[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XI.[1] ARYLGLYOXYLOHYDROXAMYL CHLORIDES[2]

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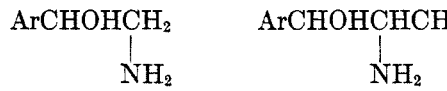
INTRODUCTION

In previous studies of the relationship between chemical structure and physiological activity of the primary amines belonging to the epinephrine-ephedrine series, it was shown that optimum circulatory activity is found in the arylethanolamines (I) and arylpropanolamines (II).



(I) (II)

Amino alcohols of both the ethane and propane derivatives may be readily obtained by the catalytic hydrogenation of the corresponding isonitroso ketones (1–4). The intermediary isonitrosopropiophenones are readily prepared by allowing the propiophenone in ether solution to react with an alkyl nitrite in the presence of hydrogen chloride,

The nitrosation reaction, which gives better than 70% yields in the case of propiophenone itself, may be employed in cases where the phenyl nucleus is substituted, even to the hydroxypropiophenones (3). Higher homologs of isonitrosopropiophenone may be prepared in a similar manner from higher alkyl aryl ketones, but unfortunately this is not true of the lower homolog, acetophenone. Consequently, it has been difficult to obtain as complete a series of arylethanolamines as has been possible in the case of the arylpropanolamines. This is regrettable, since a more complete pharmacological comparison of the amino alcohols of the corresponding ethane series is desirable. Available information on the favorable pressor activity of phenylethanolamine (5–7) and also that of norepinephrine (arterenol) (8–10)—the primary amine corresponding to that of epinephrine—indicates the desirability of a suitable general method which might be employed for the synthesis of amines of the entire arylethanolamine series.

[1] For Amino Alcohols, X, see *J. Am. Chem. Soc.*, **57**, 1091 (1935).

[2] This paper is constructed in part from a dissertation presented by Nathan Levin to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in June, 1941. A portion of this paper was presented before the Division of Organic Chemistry at the Baltimore meeting of the American Chemical Society, April, 1939.

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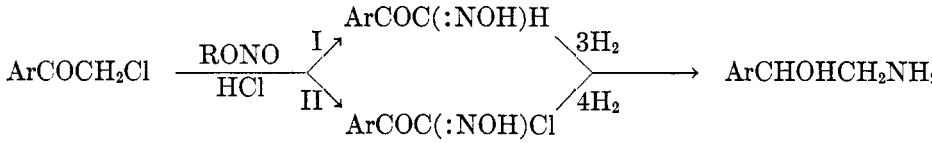
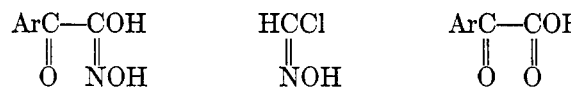
The chief objection to the use of isonitrosoacetophenones as intermediates in the synthesis of the phenylethanolamines is that these derivatives cannot be readily prepared. Thus, isonitrosoacetophenone, $C_6H_5COC(:NOH)H$, may be obtained in approximately 25% yields by allowing an absolute alcoholic solution of acetophenone, an alkyl nitrite and sodium alkoxide to stand in the cold for several days;[4] with acetophenone bearing unprotected phenolic hydroxyls, the reaction does not proceed at all. When nitrosation is carried out in the presence of hydrogen chloride, the yields of the isonitroso ketone are low or negligible (2, 11).

In quest for a procedure more broadly applicable or available for the preparation of intermediates that may readily be transformed into the corresponding arylethanolamines, the reaction between phenacyl chloride and alkyl nitrites was investigated. Nitrosation might proceed in one of two directions, either product being a potential intermediate for reduction to the arylethanolamine:



Results show that in each instance, compounds of type II, chloroisonitrosoacetophenones, are formed in excellent yields.

