

# Reductive and oxidative synthesis of saturated and unsaturated fatty aldehydes

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**Abstract** Saturated and unsaturated fatty aldehydes were synthesized 99+% pure with yields of up to 80% by the reduction of 1-acylaziridines with lithium aluminum hydride, and in yields of up to 87% by oxidation of the corresponding alcohol with 1-chlorobenzotriazole. It was found for the reduction that optimum aldehyde yield was obtained with a mole ratio of reactants, consisting of acid chloride-ethylenimine-triethylamine-LiAlH<sub>4</sub>, equal to 1:2:2:2. Optimum conditions for alcohol oxidation were found to be a mole ratio of oxidant to alcohol of 1:1.3 with refluxing for 45 min in methylene chloride containing 25% pyridine. Methods for the purification of the final product are also described. Purity criteria were thin-layer and gas-liquid chromatography and infrared and nuclear magnetic resonance spectroscopy.

**Supplementary key words** fatty alcohol · lithium aluminum hydride · 1-acylaziridines · thin-layer chromatography · gas-liquid chromatography · 1-chlorobenzotriazole

**T**HOUGH THERE ARE many published methods for synthesizing aldehydes (1), practically all of these methods deal with chain lengths of less than C<sub>8</sub>. One report has appeared on the synthesis of long-chain aldehydes by reduction of the corresponding acid chlorides with lithium aluminum tri-*t*-butoxy hydride giving a yield of 55% of purified product (2). Using two different methods we have synthesized long-chain saturated and unsaturated aldehydes, with yields of up to 87% after purification. The first method was a modification of a procedure described by Brown and Tsukamoto (3) for the LiAlH<sub>4</sub> reduction of short-chained 1-acylaziridines obtained from the corresponding acid chlorides. The second procedure was the oxidation of the corresponding fatty

alcohol with a new oxidizing agent, 1-chlorobenzotriazole (4). In this paper we describe these methods of synthesis, giving the conditions for optimum yield of fatty aldehydes and suggested mechanisms to account for our observations.

## MATERIALS

Palmitic acid and oxalyl chloride were purchased from Eastman Kodak Co., Rochester, N.Y. Thionyl chloride (purified), ether (anhydrous), and triethylamine (TEA) were purchased from J. T. Baker Chemical Co., Phillipsburg, N.J. Ethylenimine (EEI) was purchased from Matheson Coleman & Bell, Norwood, Ohio. Heptadecanoic acid, oleic acid, linoleic acid, and 14.5% EGSS-X on Gas-Chrom P were purchased from Applied Science Laboratories Inc., State College, Pa. Lithium aluminum hydride was purchased from City Chemical Corp., New York, and Ventron Corp., Beverly, Mass. Silicic acid (100 mesh) was purchased from Mallinckrodt Chemical Works, St. Louis, Mo. Silica gel G, standard palmitaldehyde, and stearaldehyde were purchased from Analabs, Inc., North Haven, Conn. Cetyl alcohol was purchased from Sigma Chemical Co., St. Louis, Mo. 1-Chlorobenzotriazole was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis. Dry ether was obtained by treating anhydrous ether with sodium. All other solvents and reagents were reagent grade. Merck hexane was used in the chromatography procedures and was purchased from Will Scientific, Inc., Ann Arbor, Mich.

## METHODS

### Preparation of acid chlorides

Acid chlorides were prepared essentially as described by Rao, Ramachandran, and Cornwell (2). When 100-mg quantities or less were used, the refluxing time was

Abbreviations: GLC, gas-liquid chromatography; TLC, thin-layer chromatography; EEI, ethylenimine; TEA, triethylamine; EGSS-X, ethylene glycol succinate-methyl silicone polymer.

reduced to 1 hr and the vacuum distillation step eliminated.

