



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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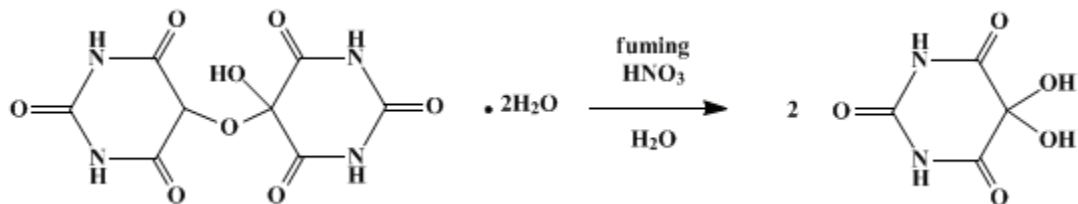
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 3, p.37 (1955); Vol. 23, p.3 (1943).

ALLOXAN MONOHYDRATE

[Alloxan]

[I. METHOD A]



Submitted by W. W. Hartman and O. E. Sheppard.

Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

In a 500-ml. flask (Note 1), fitted with a mechanical stirrer, are placed 36 ml. of water and 25 g. (0.078 mole) of finely crystalline *alloxantin dihydrate* (p. 42). The flask and contents are heated on a steam bath to 50°, and 3.6 ml. of fuming *nitric acid* (sp. gr. 1.62) is added in a fine stream while vigorous stirring is maintained and the temperature is not allowed to rise above 60° (Note 2). After all the fuming *nitric acid* has been added, the temperature is brought to 55° and the stirrer is stopped. In a few minutes a vigorous reaction begins, and large quantities of oxides of *nitrogen* are evolved. The stirrer is again started, and, if the reaction becomes too violent, the mixture is cooled somewhat; otherwise, the reaction is allowed to take its course. The reaction is complete when a current of air, introduced into the flask above the mixture, does not produce much color due to formation of *nitrogen tetroxide* (Note 3). The mixture is then heated to 60–65° for 10–15 minutes, whereupon practically all the solid dissolves. The reaction mixture is poured into a glass (Pyrex) tray and cooled overnight at 0° or below. The large triclinic, colorless crystals of *alloxan tetrahydrate* are broken up, filtered with suction, washed with ice water, and pressed as dry as possible. The crystals are then added to 25–26 ml. of *hot water* (Note 4), and the mixture is shaken until solution is complete. The solution is filtered immediately, and the filtrate is cooled overnight in a tray at 0°. The crystals are broken up, filtered, washed with ice water, and pressed as dry as possible. These moist crystals of the tetrahydrate, which weigh 22–24 g., are dried to constant weight in a glass tray over concentrated *sulfuric acid*. The resulting product is a fine white powder (Note 5) which weighs 16 g.

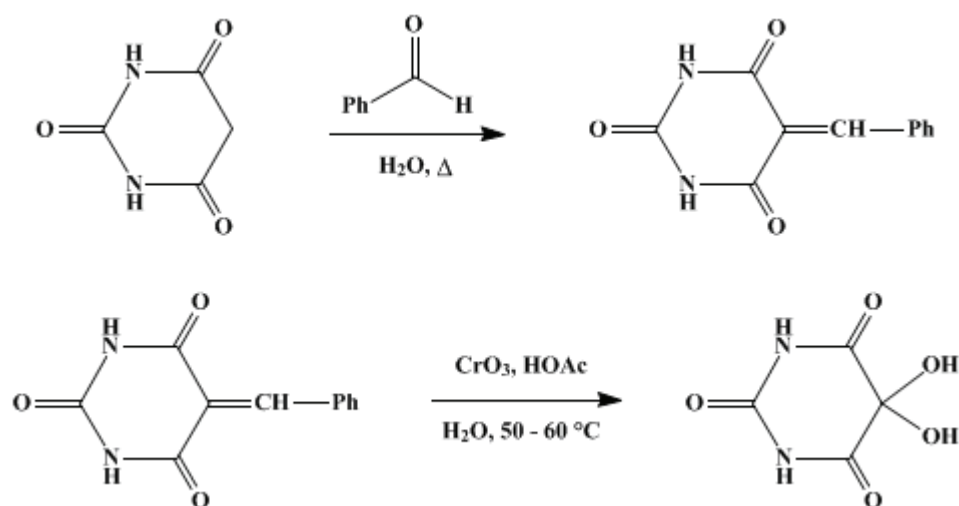
The mother liquor from the recrystallization is placed in a 250-ml. flask and is concentrated to a volume of 8–10 ml. under reduced pressure at not over 30–40° (Note 6). The concentrate, when cooled overnight at 0°, deposits a solid which is filtered, recrystallized from its own weight of boiling water, and dried over *sulfuric acid*. This solid weighs about 2 g. The mother liquors from the two crystallizations are combined with the original mother liquor from the oxidation, and the whole is evaporated to dryness under diminished pressure at not above 30–40°. This solid residue is somewhat yellow and possesses a strong odor of *nitric acid*. It is kept on a tray for several days until the odor of *nitric acid* disappears, and then it is dissolved in its own weight (2–3 g.) of boiling water, and the solution is cooled for several days below 0° (Note 7). The solid is removed, recrystallized from water, and dried over *sulfuric acid* (Note 8). This crop weighs about 0.5 g. The total yield of *alloxan monohydrate* is 18–19 g. (72–76%) (Note 9).