Structurally, these chloroisonitroso ketones form an interesting class of compounds; they are, strictly speaking, chlorides of keto-hydroximic acids of the type (III). Further, they may be considered either as aroyl derivatives of



(III) (IV) (V)

formhydroximic acid chloride (IV) or as the hydroximic acid chloride of arylglyoxylic acid (V). Accordingly, the compound, $C_6H_5COC(:NOH)Cl$, may be designated as benzoylformhydroxamyl chloride or phenylglyoxylohydroxamyl chloride,—either name is correct (12).

The first compound of this type was reported by Glutz (13), who, in 1870, treated chloroacetone with concentrated nitric acid and obtained methylglyoxylohydroxamyl chloride, $CH_3COC(:NOH)Cl$. Claisen (14) prepared the first arylglyoxylohydroxamyl chloride by saturating a cooled mixture of acetophenone and amyl nitrite with hydrogen chloride. By this method, there was obtained a small quantity of a colorless crystalline product, m.p. 133–134°, which, when heated above its melting point, decomposed with the liberation of hydrogen chloride; Claisen assumed that the reaction product was an addition compound of isonitrosoacetophenone and hydrogen chloride. Subsequently Claisen and Manasse (15) repeated the reaction and reported the isolation, in

[4] Results obtained in this laboratory. The higher yields reported by Edkins and Linnell, [*Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936)], could not be duplicated.

small amounts, of both chloroisonitrosoacetophenone and isonitrosoacetophenone. They explained the formation of these products on the basis of the following reactions,

$$RONO + HCl \longrightarrow ROH + NOCl$$

$$C_6H_5COCH_3 + NOCl \longrightarrow C_6H_5COC(:NOH)H + HCl$$

It was further indicated that any nitrous acid which might be liberated, could oxidize hydrogen chloride to "free" chlorine and this might also possibly account for the formation of the chloroisonitroso ketone (16).

Such chlorination has been successfully applied in the preparation of both phenyl- and *p*-methylphenyl-glyoxylohydroxamyl chlorides (16–18); extension of this method of synthesis is limited, however, in view of the difficulty encountered in preparing the necessary isonitrosoacetophenones themselves. Recently, Rheinboldt and Schmitz-Dumont (19) developed a process called "nitrosochlorination," which involves essentially the reaction of nitrosyl chloride with a methyl ketone,

$$RCOCH_3 \xrightarrow{NOCl} RCOC(:NOH)Cl$$

Except in the case of *tert.*-butyl methyl ketone, which formed yields of 70%, the reaction did not prove encouraging; *e.g.*, the phenyl- and *p*-tolyl- ketones gave yields of 24 and 32% respectively; the *p*-chlorophenyl ketone formed the isonitroso ketone but not the chloroisonitroso ketone.

In the present study, the nitrosation reaction was applied to phenacyl chloride and its derivatives in which the phenyl is substituted by various groups such as halogen, alkyl, alkoxyl, and hydroxyl. The yields are highly satisfactory and there is no reason to believe that the reaction is not generally applicable.

The arylglyoxylohydroxamyl chlorides dissolve in concentrated sulfuric acid with the formation of a yellow color. Heating with dilute sulfuric acid causes degradation to the corresponding benzoic acid. In cold, dilute aqueous sodium hydroxide, they dissolve slowly, forming a yellow solution; heating causes decomposition with the formation of the benzoic acid. With hydroxylamine, the arylglyoxylohydroxamyl chlorides may be converted to chloroglyoximes, ArC(:NOH)C(:NOH)Cl, and with aniline they form characteristic anilides of the general formula, $ArCOC(:NOH)NHC_6H_5$. With pyridine, all of the arylglyoxylohydroxamyl chlorides form a wine-red color with simultaneous liberation of heat; the color gradually deepens and after several minutes decomposition sets in; this characteristic color test is not obtained with oximes or other oximino ketones.

