Summary

1. In the presence of boron fluoride and organic acids, aliphatic ethers react to form esters. High temperatures are necessary for the ether cleavage.

2. In no instance did the yield of ester exceed 55%. This point is discussed.

3. An alkylation mixture containing approximately one-third mole of boron fluoride per mole of ether was found to be most satisfactory.

4. Phenol reacts with ether in the presence of boron fluoride to form a mixture of ethylphenols and phenyl ethers. Phenetole was the only constituent isolated.

5. Diphenyl ether did not react with organic acids in the presence of boron fluoride as did the aliphatic ethers.

NOTRE DAME, INDIANA

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Studies of Conjugated Systems. XIII. The Preparation and Properties of 1-Phenyl-4-bromobutadiene

BY IRVING E. MUSKAT AND LOREN B. GRIMSLEY

While studying the preparation of conjugated amines it was found desirable to prepare 1-phenyl-4-bromobutadiene. Muskat and Huggins[1] had previously prepared the corresponding 1-phenyl-4-chlorobutadiene by treating the 3,4-dichloride of phenylbutadiene with aqueous potassium hydroxide, and we therefore attempted to use a similar method for the preparation of the bromo derivative. However, this reaction is much more complicated than it first appeared. On treating the 3,4-dibromide of phenylbutadiene with aqueous alkali there is formed some phenylbutadiene, tetrabromide of phenylbutadiene, styrylacetaldehyde, and an oily residue from which we were not able to isolate pure 1-phenyl-4-bromobutadiene. The monobromide, in contrast with the corresponding monochloride, could not be distilled without considerable decomposition, even under reduced pressure.

This peculiar reaction was investigated further and it was found that on treating the 3,4-dibromide of phenylbutadiene with almost any aqueous alkaline reagent, varying amounts of phenylbutadiene and tetrabromide of phenylbutadiene in corresponding molecular quantities are formed in addition to other products. If pyridine in non-aqueous solvents or a suspension of silver oxide in benzene is used, then both bromine atoms are removed to give phenylbutadiene. The expected elimination of hydrogen bromide to give 1-phenyl-4-bromobutadiene was not observed.

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[1] Muskat and Huggins, THIS JOURNAL, **51**, 2496 (1929).

There is no apparent equilibrium between phenylbutadiene dibromide on the one hand and phenylbutadiene and the tetrabromide of phenylbutadiene on the other; for when phenylbutadiene and the tetrabromide of phenylbutadiene were treated with aqueous alkali under conditions similar to those that result in the formation of phenylbutadiene and the tetrabromide of phenylbutadiene from the 3,4-dibromide of phenylbutadiene, it was not possible to isolate any dibromide of phenylbutadiene.

The rate of bromination of phenylbutadiene was then studied and it was found that the first two atoms of bromine were absorbed almost instantly and exclusively in the 3,4-positions to give the 3,4-dibromide of phenylbutadiene, without the formation of even a trace of the tetrabromide of phenylbutadiene. After the first mole of bromine has been absorbed the rate of bromination decreases markedly and the second mole of bromine is absorbed slowly.

From the above study of the rate of bromination of phenylbutadiene it would seem that the 3,4-double bond is far more reactive toward bromination than is the 1,2-double bond; still, in the presence of aqueous alkali it appears that the 1,2-double bond of one molecule of the 3,4-dibromide of phenylbutadiene absorbs the bromine from the 3,4-double bond of a second molecule of dibromide to give one molecule of phenylbutadiene and one molecule of tetrabromide of phenylbutadiene.[2] The corresponding chlorine derivatives show similar reactions but to a much less extent.

While studying the reaction of the 3,4-dibromide of phenylbutadiene with aniline in non-aqueous solvents, it was found that one or both of the bromine atoms could be replaced by the group $—NHC_6H_5$ but the elimination of hydrogen bromide to give 1-phenyl-4-bromobutadiene was not observed. If two molecules of aniline in benzene solution are added to one mole of the 3,4-dibromide of phenylbutadiene dissolved in benzene, reaction occurs quite readily with the formation of the monoanilide, which probably has the structure $C_6H_5—CH=CH—CH(NHC_6H_5)—CH_2Br$, and the elimination of aniline hydrobromide. If four moles of aniline are similarly added to one mole of the 3,4-dibromide of phenylbutadiene, the 3,4-dianilide of phenylbutadiene is formed.

