

ORGANIC SYNTHESSES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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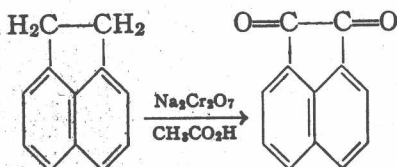
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ACENAPHTHENEQUINONE



Submitted by C. S. MAXWELL and C. F. H. ALLEN.
Checked by R. L. SHRINER and C. H. TILFORD.

1. Procedure

In a 2-l. three-necked round-bottomed flask, fitted with a mechanical stirrer, a reflux condenser, and a large-bore, short-stemmed funnel, are placed 30 g. (0.195 mole) of acenaphthene (Notes 1 and 2) and 210 ml. of glacial acetic acid. Stirring is started, and the mixture is heated to about 95° . The flame is then removed, and 130 g. (0.43 mole) of coarsely pulverized technical sodium dichromate is added through the funnel over a period of 15 to 30 minutes. The addition is made as fast as possible without causing such vigorous boiling that the reaction gets out of hand. If frothing starts, the flask is immediately surrounded by a pan of cold water. After all the dichromate has been added, the funnel is replaced by a stopper and the mixture refluxed for 15 minutes, during which time it becomes very viscous. Seven hundred milliliters of hot water is then added; the mixture is stirred for 10 minutes and filtered by suction. The red precipitate is washed on the filter with 400 ml. of hot water to remove chromium salts.

The solid is transferred to a 1-l. beaker, and 220 ml. of a 10% solution of sodium carbonate is added. The solution is heated on a steam-bath for an hour and filtered hot; this operation removes the naphthalic anhydride formed as a by-product (Note 3). The residual red solid is then placed in a 2-l. three-

necked flask fitted with a stirrer and a reflux condenser, the top of which is attached to a gas trap for absorbing sulfur dioxide. Three hundred milliliters of a 40% sodium bisulfite solution is then added, and the mixture is refluxed with stirring for 45 minutes, whereupon 500 ml. of water is added and refluxing is continued for 10 minutes. The hot solution is filtered by suction. The filtrate is then heated to boiling and acidified by the slow, cautious addition of 110 ml. of concentrated sulfuric acid (Note 4). The mixture is digested for 15 minutes over a low flame and then filtered. The yellow precipitate is washed thoroughly with 200 ml. of water and 100 ml. of dilute ammonia (1 part concentrated ammonia to 10 parts of water by volume). The washed and dried acenaphthenequinone weighs 15–21 g. (42–60%) and melts at 243–245°

2. Notes

1. The acenaphthene should be the finest grade obtainable since the technical brown variety gives tarry material from which it is difficult to isolate the quinone. The white acenaphthene obtained from the Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany, may be used. Acenaphthene produced by the Reilly Tar and Chemicals Company, Indianapolis, Indiana, is also satisfactory provided that it is recrystallized from methanol before use; the purified material melts at 94–95°.

2. Larger quantities (50–100 g.) of acenaphthene can be oxidized conveniently, but it is very difficult to extract all the quinone from the crude material. If larger quantities are oxidized, the product should be divided into small lots as described above for the bisulfite extraction. The yield is determined to a large extent by the thoroughness of the extraction.

3. The naphthalic anhydride (4–11 g.) is recovered on acidification of the filtrate. This substance is the principal product if the oxidation becomes too vigorous. Naphthalic anhydride may be prepared from the technical grade of acenaphthene.

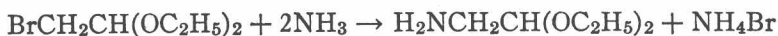
4. The acidification should be done in a hood; much sulfur dioxide is evolved. Hydrochloric acid does not precipitate all the quinone.

3. Methods of Preparation

Acenaphthenequinone has been prepared from acenaphthene by oxidation with chromic acid,^{1, 2, 3} with calcium permanganate,⁴ with air in the presence of catalysts in various solvents,^{5, 6, 7} and by the formation of an oxime with amyl nitrite followed by hydrolysis.⁸

AMINOACETAL

(Acetaldehyde, amino-, diethyl acetal)



Submitted by C. F. H. ALLEN and J. H. CLARK.

Checked by H. R. SNYDER, R. L. ROWLAND, and H. J. SAMPSON, JR.

