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Proof of Concept

Is Small-scale Production of Diethyl Ether for Anesthetic Use Possible?

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ABSTRACT

Background: Clinicians face numerous challenges when providing effective anesthesia in the setting of humanitarian crisis or armed conflict. Anesthetic supply limitations often stand as a critical gap in these environments. Due to its clinical safety profile and relatively simple production, diethyl ether (Et₂O) may offer a solution in such situations. **Methods:** The dehydration of ethanol (EtOH) using an acid-catalyzed reaction was conducted twice. Sulfuric acid was added to a solution of ethanol in a glass flask that was heated to approximately 145 °C, promoting the formation of Et₂O and water. At this temperature, Et₂O was isolated from the solution through fractional distillation and collected in a flask that was cooled in an ice bath. The distillate was analyzed using proton nuclear magnetic resonance (¹H NMR) spectroscopy. **Results:** Two samples of Et₂O were obtained using an acid-promoted dehydration of ethanol. Analysis of the samples using ¹H NMR spectroscopy led to the identification of two components, Et₂O and EtOH, whose identities were confirmed by comparison of the constituent peaks to known chemical shifts. Integration of the relevant peaks suggested a Et₂O purity of approximately 97%. **Conclusion:** This proof-of-concept study demonstrates that relatively pure Et₂O can feasibly be produced and isolated on a small scale using an acid-catalyzed dehydration reaction with fractional distillation.

KEYWORDS: *ether anesthesia; austere; ether; diethyl ether; inhalation agents*

Background

When considering healthcare in future disasters, humanitarian crises, or armed conflict with peer or near-peer adversaries, the U.S. Military will likely face challenges that were not present in

more recent conflicts. Lack of air superiority, robust resources, frequent resupply, and delayed evacuation are expected to plague healthcare systems in such situations.¹ One particular field of medicine that tends to be drastically impacted by such catastrophes is the provision of safe anesthesia. While surgical care in these settings has been well described in the literature, there is little documentation describing the provision of anesthesia under such circumstances. Previous reports suggest that use of inhaled anesthetics in these challenging environments is often limited simply by supply shortages of such medications.² Unfortunately, this often results in insufficient availability of anesthesia and analgesia or the inability to perform needed operations for many patients. Experience has led many experts to believe that in order to continue to provide effective clinical care when resources are restricted, clinicians must revert to techniques that were safely used in the past.³

Diethyl ether (Et₂O), a once commonly used anesthetic, has been replaced with inhaled general anesthetics that are far less flammable.⁴ Its previously demonstrated safety profile and simple production suggest that this agent may once again have value in resource-constrained environments.⁵ Natural disasters, armed conflict, and remote settings may force clinicians to provide prolonged field care, where conventional general anesthetic techniques may not last for necessary time periods, especially when numerous casualties are expected.^{2,6} Additionally, smaller, more mobile surgical teams are likely to become “mission incapable” if evacuation or resupply are not available.⁷ Yet, history has shown that conflict will likely limit both capabilities.⁶ As identified by previous literature, the ability to produce Et₂O, using common reagents, would certainly fill this gap. The present study aims to establish a proof of concept for producing diethyl ether using ethanol (EtOH) and sulfuric acid.

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Methods

A modification of the known acid-promoted dehydration of EtOH was used.⁸ The reaction and distillation were carried out twice using standard laboratory equipment and American Chemical Society (ACS) grade reagents. In both procedures, a 50mL two-necked, round-bottomed flask was charged with EtOH (15mL) and a magnetic stir bar.

Concentrated sulfuric acid (15mL) was slowly added dropwise. The flask was fitted with a Vigreux distilling column/condenser, and a thermometer was inserted at the top of the distilling column. The distilling column was wrapped in a layer of aluminum foil. Ice-cold water was circulated through the condenser using a commercial fish pump. The condenser outlet was fitted with a receiving flask, which was submerged in an ice water bath for cooling. (Figure 1). Once the apparatus was secure, the round-bottomed flask was submerged in a silicone oil bath that was heated to 145–150°C. As distillate was collected, additional portions of EtOH were added (6×1mL additions over a 4hr period).

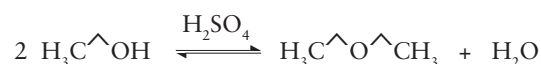


FIGURE 1 Image of equipment for the acid-catalyzed dehydration of ethanol to form diethyl ether and the fractional distillation of the diethyl ether. (A) 50mL flask in which sulfuric acid was added to a solution of ethanol. (B) distilling column, containing a thermometer. (C) condenser. (D) receiving flask, in an ice bath.



