

## SYNTHESIS OF PAREDRIE AND RELATED COMPOUNDS<sup>1</sup>

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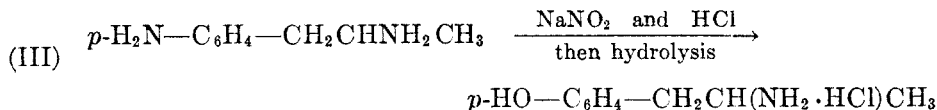
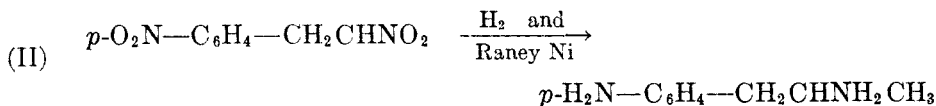
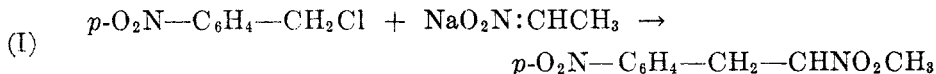
Syntheses involving the nitro alkanes may provide attractive methods for preparing amines and amino alcohols. Since nitro alkanes have now become cheap and plentiful, these methods are of particular interest for the preparation of Paredrine, Propadrine, ephedrine, and other products which possess physiological action.

Paredrine, a proprietary name for *p*-hydroxyphenyl-2-propylamine, is a synthetically-prepared, racemic mixture of the HO—C<sub>6</sub>H<sub>4</sub>—CH<sub>2</sub>CHNH<sub>2</sub>CH<sub>3</sub> bases, which is marketed as the hydrobromide. Solutions are used for shrinking the nasal mucosa in head-colds and hay fever, for sinus irrigation, and in ophthalmology as an adjuvant to 1% atropine or 4% homatropine. It has the advantage of producing practically no stimulation of the central nervous system and a minimum of side effects.

Paredrine has now been made by two series of reactions, each involving nitroethane as an intermediate.

### SYNTHESIS NUMBER ONE

In the first of these, *p*-nitrobenzyl chloride is condensed with a salt of nitroethane and the dinitro compound which results is reduced to a diamine. That amino group, which is attached to the benzene ring, is then replaced by a hydroxyl group by formation and decomposition of the diazonium salt.



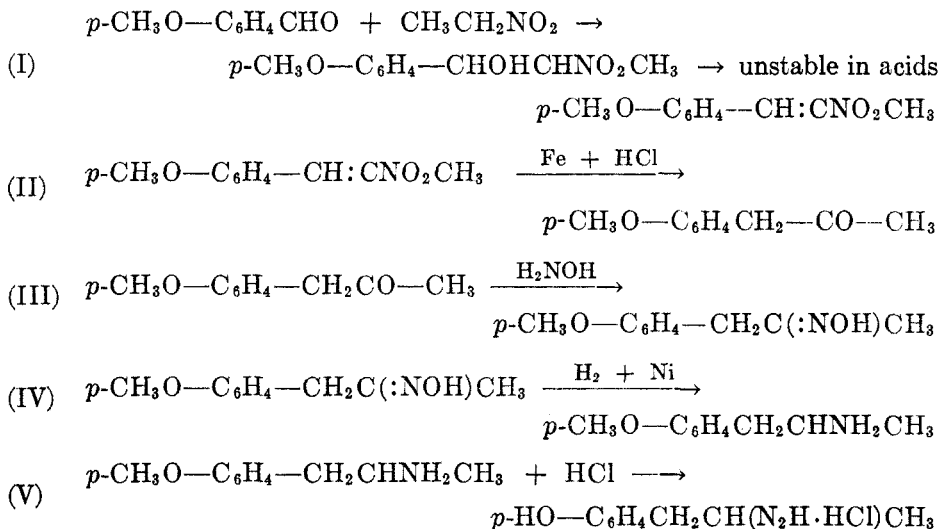
### SYNTHESIS NUMBER TWO

In this process *p*-methoxybenzaldehyde (anisaldehyde) is caused to react with nitroethane in an aldol-type condensation. The nitro alcohol which results

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loses water spontaneously, producing the nitro olefin. The nitro olefin is treated with iron and hydrochloric acid. In the course of the reduction, however, the desired oxime is hydrolyzed and the ketone, instead of the oxime, is isolated at the end of the reaction. It is therefore necessary to re-form the oxime by treating the ketone with hydroxylamine hydrochloride. The oxime is subsequently reduced, and the ether group attached to the ring is split with hydrochloric acid to yield a hydroxyl group.