The corresponding 3,4-diamine of phenylbutadiene resulted from the reaction of 3,4-dibromide of phenylbutadiene with a saturated solution of ammonia in 50% ethyl alcohol.

The 1-phenyl-4-bromobutadiene was finally prepared in almost quantitative yields by treating the 3,4-dibromide of phenylbutadiene with exactly one equivalent of alcoholic potash. The monobromide exists in two forms, probably *cis* and *trans* geometric isomers. One isomer is an

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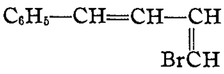
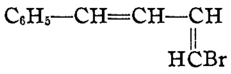
[2] This statement is made, not as an explanation of the mechanism of this reaction, but simply as a statement of fact.

oil, while the other is a solid melting at 52°.[3] The solid isomer changes into the liquid isomer upon standing at room temperature.

The addition of hydrogen bromide to each of the geometric isomers of 1-phenyl-4-bromobutadiene was studied. It was found that each isomer absorbed one mole of hydrogen bromide in the 3,4-positions to give the same 3,4-dibromide of phenylbutadiene, with a melting point of 92°. This would indicate that the geometric isomerism of the 1-phenyl-4-bromobutadiene is due to the 3,4-double bond rather than to the 1,2-double bond.



$$C_6H_5{-}CH{=}CH{-}\underset{\underset{BrCH}{\|}}{CH}$$



$$C_6H_5{-}CH{=}CH{-}\underset{\underset{HCBr}{\|}}{CH}$$

However, this is not conclusive, for the two geometric isomers of phenylbutadiene in which the isomerism is due to the 1,2-double bond, give but one 3,4-dibromide of phenylbutadiene. The rate of bromination of the two geometric isomers of phenylbutadiene is quite different, the *cis* isomer absorbing bromine more readily than does the *trans* isomer;[4] still the same 3,4-dibromide is formed. Evidently the rearrangement occurs during bromination.

Due to the orientation of the hydrogen bromide in its addition to the 1-phenyl-4-bromobutadiene, it became of interest to determine the possible electropositive character of the bromine atom in the monobromide. The electropositive character of the bromine atom in the monobromide was indicated by the fact that it quite readily oxidized potassium iodide.

The addition of bromine to 1-phenyl-4-bromobutadiene was then studied. It was found that addition occurred in the 3,4-positions to give 1-phenyl-3,4,4′-tribromo-Δ^1-butene. The position of the double bond was determined by ozonization.

From the experimental evidence presented, as well as from theoretical considerations, it appears that the electronic structure for 1-phenyl-4-bromobutadiene is best represented[5] as $C_6H_5{-}\underset{\oplus}{\overset{1}{CH}}{=}\underset{\ominus}{\overset{2}{CH}}{-}\underset{\oplus}{\overset{3}{CH}}{=}\underset{\ominus}{\overset{4}{C}}HBr$. Consequently, according to the theory developed by Muskat and his collaborators, the first step in the absorption of hydrogen bromide would be the addition of the positive hydrogen atom to the negative carbon atom (4) to give the intermediate $C_6H_5{-}CH{=}CH{-}\underset{\oplus}{CH}{-}CH_2Br$. This intermediate is identical with the intermediate which was postulated for the bromination

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[3] This may be a transition point rather than a true melting point since the melt does not resolidify, even when cooled to −10°.

[4] The *cis* phenylbutadiene is more rapidly hydrogenated and more rapidly oxidized than is the *trans* isomer. See Muskat and Knapp, *Ber.*, **64**, 779 (1931).

[5] The plus and minus signs do not imply a complete transfer of an electron from one atom to another. They indicate merely a displacement of the electrons from their central positions. We propose to use the encircled plus and minus signs to differentiate them from ionic charges.

of phenylbutadiene[6] and should therefore give the same product, namely, 1-phenyl-3,4-dibromo-Δ^1-butene. This is in accord with the actual experimental results presented in this paper. The 3,4-addition of bromine to 1-phenyl-4-bromobutadiene may be explained in a similar manner.