Distillate was collected over the course of 4 hours. At this point, heating was discontinued, and the collection flask was charged with 5% sodium hydroxide (aqueous) and swirled. The organic layer was collected and analyzed without further

purification. For the two experiments conducted, the collected volumes were 2.6 and 1.5mL, respectively.

Results

The two samples were analyzed immediately by proton nuclear magnetic resonance (¹H NMR) spectroscopy, a common analytical method in organic chemistry. In each spectrum, two components were observed. The identifying spectroscopic features for Et₂O and EtOH are known from chemical literature; this information was used to assign the constituents in the annotated spectrum (Figure 2). For the non-chemist, the lines in the spectrum provide an identifying “signature” of the analyte that can be easily compared to established standards. Integration of the relevant peaks gives the Et₂O purity level on a molar basis of approximately 97%, with the only other discernable protic component being EtOH.⁹ (The peak at 7.26 parts per million is from deuterated chloroform (CDCl₃), the solvent used to carry out the NMR analysis.) Since Et₂O has a higher molecular weight than EtOH, the Et₂O purity level on a mass basis is slightly higher than 97%.

Discussion

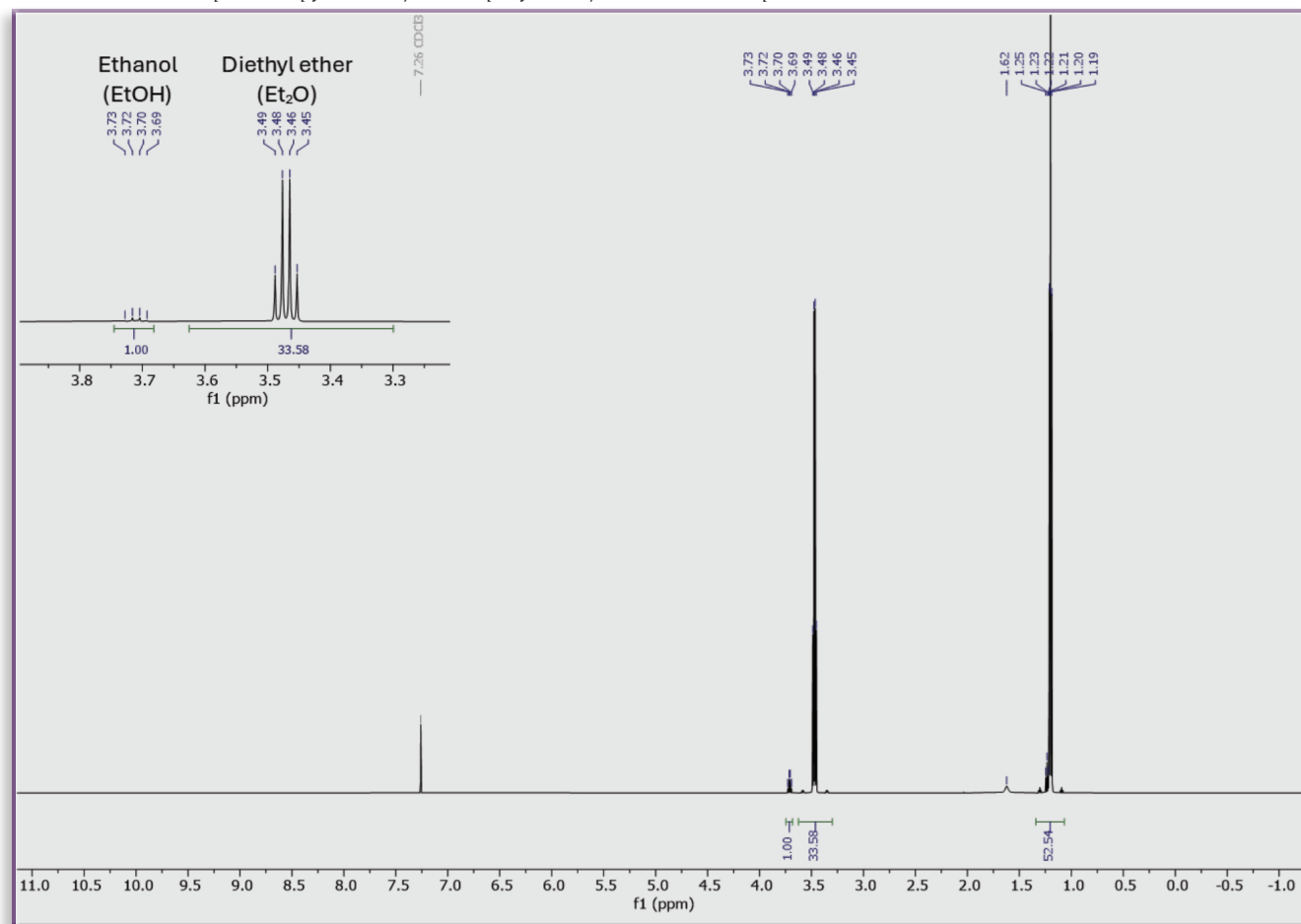
This proof-of-concept study demonstrates that Et₂O, suitable for safe clinical use as an inhaled anesthetic, can be produced with sufficient purity through an acid-catalyzed dehydration of EtOH followed by fractional distillation. The process described in this study yielded a purity of approximately 97%, which is compliant with current clinical standards.¹⁰ Furthermore, the sample was contaminated only by a small fraction of EtOH, which is likely to be of little clinical consequence when considering the small amount in the setting of an inhalational technique.¹¹

