Anal. Calcd for $C_{14}H_{20}ClNO_5$: C, 52.91; H, 6.34; N, 4.41. Found: C, 52.87; H, 6.34; N, 4.20.

5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—To a solution of 0.50 g (0.16 mmol) of 1-benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane perchlorate in 75 ml of anhydrous acetonitrile was added ketene at 0°, with stirring, by passing a dry nitrogen stream over liquid ketene at −20°. After addition of ketene for 15 min, during which the colorless solution turned yellow-orange. The solution was treated with charcoal, filtered, and concentrated to give a light yellow oil. Recrystallization from acetonitrile–ether gave colorless needles: mp 194–195° (reported[7] mp 190–195°, then mp 203–204°); yield 0.31 g (53%); ν_{max}^{KBr} 1746 cm^{-1}; ν_{max}^{Nujol} 1755, 1080, 710 cm^{-1}; nmr (CD_3CN) δ 2.20 (3 H, s, CH_3CO), 1.9–2.8 (8 H, series of multiplets, ring protons), 2.9–4.0 (4 H, series of multiplets, ring protons), 4.50 (2 H, s, benzyl CH_2), 7.53 (5 H, s, C_6H_5).

Anal. Calcd for $C_{16}H_{22}ClNO_6$: C, 53.41; H, 6.16; N, 3.89. Found: C, 53.49; H, 6.17; N, 3.98.

1-Benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane Picrate (6b).—This salt was obtained from 1-benzyl-1-azacyclooctan-5-one:[8] mp 207–208°; ν_{max}^{Nujol} 3100, 1625, 1607, 1565, 1462, 710 cm^{-1}; ν_{max}^{KBr} 3180, 1620, 1580, 1430, 1320, 710 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 54.04; H, 4.88; N, 12.21.

5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Picrate (7b).—The picrate was prepared from **6b** and ketene in the same manner as described for the perchlorate salt to yield yellow needles: mp 124–125°; yield 50%; ν_{max}^{KBr} 1750 cm^{-1}; nmr (CD_3CN) δ 2.21 (3 H, s, CH_3CO), 2.05–2.83 (8 H, series of multiplets, ring protons), 3.0–4.0 (4 H, series of multiplets, ring protons), 4.49 (2 H, s, benzyl CH_2), 7.53 (5 H, s, C_6H_5), 8.58 (2 H, s, picrate H's).

Anal. Calcd for $C_{22}H_{24}N_4O_9$: C, 54.10; H, 4.95; N, 11.47. Found: C, 54.37; H, 5.05; N, 11.77.

Acetylation of Piperidine with 5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—To 24 mg (0.28 mmol) of piperidine in 60 ml of methylene chloride was added 50 mg (0.14 mmol) of 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate at −20° with magnetic stirring. After 2 min, the solution was concentrated under vacuum pump pressure at 0° to a yellow oil. The time for concentration was less than 6 min. The presence of N-acetylpiperidine and 1-benzyl-1-azacyclooctane-5-one was evidenced by both thin-layer chromatography and by comparison of the nmr spectrum of the mixture with the spectra of the authentic samples. No starting material (**7a**) was found in the reaction mixture by either method of analysis.

Acetylation of Potassium Acetate with 5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—A sealed capillary tube containing 6 mg (16.7 μmol) of 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate and 3 mg (30.6 μmol) of vacuum dried potassium acetate[9] was heated at 195° for 1 min, during which melting occurred. The end of the tube containing the melt was cooled to −78°, and the upper two-thirds of the tube was heated with an electric dryer to cause volatile materials to condense in the lower part of the tube.

Heating of the lower third of the capillary tube then served as a gas chromatograph inlet system. Analysis of the volatile components using an 8 ft, 20% diisodecyl phthalate column on Chromosorb W led to identification of acetic anhydride as the major volatile component of the reaction mixture. Comparison of the peak areas of the reaction mixture with peak areas of known amounts of acetic anhydride generated using a similar capillary inlet system indicated that greater than 90% of the acetic anhydride expected was produced in the acetylation reaction. The presence of 1-benzyl-1-azacyclooctane-5-one was shown by thin-layer chromatographic analysis of the less volatile residue in the capillary tube.

Registry No.—**6a**, 16853-07-9; **6b**, 17555-90-7; **7a**, 16853-91-1; **7b**, 17555-92-9.

Acknowledgment.—The authors are grateful for the support of this research by the National Science Foundation (Grant GP-2012, currently GP-8407X).

(9) Attempts to powder the reagents finely prior to insertion into the capillary led to brownish mulls. This could indicate that reaction is occurring even under these conditions.

