



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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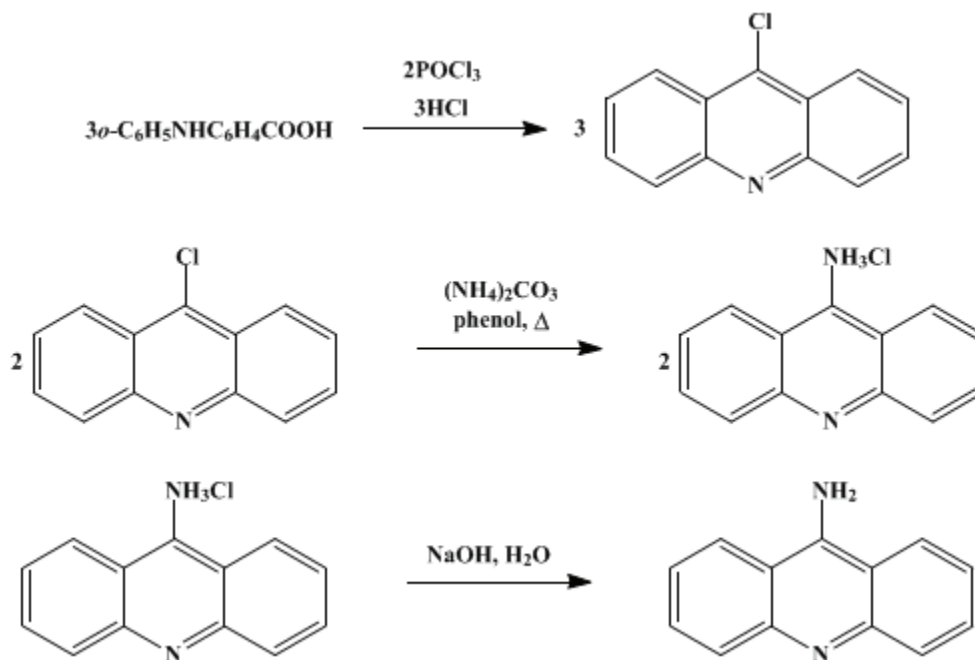
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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9-AMINOACRIDINE

[Acridine, 9-amino-]



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1. Procedure

In a 500-ml. round-bottomed flask fitted with a water-cooled condenser, 50 g. (0.23 mole) of *N*-phenylanthranilic acid (or 46 g. of acridone) is mixed with 160 ml. (270 g., 1.76 moles) of phosphorus oxychloride (Note 1). The mixture is slowly heated (about 15 minutes) to 85–90° on a water bath. A vigorous reaction sets in, and the flask is removed at once from the hot bath. If the reaction becomes too violent, the flask is immersed in a beaker of cold water for a moment. After 5–10 minutes, when the boiling subsides somewhat, the flask is immersed in an oil bath. The temperature of the bath is then raised to 135–140°, where it is maintained for 2 hours. The excess phosphorus oxychloride is removed by distillation from an oil bath at 140–150° under a vacuum of about 50 mm. The residue, after cooling, is poured into a well-stirred mixture of 200 ml. of concentrated ammonia solution, 500 g. of ice, and 200 ml. of chloroform. The flask is rinsed by shaking with a little chloroform-ammonia mixture (about 25–30 ml.). When no more undissolved solid remains (about 30 minutes is required), the chloroform layer is separated and the aqueous layer is extracted with an additional 40 ml. of chloroform. The united chloroform extracts are dried over 10 g. of calcium chloride and filtered, and the solvent is removed by distillation. The resultant greenish gray powder is dried at 70° for 20 minutes (Note 2) and (Note 3). The yield of crude 9-chloroacridine is 50 g. (practically theoretical), m.p. 117–118° (Note 4).

In a 1-l. beaker are placed 50 g. (0.23 mole) of crude 9-chloroacridine and 250 g. (2.7 moles) of phenol (Note 5). The mixture is stirred mechanically while it is heated to 70° (internal temperature) in an oil bath. Stirring is continued, and 30 g. (0.38 mole) of powdered ammonium carbonate (Note 6) is added as rapidly as the vigorous effervescence permits. The internal temperature is quickly raised to 120° and maintained there while the mixture is stirred for 45 minutes. The mixture is cooled to 30° and poured into 600 ml. of acetone in a beaker surrounded by ice. After about an hour, precipitation of 9-aminoacridine hydrochloride is complete and the product is filtered and washed free from phenol with 250 ml. of acetone (Note 7). The cake is extracted by boiling it with water three times, using

successively 800, 200, and 100 ml., the last portion containing 2 ml. of concentrated [hydrochloric acid](#). The hot solutions are filtered to remove the small amount of carbonaceous matter, and the filtrates are combined. Any precipitate is redissolved by heating, and then a solution of 60 g. of [sodium hydroxide](#) in 300 ml. of water is added. The mixture is cooled and filtered; the solid is washed with 300 ml. of cold water and dried at 120°. The yield is 34–38 g. (76–85% based on [phenylanthranilic acid](#) or [acridone](#)) of bright yellow powder, m.p. 230°. This product is pure enough for most purposes, but the crude material may be purified by boiling 38 g. of it with 1.2 l. of [acetone](#). The mixture is filtered by suction, and the filtrate is chilled in an ice-salt bath. The first crop weighs 26–27 g., and concentration of the mother liquor to 500 ml. yields an additional 6–7 g. of crystals. Both crops melt at 232–233°, and the recovery is 32–34 g. (84–89%) ([Note 8](#)).