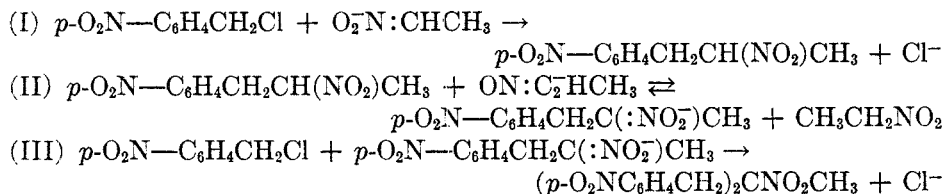
#### DISCUSSION

##### *Synthesis Number One*

The synthesis beginning with *p*-nitrobenzyl chloride involves, at the outset, an aralkylation of a salt of an aci-nitro alkane. Although the aralkylation has not been studied extensively enough to permit of prediction in all cases, Weisler (5) has shown that it is correlated with the stability of the aci-form of the nitro compound, and is probably dependent on the rate at which the aci-form tautomerizes to the normal form. If the stability of the aci-form is high, the tendency is toward aralkylation on the carbon atom instead of on oxygen. Also, the greater the reactivity of the halide selected, as evidenced by its tendency to ionize or to form free radicals, the greater is the tendency for reaction with the carbon atom.

In the reaction between the salt of aci-nitroethane and *p*-nitrobenzyl chloride, aralkylation occurs both on carbon and on oxygen, but fortunately aralkylation on carbon greatly predominates. (Reaction with an oxygen produces minor quantities of a nitronic ester or its decomposition products; *p*-nitrobenzaldehyde was therefore isolated as a by-product in step one.) Another competing reaction, which takes place to a greater extent than reaction on an oxygen atom, is the formation of 1,1-bis-(*p*-nitrobenzyl)nitroethane. If no excess nitroethane is used, this reaction predominates over the reaction desired, but formation

of the monoaralkylated product can be favored by using an excess of nitroethane so that disubstitution is largely suppressed. This effect can be explained by considering the following reactions:



Since the formation of the aralkylated product probably occurs in accordance with equation (III), the rate of its formation depends on the concentration of the ion,  $p\text{-O}_2\text{N}-\text{C}_6\text{H}_4\text{CH}_2\text{C}(:\text{NO}_2^-)\text{CH}_3$ . An excess of nitroethane will lower the concentration of this ion by affecting the equilibrium (II). The result is to decrease the yield of bis- compound and increase the yield of monoaralkylated product.

The reduction of the dinitro compound, the desired product, can be effected in any of the conventional ways, but high-pressure hydrogenation with a Raney nickel catalyst was selected and was found to give good results.

The step of diazotization was carried out according to the directions of Sal-kowski (3).

### *Synthesis Number Two*

The step of condensing *p*-methoxybenzaldehyde with nitroethane was previously reported by Alles (1), who allowed the reactants to stand for several weeks using a primary amine as a catalyst. The same reaction was found to be effected quickly by employing methanol as a solvent and refluxing for a few hours. The ketone,  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{COCH}_3$ , is readily made by the method of Hass and Susie (4), which involves reduction of the nitro olefin with iron and hydrochloric acid. Its oxime was prepared in the usual manner and reduced to the amine by high-pressure hydrogenation, using Raney nickel catalyst. Demethylation was readily accomplished by the method of Woodruff and Conger (6), which consists in heating the methoxy compound,  $\text{CH}_3\text{OC}_6\text{H}_4\text{-CH}_2\text{CHNH}_2\text{CH}_3$ , with concentrated hydrochloric acid under pressure.

