

5.49 and at 5.98 μ . The addition of 3.5 ml. of 1.0 *M* triphenylphosphine in ether solution caused the evolution of 41 ml. or 1.39 mmoles more of carbon monoxide in 30 min. and the reaction stopped. The solvent was evaporated under vacuum and the product was taken up in tetrahydrofuran. Insoluble material was removed by centrifuging, and addition of pentane and cooling to -80° gave the phosphine complex as a yellow powder. Two more recrystallizations from tetrahydrofuran-pentane gave a pure sample. The compound darkened at 80° without melting. The compound in carbon tetrachloride solution had infrared bands at 3.23(w), 3.36(w), 4.86(m), 5.02(vs), 5.07(vs), 6.07(m), 6.20(w), 6.38(m), 6.45(m), 6.77(w), 7.00(w), 8.05(w), 8.95(w), 9.14(m), 9.96(m), 10.14(m), 10.61(w), and 10.88(w) μ . There were additional bands in carbon disulfide solution at 13.40(m), 13.61(m), 14.13(m), and 14.43(m) μ .

Anal. Calcd. for $C_{28}H_{20}O_3PCo$: C, 64.21; H, 4.15. Found: C, 64.12; H, 4.45.

π -Cyclopentenonylcobalt dicarbonyl triphenylphosphine was prepared by essentially the same method as that used above for the 2-methyl- π -cyclopentenonylcobalt dicarbonyl triphenylphosphine preparation. From 60 ml. of 0.07 *M* sodium cobalt carbonylate and 2.2 ml. of 2.0 *M* 2,4-pentadienyl chloride, both in ether solution, there was obtained 0.50 g. (22.5% based upon the sodium cobalt carbonylate used) of pure π -cyclopentenonylcobalt dicarbonyl triphenylphosphine, orange-brown plates, m.p. $127-131^\circ$ dec. The compound crystallizes from tetrahydrofuran-pentane solution with one molecule of tetrahydrofuran. The infrared spectrum in carbon tetrachloride solution had infrared absorption bands at 3.23(w), 3.36(w), 3.48(w), 4.95(s), 5.08(s), 5.92(m), 6.76(w), 6.98(m), 8.10(w), 8.58(w), 9.12(m), 9.31(w), 9.70(w), 9.99(w), 10.24(w), 10.66(w), and 10.91(w) μ . In carbon disulfide solution there were additional bands at 13.40(m), 14.20(w), and 14.40(m) μ .

Anal. Calcd. for $C_{28}H_{20}O_3PCo \cdot C_4H_8O$: C, 65.66; H, 5.32. Found: C, 65.83; H, 5.26.

2-Methyl- π -cyclopentadienonecobalt Dicarbonyl Triphenylphosphine Tetrafluoroborate.—A solution of 1.7 g. of triphenylmethyl tetrafluoroborate⁷ in 10 ml. of methylene chloride at 0° was added to a solution of 2.4 g. of 2-methyl- π -cyclopentenonylcobalt dicarbonyl triphenylphosphine in 5 ml. of methylene chloride, also at 0° , under nitrogen. The solution immediately became a darker red. After 2 hr. at 0° , the solution was concentrated under vacuum to about 10 ml., and 5 ml. of ether was added. The crystals which separated were recrystallized twice more from methylene chloride-ether to give a good yield of a yellow-brown powder m.p. $170-175^\circ$ dec. The infrared spectrum in Nujol had carbonyl bands at 4.71(m), 4.78(s), and 5.98(m) μ . In methylene chloride solution there were bands at 3.27(w), 3.35(w), 4.72(m), 4.81(m), 5.92(w), 6.05(w), 6.75(w), 6.98(m), 7.38(w), 9.11(m), 9.35(m), and 9.71(m) μ .

Anal. Calcd. for $C_{28}H_{20}PBF_4O_3Co$: C, 55.94; H, 3.79. Found: C, 56.23; H, 3.71.

π -Cyclopentenonylcobalt dicarbonyl triphenylphosphine reacted with triphenylmethyl tetrafluoroborate in exactly the same way as the 2-methyl derivative did, but the product decomposed on attempted purification.

Methyl 4,6-Heptadienoate.—In a 2-l. 3-necked flask equipped with a condenser with a drying tube attached, a stirrer, and a

dropping funnel was placed 62 g. of allyltriphenylphosphonium bromide and about 1 l. of ether which had been distilled from lithium aluminum hydride. The reaction flask was flushed with nitrogen, and 58 ml. of 2.90 *M* *n*-butyllithium in pentane was added with stirring. The solution became dark red. After 1 hr., 18.6 g. of methyl, -formylpropionate⁸ in 110 ml. of ether was added dropwise. After the addition the solution was refluxed for 2 hr. Water was added and the ether phase was separated, dried over anhydrous magnesium sulfate, and distilled. There was obtained 7.2 g. of ester, b.p. $60.5-61.5^\circ$ (8 mm.).

4,6-Heptadienoic Acid.—The ester above (7.2 g.) was stirred 48 hr. with a solution of 4.0 g. of sodium hydroxide in 20 ml. of water and 20 ml. of methanol. The solution was then diluted with water, extracted three times with methylene chloride, and acidified with cold dilute hydrochloric acid. The product was extracted with several portions of methylene chloride and dried with magnesium sulfate. Distillation gave 5.8 g. of the acid, b.p. $77-80^\circ$ (3 mm.). The infrared spectrum in carbon tetrachloride solution had bands at 3.30(s), 3.73(m), 5.53(m), 5.82-(vs), 6.03(m), 6.22(w), 6.98(m), 7.08(m), 7.50(w), 7.77(m), 8.00-(m), 8.23(m), 8.72(w), 9.92(s), 10.46(m), 11.00(s), and 11.83(w) μ .