The reduction of arylglyoxylohydroxamyl chlorides to arylethanolamines is of particular interest. Suffice it to say for the present, phenylglyoxylohydroxamyl chloride has been reduced to phenylethanolamine (yields quantitative except for manipulative loss), according to the equation,

$$\underset{\parallel \atop NOH}{C_6H_5COCCl} + 4H_2 \xrightarrow[HCl]{Pd} \underset{| \atop NH_2\cdot HCl}{C_6H_5CHOHCH_2} + HOH$$

The first two molecules of hydrogen are taken up rapidly with the formation of a product characterized as an α-amino ketone, which on treating with aqueous ammonia gives 2,5-diphenylpyrazine; the third molecule generally is taken up more slowly, and the fourth enters with considerable difficulty. A more detailed description of this reduction procedure will be given later.

EXPERIMENTAL

Preparation of chloromethyl ketones. Phenacyl chloride and its various derivatives were prepared by either the Friedel-Crafts reaction or the Fries rearrangement from appropriate starting materials. The data are summarized in Table I.

3,4-Dihydroxyphenacyl chloride. This important intermediate has been prepared in varying yields (40–65%) by various modifications of the reaction between catechol, chloroacetic acid, and phosphorus oxychloride (20). The extensive study by Ott (20), which indicates that ketone formation is catalyzed by the presence of phosphorus oxychloride, suggested a further modification of the previously described procedures. In the course of

TABLE I

CHLOROMETHYL KETONES[a]

KETONE	M.P., °C	PER CENT YIELD
Phenacyl chloride	56–57	88.2
p-Methylphenacyl chloride	55–56	82
p-Phenylphenacyl chloride	124–126	84
p-Chlorophenacyl chloride	100–101	88.5
p-Methoxyphenacyl chloride	97–98	65
p-Hydroxyphenacyl chloride	147–148[b]	28.2
3,4-Dihydroxyphenacyl chloride	173[b]	60

[a] These ketones are described in Beilstein.

[b] Decomposes on heating.

this investigation it was found that yields of 60% of pure, colorless product may be consistently obtained by the following procedure: A mixture of 83.3 g. (0.4 mole) of phosphorus pentachloride and 42.5 g. (0.45 mole) of chloroacetic acid is allowed to react by refluxing in a boiling water-bath for three hours. The clear solution thus obtained is distilled and the portion coming over up to 115° is added to a suspension of 44.0 g. (0.4 mole) of catechol in 200 cc. of benzene (anhydrous). After refluxing on a water-bath for fifteen hours, the solvent is recovered by distillation, using slightly reduced pressure toward the end. The dark purple residue thus obtained is then dissolved in 400 cc. of boiling water; on cooling and with rapid stirring, the crude product crystallizes out. After standing overnight in the refrigerator, the precipitated material is filtered off and dried with suction; recrystallization from boiling water with the addition of 5.0 g. of Norit, gives 41.5 g. (60%) of colorless needles, decomposing at 173°.[5]

Nitrosation of chloromethyl ketones. The general procedure adopted for the preparation of arylglyoxylohydroxamyl chlorides is as follows: In a three-neck, round-bottom flask (of suitable size), provided with a sealed mechanical stirrer, a reflux condenser (connected to a gas-absorption trap), a delivery tube for hydrogen chloride, and a small dropping-funnel, is placed the chloromethyl ketone and ether (U.S.P.). The stirrer is set in motion, and after (complete or partial) solution of the ketone, anhydrous hydrogen chloride is intro-

[5] All melting points reported were taken with an Anschütz thermometer (entire stem immersed in bath).

duced into the reaction mixture at the rate of 2–3 bubbles per second, stirring and addition of hydrogen chloride being continued throughout the reaction. Then freshly-distilled alkyl nitrite (in slight molecular excess) is added from the dropping-funnel, in 0.5–1.0-cc. portions. After addition of the first portion, the reaction mixture becomes an orange-brown and after several minutes, light yellow in color; after this, a second portion of nitrite is added and a similar color change takes place, whereupon a third portion is added. The reaction mixture gradually warms up and the ether begins to reflux gently. After all of the nitrite is added (about thirty to forty minutes are usually required), stirring and addition of hydrogen chloride are continued for another fifteen minutes, after which the reaction mixture is allowed to stand for one to two hours, or overnight if more convenient. The reflux condenser is then inverted, stirring is resumed, and the solvent recovered by distillation from a bath maintained at 60–80°. When practically all of the solvent is removed, distillation is continued using slightly reduced pressure, until no further appearance of crystals is noted. The residue is then allowed to stand until dry in a vacuum desiccator over concentrated sulfuric acid, soda-lime, and anhydrous calcium chloride. The crude product is recrystallized from a suitable solvent.

