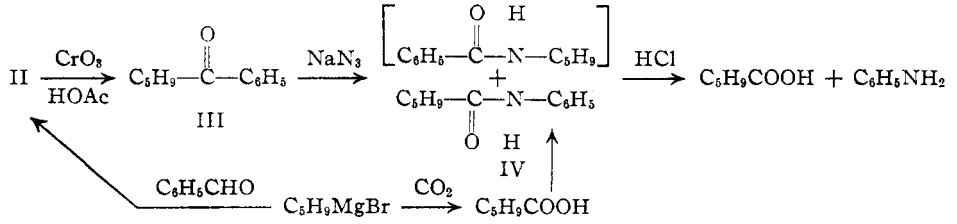
The Action of Nitrous Acid on 2-Phenylcyclohexylamine

BY DOROTHY V. NIGHTINGALE AND MILLARD MAIENTHAL[1,2]

2-Phenylcyclohexylamine (I) reacted with nitrous acid in acid solution to yield cyclopentylphenylcarbinol (II). There was little evidence for the presence of cyclohexanols or cyclohexenes among the reaction products.

The structure of II was established by the following series of reactions



The 2,4-dinitrophenylhydrazones of the ketone III obtained by the two procedures were identical. The aniline was identified by its benzoyl derivative and the cyclopentanecarboxylic acid was reconverted to its anilide. The low melting point and analyses of the amide obtained from the Schmidt reaction indicated that it was a mixture of the two isomeric amides, but it was not possible to isolate N-cyclopentylbenzanilide or its hydrolysis products from the mixture.

The product from the reaction of 2-phenyl-4,5-dimethylcyclohexylamine and nitrous acid distilled over a 30° range and appeared to be a mixture of unsaturated hydrocarbon, phenyldimethylcyclohexanol and/or dimethylcyclopentylphenylcarbinol. Carbon–hydrogen analyses of the carbinol fraction, a mushy solid, agreed with the formula $C_{14}H_{20}O$. Oxidation of this material yielded a ketone, $C_{14}H_{18}O$, but the amide obtained from this ketone would not crystallize and aniline was the only identifiable product obtained from its hydrolysis. Further work will be necessary to identify the reaction products.

Demjanow[3] has stated that ring contraction may take place when an alicyclic amine reacts with nitrous acid, but the only examples in the literature are the reactions of cyclobutylamine[4] and of the cyclobutylamines derived from truxillic and truxinic acids[5] to yield cyclopropane derivatives.

Anziani and Cornubert[6] obtained only *trans*-2-methylcyclohexanol from *trans*-2-methylcyclohexylamine, but the *cis* isomer yielded a small amount of *trans*-2-methylcyclohexanol along with another unidentified alcohol which they state is not cyclopentylmethylcarbinol.

Hückel[7] found no evidence of ring contraction in the reactions of nitrous acid with *trans*-2-methylcyclohexylamine, or with amines derived from some of the monocyclic terpenes, and he reported only cyclohexanol and cyclohexene from cyclohexylamine.

Experimental[8]

The 2-phenylcyclohexylamine and the 2-phenyl-4,5-dimethylcyclohexylamine were prepared by reduction of the corresponding nitro compounds.[9]

2-Phenylcyclohexylamine and Nitrous Acid.—A solution of 39 g. (0.22 mole) of 2-phenylcyclohexylamine in 150 cc. of water and 30 cc. of concd. hydrochloric acid was maintained at 0° and mechanically stirred while a concentrated aqueous solution of 25 g. of sodium nitrite was added slowly. After the addition of the sodium nitrite, the solution was allowed to stand twenty hours at room temperature with occasional stirring and then heated to 70° for one hour. The separated oil was extracted with ether and the ether extract was washed successively with 10% hydrochloric acid, 10% sodium carbonate and finally with water. The ether solution was dried over Drierite and distilled; yield of II, 25 g. (65%); b. p. 100–110 (5 mm.); $n^{20}D$ 1.5425. *Anal.* Calcd. for $C_{12}H_{16}O$: C, 81.78; H, 9.15. Found: C, 81.78; H, 9.23.