Improved Synthesis of *anti*-Benzaldoxime. Concomitant Cleavage and Formylation of Nitrones

ERWIN F. SCHOENEWALDT, ROBIN B. KINNEL, AND PAUL DAVIS

Merck Sharp & Dohme Research Laboratories, Merck & Company, Inc., Rahway, New Jersey

Received June 11, 1968

Recent interest in alkylation of *anti*-benzaldoxime[1] to form nitrones[2,3] and in the hydrolysis of nitrones to N-hydroxyamino compounds[3,4] has emphasized the fact that no satisfactory procedure is available in the literature for the preparation of this starting material. The published procedures[5-7] involving sodium carbonate neutralization of the oxime hydrochloride have not been successfully carried out on a large scale[2] and are suitable only for the preparation of a few grams of transiently stable[6] *anti*-oxime, rapid reversion to the low-melting *syn*-oxime occurring during work-up and handling.

In connection with our synthetic program on hadacidin, a growth inhibitor isolated from *Penicillium frequentans* Westling,[8] it was necessary to develop a procedure for the preparation and use of *anti*-benzaldoxime on a large scale.

The *syn*-oxime, obtained by conventional means from benzaldehyde and hydroxylamine, is converted into a hydrochloride on treatment with anhydrous hydrogen chloride in a variety of solvents. Brady and Dunn described[6] the preparation of two isomeric hydrochlorides, the β hydrochloride, prepared at higher temperatures, affording the very unstable *anti*-oxime on neutralization.

We have developed a procedure in which the hydrochloride is prepared in refluxing benzene to ensure complete conversion into the β form, which is isolated with exclusion of atmospheric moisture and is then neutralized in a rapid sequence of dissolution in excess caustic, reacidification with ammonium chloride, and extraction with ethyl ether. Both the preparation of the hydrochloride in hot solvent and the particular mode of neutralization are critical to the process. By this means, *anti*-benzaldoxime can be prepared conveniently in large quantities in 88% over-all yield from benzaldehyde. The method is described below on a 2-mol scale and has been carried out on a scale many fold larger. Oxime so produced is free of *syn* isomer and has remained stable for several weeks. The nmr spectrum in tetrahydrofuran showed the —CH=N— proton as a singlet at 7.27 ppm relative to TMS, a value identical

(1) *anti*-Benzaldoxime has been referred to as β-benzaldoxime in the older literature. The name (Z)-benzaldoxime has been proposed by *Chemical Abstracts Service* [J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968)].

(2) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).

(3) E. Falco and G. B. Brown, *J. Med. Chem.*, **11**, 142 (1968).

(4) E. Buehler and G. B. Brown, *J. Org. Chem.*, **32**, 265 (1967).

(5) E. Beckmann, *Chem. Ber.*, **23**, 1684 (1890).

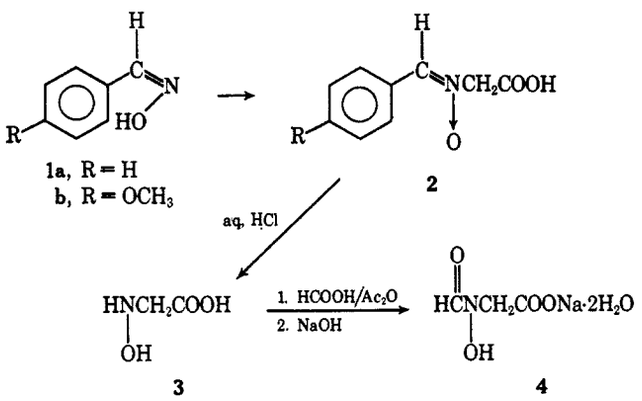
(6) O. Brady and F. Dunn, *J. Chem. Soc.*, 1783 (1923). In this reference, the designations *syn* and *anti* are interchanged.

(7) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed., Longmans, Green and Co., Ltd., London, 1956, p 719.