1. Procedure

To a solution of 197 g. (1 mole) of bromoacetal¹ in 250 ml. of absolute alcohol, cooled in a hydrogenation bomb of about 1.1-l. capacity to the temperature of a Dry Ice-acetone bath, is added approximately 300 g. (about 18 moles) of liquid ammonia (Note 1). The bomb is closed, connected with a pressure gauge, and heated at 120–130° with shaking for 12 hours. The pressure rises to about 2300 pounds.

After the bomb has cooled, the ammonia is allowed to escape (Note 2) and the solution is poured out. The bomb is rinsed with

¹ Gräbe, *Ber.*, **20**, 659 (1887); **25**, 654 (1892); *Ann.*, **276**, 3 (1893).

² Dashevskii and Karishin, *Org. Chem. Ind. (U.S.S.R.)*, **1**, 729 (1936) [*C.A.*, **31**, 679 (1937)].

³ Kiprianov and Dashevskii, *J. Applied Chem. (U.S.S.R.)*, **7**, 944 (1934) [*C.A.*, **29**, 2530 (1935)].

⁴ Morgan, *J. Soc. Chem. Ind.*, **49**, 420 (1930).

⁵ Jaeger, Brit. pat. 318,617 [*C.A.*, **24**, 2145 (1930)].

⁶ Duckert, *Arch. sci. phys. nat.*, **15**, 244 (1933) [*C.A.*, **28**, 1255 (1934)].

⁷ Paillard, *Helv. Chim. Acta*, **16**, 775 (1933).

⁸ Reissert, *Ber.*, **44**, 1750 (1911).

¹ *Org. Syntheses*, **23**, 8 (1943); Bedoukian, *J. Am. Chem. Soc.*, **66**, 651 (1944).

two 200-ml. portions of absolute alcohol (Note 3), and the combined solution and washings are filtered. The alcohol is distilled from the filtrate at atmospheric pressure on the steam bath (Notes 4 and 5). The liquid residue is dissolved in 1.5 l. of ether, the inorganic solid which separates is filtered, and the ether is dried over 125 g. of potassium hydroxide pellets. The ether is evaporated and the residue is distilled at reduced pressure (Note 6). The material which distills below $180^{\circ}/15$ mm. is fractionated at atmospheric pressure in a modified Claisen flask. The material distilling below 161° , amounting to 15 g., is discarded. The aminoacetal distilling at 161 – 162° amounts to 43–52 g. (32–39%). The residue amounts to about 18 g. (Notes 7, 8, and 9).

2. Notes

1. The bomb is cooled by placing it in an iron pot of about two-thirds the height of the bomb. The pot is half filled with acetone, and pieces of Dry Ice are added until the vigorous evolution of carbon dioxide accompanying the addition of each new piece is no longer observed. If liquid ammonia is added to an insufficiently cooled solution of bromoacetal and alcohol, the ammonia is volatilized so vigorously that much of the starting material is lost. The checkers forced the ammonia from a small bomb into the bomb containing the alcohol and bromoacetal, at room temperature, by the aid of compressed hydrogen.²

2. Some of the reaction mixture may be carried from the bomb by the escaping ammonia. If the ammonia is allowed to escape through a tube leading into a beaker or flask, this material can be collected.

3. An appreciable amount of a slimy solid collects on the walls of the bomb. It appears to consist of ammonium bromide together with a small amount of iron salts dissolved from the walls of the bomb by the action of the ammonia. The amount of product recovered by careful working of this material is less than 2 g.

² *Org. Syntheses*, **23**, 69 (1943).

4. If much of the alcohol is left in the residue, the ether solution will deposit considerable amounts of inorganic salt during the drying over potassium hydroxide, and it will be desirable to filter rather than decant the ether solution. The yield is not affected.

5. A more elaborate procedure for working up this residue is as follows.

The residue is added to an equal volume (about 175 ml.) of water; the oil which separates is removed; and the water layer is extracted with two 150-ml. portions of ether. The water layer (A) is treated as described below. The extracts are dried over potassium hydroxide pellets, the ether distilled, and the residue fractionated. That portion (40 g.) of the distillate which comes over below $150^{\circ}/15$ mm. is refractionated at atmospheric pressure. The material (B) distilling below 180° , amounting to 19 g., is combined with the main portion of the product as indicated below.

