Reduction Studies on 3,4-Dihydroxyphenylglyoxylohydroxamyl Chlorides and Related Compounds

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The preparation of four new phenylglyoxylohydroxamamides is described; however, only two of these products are fully characterized. The reduction of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride and N-α-methylbenzylphenylglyoxylohydroxamamide with platinum-palladium catalyst under low pressure has been studied and conclusions drawn from chemical, physical, and analytical data.

In 1951, LaRocca, *et al.* (1), were able to reduce successfully phenylglyoxylohydroxamyl chloride to phenethanolamine by utilizing a mixed palladium-platinum catalyst. In addition, they prepared and reduced several arylglyoxylohydroxamamides. Efforts to prepare norepinephrine, either by reduction of the corresponding 3,4-dihydroxyphenylgloxylohydroxamyl chloride or by 3,4-dihydroxyphenylglyoxylohydroxamamide were unsuccessful, since the reduction products could not be identified. The purpose of this investigation is to study these reductions in an attempt to clarify the reaction.

EXPERIMENTAL

Low pressure (approx. 4 Atm.) and room temperature were used for all reductions. These were carried out in a Parr series 3910 hydrogenation apparatus. The platinum oxide used for the preparation of the mixed catalyst itself was prepared from platinum chloride by fusion with potassium nitrate as described in Reference 2. The mixed catalyst used in all reductions was composed of: 10.00 Gm. activated charcoal, 1.00 Gm. palladium chloride, 0.15 Gm. platinum oxide.

The catalyst was prepared by suspending these materials in 100 ml. of 1 *N* sodium acetate solution and shaking under 1 atmosphere of hydrogen until hydrogen uptake ceased. The catalyst was then filtered off and washed with several portions of distilled water, followed by ethyl alcohol. Attempts to dry the catalyst by suction usually resulted in spontaneous ignition of the catalyst so it was used while still damp.

Reduction of 3,4-Dihydroxyphenylglyoxylohydroxamyl Chloride.—The reduction of 4.27 Gm. (0.02 mole) of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride was carried out by shaking (under 4 Atm. of hydrogen) an acidified hydroalcoholic solution (95 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid) of the compound with the mixed catalyst described above.

The first mole of hydrogen was absorbed in 2 minutes, the second in 20 minutes, the third in 3 hours, and the fourth in 6 hours. From the reduction mixture, 2.9 Gm. (77.5% yield based on 3,4-dihydroxyphenethylamine hydrochloride) of a colorless solid was obtained. Repeated recrystallizations from hot absolute alcohol and benzene gave colorless plates which melted at 243°dec. The melting point of norephinephrine hydrochloride is 141°. This reduction was repeated 10 times with similar results. The reduction product was soluble in water, slightly soluble in alcohol, and insoluble in benzene and ether. It gave an emerald green color with ferric chloride solution, indicating an *o*-dihydroxyphenyl nucleus and (with aqueous silver nitrate) a precipitate of silver chloride which is quickly reduced to free silver. It is very susceptible to oxidation in alkaline solution, first giving a rose colored solution which darkens on standing.

Anal.—Found: C, 50.99 and 51.00; H, 6.45 and 6.45; Cl, 18.78 and 18.78; N, 7.15 and 7.24.[1] The best emprical formula obtained from this information is $C_8H_{12}ClNO_2$.

A quantitative determination of acetylatable groups by the method described by Siggia (3) indicated the presence of two such groups. However, the development of a rose color in alkaline solution indicated that at least one functional group had not been acetylated.

The infrared spectrum of the reduction product was determined on a 500-mg. potassium bromide disk containing 50 mg. of sample. This spectrum was determined on a Perkin Elmer model 112, double pass, single beam spectrophotometer. The interpretation of the spectrum was made from an energy transmission record. The presence of a NH_3^+ group was indicated by bands at 3.29, 6.18, and 6.78 μ; a hydroxy (or secondary amine) group gave a strong band at 3.02 μ. Bands at 6.24, 6.32, 6.56, 7.90, 9.05, 9.26, 10.38, 11.43, and 12.27 μ confirm the presence of a 1, 2, 4-trisubstituted benzene ring. Strong bands at 7.78 and either 7.46 or 7.58 μ show the presence of one or more phenolic hydroxyl groups.[2] The above data coupled with the ease of reducibility of hydroxyl groups on carbon atoms adjacent to the benzene ring seem to establish fairly conclusively that the reduction product is 3,4-dihydroxyphenethylamine hydrochloride. This is an agreement with the best empirical formula as determined from the analytical data. The injection of 1.0 ml. of a 1/200 *N* solution of the reduction product into a dog under pentobarbital anesthesia

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[1] All microanalyses by Oakwold Laboratories, Alexandria, Va.

[2] The infrared spectrum of this compound was determined and interpreted by Dr. George E. Philbrook University of Georgia Chemistry Department, Athens.