## EXPERIMENTAL

### *Synthesis Number One*

*Preparation of 1-p-nitrobenzylnitroethane.* Sodium nitroethane (24.45 g., 0.25 mole) was prepared in the reaction flask by dissolving sodium (5.75 g., 0.25 mole) in a small amount of ethanol, then adding nitroethane (131.2 g., 1.75 moles). *p*-Nitrobenzyl chloride (42.9 g., 0.25 mole) and 500 ml. of absolute ethanol were added and the mixture was refluxed eleven hours on a steam-bath, during which the solution turned red and a precipitate formed. After filtering, the filtrate was evaporated on a hot plate. The residue was dissolved in benzene and the solution was extracted with sodium bisulfite solution to remove *p*-nitrobenzaldehyde. (Free *p*-nitrobenzaldehyde was isolated from this extract, recrystallized and identified.) After removing the benzene, the residue was distilled (b.p. 145-

160° at 0.5 to 0.6 mm.) from a Claisen flask; yield 28 g., 83%. The viscous oil was dissolved in alcohol and crystallized, m.p. 51°.

*Anal.* Calc'd for  $C_9H_{16}N_2O_4$ : C, 51.4; H, 4.8; N, 13.0.

Found: C, 51.6; H, 4.7; N, 13.0.

The precipitate which had been filtered out was extracted with water to remove sodium chloride (0.24 mole of silver chloride was obtained from the extract upon adding silver nitrate). A grayish residue remained. This melted at 214° after recrystallization from nitrobenzene and was identified as 1,1-bis(*p*-nitrobenzyl)nitroethane.

*Anal.* Calc'd for  $C_{16}H_{18}N_3O_6$ : C, 55.67; H, 4.38; N, 12.2.

Found: C, 55.48; H, 4.38; N, 12.0.

*Preparation of 1-p-aminophenyl-2-propylamine.* Distilled 1-*p*-nitrophenyl-2-nitropropane (30 g., 0.142 mole), 150 ml. of absolute ethanol, and 5 g. Raney nickel were placed in a Parr hydrogenation bomb under hydrogen pressure of 1400 lbs./sq. in. at 50–70°. Under these conditions, reduction was complete in one-half hour but at room temperature (25–30°) several hours were necessary for complete reduction.

After the pressure had become constant the material was removed, filtered, and the solvent evaporated. The residue was dissolved in hydrochloric acid solution and extracted with benzene to remove the non-basic portions. It was made strongly basic with a large excess of sodium hydroxide (50% solution) and the diamine was extracted with benzene. Benzene was removed and the base was distilled from a Claisen flask; yield 15.6 g., 71%. It was redistilled from a precision column (b.p. 126° at 2 mm.,  $n_D^{20}$  1.5723,  $d_4^{25}$  1.022). The dihydrochloride, obtained by adding excess hydrochloric acid and evaporating, was recrystallized from alcohol-ether. The diamine dihydrochloride is readily oxidized in solution but oxidation can be largely suppressed by using excess acid. The dihydrochloride is a white solid melting above 270°.

*Anal.* Calc'd for  $C_9H_{16}Cl_2N_2$ : Cl, 31.80. Found: Cl, 31.86.

*Preparation of 1-p-hydroxyphenyl-2-propylamine hydrochloride.* The procedure of Sal-kowski (3) was followed. The reaction does not proceed very smoothly and a considerable amount of a brownish by-product results. 1-*p*-Aminophenyl-2-propylamine dihydrochloride (30.17 g., 0.135 mole), 60 ml. of concentrated hydrochloric acid, and 20 ml. of water were mixed and cooled to –3°. Sodium nitrite (9.6 g., 0.139 mole), in 40 ml. of water, was slowly added with adequate stirring. A temperature of 3° or less was maintained throughout the reaction. Agitation was continued for one hour after all the sodium nitrite was added, then the temperature was gradually raised to 70° and was maintained at 70–90° until the evolution of nitrogen ceased. The resulting red solution was extracted with benzene to remove non-basic impurities, and the water layer was evaporated. The gummy, brown residue was dissolved in alcohol, the sodium chloride which precipitates was filtered off, and a large excess of ether was added. The yellow precipitate dissolved in hydrochloric acid with a marked darkening in color, and on cooling, 10–12 g. (40–50%) of a solid separated, m.p. 171–172° after three recrystallizations from concentrated hydrochloric acid. A mixture with a known sample melted at 171–172°. The free amine, prepared from the salt by treating it with concentrated ammonia, was recrystallized from benzene, and melted at 125°. [Mannich and Jacobson (2) have reported 125–126°]. A mixture with an authentic sample melted at 125°.

