The Synthesis and Resolution of alpha-o-Chlorobenzylethylamine[1]

BY I. B. JOHNS AND J. M. BURCH

The synthesis of certain primary amines by heating ketones with excess ammonium formate was first described by Leuckart.[2] More recently Ingersoll[3] and his co-workers have published a review of the Leuckart synthesis and have reported the preparation of a series of α-substituted ethylamines by the use of an improved modification of the Leuckart method. Some work[4] in this Laboratory is in agreement with Ingersoll in that the effective reagent is formamide. dl-α-Phenylethylamine, dl-α-benzylethylamine and dl-α-p-tolylethylamine were prepared in 50–60% yields by simply substituting formamide for ammonium formate. The yields obtained in this Laboratory are 10–20% less than those reported by Ingersoll[2] and may be explained by the fact that no provision was made for the recovery of the unreacted ketones. dl-α-o-Chlorobenzylethylamine was prepared in a like manner and the yield was 52% of the theoretical based on the ketone charged to the reaction.

Ingersoll[5] has reported some excellent work on the resolution of a number of α-substituted ethylamines by the classical method of fractional crystallization of the amine salts of optically active acids. For the resolution of dl-α-o-chlorobenzylethylamine we have used d-tartaric acid with 50% ethyl alcohol as the solvent. The d-α-o-chlorobenzylethylamine d-tartrate crystallizes at room temperature and leaves the salt of the l-base-d-acid in the mother liquor.

By the catalytic reduction of active α-phenylethylamine to form α-cyclohexylethylamine, Leithe[6] has shown that the dextro isomer of the former and the levo isomer of the latter have the same relative configuration. Likewise he proved that the dextro isomer of α-benzylethylamine and the dextro isomer of α-hexahydrobenzylethylamine have the same configuration. We have replaced the chlorine in d-α-o-chlorobenzylethyl-

amine by catalytic hydrogenation in the presence of palladium oxide catalyst to form d-α-benzylethylamine.

The active α-benzylethylamine obtained by the reduction was isolated as the benzoyl derivative. The melting point and the rotatory power in ethyl alcohol and in chloroform agree with the constants reported by Leithe[6] for the benzoyl derivative of the dextro isomer. Therefore it can be concluded that d-α-o-chlorobenzylethylamine and d-α-benzylethylamine have the same configuration.

Experimental[7]

o-Chlorobenzyl Methyl Ketone.—o-Chlorobenzyl cyanide, b. p. 120° (9 mm.), was prepared from o-chlorobenzyl chloride in the usual manner. Hydrolysis of o-chlorobenzyl cyanide with 45% H_2SO_4 gave a 95% yield of o-chlorophenylacetic acid. o-Chlorophenylacetyl chloride, b. p. 130–135° (20–30 mm.), was prepared by the method of Metzner[8] in 83% yield. One hundred and sixty-five grams of the acid chloride dropped into an equivalent of zinc methyl iodide and subsequent hydrolysis of the addition product gave 105 g. of o-chlorobenzyl methyl ketone, b. p. 125–130° (15 mm.). The oxime was recrystallized from petroleum ether and melted at 120°.

Anal. Calcd. for $C_9H_{10}ONCl$: N, 7.63. Found: N, 7.69.

α-o-Chlorobenzylethylamine.—Twenty-four grams of o-chlorobenzyl methyl ketone, and 50 g. of formamide were refluxed for thirty hours. One hundred cc. of 30% sodium hydroxide solution was added and the reaction mixture was refluxed for twelve hours longer to hydrolyze the formyl derivative of the amine. After cooling to room temperature the reaction mixture was extracted with several portions of ether. The combined ether extract was shaken with 10% hydrochloric acid solution. Unreacted ketone may be recovered from the ether layer. The amine was regenerated from the acid layer by the addition of sodium hydroxide and then extracted with ether. The ether solution of the amine was dried over potassium hydroxide sticks and filtered. Dry hydrogen chloride gas was passed into the ether solution and the hydrochloride of α-o-chlorobenzylethylamine was filtered off and dried in a vacuum desiccator; yield, 15 g. of amine hydrochloride, m. p. 175–176°.

The free base, regenerated and dried over solid potassium hydroxide, gave the following constants: b. p. 75–80° (8 mm.); d^{25}_4 1.0789; n^{25}D 1.5418.

Anal. Calcd. for $C_9H_{12}NCl$: N, 8.27. Found: N, 8.22, 8.16.

(1) Supported in part by a grant from the Industrial Science Research funds of the Iowa State College and also in part by a grant from the Rockefeller Fluid Research Fund.·

(2) Leuckart, Ber., 18, 2341 (1885); 19, 2128 (1886); 20, 104 (1887); 22, 1409, 1851 (1889).

(3) Ingersoll, et al., THIS JOURNAL, 58, 1808 (1936).

(4) J. M. Burch, unpublished Doctoral Thesis, Iowa State College, June, 1935.

(5) Ingersoll, et al., THIS JOURNAL, 47, 1168 (1925); 54, 274, 4712 (1932).

(6) Leithe, Ber., 65, 665 (1932).

(7) We are indebted to Mr. Morton Rayman, then a senior student, for assisting in the preparation of some of these compounds.

