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 electromeric effect, is strongly electron attracting. 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, *viz.*, 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.

(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).

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.

MADISON, WISCONSIN RECEIVED JANUARY 26, 1940

[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 paper[1] 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 contain the unreactive isobutyl bromide[3] 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 paper[3] 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-

(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).

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

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

late[6] with phosphorus tribromide according to the procedure of Lease and McElvain[6] gives only a poor yield of the desired ester. The ethyl bromopivalate used boiled at 62–63°[4] (7 mm.); d^{25}_4 1.2713; $n^{25}D$ 1.4469; M_D calcd., 43.91; found, 44.21.

Ethyl α,α-Dimethyl-β-bromobutyrate.—After chilling each in an ice-bath, a solution of 54 g. of phosphorus tribromide in 100 ml. of benzene was added to a solution of 80 g. of ethyl α,α-dimethyl-β-hydroxybutyrate[7] in 100 ml. of benzene. The mixture was allowed to stand in an ice-bath and gradually to come to room temperature as the ice melted. After standing for six days at room temperature, the benzene solution was poured into 500 ml. of ice water and the benzene layer separated, washed with water, then with a saturated solution of sodium bicarbonate and finally with water. On fractionation 28 g. (25% of the theoretical) of the bromo-ester, boiling at 90–92° (20 mm.) was obtained. In addition to this product 36 g. of the phosphite ester of the starting hydroxy ester remained as an undistilled residue. From this residue additional α,α-dimethyl-β-bromobutyric acid could be recovered by slow distillation with 48% hydrobromic acid.

The bromo-ester as prepared above was found to contain some of an isomeric ester, presumably ethyl α,β-dimethyl-α-bromobutyrate, a rearrangement product analogous to that obtained by Whitmore and Johnston[8] by the replacement of the hydroxyl group of methylisopropylcarbinol by halogen. This isomeric bromo-ester was removed readily from the desired product by reaction with piperidine. A solution of 20 g. of the crude bromo-ester and 25 ml. of piperidine in 50 ml. of benzene was refluxed for two hours. After this time the benzene solution was fractionated, whereupon 4 g. of a product boiling at 145–150° and 12 g. of a product boiling at 70–74° (8 mm.) were obtained. The lower boiling fraction was unsaturated and corresponded in properties to trimethylacrylic ester.[9] On refractionation the desired ethyl α,α-dimethyl-β-bromobutyrate boiled at 72–74° (8 mm.); d^{25}_4 1.2430; $n^{25}D$ 1.4531; M_D calcd., 48.51; found, 48.58.

Anal. Calcd. for $C_8H_{15}O_2Br$: Br, 35.8. Found: Br, 35.4.

Ethyl β-Bromoisocaproate.—In a 3-liter round-bottomed flask were placed 960 g. (6 moles) of diethyl malonate, 50 g. of piperidine acetate and 432 g. (6 moles) of isobutyraldehyde. After stirring until homogeneous, the mixture was allowed to stand for forty-two hours at room temperature. Then 600 ml. of benzene was added and the aqueous layer separated. The benzene layer was washed with four 200-ml. portions of water and then fractionally distilled.

The yield of isobutylidene malonic ester[10] boiling at 117–119° (13 mm.) amounted to 629 g. (48% of the theoretical). To a hot solution of 450 g. of potassium hydroxide in 450 ml. of water was added slowly with stirring 428 g. (2 moles) of isobutylidenemalonic ester. After standing for two hours on the steam-bath without a reflux condenser, the hydrolysis mixture was chilled in an ice-bath and a cold solution of 450 g. of concentrated sulfuric acid in 450 ml. of water added. The precipitated potassium sulfate was filtered off and washed thoroughly with isopropyl ether. The aqueous solution was extracted with four 250-ml. portions of isopropyl ether and the combined ethereal extracts washed once with a little saturated sodium sulfate solution and then dried over anhydrous sodium sulfate. After removal of the ether, the malonic acid was decarboxylated by heating at 150° in an oil-bath and under a pressure of 20 mm. The monocarboxylic acid which distilled over was then fractionally distilled under reduced pressure. A yield of 46 g. (20.2%) of isocaprolactone[11] boiling at 96–98° (18 mm.), $n^{25}D$ 1.4312, and 48 g. (21%) of isobutylideneacetic acid[11] boiling at 114–115° (18 mm.), $n^{25}D$ 1.4466, neutral equivalent 114, was obtained. A portion of the acid on oxidation with cold 2% potassium permanganate yielded isobutyric acid, which was identified through its *p*-bromophenacyl ester. The isobutylideneacetic acid (42 g.) was esterified by refluxing it for two hours with 100 ml. of absolute ethanol using 2 ml. of concentrated sulfuric acid as a catalyst. The yield of ethyl isobutylideneacetate,[12] boiling at 171–173°, $n^{25}D$ 1.4301, amounted to 44 g. (84% of the theoretical).