The water layer (A) remaining from the ether extraction described above is treated with 175 g. of anhydrous potassium carbonate. The oil which separates is removed, and the water layer is extracted twice with 150-ml. portions of ether. The combined oil and extracts are dried over potassium hydroxide pellets and distilled at 15 mm. pressure. The material boiling below 180° at this pressure amounts to 63 g. This material is combined with the distillate (B) obtained above, and the whole is fractionated at atmospheric pressure. The material of b.p. $161\text{--}162^{\circ}$ amounts to 50 g. (37%).

6. This material contains a considerable amount of dissolved solids from which it is desirable to remove the product at as low a temperature as possible.

7. The low-boiling fraction was not investigated. The residue is largely diacetylamine (b.p. $124\text{--}127^{\circ}/7$ mm.) (11–14%).

8. Aminoacetal has been prepared from chloroacetal by this same procedure in a yield of 46%.

9. A procedure similar to the present one, in which potassium iodide is added to the reaction mixture, is reported to give slightly better yields.³ The checkers found that addition of potassium

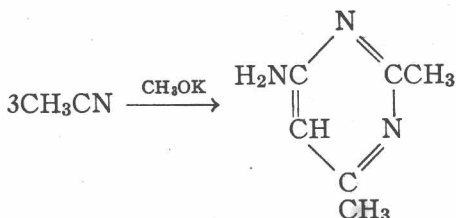
³ Cass, *J. Am. Chem. Soc.*, **64**, 785 (1942).

iodide to the reaction mixture in the present procedure had no beneficial effect.

3. Methods of Preparation

Aminoacetal has been prepared by the action of ammonia on haloacetals,^{3, 4, 5, 6, 7, 8, 9} by the reduction of nitroacetal using sodium in boiling alcohol,¹⁰ and by the reduction of glycine ester hydrochloride with sodium amalgam.¹¹

4-AMINO-2,6-DIMETHYLPYRIMIDINE



Submitted by ANTHONY R. RONZIO and WILLIAM B. COOK.
Checked by C. G. STUCKWISCH and HENRY GILMAN.

1. Procedure

Seventy grams (1 mole) of freshly prepared potassium methoxide (Note 1) and 41 g. (1 mole) of freshly purified acetonitrile (Note 2) are placed in a 500-ml. distilling flask. A cold-finger condenser which extends into the bulb of the flask is inserted through a rubber stopper in the neck of the flask, and a short

⁴ Wohl, *Ber.*, **21**, 617 (1888); **39**, 1953 (1906).

⁵ Wolff, *Ber.*, **21**, 1482 (1888); **26**, 1832 (1893).

⁶ Wolff and Marburg, *Ann.*, **363**, 179 (1908).

⁷ Marckwald, *Ber.*, **25**, 2355 (1892).

⁸ Hartung and Adkins, *J. Am. Chem. Soc.*, **49**, 2521 (1927).

⁹ Buck and Wrenn, *J. Am. Chem. Soc.*, **51**, 3613 (1929).

¹⁰ Losanitsch, *Ber.*, **42**, 4049 (1909).

¹¹ Fischer, *Ber.*, **41**, 1021 (1908).

piece of rubber tubing carrying a Hofmann clamp is connected to the side arm of the flask. The tubing is connected to an aspirator, and suction is applied until the acetonitrile begins to boil, whereupon the tubing is closed by means of the clamp and the flask is heated for 5 hours in an oil bath maintained at 140°.

At the end of the heating period the contents of the flask will have solidified. To the cold mixture 40 ml. of water is added to hydrolyze the potassium methoxide and precipitate the pyrimidine; the fine crystals are filtered and dried. The crude product is placed in a 500-ml. distilling flask with 250 ml. of purified kerosene (Note 3). On distilling the kerosene, the pyrimidine co-distills and solidifies in the receiving flask to a snow-white mass of crystals. These are filtered, washed well with petroleum ether, and dried in an oven at 100°. The yield of pure material, melting at 182–183°, is 27.5–28.7 g. (67–70%) (Note 4).

2. Notes

1. To prepare the potassium methoxide 39 g. (1 gram atom) of metallic potassium, cut *under toluene* (see p. 100) in 1-cm. cubes, is placed in a 1-l. three-necked flask which has been swept with nitrogen. The flask, fitted with a reflux condenser, mechanical stirrer, and dropping funnel, is immersed in a cooling bath at –30°, and absolute methanol is added through the funnel until all the potassium has dissolved. The excess methanol is removed by heating on the steam bath, finally under reduced pressure, and the potassium methoxide is dried overnight in a vacuum desiccator over sulfuric acid.