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.30; H, 8.07. Found: C, 66.64; H, 7.99.

The acid chloride was obtained by dissolving 5.7 g. of the acid in 30 ml. of dry ether, adding 13.5 g. dicyclohexylethylamine, cooling to 0° , and adding 4.0 ml. of thionyl chloride during 30 min. After the mixture was let stand at 25° for an hour more, the salts were removed by centrifuging and the solution was distilled. There was obtained 3.75 g. of the acid chloride, b.p. $46.5-48^\circ$ (5.5 mm.). The ultraviolet spectrum taken in methanol solution (methyl ester formed), had a λ_{max} of 224 m μ with ϵ 24,000.

4,6-Heptadienylcobalt Tricarbonyl Triphenylphosphine.—In a carbon monoxide-filled, magnetically stirred reaction flask at 0° attached to a thermostated gas buret¹⁰ were placed 30 ml. of 0.07 *M* sodium cobalt carbonylate in ether and 3.0 ml. of 1.0 *M* 4,6-heptadienyl chloride in ether. The solution turned red, and in 3 hr., 41 ml. (1.38 mmoles) of carbon monoxide was evolved and the reaction stopped. To this solution at 0° was added 3.0 ml. of 1.0 *M* triphenylphosphine in ether. When the reaction was complete, 21 ml. or 0.71 mmole more of carbon monoxide had been evolved. The solution was evaporated to dryness under vacuum and the product was recrystallized three times from ether-pentane solution. There was obtained a good yield of yellow prisms which melted at $89-90^\circ$ dec.

Anal. Calcd. for $C_{28}H_{24}O_4PCo$: C, 65.38; H, 4.70. Found: C, 65.56; H, 4.97.

An ether solution of the above complex in a capped tube was heated in boiling water for about an hour. The infrared spectrum now showed carbonyl bands only at 4.85(w), 5.02(s), and 5.13(s) μ . There were no significant bands in the 5.5-6.2 μ region. Only yellow-orange oils could be isolated from the reaction mixture.

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gem-Dihalides from α -Haloamides. II. Rearrangement of *N*-Bromo- α -haloamides Utilizing Bromide-82 Tracer¹

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Two *N*-bromo- α -haloamides were allowed to react in the presence of sodium hydroxide and bromide ion to form *gem*-dihalides. Potassium bromide-82 was utilized internally and externally in separate experiments to establish (1) the degree of retention of bromine in the *gem*-dihalide product and (2) the extent to which external bromide ion was incorporated in the *gem*-dihalide. With *N*-bromo- α -chloroisobutyramide under cold, 0° , conditions, retention was $100.0 \pm 1.0\%$ and incorporation was $0.2 \pm 0.2\%$. With *N*-bromo- α -bromoisovalerylamide, under hot distillation conditions, retention was $99.4 \pm 1.0\%$ and incorporation was $0.6 \pm 0.3\%$. The *gem*-dihalides were stable under the experimental conditions and no isotopic exchange with bromide-82 was detected. The results indicate the reaction is almost exclusively intramolecular in character and offer additional support for a stereospecific four-center mechanism.

In the first paper of this series,² the limited literature relating to the conversion of the α -haloamides to *gem*-

dihalides under conditions similar to those employed in the Hofmann rearrangement reaction was reviewed.

(1) This work was supported by the National Science Foundation, Research Grant G-14630.

(2) C. L. Stevens, T. K. Mukherjee, and V. J. Traynelis, *J. Am. Chem. Soc.*, **78**, 2264 (1956). This reference is considered paper I of this series.

In brief, the initial observation is due to Kishner,³ who, in 1905, isolated a product believed to be 1,1-dibromocyclobutane from α -bromocyclobutanecarboxamide. In 1954, Husted and Kohlhas⁴ isolated *gem*-dihalides by the rearrangement of aliphatic perfluoroamides with alkaline hypobromite and indicated that the reaction proceeded through the N-bromoamide intermediate. Barr and Haszeldine dissolved heptafluorobutyramide in hot alkaline sodium hypobromite and obtained an 81% yield of heptafluoropropyl bromide and an 80% yield of cyanate ion.⁵ They also prepared the N-bromo derivative and its sodium salt and rearranged these in good yield.

Previous work in this Laboratory has shown that the rearrangement of aliphatic α -haloamides to *gem*-dihalides in the presence of alkaline hypobromite is broad in scope; and insight into the essential features of the reaction was gained by the conversion of α -chloroisobutyramide to 2-bromo-2-chloropropane in 95% yield at 0° using alkaline sodium hypobromite.² The N-bromo derivative gave the same result when placed in base containing bromide ion, but no *gem*-dihalide was formed when the N-bromoamide was placed in water containing only bromide ion. Further, the corresponding α -chloroisocyanate in base gave only ketone and no *gem*-dihalide. These results show that the N-bromo anion is an essential intermediate and the isocyanate is not an intermediate in the formation of *gem*-dihalide.²

In view of these results, two possible mechanisms were suggested which were compatible with the observations. They were (1) an intramolecular four-center reaction or (2) an intermolecular reaction involving participation by external bromide ion as shown in Fig. 1.

