

appears the best method of converting them into acids, since hydrolysis is effected with difficulty.

The ester and acetamide were distilled slowly at 200–210° for three hours to discover whether an interchange of groups would take place. Twenty-eight per cent. of the ester was converted into *m*-dichlorobenzene and the rest was recovered. The temperature used (200–210°) was below that at which the acid first loses carbon dioxide (235°).

Phenyl Tollyl Ketones from Toluene and Benzoic Acid.—Groggins⁶ has shown that chlorobenzophenone can be prepared by condensing chlorobenzene with benzoic acid by means of aluminum chloride. We have applied the reaction to toluene. A mixture of 0.20 mole of benzoic acid, 0.40 mole of aluminum chloride and 0.44 mole of toluene was refluxed for six hours. About two-thirds of the 60% yield of ketones was a mixture which contained *p*-tolyl phenyl ketone and a smaller amount of the ortho isomer. When benzene was used with benzoic acid about 90% of the acid was recovered.

Summary

1. Eleven examples are given of the preparation with excellent yields of nitriles by the reaction

(6) Groggins, Nagel and Stearton, *Ind. Eng. Chem.*, **26**, 1317 (1934).

between amides and aluminum chloride or the compound NaCl·AlCl₃. The process can be used on a semi-micro scale as an aid in the identification of amides.

2. It has been shown that a reversible reaction takes place between an acid and an amide as the result of which the NH₂ and OH groups exchange places.

3. 2,6-Dichlorobenzoic acid loses its carboxyl group quantitatively when heated with acetamide at a temperature at which it is relatively stable when heated alone. The ester of the acid is quantitatively converted into the acid and ethyl chloride when it is heated at 110° with aluminum chloride.

4. The following are described: the reaction between benzoyl chloride and ammonium chloride, the use of the compound NaCl·AlCl₃ in the Friedel and Crafts reaction and the condensation of benzoic acid with toluene by means of aluminum chloride.

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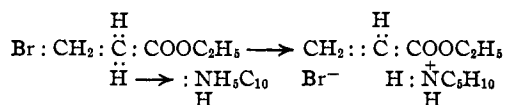
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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of Organic Halides with Piperidine. V. Negatively Substituted Ethyl Bromides

BY E. LEON FOREMAN AND S. M. McELVAIN

In the preceding paper¹ of this series it was shown that esters with a β -bromo substituent are very much more reactive toward piperidine than are other types of bromo-esters. Also it was shown that the reaction involves, first, the elimination of hydrogen bromide from the β -bromo-ester, and then the addition of piperidine to the resulting acrylic ester. The mechanism by which the acrylic ester is formed was thought to be the removal of a proton from the α -carbon atom of the bromo-ester by the nucleophilic reagent, piperidine, followed by the release of the bromide ion from the molecule,² thus



(1) Drake and McElvain, *THIS JOURNAL*, **56**, 697 (1934).

(2) A similar idea as to the mechanism of this type of elimination reaction has been expressed in a footnote of a paper by Noller and Dinsmore, *ibid.*, **54**, 1025 (1932), and also by Hauser and co-workers, *ibid.*, **57**, 1056 (1935); **59**, 1823 (1937).

On the basis of such a mechanism it is obvious that the reactivity of β -substituted ethyl bromides, YCH₂CH₂Br, should parallel the electro-negativity of the group Y.

The present paper reports the preparation and reactivity of a number of such negatively substituted ethyl bromides with piperidine. In the cases that Y is carbethoxy, cyano or benzoyl the rate of reaction of the bromide with piperidine is so rapid (*e. g.*, ethyl β -bromopropionate reacts to the extent of 94% in fifteen minutes at room temperature) that it cannot be measured readily. For this reason negatively substituted phenylethyl bromides, YC₆H₄CH₂CH₂Br, were used. These vinylogs of the more simply substituted ethyl bromides are, in most cases, more easily prepared and generally show a lower and more readily determined reaction rate.

