

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MCGILL UNIVERSITY]

The Reduction of α -Bromo-ketones by Aluminum Isopropylate with a Note on the Isomeric Amino-alcohols of the Ephedrine Series

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In an earlier communication we¹ reported the reduction of α -bromo-ketones with aluminum isopropylate. Thus α -bromopropiophenone yielded the bromohydrin and halogen-free products. The former with methylamine gave a mixture of isomeric amino-alcohols, one of which was *dl*-pseudo-ephedrine. No *dl*-ephedrine was isolated.² The other isomeric amino-alcohol has now been found to be the *dl*-isoeephedrine of Emde and Runne.³ Inasmuch as this substance and *dl*-pseudo-ephedrine yield the same oxide, according to the boiling points recorded by Rabe and Hallensleben,⁴ very likely it has the pseudo configuration, and so should be called *dl*-pseudo-isoeephedrine.

In view of the discovery of Winstein and Lucas⁵ that replacement by bromine of the hydroxyl group of certain bromohydrins involves a cyclic intermediate, with net retention of configuration, we believe that a similar series of reactions takes place here, rather than direct replacement with inversion. This would mean that both isomeric amino-alcohols are derived from the *threo*-bromohydrin through the *erythro*-oxide. We have no satisfactory explanation for the failure to obtain *dl*-ephedrine, unless the bromohydrin was principally the *threo*-form, or the *threo*-oxide gave complex products instead of the expected *dl*-ephedrine.⁶ Work on this problem is now in progress.

The secondary reduction products of the bromo-ketone are lower boiling, and bromine-free. The higher boiling of these turned out to be a mixture of carbinols, one of which was methylbenzylcarbinol. This carbinol undoubtedly arises from further action of aluminum isopropylate on the bromohydrin for, actually, purified bromohydrin yields appreciable amounts of the carbinol when treated separately with the alcoholate. Probably this transformation involves the oxide as an intermediate, which then must rearrange to phenyl-

acetone,⁷ followed by further reduction. It was puzzling, however, to understand how this could occur so easily in an aluminum isopropylate solution, until we found that part of the hydrobromic acid removed from the reaction products appeared as isopropyl bromide. The acid could not then be completely neutralized, and was still available, possibly in the form of $\text{AlBr}(\text{OC}_3\text{H}_7\text{-}i)_2$, for either reactions with alcohols, or isomerization of the oxide.

To test this, we treated the oxide with the isopropylate containing aluminum bromide. Rearrangement and simultaneous reduction occurred readily, and the products appeared to be the same mixture of carbinols with methylbenzylcarbinol predominating. We therefore prefer this oxide-rearrangement mechanism in this case, to that suggested by Winstein,⁸ which would involve disproportionation of the bromo-ketone to propiophenone and the dibromo-ketone, because this should yield ethylphenylcarbinol and not methylphenylcarbinol. While it is possible that such disproportionation occurred, yet it must have been to a very small extent only, since Kröhnke⁹ has shown that the equilibrium between dibromopropiophenone and propiophenone in the presence of hydrobromic acid is almost completely on the side of the monobromo ketone.

The carbinol fraction obtained both from reduction of the bromo-ketone and the oxide boiled over a wide range. This was not due to the other possible rearrangement reduction product of the oxide, hydratropic alcohol,¹⁰ but to another non-isomeric hydroxy compound. This substance was obtained almost exclusively from the oxide and aluminum isopropylate without any aluminum bromide. Its composition corresponded to $\text{C}_{12}\text{H}_{18}\text{O}_2$, and it formed a *p*-nitrobenzoate and phenylurethan melting¹¹ at 100 and 95.5°, re-

(7) Compare Fournneau and Tiffeneau, *Compt. rend.*, **141**, 663 (1905); also Lévy and Dvoletzka-Gombinska, *Bull. soc. chim.*, [4] **49**, 1765 (1931).

(8) After our first paper appeared, Winstein [THIS JOURNAL, **61**, 1610 (1939)] reported the reduction of α -bromocyclohexanone with aluminum isopropylate to about equal amounts of bromohydrin and cyclohexanol.

