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# Studies on the Preparation of Quinoline-2-Aldehyde\*

### By VIRGINIA G. RAMSEY

A study has been made of the effect of the purity of the oxidizing agent upon the yield of quinoline-2-aldehyde obtained from the oxidation of 2-methylquinoline with selenium dioxide. Other conditions are described which result in increasing the yield of aldehyde in this reaction.

UINOLINE-2-ALDEHYDE was an important intermediate in the preparation of compounds which were evaluated as antimalarial and antitubercular drugs.

A number of procedures for preparing quinoline-2-aldehyde may be found in the literature.  $\alpha$ -(2-Quinoline)- $\beta$ -hydroxy- $\gamma$ -trichloro-propane, which was prepared readily from 2-methylquinoline and chloral by the method of Alberts and Bachman (1), was converted to  $\beta$ -(2-quinolyl)-acrylic acid following the work of Einhorn and Sherman (2), and this then was oxidized to quinoline-2-aldehyde according to the procedure described by Clemo and Hogarth (3). Henze (4) and Kaplan (5) reported the preparation of quinoline-2-aldehyde by the oxidation of 2methylquinoline with selenium dioxide. All oxidation methods for the preparation of the aldehyde were accompanied by the formation of carboxylic acids and condensation by-products (3, 5, 6). In this laboratory the most direct method and the most satisfactory with respect to yield was the oxidation of the corresponding methylquinoline to quinoline-2-aldehyde with selenium dioxide. When the method of Kaplan (5) was extended to amounts of 2-methylquinoline larger than those described, the yield of aldehyde decreased appreciably. The procedure developed by Hamilton (7) for the preparation of quinoline-4-aldehyde was applied to the preparation of the 2-aldehyde, but gave poorer yields of this aldehyde than the Kaplan method.

This paper describes a study of the effect of the degree of sublimation of the selenium dioxide on the yield of quinoline-2-aldehyde. Modifications of selenium dioxide oxidation procedures which increased the yield of quinoline-2-aldehyde are reported also.

#### EXPERIMENTAL

The Effect of the Degree of Sublimation of Selenium Dioxide on the Yield of Quinoline-2-aldehyde.--Selenium dioxide was prepared as described in "Organic Syntheses" (8) and sublimed using the method of Hill, Soth, and Ricci (9).

In each of the tabulated runs the procedure was the same. Quinaldine (10 Gm.) was dissolved in dioxane (17 cc.) and added to a mixture of selenium dioxide (9 Gm.), dioxane (80 cc.), and water (3.2 cc.). The method followed was essentially that of Kaplan (5), only the following changes were introduced: (a) During the removal of dioxane from the filtrate under reduced pressure, care was taken to keep the temperature of the bath below  $70^{\circ}$ . (b) Before steam distillation the aqueous solution was made alkaline to phenolphthalein with sodium bicarbonate. Results of the study are summarized in Table Ι.

Quinoline-2-aldehyde .-- The procedure for the oxidation of 2-methylquinoline to quinoline-2-aldehyde with selenium dioxide which was found to be most satisfactory is described below. Quinoline-2aldehyde decomposed when distillation was attempted; the decomposition occurred at a bath temperature of 170° and a pressure of 2 mm.

Quinaldine (51.6 Gm.) was dissolved in dioxane (400 cc.) and heated to 60° in an oil bath on a hotplate in a flask carrying an efficient stirrer and reflux condenser. Selenium dioxide (40 Gm.), which had been freshly prepared and immediately sublimed, was added in small portions over one-half hour. The temperature during the addition rose to 88°.

<sup>\*</sup> Received July 5, 1951, from the Department of Research in Organic Chemistry, Mellon Institute, Pittsburgh, Pa.

Run	Degree of Purification of SeO2	Temperature of Reaction Mixture, °C.	Temperature of Bath, °C.	Weight of Crude Aldehyde Hydrate, Gm.	Yield, %
1	Unsublimed	95	110 - 115	5.0	41
2	Once sublimed	95	110 - 115	4.5	37
3	Once sublimed	80-85	8085	4.6	38
4	Once sublimed then washed with 3 portions of dioxane	95	110 - 115	4.0	33
5	Twice sublimed	95	110 - 115	4.4	36
6	Residue from sublimations	95	110-115	3.2	26

TABLE I.—THE EFFECT OF THE PURITY OF THE SELENIUM DIOXIDE ON THE YIELD OF QUINOLINE-2-ALDEHYDE

TABLE II.—COMPARISON OF YIELDS OBTAINED BY VARIOUS M	ethods
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Method	2-Methylquinoline, Gm.	Yield of Crude Quinoline-2- aldehyde, %	Yield of Purified Quinoline-2- aldehyde, %	Melting Point, °C.
Hamilton (7)	80.0		11	67-69
Kaplan (5)	77.0	19		
Modified	51.6	30	22	67-69
Modified	59.3	30	20	67-68

After the addition of all the selenium dioxide the reaction was continued at a temperature of 75-88° for one-half hour and then the solution was filtered hot to remove the precipitated selenium. Dioxane was removed under reduced pressure at a temperature which was maintained below 70°. Water (400 cc.) was added to the residue which remained after evaporation of the solvent. The solution was made alkaline to litmus with sodium bicarbonate and steam distilled. The distillate was chilled overnight in a refrigerator before filtering off the quinoline-2aldehyde hydrate.

On drying the hydrate in a desiccator over phosphorus pentoxide, 17.0 Gm. of crude quinoline-2aldehyde was obtained; yield, 30%. This material was crystallized from Skellysolve (3 cc. of Skellysolve to 1 Gm. of aldehyde) and dried to constant weight in a desiccator over phosphorus pentoxide and paraffin. The crystallized quinoline-2-aldehyde was found to weigh 12.5 Gm. and melt at 67-69°; yield, 22%.

A comparison of the yields obtained using the different selenium dioxide oxidation procedures is given in Table II. In all cases the selenium dioxide had been freshly prepared and once sublimed.

#### SUMMARY

1. The effect is shown of the purity of the selenium dioxide upon the yield of quinoline-2aldehyde for the reaction in which quinoline-2aldehyde is prepared by the oxidation of 2methylquinoline with selenium dioxide.

2. Conditions are described for the preparation of quinoline-2-aldehyde, from 2-methylquinoline by oxidation with selenium dioxide, in improved yields.

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## American Association for the Advancement of Science-Pharmacy Subsection Meeting

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The next meeting of the American Association for the Advancement of Science will be held in Philadelphia on December 26-31, 1951. The program of the Pharmacy Subsection of the Medical Sciences has been made up. Six sessions of this Subsection will be held. Members are invited to attend the meetings of the Section on Medical Sciences, Subsection on Medicine, and the Section on Chemistry.