Experimental

Preparation of β -Substituted Ethyl Bromides.—Ethyl β -bromopropionate was prepared from ethylene cyano-

hydrin.³ β -Bromopropionitrile⁴ was prepared by the reaction of ethylene cyanohydrin with phosphorus tribromide in benzene solution. The yield of product, boiling at 68–69° (7 mm.), d^{25} , 1.6234, n^{25}_D 1.4789, was 43% of the theoretical. β -Bromopropiophenone. This compound had been prepared several years ago in this Laboratory by Frederick Beyerstedt and William Rinelli according to the following procedure. In a 2-liter round-bottom, 3-neck flask, fitted with a reflux condenser, an efficient stirrer and a dropping funnel were placed 500 ml. of carbon bisulfide, 100 g. of thiophene-free benzene and 260 g. of anhydrous aluminum chloride. The flask was set in an ice-salt mixture, stirring started, and 171 g. of β -bromopropionyl chloride⁵ added through the dropping funnel at such a rate that the carbon bisulfide refluxed gently. After the addition of the halide, the ice-bath was removed and stirring continued until no more halogen acid was evolved. The reaction mixture then was poured carefully onto a mixture of ice and hydrochloric acid and, after thorough stirring, the carbon bisulfide layer separated. This layer was washed well with water and the solvent removed by distillation from a steam-bath. The remaining residue on cooling solidified. The yield of crude product amounted to 200 g. (93%). After recrystallization from petroleum ether the product melted at 58–59°.

Anal. Calcd. for C_9H_9OBr : Br, 37.5. Found: Br, 37.7.

Preparation of Substituted β -Phenylethyl Bromides. β -Phenylethyl Bromide.—This compound was prepared from Eastman Kodak Co. β -phenylethyl alcohol by the procedure of Norris.⁶ The product boiled at 86° (8 mm.); n^{25}_D 1.5545.

o- and *p*-Nitrophenylethyl Bromide.—A mixture of 204 g. of acetic anhydride and 120 g. of acetic acid was chilled to 0° in a 1-liter 3-necked flask equipped with a stirrer, thermometer and dropping funnel. There was added slowly 126 g. of fuming nitric acid, after which the mixture was chilled to –5°. One hundred and eighty-five grams of phenylethyl bromide was added slowly (three hours) through the dropping funnel, while the temperature was maintained below 0°. Stirring was continued for two and one-half hours after the addition was complete. The reaction mixture was then poured into a suspension of 265 g. of sodium carbonate in 2 liters of ice water. The yellow product was taken up in benzene and thoroughly washed with water and then with a saturated sodium bicarbonate solution. The benzene was removed as completely as possible on the steam-bath, the final portion under reduced pressure. The remaining product was recrystallized from 3 liters of petroleum ether (b. p. 60–68°). A yield of 124 g. (54% of the theoretical) of the *p*-nitro compound, m. p. 69–70°,⁷ was obtained.

The solvent was removed from the mother liquors and the residue fractionally distilled under reduced pressure. Seventy grams (30.4% of the theoretical) of the *o*-nitro compound boiling at 115–120° (0.5 mm.) with some decomposition was obtained. After recrystallizing from

petroleum ether, the product melted at 36–38°. This product on oxidation with potassium permanganate yielded *o*-nitrobenzoic acid. An additional 18 g. of the *p*-nitro compound may be recovered from the still residues, if desired. These two compounds were previously prepared by Sobotka,⁷ who, however, did not obtain the ortho isomer in pure form.

Anal. Calcd. for $C_8H_9NO_2Br$: Br, 34.7. Found: Br, (ortho) 34.3, (para) 34.5.

