[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Aryloxyacetones[1]

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All recorded yields of phenoxyacetone in its synthesis from phenol and chloroacetone are very poor. When sodium phenoxide and chloroacetone reacted in toluene as solvent the yield[2] was 16%, whereas a 23% yield was found[3] when phenol, chloroacetone and potassium carbonate interacted using acetone as solvent. Even with bromoacetone the yields from phenol[4] (53%) or *p*-cresol[5] (27–37%) leave much to be desired.

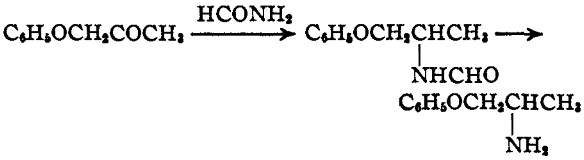
The story with β-naphthol and its tetrahydro derivative is much the same. β-Naphthoxyacetone is formed in 21% yield[2] by interaction of β-naphthol, chloroacetone and potassium carbonate in acetone. Thoms and Kross[6] in a study of 5,6,7,8-tetrahydro-2-naphthol, reported a poor yield of the aryloxyacetone when the sodium salt was brought into reaction with chloroacetone in benzene; but that no ketone was formed when alcohol, chloroform or ether were used as solvent, or when pyridine was used as the base with the phenol and chloroacetone.

A study of this general problem has revealed the interesting observation that 90–95% yields of phenoxyacetone from chloroacetone may be obtained if a small amount of potassium iodide is present in the reaction mixture. Undoubtedly this catalyst functions by converting chloroacetone into iodoacetone. This catalytic method was used also to obtain an 85% yield of β-naphthoxyacetone.

Several reactions of phenoxyacetone were investigated: catalytic hydrogenation, conversion to its oxime and hydrogenation of the latter, Leuckart reaction, Grignard reaction, bromination and pyrolysis. The first two of these reactions were also carried out on β-naphthoxyacetone.

1-Phenoxy-2-propanol, $CH_3CHOHCH_2OC_6H_5$, was prepared in good yields by hydrogenation at 1400 pounds pressure in the presence of nickel catalyst. This compound has been made previously[7] only by interaction of 1-chloro-2-propanol and sodium phenoxide. Reduction of β-naphthoxyacetone in the same manner to 1-β-naphthoxy-2-propanol was also achieved in good yield. The melting point of this substance, 82–83°, is the same as that reported by Boyd and Marle[8] for the product of reaction of propylene oxide and sodium β-naphthoxide. These authors regarded their product as a mixture of 1-β-naphthoxy-2-propanol and 2-β-naphthoxy-1-propanol but the present work makes it evident that it must have been a reasonably pure sample of the former.

Oximes of phenoxyacetone and β-naphthoxyacetone were prepared by reaction with hydroxylamine. Hydrogenation of the oximes gave rise to 2-phenoxyisopropylamine and 2-β-naphthoxyisopropylamine, respectively, in yields of about 65%. 2-Phenoxyisopropylamine was prepared, also, but in poorer yield by refluxing the ketone with formamide by the Leuckart reaction[9]



$$C_6H_5OCH_2COCH_3 \xrightarrow{HCONH_2} C_6H_5OCH_2\underset{NHCHO}{C}HCH_3 \longrightarrow C_6H_5OCH_2\underset{NH_2}{C}HCH_3$$

The structural similarity of 2-phenoxyisopropylamine, $C_6H_5OCH_2\underset{NH_2}{C}HCH_3$, and benzedrine, $C_6H_5CH_2\overset{NH_2}{C}HCH_3$, made it interesting to study its pharmacology. We are indebted to Dr. Oliver Kamm and Mr. L. R. Rowe of Parke, Davis and Company for the following report.

