow stream of nitrogen bubbled through. The reddish-purple cuprous precipitate then was collected on a sintered glass funnel of medium porosity and washed with about 0.5 l. of water until the washings no longer changed the color of a drop of 0.1 *N* permanganate (the filter cake should not be allowed to dry out, even temporarily, during this operation). The wet precipitate was dissolved in 15 ml. of a solution containing, per liter, 100 g. of "desiccated" ferric sulfate and 200 g. of concd. sulfuric acid; an additional 5 ml. of the acid ferric solution was required to dissolve some acetylides adhering to the glass walls of the traps. The resulting greenish solution was rinsed over into an erlenmeyer flask. Two ml. of 85% phosphoric acid then was added and the ferrous ion titrated with 0.1 *N* permanganate until the pink coloration persisted for a second or two throughout the solution.<sup>12</sup>

**Formation of Acetylene Tetrabromide and Diacetylene Hexabromide.**—The ultrasonically obtained precipitate was treated with acid in the all-glass apparatus mentioned in the same manner as described, but in this instance each trap was filled with 2–3 ml. of a 25% bromine solution in chloroform. After the conclusion of the 2-hr. experiment the resulting solution was kept standing for 2 more hr. The excess bromine then was distilled off by heating in a steam-bath, the oily residue was dissolved in ether (sufficient to make the solution lighter than water) and the ether solution was freed from bromine by repeated shaking with ferrous sulfate or ammonia. (If ammonia was used, the resulting emulsion had to be broken up by means of a few drops of dilute nitric acid.) The ether solution (about 5 ml.) was washed twice with water, dried with magnesium sulfate and filtered through a glass-wool plug into a tared 25-ml. erlenmeyer flask. The ether was driven off first at the water-pump, then high vacuum was applied for a minute, and, finally, the yellow, oily residue was weighed.

On standing, this residue deposited colorless rhombohedra which, upon two recrystallizations from abs. alcohol, melted at 182–183° (cor.) and did not give any melting point depression with an authentic sample of diacetylene hexabromide.<sup>13</sup> This identification was carried out with samples *ex bromobenzene*, iodobenzene,  $\alpha$ -bromothiophene,  $\alpha$ -iodothiophene and  $\alpha$ -bromofuran.

*Anal.* Calcd. for C<sub>4</sub>H<sub>2</sub>Br<sub>6</sub>: C, 9.07; H, 0.38; Br, 90.55; mol. wt., 530. Found: C, 8.44; H, 0.34; Br, 91.33 (Carius); mol. wt. (Rast), 584.

**Separation and Estimation of Acetylene Tetrabromide and Diacetylene Hexabromide.**—An all-glass semi-micro

(11) L. von Ilosvay, *Ber.*, **32**, 2697 (1899).

(12) The eventual disappearance of this color is caused by some reducing substances, most of which may be eliminated by a pre-extraction with methylene chloride; however, such stabilization of the titrimetric end-point was not required for our purposes.

(13) 2-Butyne-1,4-diol was converted into 2-butyne-1,4-dichloride, and the diacetylene, obtained by alkaline dehydrohalogenation of the latter, was passed into bromine water. The precipitate was recrystallized from hot alcohol (*cf.* A. W. Johnson, *J. Chem. Soc.*, 1009 (1946); J. B. Armitage, E. R. H. Jones and M. C. Whiting, *ibid.*, **44** (1951)).

steam distillation device of the type described by Fieser,<sup>14</sup> with a small condenser sealed on, was used. The condenser arm (length, 4.5 cm.) was cooled by ice-water during the experiment. The brominated mixture (see above) was transferred with some ether into the inner tube of this apparatus and the ether was blown off with nitrogen. The boiler flask, half-filled with dist. water, was then heated to allow the collection of about 1 ml. of distillate per min. When practically all of the acetylene tetrabromide had gone over, crystals of diacetylene hexabromide began to appear in the condenser arm. At this point the steam-distillation was stopped and the crystals were freed from water by draining as completely as possible. The flask was then kept in a vacuum desiccator for half a day and weighed.

The collected crude acetylene tetrabromide was extracted from the distillate with ether, and the solution was dried and evaporated *in vacuo*. The oily residue showed  $n_D^{20}$

(14) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 161.

1.6343, while a redistilled commercial sample, after having gone through the described operations, gave the value 1.6340.

Anal. Calcd. for  $C_2H_2Br_4$ : Br, 91.95. Found: Br, 92.18 (Carius).