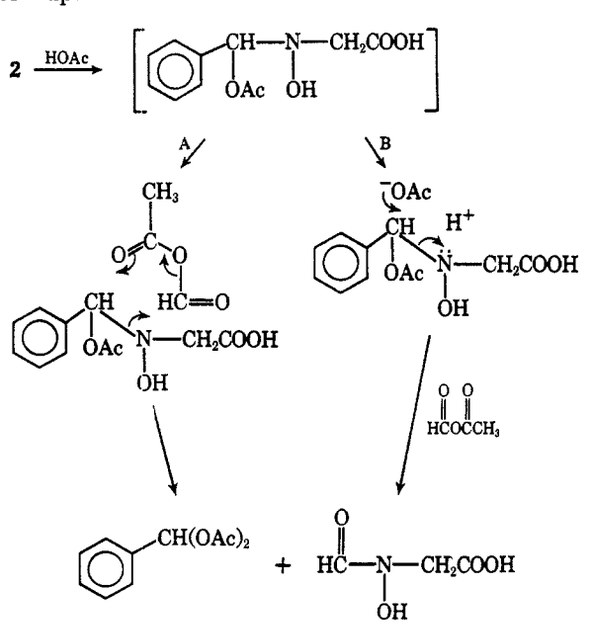
(8) E. A. Kaczka, C. O. Gitterman, E. L. Dulaney, and K. Folkers, *Biochemistry*, **1**, 340 (1962).

with that obtained by interpolation of data[9] relating the chemical shift of this resonance in aromatic oximes to the substituent constant σ. The generality of the method is shown by the conversion of anisaldehyde into *anti*-anisaldoxime (79% yield).

These *anti*-oximes have been converted into the N-(carboxymethyl)-α-arylnitrones (2) by known means[10] and have been used for the preparation of hadacidin (4, sodium N-formylhydroxyaminoacetate dihydrate) by hydrolysis to N-hydroxyaminoacetic acid[4,10] followed by formylation.[8]



As isolation of N-hydroxyaminoacetic acid from the aqueous hydrolysate is difficult, a more direct conversion of 2 into hadacidin was sought. We have found that these nitrones can be cleaved with concomitant formylation by treatment with formic acetic anhydride at room temperature. This reaction can be best formulated as an initial addition of acetic acid followed by either a concerted formylation cleavage (A) or an acid-catalyzed cleavage followed by formylation (B). The aromatic aldehyde appears as a by-product during work-up.



Experimental Section[11]

β-Benzaldoxime Hydrochloride.—Benzaldehyde (212 g, 2.0 mol) was added with stirring to a solution of 200 g (5.0 mol) of sodium hydroxide in 600 ml of water at room temperature. Hydroxylamine hydrochloride (144 g, 2.06 mol) was added in one portion. The temperature rose to 70°, and a clear solution was obtained. The solution was cooled to 30–35°, and carbon dioxide was passed in until the pH fell to 10. Alizarin yellow (1 mg) can be added during the carbonation to serve as a convenient internal indicator (rose to yellow). The free (*syn*) oxime which separated was extracted with 800 and 400 ml of benzene. The combined extracts were dried ($MgSO_4$) and filtered.

A small sample was evaporated *in vacuo* to constant weight. The ir spectrum ($CHCl_3$) of the resultant oil showed 3570 (s), 3300 (s, br), 1620 (w), 1565 (w), 1480 (m), 1255 (s), and 860 cm^{-1} (vs). The nmr spectrum (tetrahydrofuran) showed the —CH=N— proton singlet at 8.04 ppm relative to TMS.[12] The benzene solution was placed in a 2-l. three-necked flask equipped with a large-bore gas-inlet tube set for subsurface delivery, stirrer, thermometer, distillation head, and heating mantle. The solution was heated with stirring, and about 100 ml of solvent was distilled out to ensure dryness. An efficient condenser with a drying tube was set for reflux; the solution was reheated to boiling; the heating mantle was removed; and a strong flow of anhydrous hydrogen chloride gas was sparged through the vigorously stirred hot solution. The heat of reaction maintained vigorous reflux with a liquid temperature of 77–80°. Addition of hydrogen chloride was continued until the oil which first separated had crystallized and the liquid temperature had fallen to 50°.

The resultant slurry was cooled to 10° and filtered, and the crystalline hydrochloride was washed with two 200-ml portions of benzene and two 500-ml portions of *n*-hexane. Care must be taken to avoid exposure to atmospheric moisture, and air should not be allowed to be drawn through the filter cake. The hydrochloride, wet with solvent, may be stored in a desiccator over potassium hydroxide pellets. No attempt was made to weigh this intermediate.