"Comparisons between the samples of 2-phenoxyisopropylamine and 2-β-naphthoxyisopropylamine were made several times on five or six dogs anesthetized with chloretone, and one dog under Sodium Pentobarbital was injected several times. Usually benzedrine was included for comparison. In every case 2-phenoxyisopropylamine showed a definite pressor and respiratory stimulating action similar to that of benzedrine, but only one-half as strong. In other words, it required an intravenous dose of 20 mg. to produce the same effect as would have been obtained by 10 mg. of benzedrine in the same animal. The 2-β-naphthoxyisopropylamine does not exhibit a benzedrine-like effect, even in doses as high as 50 mg. Almost invariably it causes a depressor action with no evidence of cardiac or respiratory stimulation. The toxicity of each compound is about the same intraperitoneally to white mice (M. L. D. being 0.15 mg. per g.). That of benzedrine is 0.10 mg. per g., so these compounds are somewhat less toxic than benzedrine."

No difficulty was encountered in converting phenoxyacetone into 1-phenoxy-2-methyl-2-pro-

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[1] This communication was presented at the Memphis meeting of the American Chemical Society, April, 1942. It is abstracted from a dissertation submitted by P. Perletz in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Northwestern University, June, 1940.

[2] Whitney and Henze, THIS JOURNAL, **60**, 1148 (1938).

[3] Bradsher and Tess, *ibid.*, **61**, 2184 (1939).

[4] Calaway and Henze, *ibid.*, **61**, 1356 (1939).

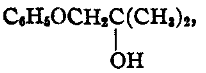
[5] Tarbell, *J. Org. Chem.*, **7**, 251 (1942).

[6] Thoms and Kross, *Arch. Phar.*, **265**, 342 (1927); see also Sabetay, *Bull. soc. chim.*, **45**, 534 (1929).

[7] F. Bayer and Co., German patent 282,991; *Chem. Zentr.*, **86**, I, 815 (1915).

[8] Boyd and Marle, *J. Chem. Soc.*, **105**, 2117, 2135 (1914).

[9] Leuckart and co-workers, *Ber.*, **18**, 2341 (1885); **19**, 2128 (1886); **20**, 104 (1887).

panol,  $C_6H_5OCH_2C(OH)(CH_3)_2$, by the reaction with methylmagnesium iodide. The same tertiary alcohol was prepared by Stoermer[10] from phenoxyacetic ester and methylmagnesium halide.

Cleavage of the ether linkage was encountered during bromination of phenoxyacetone in glacial acetic acid solution. Tribromophenol was the product obtained. This scission of a phenyl ether is in contrast with the non-cleavage of a phenyl acetal, namely, the direct bromination in acetic acid of phenyl tetraacetyl-β-D-glucoside[11] to *p*-bromophenyl tetraacetyl-β-D-glucoside.

Tarbell[5] has reported the non-rearrangement of *p*-tolyloxyacetone at 250°. We observed a similar non-rearrangement of phenoxyacetone when it was refluxed for five hours in a mixture of acetic anhydride and diethylaniline. The latter conditions have been used successfully, for example, in effecting the Claisen-type rearrangement of 1,4-naphthohydroquinone diallyl ether.[12]

Pyrolysis of phenoxyacetone at 650° brought about rupture of the compound into phenol. Carbon monoxide and methane predominated among the gaseous decomposition products and the inside of the reaction tube became coated with tar and carbon. The reaction may be summarized

$$C_6H_5OCH_2COCH_3 \longrightarrow C_6H_5OH + C + CO + CH_4$$

No evidence was obtained for ketene, methylketene or hydrogen as reaction products.

The temperature of 650° is in the range where free radicals might be formed to play a part in the mechanism. If so, one would expect both radicals $PhOCHCOCH_3(R')$ and $PhOCH_2COCH_2(R^2)$ to participate. The absence of ketene suggests, at least, that R^2 was not involved.

Experimental

Chloroacetone was generously supplied for this work by Commercial Solvents Corporation.

