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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the range of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

Procedures should be written in the style and format employed in the latest published volume of *Organic Syntheses*. Copies of

the current style sheet may be obtained from the Secretary of the Editorial Board. In Section 3, **Methods of Preparation,** there should be described other practical methods for preparing the compound which have appeared in the literature. It is unnecessary to mention methods which have been published but are of no practical synthetic value. In Section 4, **Merits of the Preparation,** a statement should be made indicating why the preparation is published in *Organic Syntheses*. Among the obvious reasons for publication would be the novelty of the procedure, general scope of the synthetic method, specific interest in the compound or its use as an intermediate for preparing other compounds, convenience of the method, and improvement in yields. Two copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparation which are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

The preparations presented in this volume of *Organic Syntheses* were selected from those manuscripts submitted voluntarily, and those received in response to the solicitation program. The choices reflect the continuing policy by the editors of presenting examples which illustrate new or general methods of organic synthesis, significant improvements in older methods of synthesis, and the preparation of compounds of wide general interest.

This volume contains a relatively large number of preparations which illustrate new or general methods, including: a method for carboxylating saturated hydrocarbons containing a tertiary hydrogen (1-adamantanecarboxylic acid); a general method for the synthesis of aldehydes (*o*-anisaldehyde); a method for the conversion of carbonyl groups to difluoromethylene groups (α,α-difluorotoluene); a method for the conversion of 2,6-dialkylphenols to 1,3-dihydro-2H-azepin-2-ones (1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one); a method for the conversion of olefins and *t*-alcohols to *t*-amines by the Ritter reaction (α,α-dimethyl-β-phenethylamine); a general method for the synthesis of ketimines (diphenyl ketimine); the use of lithio-esters for the preparation of β-hydroxy esters (ethyl β-hydroxy-β,β-diphenylpropionate); a method for the synthesis of N-alkylallenimines by ring closure of N-(2-bromoallyl)-alkylamines by action of sodium amide; the use of ethylene bromide as an entrainment agent in Grignard syntheses (pentachlorobenzoic acid); a method for the synthesis of azulenes (4,6,8-trimethylazulene); and the Decker reaction for the preparation of N-methylalkylamines (N-methylbutylamine and N-methylethylamine).

Certain preparations—mesitoic acid, 7-*t*-butoxynorbornadiene, cyclopentanecarboxaldehyde, *t*-butyl azidoformate, indole-

3-acetic acid, 2,3-diaminopyridine, and 2,4,6-trimethylpyrylium perchlorate—illustrate new or improved methods for the synthesis of compounds of wide general interest. In including the preparation of 2,4,6-trimethylpyrylium perchlorate, it was felt that standard procedures which have been tested in more than one laboratory without difficulty and which attempt to point out as clearly as possible the potential hazards involved would serve a useful function for those who, despite the hazards, find this a necessary and important starting material.

The editors express their appreciation to chemists in this country and throughout the world for their contributions to this series, as reflected by the high quality of the preparations received through the voluntary submission program. The editors will welcome recommendations by readers of *Organic Syntheses* of preparations to be included in subsequent volumes. For this purpose, submission of a brief description of the reaction and the merits of the preparation will permit preliminary evalution by the members of the Board of Editors.

WILLIAM E. PARHAM

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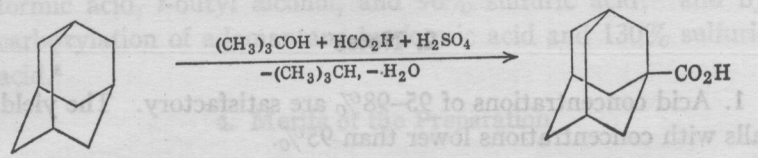
1-ADAMANTANECARBOXYLIC ACID



Submitted by H. Koch and W. Haaf[1]
Checked by W. W. Prichard and B. C. McKusick

1. Procedure

Caution! Because carbon monoxide is evolved, the reaction should be carried out in a good hood.