***anti*-Benzaldoxime.**—Ethyl ether (2.0 l.) and 1.5 l. of an aqueous solution of sodium hydroxide (160 g, 4 mol) were mixed and cooled to 10° with good stirring. Maintaining vigorous agitation, the oxime hydrochloride prepared above was rapidly added. As soon as all solids had dissolved (*ca.* 1 min), a solution of 400 g of ammonium chloride in 1.5 l. of water was added. When the precipitated solids had redissolved (*ca.* 1 min), the stirring was stopped, the layers separated, and the aqueous layer was reextracted with 800 ml of ethyl ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to a very thick slurry. *n*-Hexane (300 ml) was added, and the mixture was again vacuum concentrated to a thick slurry. Another 300-ml portion of *n*-hexane was added, and the *anti*-oxime was filtered, using the mother liquor to aid in transfer. The filter cake was washed liberally with *n*-hexane. The product was air dried to constant weight. The *anti*-oxime, obtained as white needles, mp 129.5–130°, weighed 213 g (88% of theory from benzaldehyde). The ir spectrum ($CHCl_3$) showed 3570 (s), 3240 (s, br), 1630 (w, br), 1565 (w), 1480 (m), 1175 (w), and 840 cm^{-1} (s). The nmr spectrum (tetrahydrofuran) showed a proton as a singlet at 7.27 ppm relative to TMS.

Anal. Calcd for C_7H_7NO: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.80; H, 5.89; N, 11.60.

***anti*-Anisaldoxime.**—The same procedure was used to convert anisaldehyde (68.07 g, 0.5 mol) into β-anisaldoxime hydrochloride which was dried to constant weight *in vacuo* yielding 87.3 g (93.2% of theory), mp 133–133.5° dec. On neutralization as above, there was obtained 59.80 g (79% from anisaldehyde) of *anti*-anisaldoxime, mp 131–137° (lit. mp 130–130.5°[5] and 131.5°[6]).

N-(Carboxymethyl)-α-phenylnitrone.—*anti*-Benzaldoxime was converted into N-(carboxymethyl)-α-phenylnitrone by the procedure of Hantzsch and Wild.[10] The product was obtained in 81% yield, mp 176–179° (lit.[4] mp 178–179°).

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.18; N, 8.04.

(9) I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **48**, 1157 (1965).

(10) A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896).

(11) All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer 421 grating spectrophotometer. The nmr spectra were obtained through the use of a Varian Associates Model 4300B high resolution spectrometer and tetramethylsilane (TMS) as an internal standard.

(12) Interpolation of the data of ref 9 gives 8.07 ppm relative to TMS for the chemical shift of this proton in *syn*-benzaldoxime.

N-(Carboxymethyl)-α-(p-methoxyphenyl)nitrone.—In a similar fashion, *anti*-anisaldoxime (54.8 g, 0.362 mol) was converted into 53.2 g (70.4%) of the nitrone, mp 165–165.5° dec. A sample which recrystallized from aqueous ethanol had mp 165.5–166° dec.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.51; H, 5.13; N, 6.98.

Sodium N-Formylhydroxyaminoacetate Dihydrate.[13]—To 65.6 ml (1.7 mol) of 98% formic acid in a three-necked flask maintained at 25–30° was added 87.5 ml (0.925 mol) of acetic anhydride over 30 min with stirring. The solution was aged 15 min at 25° and then treated with 35.0 g (0.195 mol) of N-carboxymethyl-α-phenylnitrone portionwise over 15 min. The resultant slurry was stirred over 25° until the solid dissolved (1.5 hr) and then for an additional hour. Versene (0.2 g) was added;[14] the solution cooled to 5° and partially neutralized, at a temperature kept below 30°, by dropwise addition of 122 ml of 8 *N* aqueous NaOH. The final pH was 3.7. The solution was washed with 50 ml of ethyl ether to remove benzaldehyde. The product was crystallized by slow addition of 720 ml of ethanol, with stirring and seeding. The resulting slurry was cooled to 0–5°, aged at that temperature for 30 min, and filtered. The cake was washed with three 35-ml portions of 95% ethanol, sucked damp dry, and dried under forced air at 35°. There was obtained 24.2 g of sodium N-formylhydroxyaminoacetate dihydrate (70% of theory) mp 191–193° dec.

Anal. Calcd for $C_3H_4NO_4Na \cdot 2H_2O$: C, 20.34; H, 4.55. Found: C, 20.56; H, 4.57.

Very similar results were obtained when N-carboxymethyl-α-(p-methoxyphenyl)-nitrone was employed in this reaction.

Registry No.—**1a**, 13830-84-7; **2a**, 3884-90-0; **2b**, 17556-16-0; **4**, 2618-22-6.

Acknowledgments.—We wish to thank Dr. Byron H. Arison and Dr. Nelson R. Trenner for the nmr spectra, Mr. Robert Walker for the infrared spectra, and Mr. Richard N. Boos and his staff for the elemental analyses.

(13) The procedure as originally developed used a larger volume of formic acid and acetic anhydride, and the reaction mixture was evaporated to a syrup at reduced pressure below 40°. Under these conditions a possibly hazardous exotherm was sometimes observed. We are indebted for this modification, in which smaller initial volumes obviate the vacuum concentration, to Mr. William F. Elmendorf and Dr. David F. Hinkley of these laboratories.

