Amino Alcohols. XVIII. Reduction Studies on Arylglyoxylohydroxamyl Chlorides and Amides*

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A method for the preparation of arylglyoxylohydroxamamides from aliphatic and aromatic amines is described. The reaction has been applied to two aromatic amines, eight aliphatic amines, and to ammonia. Reduction studies of the compounds prepared are reported.

In 1942 Levin and Hartung (1) described the synthesis of arylglyoxylohydroxamyl chlorides, Ar—CO—C—(:NOH)—Cl. They reported a successful reduction of the phenyl compound to phenylethanolamine, C_6H_5—CHOH—CH_2NH_2, but indicated that the reduction did not proceed normally as desired. A further study of these reductions now shows that with palladium alone it is extremely difficult, and next to impossible, to reduce these hypothetically attractive intermediates to the desired corresponding arylethanolamines. Usually two moles of hydrogen are taken up quite rapidly; the third enters much slower and, as mentioned, the fourth enters rarely, even if the catalyst is fortified by the addition of more palladium.

It was anticipated, in view of Rosenmund's procedure for reducing acid chlorides to aldehydes, that the chlorine atom should be easily removed, resulting (for phenylglyoxylohydroxamyl chloride) in the well-known oximino ketone, C_6H_5—CO—CH:NOH, which may be converted, via the amino ketone, into phenylethanolamine (2). The third molecule of hydrogen, then, would be expected to form phenacylamine. In agreement with these expectations is the finding (1) that the partially reduced intermediate treated with alkali forms diphenylpyrazine; this suggests the presence of the amino ketone (2). The yield of crude diphenylpyrazine is good, but with a low melting point, and much of it is lost in purifying to maximum melting point. In any case, the ready absorption of two molecules of hydrogen and the further absorption of a third molecule would suggest that the reduction proceeds in stages, hence one would expect to isolate in good yields products which are intermediate between the hydroxamyl chloride and the arylalkanolamine. However, such is not the case. When the products were isolated at the several stages of hydrogenation, they were not homogeneous, and during the attempts to isolate pure materials, most of the product was lost. Furthermore, any products which could be isolated did not prove to be any of the intermediate stages which might be constructed, and they resisted further hydrogenation. This is even more surprising now that it has been found possible to obtain good yields of the corresponding amino alcohols from the starting materials.

Several other approaches were tried, namely: conversion of the hydroxamyl chloride into corresponding amides, Ar—CO—Cl(:NOH)—NRR, and a modification of the catalyst. This latter proved effective; several arylethanolamines have been prepared by this adaptation, described below, and it is believed that others will likewise be obtainable where the glyoxylohydroxamyl halide is available. Meanwhile the work via the amides had progressed to the point where these reduction studies also deserve mention.

Levin and Hartung (1) found that the arylglyoxylohydroxamyl chlorides behave as acid chlorides, and may be converted into amides as expected. For the present study a series of amides was prepared, for which the data are summarized in Table I. Several of these were then subjected to catalytic hydrogenation. Any one or a mixture of three possible reduction products might be expected (see compounds I, II, and III). Compound III was not expected since compounds in which two amino groups are attached to a single carbon are but little known; structurally they are ammono analogs of the hydrated form of an aldehyde, and would therefore be expected to be amenable to further reduction, forming in this instance I or II, or both. In the reduction of the simple amide C_6H_5—CO—C(:NOH)—NH_2 four moles of hydrogen was absorbed and the product was phenylethanolamine. But with the N-substituted amides, only three moles of hydrogen was taken up; analytical data for the hydrochloride of the reduction product from phenylglyoxylohydroxanilide indicate the formula $C_{14}H_{16}N_2O \cdot 2HCl$; analysis for the salt of

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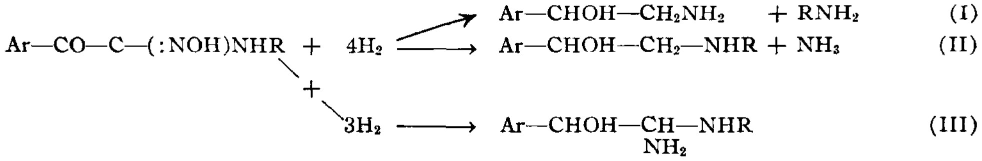

$$\begin{array}{llr} \text{Ar—CO—C—(:NOH)NHR} + 4\text{H}_2 & \longrightarrow \text{Ar—CHOH—CH}_2\text{NH}_2 + \text{RNH}_2 & \text{(I)} \\ & \longrightarrow \text{Ar—CHOH—CH}_2\text{—NHR} + \text{NH}_3 & \text{(II)} \\ \quad + 3\text{H}_2 & \longrightarrow \text{Ar—CHOH—}\underset{\text{NH}_2}{\text{CH}}\text{—NHR} & \text{(III)} \end{array}$$

the product from the N-butyl analog suggests the formula $C_{12}H_{19}N_2O \cdot 2HCl$. Whether these have structures corresponding to III has not yet been established, and there is no explanation for the formation, apparently, of a dihydrochloride from the anilide and a monohydrochloride from the N-butyl intermediate.