A 1-l. three-necked flask equipped with stirrer, thermometer, dropping funnel, and gas-outlet tube is charged with 470 g. (255 ml., 4.8 moles) of 96% sulfuric acid (Note 1), 100 ml. of carbon tetrachloride (Note 2), and 13.6 g. (0.100 mole) of adamantane.[2] The well-stirred mixture is cooled to 17–19° in an ice bath, and 1 ml. of 98% formic acid is added. Then a solution of 29.6 g. (38 ml., 0.40 mole) of *t*-butyl alcohol in 55 g. (1.2 moles) of 98–100% formic acid is added dropwise; the rate of addition and the cooling are regulated so that the addition requires 1–2 hours, and the temperature of the reaction mixture is kept at 17–25°. The reaction mixture is stirred for an additional 30 minutes and poured onto 700 g. of crushed ice. The layers are separated, and the upper, acid layer is extracted with three 100-ml. portions of carbon tetrachloride.

The combined carbon tetrachloride layers are shaken with 110 ml. of 15*N* ammonium hydroxide (Note 3), and the crystalline ammonium 1-adamantanecarboxylate that separates is collected on a Büchner funnel having a coarse fritted disk. The salt is washed with 20 ml. of cold acetone and suspended in 250 ml. of water. The suspension is made strongly acidic with 25 ml. of 12*N* hydrochloric acid and extracted with 100 ml. of chloroform. The chloroform layer is dried over anhydrous sodium sulfate and

evaporated to dryness on a steam bath (Note 4). The residue is crude 1-adamantanecarboxylic acid; weight 12–13 g. (67–72%) (Note 5); m.p. 173–174°. Recrystallization of this product from a mixture of 30 ml. of methanol and about 10 ml. of water gives 10–11 g. (56–61%) of pure acid, m.p. 175–176.5° (Note 6).

2. Notes

1. Acid concentrations of 95–98% are satisfactory. The yield falls with concentrations lower than 95%.

2. Cyclohexane or *n*-hexane can be used in place of carbon tetrachloride. Technical "normal hexane" may contain substantial amounts of methylcyclopentane and isohexane that lower the yield through formation of C_7-acids that are hard to remove.

3. A large amount of trimethylacetic acid and a small amount of at least one C_9-acid and one C_{13}-acid are formed from the *t*-butyl alcohol. The treatment with ammonia separates 1-adamantanecarboxylic acid from these acids, the ammonium salts of which remain in solution.

4. Acid that is satisfactory for most purposes may be obtained by interrupting the evaporation of the chloroform solution when crystals start to appear, cooling the concentrated chloroform solution to 0–5°, and collecting the acid on a Büchner funnel. The acid melts at 173–174°.

5. The checkers obtained similar yields when the quantity of reactants was increased fivefold.

6. As an alternative purification procedure, the checkers have esterified the crude acid by refluxing it for 2 hours with three times its weight of methanol and 2 ml. of 98% sulfuric acid. The solution is poured into 10 volumes of water and extracted with the minimum amount of chloroform required to give a clean separation of layers. The chloroform solution is washed with water, dried over calcium chloride, and distilled from a Claisen flask with an indented neck. Methyl 1-adamantanecarboxylate is collected at 77–79° (1 mm.); m.p. 38–39°. Hydrolysis of the ester with the calculated amount of 1*N* potassium hydroxide followed by acidification yields 1-adamantanecarboxylic acid; m.p. 175–176.5°; 90% overall recovery.

3. Methods of Preparation

1-Adamantanecarboxylic acid can be prepared by carboxylation of 1-adamantanol[3] or 1-bromoadamantane[3,4] by formic acid and 96% sulfuric acid; by carboxylation of adamantane by formic acid, *t*-butyl alcohol, and 96% sulfuric acid;[5] and by carboxylation of adamantane by formic acid and 130% sulfuric acid.[6]