2. Notes

1. The large flask is necessary because the mixture foams greatly during the reaction.
2. Very little reaction occurs during the addition of the *nitric acid*, and consequently there is very little rise in temperature. The acid is added during a few minutes.
3. The reaction is complete in about 30 minutes.

4. The water must not be boiled during the addition of the crystals or afterwards as this will cause decomposition of the **alloxan** to **carbon dioxide**, **parabanic acid**, and **alloxantin**.
5. The tetrahydrate effloresces readily, gradually loses part of its water, and becomes moist when allowed to stand at room temperature. For this reason it is not suitable for storage. The monohydrate results when the material is dried over **sulfuric acid**. Drying in an oven is likely to result in local overheating and decomposition, which starts slightly above 100°; it is also likely to result in reddening if even a trace of **ammonia** or amines is present in the air.
6. A higher temperature is likely to cause oxidation and to result in a violent reaction which may become explosive as the **nitric acid** becomes concentrated.
7. **Alloxan tetrahydrate** crystallizes from solution much more slowly when it is nearly free of **nitric acid** and when other soluble substances are present; it is, however, less soluble in **nitric acid** solution than in water.
8. A little **alloxan** still remains in solution. The mother liquor still slowly colors the skin red and on standing deposits **alloxantin**. The **alloxantin** can be removed and used in another oxidation. About 0.3–0.5 g. of it may deposit after the filtrate has stood for some time.
9. The submitters obtained the same yields (per cent) when approximately 65 times these amounts of materials were used. Thus, carrying out the oxidation of 1610 g. (5 moles) of **alloxantin dihydrate** in a 22-l. flask, the submitters obtained 1085 g. of the first crop, 160 g. of the second, and 28 g. of the third, a total of 1273 g.

[II. METHOD B]



Submitted by John H. Speer and Thomas C. Dabovich.
 Checked by W. E. Bachmann and R. O. Edgerton.

1. Procedure

A. *Benzalbarbituric acid*. A mixture of 128 g. (1 mole) of **barbituric acid** and 1250 ml. of water in a 2-l. three-necked round-bottomed flask equipped with an efficient stirrer and a reflux condenser is heated on a steam bath to effect solution (**Note 1**). When the acid has dissolved, 115 g. (110 ml., 1.08 moles) of **benzaldehyde** is added while heating and stirring are continued. The solution rapidly fills with the insoluble **benzalbarbituric acid**. The mixture is heated for 1 hour on the steam bath to complete the reaction, and then is filtered by suction (**Note 2**). The filter cake is washed with several portions of hot water and dried at 100°. The yield is 190–205 g. (88–95%) of product possessing a very pale yellow color. The substance melts at 254–256° and needs no further purification.

B. *Alloxan monohydrate*. A mixture of 730 ml. of **acetic acid**, 95 ml. of water, and 162 g. (1.62 moles) of **chromium trioxide** (**Note 3**) is placed in a 2-l. three-necked round-bottomed flask fitted with a stirrer and a thermometer; the stirrer is started, and the mixture is warmed to 50°. To the solution 180 g. (0.83 mole) of **benzalbarbituric acid** is added in small portions during the course of 30 minutes, a cold

water bath being used to maintain the temperature at 50–60°. After all the acid has been added, stirring is continued and the temperature maintained at 50–60° by a warm water bath for another 30 minutes to complete the reaction. [Alloxan monohydrate](#) generally starts to crystallize from the warm solution. The mixture is cooled to 15° and filtered. The product is washed on the filter with cold glacial [acetic acid](#) until the washings are no longer green, and then is dried by washing with [ether](#). The yield is 105–112 g. (79–84%) of yellow crystals which melt at about 254° ([Note 4](#)) with decomposition and are sufficiently pure for most purposes.