Reduction of Cyclopentylphenylcarbinol.—A solution of II (9.7 g.) in 50 cc. of absolute ethyl alcohol and 3 g. of copper–chromium oxide catalyst were placed in the copper liner of the conventional high pressure reduction equipment and reduced with hydrogen at 185° and 230 atm. After removal of the catalyst and solvent, the cyclopentylphenylmethane distilled at 70–72° (5 mm.); $n^{20}D$ 1.5200; reported $n^{18}D$ 1.5206.[10]

Oxidation of II.—To a mechanically stirred solution of 15 g. (0.085 mole) of the cyclopentylphenylcarbinol dissolved in 25 cc. of glacial acetic acid was added dropwise a solution of 7 g. of chromic oxide in 25 cc. of 80% acetic acid at such a rate that the temperature did not rise above 50°. After standing 24 hours at room temperature the reaction mixture was poured into 125 cc. of water and extracted with benzene. The benzene extract was washed with dilute sodium bicarbonate solution and then with water, dried over Drierite and distilled; yield of III 9.5 g. (64%); b. p. 105–110° (5 mm.). The ketone was purified by means of Girard "T" reagent; b. p. 103–105° (5 mm.); $n^{20}D$ 1.5452. *Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.65; H, 8.27. The 2,4-dinitrophenylhydrazone of the cyclopentylphenyl ketone melted at 144.5–145.5°. *Anal.* Calcd. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 60.78; H, 4.79.

The Schmidt Reaction.—A solution of 3 g. of cyclopentyl phenyl ketone III and 25 g. of chloroacetic acid was heated to 60° and 1.5 g. of sodium azide was added at once, while the solution was cooled externally with ice to prevent the temperature from rising above 60°. The

(1) Abstract of a portion of the Ph.D. dissertation of Millard Maienthal, June, 1949. Presented in part at the Philadelphia meeting of the American Chemical Society, April, 1950.

(2) Gregory Fellow, 1948–1949.

(3) Demjanow, *Uspekhi Khimii* (*U. S. S. R.*), **3**, 493 (1934); *C. A.*, **29**, 458 (1935).

(4) Demjanow, *Ber.*, **40**, 4961 (1907).

(5) Stoermer, Scheneck and Panesgrau, *ibid.*, **60B**, 2566 (1927).

(6) Anziani and Cornubert, *Compt. rend.*, **221**, 6059 (1945).

(7) Hückel, *Ann.*, **533**, 9 (1937); Hückel and Wilip, *J. prakt. Chem.*, **158**, 21 (1941).

(8) The carbon and hydrogen analyses were performed by R. A. Carpenter and J. S. Finney.

(9) Nightingale and Tweedie, THIS JOURNAL, **66**, 1960 (1944).

(10) Zelinsky and Titz, *Ber.*, **64B**, 183 (1931).

solution was stirred at intervals and maintained at 60–70° for six hours, then poured into iced water. The mixture was extracted with benzene and the benzene extract washed with 10% hydrochloric acid, 10% sodium hydroxide, and finally with water. After removal of the benzene, the solid residue was recrystallized from aqueous alcohol to yield an amide which melted at 132–133°, the analytical sample. Other samples of this amide melted at 135–137° and 139–142°. *Anal.* Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99. Found: C, 75.98; H, 8.27. The amide was probably a mixture of the anilide of cyclopentanecarboxylic acid (IV), m. p. 159–160°,[11] and N-cyclopentylbenzanilide, m. p. 157–158°.[12]

The amide was hydrolyzed with alcoholic hydrochloric acid to yield finally aniline and cyclopentanecarboxylic acid. The aniline was identified by its benzoyl derivative, m. p. 163.5–164.5° and mixed m. p. with an authentic sample of benzanilide 162.5–163.5°. The cyclopentanecarboxylic acid was converted to its anilide IV, m. p. 159–161°; mixed m. p. with an authentic sample of cyclopentanecarboxylic acid anilide, 161–162.5°.

Cyclopentanecarboxylic acid was synthesized from cyclopentylmagnesium bromide by carbonation and converted to the anilide IV, m. p. 162.5–163.5°, literature 159–160°.[11]

Synthesis of Cyclopentylphenylcarbinol II, and Cyclopentylphenyl Ketone III.—The carbinol was synthesized from 0.7 mole of benzaldehyde and 0.7 mole of cyclopentylmagnesium bromide[13]; yield 50 g. (40%); b. p. 110–112° (5 mm.); $n^{20}D$ 1.5412. *Anal.* Calcd. for $C_{12}H_{16}O$: C, 81.78; H, 9.15. Found: C, 81.80; H, 9.45.

The carbinol II was oxidized to cyclopentyl phenyl ketone III as described above; b. p. 100–108° (5 mm.); $n^{20}D$ 1.5422. The 2,4-dinitrophenylhydrazone melted at 144–144.5°. A mixture of this 2,4-dinitrophenylhydrazone and that of the ketone derived from the 2-phenylcyclohexylamine reaction melted at 144–145°.

(11) Haworth and Perkin, *J. Chem. Soc.*, **65**, 100 (1894).