TABLE I.—SUMMARY OF ARYLGLYOXYLOHYDROXAMAMIDES

$C_6H_5 \cdot CO \cdot C(NOH) \cdot NR'R''$ R′	R″	M. p.[a]	Description	Yield, %	Nitrogen—Calcd.	Nitrogen—Found
Cyclohexyl	H	...	Brown oil	98.3	...	...
Ethyl	Ethyl	...	Yellow oil	119.0	...	...
						10.78
p-Methylphenyl	H	154°	Tan needles	74.0	11.01	11.03
						9.59
α-Methylbenzyl	H	128°	Yellow plates	88.0	10.44	9.67

[a] All melting points are uncorrected.

produced a pressor response similar to that obtained by Barger and Dale (4) with an equal dose of 3,4-dihydroxyphenethylamine hydrochloride. The melting points of the reduction product and 3,4-dihydroxyphenethylamine hydrochloride are in close agreement: literature value for 3,4-dihydroxyphenethylamine hydrochloride 240–241° dec. (5), reduction product 243° dec. The picrate of 3,4-dihydroxyphenethylamine is reported to melt at 189° (5); the picrate of the reduction product melts at 190–193°. In all instances reduction of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride gave a small amount of a yellow oil in addition to the colorless crystalline 3,4-dihydroxyphenethylamine hydrochloride. This oil was found to be extremely hygroscopic, and it underwent color change in alkaline solution. Upon addition of a base, the solution became cherry red in color and changed to yellow when an acid was added. These properties were not possessed by either 3,4-dihydroxyphenylglyoxylohydroxamyl chloride or the 3,4-dihydroxyphenethylamine hydrochloride produced in the reduction reaction.

Preparation of Arylglyoxylohydroxamamides.—The arylglyoxylohydroxamamides were prepared by essentially the same method reported by LaRocca, *et al.* (1). As was expected, the aromatic amides were found to be crystalline solids, and the aliphatic amides to be resinous solids or oils. Attempts to prepare the hydrochlorides of the aliphatic amides failed to give crystalline solids. (See Table I.)

Reduction of N-α-methylbenzylphenylglyoxylohydroxamamide.—In a reduction solution identical with that previously described, 5.26 Gm. (0.02 mole) of N-α-methylbenzylphenylglyoxylohydroxamamide was shaken under 4 Atm. of hydrogen for 40 hours. During this time 3.5 moles of hydrogen were taken up. Removal of the catalyst and evaporation of the solvent under reduced pressure gave 4.5 Gm. of a yellowish white solid which melted at 154°. Repeated recrystallizations gave colorless plates which melted at 169–171.°

Anal.—Found: Cl, 11.73 and 11.56; N, 9.18 and 9.17. The best empirical formula which can be assigned from the analytical data is $C_{16}H_{19}Cl\ N_2O_2$ which indicates the reduction of the ketone group.

An infrared spectrum was determined on a Nujol mul of the compound. This spectrum showed a band at 3.02 μ (which is characteristic of a hydroxyl or secondary amino group), a strong band at 6 μ (indicative of a C=O or C=N), and bands at 6.29, 6.32, and 6.56 μ (indicative of a phenyl group).[3] These data indicate that the oximino alcohol is the product of the reduction. Attempts to reduce this compound further by the above procedure were unsuccessful.

[3] The infrared spectrum of this compound was determined and interpreted by the Department of Research in Chemical Physics, Mellon Institute of Industrial Research, Pittsburgh, Pa.

DISCUSSION AND CONCLUSIONS

The successful reduction of phenyl-, *p*-xynyl-, *p*-methylphenyl-, and probably 3,4-dihydroxyphenyl, glyoxylohydroxamyl chlorides to the corresponding arylethanolamines by the use of hydrogen under high pressure with a platinum-palladium catalyst has been reported (1). Attempts to reduce 3,4-dihydroxyphenylglyoxylohydroxamyl chloride with the same type catalyst under low pressure failed to give the corresponding phenethanolamine. The pharmacological, chemical, analytical, and physical data indicate that the reduction product is 3,4-dihydroxyphenethylamine. The same type data for the reduction product of N-α-methylbenzylphenylglyoxylohydroxamamide strongly indicates the formation of the corresponding oximino alcohol. These data indicate that, in the reduction of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride, the oxygen atom on the carbon adjacent to the aromatic nucleus is removed by the reduction. In the case of phenyl-, *p*-xenyl-, *p*-methyl- phenylglyoxylohyoroxamyl chlorides and N-α-methylbenzylphenylglyoxylohydroxamamide it appears that this oxygen undergoes normal reduction to the corresponding alcoholic group. The most obvious explanation of this phenomena is that certain types of substituents in the aromatic nucleus (at least 3,4-dihydroxy substitution) tend to increase the susceptibility of the oxygen on the α carbon to over-reduction.

Hartung, *et al.* (6), report the reduction of α-isonitrosopropiophenone with palladium-charcoal catalyst proceeds to the amino-ketone first and then to the amino alcohol. All data acquired in this study indicate that, with a platinum-palladium-charcoal catalyst, reduction of the ketone group precedes the reduction of the oximino group. This conclusion is strengthened by the typical oxime color changes in acid and alkaline solution exhibited by the yellow oil by-product obtained from reduction of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride.

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