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

The Reaction of Organic Halides with Piperidine. III. Cyclohexyl Bromide and the Butyl Bromides

BY W. V. DRAKE AND S. M. MCELVAIN

In the first paper[1] of this series cyclohexyl bromide was found to differ very markedly from other secondary bromides both in the rate and the course of its reaction with piperidine. It was suggested then that the greater reactivity of the open chain secondary bromides might be due to their rearrangement to the more reactive primary structure, a transformation which cyclohexyl bromide cannot undergo without rupture of a carbon to carbon linkage. The validity of this hypothesis has now been tested by an investigation of the tertiary amines produced in the reaction of piperidine with cyclohexyl bromide and each of the four butyl bromides. This work has led to the isolation of four different N-butyl-piperidines, a result which definitely shows that the above explanation for the relative inertness of cyclohexyl bromide has no experimental justification.

Experimental

Materials Used.—The piperidine and petroleum ether were prepared as previously described.[1] Isobutyl bromide was prepared according to Noller[2] and cyclohexyl bromide by the procedure of Kamm and Marvel.[3] *n*-Butyl, *sec*-butyl and *tert*-butyl bromides were prepared by the Norris procedure.[4] The tertiary butyl alcohol which was used melted at 22–25°.[5]

General Procedure

The procedure which has been described[1] for carrying out the reaction of piperidine with various alkyl bromides was used with the following modifications: (a) the larger quantities of reactants used in the work now reported required Pyrex bomb tubes instead of test-tubes for the reaction; (b) the temperature of the reaction was raised to 150–155° in order that a greater amount of reaction might take place within a given time; (c) after removal of the piperidine hydrobromide, the unreacted piperidine was precipitated as piperidine thiocarbamate[6] with carbon bisulfide;[7] (d) when all of the

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

(2) Noller, *ibid.*, **53**, 635 (1931).

(3) "Organic Syntheses," Vol. I, 1921, p. 1.

(4) Norris, *Am. Chem. J.*, **38**, 639 (1907).

(5) In some earlier experiments tertiary butyl alcohol melting at 10–16° was used to prepare the bromide. This bromide, however, gave a tertiary amine hydrochloride which after recrystallization gave analyses corresponding to a N-propylpiperidine hydrochloride. By comparison with an authentic specimen, this hydrochloride was found to be N-isopropylpiperidine hydrochloride, m. p. 272–273°; Cl, calcd.: 21.67; found, 21.64. This compound undoubtedly resulted from small amounts of isopropyl alcohol in the tertiary butyl alcohol. The tertiary amine hydrochloride prepared from tertiary butyl alcohol, m. p. 22–25°, not only gave correct analyses, but when mixed with N-isopropylpiperidine hydrochloride melted at 260–264°.

(6) Ladenburg and Roth, *Ber.*, **17**, 514 (1884).

(7) This procedure was found to give just as satisfactory results as the one using phenyl isocyanate as a precipitant for the unreacted piperidine.[1] The handling of the carbon bisulfide precipitate was the same as that used for piperidinoformanilide. Several precipitations of known quantities of piperidine from a petroleum ether solution by carbon bisulfide showed that 95% of the piperidine could be recovered.

piperidine had been removed from the petroleum ether solution the tertiary amine was precipitated as the hydrochloride with dry hydrogen chloride. These hydrochlorides then were recrystallized from an alcohol-ether mixture.

Table I summarizes the pertinent data which were obtained. Column A shows the amount of piperidine used with each bromide. A relatively large amount of reactants was necessary in the case of tertiary butyl bromide in order that sufficient tertiary amine could be obtained. The ratio of one mole of the bromide to two moles of piperidine was used in each reaction. Column C shows the moles of piperidine hydrobromide which precipitated from the reaction; therefore the percentages in parentheses indicate the extent of each reaction. Column D shows the amounts of piperidine precipitated by carbon bisulfide as piperidine thiocarbamate and the percentage values in parentheses are based on one-half of the piperidine used. Column E gives the yields in moles and percentage of the tertiary amines. Column F shows the amounts in moles and the percentage of the total piperidine used which was accounted for as piperidine hydrobromide, piperidine thiocarbamate and N-alkylpiperidine hydrochloride.