Preparation of Phenoxyacetone.—In a three-necked, 2-liter flask was placed 100 g. (1.06 moles) of phenol, 34 g. of potassium carbonate and 140 ml. of dry acetone. A mixture of 138 g. (1.5 moles) of chloroacetone, 130 ml. of acetone and 3 g. of potassium iodide was placed in a 500-cc. separatory funnel and allowed to stand overnight. The mixture in the flask was stirred and refluxed for fifteen minutes and then the chloroacetone mixture was added very slowly. After one fourth of this mixture was added, 34 g. of potassium carbonate and enough dry acetone to thin the mixture was added. The second portion of chloroacetone was added dropwise. This procedure was repeated two more times until 138 g. of potassium carbonate and all the chloroacetone had been added. The mixture was then stirred for fifteen hours. A good indication that the reaction was completed was the disappearance of the granules of potassium carbonate.

The mixture was filtered through a sintered glass funnel and the precipitate was washed with acetone. The filtrate was concentrated and the residue distilled under reduced pressure. The fraction which distilled at 117–120° (19 mm.) weighed 147.5 g., or a yield of 92.5%. The residue weighed 15 g. The phenoxyacetone distilled nearly colorless but became colored on standing.

Less satisfactory yields were obtained if the potassium iodide was first mixed with the phenol or if an excess of chloroacetone was not used or if there was no initial period of standing of the chloroacetone with the potassium iodide.

Oxime.—Stoermer[13] simply described this oxime as an oil. We obtained this same oil and found that some decomposition attended its vacuum distillation at 12–17 mm. The fraction, twice distilled and collected at 160° (17 mm.), possessed these constants: $n^{20}D$ 1.5444, d^{20}_4 1.1214. It was a viscous oil which became colored on standing.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 7.83.

β-Naphthoxyacetone.—Into a stirred mixture of 59 g. of β-naphthol, 57 g. of potassium carbonate and 150 ml. of dry acetone was slowly dropped a mixture of 50 g. of chloroacetone, 3 g. of potassium iodide and 50 ml. of dry acetone. Stirring and refluxing were continued for six hours after the addition, then stirring at room temperature for twenty hours more. The mixture was filtered and the salt was washed well with acetone. To obtain the β-naphthoxyacetone from the filtrate it was diluted with water and the precipitate recrystallized once from methanol and water, yield 70 g. or 85%; m. p. 69–73°. Two recrystallizations from cyclohexane brought the m. p. to 75–77°.

The oxime,[13] prepared in 87% yield from the crude ketone, melted at 122–123°.

1-Phenoxy-2-propanol.—Grateful acknowledgment is made to Dr. V. N. Ipatieff and Vladimir Haensel of this Laboratory for assistance in this and other hydrogenations reported in this paper.

Twelve grams of phenoxyacetone was dissolved in cyclohexane to make the solution up to 50 cc. Five grams of nickel catalyst[14] in pellet form was pulverized in a mortar under 5 cc. of the solution. This mixture was poured into a 125-cc. steel bomb. The remainder of the solution, followed by 5 cc. of cyclohexane, was used to wash the catalyst into the bomb. The bomb was first flushed out with hydrogen and then filled with this gas until the initial pressure was 92 atmospheres. It was rotated at room temperature until the pressure became constant at 67 atmospheres. The contents of the bomb were filtered, washed with ether, and the filtrate distilled at 21 mm. leaving no residue: 1.3 g. collected at 125–130°; 9.0 g. at 130°, $n^{20}D$ 1.5232, d^{20}_4 1.0622. The molar refraction using the Lorenz and Lorentz formula was 43.73; calculated, 43.3. The yield of the second fraction was 75%. The substance reacted with sodium metal and acid chlorides. It did not form a semicarbazone. It was insoluble in water.

Reduction of phenoxyacetone or β-naphthoxyacetone by the sodium and ethanol method resulted only in tarry products.