(8) Metzner, Ann., 298, 375 (1897).

The benzoyl derivative of the inactive amine was prepared by shaking the amine with benzoyl chloride in a weak potassium hydroxide solution and recrystallizing the precipitate from ethyl alcohol, m. p. benzoyl derivative, 135–136°. *Anal.* Calcd. for $C_{15}H_{16}ONCl$: N, 5.12. Found: N, 5.27, 5.23.

Dextro-α-o-chlorobenzylethylamine.—Twelve grams of *dl*-α-*o*-chlorobenzylethylamine and 10 g. of *d*-tartaric acid were dissolved in a boiling solution of 100 cc. of water and 100 cc. of ethyl alcohol. The solution was allowed to cool slowly to room temperature and at the end of three days 16 g. of crystals was filtered. This fraction was recrystallized twice from a solution of equal parts ethyl alcohol and water. Seven and one-half grams of the *d*-base-*d*-acid salt was obtained: m. p. 175°; $[\alpha]^{24}D$ (in water c, 2.74) +21.1°. *Anal.* Calcd. for $C_{13}H_{18}O_6NCl$: N, 4.38. Found: N, 4.34, 4.48.

The dextro base, regenerated and dried over solid potassium hydroxide gave the following constants: b. p. 75–77° (6 mm.); d^{25}_4 1.0789; α_D +14.9 at 25° in a 1-dm. tube; $[\alpha]^{25}D$ +13.8°; $[\alpha]^{25}D$ (methanol, c, 10.3) +11.4°; (hexane, c, 13.0) +12.7°.

The hydrochloride of the dextro base gave the following constants: m. p. 175–176°; $[\alpha]^{25}D$ (in water, c, 3.78) +9.0°, $[\alpha]^{25}D$ (in methanol, c, 8.66) +4.1°.

The benzoyl derivative of the dextro base gave the following constants: m. p. 166°, $[\alpha]^{28}D$ (in ethyl alcohol, c, 0.97) 97.6°. *Anal.* Calcd. for $C_{16}H_{16}ONCl$: N, 5.12. Found: N, 5.15.

Catalytic Reduction of Dextro-α-o-chlorobenzylethylamine.—Sixty-three hundredths gram of the pure dextro amine dissolved in 25 cc. of ethyl alcohol and 5 cc. of gla-cial acetic acid was reduced catalytically using 0.1 g. of palladium oxide catalyst. The catalyst was prepared by the method of Shriner and Adams.[9] The hydrogenation was carried out at room temperature and under six atmospheres of hydrogen for five hours. A test with silver nitrate showed the chloride ion to be present at the end of this time. The solution was filtered and evaporated nearly to dryness on the steam-bath. The amine was liberated with potassium hydroxide and extracted with ether. After the ether was distilled off the benzoyl derivative was prepared by shaking with benzoyl chloride in weak potassium hydroxide solution. The precipitate was recrystallized from alcohol and was shown to be the benzoyl derivative of dextro-α-benzylethylamine by the following constants: m. p. 160°; $[\alpha]^{22}D$ (in ethyl alcohol, c, 1.66) +69°; $[\alpha]^{22}D$ (in chloroform, c, 3.00) −13.7°. *Anal.* A qualitative test for chlorine was negative. Calcd. for $C_{16}H_{17}ON$: N, 5.85. Found: N, 5.80.

Summary

1. Racemic α-*o*-chlorobenzylethylamine has been synthesized and resolved.

2. Constants of *d*-α-*o*-chlorobenzylethylamine have been reported.

3. *d*-α-*o*-Chlorobenzylethylamine and *d*-α-benzylethylamine have been shown to have the same configuration.

(9) Shriner and Adams, THIS JOURNAL, **46**, 1683 (1924).

The Volatile Oil of Amur Cork Tree Fruit[1]

BY E. K. NELSON

The Amur cork tree (*Phellodendron amurense*), is a native of North China and Manchuria. It was introduced in this country about 1856. The dioecious flowers appear in June and the fruit ripens in September and October.

The fruit, when crushed, has a pronounced aromatic odor, described in some textbooks on botany as "turpentiny."

No record was found in the literature on the constituents of the fruit. Wehmer, "Die Pflanzenstoffe," states that the bark of the tree is used in Japan as a tonic and stomachic, containing about 1.6% berberin besides other constituents.

Fruit for the present investigation of the volatile oil was collected from a heavily bearing tree located in the grounds of the Congressional Li-brary in Washington, D. C. The fruit was collected in October when still green, but on the verge of ripening, and also in November when fully ripe. No difference was found in the composition of the oils from the two lots of fruit, though the ripe fruit gave a somewhat higher yield of oil.

Three kilograms of the green fruit was minced and distilled with steam. Sixty-six cubic centimeters of oil was obtained, a yield of 2.16 cc. per 100 g. of fruit. Eight kilograms of ripe fruit, similarly distilled, afforded 242 cc. of oil, or 3 cc. per 100 g. of fruit. The oil has the following physical characteristics:

Specific gravity 15/15	0.7984
Optical rotation	−.7°
Refractive index at 20°	1.4693

The oil was fractionated at 10 mm. through an efficient column, over 92% boiling at 53–54°, having specific