### Reduction of acid chlorides to aldehydes

Acid chlorides were reduced essentially as described by Brown and Tsukamoto (3). The acid chlorides (0.5 mmole) were cooled in an ice-salt mixture and a stirred solution of 1 mmole of EEI and 1 mmole of TEA in 1 ml of cold, dry ether was added with continuous shaking and cooling over a period of 1 hr. After another half hour of shaking, the precipitated TEA hydrochloride was filtered off and washed thoroughly with dry ether. The combined ether solutions were reduced in volume using a rotary evaporator and cooled to  $-5^{\circ}\text{C}$  in an ice-salt mixture. 1 mmole of lithium aluminum hydride suspended in 5 ml of cold, dry ether was added to the stirred solution over a period of 1 hr. The mixture was continuously shaken while cooling over a period of another hour. Cold 5 N sulfuric acid was cautiously added until two layers, equal in volume, were obtained. The aqueous layer was removed and reextracted with dry ether several times. The combined ether layers were washed first with water, then with a saturated sodium bicarbonate solution, and finally several times with water. Occasionally, the ether layer foamed on addition of water; it was allowed to separate by standing overnight at  $2-5^{\circ}\text{C}$ . Finally, the crude product was dried overnight over sodium sulfate.

### Analysis and purification

The crude products were analyzed by GLC using a Packard gas chromatograph, model 7500, equipped with a dual hydrogen flame ionization detector. A 6-ft glass column containing 14.5% EGSS-X on 100-120 mesh Gas-Chrom P was used. The analyses were run at either  $150$  or  $180^{\circ}\text{C}$  with nitrogen as the carrier gas at a flow rate of 110 ml/min, with an inlet pressure of 31 psi. Peaks on the chromatograms were identified by co-chromatography with available standards or by relative retention times. Triangulation of peak areas was used to calculate percentage distributions. The instrument was calibrated using mixtures of known percentages of saturated aldehydes and alcohols from  $\text{C}_{12}$  to  $\text{C}_{19}$ .

The aldehyde and by-products were separated by either TLC or column chromatography on silicic acid. Aliquots of the crude product were applied to neutral thin-layer plates (5) of silica gel G and developed in hexane-chloroform-methanol 73:25:2 (v/v/v) (6). The plates were visualized under UV light after spraying them with 0.05% rhodamine G in 80% aqueous methanol. The bands corresponding to standard aldehyde and alcohol were scraped off, eluted with chloroform, and stored in fresh carbon disulfide at  $4^{\circ}\text{C}$  under nitrogen (7). Rhodamine G is not eluted with chloro-

form. Crude aldehyde was also purified on a column packed with 10 g of 100-mesh silicic acid previously heated at  $110^{\circ}\text{C}$  in an oven for 12 hr. The column was thoroughly prewashed with hexane-ether 9:1 (v/v) before applying the samples. Crude saturated aldehydes were applied to the column in hexane-ether 9:1 (v/v) and were eluted pure with about 65 ml of the same solvent; unsaturated aldehydes were eluted with about 100 ml of solvent. The purity of the aldehydes was assessed by IR and NMR spectroscopy as previously described (6, 8).

### Oxidation of alcohols to aldehydes with 1-chlorobenzotriazole

Cetyl alcohol was oxidized to palmitaldehyde essentially as described by Rees and Stoor (4). 500 mg of cetyl alcohol (2.06 mmoles) and a slight excess (400 mg) of 1-chlorobenzotriazole were dissolved in 5 ml of methylene chloride containing 25% pyridine. The mixture was refluxed for 45 min to 1 hr. After refluxing, the solution was cooled in ice and the precipitated benzotriazole hydrochloride separated. The precipitate was filtered off below  $0^{\circ}\text{C}$ . Because the precipitated benzotriazole hydrochloride is soluble in both methylene chloride and pyridine, one of two additional methods was used to purify the crude product.

(a) Aliquots of the crude product were applied to neutral thin-layer plates of silica gel G and developed in hexane-isobutanol-methanol 100:3:3 (v/v/v) (6). The aldehydes and alcohols are not separated well in this solvent system, but they are separated from other components of the crude mixture. The aldehyde and alcohol areas were scraped together from the plate, eluted with chloroform, and applied to a second plate, which was developed in hexane-chloroform-methanol 73:25:2 (v/v/v) (6).

(b) Aliquots of the crude product were applied to a thin-layer plate of aluminum oxide H which was developed in hexane-ether-acetic acid 70:30:1 (v/v/v). All the impurities including alcohols separated from the aldehyde in this system.