(9) Kröhnke, *Ber.*, **69**, 921 (1936).

(10) Compare Ref. 7.

(11) The *p*-nitrobenzoate of hydratropic alcohol melts at 65° (Cohen, Marshall and Woodman, *J. Chem. Soc.*, **107**, 887 (1915)).

(1) Stevens, THIS JOURNAL, **60**, 3089 (1938).

(2) Compare Fournneau, *J. Pharm. Chim.*, [6] **20**, 481 (1904).

(3) Emde and Runne, *Arch. Pharm.*, **249**, 369 (1911).

(4) Rabe and Hallensleben, *Ber.*, **43**, 2622 (1910).

(5) Winstein and Lucas, THIS JOURNAL, **61**, 2845 (1939).

(6) Compare Schmidt, *Arch. Pharm.*, **253**, 60 (1915).

solution of 33.0 g. of aluminum as isopropylate in 1200 cc. of isopropyl alcohol, and the solution boiled under a reflux distilling column for nine hours. The acetone was removed by fractional distillation. The combined distillate on treatment with alcoholic silver nitrate gave a precipitate of silver bromide equivalent to approximately 8% of the total bromine, indicating the presence of isopropyl bromide. Propylene was also present as evidenced by rapid reduction by aqueous permanganate. Most of the isopropyl alcohol was removed *in vacuo*, and the residual pasty mass poured onto ice and dilute sulfuric acid, extracted with ether, washed with dilute acid, water, potassium carbonate, sodium hydroxide, water, dried over anhydrous potassium carbonate and distilled: first fraction up to 75° (0.1 mm.), second fraction, 44 g., b. p. 75–95° (0.1 mm.). The black tarry residue weighed 42.7 g. Redistillation of the second fraction yielded the bromohydrin, a somewhat viscous yellow-brown oil, b. p. 73–75° (0.1 mm.), n_D^{25} 1.5611. *Anal.* Calcd. for $C_6H_{11}OBr$: Br, 37.2. Found: Br, 34.8.

Another reduction was made using 60 g. of bromo-ketone, 26 g. of aluminum and 1730 ml. of isopropyl alcohol, the solution being approximately one-half as concentrated as above. The solution was boiled for nine hours. Very little isopropyl bromide was formed. The reaction product was worked up as before, and yielded 45 g. of a distillate passing at 70–73° (0.03 mm.). This was not homogeneous, however, and redistillation at 0.02 mm. of 69.5 g. gave the following fractions: (1) 5 g., 45–57°; (2) 7.8 g., 57–58°; (3) 20.8 g., 58–62°; (4), 25 g., 62–68°. The first two fractions were mainly the carbinols, etc., and the last was fairly pure bromohydrin, n_D^{25} 1.5643; d_4^{25} , 1.429; MR calcd., 49.45; found, 48.96. *Anal.* Calcd. for $C_6H_{11}OBr$: C, 50.2; H, 5.1; Br, 37.2. Found: C, 49.9; H, 5.1; Br, 38.0. The bromohydrin was not very stable, redistillation always yielding considerable tarry residue. Freshly distilled bromohydrin was yellowish, but turned dark green on standing.

The Reduction Side-Reaction Products.—The more volatile material from the reduction of 126 g. of bromo-ketone boiled from 73–98° (8 mm.) of which the carbinol fraction boiled at 104–111° (16 mm.). This was redistilled taking the fraction b. p. 106–108° (16 mm.). Treatment with phenyl isocyanate yielded the phenylurethan of methylbenzylcarbinol, crystallizing from Skelly Solve B in fine silky needles, m. p. 87.0–87.5° (mixed m. p., 87–88°). The lower boiling substance was not investigated further.