Barr and Haszeldine⁵ also favor a cyclic mechanism similar to that proposed above. Features of the reaction have also been discussed by Husted and Kohlhas⁴ and by Beecham.⁶

The present work was undertaken to establish the inter- and/or intramolecular nature of the reaction and the degree of stereospecificity of either mechanism. Bromide-82 ion was employed as a powerful tool to establish both the extent of the retention of the bromine and the extent of incorporation of external bromide ion into the product *gem*-dihalide. N-Bromo- α -chloroisobutyramide (I) and N-bromo- α -bromoisovalerylamide (II) were studied, the latter undergoing conversion to *gem*-dihalide only under forcing conditions. In view of the relatively severe conditions, participation by external bromide and/or an alternate mechanism leading to rearranged dihalides would not be unexpected.

N-Bromo- α -chloroisobutyramide (I) was prepared in pure form² and dissolved in two molar equivalents of aqueous sodium hydroxide at 0°, followed by the addition of two molar equivalents of 4.0 *N* sodium bromide enriched with bromide-82 ion. After 18 hr. at 0°, the *gem*-dihalide was isolated and gave a single peak by vapor chromatography. The *gem*-dihalide was counted against an aliquot of the enriched 4.0 *N* sodium bromide as standard, giving uncorrected values for the bromine-82 content of 0.13 and 0.11% in two experiments. Correcting for the ratio of bromide-82 to total available bromide of 2 to 3 and considering the probable error, the extent of incorporation of external bromide into the product *gem*-dihalide is $0.2 \pm 0.2\%$.

To confirm this result, compound I was prepared with labeled bromine-82 and the rearrangement reaction

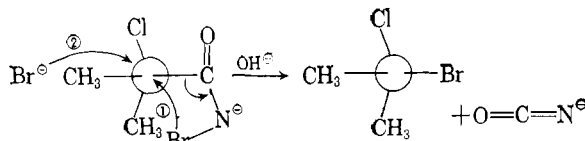


Fig. 1.—Two possible rearrangement paths.

carried out in the presence of nonradioactive sodium bromide. The isolated pure *gem*-dihalide was then counted against the labeled amide as standard. The results of two runs were 100.5 and 100.8%. Considering the probable error, the degree of retention is $100.0 \pm 1.0\%$. Exposure of the *gem*-dihalide to bromide-82 ion and sodium hydroxide under the conditions of the experiment indicated no isotopic exchange.

As an interesting sidelight, it was observed that, if compound I was added to base which had been inoculated with bromide-82, some incorporation of the bromide-82 label into the *gem*-dihalide was observed. Further, if I is mixed with bromide-82 ion for 1 min. in an aqueous solution in the absence of base, complete incorporation of the label results. Although the N-bromoamide anion is resistant to exchange in the presence of external bromide, the N-bromoamide exchanges rapidly. To establish whether the rapid exchange involves nucleophilic attack of bromide on nitrogen displacing bromide, or a frontal attack on the bromine atom attached to nitrogen by bromide ion yielding amide ion and bromine, compound I was exposed to a molar equivalent of cyanide ion at 0°. In two experiments, 22 and 42% cyanogen bromide and 74 and 55% of α -chloroamide, respectively, were isolated, indicating a frontal attack of cyanide ion on the bromine atom attached to nitrogen.

N-Bromo- α -bromoisovalerylamide (II).—The conversion of α -bromoisovalerylamide to *gem*-dihalide proved to be unusually difficult. Best results were secured by isolating the N-bromo derivative II in relatively pure form and dissolving it in 8 moles of 16.7% sodium hydroxide containing 1.05–1.10 moles of bromine. Successive small 4 to 10-ml. portions of the solution were then rapidly heated to the boiling point in a short-path distillation apparatus, co-distilled oil and water being collected in a chilled receiver. Purification of the *gem*-dihalide gave an isolated yield of 2.8% and an estimated conversion of 3.3%. Purity and identity were established by vapor chromatography and infrared measurements. The alkaline reaction liquors were analyzed for cyanate ion, 18%, and α -hydroxyisovaleric acid, 23% (see Table I). In a modified procedure, a solution of α -bromoisovalerylamide in sodium hypobromite and alkali was added in a steady stream to distilling aqueous alkali. No *gem*-dihalide was found, but cyanate ion formation in excess of 50% was observed, whereas α -hydroxy acid formation was only 3%, as shown in Table I. Further, no *gem*-dihalide or cyanate was formed at 0° or at room temperature.

TABLE I
REARRANGEMENT OF α -BROMOAMIDES. COMPARATIVE DATA

	α -Bromoamide, %		
	<i>n</i> -Bu ^a	<i>i</i> -Val ^a	<i>i</i> -Val ^b
1 Cyanate (<i>gem</i> -dihalide)	21	3	0
2 Excess cyanate ^c	14	15	48
3 α -Hydroxy acid	53	23	3
4 Unaccounted for	12	59	49

^a Standard "hot" procedure. ^b Addition of N-bromoamide solution to distilling aqueous alkali (average values). ^c Total cyanate less *gem*-dihalide.

The radiobromine studies with II utilized the same general technique as with I. To measure the extent of

(3) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **35**, 105 (1905); *Chem. Zentr.*, **56**, 1, 1219, 1220 (1905).

(4) D. R. Husted and W. L. Kohlhas, *J. Am. Chem. Soc.*, **76**, 5141 (1954).