2. Notes

1. The [phosphorus oxychloride](#) should be freshly distilled.
2. [9-Chloroacridine](#) is readily hydrolyzed in neutral and acid solutions; hence it must not be exposed to the air after removal of the [phosphorus oxychloride](#) and before treatment with [ammonia](#). If the drying is carried out at a higher temperature, loss results through sublimation. Care should be taken to keep [9-chloroacridine](#) from entering the eyes, as it is distinctly irritating.
3. It was found convenient to dry the [chloroacridine](#) by pouring the concentrated [chloroform](#) extract directly into the 1-l. beaker to be used for the next step, and heating the oil bath to 70° for the required 20 minutes.
4. If pure [9-chloroacridine](#) is desired, the crude product is dissolved in a little boiling alcohol, and 0.5% [ammonia](#) is added until the solution becomes milky. About 0.5 g. of [Norit](#) is then added; the solution is quickly filtered and at once cooled in an ice bath. White crystals, melting at 119–120°, are obtained. The product keeps best in a desiccator over [potassium carbonate](#). By warming [9-chloroacridine](#) with various primary and secondary amines, many substituted [9-aminoacridines](#) are readily obtained.
5. [9-Phenoxyacridine](#) appears to be an intermediate in this reaction.
6. The [ammonium carbonate](#) should analyze for 30% [ammonia](#). Baker's analyzed [ammonium carbonate](#) (lump) is suitable.
7. The [acetone](#) and the [phenol](#), recovered from the filtrate by simple distillation and by vacuum distillation, respectively, may be used again.
8. [9-Aminoacridine hydrochloride](#) is one of the most highly fluorescent of substances. The 1:1000 aqueous solution is pale yellow with only a faint green fluorescence, but the 1:100,000 solution is colorless with an intense blue fluorescence. [9-Aminoacridine](#) is a moderately strong base;¹ the dissociation constant is 3×10^{-5} ([aniline](#) = 5×10^{-10}).

3. Discussion

[9-Chloroacridine](#) has been prepared by heating [thioacridone](#),¹ [acridone](#),² or [N-phenylanthranilic acid](#)^{3,4,5} with [phosphorus pentachloride](#), [phosphorus oxychloride](#), or a mixture of the two phosphorus halides, with and without the addition of hydrocarbon solvents. The present method is essentially that of [Magidson](#),³ but the troublesome filtration of the glutinous and easily hydrolyzed [9-chloroacridine](#) has been avoided by the use of [chloroform](#).

The method described for converting [9-chloroacridine](#) to [9-aminoacridine](#) was developed after experience with the methods given in the literature, namely: conversion of [9-chloroacridine](#), through [9,9-diphenoxyacridan](#), to [9-phenoxyacridine](#), which is then heated with [ammonium chloride](#);⁶ heating [9-chloro-](#), [9-ethoxy-](#), or [9-phenoxyacridine](#) with [ammonia](#) and a [copper](#) compound under pressure,⁷ or with [phenylhydrazine](#) followed by acid reduction.⁸ [9-Aminoacridine](#) has also been prepared by hydrolyzing [9-cyanoacridine](#) (from [acridine](#) or [9-chloroacridine](#)) to the corresponding acid amide, and subsequent degradation to the required amine;⁹ and by the decomposition of the acid [azide](#).¹⁰ Some methods developed for preparing aminoethoxyacridines¹¹ are also of interest. [9-Aminoacridine](#) has also been obtained by the reaction of [acridine](#) with [sodium amide](#).¹²

References and Notes

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 11. Meister, Lucius, and Bruning, Ger. pat. 393,411 [*Frld.*, **14**, 807 (1921–1925)]; Ger. pat. 395,683 [*Frld.*, **14**, 812 (1921–1925)].
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

9-chloro-, 9-ethoxy-, or 9-phenoxyacridine

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonium carbonate (506-87-6)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

phenol (108-95-2)

Phenylhydrazine (100-63-0)

copper (7440-50-8)

acetone (67-64-1)

Norit (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

Acridone (578-95-0)

N-Phenylanthranilic acid,
phenylanthranilic acid (91-40-7)

azide

sodium amide (7782-92-5)

9-Aminoacridine,
Acridine, 9-amino- (90-45-9)

chloroform-ammonia

9-Chloroacridine (1207-69-8)

9-aminoacridine hydrochloride

chloroacridine

9-Phenoxyacridine

thioacridone

9,9-diphenoxyacridan

9-cyanoacridine

acridine (260-94-6)