In order to obtain practically colorless [alloxan monohydrate](#) ([Note 5](#)), 25 g. of the yellow crystals is dissolved in 37 ml. of hot water, the solution is boiled with [Norit](#), and the hot solution is filtered into a 500-ml. round-bottomed flask. About 15–20 ml. of water is removed by distillation under reduced pressure on a water bath. The colorless crystalline residue is dissolved in the minimal volume of hot water, the solution is cooled somewhat, and to it is added 250 ml. of glacial [acetic acid](#). After the mixture has been kept cold (5–10°) for 4–6 hours, the [alloxan monohydrate](#) is filtered. The yield is 20–21 g. (80–84% recovery) ([Note 6](#)) of practically colorless crystals which melt at about 254° ([Note 7](#)) with decomposition.

2. Notes

1. The submitters report that a single attempt to use the aqueous-ethanolic solution of [barbituric acid](#) obtained in *Org. Syntheses*, **18**, 8, before recrystallization of the product gave an excellent yield of an apparently isomeric product unsuited for the preparation of [alloxan](#).
2. This filtration may be done hot or cold at the convenience of the operator.
3. The technical grade (flakes) was found quite satisfactory.
4. This value is obtained in a Pyrex capillary tube; the solid remains yellow until about 254°, when it suddenly decomposes to a red melt with vigorous evolution of gas. When a soft-glass capillary tube is used, the solid assumes a red color at about 180–200° and melts between 240° and 250°.
5. By recrystallization of the yellow product from glacial [acetic acid](#) (12 ml. per g.), using [Norit](#), the checkers invariably obtained yellow crystals (75–80% recovery) instead of the practically colorless crystals reported by the submitters. By adding a volume of water equal to the weight of crystals to the hot [acetic acid](#) solution, the checkers obtained a pale yellow product.
6. This represents the first crop of crystals.
7. This value is obtained in a Pyrex capillary tube. The colorless solid begins to turn yellow at about 180° and melts at about 254° (occasionally 258–260°) to a red liquid with vigorous evolution of gas.

3. Discussion

[Alloxan monohydrate](#) has been prepared by the oxidation of [uric acid](#) with [chlorine](#),^{1,2} or [potassium chlorate](#) and [hydrochloric acid](#);³ by the oxidation of [alloxantin](#),⁴ [xanthine](#),⁵ [uramil](#),⁴ and [thiouramil](#);⁶ and by the hydrolysis of [dibromobarbituric acid](#).⁷ The method here described is originally due to Biilmann and Berg.⁸

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 4, 23](#)

References and Notes

1. McElvain, *J. Am. Chem. Soc.*, **57**, 1303 (1935).
2. Biltz and Heyn, *Ann.*, **413**, 60 (1917).
3. Fischer and Helferich, *Anleitung zur Darstellung organischer Präparate*, 10th ed., p. 66, Braunschweig, 1922.
4. Wöhler and Liebig, *Ann.*, **26**, 256 (1838).
5. Fischer, *Ann.*, **215**, 310 (1882).
6. Fischer and Ach, *Ann.*, **288**, 160 (1895).

7. Baeyer, *Ann.*, **127**, 230 (1863); **130**, 131 (1864).
 8. Biilmann and Berg, *Ber.*, **63B**, 2201 (1930).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

benzaldehyde (100-52-7)

Norit (7782-42-5)

chlorine (7782-50-5)

potassium chlorate (3811-04-9)

nitrogen tetroxide

uric acid

Barbituric acid (67-52-7)

chromium trioxide (1333-82-0)

Uramil (118-78-5)

alloxantin (76-24-4)

Alloxan monohydrate (2244-11-3)

Alloxan (50-71-5)

Alloxantin dihydrate (6011-27-4)

alloxan tetrahydrate

Benzalbarbituric acid (27402-47-7)

xanthine

thiouramil

dibromobarbituric acid (511-67-1)

Parabanic acid (120-89-8)