(5) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 30 (1957).

(6) A. F. Beecham, *Chem. Ind. (London)*, 392 (1957).

incorporation of external bromide, II, 99.4% pure by active halogen assay, was dissolved in eight molar equivalents of aqueous sodium hydroxide at 0°. To this solution was added three molar equivalents of bromide ion in the form of 6.13 *N* sodium bromide inoculated with potassium bromide-82. The reaction, performed as described above, yielded *gem*-dihalide of 97.0 ± 1.0% purity. The *gem*-dihalide was then counted against an aliquot of the inoculated 6.13 *N* sodium bromide as standard, giving an uncorrected value for incorporation of 0.39%. Applying corrections for the purity of the isolated *gem*-dihalide and the mole ratio of bromide-82 to total available bromide (0.75), a corrected value of 0.54% is obtained. As bromine balance studies had shown that all the bromine present in the molecule was hydrolyzed completely to bromide ion, except that retained in the *gem*-dihalide, all or part of the liberated β -bromine anion could be available for external participation. Inclusion of this source of bromide ion gives a mole ratio factor of 0.61 instead of 0.75 and a corrected value of 0.66%. In view of this and considering other sources of error, the value for incorporation of external bromide into the product *gem*-dihalide is expressed at 0.6 ± 0.3%.

To confirm this result, labeled II was prepared by the addition of α -bromoisovalerylamide to sodium hypobromite which had been inoculated with potassium bromide-82. The product, collected after acidification with cold 25% acetic acid and thoroughly washed with water, assayed 99.8% by active halogen titration and possessed a high specific count. This product was then rearranged in the presence of unlabeled bromide ion. The isolated *gem*-dihalide, 98.7 ± 1.0% pure by vapor chromatography, was counted against labeled II as standard and gave an uncorrected retention of labeled bromine of 98.26%. The corrections in this case are only for purity of the *gem*-dihalide and labeled II; considering the probable error, the corrected value for retention is 99.4 ± 1.0%.

Exposure of the *gem*-dihalide to aqueous sodium hydroxide and bromide-82 under the conditions of the experiment indicated no isotopic exchange. Exposure of the *gem*-dihalide to alkaline attack under conditions of the experiment indicated less than 2% loss of the *gem*-dihalide, calculated as conversion to aldehyde.

The structure of the *gem*-dihalide was established unequivocally as the expected 1,1-dibromo-2-methyl propane by elemental analysis and a comparison with authentic samples of 1,2-dibromo-2-methylpropane and 2,3-dibromobutane. Physical properties of the three isomers were significantly different. Infrared spectrograms showed the expected *gem*-dimethyl doublet at 7.22 and 7.32 μ for the *gem*-dihalide and 1,2-dibromo-2-methylpropane, absent in 2,3-dibromobutane. Distinct retention times were obtained for the three isomers by vapor chromatography and synthetic mixtures were readily separated on the column; symmetrical peaks were obtained with no evidence of decomposition. Vapor chromatograms of the 1,1-dibromo-2-methyl propane from the radiobromine studies indicated no impurities other than hydrocarbon contaminants from the pentane solvent.

Discussion

The data for the rearrangement of *N*-bromo- α -chloroisobutyramide (I) at 0° (95% yield) and *N*-bromo- α -bromoisovalerylamide (II) at ca. 105–110° (3% yield) may be summarized as

<i>N</i> -Bromo- α -haloamide	External bromide-82 incorporation, %	Retention of label, %
Isobutyr-	0.2 ± 0.2	100.0 ± 1.0
Isovaleryl-	0.6 ± 0.3	99.4 ± 1.0

In addition, no isotopic exchange of bromide-82 with *gem*-dihalide was observed and the *gem*-dihalide was substantially stable to alkaline attack under conditions of the experiments.

The results prove unequivocally that the rearrangement of α -haloamides to *gem*-dihalides in the presence of alkaline hypobromite proceeds almost exclusively by an intramolecular mechanism. Participation by external bromide ion is shown to be 1% or less in both examples studied. A clear distinction between the two reaction pathways of Fig. 1 can now be settled in favor of mechanism 1. It is our conviction that the minor extent (1% or less) of external participation strongly suggests a high degree of stereospecificity with probable retention of configuration as portrayed in Fig. 1. This conviction is strengthened by parallel work in this Laboratory utilizing an optical center, the results of which are presented and discussed in terms of mechanistic implications in the subsequent paper of this series.⁷

Certain other features of the hot reaction of α -haloamides observed in this study are of interest. Data are presented in Table I.

The nonequivalence of *gem*-dihalide and cyanate ion is probably best explained by *prior* attack of base at the α -carbon, forming the α -hydroxy-*N*-bromoamide, an intermediate known to generate cyanate and aldehyde rapidly.^{2,8} Selective attack at the α -carbon atom is understandable in view of negative charge on the amide function. The marked difference in results obtained with α -bromoisovaleryl amide by the two methods studied is not well understood at present and further study is required. Similarly, the reluctance of the isovaleryl compound to form *gem*-dihalide is not clear at present, although partial blocking of the α -carbon by the β -methyl groups to attack by the large bromine atom may play a role.

Experimental

The preparation of the α -haloamides has been described elsewhere.² α -Bromoisovalerylamide was kindly supplied by Dr. Harold Scheer of Ohio State University as white fluffy crystals, m.p. 125.5–127.5°. All melting points are uncorrected.