1-β-Naphthoxy-2-propanol.—Eight grams of β-naphthoxyacetone, dissolved in 50 ml. of benzene was reduced with hydrogen at an initial pressure of 100 atm. over 4 g. of nickel catalyst. The reduction took place at room temperature and was complete after a pressure drop of 18 atmospheres. After the benzene solution was freed from the catalyst, the excess solvent was removed by distillation. The residue, after the first recrystallization from methanol and water, weighed 7.0 g., melted at 80–82°, and the yield was 87.5%. After recrystallization from cyclohexane the 1-β-naphthoxy-2-propanol melted[8] at 82–83°.

This substance did not form a semicarbazone. It reacted slowly with sodium metal. In the absence of a solvent there was no apparent reaction with the acid chlorides. When pyridine was present a reaction took place with benzoyl chloride.

2-Phenoxyisopropylammonium Chloride.—The amine was prepared by reducing 7.5 g. of phenoxyacetone oxime in 40 ml. of cyclohexane (a cloudy solution) and 5 ml. of ether with 2 g. of nickel and hydrogen at an initial pressure

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[10] Stoermer, *Ber.*, **39**, 2296 (1906).

[11] Hurd and Bonner, THIS JOURNAL, **67**, 1764 (1945).

[12] Fieser, Campbell and Fry, *ibid.*, **61**, 2215 (1939).

[13] Stoermer, *Ber.*, **28**, 1253 (1895); *Ann.*, **312**, 273, 312 (1900).

[14] This catalyst was developed by Ipatieff and Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938), and may be obtained from the Victor Chemical Company.

of 100 atmospheres. The reduction took place slowly at room temperature and was, therefore, kept at 45°. The total pressure drop in the 125-cc. bomb was 26 atmospheres. There was a distinct odor of ammonia when the tube was opened. The cyclohexane solution was extracted with dilute hydrochloric acid. The acid solution was made alkaline with dilute sodium hydroxide solution and extracted with ether. The extract was dried and then concentrated. A yellow oil was left as a residue which was taken up in dry ether and the salt precipitated by hydrogen chloride. It was recrystallized from acetone: m. p. 147–148°. The yield was 5.5 g. or 65%.

Anal. Calcd. for $C_9H_{14}ClNO$: Cl, 18.89. Found: Cl, 18.89.

2-Phenoxyisopropylamine.—The above hydrogenation was repeated on 6.5 g. of oxime in 60 ml. of benzene with 2 g. of nickel catalyst. Instead of preparing the salt the free amine was distilled but decomposition was extensive. Only 1.1 g. (18.5%) was collected at 117–120° (13 mm.); $n^{20}{}_D$ 1.5237, $d^{20}{}_4$ 1.0146. Another 0.8 g. was collected at 150–205°.

Anal. Calcd. for $C_9H_{13}NO$: N, 9.26; mol. ref., 45.1. Found: N, 8.72; mol. ref., 45.6.

This amine was also prepared by the Leuckart synthesis. A mixture of 7 g. of phenoxyacetone and 16 g. of formamide was heated for twelve hours to just below the boiling point. The dark solution was decomposed by refluxing with 50 ml. of concentrated hydrochloric acid for twenty-eight hours. The mixture was extracted with ether. The acid solution was made alkaline with 10% sodium hydroxide solution, extracted with ether, the extract dried over potassium carbonate, and then distilled under reduced pressure. The distillate came over at 126° (23 mm.). The yield was 2 g. or 25%. This amine was taken up in ether and the salt precipitated by hydrogen chloride. The precipitate was recrystallized from absolute alcohol and petroleum ether, m. p. 145–146°.