2. Commercial acetonitrile is treated with solid sodium carbonate until no more carbon dioxide is evolved. The nitrile is then distilled over phosphorus pentoxide and stored in tightly stoppered bottles. Before use, the nitrile is redistilled over phosphorus pentoxide.

3. Kerosene is purified by shaking for 24 hours with concentrated sulfuric acid. The kerosene is separated from the acid, washed several times with dilute sodium hydroxide, then with water, and finally dried over calcium chloride and distilled using

an air condenser. Purified kerosene is a water-white, sweet-smelling liquid.

4. The percentage yield decreases when larger or smaller quantities of material are used.

3. Methods of Preparation

4-Amino-2,6-dimethylpyrimidine has been prepared by heating the reaction product obtained from acetic anhydride and acetamidine;¹ by treating 4-chloro-2,6-dimethylpyrimidine with ammonia;² and by heating acetonitrile either with sodium ethoxide in a sealed tube³ or with sodium.^{4, 5}

¹ Pinner, *Ber.*, **22**, 1600 (1889).

² Schmidt, *Ber.*, **35**, 1577 (1902).

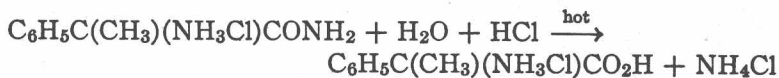
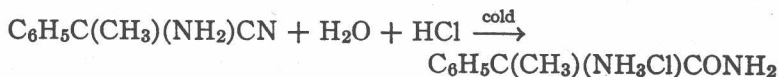
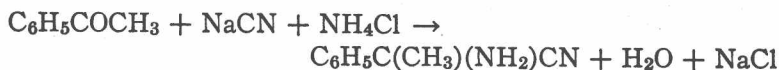
³ Schwarze, *J. prakt. Chem.*, (2) **42**, 3 (1890).

⁴ Keller, *J. prakt. Chem.*, (2) **31**, 365 (1885).

⁵ von Meyer, *J. prakt. Chem.*, (2) **27**, 153 (1883).

***dl*- α -AMINO- α -PHENYLPROPIONIC ACID**

(*dl*-Alanine, α -phenyl-)



Submitted by ROBERT E. STEIGER.

Checked by R. L. SHRINER and S. P. ROWLAND.

1. Procedure

In a 2-l. round-bottomed flask are placed, in the order mentioned, 50 g. (1 mole) of 98% sodium cyanide in 100 ml. of water, 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water (about 35°), and 134 ml. (2 moles) of aqueous ammonia (sp. gr. 0.90). The mixture is shaken while 120 g. (1 mole) of acetophenone in 300 ml. of 95% ethyl alcohol is added. The flask is stoppered with a rubber stopper, which is wired in place (Note 1), and is then immersed in a water bath maintained at 60°. The flask is shaken from time to time, and a homogeneous solution results within half an hour. The reaction mixture is heated for 5 hours at 60°, then well cooled in an ice-water mixture, and poured, with precautions (under a well-ventilated hood), into a 5-l. round-bottomed flask which is immersed up to the neck in an ice-water mixture and which contains 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18–1.19). The reaction flask is rinsed with two 25-ml. portions of water, which are added to the hydrochloric acid solution. The solution of the aminonitrile is satu-

rated at 0–5° with dry hydrogen chloride (Note 2) and is then set aside overnight in the ice-water bath, which is allowed to melt and come to the temperature of the room. The mixture of solid and liquid material is diluted with 1 l. of water and boiled vigorously for 2.5 hours under a reflux condenser in a well-ventilated hood (Note 3). The dark hydrolysate is concentrated under reduced pressure to remove the acetophenone and other volatile impurities. The solution is finally transferred to a 10-in. evaporating dish and is stirred occasionally while it is evaporated almost to dryness. Once a heavy deposit of inorganic salts has formed, very little bumping occurs. The solid residue is evaporated on a water bath twice with 100-ml. portions of water in order to remove as much hydrochloric acid as possible. The residue is crushed, and 600 ml. of absolute ethyl alcohol is added. The suspension is warmed for a short time on a steam bath; it is shaken thoroughly and then chilled in an ice-water mixture. The inorganic salts are removed by filtration through a 15-cm. Büchner funnel, and the cake is washed with small portions of absolute alcohol until 600 ml. has been used. The combined filtrates and washings are placed in a 3-l. beaker, and pyridine is added while the mixture is stirred by hand with a thick glass rod. The addition of pyridine is continued until the solution is nearly neutral to Congo red paper, and then an additional 50 ml. is added; the total amount of pyridine required is 80–100 ml. (Note 4).