***p*-Acetylphenylethyl Bromide.**—In a 1-liter 3-necked flask equipped with an efficient stirrer, dropping funnel, and reflux condenser were placed 83 g. of anhydrous aluminum chloride, 300 ml. of carbon disulfide, and 47 ml. of acetyl chloride. The flask was set in an ice-bath and a solution of 124 g. of phenylethyl bromide in 95 ml. of acetyl chloride added as rapidly as possible. Stirring was continued until no more hydrogen chloride was evolved (two to two and one-half hours), after which the reaction product was decomposed with a mixture of concentrated hydrochloric acid and crushed ice. The carbon disulfide layer was removed and the aqueous layer extracted twice with benzene. The combined benzene and carbon disulfide layers were washed with dilute hydrochloric acid, water, 10% sodium hydroxide solution, and again with water. The solvent was removed and the product fractionally distilled under reduced pressure. A recovery of 22.5 g. of phenylethyl bromide was effected, so that the 101.5 g. of product boiling at 117–118° (0.1 mm.) amounted to 83% of the theoretical based on the phenylethyl bromide actually used; n^{25}_D 1.5724; d^{25} , 1.3784; *M*_D calcd. 53.26, found 52.91. Permanganate oxidation converts this product to terephthalic acid.

Anal. Calcd. for $C_{10}H_{11}OBr$: Br, 35.2. Found: Br, 35.2.

***p*-Carboxyphenylethyl Bromide and *p*-Carboxyphenylethyl Bromide.**—An alkaline hypobromite solution prepared in a 1-liter 3-necked flask from 48 g. of the bromine and 33 g. of sodium hydroxide dissolved in 280 ml. of water and 200 ml. of dioxane, was chilled to 0° and 23 g. of *p*-acetylphenylethyl bromide added with stirring. Stirring was continued until the hypobromite was exhausted (2 hours), the temperature being maintained below 0°. The solution was acidified with an excess of hydrochloric acid and the precipitated acid filtered from the aqueous solution and bromoform, washed with water and dried. The yield of *p*-carboxyphenylethyl bromide was 20 g. (87%). After crystallization from a mixture of petroleum ether and benzene, the acid melted at 205–207°.

Anal. Calcd. for $C_8H_7O_2Br$: Br, 34.9. Found: Br, 35.0.

The acid was converted to the ester in 79% yield by first converting it to the acid chloride with a slight excess of thionyl chloride, then refluxing the crude chloride with ethanol. The ester boils at 111–114° (0.1 mm.); d^{25} , 1.2918; n^{25}_D 1.5404; *M*_D calcd., 59.19; obsd. 62.84.

Anal. Calcd. for $C_{11}H_{13}O_2Br$: Br, 31.1. Found: Br, 30.5.

***p*-Cyanophenylethyl Bromide.**—*p*-Carboxyphenylethyl bromide (64 g.) was converted to the corresponding acyl chloride by refluxing with a slight excess of thionyl chloride. This crude chloride was poured into cold concentrated ammonia water. The precipitated amide was

(3) "Organic Syntheses," Coll. Vol. I, 1932, p. 241.

(4) Moureu and Brown, *Bull. soc. chim.*, [4] 27, 901 (1920).

(5) Hamilton and Simpson, *This Journal*, 51, 3158 (1929).

(6) Norris, Walt and Thomas, *ibid.*, 38, 1071 (1916).

(7) Sobotka, *Ber.*, 62, 2191 (1929).

TABLE I
RATE AND COURSE OF THE REACTION OF PIPERIDINE WITH NEGATIVELY SUBSTITUTED β -PHENYLETHYL BROMIDES, $YC_6H_4CH_2CH_2Br$, AT 60°

Y is	Reaction time, hr.	A % Reaction	B Moles $\times 10^2$ piperidine HBr	C Moles $\times 10^2$ unreacted piperidine	D % Tertiary amine calcd.	E % Olefin calcd.
1 <i>o</i> -NO ₂	0.25	78	0.78	1.01	21	57
	2.0	98	.98	0.62	40	58
2 <i>p</i> -NO ₂	0.25	83	.83	.90	27	56
	2.0	98	.98	.55	47	51
3 <i>p</i> -CN	0.25	58	.58	1.11	31	27
	2.0	91	.91	0.62	47	44
4 <i>p</i> -CH ₃ CO	0.25	40	.40	1.26	34	6
	2.0	80	.80	0.58	62	18
5 <i>p</i> -CO ₂ C ₂ H ₅	0.25	26	.26	1.52	22	4
	2.0	67	.67	0.81	52	15
6 H	0.25	16	.16	1.62	24	..
	2.0	55	.55	0.86	59	..
	48 ^a	95	.95	.05	100	..