Dry hydrogen bromide was passed into a cold solution of 14.2 g. (0.1 mole) of ethyl isobutylideneacetate in 100 ml. of chloroform until twice the amount theoretically required for addition to the unsaturated ester had been absorbed. The flask was then tightly stoppered, allowed to stand in the ice-bath and gradually to come to room temperature after the ice had melted. After six hours, the reaction mixture was poured into cold water and the chloroform layer separated, washed with water, then sodium bicarbonate solution, and finally with water. After drying over calcium chloride, the chloroform was removed at room temperature under reduced pressure and the product distilled at 0.1 mm. pressure so as to minimize the possibility of thermal rearrangement. The yield of ethyl β-bromoisocaproate amounted to 19.3 g. (86.5%); b. p. 63–64° (0.1 mm.); d^{25}_4 1.2464; $n^{25}D$ 1.4557; M_D calcd., 48.51; found, 48.89.

Anal. Calcd. for $C_8H_{15}O_2Br$: Br, 35.8. Found: Br, 35.3.

An attempted preparation of this ester from the corresponding hydroxy ester and phosphorus tribromide yielded a product which appeared to be a mixture of the β- and γ-bromo-isocaproic esters, judging from the incompleteness of the reaction of this product with piperidine. In order to make the comparison, ethyl γ-bromo-isocaproate was prepared from isocaprolactone by the procedure of Bredt.[13] This bromo-ester distilled with some decomposition at 57–58° (0.1 mm.) and was found to contain 34.6% instead of the required 35.8% bromine. Previous workers[13,14] have reported it as undistillable. When this γ-bromo-ester was allowed to react with piperidine under the conditions used for the other bromo-esters listed in Table I it showed only 31% reaction in four hours.

Ethyl γ,γ-Dimethyl-β-bromovalerate.—Trimethylacetaldehyde[15] was condensed with diethyl malonate in 50%

(5) Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 110 (1904).
(6) Lease and McElvain, THIS JOURNAL, **55**, 806 (1933).
(7) Adkins, Connor and Cramer, *ibid.*, **52**, 5192 (1930).
(8) Whitmore and Johnston, *ibid.*, **60**, 2265 (1938).
(9) Von Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **82**, 167 (1910).
(10) Shryver, *J. Chem. Soc.*, **63**, 1344 (1893).
(11) Braun, *Monatsh.*, **17**, 207 (1896).
(12) Howles, Thorpe and Udall, *J. Chem. Soc.*, **77**, 942 (1900).
(13) Bredt, *Ber.*, **19**, 513 (1886).
(14) Jones and Tattersall, *J. Chem. Soc.*, **85**, 1691 (1904).
(15) The authors are indebted to Mr. E. W. Reeve of this Laboratory for the trimethylacetaldehyde used in this preparation. The catalytic dehydrogenation process used in its preparation will be described in a forthcoming publication.

TABLE I

RATE AND COURSE OF THE REACTION OF PIPERIDINE WITH CERTAIN β-BROMO-ESTERS AT 90°

	Bromo-ester (Y = $COOC_2H_5$)	Reaction time, hr.	A % Reaction	B Moles × 10^2 piperidine HBr	C Moles × 10^2 unreacted piperidine	D % t-amine calcd.	E % Olefin calcd.
1.	$BrCH_2C(CH_3)_2Y$	48	4	0.04	1.84	12[a]	..
		96	7	.07	1.71	20[a]	..
2.	$CH_3CHBrC(CH_3)_2Y$	96	9	.09	1.79	11	..
3.	$(CH_3)_2CHCHBrCH_2Y$	0.25	93[b]	.93	0.99	8	85
		4	94	.94	.97	9	85
4.	$(CH_3)_3CCHBrCH_2Y$	0.25	97[b]	.97	.94	9	88
		4.0	96	.96	.91	13	83
5.	$BrCH_2CH_2Y$	0.25	97[b]	.97	.18	84	13
6.	1,2-$C_6H_{10}BrY$	.25	74	.74	1.21	4	70
		4	90	.90	1.09	2	88

[a] For some reason, as yet undetermined, the values of unreacted piperidine in column C, from which the yields of tertiary amine in column D were calculated, were consistently low. The most obvious explanation of such a result, *viz.*, amide formation, could not be substantiated.