Experimental Part

Rate of Bromination of the Geometric Isomers of Phenylbutadiene.—*Cis* and *trans* phenylbutadiene were prepared according to the method of Muskat and Herrman[7] and the freshly distilled products were used in the bromination experiments. The rate of bromination of each of the geometric isomers was determined in chloroform solution at 0 and 25°. The phenylbutadiene was dissolved in chloroform and two moles of bromine also dissolved in chloroform were added. The reaction mixtures were maintained at the proper temperature by keeping the reaction vessels immersed in a constant temperature bath. Aliquot samples were removed at definite time intervals and titrated with standard sodium thiosulfate for unreacted bromine. The experimental data thus obtained for each of the geometric isomers are shown in Fig. 1.

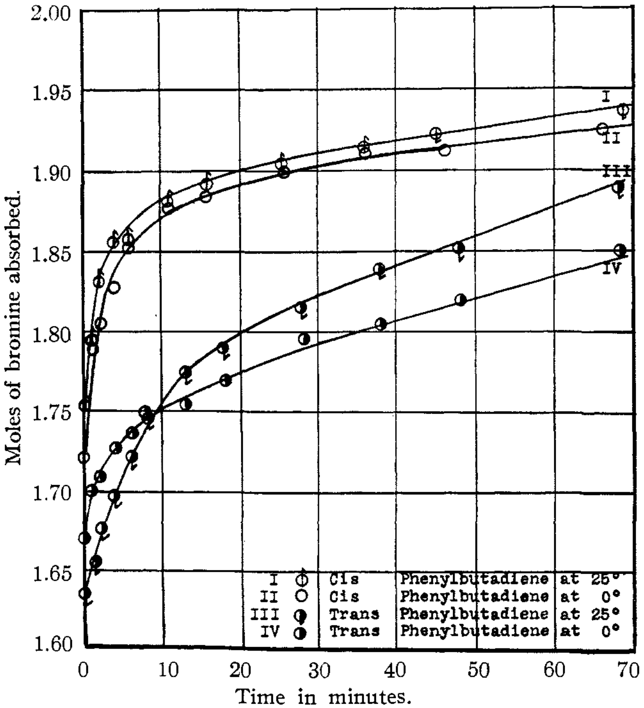

Fig. 1.

The 3,4-dibromide of each of the geometric isomers of phenylbutadiene was prepared. Since the geometric isomerism of phenylbutadiene must be due to the 1,2-

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[6] See Muskat and Northrup, THIS JOURNAL, **52**, 4049 (1930). In this paper the electronic explanation for the chlorination of phenylbutadiene is developed. The bromination of phenylbutadiene is similarly explained.

[7] Muskat and Herrman, *ibid.*, **53**, 252 (1931).

double bond we expected to find two geometric isomers of the 3,4-dibromide of phenylbutadiene. However, only one product was obtained even though the bromination was carried out at about −80°. The identity of the two dibromides was determined by the melting point of mixtures and by the rate of bromination to the tetrabromides.

Reactions of the 3,4-Dibromide of Phenylbutadiene.—In order to determine under what conditions the 3,4-dibromide of phenylbutadiene yielded phenylbutadiene and the tetrabromide of phenylbutadiene, a considerable number of experiments with different aqueous alkaline reagents and under varying conditions as to temperature and time of reaction were performed. We shall list the results of only a few of these reactions.

Reagent	Temp., °C.	Time, min.	Bromide ion formed	Phenylbutadiene and tetrabromide of phenylbutadiene indicated
None	100	30	No	No
5% NaOH	0	60	No	No
5% NH_4OH	0	60	No	No
8% Pyridine	0	60	Yes	No
5% NaOH	100	25	Yes	Yes
10% NH_4OH	100	25	Yes	No
10% Pyridine	100	25	Yes	Yes

The tetrabromide of phenylbutadiene is much less soluble in low boiling ligroin (30–60°) than is the 3,4-dibromide of phenylbutadiene. Advantage was taken of this fact in detecting small amounts of the tetrabromide of phenylbutadiene in the presence of larger amounts of the 3,4-dibromide of phenylbutadiene, and conversely in detecting small amounts of the 3,4-dibromide of phenylbutadiene in the presence of larger amounts of the tetrabromide of phenylbutadiene. In this manner, 0.2 g. of tetrabromide was readily isolated and identified in the presence of much larger amounts of 3,4-dibromide of phenylbutadiene, and, conversely, 0.2 g. of 3,4-dibromide of phenylbutadiene was readily isolated and identified in the presence of much larger amounts of the tetrabromide of phenylbutadiene.