^a The values for this time are taken from a table in ref. 9 and were determined at 90° .

filtered off, dried, and converted to the nitrile by refluxing with a mixture of 100 ml. of benzene and 100 ml. of thionyl chloride according to the procedure of Michaelis and Siebert.⁸ When the reaction was complete, the excess thionyl chloride and solvent was removed on the steam-bath, the remaining product taken up in benzene and the insoluble residue discarded. The benzene solution was washed with water and saturated sodium bicarbonate solution, after which the solvent was removed by distillation. The yield of *p*-cyanophenylethyl bromide amounted to 35.5 g. (60% of theoretical) after recrystallization from petroleum ether and melted at $49-50^\circ$.

Anal. Calcd. for C₉H₈NBr: Br, 38.1. Found: Br, 38.5.

Reaction of Negatively Substituted Ethyl Bromides with Piperidine.—Ethyl β -bromopropionate, β -bromopropionitrile and β -bromopropiophenone each react too rapidly with piperidine to allow for rate determinations. The least reactive of these compounds, ethyl β -bromopropionate, was found to react practically completely with piperidine in fifteen minutes at room temperature. Determinations of the course of these reactions by the procedure described below in each case showed that the rate at which piperidine added to the resulting unsaturated compound to form the tertiary amine was practically as rapid as that at which the unsaturated compound was formed from the bromide. As may be seen from the table such is not the case with the negatively substituted phenylethyl bromides.

Reaction of Substituted Phenylethyl Bromides with Piperidine.—Due to the insolubility of these compounds in petroleum ether, the procedure used to follow the course and extent of the reaction was modified slightly from that previously reported.¹

To 10 ml. of *M* solution of the bromide in benzene, contained in a test-tube prepared for sealing, was added two equivalents of piperidine by means of a calibrated pipet. The tubes were then sealed and immersed in the thermostat for the desired length of time, after which they were cooled and opened. The precipitated piperidine hydrobromide was washed onto a filter with petroleum ether and

the washings made up to 50 ml. with petroleum ether. Unreacted piperidine was determined by treating an aliquot of this solution with phenyl isocyanate and collecting the piperidinoformanilide as described previously,⁹ except that no corrections were applied.

After drying, the piperidine hydrobromide was dissolved in water and made up to 100 ml. An aliquot of this solution was titrated for bromide ion with standard silver nitrate solution.

It is believed that the results in column B of Table I are accurate to about 1%, while those in column C are probably less than 5% in error.

Discussion of Results

It may be seen from columns A and B of Table I that the reactivity of the substituted phenylethyl bromides increases with the negativity of the substituent in the benzene nucleus. Such a result would be expected from a reaction mechanism of the type postulated in the introductory portion of the paper. Inspection of columns D and E in the above table shows that the percentage of tertiary amine in the amine-olefin mixture of reaction products increases with a decrease in the negativity of the substituent groups. This fact indicates that the mechanism involving the elimination of hydrogen bromide is replaced, to an increasing extent, by one that operates directly at the carbon atom holding the bromine.¹⁰ This

(9) Semb and McElvain, *THIS JOURNAL*, **53**, 690 (1931).

(10) Another alternative, which would require the rate of addition of piperidine to the olefin to increase with a lowering of the negativity of the substituent, was readily eliminated by the failure of piperidine to add to styrene under the conditions of the reaction. Also the high yields of tertiary amine (the formation of which certainly involves the addition of piperidine to the olefin (*cf. ref. 1*)) in the cases of negatively substituted ethyl bromides, which were discussed in the experimental part of the paper, show that the strongly negative group promotes rather than hinders the addition of piperidine to an adjacent carbon to carbon double bond.