TABLE I

REACTION OF PIPERIDINE WITH VARIOUS ALKYL BROMIDES AT 150-155°

Alkyl group	A Moles × 10 piperidine used	B Reaction time, hr.	C Moles × 10 piperidine hydrobromide (%)	D Moles × 10 unreacted piperidine (%)^a	E Moles × 10 tertiary amine hydrochloride (%)	F Total piperidine recovered C + D + E (%)
n-Butyl	0.4	48	0.20 (100)	0.00	0.179 (89)	0.379 (95)
Sec-butyl	0.4	48	0.195 (98)	.027 (13)	.154 (77)	0.376 (94)
Isobutyl	0.4	48	0.193 (98)	.00	.180 (90)	0.373 (93)
Tert-butyl	2.4	48	1.11 (92)	.838 (70)^b	.036 (3)	1.982 (83)
Cyclohexyl	0.8	120	0.386 (97)	.267 (67)	.111 (28)	0.764 (95)

[a] Determined as piperidine thiocarbamate by precipitation with carbon bisulfide. [b] This value is probably low because of the pressure developed in the reaction tube and consequent loss of piperidine when the tube was opened and this pressure released.

The properties and analyses of the tertiary amine hydrochlorides (Column E, Table I) are summarized in Table II.

TABLE II

N-ALKYLPIPERIDINE HYDROCHLORIDES^a

			Analyses, %					
			Calcd.			Found		
Alkyl group	Formula	M. p., °C.	C	H	Cl	C	H	Cl
n-Butyl	$C_9H_{20}NCl$	239-240	60.81	11.35	19.96	60.80	11.22	19.98
Sec-butyl	$C_9H_{20}NCl$	208-209	60.81	11.35	19.96	61.01	11.25	20.02
Isobutyl	$C_9H_{20}NCl$	257-258^b	60.81	11.35	19.96	60.75	11.40	19.93
Tert-butyl	$C_9H_{20}NCl$	268-269^b	60.81	11.35	19.96	60.75	11.26	20.14
Cyclohexyl	$C_{11}H_{22}NCl$	292-293^b	64.33	10.90	17.49	64.40	10.93	17.44

[a] These compounds were obtained by recrystallization of the hydrochlorides of Column E, Table I, from an alcohol-ether mixture. The recovery of the recrystallized products varied from 65-85%. It is believed that these recrystallization losses were largely manipulative. [b] These compounds melt with decomposition.

The free tertiary amines were isolated from the above hydrochlorides in the cases of *n*-butyl, *sec*-butyl and isobutyl piperidine. The amounts of N-tertiary-butylpiperidine hydrochloride obtained from the reaction of tertiary butyl bromide were so small that the isolation of the free base was not attempted.[8] The properties and analyses of these tertiary amines are given in Table III.

Table III

N-Butylpiperidines

N substituent	B. p., °C. (740 mm.)	d^{25}_{25}	n^{25}_{D}	N analyses, % Calcd.	Found
n-Butyl[a]	171–172	0.8210	1.4442	..	..
Sec-butyl	169–170	.8334	1.4468	9.92	9.73
Isobutyl[b]	160–161	.8161	1.4382	9.92	9.87

[a] This compound has been reported by Gibson and Macbeth [*J. Chem. Soc.*, 119, 438 (1921)] as boiling at 170–172°. [b] Hjortdahl, *Jahresb.*, 1085 (1882), reports the chloroplatinate of this amine.