As indicated, it is now found possible to reduce by catalytic methods the arylglyoxylohydroxamyl chlorides directly according to the equation Ar—CO—C(:NOH)—Cl + $4H_2$ → Ar—CHOH—$CH_2NH_2 \cdot HCl$ + H_2O. The catalyst was modified by the addition of platinic oxide, and the hydrogenation was carried out at pressures varying from 10 to 20 atmospheres. Repeated experiments with phenylglyoxylohydroxamyl chloride showed that slightly more than the calculated (0.003 to 0.005 mole for 0.02 mole substrate) for complete reduction was absorbed in approximately ninety minutes. The product was phenylethanolamine. In a similar manner, the *p*-methyl- and the *p*-phenyl-phenylethanolamines were obtained from the corresponding hydroxamyl chlorides.

EXPERIMENTAL

The synthesis of arylglyoxylohydroxamyl chlorides has already been described. The amides were prepared as follows:

Separate solutions in anhydrous ether were prepared of two moles of amine and one mole of hydroxamyl chloride; the solution of the amine was added dropwise with vigorous stirring to the solution of the chloride. Reaction occurred instantaneously, as noted by the precipitation of the amine hydrochloride. The hydrochloride was filtered off, and the ethereal solution evaporated to dryness. The aromatic hydroxamamides were found to be solid. However, those formed with aliphatic amines were semisolid or oily in nature, and all attempts to crystallize them were unsuccessful. Phenylglyoxylohydroxamamide was prepared by bubbling ammonia gas (generated by heating concentrated ammonium hydroxide) through an ethereal solution of the chloride.

Hydrochlorides of the phenylglyoxylohydroxamamides were prepared by spraying an ethereal solution of the hydroxamamide with hydrogen chloride. The hydrochlorides were found to be white powders having sharp melting points and were used to identify the respective hydroxamamides. These salts were found to be fairly unstable and, on treatment with water, hydrolyzed readily to give the original hydroxamamide and hydrochloric acid. Table I summarizes the arylglyoxylohydroxamamides and their hydrochlorides, which were prepared by the procedures described.

The palladium chloride and platinic oxide were obtained from J. Bishop and Company. The palladium charcoal catalyst was prepared by essentially the same method as described by Hartung (3). To this catalyst, 0.150 Gm. of platinum oxide was added so that final composition of the catalyst

TABLE I.—SUMMARY OF ARYLGLYOXYLOHYDROXAMAMIDES

Ar·CO·C(:NOH)NHR						Nitrogen, %	
Ar—	R—	Melting Point, °	Melting Point of Hydrochloride, °	Characteristics	Yield, %	Calcd.	Found[a]
Phenyl	Phenyl	142	123–124	Yellow flakes	62	11.60	11.69 11.57
Phenyl	*β*-Naphthyl	178–179	...	Yellow crystals	93	9.65	9.91 9.98
Phenyl	Hydrogen	129–131	...	Yellow prisms	56	17.08	17.23 17.15
Phenyl	Morpholino	98	...	Yellow flakes	2	11.96	12.20 12.08
Phenyl	Isopropyl	...	...	Semisolid	90		
Phenyl	*n*-Propyl	...	...	Semisolid	68		
Phenyl	Ethyl	...	...	Viscous oil	79		
Phenyl	Benzyl	...	...	Semisolid	82		
Phenyl	Methyl	...	132–133	Yellow oil	80	13.05[b]	13.53 13.79
Phenyl	*n*-Butyl	...	120–125	Viscous oil	85	10.99[b]	10.82 10.53
Phenyl	Heptyl	...	123–125	Yellow oil	70	9.39[b]	9.51 9.79
p-Methylphenyl	Phenyl	163–164[c]	...	Colorless needles	95		
p-Methylphenyl	Methyl	124	...	Colorless needles	75		

[a] Microanalyses by Oakwold Laboratories, Alexandria, Va.
[b] Assayed as hydrochloride.
[c] Agrees with value given in the literature.

was as follows: 10.0 Gm. palladium-Nuchar catalyst (3) and 0.150 Gm. platinum oxide.