Synthesis of Methylbenzylcarbinol.—This carbinol, b. p. 102–103° (16 mm.), n_D^{25} 1.5191, was prepared from phenylacetaldehyde and methylmagnesium iodide. The yield was poor, due to the formation of condensation products. The phenylurethan crystallized as fine needles from Skelly Solve B, m. p. 87–88°. ¹⁶

One of the condensation products crystallized from ether and Skelly Solve A as fine long needles, m. p. 126.5–127.0°. *Anal.* Calcd. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.8. Found: C, 79.8; H, 7.6. Its composition and reactions indicated a glycol structure. Oxidation with chromic acid yielded a yellow-brown oil which gave a deep wine color with ferric chloride, but no copper derivative with copper

acetate. Very likely the substance is the aldol condensation product of phenylacetaldehyde which has reacted with methylmagnesium iodide, with the structure $C_6H_5CH_2CHOHCH=CHOHCH_3$.



Action of Methylamine on the Bromohydrin.—27.2 grams of bromohydrin (34.8% Br) was treated with 40 g. of methylamine dissolved in absolute methanol. After twenty-eight days in the dark at 20–25°, the excess amine was removed *in vacuo*. The entire mass, now solid, was shaken with ether and water, and then extracted four times with dilute hydrochloric acid. The acid solution was extracted twice with ether, and then neutralized with cold concentrated sodium hydroxide. The liberated amine, partially crystalline, was extracted thrice with ether, dried over anhydrous potassium carbonate and the ether evaporated, thus yielding crystals. These were washed with cold Skelly Solve A, weight 7.7 g., yield 33%. After four recrystallizations from Skelly Solve B, the silky crystals melted 116.5–117° with preliminary sintering. A mixed melting point with an authentic sample of *dl*-pseudoephedrine (prepared from *dl*-ephedrine by heating with 25% hydrochloric acid, and recrystallized from Skelly Solve B, m. p. 116.5–117.2°) was 116.5–117°. Recrystallized from water, the melting point was 117–117.7°. The hydrochloride crystallized from alcohol and ether as needles, m. p. 162–163°.

The filtrate from the *dl*-pseudoephedrine was evaporated, yielding 10 g. of a red oil, 43% yield. This was taken up in ether, extracted with dilute hydrochloric acid, neutralized to a faint acid reaction using congo red, and evaporated in a current of air, then over potassium hydroxide *in vacuo*, yielding 13 g. of a dry salt. This salt was crystallized from isopropyl alcohol from which after 6–8 recrystallizations it separated as hexagonal plates, m. p. 188–190.5°. It was much more soluble than *dl*-ephedrine hydrochloride. *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 59.6; H, 7.9. Found: C, 59.8; H, 8.1. A mixed melting point with an authentic specimen¹⁷ of *dl*-pseudo-isoeephedrine hydrochloride (m. p. 188–190°) was 188–190°. A mixed melting point with *dl*-ephedrine hydrochloride, m. p. 184–185°, was 155–175°. The mother liquors contained in substantial amounts the basic complex products, which did not lend themselves to purification, and so were not further investigated.

Action of Aluminum Isopropylate on the Bromohydrin.—A solution of 10.75 g. of bromohydrin, b. p. 62–68° (0.02 mm.) in 150 cc. of isopropyl alcohol containing 4 g. of aluminum was boiled for fifteen hours. At first the distillate gave a heavy silver bromide precipitate with silver nitrate, and a copious test for acetone. At the end of the reaction these tests were faint. The products were worked up as usual and distilled at 16 mm., yielding 2.8 g. of a liquid, b. p. 66–120°, and much tar; redistillation at 16 mm., first fraction 0.7 g., b. p. 68–100° (mostly 72–74°); second, 1.1 g., 100–109°. This fraction formed a phenylurethan, m. p. 86–87° (mixed m. p. 86.5–88.0°).

α -Methyl- β -phenylethylene Oxide.—21.5 grams of α -phenylpropylene (prepared by the method of Gauthier¹⁸

(17) Prepared according to the direction of Emde and Runne, ref. 3.

(18) Gauthier and Gauthier, *Bull. soc. chim.*, [4] 53, 323 (1933).

(16) Emde and Runne reported 88–89° (ref. 3).

and Gauthier) b. p. 79–82° (20 mm.) was added to 37 g. of perphthalic acid (prepared following the directions of Böhme¹⁹), dissolved in one liter of ether. After twenty-four hours at –1°, and four days at 20–25°, the ether solution was decanted from the phthalic acid, washed thoroughly with aqueous sodium carbonate and water, dried over anhydrous potassium carbonate, and distilled. The oxide fraction, b. p. 74–75° (9 mm.) weighed 15 g., 61% yield. Several batches of oxide were combined and redistilled, b. p. 77–78.8° (10 mm.), n_D^{20} 1.5207, n_D^{25} 1.5189.