This procedure may be employed for the nitrosation of the various ketones. Where the chloromethyl ketone is not readily soluble in ether, suspensions of the material nitrosate equally well; solution gradually takes place during the course of reaction since the products are, in general, more soluble than the ketones from which they are prepared. Any alkyl nitrite may be employed as nitrosating agent; in this reaction, isopropyl nitrite is preferred because it is a liquid, may be conveniently handled and moreover, the alcohol which it forms boils relatively low and hence may be removed with comparative ease.

Oximation. The chloroglyoximes are prepared by treating 0.02 mole of the arylglyoxylohydroxamyl chloride in 25 cc. of alcohol with a solution of 0.04 mole of hydroxylamine hydrochloride dissolved in 25 cc. of water. Sufficient alcohol is then added, drop by drop, until a clear solution results. After allowing the reaction mixture to stand for three to four days, crystals begin to precipitate out; after two weeks, the product is filtered off and dried with suction. The glyoximes prepared in this investigation are colorless, crystalline compounds, melting with decomposition.

Phenylglyoxylohydroxamyl chloride. Nitrosation of phenacyl chloride, 15.5 g. (0.1 mole), using 12.6 cc. (0.11 mole) of butyl nitrite in 100 cc. of ether, gives 15.7 g. (85.6%) of phenylglyoxylohydroxamyl chloride, after recrystallization from boiling carbon tetrachloride, m.p. 130–133°. A second recrystallization gives long, glistening colorless needles, m.p. 132–133°.

The chloroglyoxime, after recrystallization from hot isoamyl alcohol, decomposes at 186–187° (19).

p-*Methylphenylglyoxylohydroxamyl chloride.* From 50.6 g. (0.3 mole) of *p*-methylphenacyl chloride, 36.7 cc. (0.32 mole) of butyl nitrite in 200 cc. of ether, there is obtained, after recrystallization from hot carbon tetrachloride, 44.0 g. (74.2%) of chloroisonitroso ketone, m.p. 119–126°; a second recrystallization forms long, colorless needles, m.p. 126–128°.

Anal. Calc'd for $C_9H_8ClNO_2$: N, 7.10. Found: N, 6.88.

p-Tolyl chloroglyoxime, recrystallized from hot isoamyl alcohol, decomposes at 185–186°.

Anal. Calc'd for $C_9H_9ClN_2O_2$: N, 13.17. Found: N, 12.7.

p-*Xenylglyoxylohydroxamyl chloride.* *p*-Phenylphenacyl chloride is nitrosated by treating a rapidly-stirred suspension of 23.1 g. (0.1 mole) of ketone in 300 cc. of ether with 11.6 cc. (0.11 mole) of isopropyl nitrite. As reaction proceeds, the ketone gradually goes into solution, and after approximately three-fourths of the required nitrite is added, a homogeneous solution results. Recrystallization of the crude product from boiling benzene gives 21.2 g. (81.6%) of pale yellow crystals of *p*-xenylglyoxylohydroxamyl chloride, which forms a red melt at 157–158°.

Anal. Calc'd for $C_{14}H_{10}ClNO_2$: N, 5.4. Found: N, 5.32.

p-Xenyl chloroglyoxime, prepared in the usual manner, is recrystallized from hot butyl alcohol; dec. 177°.