*Anal.* Calc'd for  $C_9H_{14}ClNO$ : Cl, 18.93. Found: Cl, 19.14.

#### Synthesis Number Two

*Preparation of 1-p-methoxyphenyl-2-nitropropene.* A mixture of *p*-methoxybenzaldehyde (anisaldehyde, 27.2 g., 0.2 mole) and nitroethane (15.0 g., 0.2 mole) in 35 ml. of absolute alcohol and 4.0 ml. of butylamine was refluxed six hours. After cooling in ice and salt, filtering, concentrating, and cooling again, a total of 20 g. (51.8% conversion) was obtained; 3 g. of additional nitro olefin and 9 g. of *p*-methoxybenzaldehyde were recovered by distilling the filtrate. The product melts at 43–44°, conversion 59.6%, yield 87.2%.

*Preparation of 1-p-methoxyphenyl-2-propanone.* A mixture of 1-p-methoxyphenyl-2-nitropropene (96.5 g., 0.5 mole), iron filings (40 mesh, 200 g.), 500 ml. of water, and 1 g. of ferric chloride was refluxed for eight hours with good agitation, and 90 ml. of concentrated hydrochloric acid was added in the course of the eight hours. The mixture was steam distilled until four liters of water had been collected. The distillate was extracted with ether. Upon distillation, the extract provided 48 g. of 1-p-methoxyphenyl-2-propanone, b.p. 117-122° at 5 to 6 mm.; yield 59%.

*Preparation of 1-p-methoxyphenyl-2-propanone oxime.* An alcoholic solution containing 1-p-methoxyphenyl-2-propanone (21 g., 0.128 mole) was mixed with an aqueous solution containing hydroxylammonium chloride (21 g., 0.30 mole). After adding sufficient sodium hydroxide (20% solution) to render the mixture just basic, it was refluxed five minutes, precipitated by adding water and cooling. The oxime (20 g., yield 87%) was a mixture of syn- and anti- isomers, m.p. 56-61°.

*Preparation of 1-p-methoxyphenyl-2-propylamine.* 1-p-Methoxyphenyl-2-propanone oxime (42 g., 0.234 mole), 300 ml. of 95% ethanol, and 5 g. of Raney nickel in a Parr hydrogenation bomb were subjected to an initial hydrogen pressure of 1940 lbs./sq.in. Approximately two hours were required for complete reduction. 1-p-Methoxyphenyl-2-propylamine was formed. The hydrochloride m. 208°. The yield was 30 g. of pure amine (78%).

*Preparation of 1-p-hydroxyphenyl-2-propylamine.* The method of Woodruff and Conger (6) was used to split the ether. 1-p-Methoxyphenyl-2-propylamine hydrochloride (7 g., 0.034 mole) and 25 ml. concentrated hydrochloric acid were heated in a Carius tube at 140-160° for two hours. The brown, solid residue remaining after evaporation of the acid was dissolved in alcohol, decolorized with Norit, and precipitated by adding ether. 1-p-Hydroxyphenyl-2-propylamine hydrochloride, m.p. 171-172°, resulted; yield 5.5 g. (80%).

#### ACKNOWLEDGMENTS

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#### SUMMARY

Two syntheses for 1-p-hydroxyphenyl-2-propylamine (Paredrine) are described. One synthesis utilizes *p*-nitrobenzyl chloride and a salt of nitroethane; the other employs *p*-methoxybenzaldehyde (anisaldehyde) and nitroethane as initial materials. Among the intermediates and by-products there are three new compounds, namely, 1-*p*-nitrophenyl-2-nitropropane, 1,1-bis(*p*-nitrobenzyl)-1-nitroethane, and 1-*p*-aminophenyl-2-propylamine.

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