

and turned a straw color on standing. The physical properties of the product are given in Table III and exclude the possibility that it is the isomeric 2-methylcoumaran. The following properties have been reported for chroman⁸ and 2-methylcoumaran,¹⁵ respectively: b. p. 93.5° (8 mm.), 208–212°; n_D 1.54437 (20°), 1.5302 (25°); d , 1.0587 (20°), 1.028 (25°).

Omission of the treatment with alkali described above reduced the yields of chroman to 70–75%. None of the expected bromide was isolated but the chroman fraction contained large amounts of halogen. However, treatment of γ -(*o*-hydroxyphenyl)-propyl alcohol (V) with hydrobromic acid-sulfuric acid mixture as described¹⁶

(15) Niederl and Storch, *THIS JOURNAL*, **55**, 4554 (1933).

(16) Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1932, p. 27.

for lauryl bromide gave a 50% yield of chroman and 10% of what was probably γ -(*o*-hydroxyphenyl)-propyl bromide, b. p. 165° (23 mm.). The latter could not be purified, since hydrogen bromide was evolved slowly during distillation.

Summary

Products obtained by the hydrogenation of coumarin, or from its hydrogenation products, include dihydrocoumarin, octahydrocoumarin, chroman, hexahydrochroman and a substance believed to be a polymeric ester. Of especial interest is the conversion of δ -lactones and of a 1,5-glycol to cyclic ethers over Raney nickel.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF YENCHING UNIVERSITY]

Ephedrine. III. Di-(α -hydroxyl- β -methylaminopropyl)-benzenes

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Although a large number of derivatives and homologs of ephedrine have been reported by numerous investigators, we can find no record of such derivatives with two α -hydroxyl- β -methylaminopropyl side chains. This paper reports the preparation of the meta and para compounds of this type. These compounds were prepared from the 1,3- and 1,4-dipropionylbenzenes, respectively, which we made from the corresponding phthalyl chlorides by modifications of Mixin's¹ method. According to this method the phthalyl chlorides were first converted into the diethyl-diamides by treatment with diethylamine. These diethyl acid amides were then treated with ethylmagnesium bromide, which converted them into the desired dipropionyl compounds. In the first step Mixin employed ether as a solvent with the para compound but used benzene with the meta compound. The substitution of ether for the benzene in the case of the meta compound resulted in better yields and much greater ease in purification of the product. Mixin reports a yield of 25–30% in the second step from the Grignard reaction when he refluxed for four hours. We obtained yields of 35–40% by refluxing for nine hours.

The dipropionylbenzenes were next treated with bromine, which converted them into two new derivatives: 1,3- and 1,4-di-(α -bromopropionyl)-benzenes. When the bromo compounds were

treated with methylamine they were converted into the corresponding di-(α -methylaminopropionyl)-benzenes which also have not been described previously. These amino compounds were then reduced by hydrogen in the presence of platinum to give the desired new ephedrine. The last three reactions have been employed in the preparation of the more normal types of ephedrine homologs by Späth and Göhring,² Hyde, Browning and Adams,³ Wilson and Sun⁴ and others.

The free base of the new para ephedrine was a thick oil but that of the meta compound was an amorphous solid. The salts of the para compound crystallized well and had high melting points, while the hydrochloride, sulfate, oxalate, and phosphate of the meta derivative were thick liquids, but the picrate was a somewhat gummy amorphous solid. This agrees with Koller's⁵ finding, that salts of *p*-methoxyephedrine were crystalline and had melting points while the salts of *m*-methoxy-*p*-hydroxyephedrine were liquids. These compounds contain four asymmetrical carbons and their resolution into their optical isomers would be an interesting problem.

Experimental Part

Preparation of 1,4-Di-(α -bromopropionyl)-benzene.—8.41 g. of bromine was added gradually to 5 g. of 1,4-

(2) Späth and Göhring, *Monatsh.*, **41**, 319 (1920).

(3) Hyde, Browning and Adams, *THIS JOURNAL*, **50**, 2287 (1928).

(4) Wilson and Sun, *J. Chinese Chem. Soc.*, **2**, 243 (1934).

(5) Koller, *Monatsh.*, **47**, 397 (1926).

(1) Mixin, *Ann. Chim.*, **9**, 55 (1928).

dipropionylbenzene dissolved in 100 cc. of glacial acetic acid while the solution was heated on the water-bath under a reflux condenser. After the hydrogen bromide was nearly all expelled, the solution was cooled in an ice-bath. The bromo compound separated in colorless plates, which were recrystallized from alcohol, yield 95%, m. p. 109–110°. The compound is insoluble in water, moderately soluble in alcohol and very soluble in benzene and ether.