Anal. Calc'd for $C_{14}H_{11}ClN_2O_2$: N, 10.2. Found: N, 10.08.

p-*Chlorophenylglyoxylohydroxamyl chloride.* From 19.0 g. (0.1 mole) of *p*-chlorophenacyl chloride, 11.6 cc. (0.11 mole) of isopropyl nitrite, and 200 cc. of ether, pale yellow crystals of crude product are obtained, which after recrystallization from boiling carbon tetrachloride gives 16.7 g. (76.6%) of colorless, glistening needles, m.p. 120–121°. *p*-Chlorophenylglyoxylohydroxamyl chloride is soluble in cold alcohol and ether; in benzene and toluene, on heating, but insoluble in petroleum benzine and ligroin.

Anal. Calc'd for $C_8H_5Cl_2NO_2$: N, 6.42. Found: N, 6.3.

The chloroglyoxime forms colorless platelets from hot glacial acetic acid; dec. 181–182°.

Anal. Calc'd for $C_8H_6Cl_2N_2O_2$: N, 12.01. Found: N, 12.14.

p-*Methoxyphenylglyoxylohydroxamyl chloride.* When nitrosation is applied to *p*-methoxyphenacyl chloride, the characteristic color changes are not observed, and reaction does not appear to occur. It was found that the addition of a few drops of water is necessary to initiate nitrosation; thereafter reaction proceeds as usual. The yield of *p*-methoxyphenylglyoxylohydroxamyl chloride obtained from 9.2 g. (0.05 mole) of ketone, 5.8 cc. (0.055 mole) of isopropyl nitrite, and 100 cc. of ether (to which is added 0.2 cc. of water), is 8.8 g. (82.0%), after recrystallization from hot carbon tetrachloride. The colorless needles thus obtained melt at 137–139°, and are soluble in ether, alcohol, and ethyl acetate, but dissolve in ligroin, benzene, and carbon tetrachloride only on heating.

Anal. Calc'd for $C_9H_8ClNO_3$: N, 6.56. Found: N, 6.65.

p-*Hydroxyphenylglyoxylohydroxamyl chloride.* To a suspension of 17.1 g. (0.1 mole) of *p*-hydroxyphenacyl chloride in 250 cc. of ether is added 12.6 cc. (0.11 mole) of butyl nitrite. Recrystallization of the crude product from ether-benzin (1:3) gives 18.5 g. (95.5%) of fine, colorless crystals, decomposing at 158–159°. *p*-Hydroxyphenylglyoxylohydroxamyl chloride is characterized by a violent sternutatory action. The chloroisonitroso ketone is readily soluble in alcohol, ether, acetone, and ethyl acetate; in *n*-amyl acetate on heating, but is insoluble in benzene, toluene, and carbon tetrachloride.

Anal. Calc'd for $C_8H_6ClNO_3$: N, 7.02. Found: N, 7.01.

Oximation by the general procedure gives colorless crystals of *p*-hydroxyphenyl chloroglyoxime, which, after recrystallization from a mixture of dioxane and heptane, decomposes at 183–184°.

Anal. Calc'd for $C_8H_7ClN_2O_3$: N, 13.52. Found: N, 13.33.

3,4-*Dihydroxyphenylglyoxylohydroxamyl chloride.* Eighteen and seven-tenths grams (0.1 mole) of the dihydroxyphenacyl chloride suspended in 400 cc. of ether (to which is added 3 cc. of water) is treated with 12.6 cc. (0.11 mole) of butyl nitrite according to the general nitrosation procedure. The reaction mixture darkens gradually as the nitrite is added; complete solution of the ketone occurs after approximately one-half of the required nitrite is added. The reaction mixture is then concentrated to one-half its volume by distillation from a water-bath and 200 cc. of benzene is added to precipitate the chloroisonitroso ketone. The yield of yellow crystals obtained is 17.8 g. (82.4%); dec. 184–185°.

Anal. Calc'd for $C_8H_6ClNO_4$: N, 6.47. Found: N, 6.38.

Isolation of the chloroglyoxime, when the general procedure is employed, proved difficult.