N-Bromo- α -chloroisobutyramide (I) was prepared as described, previously² and purified by sublimation without heating at 40° (0.1 mm.), 77%, m.p. 69–71; recrystallized from chloroform-hexane, m.p. 72–73°.

Anal. Calcd. for C₄H₆BrClNO: C, 23.96; H, 3.52; Br, 39.89; N, 6.99. Found: C, 23.99; H, 3.55; Br, 40.15; N, 7.03.

Rearrangement of I in the Presence of Bromide-82 Ion.—To an ice-cooled separatory funnel, containing 5 ml. (0.02 mole) of 4 *N* sodium hydroxide, was added 2.0 g. (0.01 mole) of *N*-bromo- α -chloroisobutyramide, followed by 5 ml. (0.02 mole) of 4.0 *N* sodium bromide solution inoculated with potassium bromide-82.⁹ After the solution stood at 0° for 18 hr., the *gem*-dihalide was collected, washed with cold concentrated sulfuric acid, and transferred to a small distilling flask containing a crushed pellet of sodium hydroxide. After swirling for 30 sec., the oil was distilled under aspirator pressure into a cooled receiver, yielding pure 2-chloro-2-bromopropane, b.p. 90–91°, n_D^{20} 1.4545 (lit.¹⁰ b.p. 91.0–91.2°, n_D^{20} 1.4575). The γ -activity of the *gem*-dihalide was then counted against 100 λ of the inoculated 4.0 *N* sodium bromide as standard.

In the first of two experiments, 4.240 mmoles of *gem*-dihalide was counted against 0.400 mmole of standard bromide-82. Cor-

(7) C. L. Stevens, H. Dittmer, and J. Kovacs, *J. Am. Chem. Soc.*, **85**, 3394 (1963).

(8) C. L. Arcus and D. B. Greenwald, *J. Chem. Soc.*, 1937 (1953); also Ault, *et al.*, *ibid.*, 1722 (1934), and Haworth, *et al.*, *ibid.*, 1975 (1938).

(9) Bromide-82, a γ -emitter with half-life of 35.9 hr., is obtained as 0.5 ml. of aqueous potassium bromide with an activity of >0.5 mc. per ml. from Oak Ridge National Laboratory, Oak Ridge, Tenn., at nominal cost. The solution is conveniently diluted with ca. 10 ml. of water and 100 to 200 λ (0.1–0.2 ml.) are taken for inoculation purposes as required to give a suitable count in relation to the counting efficiency to the equipment. A nuclear Chicago Corp. Model 186 scintillation counter in combination with a NR1 Instrument Co. Model L-6 well was employed.

(10) M. S. Kharasch, H. Engelman, and F. R. Mayo, *J. Org. Chem.*, **2**, 300 (1937).

rected for background, 437 counts per minute (c.p.m.), the *gem*-dihalide measured 17 c.p.m./mmole and the standard 13,100 c.p.m./mmole; incorporation is 0.13% (uncor.). A second experiment gave 0.11%, average 0.12% (uncor.). After correction for the ratio of 2:3 for bromide-82 to total available bromide, and considering the probable error, the average incorporation is $0.2 \pm 0.2\%$.

Rearrangement of Labeled I in the Presence of Bromide Ion.—Labeled I was prepared using bromine which had been equilibrated with a small amount of bromide-82 concentrate. From 12.2 g. (0.1 mole) of α -chloroisobutyramide there was obtained 11.4 g. (57%) of labeled I, m.p. 72–73°. This was rearranged in the presence of base and unlabeled external bromide ion in the same manner as above. Vapor chromatography gave only one peak and the *gem*-dihalide was considered pure. In the first of two experiments, 6.563 mmoles of *gem*-dihalide was counted against 2.374 mmoles of labeled I as standard. Corrected for background, 465 c.p.m., the *gem*-dihalide measured 1843 c.p.m./mmole and the standard measured 1833 c.p.m./mmole; retention of label is 100.5%. In the second experiment, retention of label was 100.8%. Considering the probable error, which is inherently greater than in the incorporation studies, the result is expressed as $100.0 \pm 1.0\%$.

Equilibration between 2-Bromo-2-chloropropane and Bromide-82.—To 5.0 ml. (0.020 mole) of labeled sodium bromide solution and 5.0 ml. (0.020 mole) of 4 *N* sodium hydroxide solution was added 1.78 g. (0.0131 mole) of 2-bromo-2-chloropropane. After 20 hr. at 0°, the *gem*-dihalide was isolated and purified to give 1.1087 g. (62%) of pure product. The average value of successive readings of the total weight of product was 422 c.p.m. vs. an average background of 437 c.p.m.; no isotopic exchange was evident.

Isotopic Exchange of I with Bromide-82.—In exploratory experiments, compound I was added to a solution containing two molar equivalents of 4 *N* sodium hydroxide and two molar equivalents of 4.0 *N* sodium bromide inoculated with potassium bromide-82. Compound I was recovered after neutralizing the solution with acetic acid and the recovered N-bromoamide was found to contain an average of $69.2 \pm 0.8\%$ of labeled bromine. Similar results were obtained in the absence of base using 33% acetone in water as solvent. With a 60-sec. exposure, 68.3 and 67.4% incorporation was observed, and in 30 sec. 64.7% incorporation was observed. The data indicated that exchange in the initial case occurred after neutralization with acetic acid. The exchange between I and external bromide ion is rapid and is complete in less than 1 min. (In a separate experiment N-bromoacetamide gave 64.7% incorporation after 90 sec. exposure.) Deviations from the expected value of 66.7% are ascribed mainly to the relative purities of starting and isolated I (not determined). The experiments in the next paragraph were performed to elucidate the mechanism of this rapid exchange.