Limitations

As a proof-of-concept study, using only two samples, this study has several limitations. First, in our study, we used standard laboratory equipment and ACS grade reagents. When providing care in austere or prolonged field care settings, such materials may not be available. In these settings, providers would likely rely on obtaining commercially available products, such as glass or copper containers and columns (pipes) from a local hardware store, cleaning solutions containing sulfuric acid, and food-grade sodium hydroxide. Second, as we only obtained two samples, our outcomes would need to be tested further to confirm generalizability. Third, our project did not seek to use the isolated sample in a clinical setting. Lastly, our sample was immediately analyzed, which did not allow for the assessment of how stable the Et₂O would be during storage. For example, during prolonged periods of storage, Et₂O tends to form peroxides when exposed to air, moisture, and light.¹² Additional environmental variables such as ambient temperature and atmospheric pressure, or altitude are also likely to impact the stability of Et₂O.¹³

Inhaled anesthetics have already shown promise in both civilian and military prehospital settings.^{14,15} Inhaled methoxyflurane has demonstrated feasibility and usability in the combat environment, while also providing more rapid analgesia compared to standard parenteral analgesics in the civilian prehospital environment. Inhaled anesthetics have a good safety profile and do not require placement of an intravenous catheter. These

FIGURE 2 ^1H NMR spectroscopy results of the sample yielded from the second experiment.



properties collectively enable inhaled anesthetics to overcome many of the barriers that restrict delivery of typical analgesics in the prehospital setting.

Adherence to proper safety measures is of utmost concern when conducting this reaction and distillation process. First, both EtOH and Et₂O are highly flammable. This is one of the reasons that ether fell out of favor as an anesthetic agent.^{4,5} Clinicians would therefore need to ensure that these vapors did not come into contact with an open flame or spark during the reaction, distillation, or clinical use of Et₂O. A separate concern during this process is the addition of the corrosive acid (sulfuric acid) to the solvent (EtOH). The solvation process generates heat and can result in dangerous splashing if addition is carried out too rapidly or if the order of addition is reversed. Therefore, to allow for more controlled heat distribution, sulfuric acid was added slowly to the ethanol.

Further investigation is needed to ensure reliability and safety in the small-scale production of Et₂O for use as a general anesthetic. Future studies using commercially available off-the-shelf (COTS) equipment and reagents, which would likely be of lower standard and purity respectively, may yield findings that are more applicable to operational medicine. Larger sample sizes would produce more generalizable findings. Additionally, analyses of samples stored for prolonged periods may provide insights into proper storage techniques after the Et₂O is produced.

Conclusion

As disasters, conflict, and humanitarian crises leave numerous patients in need of effective anesthesia and analgesia, supply limitations often prevent this need from being met. The lack of anesthetic medications around the world is a glaring gap in medicine that needs to be addressed. This study offers initial insight into a means for the small-scale production of Et₂O, a once used, but not forgotten, anesthetic agent.

Author Contributions

SD conceived the study concept. KK and SD carried out the procedure. KK and JJ analyzed the data. SD, JJ, DJ, and KK wrote the manuscript, and all authors read and approved the final draft.

Disclaimer

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Disclosures

The authors have nothing to disclose.

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