The reductions were carried out under 10 to 20 atmospheres of hydrogen. The apparatus used was a steel reaction bomb, fitted with a pressure gauge and automatic shaking attachment of the type manufactured by the American Instrument Company.

In all the reductions performed the reaction solvent used was 95 ml. of 95% alcohol to which 5 ml. of concentrated hydrochloric acid had been added.[1]

The reduction products were isolated by removing the catalyst by filtration and evaporating the reduction mixture to dryness in a vacuum desiccator over P_2O_5.

Reduction of N-Phenylphenylglyoxylohydroxamamide.—From the reduction of 2.4 Gm. of N-phenylphenylglyoxylohydroxamamide, 2.2 Gm. of greenish crystals were obtained. The product was very hydroscopic and the highest melting point determined was 80–85°.

Anal.—Calcd. for $C_{14}H_{16}ON_2 \cdot 2HCl$: N, 9.35%. Found: N, 9.29% and 9.12%.

Reduction of N-Butylphenylglyoxylohydroxamamide.—From the reduction of 4 Gm. of N-butylphenylglyoxylohydroxamamide, 2.1 Gm. of white hydroscopic crystals, m. p. 140–145°, were obtained.

Anal.—Calcd. for $C_{12}H_{20}ON_2 \cdot HCl$: N, 11.49%. Found: N, 11.21% and 11.24%.

Reduction of Phenylglyoxylohydroxamamide.—Phenylethanolamine hydrochloride, (1.1 Gm.) m. p. 210–215° (decompd.) was obtained from the reduction of 3.3 Gm. of phenylglyoxylohydroxamamide.

Reduction of Phenylglyoxylohydroxamyl Chloride.—Colorless crystals, melting at 209–210°, were obtained from the reduction of phenylglyoxylohydroxamyl chloride. This melting point agrees with that given in the literature for phenylethanolamine hydrochloride (4). The compound is water-soluble, giving a positive chloride ion test with aqueous silver nitrate test solution. The picrate softens at 154°, melting at 158° (decompd.). The melting point of the picrate of phenylethanolamine is reported at 154° in the literature. The yields obtained in three reductions were 86, 91, and 85%.

Anal.—Calcd. for $C_8H_{11}ON \cdot HCl$: N, 8.07%. Found: N, 8.37% and 8.47%.

Reduction of *p*-Xenylglyoxylohydroxamyl Chloride.—From the reduction of 5.2 Gm. (0.02 mole) of the chloride, in which 4 moles of hydrogen were absorbed in five hours, 4.1 Gm. (84%) of *p*-xenylethanolamine (*p*-phenylphenylethanolamine) hydrochloride was obtained, m. p. 191–192°. The picrate of this product melts at 114–115°.

Anal.—Calcd. for $C_{14}H_{15}ON \cdot HCl$: Cl, 14.06; N, 5.64%. Found: Cl, 13.44, 13.53%; N, 5.73% and 5.69%.

An aqueous solution of the hydrochloride was made alkaline and extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and evaporated to dryness in a desiccator under vacuum. A white solid, m. p. 126–129°, was obtained.

Reduction of *p*-Methylphenylglyoxylohydroxamyl Chloride. — *p* - Methylphenylglyoxylohydroxamyl chloride was reduced to the corresponding ethanolamine, four moles of hydrogen being absorbed in two and one-half hours. A white compound was obtained, which on recrystallization from hot absolute alcohol gave colorless platelets. From 3.9 Gm. (0.02 mole) of the chloride, 2 Gm. (54%) of colorless platelets, m. p. 189–190°, was obtained. The picrate melts at 155°.

Anal.—Calcd. for $C_9H_{13}ON \cdot HCl$: N, 7.49%. Found: N, 7.82% and 7.98%.

SUMMARY

1. The formation of arylglyoxylohydroxamamides from aliphatic and aromatic amines is described; the reaction has been applied to two aromatic amines, eight aliphatic amines, and to ammonia.

2. The hydrochlorides of some of these hydroxamamides have been prepared and utilized in characterizing the corresponding hydroxamamides.

3. Reduction studies of arylglyoxylohydroxamamides were undertaken. It has been found that the simple amide $C_6H_5 \cdot CO \cdot C(:NOH)NH_2$ takes up the calculated four moles of hydrogen to form the expected phenylethanolamine. The substituted amides take up but three moles, and indications are that in the product both nitrogen atoms are still present.

4. Arylglyoxylohydroxamyl chlorides have been successfully reduced to the corresponding amino alcohols by using a mixed palladium-platinum catalyst.

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[1] All reductions carried out at the Naval Research Laboratory, Washington, D. C.