(14) Hadacidin forms an intensely colored chelate with iron, and an off-color product may be obtained unless a sequestering agent is used.

Diazomethane and Deuteriodiazomethane by the Base-Catalyzed Reaction of Hydrazine with Chloroform

SAMUEL P. MCMANUS, JOHN T. CARROLL, AND CHARLES L. DODSON

Department of Chemistry, University of Alabama in Huntsville, Huntsville, Alabama 35807

Received March 11, 1968

The record number of preparations for diazomethane which appear in "Organic Syntheses"[1] accentuates not only its importance to the synthetic organic chemist, but also its lability. Despite its many years in the chemists repertory of reagents, the explosive nature[2] of diazomethane is not understood. In the course of another study,[3] pure deuterated diazomethane was required. Although the best preparative methods[4] avoid concentrated solutions of diazomethane,[2] the solvent-free gas and a procedure easily adaptable for preparation of deuteriodiazomethane was desired for the above mentioned study.

Demore, Pritchard, and Davidson,[5] and others[6,7] report the preparation of deuterated diazomethane by direct exchange with D_2O. An ir spectrum shown by Demore, *et al.*, indicates the presence of approximately 40% CD_2N_2, 40% $CHDN_2$, and 20% CH_2N_2. In the present work, this technique was extended to two 30-min exchanges and resulted in the loss of 95% of the original diazomethane sample due to the reaction of diazomethane with water to produce methyl ether.

Leitch, Gagnon, and Cambron[8] have prepared a relatively pure sample of deuterated diazomethane by decomposing methyl-d_3-nitrosourea in NaOD–D_2O. Although the presence of CH_2N_2 was negligible, the end product contained a large quantity of $CHDN_2$. The rather lengthy procedure required to produce all the deuterated intermediate reactants and solvents illustrated the necessity of having such species deuterated in all positions.

Utilization of the technique of Staudinger and Kupfer[9] to prepare deuterated diazomethane is more straightforward since deuterated hydrazine and chloroform are commercially available, and the preparation of deuterated solvent and potassium hydroxide are moderately simple. The relatively low yields of diazomethane (≈20%) and the impurities produced must be considered before utilizing this technique.

With reaction conditions as formulated by Staudinger and Kupfer[9] (eq 1), ammonia and ethylene are

$$NH_2NH_2 \cdot H_2O + CHCl_3 + 3KOH \xrightarrow{CH_3CH_2OH} CH_2N_2 + 3KCl + 4H_2O \quad (1)$$

gaseous contaminants in diazomethane by ir analysis. If methyl alcohol is substituted for ethyl alcohol as the solvent, methyl ether is an additional gaseous product. With no solvent, chloroacetylene has been identified as a minor product.[10] Variation of the reactants as shown in Table I causes a considerable variation in the products observed.

Although all of the gaseous products probably arise by interesting mechanisms, we were particularly fascinated with the formation of chloroacetylene. It was identified in the following way. Diazomethane

(1) (a) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 165; (b) C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, ref 1a, Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y. 1955, p 244; (c) Th. J. deBoer and H. J. Backer, ref 1a, Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250; (d) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(2) Diazomethane is unpredictably dangerous. For leading references and representative warnings concerning its use, see ref 1d and the following: (a) I. T. Millar and H. D. Springall, "Sidgewick's Organic Chemistry of Nitrogen," 3rd ed, Clarendon Press, London, 1966, pp 478–479; (b) P. A. S. Smith, "The Chemistry of Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 212–215.

(3) C. L. Dodson, Ph.D. Thesis, University of Tennessee, 1963.

(4) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, pp 191–195.

(5) W. B. Demore, H. O. Pritchard, and N. Davidson, *J. Amer. Chem. Soc.*, **81**, 5874 (1959).

(6) G. W. Robinson and M. McCarty, Jr., *ibid.*, **82**, 1859 (1960).

(7) T. D. Goldfarb and G. C. Pimentel, *ibid.*, **82**, 1865 (1960).

(8) L. C. Leitch, P. E. Gagnon, and A. Cambron, *Can. J. Res.*, **28B** 256 (1950).

(9) H. Staudinger and O. Kupfer, *Ber.*, **45**, 505 (1912).

(10) We suspect chloroacetylene as a product with solvent also; its solubility may keep it from codistilling with diazomethane. In one experiment a mixture of CH_2N_2 and chloroacetylene was bubbled through ethyl alcohol which removed chloroacetylene, but CH_2N_2 reacted with the solvent to produce methyl ethyl ether.