Discussion of the Results

It is seen from Tables I and II that four different N-butylpiperidines are formed from the reaction of piperidine with the four butyl bromides. This fact seems to be definite proof that these bromides react to form tertiary amines without previous rearrangement. A comparison of the data for secondary butyl bromide and cyclohexyl bromide given in Table I shows that the difference in behavior of these secondary bromides is one of degree rather than kind. When the reaction of secondary butyl bromide with piperidine is forced practically to completion, a yield of tertiary amine lower than those from the primary butyl bromides is obtained and the amount (13%) of unreacted piperidine (Column D) shows that some loss of hydrogen bromide to form the unsaturated hydrocarbon has taken place. This latter reaction is confirmed by the fact that the petroleum ether solution, after removal of the unreacted piperidine, rapidly decolorizes a bromine solution. Cyclohexyl bromide also shows these two types of reaction, only in this case the relative amounts of tertiary amine formation and loss of hydrogen bromide are the reverse of those obtained from secondary butyl bromide. On the basis of these data the results reported in the first paper[1] of this series do not appear anomalous. It should be noted that the tertiary amines are formed directly from the reaction of the bromide with piperidine rather than through the addition of the latter compound to the unsaturated hydrocarbon, since it was found that the substitution of cyclohexene for cyclohexyl bromide gave no isolable quantity of tertiary amine under the same conditions of reaction that produced a 28% yield of the tertiary amine from the bromide.

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(8) Velghe [*Bull. Sci. Acad. Roy. Belg.*, [5] 11, 301 (1925); *Chem. Abstracts*, **20**, 1053 (1926)] reports N-tertiary-butylpiperidine, b. p., 166°, from the reaction of α-piperidinoisobutyronitrile with methylmagnesium bromide.

Noller and Dinsmore,[9] in a recent study of the reaction of alkyl bromides with pyridine, have shown that the loss of hydrogen bromide and the formation of alkyl pyridinium bromides are distinct, but simultaneously occurring reactions. It is quite probable also that in the reaction of alkyl halides with secondary amines the relative rates of two independent reactions, the loss of halogen acid and tertiary amine formation, determine the course of the reaction, since the data for the reaction of alkyl bromides with piperidine in Table I appear, in general, to be quite similar to those reported by Noller and Dinsmore.

Summary

The isolation of four different N-butylpiperidine hydrochlorides from the reaction of piperidine with the butyl bromides has demonstrated that these bromides, in this reaction, do not rearrange previous to reaction. The difference between the behavior of cyclohexyl bromide and other secondary bromides has been found to be one of degree rather than kind.

[9] Noller and Dinsmore, THIS JOURNAL, 54, 1025 (1932).

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Diarsyls. V. Reactions of Tetraphenyldiarsyl

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Tetraphenyldiarsyl reacts with sulfur to form tetraphenylarsyl sulfide; with sulfur chloride, diphenylchloroarsine and sulfur were obtained; with thionyl chloride the reaction products were diphenylchloroarsine, sulfur dioxide and sulfur.

Bromocyanogen and the diarsyl yield diphenylbromoarsine; triphenylarsine is formed when the diarsyl reacts with phenylmagnesium bromide.

Interaction with arsenic trichloride proceeds rapidly with the formation of diphenylchloroarsine and arsenic in practically quantitative yield; when phenylarsine oxychloride was used the reaction products were diphenylchloroarsine and phenylarsine oxide.

Phosphorus trichloride and the diarsyl yield diphenylchloroarsine.

Tetraphenyldiarsyl, dissolved in benzene, was shaken with liquid sodium–potassium alloy. The colorless benzene layer soon became intensely yellow-brown in color and a very decided change was noticed in the appearance of the alloy, a change which we attribute to the formation of the potassium, or sodium derivative of diphenylarsine. Bromobenzene was added to the mixture and, after some time, evaporation of the benzene layer yielded oily triphenylarsine; the latter was isolated in the form of the methyl iodide addition product, methyltriphenylarsonium iodide, since this substance is easier to purify, in small amounts, than triphenylarsine.