The resulting rather stiff paste is chilled in an ice-water mixture for 1 hour. The solid is collected on a 15-cm. Büchner funnel and washed with 25-ml. portions of absolute ethyl alcohol until it is white and until the filtrate becomes colorless (100–200 ml. of alcohol is required). The fluffy material, after it is dried in a vacuum desiccator over flake sodium hydroxide, weighs 66 g. (40%).

The amino acid contains a small amount of ammonium chloride, which can be removed by dissolving the product in 21 times its weight of water and precipitating it by the addition of 42 times its weight of absolute ethyl alcohol (Note 5). The mixture is allowed to stand overnight in a refrigerator. The amino acid

is collected on a Büchner funnel and washed with an ethyl alcohol-water mixture containing 80% by weight of ethyl alcohol. The amino acid is dried in a vacuum desiccator over flake sodium hydroxide. The recovery is about 70% (Note 6).

2. Notes

1. A flask fitted with a ground-glass stopper is convenient for carrying out this step. The ground-glass stopper should be slightly lubricated with stopcock grease. It must be firmly secured in place by means of adhesive tape, as some pressure develops when the reaction mixture is heated.

2. From 500 to 600 g. of dry hydrogen chloride gas is required. Since this gas is very rapidly absorbed, a high-speed generator can be used.

3. The hydrolysis of the aminonitrile must be carried out under a good hood. The top of the reflux condenser should be connected with the ventilating pipe by means of a piece of glass tubing.

4. The minimum amount of pyridine necessary is determined by the amount of hydrochloric acid remaining in the residue.

5. The material does not readily become wet in contact with water, and it dissolves very slowly. The finely powdered material is best suspended in a large excess of water, e.g., about 30 times its weight. The suspension is boiled under a reflux condenser and frequently shaken until the solid is dissolved. The excess water is then boiled off at atmospheric pressure until a solution of the amino acid in 21 times its weight of water is obtained. The solution is then cooled and treated with absolute alcohol.

6. The amino acid does not have a sharp melting point. It sublimes with decomposition at about 265–270°.

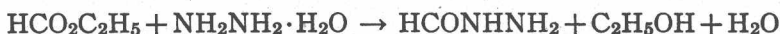
3. Methods of Preparation

α -Amino- α -phenylpropionitrile has been prepared by heating acetophenone cyanohydrin for 6 to 8 hours in a closed vessel with

1 equivalent of ethyl alcoholic ammonia at 70°;^{1,2} and by heating acetophenone for 4 hours in a closed vessel with an ethyl alcoholic solution of ammonium cyanide to 80°.³ α -Amino- α -phenylpropionitrile has been hydrolyzed by the action of, first, fuming hydrochloric acid at room temperature, and then dilute hydrochloric acid at boiling temperature, in the presence of some ethyl alcohol. This procedure gives a good yield of the amino acid hydrochloride. The amino acid has usually been liberated from its hydrochloride by means of ammonium hydroxide.^{1,2,3} The process of isolating the amino acid by treating an alcoholic solution of its hydrochloride with pyridine is essentially the same as that developed for the preparation of glycine⁴ and of α -aminoisobutyric acid.⁵

4-AMINO-1,2,4-TRIAZOLE

(1,3,4-Triazole, 1-amino-)



Submitted by C. F. H. ALLEN and ALAN BELL.

Checked by W. E. BACHMANN and G. DANA JOHNSON.

1. Procedure

In a 1-l. round-bottomed flask, equipped with an efficient water condenser, are placed 148 g. (2 moles) of ethyl formate (b.p. 52–53°) and 150 ml. of 95% ethanol. One hundred and twenty grams (2 moles) of 85% hydrazine hydrate is added

¹ Tiemann and Köhler, *Ber.*, **14**, 1981 (1881).

² McKenzie and Clough, *J. Chem. Soc.*, **101**, 395 (1912).

³ Jawelow, *Ber.*, **39**, 1195, 1197 (1906).