The 3,4-dibromide of phenylbutadiene was treated with a large excess of dry pyridine in benzene solution. The solution was heated on the water-bath for about twenty-four hours. The excess pyridine was neutralized with cold dilute hydrochloric acid and the resulting mixture was extracted with ether. The ether extract was washed free of acid and of halide ion and dried over anhydrous sodium sulfate. The ether was removed by means of suction and the residue was distilled under reduced pressure. A small amount of a light yellow oil distilled at 90° under 14 mm. pressure. This distillate was identified as phenylbutadiene by the melting point of its tetrabromide and the melting point of a mixture with a known sample of the tetrabromide of phenylbutadiene.

The 3,4-dibromide of phenylbutadiene, in benzene solution, was treated with silver oxide, and the suspension heated gently for about forty-eight hours. The reaction product was extracted with low boiling ligroin. Some crystals, which proved to be the unreacted dibromide rather than the tetrabromide of phenylbutadiene, were isolated. Distillation of the residue left by the removal of the solvent gave a small amount of a light yellow liquid, which distilled at 85° under 10 mm. pressure. This distillate was identified as phenylbutadiene by the melting point of its tetrabromide and by the melting point of a mixture with known tetrabromide of phenylbutadiene.

1-Phenyl-3-anilido-4-bromo-Δ^1-butene.—The 3,4-dibromide of phenylbutadiene, in benzene solution, was treated with exactly two moles of aniline also in benzene solution, and the reaction mixture was allowed to stand at room temperature until there was no further precipitation of aniline hydrobromide. The reaction mixture was diluted with ether and washed with water to remove the bromide ion. The solution was dried over anhydrous sodium sulfate and the ether was removed by means of suction. A yellowish-orange crystalline mass remained which was soluble in benzene, chloroform, alcohol, and acetone. It melted at 110°.

Anal. Calcd. for $C_{16}H_{16}NBr$: Br, 26.49. Found: Br, 26.36, 26.36.

Although no effort was made to determine the position of the $—NHC_6H_5$ group, it is thought most likely to have the structure $C_6H_5—CH{=}CH—CH(NHC_6H_5)—CH_2Br$.

The 1-phenyl-3-anilido-4-bromo-Δ^1-butene was dissolved in dry benzene and dry hydrogen bromide was passed into it. The hydrogen bromide salt was precipitated. The crystals were filtered off by means of suction, washed with anhydrous ether to remove the excess hydrogen bromide and, dried in a vacuum desiccator over anhydrous calcium chloride. These crystals were slightly yellow in color and hydrolyzed slowly when exposed to the air. The crystals melted at 124°.

Anal. Calcd. for $C_{16}H_{17}NBr_2$: Br, 41.78. Found: Br, 41.83, 41.75.

The compound is therefore the hydrobromide salt of the 1-phenyl-3-anilido-4-bromo-Δ^1-butene.

The 1-phenyl-3-anilido-4-bromo-Δ^1-butene was dissolved in chloroform and an excess of bromine was added. The crystals formed were filtered from the mother liquor, and washed several times with chloroform, leaving the crystals pure white. The crystals melted at 215°.

Anal. Calcd. for $C_{16}H_{14}NBr_7$: Br, 71.79. Found: Br, 71.70, 71.61.

The compound is therefore the hydrobromide salt of the 1-phenyl-1,2,4-tribromo-3-tribromoanilido-butane.