Anal. Calcd. for $C_{12}H_{12}O_2Br_2$: Br, 45.93. Found: Br, 45.97.

Preparation of 1,4-Di-(α -methylaminopropionyl)-benzene Hydrogen Chloride.—Seven grams of the 1,4-di-(α -bromopropionyl)-benzene dissolved in 200 cc. of benzene was added drop by drop to 3 g. of methylamine in 200 cc. of benzene. The reaction mixture was allowed to stand at room temperature for one hundred hours. Crystals of methylamine hydrobromide separated and were filtered off. A portion of the benzene and the excess of the methylamine were removed by distillation. The residual solution was then treated with a current of dry hydrogen chloride at room temperature. The 1,4-di-(α -methylaminopropionyl)-benzene hydrochloride which separated out was recrystallized from methyl alcohol and ether to give fine colorless plates, which did not melt but decomposed above 320°. The product is slightly soluble in ether, moderately soluble in alcohol and very soluble in water. The yield was 3 g. or 62%.

Anal. Calcd. for $C_{14}H_{22}N_2O_2Cl_2$: C, 52.32; H, 6.91; Cl, 22.08. Found: C, 52.50; H, 6.70; Cl, 21.64.

Preparation of 1,4-Di-(α -hydroxyl- β -methylaminopropyl)-benzene Hydrochloride.—Two grams of the 1,4-di-(α -methylaminopropionyl)-benzene hydrochloride dissolved in 100 cc. of 95% alcohol was reduced by hydrogen in the presence of platinum catalyst. The catalyst was removed by filtration and the solution concentrated by evaporation of a portion of the ethyl alcohol. Upon addition of ether, the new compound separated in a yield of 1.8 g. On recrystallization from methyl alcohol and ether it formed rosetts, m. p. 285–287°. The product was insoluble in benzene and ether, moderately soluble in alcohol and very soluble in water.

Anal. Calcd. for $C_{14}H_{26}N_2O_2Cl_2$: C, 51.67; H, 8.06. Found: C, 51.65; H, 8.03.

Preparation of the Free Base.—It was difficult to separate and purify the free base when it was set free from the hydrochloride by addition of potassium hydroxide. On the other hand, the free base of the corresponding ketone was easily obtained by the same treatment and

gave the corresponding ephedrine on catalytic reduction. Both bases were slightly brownish, somewhat gummy amorphous substances which decomposed on heating. The sulfate (decomposed above 320°), mandelate (m. p. 214°), and tartrate (m. p. 167–168°), of the ephedrine were prepared easily by treating an alcoholic solution of the base with an alcoholic solution of the corresponding acids. They were recrystallized from mixtures of alcohol and ether. All were white nicely crystallized products.

Preparation of 1,3-Di-(α -hydroxyl- β -methylaminopropionyl)-benzene Hydrochloride.—This compound was prepared from the corresponding 1,3-dipropionylbenzene by an analogous series of reactions. It was found more satisfactory to substitute carbon tetrachloride as a solvent during the bromination of the dipropionyl compound. The bromo compound, the hydrochloride of the amino ketone and the hydrochloride of the ephedrine were all liquids which did not solidify even at -20° . The solubilities were very similar to those of the corresponding 1,4-derivatives.

Anal. Calcd. for $C_{14}H_{26}N_2O_2Cl_2$: C, 51.67; H, 8.06; Cl, 21.81. Found: C, 51.38; H, 7.61; Cl, 22.94.

The Free Base.—In this case the free base was prepared by treating a water solution of the hydrochloride of the ephedrine with potassium hydroxide. It proved to be an amorphous solid which decomposed on heating. This product is soluble in alcohol and benzene but insoluble in water. Treatment of saturated alcoholic solutions of the base with alcoholic oxalic, sulfuric and phosphoric acids gave only liquid products which did not solidify even at -20° . The picrate was an amorphous solid which decomposed on heating.

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Summary

1. Two new ephedrine homologs, 1,3- and 1,4-di-(α -hydroxyl- β -methylaminopropyl)-benzene, have been prepared.
2. Four new intermediate compounds were obtained: the 1,3- and 1,4-di-(α -bromopropionyl)-benzenes and the 1,3- and 1,4-di-(α -methylaminopropionyl)-benzenes.

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