## RESULTS

### Reduction of 1-acylaziridines

The earlier work of Brown and Tsukamoto (3) showed that the 1-acylaziridines, formed by adding the corresponding acid chloride to an equimolar mixture of EEI and TEA, need not be isolated before the addition of  $\text{LiAlH}_4$ , and that a 100% excess of  $\text{LiAlH}_4$  made no difference in the reaction. In contrast, however, we have found that for long-chain aldehydes, the reaction is very sensitive to both the amount and the source (perhaps this

was due to storage time) of the hydride. Our best results were obtained with  $\text{LiAlH}_4$  purchased from City Chemical Corp. The percentage distributions of the products were calculated from GLC analysis of the crude mixture following the reaction. The yield of aldehyde was determined after purification by *p*-nitrophenylhydrazone formation as described previously (9), and by quantitative GLC. The identity of the products, which consisted of aldehyde, the corresponding alcohol, and 1-alkylaziridine, was determined by cochromatography (GLC) with standards, and by IR and NMR spectroscopy following their isolation from the crude mixture. For less than 100-mg quantities, pure aldehydes were obtained by TLC on silica gel G as described previously (6). Larger amounts of aldehydes were purified on a silicic acid column using hexane-ether 9:1 (v/v) as the developing solvent. Saturated aldehydes were eluted from this column in the first 50–60 ml and unsaturated aldehydes in the first 85–100 ml; the saturated alcohols came off in the 85–150-ml fraction and unsaturated alcohols in the 130–300-ml fraction. The 1-acylaziridines are insoluble in this solvent and were readily obtained by washing the column with chloroform.

A second series of experiments was carried out by varying the amounts of EEI and TEA. Aldehyde yields of 80% or better were achieved using a mole ratio of acid chloride-EEI-TEA- $\text{LiAlH}_4$  equal to 1:2:2:2. Even a slight deviation in this ratio to 1:2.5:2.5:1 gave only a 30% yield of aldehyde, the 1-hexadecylaziridine being the major product. This is shown in Fig. 1. In addition to

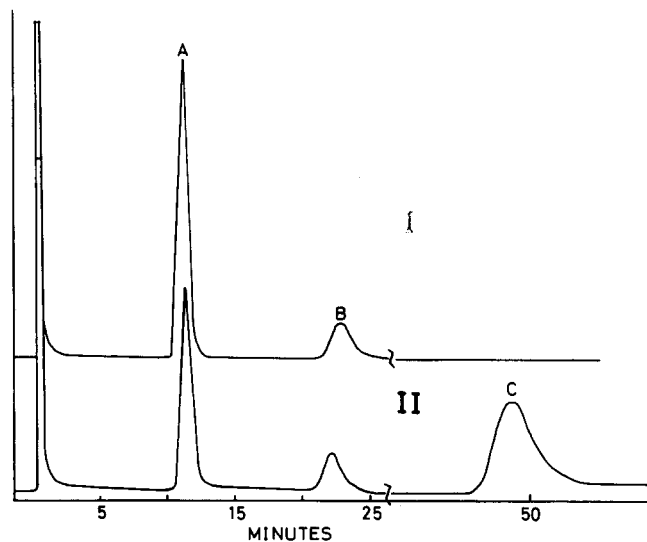


FIG. 1. Gas-liquid chromatogram showing the effect of the mole ratio of product distribution during the synthesis of palmitaldehyde from 1-palmitoylaziridine. The 6-ft column contained 14.5% EGSS-X on Gas-Chrom P, and the temperature was 150°C. Peak identification: A, palmitaldehyde; B, cetyl alcohol; C, 1-palmitoylaziridine. Reactant ratio of palmitoyl chloride-EEI-TEA- $\text{LiAlH}_4$  for curve I, 1:2:2:2; for curve II, 1:2.5:2.5:1.

TABLE 1. Reduction of saturated and unsaturated fatty acids to the corresponding aldehydes with  $\text{LiAlH}_4$

Starting Material	Amount	Distribution of Products		Yield of Aldehyde
		Aldehyde	Alcohol	
	mmoles	%	%	%
Hexadecanoic acid	0.50	86	14	82
Heptadecanoic acid	0.40	90	10	65
Oleic acid	3.54	75	25	72
Linoleic acid	3.50	60	40	55

palmitaldehyde we have synthesized odd-chain and unsaturated fatty aldehydes in acceptable yields, using the optimum ratio of reactants described above. These results are given in Table 1. Under the optimum conditions used, no 1-alkylaziridine was obtained.