1-Phenyl-3,4-dianilido-Δ^1-butene.—The 3,4-dibromide of phenylbutadiene was dissolved in benzene, four moles of aniline added, and the reaction mixture allowed to stand at room temperature until there was no further precipitation of aniline hydrobromide. The crystals of aniline hydrobromide were filtered off, the filtrate diluted with ether, washed free of bromide ion, and then dried over anhydrous sodium sulfate. Dry hydrogen chloride was then passed into the solution. The dihydrochloride salt of the dianilide was precipitated. The crystals were filtered off by means of suction, washed with anhydrous ether to remove the excess hydrogen chloride, and then dried in a vacuum desiccator over anhydrous calcium chloride. The crystals were slightly yellow in color and hydrolyzed slowly when exposed to the air. The crystals melted at 113°.

Anal. Calcd. for $C_{22}H_{24}N_2Cl_2$: Cl, 18.34. Found: Cl, 18.50, 18.45.

The compound is therefore the dihydrochloride salt of 1-phenyl-3,4-dianilido-Δ^1-butene.

1-Phenyl-3,4-diamino-Δ^1-butene.—The 3,4-dibromide of phenylbutadiene was dissolved in alcohol, the alcoholic solution treated with concentrated ammonium hydroxide and then gaseous ammonia passed into the reaction mixture to saturation. The reaction mixture was allowed to stand for six days at room temperature. It was then diluted with a large amount of water, extracted with ether, the ether extract washed free of ammonia and of bromide ion, and then dried over anhydrous sodium sulfate. Dry hydrogen chloride was passed into the solution. A white crystalline precipitate resulted. The crystals were filtered off by means of suction, washed with anhydrous ether to remove the excess hydrogen chloride, and then dried in a vacuum desiccator over anhydrous calcium chloride. The crystals were soluble in water, alcohol, acetone, and slightly soluble in ether. They melted at 124° and hydrolyzed only very slowly when exposed to the air.

Anal. Calcd. for $C_{10}H_{16}N_2Cl_2$: Cl, 30.18. Found: Cl, 30.22, 30.07.

The compound is therefore the dihydrochloride salt of 1-phenyl-3,4-diamino-Δ^1-butene.

1-Phenyl-4-bromobutadiene.—The 3,4-dibromide of phenylbutadiene was dissolved in ether and exactly one mole of alcoholic potassium hydroxide added. Sufficient alcohol was then added to prevent the separation of the reaction mixture into two layers, and it was then allowed to stand at room temperature until the mixture was neutral to litmus. Care should be taken to press the precipitated potassium bromide against the sides of the reaction vessel until quite granular so that it does not occlude any potassium hydroxide. The reaction mixture was then diluted with a large volume of water, extracted with ether, the ethereal extract washed several times with water, and then dried over anhydrous calcium chloride. The ether was removed by means of suction, without heating. There was left a residue of pure white, needle-like crystals, which even upon standing at room temperature slowly changed over to a light yellow, somewhat viscous oil. The crystals melted at 52° but did not recrystallize, even when cooled to $-10°$. The crystals were analyzed for bromine.

Anal. Calcd. for $C_{10}H_9Br$: Br, 38.23. Found: Br, 38.23, 38.15.

The oil was likewise analyzed for bromine.

Anal. Calcd. for $C_{10}H_9Br$: Br, 38.23. Found: Br, 37.90, 38.10.

Both compounds evidently have the structure 1-phenyl-4-bromobutadiene.[8]

An attempt to distil this oil resulted mainly in decomposition although a small amount of a light yellow oil distilled at 137° under 6 mm. pressure. Analysis of this distillate for bromine showed it to be 1-phenyl-4-bromobutadiene. The residue left in the distilling flask was washed thoroughly with ether. A fine, light yellow powder remained.

Anal. Calcd. for $C_{10}H_9Br$: Br, 38.23. Found: Br, 38.37.

Molecular weight determinations indicate that the compound is a dimer of 1-phenyl-4-bromobutadiene. The compound melted at 138°.