Action of Aluminum Isopropylate on the Oxide. (a) **Without Aluminum Bromide.**—Fifteen grams of the oxide was added to a 1 molar solution of aluminum isopropylate (9 g. of aluminum), and the solution boiled under a reflux column for twelve hours. Fractions were removed at intervals. The reaction of the oxide was very slow, as evidenced by the slow formation of acetone. After eight hours, no more acetone could be detected. The products were worked up as usual. There was no odor of any remaining oxide. Distillation at 16 mm.: first fraction, 1 g., b. p. 118–121°; second, 14 g., 121–124°, viscous residue 1–2 g. Obviously there was very little if any methylbenzylcarbinol, b. p. 102–103° (16 mm.), or hydratropic alcohol, b. p. 111–112° (16 mm.). Redistillation at 11 mm.: b. p. 114–116°, n_D^{25} 1.4924, d_4^{25} 0.9877; MR calcd. 57.18; found 57.05. *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 73.4; H, 9.1. The substance contained a hydroxyl group, as it formed a *p*-nitrobenzoate, crystallizing from ethyl alcohol, m. p. 99.5–100°. *Anal.* Calcd. for $C_{19}H_{21}O_3N$: N, 4.1. Found: N, 4.2. The phenylurethan crystallized from Skelly Solve A as feathery needles, m. p. 94.5–95.5°. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: N, 4.5. Found: N, 4.6. The ease of formation of these derivatives suggests the α -ether structure rather than the β .

(b) **With Aluminum Bromide.**—The same quantities were used here as in (a), adding 4.5 g. of aluminum bromide. The isomerization and reduction were quite rapid, as acetone was evolved readily. After thirteen hours of boiling, the products were worked up in the same way and distilled at 16 mm., first fraction, 0.2 g., b. p. 85–107; second fraction, 9.35 g., b. p. 107–118°, third fraction, 3.85 g., b. p. 118–124°. There was very little residue. Obviously here the product was essentially a mixture of methylbenzylcarbinol, and the higher boiling so-called glycol ether. Fraction 2 was converted to the phenylurethan, m. p. 87–88° (mixed m. p. 87–88°).

Reduction of α -Bromoisobutyrophenone. (a) **At 80–85°.**—This bromo-ketone is easily prepared from isobutyrophenone by simple bromination. In spite of its tertiary bromine atom it reacts extremely slowly with alcoholic silver nitrate, a faint opalescence appearing only after fifteen to twenty minutes at 20–25°. This inactivity, it appears, is quite normal for α -bromo-ketones, for α -bromopropiophenone and α -bromopentamethylacetone likewise react very slowly. Unlike the former, but similar to the latter, α -bromoisobutyrophenone has almost no lachrymatory power. It boils about 10° lower than α -bromopropiophenone, b. p. 119–120° (10 mm.), n_D^{25} 1.5550, d_4^{25} 1.3663.

Sixty-eight grams of bromo-ketone was reduced by boil-

ing with 27.5 g. of aluminum as isopropylate in 1000 cc. of isopropyl alcohol for seven hours. The amount of isopropyl bromide formed was approximately 30%. The products were worked up as usual, and distilled, b. p. 25–75° (0.03 mm.). This product was separated by repeated distillation into two fractions, (1) b. p. 81–87° (9 mm.) and (2) b. p. 100–103.5° (9 mm.). The first was refracted through a reflux column packed with glass helices, and so yielded a substance with an odor somewhat reminiscent of geraniol, b. p. 83.8–84.5° (9 mm.), n_D^{25} 1.4756, d_4^{25} 0.8985. It gave no precipitate with hot alcoholic silver nitrate, but reduced aqueous permanganate to some extent. *Anal.* Calcd. for $C_{13}H_{20}O$: C, 81.2; H, 10.4. Found: C, 81.0; H, 10.3.