Reaction of I with Cyanide Ion.—To a solution of 2.0 g. (0.01 mole) of the N-bromoamide in 3 ml. of diglyme at 0° was added a solution of 0.49 g. (0.01 mole) of sodium cyanide in 3 ml. of water. The solution was swirled at 0° for 2 min., then flash distilled under water aspirator vacuum into a cold trap. After collecting ca. 2 ml. of distillate, 10 g. of Drierite was added to the receiver and the cyanogen bromide was redistilled at water aspirator pressure to give 0.44 g. (42%) of cyanogen bromide, m.p. 51–52°, mixture m.p. unchanged. The diglyme solution was diluted with 20 ml. of water and extracted with chloroform. The chloroform was removed, leaving an oil which, when diluted with water, gave 0.67 g. (55%) of crystalline α -chloroisobutyramide, m.p. 118–120°. The experiment was repeated using 10 ml. of water instead of the diglyme-water mixture. The yield of α -chloroisobutyramide was increased to 74%, but the yield of cyanogen bromide was decreased to 22%. In a similar experiment with N-bromoacetamide, a 30% yield of cyanogen bromide was obtained.

N-Bromo- α -bromoisovalerylamide (II).—Bromine (8.8 g., 0.055 moles) was dissolved at -5 to 0° in 60.0 g. (0.15 mole) of 10% sodium hydroxide, followed by 9.0 g. (0.05 mole) of II. The solution was filtered and the filtrate was neutralized at 0 to 5° with 12 g. of 50% acetic acid to ca. pH 5. The precipitate tends to become lumpy in the early stage, but the lumps largely break up as more acid is added; hard lumps were broken up with a glass rod. The mixture was filtered through sintered glass and the precipitate washed thoroughly with cold water. The product was air-dried for 20 min. and then dried to constant weight *in vacuo*. The average yield for three batches was 87% and active halogen assay of the blend indicated a purity of 99.4%.

Rearrangement of II in the Presence of Bromide-82 Ion.—Compound II (12.95 g., 0.05 mole) was dissolved in 75.6 g. (0.4 mole) of 21.2% sodium hydroxide held at 3–8°; 25 ml. of 6.130 *N* sodium bromide (0.1533 mole) inoculated with bromide-82 was then added giving a final concentration of sodium hydroxide of 16.7% based on water. Individual 4-ml. portions of the cold (5°) filtered solution were placed in a reaction flask connected with a short gooseneck to a condenser and chilled receiver. The oil-water distillate was collected in a chilled receiver with bottom

drain and the distillate was allowed to accumulate until three 0.05-mole batches had reacted.

Water was removed by pipet from the distillate, 2 ml. of cold distilled *n*-pentane was added, and the oil (upper) layer was washed with cold distilled water to remove entrained bromide; none was detected by neutral silver nitrate. The water layer was carefully withdrawn and the cold pentane solution was washed successively with cold concentrated sulfuric acid from a micropipet, cold water, bicarbonate, and water until neutral to litmus. The dried *gem*-dihalide solution was distilled in an all-glass apparatus using 0.8-inl. receivers with ground joints. The receiver system was chilled at -30° and the pentane slowly removed by reducing the pressure from 90 to 30 mm., with the bath temperature at 40° . A 0.20-g. fraction was removed at 30 min., n_D^{25} 1.440, containing an estimated 50% of *gem*-dihalide. The bath temperature was raised to 80° and a second fraction weighing 0.889 g., n_D^{25} 1.4992, was isolated (2.8% yield). The infrared curve was identical with an analytical sample. Purity by vapor chromatography was estimated at $97.0 \pm 1.0\%$ by area ratios. A third fraction, 0.170 g., n_D^{25} 1.4562, was removed by microflame with an estimated purity of 60%. The total conversion to *gem*-dihalide was approximately 3.3%.

Redistillation gave an analytical sample, n_D^{25} 1.5025, b.p. 66° (60 mm.), 52° (30 mm.). The infrared absorption spectrum showed the expected *gem*-dimethyl doublet at 7.22 and 7.32 μ .

Anal. Calcd. for $C_4H_5Br_2$: C, 22.23; H, 3.54. Found: C, 22.25; H, 3.73.

Fraction 2 (0.889 g., 4.12×10^{-3} mole) was used for counting against the inoculated 6.130 *N* sodium bromide (0.100 ml., 6.13×10^{-4} moles) as standard. Counting was performed in a well-type counter in the sequence [background (B), *gem*-dihalide (G), standard (S)]: B, G, S, B, G, S, and B. The background was counted for 5 min., the halide to 10,000 counts, and the standard to 100,000 counts. Background readings were 386, 390, 389, and 395 c.p.m., average 390 c.p.m. The standard measured 22,600, 22,500, and 32,400 c.p.m., average 22,500 c.p.m., or 22,110 c.p.m. corrected for background. *gem*-Dihalide readings were 972, 970, 971 c.p.m., average 971 c.p.m., or 581 c.p.m. corrected for background. Accordingly, *gem*-dihalide calculated 141 c.p.m./mmole and the standard 36,000 c.p.m./mmole indicating that 0.39% (uncor.) of external bromide had been incorporated in the *gem*-dihalide. The ratio of bromide-82 to total bromide employed experimentally was 0.75. Although bromine-balance studies indicated that all bromide appeared as bromide ion in the mother liquor except that present in the *gem*-dihalide, the maximum effect would be to reduce the ratio to 0.61. As discussed in the text earlier, the application of corrections for this range of ratios and for the purity of the *gem*-dihalide (97%) results in a corrected value of $0.6 \pm 0.3\%$.