Reactions of 1-Phenyl-4-bromobutadiene.—The liquid isomer of the 1-phenyl-4-bromobutadiene was dissolved in dry ether and dry hydrogen bromide was passed into the solution for about an hour. The ether was removed by means of suction and the crude crystals remaining were extracted with warm, low boiling ligroin. The crystals obtained from the ligroin extract melted at 92°, as did a mixture with a sample of known 3,4-dibromide of phenylbutadiene. The solid isomer of 1-phenyl-4-bromobutadiene also gave the same 3,4-dibromide of phenylbutadiene after being treated with hydrogen bromide in a similar manner.

A dilute potassium iodide solution was added to an aqueous suspension of 1-phenyl-4-bromobutadiene. Iodine was immediately liberated, showing that the potassium iodide was oxidized by the 1-phenyl-4-bromobutadiene. In order to obtain a rough estimate of the extent of the oxidation, the following experiment was conducted. Three grams of 1-phenyl-4-bromobutadiene, dissolved in a little ether, was added to an aqueous solution of potassium iodide and the mixture warmed on the water-bath to expel the ether. The reaction mixture was cooled and two or three drops of glacial acetic acid was added. The solution was then titrated with standard sodium thiosulfate for iodine. Assuming that the oxidation was due to the positive bromine atom in 1-phenyl-4-bromobutadiene, approximately 3% oxidation occurred in thirty hours. Of course, air was excluded during the entire reaction.

The 1-phenyl-4-bromobutadiene was dissolved in carbon tetrachloride and one mole of bromine also dissolved in carbon tetrachloride was added. The carbon tetrachloride was removed by means of suction. The viscous liquid which remained crystallized upon standing. The crude crystals were washed with small portions of low boiling ligroin. The compound, which was slightly gray in color, melted at 140–140.5°.

Anal. Calcd. for $C_{10}H_9Br_3$: Br, 65.04. Found: Br, 64.74, 64.70.

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[8] The proof of the position of the bromine atom is given in paper XIV of this series.

The compound is therefore the dibromide of 1-phenyl-4-bromobutadiene.

These crystals were dissolved in chloroform and a current of ozonized oxygen passed through the solution for about twenty-four hours. The chloroform was removed by means of suction and the residual ozonide decomposed with water. It was possible to isolate benzoic acid from the ozonization products. The benzoic acid was identified by its melting point and by the melting point of a mixture with known benzoic acid. The compound is therefore 1-phenyl-3,4,4′-tribromo-Δ^1-butene.

Summary

1. The two geometric isomers of 1-phenyl-4-bromobutadiene were isolated.
2. Hydrogen bromide is absorbed by each of the geometric isomers of 1-phenyl-4-bromobutadiene in the 3,4-positions to give the same 3,4-dibromide of phenylbutadiene.
3. 1-Phenyl-4-bromobutadiene absorbs a mole of bromine in the 3,4-positions to give 1-phenyl-3,4,4′-tribromo-Δ^1-butene.
4. The reactions of the 3,4-dibromide of phenylbutadiene with various alkaline reagents were studied and a number of new derivatives isolated.

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Aminoguanidine Derivatives

BY VERA A. CONARD AND R. L. SHRINER

The most important types of compounds which have been studied in order to find pure substances possessing an action similar to that of insulin have been derivatives of guanidine. An excellent review of proposed insulin substitutes has been given by Braun.[1] Most of these compounds contain a guanidine and an amino group or two guanidine nuclei. The possibility that the guanidine grouping may be connected with the hypoglycemic action of insulin is suggested by the fact that arginine is one of the amino acids produced by the hydrolysis of insulin.[2] Since aminoguanidine appears to be less toxic than guanidine it was thought that certain of its derivatives might prove of value.

Accordingly aminoguanidine hydrochloride, prepared by the reduction of nitroguanidine, was condensed with *p*-dimethylaminobenzaldehyde in the presence of sodium carbonate. Both the mono and di condensation products were formed.

The two compounds were separated by fractional crystallization and their hydrochlorides prepared. The monohydrochlorides were used for the pharmacological tests since their aqueous solutions were nearly neutral and hence less irritating than the acidic solutions of the dihydrochlorides.

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(1) C. E. Braun, *J. Chem. Ed.*, **8**, 2175 (1931).

(2) H. Jensen, O. Wintersteiner and V. du Vigneaud, *J. Pharmacol. and Exptl. Ther.*, **32**, 387 (1928).