Alkaline decomposition of the arylglyoxylohydroxamyl chlorides. Decomposition of the arylglyoxylohydroxamyl chlorides, by refluxing with aqueous alkali, gives excellent yields of the corresponding benzoic acids, varying from 80–99%; attempts to prepare protocatechuic acid by the decomposition of the glyoxylohydroxamyl chloride, however, proved difficult, due to the ease of oxidation of the acid and also its extremely high solubility in water.

Arylglyoxylohydroximic acid anilides. The general procedure employed for the preparation of these anilides, is essentially that of Rheinboldt and Schmitz-Dumont (19). To 0.03 mole of arylglyoxylohydroxamyl chloride dissolved in 100 cc. of anhydrous ether is added 0.06 mole of freshly-distilled aniline. The flask is securely stoppered and allowed to stand at room temperature, with occasional shaking, for four days. The precipitated aniline hydrochloride is filtered off with suction and the filtrate evaporated to dryness in

a vacuum desiccator. Recrystallization from an appropriate solvent gives a pure product. The anilides obtained from *p*-hydroxy- and 3,4-dihydroxyphenyl-glyoxylohydroxamyl chlorides are insoluble in ether; these are freed of the precipitated aniline hydrochloride by washing with cold water.

Arylglyoxylohydroximic acid anilides melt with decomposition; with concentrated sulfuric acid, cold, they decompose, with the formation of a dark purple color. On heating with dilute aqueous alkali, the anilides yield isocyanides, recognized by the characteristic odor; a similar observation is made in attempts to recrystallize these from the higher-boiling solvents, *viz.* xylene, amyl acetate, etc. A summary of the various arylglyoxylohydroximic acid anilides is presented in Table II.

TABLE II

ARYLGLYOXYLOHYDROXIMIC ACID ANILIDES

Ar=	M.P. (DEC) °C.	RECRYSTALLIZED FROM	CRYSTALLINE FORM	FORMULA	ANAL., N	
					Calc'd	Found
C_6H_5— [a]	145-146	Toluene	Yellow flakes	$C_{14}H_{12}N_2O_2$		
p-$CH_3C_6H_4$—	163-164	Isopropyl alcohol	Fine, colorless needles	$C_{15}H_{14}N_2O_2$	11.02	11.00
p-$C_6H_5C_6H_4$— [b]	135-136	Isopropyl alcohol	Yellowish-brown flakes	$C_{20}H_{16}N_2O_2$		
p-ClC_6H_4—	145-146	Isopropyl alcohol	Large, yellow flakes	$C_{14}H_{11}ClN_2O_2$	10.2	10.01
p-$CH_3OC_6H_4$—	148-150	Dilute alcohol (50%)	Fine, pale yellow needles	$C_{15}H_{14}N_2O_3$	10.4	10.22
p-HOC_6H_4—	164-165	Dilute alcohol (50%)	Fine, pale yellow needles	$C_{14}H_{12}N_2O_3$	10.9	11.10
3, 4-$(HO)_2C_6H_3$—	155[c]	Acetone-toluene (1:3)	Small, yellow needles	$C_{14}H_{12}N_2O_4$	10.26	10.0

[a] Previously described by Rheinboldt and Schmitz-Dumont (19).

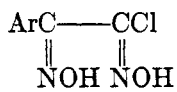
[b] Not pure for analysis

[c] Darkens at this temperature.

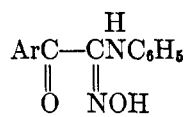
SUMMARY

1. A general method is described for the preparation, in good yields, of arylglyoxylohydroxamyl chlorides by the nitrosation of chloromethyl ketones.

2. These products may be converted into glyoximes of the general structure,



3. Arylglyoxylohydroxamyl chlorides show properties of acid chlorides, *e.g.*, they react with amines; with aniline, they form characteristic anilides of the type,



4. Preliminary studies indicate that arylglyoxylohydroxamyl chlorides are of value as intermediates, by catalytic hydrogenation, for the synthesis of phenylethanolamine and its phenyl substituted derivatives.

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