The extent of the reliability of the procedure may be illustrated by the following results obtained by steam distilling two artificial mixtures: (a) applied, 20 mg. of diacetylene hexabromide mixed with about 14 parts of acetylene tetrabromide; recovered, 19.8 mg. (99%); (b) applied, 75.6 mg. of hexabromide and 2.5 parts of tetrabromide; recovered, 78 mg. (103%).

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[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

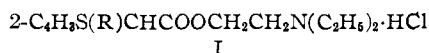
### Antispasmodics. III. Basic Alkyl Ester Acid Addition and Quaternary Ammonium Salts of $\alpha$ -(2-Cycloalken-1-yl)-2-thienylacetic Acids

BY FREDERICK LEONARD<sup>1</sup> AND LEON SIMET

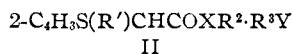
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A large number of basic alkyl esters of  $\alpha$ -(2-cycloalken-1-yl)-2-thienylacetic acids of the general formula II have been prepared for pharmacological evaluation in the form of their acid addition and quaternary ammonium salts. Several have been found to possess anticholinergic activity of a high order.

The synthesis, antispasmodic activity and toxicity of a number of 2-diethylaminoethyl ester hydrochlorides of  $\alpha$ -substituted 2-thienylacetic acids were reported in the first paper<sup>2</sup> of this series. Two of the compounds described therein, namely, 2-diethylaminoethyl  $\alpha$ -(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride [I, R = 1-(2-C<sub>5</sub>H<sub>7</sub>)<sup>3</sup>] and its 2-cyclohexen-1-yl homolog [I, R = 1-(2-C<sub>6</sub>H<sub>9</sub>)] were found to possess *in vitro* and *in vivo* antispasmodic activity in the clinically useful range. The preparation was therefore undertaken, with these substances as model compounds, of a



variety of basic alkyl ester, thiol ester and N-basic alkyl amide acid addition and quaternary ammonium salts of the general formula II. These substances may be regarded as having been derived from the esters I, by expansion of the alcoholic ethylene group with or without branching and/or



replacement of the diethylamino residue by other dialkylamino radicals, by incorporation of the diethylaminoethyl chain into a nitrogenous ring system, by replacement of the alcoholic carboxyl oxygen atom by sulfur or nitrogen.

The parent basic alkyl esters of the acid addition and quaternary ammonium salts II were obtained by (1) condensation of  $\alpha$ -(2-cycloalken-1-yl)-2-thienylacetic acids (III) with tertiary amino alkyl

(1) Nepera Chemical Co., Yonkers, New York.

(2) F. Leonard, *THIS JOURNAL*, **74**, 2915 (1952).

(3) "Neotropine Hydrochloride Warner," U. S. Patent 2,561,385, July 24, 1951.

halides in the presence of anhydrous potassium carbonate, (2) reaction of  $\alpha$ -(2-cycloalken-1-yl)-2-thienylacetyl chlorides (IV) with basic alcohols, or (3) amination of  $\omega$ -bromoalkyl  $\alpha$ -(2-cycloalken-1-yl)-2-thienylacetates (V). The  $\omega$ -bromoalkyl esters (V) were prepared either by interaction of the acids (III) with alkylene dibromides in the presence of potassium carbonate or by treatment of the acid chlorides (IV) with alkylenebromohydrins. Interaction of 2-diethylaminoethylmercaptan with the acid chlorides IV gave thiol esters. Two N-diethylaminoethyl amides were obtained when the substituted acetyl chlorides (IV) were treated with N,N-diethylethylenediamine.

These reactions are illustrated in the flow chart. Crude hydrochlorides were converted to the free bases for purification. With very few exceptions the bases were fractionated *in vacuo* prior to conversion to acid addition and quaternary ammonium salts. In a number of instances particularly "clean" bases were isolated. These were, therefore, converted without distillation to the desired final products.

Quaternization of the free bases of the ester hydrochlorides I was attempted with several different types of halides. Methyl iodide, benzyl bromide, ethyl bromoacetate and *n*-butyl  $\gamma$ -bromocrotonate reacted rapidly when refluxed in acetone or benzene with I base. Addition of ethyl iodide to I base [R = 1-(2-C<sub>5</sub>H<sub>7</sub>)] was only about 30% complete after 72 hours of reflux in benzene solution, but addition of ethyl bromide to I base [R = 1-(2-C<sub>6</sub>H<sub>9</sub>)] was practically quantitative when the reagents dissolved in acetone were heated in a pressure bottle at 100° for 24 hours. *p*-Xylene dibromide quaternized rapidly with two molecules of the basic