The carbinol fraction contained about 5% bromine, and so was purified through the phthalate. It still boiled over the range 100–104° (9 mm.) but was bromine-free. The fraction of b. p. 101–103° (9 mm.) was possibly a mixture of carbinols. *Anal.* Calcd. for $C_{10}H_{14}O$: C, 80.0; H, 9.3. Found: C, 80.2; H, 9.5.

(b) **At 33° in vacuo.**—Thirty-four grams of bromo-ketone was added to a solution of 13.8 g. of aluminum in 865 cc. of isopropyl alcohol, and distilled through a reflux column at 63–65 mm. The bath temperature was 33–34°. The distillation was continued for about fifteen hours, and the reaction products stood two nights at 20–25°. Finally the test for acetone in the distillate was very faint. Very little if any isopropyl bromide could be detected. The product was worked up as usual and distilled, yielding 28.5 g. of an oil, b. p. 65–85° (0.02 mm.). The residue was only 1.7 g. Redistillation in a modified Claisen flask at 0.04 mm. yielded the following fractions, (1) 2.0 g., b. p. 30–64°; (2) 4.6 g., b. p. 64–73°; (3) 18.9 g., b. p. 73–74°. This last was redistilled at 8 mm. taking the following fractions (1) b. p. 80–107°, (2) b. p. 107–115°, (3) b. p. 115–117°. The third fraction represented 70% of the total, n_D^{25} 1.5921, d_4^{25} 1.323, MR calcd. 52.08, found 52.72. The bromohydrocarbon, a mild lachrymator, reacts instantly with alcoholic silver nitrate, and reduces permanganate rapidly. It did not absorb bromine in carbon tetrachloride, but did so slowly in acetic acid. *Anal.* Calcd. for $C_{12}H_{11}Br$: C, 56.9; H, 5.2; Br, 37.9. Found: C, 56.9; H, 5.1; Br, 37.2. Oxidation with chromic acid in hot acetic acid was rapid, and a lachrymator was evolved. The acid fraction was isolated in the usual way, yielding copious amounts of benzoic acid, m. p. 121–122°.

Hydrolysis of the Unsaturated Bromide.—One gram of the bromide was boiled for several hours with dilute aqueous sodium hydroxide, the oil extracted with ether, dried, the ether evaporated, and the residual oil distilled *in vacuo*. The distillate was colorless, bromine-free, and had a fine odor. It reduced permanganate instantly, and absorbed bromine in carbon tetrachloride rapidly. The dibromide crystallized from Skelly Solve B as needles, m. p. 86–87° (mixed m. p., 86–87°). The phenylurethan crystallized in long needles from Skelly Solve B, m. p. 78.2–78.8° (mixed m. p. 78.2–78.8°).

2-Methylcinnamic Aldehyde.—This aldehyde was prepared from propionaldehyde and benzaldehyde according to the directions of Miller and Kinkelin²¹ with only slight

(19) Böhme, *Ber.*, **70**, 379 (1937).

(20) α , α -Dimethyl- β -phenylethylene oxide boils at 74° (10 mm.).

(21) Miller and Kinkelin, *Ber.*, **19**, 526 (1886).

modifications. The aldehyde, purified through the semicarbazone, m. p. 206–208°, boiled at 113° (12 mm.).

2-Methylcinnamyl Alcohol.—Reduction of the above aldehyde was carried out with aluminum isopropylate. The unsaturated alcohol boiled at 124–124.3° (8 mm.), n_D^{25} 1.5697, d_4^{25} 1.034, MR calcd. 45.84, found 46.94. On cooling it solidified, m. p. 19–21°. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.1; H, 8.1. Found: C, 80.9; H, 8.1. The dibromide crystallized from Skelly Solve A as needles, m. p. 86.0–87.0°. Anal. Calcd. for $C_{10}H_{12}OBr_2$: Br, 51.9. Found: Br, 51.8. The phenylurethan crystallized from Skelly Solve B, m. p. 78.5–79.3°. Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.6. Found: N, 5.5.