Rearrangement of Labeled N-Bromo- α -bromoisovalerylamide in the Presence of Bromide Ion.—The labeled N-bromoamide in this case was prepared by addition of 100 λ of potassium bromide-82 to 10% sodium hydroxide, followed by addition of bromine and N-bromoamide. The N-bromo-82-amide was isolated as before except the initial precipitate was dried, ground, and rewashed with water containing a little acetic acid and finally water. The active halogen assay was 99.8%, m.p. 105–106° (uncor.). Labeled amide was dissolved in eight molar equivalents of sodium hydroxide and three molar equivalents of noninoculated 6.02 *N* sodium bromide and rearranged as before. A sample of 0.2055 g. of *gem*-dihalide was used for counting against a 0.07960-g. sample of N-bromo-82-amide as standard.

The counting was performed in the following sequence without appreciable time delays: *gem*-dihalide, background, standard, background. Both the *gem*-dihalide and standard were timed to 10^6 counts. The background average was 340 c.p.m. for six readings. The results are shown below as counts per minute per millimole, corrected for background.

(1) GDH	376,750
(2) Standard	378,200
(3) GDH	369,470
(4) Standard	373,000
(5) GDH	361,820
(6) Standard	365,920

The percentage retention was calculated by the ratio of the averages of 1, 3, and 5 to 2 and 4, and the averages of 3 and 5 to 2, 4, and 6. The two values are 98.34% and 98.19%, average 98.3%. The purity of the *gem*-dihalide by vapor chromatography was $98.7 \pm 0.5\%$. (The impurity, 1.3%, as in the incorporation experiment, appeared to be a hydrocarbon from the pentane used as solvent in the work-up.) The purity of the standard was 99.8% by titration assay. The corrected retention value considering the probable error is expressed as $99.4 \pm 1.0\%$. A repeat count, made later in a lower count range, was substantially the same, an uncorrected value of 98.4% being obtained.

Equilibration between 1,1-Dibromo-2-methylpropane and Bromide-82.—*gem*-Dihalide (193.4 mg., 0.9 mmole), isolated from the incorporation study above, was covered with 39.4 g. (215

mmoles) of 21.2% sodium hydroxide and 12.63 ml. of 6 *N* sodium bromide-82 in a 100-ml. flask equipped with stirrer, downward condenser, and receiver. (The large molar excess of base is to correct for the yield of *gem*-dihalide.) The reaction flask was gently heated until the *gem*-dihalide co-distilled with water. The work-up was the same except the oil was washed ten times with distilled water and the sulfuric acid wash was omitted. For counting, 0.0810 g. (0.375 mmole) was used *vs.* 0.4020 g. (1.86 mmoles) of original *gem*-dihalide and products were essentially identical. The average value of the *gem*-dihalide recovered was 335 c.p.m./mmole compared to 340 c.p.m./mmole for the starting *gem*-dihalide. The results indicate no exchange in the limits of experimental error. (Note: Nonradioactive *gem*-dihalide would have been employed, preferably, except that none was available at the time.)

Alkaline Stability of 1,1-Dibromo-2-methylpropane.—*gem*-Dihalide (66.7 mg., 0.209 mmole) was weighed into a 50-ml. flask equipped with stirrer and downward condenser and covered with 17.9 g. (74.5 mmoles) of 16.7% sodium hydroxide. The flask was slowly and carefully heated until the *gem*-dihalide had completely co-distilled with water. The hydrolysate was drained and rinsed into a 250-ml. beaker and bromide determined gravimetrically in the usual manner. The silver bromide weighed 1.9 mg., equivalent to 1.67% hydrolysis to aldehyde. A comparative experiment with 1,1-dibromopropane gave 0.44% hydrolysis, calculated to the aldehyde.

Rearrangement of α -Bromobutyramide and α -Bromoisovalerylamine. Standard Hot Procedure.—The standard hot procedure follows that described by Stevens, *et al.*, and designated by them as Procedure B.² This is essentially the procedure described above for the radiobromine studies except that the earlier work prepared the *N*-bromoamide *in situ*. This method was used for exploratory studies with α -bromoisovalerylamine. Two runs were made with α -bromobutyramide, repeating earlier work,² to acquire the comparative data reported in Table I.

Bromine balance data were obtained for two runs using Procedure B. An aliquot of the alkaline liquors was neutralized with nitric acid, filtered, a slight excess of nitric acid was added, and the solution boiled to destroy cyanate. Bromine ion, 83 mmoles, was found in the alkaline liquors out of a total of 85 mmoles, including the α -bromo atom. The *gem*-dihalide accounted for *ca.* 0.8 mmole leaving 1.2 mmoles unaccounted for. In a repeat run, 146.1 mmoles out of a possible 150.0 mmoles was found, 145.8 mmoles in the alkaline mother liquors.