2-β-Naphthoxyisopropylamine and its Hydrochloride.—This amine was prepared by the reduction of 10.5 g. of β-naphthoxyacetone oxime dissolved in 100 ml. of benzene with hydrogen at an initial pressure of 94 atm. over 3 g. of nickel catalyst. The temperature never exceeded 52° in the 400-cc. bomb during the reduction. After working up in the usual manner, a tan solid residue remained which weighed 6.5 g. This represented a yield of 66.3%. As with the phenoxy compound, there was a strong odor of ammonia emanating from the benzene solution. Four grams of the amine was distilled. Three grams was collected at 148° (5 mm.). The decomposition was slight. It solidified and melted at 40–42°.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 6.96. Found: N, 6.53.

Two grams of the amine was taken up in dry ether. Hydrogen chloride was passed in until precipitation was complete. The salt obtained melted at 200–202°.

Anal. Calcd. for $C_{13}H_{16}ClNO$: Cl, 14.93. Found: Cl, 14.91.

1-Phenoxy-2-methyl-2-propanol.—Methylmagnesium iodide solution was prepared (5 ml. of methyl iodide, 2.4 g. of magnesium, 40 ml. of ether). Into it was dropped a solution of 8 g. of phenoxyacetone in 75 ml. of ether. After hydrolysis with cold hydrochloric acid the product was obtained from the ether solution. On distillation, 9 g. was collected at 126–129° (22 mm.). Redistillation yielded 7.1 g. or 88% yield of the alcohol, collected[10] at 125.0–125.5° (21 mm.); $n^{20}{}_D$ 1.5100.

The 1-phenoxy-2-methyl-2-propanol was found to be indifferent to acid chlorides. It was not dehydrated when vacuum distilled in the presence of a crystal of iodine. A slow reaction was observed with metallic sodium.

Bromination in Glacial Acetic Acid.—Five grams of bromine was added to a glacial acetic acid solution of 0.5 g. of phenoxyacetone. There was copious fuming. After the red solution had stood for two hours, it was poured into 150 cc. of water. Solid sodium bisulfite was added to destroy the excess bromine. The white precipitate weighed 0.64 g. It melted at 89–91° after recrystallization from alcohol and water. This was tribromophenol.

Pyrolysis of Phenoxyacetone.—The ketone (26.8 g.) was delivered by mercury displacement into the top of a 105-cc. Pyrex tube, heated electrically to 650°, at a rate of 1.17 g. per minute. Gaseous products were passed through an aniline trap. No acetanilide was formed. The volume of gas obtained was 3040 cc. at N. T. P. Gas analysis revealed (%): carbon dioxide 4.2, unsaturated hydrocarbons 6.1, carbon monoxide 57.7, methane 32.0.

The inner surface of the Pyrex tube became coated with tar and carbon. The liquid condensate weighed 20.5 g. It was taken up in ether, filtered to remove carbon, and distilled. Three grams was collected up to 85° (16 mm.) then 7.0 g. of phenol was taken off at 85–87° (16 mm.). About 2.5 g. was obtained between 87–160° (16 mm.), and there was 6 g. of residue. The phenol fraction solidified on cooling and gave a derivative, m. p. 89–91°, with bromine water.

Thus, the 0.17 mole of phenoxyacetone gave rise to 0.074 mole of phenol, 0.078 mole of carbon monoxide, 0.043 mole of methane and less than 0.01 mole each of carbon dioxide and olefins.

Summary

Directions are presented for improving the yield of phenoxyacetone from chloroacetone and phenol from 16–23% to over 90%. The chief feature of the improvement is the use of potassium iodide as catalyst. β-Naphthoxyacetone is prepared similarly.

Catalytic hydrogenation of these compounds gives rise to 1-phenoxy-2-propanol and 1-β-naphthoxy-2-propanol. Catalytic hydrogenation of the oximes yields 2-phenoxyisopropylamine and 2-β-naphthoxyisopropylamine, for which pharmacological data are presented. 2-Phenoxyisopropylamine may be made also by the Leuckart reaction.

The report also includes these reactions of phenoxyacetone: Grignard reaction, bromination, pyrolysis.

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