⁴ Clarke and Taylor, *Org. Syntheses*, **4**, 31 (1925); Coll. Vol. I, 298 (1941).

⁵ Clarke and Bean, *Org. Syntheses*, **11**, 4 (1931); Coll. Vol. 2, 29 (1942).

cautiously to this solution (Note 1) with shaking over a period of 10 minutes. After the reaction has subsided, the solution is refluxed on a steam bath for 18 hours. The bulk of the water and alcohol is now removed by evaporation under reduced pressure until the volume in the flask is about 150 ml. The resulting syrupy crude formhydrazide, is heated under atmospheric pressure for 3 hours, during which time the temperature of the bath is raised from 150° to 200°. After cooling to about 100°, the oil is taken up in 50 ml. of 95% ethanol, and 5 g. of Norite is added. The filtered solution is then diluted with 75 ml. of ether and placed in an icebox to cool. The crystalline product is filtered, washed with 50 ml. of 1 : 2 alcohol-ether, and dried. The yield of aminotriazole, melting at 77–78°, is 55–60 g. (65–71%) (Note 2). If a purer product is desired, the crude, washed material may be recrystallized, using 2 ml. of warm 95% ethanol per gram of compound followed by addition of 2.5 ml. of ether, and chilling. The melting point of the purified product is 81–82°.

The residual amine in the filtrate may be isolated in the form of the hydrochloride. The combined solutions are evaporated on a steam bath, 50 ml. of concentrated hydrochloric acid is added, and heating is continued for 2 hours. On cooling, the syrupy solution crystallizes. It is triturated with 50 ml. of ethanol, and the 4-amino-1,2,4-triazole hydrochloride is filtered, washed with a little ethanol, and dried. The yield of the hydrochloride is 10–18 g. (8–15%); the salt melts at 147–148° and may be recrystallized from 95% ethanol, using 10 ml. per gram; the melting point is thus raised to 151–152°.

2. Notes

1. The reaction is very vigorous, but, if the hydrazine hydrate is added carefully, no difficulty of control is encountered.
2. The combined yield of base and hydrochloride is always about 80–81%. When the amount of base is low, that of the hydrochloride is high.

3. Methods of Preparation

4-Amino-1,2,4-triazole has been obtained from orthoformic ester and hydrazine hydrate in a sealed tube at 120°;¹ by heating formylhydrazine at 150–210°;^{2,3,4} by heating N,N'-diformylhydrazine at 160°;⁵ by decarboxylation of 4-amino-1,2,4-triazoldicarboxylic acid;⁶ by fusion of 1,2-dihydro-1,2,4,5-tetrazine;⁶ and by heating 1,2-dihydro-1,2,4,5-tetrazinedicarboxylic acid above its melting point.^{4,6,7}

BENZOYL CYANIDE



Submitted by T. S. OAKWOOD and C. A. WEISGERBER.

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1. Procedure

In a 500-ml. distilling flask (Note 1) fitted with a thermometer extending to within 0.5 in. of the bottom are placed 110 g. (1.2 moles) of cuprous cyanide (Note 2) and 143 g. (118 ml., 1.02 moles) of purified benzoyl chloride (Note 3). The flask is shaken to moisten almost all the cuprous cyanide and is placed in an oil bath (Note 4) which has been previously heated to 145–150°. The temperature of the bath is raised to 220–230° and maintained between these limits for 1.5 hours. During the heating the flask is frequently removed from the bath (about every 15 minutes) and the contents are thoroughly mixed by vigorous shaking (Note 5). At the end of the 1.5 hours the flask

¹ Stolle, *J. prakt. Chem.*, (2) **68**, 467 (1903).

² Ruhemann and Stapleton, *J. Chem. Soc.*, **75**, 1132 (1899).

³ Ruhemann and Merriman, *J. Chem. Soc.*, **87**, 1772 (1905).

⁴ Hantzsch and Silberrad, *Ber.*, **33**, 85 (1900).

⁵ Pellizzari, *Atti accad. Lincei*, (5) **8** (I), 331 (*Chem. Zentr.*, **1899**, I, 1240); *Gazz. chim. ital.*, **39** (I), 530 (1909).

⁶ Curtius, Darapsky, and Müller, *Ber.*, **40**, 835, 1194 (1907).

⁷ Curtius and Lang, *J. prakt. Chem.*, (2) **38**, 549 (1888).