α -Bromoisovalerylamine. Hot "Drop-In" Method.—In a typical run, 8.8 g. of bromine was added to 66 g. of 10% sodium

hydroxide at 3–8° followed by 9.0 g. of α -bromoisovalerylamine. The cold solution was added dropwise to a boiling solution of 100 g. of 10% sodium hydroxide which was distilling, prior to addition, through a downward condenser. The addition was complete in 18 min. with heating continued for 3 more minutes; 68 g. of water plus oil was collected. The separated oil weighed 1.2 g., n_D^{25} 1.4425. Infrared analysis and subsequent work-up of the distillate indicated that the product was predominantly isobutyraldehyde, 26% isolated, and high-boiling polymers. (No *gem*-dihalide was found in a combined work-up and fractional distillation of 2.55 g. of oil from 0.23 mole of α -bromoamide.) Aliquots of the filtered mother liquor were analyzed for cyanate ion⁵ and α -hydroxyisovaleric acid by usual means. Results are reported in Table I.

Rearrangement of α -Bromoisovalerylamine. Cold Studies.—Bromine (16 g., 0.1 mole) was added at –5° to 120 g. (0.3 mole) of 10% sodium hydroxide, followed by 16.2 g. (0.09 mole) of α -bromoisovalerylamine. The batch was split and one portion (0.044 mole) was placed in the refrigerator for 21 days. After neutralization, approximately 7.0 g., 60%, of crude *N*-bromoamide was isolated. No *gem*-dihalide and no cyanate ion was found. The second portion was held at room temperature for 4 days and filtered to recover, after washing with cold water, 5.1 g., 61%, of pure α -bromoisovalerylamine, m.p. 129–130.5°. No *gem*-dihalide and no cyanate were found. A second experiment gave similar results.

Vapor Chromatography.—The column was prepared with Dow 702 silicone, 20% on 42–60 mesh firebrick. Studies with 1,1-dibromo-2-methylpropane and the comparison with 1,2-dibromo-2-methylpropane and 2,3-dibromobutane all were carried out under the conditions: helium pressure 7.8 p.s.i., preheater temperature 150°, and column temperature 135–136°. Symmetrical peaks and excellent separations were achieved. The pentane solvent showed six components (peaks) and two of these were the apparent contaminants in the 1,1-dibromo-2-methylpropane isolated from the rearrangement experiments.

Cyanate Ion.—Aliquots of the alkaline mother liquor were filtered, if necessary, neutralized with 25–50% acetic acid to methyl red end point, and filtered again, if necessary. Sodium acetate, 2 g., was added, followed by 1 g. of semicarbazide hydrochloride.³ The solution was shaken vigorously and placed in the refrigerator overnight. The filtered hydrazodicarboxamide was washed with cold water and dried at 105° for 2 hr. The melting points were within 3 to 6 degrees of the pure compound, 249° (252°).⁵ Cyanate recovery was measured at 90–95%, but further study and refinement of the method is desirable.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

gem-Dihalides from α -Haloamides. III. Rearrangement of Optically Active α -Chlorohydrocinnamamides¹

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Additional evidence for the stereospecific nature of the conversion of α -haloamides to *gem*-dihalides was gained by the isolation of an optically active *gem*-dihalide from an optically active α -haloamide. *D*- α -Chlorohydrocinnamamide, $[\alpha]_D^{25} +11.0^\circ$, was dissolved in alkaline sodium hypobromite and steam distilled to yield *D*-*gem*-dihalide, $\alpha_D^{25} -0.065^\circ$, determined as a neat liquid with *DL*-*gem*-dihalide as reference. Similarly, *L*- α -chlorohydrocinnamamide, $[\alpha]_D^{25} -10.7^\circ$, gave *L*-*gem*-dihalide, $\alpha_D^{25} +0.066^\circ$, the reading of which was essentially doubled in a 2-dm. tube. A maximum racemization of 40% due to hydrogen exchange at the α -carbon atom was established by rearrangement of *DL*- α -chlorohydrocinnamamide in the presence of heavy water and determining the deuterium content of the isolated *gem*-dihalide. The signs of rotation of the *gem*-dihalides agree with prediction and the values are of the expected order of magnitude.

Work in this Laboratory has continued to provide additional insight into the conversion of α -haloamides to *gem*-dihalides^{2,3} in the presence of alkaline hypobromite. The previous paper² in this series reviewed the progress of this program and provided additional evidence that the reaction proceeds almost exclusively by an intramolecular mechanism. The mechanism² predicts retention of configuration and additional evidence for the stereospecific character of the rearrangement forms the subject matter of this paper.

(1) This work was supported by the National Science Foundation, Research Grant G14630.

(2) Paper II of this series: C. L. Stevens, M. E. Munk, A. B. Ash, and R. D. Elliott, *J. Am. Chem. Soc.*, **85**, 3390 (1963).

(3) C. L. Stevens, T. K. Mukherjee, and V. J. Traynelis, *ibid.*, **78**, 2264 (1956).

The objective of the present program was to utilize the optical center at the α -carbon atom of *D*- and *L*- α -chlorohydrocinnamamides and subject the enantiomers to the rearrangement reaction. Isolation of the resulting *gem*-dihalides and measurement of their optical rotation should provide evidence relative to the stereospecificity of the reaction. The preparation of the desired starting amides followed generally the methods of Greenstein and co-workers in the alanine series.⁴

D-, *L*-, and *DL*-phenylalanine were dissolved in hydrochloric acid at 5° and treated with sodium nitrite to form the corresponding α -chloro-hydrocinnamic acids. The latter were treated with excess thionyl chloride at

(4) S. C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **76**, 6054 (1954).