1-Phenylmethallyl Alcohol.—This isomeric alcohol was prepared from α -methylacrolein and phenylmagnesium bromide in the usual way, b. p. 99.8–100.0° (8 mm.), n_D^{25} 1.5361, d_4^{25} 1.010, MR calcd. 45.84, found 45.70. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.1; H, 8.1. Found: C, 81.2; H, 8.3.

The dibromide was an oil. The phenylurethan crystallized from Skelly Solve B, m. p. 79.5–79.9° (mixed m. p. with the phenylurethan of its isomer above (m. p. 78.5–79.3°) was 57–65°). Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.6. Found: N, 5.6.

Action of Hydrobromic Acid on 1-Phenylmethallyl Alcohol.—Fifteen grams of the alcohol was treated with 30 ml. of constant boiling hydrobromic acid for one hour, with frequent shaking. The alcohol layer became olive-green. The upper layer was separated, washed with cold sodium bicarbonate, dried over sodium sulfate and distilled, b. p. 165–165.5° (30–26 mm.), 10.3 g. The bromide was now boiled with dilute aqueous sodium hydroxide for four hours, and then worked up as usual. The unsaturated alcohol was distilled, b. p. 147–150° (33 mm.),

and converted to the phenylurethan, m. p. 78.0–78.5° (mixed m. p. with the phenylurethan of 2-methylcinnamyl alcohol (m. p. 78.5–79.3°) 78.5–79.0°).

Reduction of 2-Bromocholestanone.—One-half gram of the bromo-ketone, m. p. 169–170°, prepared according to the directions of Butenandt and Wolff¹⁵ was treated with 55 ml. of a 0.2 molal aluminum isopropylate solution. The ketone did not appear to dissolve even after four and one-half hours boiling. The product, recovered in the usual way, was a gum, which gave only a faint opalescence with boiling alcoholic silver nitrate. It was not investigated further.

Summary

1. Reduction of α -bromopropiophenone yielded the bromohydrin and halogen-free products, one of which was methylbenzylcarbinol.
2. The bromohydrin with methylamine gave *dl*-pseudo-ephedrine and *dl*-pseudo-isoeephedrine. No *dl*-ephedrine was isolated.
3. Reduction of α -bromoisobutyrophenone at 80–85° yielded principally bromine-free compounds.
4. Reduction of α -bromoisobutyrophenone at 33° *in vacuo* yielded 2-methylcinnamyl bromide, the result of a loss of hydrogen bromide, reduction and replacement by halogen accompanied by an allylic rearrangement.
5. Reduction of 2-bromocholestanone occurred with complete removal of bromine.

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Intermediate Complexes in the Friedel and Crafts Reaction

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In a former paper² a number of complexes were described which contained aluminum halides, aromatic hydrocarbons and hydrogen halides. The complexes differed in stability when submitted to diminished pressure. When the one having the composition $Al_2Br_6 \cdot 2C_6H_5(C_2H_5)_3HBr$ was held at 0.002 mm. pressure until constant weight was obtained, one-half of the hydrocarbon was lost. We accordingly attempted to prepare directly a complex which contained its components in molecular ratio of $1Al_2Br_6$ to $1s-C_6H_5(C_2H_5)_3$. When a mixture of these compounds in

the above ratio was treated with hydrogen bromide, a compound was formed which was shown by analysis to have the composition represented by the formula $Al_2Br_6 \cdot s-C_6H_5(C_2H_5)_3HBr$. A compound of similar composition containing aluminum bromide, mesitylene and hydrogen bromide also was prepared.

The previous work of Norris and Ingraham indicated that a complex could be formed in which ethyl bromide replaced the hydrogen bromide. We have isolated complexes which have the formulas $Al_2Br_6 \cdot s-C_6H_5(C_2H_5)_3$, C_2H_5Br and $Al_2Br_6 \cdot s-C_6H_5(CH_3)_3 \cdot C_2H_5Br$. We were unsuccessful in attempts to prepare complexes of definite composition containing only aluminum halides and

(1) From the thesis of John Edward Wood, III, presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1939.

(2) Norris and Ingraham, *THIS JOURNAL*, **62**, 1298 (1940).