[b] These values carry no rate significance. As pointed out in the fifth paper of this series (ref. 1b) an ethyl bromide with a carbethoxy, cyano or benzoyl group as a β-substituent is much too reactive toward piperidine to allow for rate determinations at or above room temperature. The values are included in the above table to show that the reaction is complete insofar as the elimination of bromine from the ester molecule is concerned.

yield, using the process of Cope and Hancock,[16] except that the refluxing time was reduced from sixty to thirty-six hours. Trimethylethylidenemalonic ester boils at 138–140° (23 mm.); $n^{25}D$ 1.4449; d^{25}_4 0.9347; M_D calcd., 60.46; found, 65.24; exaltation, 4.78.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.12; H, 8.83. Found: C, 63.13; H, 8.86.

The malonic ester was saponified and the acid decarboxylated in 89% yield, using the procedure described above for the preparation of isobutylideneacetic acid. The 4,4-dimethyl-2-pentenoic acid boils at 126–131° (23 mm.), and melts at 62–63° after recrystallization from petroleum ether. The yield of recrystallized acid, neutral equivalent 127, amounted to 73% of the theoretical. A portion of the acid on oxidation with cold 2% potassium permanganate yielded trimethylacetic acid, which was identified by its *p*-bromophenacyl ester.

A solution of 25.6 g. (0.2 mole) of the dimethylpentenoic acid in 100 ml. of absolute ethanol was chilled in an ice-salt-bath and saturated with dry hydrogen bromide. After standing at room temperature for twelve hours, the reaction mixture was poured onto crushed ice, extracted with benzene, and worked up as described above for ethyl β-bromo-isocaproate. The yield amounted to 35.5 g. (75% of theoretical) of product boiling at 65–66° (0.1 mm.); d^{25}_4 1.2149; $n^{25}D$ 1.4588; M_D calcd., 53.29; found, 53.17.

Anal. Calcd. for $C_9H_{17}O_2Br$: Br, 33.8. Found: Br, 32.9.

Ethyl 2-bromocyclohexanoate was prepared in 50% yield from ethyl hexahydrosalicylate[17] by the procedure used above for ethyl α,α-dimethyl-β-bromobutyrate. It boils at 75–76° (0.1 mm.); d^{25}_4 1.3272; $n^{25}D$ 1.4909; M_D calcd., 51.17; found, 53.66.

Anal. Calcd. for $C_9H_{15}O_2Br$: Br, 34.0. Found: Br, 33.8.

(16) Cope and Hancock, THIS JOURNAL, **60**, 2901 (1938).

(17) Connor and Adkins, *ibid.*, **54**, 4678 (1932).

Reaction of Bromo-esters with Piperidine.—A ratio of two moles of piperidine to one of the bromo-esters was used. The general procedure for the determination of the extent and course of this reaction was the same as that described in the fifth paper of this series.[1b] The results of these determinations are summarized in Table I. It is believed that the values in column A can be duplicated within 1%, and that the maximum error for the values in column C is 5%.

Discussion of Results

It is apparent that those β-bromo-esters (1 and 2) that have no hydrogen on the α-carbon atom are very unreactive toward piperidine. It also should be noted that these particular bromo-esters show practically the same amount of reaction after ninety-six hours, even though one is a primary and the other a secondary bromide. With the simple alkyl halides there is a considerable difference in the reactivity of these two types.[3] In this connection mention should be made of Bouveault's observation[18] that ethyl α,α-dimethyl-β-chlorobutyrate is not attacked by alcoholic potassium hydroxide.

The high reactivities of the bromo-esters 3 and 4 show that the neopentyl bromide type of structure is not responsible for the low reactivity of esters 1 and 2. There is practically no difference in the rate at which esters 3 and 4 and ethyl β-bromopropionate[5] lose their bromine when allowed to react with piperidine. This fact definitely shows the powerful effect of the presence of an α-hydrogen, as well as the negligible effect of substitution

(18) Bouveault, *Bull. soc. chim.*, [3] **21**, 1064 (1899).

of such generally deactivating groups as isopropyl or *t*-butyl for a β-hydrogen atom of ethyl β-bromopropionate, on the reactivity of the halogen of β-bromoesters. It should be noted, however, that while the presence of these alkyl groups does not materially affect the rate at which these esters give up their bromine, such substitution does greatly affect the rate of addition of piperidine to the olefinic ester to form a tertiary amine.