(8) Michaelis and Siebert, *Ann.*, **274**, 312 (1893).

other mechanism may involve the approach of the reagent to the carbon holding the bromine, the ionization of the bromine, or some other mode of reaction. Similar transitions from one mechanism to another have been noted in other series of variously substituted bromides.¹¹

A strong indication that the elimination reaction under discussion first involves a removal of a proton from the carbon in the β -position to the bromine is the striking difference in the reactivities of the negatively substituted phenylethyl bromides of the present paper and similarly substituted benzyl bromides. With the latter type of bromide it has been found that an increase in the negativity of the substituent group causes a *decrease* in the reactivity of the benzyl bromide with such bases as pyridine and aniline^{11a} as well as with aqueous alcohol.¹² This behavior has been taken to indicate that the bromine is removed from the molecule of the benzyl bromide as a negative ion because such an ionization would be hindered by the presence of a substituent in the benzene ring which, by both an inductive and an electro-meric effect, is strongly electron attracting.

(11) (a) Baker, *J. Chem. Soc.*, 1128 (1933); (b) Gleave, Hughes and Ingold, *ibid.*, 238 (1935).

(12) Shoesmith and Slater, *ibid.*, 214 (1926); Olivier, *Rec. trav. chim.*, **42**, 775 (1923).

The fact that such a negative group has just the opposite effect on the reactivity of a phenylethyl bromide with piperidine suggests that the opposite type of ion, *vis.*, a positive proton, is removed from the carbon adjacent to the benzene nucleus by the reagent. There seems to be no reason to believe that the electrophilic character of such a substituent group would not exert some of the same hindering effect on the reactivity of a bromine in the β -position to the ring as it does on the bromine of a benzyl bromide. If this be true, then a carbon-hydrogen bond adjacent to the aromatic nucleus is the only apparent point at which a negative substituent in the nucleus can activate a phenylethyl bromide for reaction with a base such as piperidine.

Summary

The rate and course of the reaction of some negatively substituted ethyl bromides with piperidine have been determined. Evidence is presented to show that the removal of a proton from the carbon atom in the α -position to the negative substituent (and in the β -position to the bromine) is the initial step in the elimination of hydrogen bromide from such a negatively substituted bromide.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of Organic Halides with Piperidine. VI. Some Branched Chain β -Bromo-esters

BY E. LEON FOREMAN AND S. M. McELVAIN

If the high reactivity of the β -bromo-esters with piperidine, reported in the fourth paper¹ of this series, is due, as suggested, to the presence of a hydrogen on the α -carbon atom of the ester, a study of the behavior of branched chain β -bromo-esters, particularly those having no α -hydrogen, should be of some interest. The present paper reports the behavior of two such esters, ethyl bromopivalate and ethyl α,α -dimethyl β -bromobutyrate (1 and 2 in the table below) in this reaction. Since such esters are halides of the neopentyl type, which are known to be very unreactive,² it seemed necessary to study also ethyl β -bromo-isocaproate and ethyl γ,γ -dimethyl- β -bromovalerate (3 and 4). These esters

(1) (a) Drake and McElvain, *THIS JOURNAL*, **56**, 697 (1934); (b) Paper V is Foreman and McElvain, *ibid.*, **62**, 1435 (1940).

(2) Whitmore, Wittle and Popkin, *ibid.*, **61**, 1586 (1939).

contain the unreactive isobutyl bromide³ and neopentyl bromide structure, respectively, and also have hydrogens on the α -carbon atom and a bromine on the β -carbon atom to the carbethoxy group.

In the first paper³ of this series cyclohexyl bromide, of all that were studied, was found to be the most inert toward piperidine. In order to ascertain the effect of a carbethoxy group in the β -position to the bromine atom on the reactivity of this bromide, ethyl 2-bromocyclohexanoate (no. 6) was included in the present study.

Experimental

Preparation of the Bromo-esters

Ethyl bromopivalate is best prepared by esterification of bromopivalic acid.⁴ The treatment of ethyl hydroxypiva-

(3) Cf. Semb and McElvain, *ibid.*, **53**, 690 (1931).

(4) Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 158 (1904).