(12) Markownikow and Kaschirin, *Ber.*, **30**, 975 (1897).

(13) Edwards and Reid (THIS JOURNAL, **53**, 3234 (1930)) reported a synthesis of cyclopentylphenylcarbinol from cyclopentylmagnesium chloride and benzaldehyde in 7% yield. They give the boiling point as 129–131° (5 mm.) but state that their product was rather impure as indicated by their analyses.

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Synthesis of α-D-Glucose-1-phosphate and α-D-Galactose-1-phosphate

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Until recently, the only method of synthesis of α-aldose-1-phosphates was the one devised by Cori, Colowick and Cori.[2,3] According to their procedure, an α-acetobromo-aldose is treated with trisilver phosphate. The condensation product, which seems to be composed mainly of a tertiary ester, is partially hydrolyzed with acid in order to remove two sugar residues, and then deacetylated. The over-all yield is poor because the reaction involves the loss of two-thirds of the starting sugar.

In the synthesis of α-D-glucose-1,6-diphosphate,[4] another procedure has been successfully used. It depends upon treating an α-acetobromo-aldose with silver diphenylphosphate. The phenyl groups are then removed from the condensation product by catalytic hydrogenation and the acetyl groups by alkali. Thus, an aldose-1-phosphate is formed which, in the case of glucose-1,6-diphosphate, is mainly the α-form.

The application of this new method to the synthesis of two biochemically important sugar phosphates, glucose-1-phosphate and galactose-1-phosphate, is described here. In these cases, again, the naturally occurring α-forms were obtained as the principal reaction products. It has already been pointed out[4] that silver diphenylphosphate differs markedly from other monosilver phosphate derivatives, in that it condenses with α-acetobromo sugars without inversion, while silver dibenzylphosphate[5] and "monosilver phosphate"[6] condense chiefly with inversion. In this work α-D-glucose-1-phosphate and α-D-galactose-1-phosphate were obtained as crystalline potassium salts, in 37% and 44% over-all yields, respectively. The best reported yields obtained by the trisilver phosphate procedure are one-fourth to one-sixth as large.[3,7]

Another method of preparing α-aldose-1-phosphates was also investigated. β-D-glucose-2,3,4,6-tetraacetate was dissolved in pyridine and left at room temperature. The final rotation indicated the presence of an equilibrium mixture containing about 20% of β- and 80% of α-D-glucose-2,3,4,6-tetraacetate. This solution was then treated with diphenyl chlorophosphonate. After the removal of the phenyl groups by catalytic hydrogenation and deacetylation with alkali, α-D-glucose-1-phosphate was isolated as the crystalline potassium salt. However, the over-all yield (10%) was much lower than by the first new procedure.

Grateful acknowledgment is expressed to Prof. C. F. Cori for his interest in this work.

Experimental

Barium α-D-Glucose-1-phosphate and Barium α-D-Galactose-1-phosphate.—A solution of 0.6 g. (0.00146 mole) of α-acetobromoglucose or of α-acetobromogalactose was prepared in 2 ml. of dry benzene. After the addition of 0.52 g. (0.00146 mole) of dry, finely powdered silver diphenylphosphate,[4] the mixture was refluxed for half an hour with exclusion of moisture. Then 0.25 g. of silver diphenylphosphate was added and the mixture was refluxed again for half an hour. After centrifugation and thorough washing of the silver salts with dry benzene, the solvent was evaporated under reduced pressure. The residue was dried *in vacuo*, and then dissolved in 8 ml. of absolute ethanol. The filtered solution was exhaustively hydrogenated at room temperature and atmospheric pressure in the presence of 100 mg. of platinic oxide.

For the deacetylation of the glucose derivative, 1 *M* sodium hydroxide was added dropwise until a permanent pink color was obtained with phenolphthalein. However, the deacetylation of the galactose derivative had to be carried out under more drastic conditions: following the

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(2) (a) C. F. Cori, S. P. Colowick and G. T. Cori, *J. Biol. Chem.*, **121**, 465 (1937); (b) S. P. Colowick, *J. Biol. Chem.*, **124**, 557 (1938).

(3) M. E. Krahl and C. F. Cori in "Biochemical Preparations," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1949.

(4) T. Posternak, *J. Biol. Chem.*, **180**, 1269 (1949).

(5) M. L. Wolfrom, C. S. Smith, D. E. Pletcher and A. E. Brown, THIS JOURNAL, **64**, 23 (1942).

(6) F. J. Reithel, *ibid.*, **67**, 1056 (1945).

(7) H. W. Kosterlitz, *Biochem. J.*, **33**, 1087 (1939).