The substitution of a carbethoxy group in the β-position to the halogen of cyclohexyl bromide changes it from an extremely inert halide to one with a quite high reactivity toward piperidine However, the ethyl 2-bromocyclohexanoate is not as reactive as the other β-bromo-esters with an α-hydrogen that have been studied and the resulting olefin, ethyl cyclohexenoate, shows a surprising inability to add piperidine across its double bond.

Summary

The rate and course of the reaction between piperidine and a number of β-bromo-esters with branched chains are reported. It is shown that those β-bromo-esters that have no α-hydrogen atom are extremely inert, while those that have such a hydrogen atom are very reactive regardless of the nature of the branching of the carbon chain. Such branching, however, greatly reduces the ability of the unsaturated ester that is formed from the bromo-ester to add piperidine to form a tertiary amine.

MADISON, WISCONSIN RECEIVED JANUARY 26, 1940

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF NORTH CAROLINA]

Vicinal Substituted Resorcinols. I. Alkyl Resorcinols. The Synthesis of γ-Ethyl, γ-*n*-Propyl and γ-*n*-Butyl Resorcinols

BY ALFRED RUSSELL, JOHN R. FRYE AND WM. L. MAULDIN

The occurrence of γ-isoamylresorcinol as a fission product of natural rotenone, the possible value as antiseptics of γ-alkyl resorcinols and the potential usefulness as initial materials in various types of syntheses of γ-substituted resorcinols make it of considerable interest to exploit possible routes to such compounds.

It is comparatively easy to obtain good yields of β-substituted derivatives of resorcinol; thus by treatment of resorcinol by a modification of the Gattermann process[1] it is possible to obtain upward of 90% of the theoretical amount of β-resorcylaldehyde; by carboxylation of resorcinol[2] some 60% of the theoretical amount of β-resorcylic acid may be obtained; again treatment of resorcinol with aliphatic acids and anhydrous zinc chloride gives good yields of alkyl β-resorcyl ketones, a process that involves ester formation followed by a Fries rearrangement; moreover, the ketones so obtained reduce readily by the Clemmensen method to the corresponding β-alkylresorcinols and this process is actually used in the manufacturing of hexylresorcinol.[3] There has also recently been described[4] the synthesis of some *n*-5-(or α)-alkyl resorcinols through the intermediate ketones obtained by the action of appropriate Grignard reagents on 3,5-dimethoxybenzamide.

However, the preparation of vicinal (or γ) substituted resorcinols has been attended with such difficulty that very few such compounds have been made and the yields have been poor. The tedious synthesis of 2,6-dihydroxyacetophenone[5] or vicinal resacetophenone starting with *m*-dinitrobenzene gives a yield amounting at the best to only a few per cent. of the theoretical. The synthesis of γ-resorcylaldehyde which has been described recently gives only a small yield of aldehyde.[6]

The synthesis of 4-methyl-7-hydroxy-8-acetylcoumarin (III, R = CH_3) is on record[7] and from this compound by fission with alkali 2,6-dihydroxyacetophenone[8] is obtained in better than 90% yield. It is obvious that a Clemmensen reduction of 2,6-dihydroxyacetophenone would give γ-ethylresorcinol and such a reduction of 2,6-dihydroxyisovalerophenone recently has been described[9] yielding γ-isoamylresorcinol.

(1) Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).
(2) "Organic Syntheses," Volume X, John Wiley and Sons, Inc., New York, N. Y., 1930, p. 94.
(3) U. S. Patents 1,649,667 and 1,197,168.
(4) Suter and Weston, THIS JOURNAL, **61**, 234 (1939).
(5) Mauthner, *J. prakt. Chem.*, **139**, 290 (1934).
(6) Shah and Laiwalla, *J. Chem. Soc.*, 1828 (1938).
(7) Limaye, *Ber.*, **65**, 375 (1932).
(8) Baker, *J. Chem. Soc.*, 1954 (1934).
(9) Robertson and Subramanian, *ibid.*, 278 (1937).