#### Oxidation of cetyl alcohol with 1-chlorobenzotriazole

Our results with cetyl alcohol, using the procedure of Rees and Storr (4), have shown, as in the previous experiments, that the conditions for long-chain alcohols had to be modified. We tested their procedure using benzyl alcohol and achieved essentially the same results. With cetyl alcohol, however, less than 10% conversion to palmitaldehyde had occurred even after refluxing for 72 hr. This was shown by periodic GLC analysis of the refluxing mixture. We examined various mole ratios of oxidant to cetyl alcohol, as well as refluxing times, and obtained optimum yields of aldehyde with a 10:1 excess of 1-chlorobenzotriazole refluxed for 7 hr.

It was further found that when a small amount of pyridine (0.5 ml) was added to the reaction mixture containing the 10:1 excess of oxidant in 5 ml of methylene chloride, 90% conversion to the aldehyde occurred in 3 hr rather than in the 7 hr required without pyridine. Carrying out the reaction with pyridine as the solvent and only a slight excess of oxidant relative to cetyl alcohol gave only 34% conversion to the aldehyde. The best yields, in the shortest time, were obtained with a mole ratio of oxidant to alcohol of 1:1.3 in a medium of methylene chloride containing 25% pyridine, with refluxing for 45 min. The yield of aldehyde under these conditions was 82%.

#### DISCUSSION

Our findings for the reduction of acylaziridines are consistent with the proposed mechanism for the reduction of substituted amides (10).

Decomposition or hydrolysis of the acylaziridine molecule at the moment of reaction with the  $\text{LiAlH}_4$  has been offered to explain the formation of alcohol (11). Formation of the 1-alkylaziridine has been attributed to

attack by the aluminumhydride ion,  $\text{AlH}_4^-$ , which apparently exists in ether solution (12).

Pyridine has been shown to enhance the reactivity of  $\text{LiAlH}_4$  (13), while in the work reported here, TEA seems to play a similar role, as evidenced by the fact that the 1-alkylaziridine was the major product when TEA was in excess.

The oxidation of alcohols with 1-chlorobenzotriazole has been suggested to proceed by a radical mechanism (4). The fact that carrying out the reaction under the recommended conditions allowed total recovery of the starting alcohol argues against the homolytic reaction mechanism suggested. Such a mechanism implies that chlorine atoms generated in the chain-initiatory step would react in some manner with the cetyl alcohol, whether it is at the  $\alpha$ -H or elsewhere along the chain. The essentially total recovery of alcohol, however, argues in favor of a  $\text{S}_{\text{N}}2$  type reaction, probably on the nitrogen of 1-chlorobenzotriazole.

In agreement with this mechanistic conclusion is the observation that the presence of pyridine caused a significant increase in the rate of the reaction. This is probably because it either aids in the generation of the more nucleophilic alkoxide ion or prevents the formation of oxonium salts which would further deactivate the acetyl alcohol. Rees and Storr (4) in their work did not use any primary alcohols. When one examines the substrates used by these workers, it is quite logical to conclude that, in their case, a homolytic mechanism was operating. With primary alcohols, however, our evidence indicates a heterolytic mechanism.

We have successfully used both of the procedures described in this paper for the synthesis of  $[1-^{14}\text{C}]$ palmitaldehyde. The method of choice for synthesizing radio-labeled fatty aldehydes is obviously the oxidation of the corresponding  $^{14}\text{C}$ -labeled fatty alcohol with 1-chlorobenzotriazole, due to the better yields and shorter reaction time. The synthesis of  $[1-^3\text{H}]$ palmitaldehyde using the method of Brown and Tsukamoto (3) has been described previously (14), although these workers made no comments as to yield or problems encountered.

This investigation was supported, in part, by a Public Health Service Research Grant HE13361-01 from the National Heart and Lung Institute, National Institutes of Health.

Helpful suggestions from Dr. H. Harry Szmant are gratefully acknowledged.

*Manuscript received 26 March 1971; accepted 22 July 1971.*

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