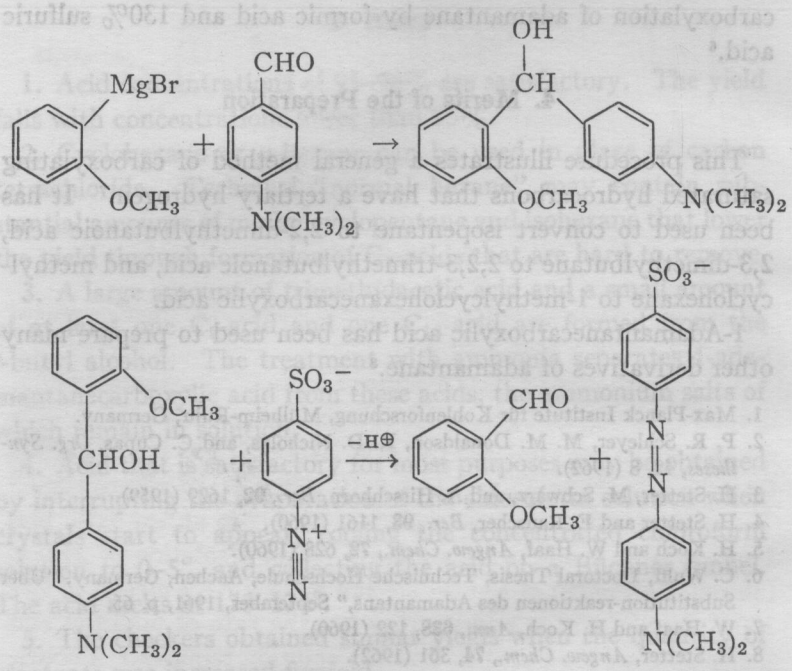
4. Merits of the Preparation

This procedure illustrates a general method of carboxylating saturated hydrocarbons that have a tertiary hydrogen.[7] It has been used to convert isopentane to 2,2-dimethylbutanoic acid, 2,3-dimethylbutane to 2,2,3-trimethylbutanoic acid, and methylcyclohexane to 1-methylcyclohexanecarboxylic acid.

1-Adamantanecarboxylic acid has been used to prepare many other derivatives of adamantane.[8]

1. Max-Planck Institute für Kohlenforschung, Mülheim-Ruhr, Germany.
2. P. R. Schleyer, M. M. Donaldson, R. D. Nicholas, and C. Cupas, *Org. Syntheses*, **42**, 8 (1962).
3. H. Stetter, M. Schwarz, and A. Hirschhorn, *Ber.*, **92**, 1629 (1959).
4. H. Stetter and E. Rauscher, *Ber.*, **93**, 1161 (1960).
5. H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).
6. C. Wulff, Doctoral Thesis, Technische Hochschule, Aachen, Germany, "Uber Substitution-reaktionen des Adamantans," September, 1961, p. 65.
7. W. Haaf and H. Koch, *Ann.*, **638**, 122 (1960).
8. H. Stetter, *Angew. Chem.*, **74**, 361 (1962).

o-ANISALDEHYDE



Submitted by A. J. Sisti [1]
Checked by G. L. Walford and Peter Yates

1. Procedure

A. *4-Dimethylamino-2'-methoxybenzhydrol.* An ethereal solution of *o*-methoxyphenylmagnesium bromide is prepared in the usual manner [2] with 250 ml. of anhydrous ether, 14.5 g. (0.60 g. atom) of magnesium, and 100 g. (0.53 mole) of *o*-bromoanisole (Note 1). A solution of 60 g. (0.40 mole) of *p*-dimethylaminobenzaldehyde (Note 2) in 200 ml. of anhydrous benzene is added dropwise to the Grignard reagent (Note 3). After the addition is completed, the reaction mixture is stirred for 10 hours at room

temperature. The magnesium complex, which forms a very thick suspension, is decomposed with a solution of 75 g. of ammonium chloride in 450 ml. of water. The ether-benzene layer is separated, washed with 100 ml. of water, and dried over calcium sulfate (Note 4). The solvent is removed under reduced pressure, and the residue is induced to crystallize by trituration with a little petroleum ether (30–60°). Recrystallization of the solid from benzene-petroleum ether (30–60°) gives 4-dimethylamino-2′-methoxybenzhydrol (59–60 g., 57–58%), m.p. 75–80°.

B. *o-Anisaldehyde.* In a 3-l. three-necked flask fitted with a mechanical stirrer and a nitrogen inlet tube are placed 60 g. (0.35 mole) of sulfanilic acid (Note 5), 18 g. (0.17 mole) of anhydrous sodium carbonate, and 400 ml. of water. Stirring is started, and the resulting solution is cooled to 0–5° in an ice bath. Nitrogen is passed into the reaction flask, and a nitrogen atmosphere is maintained throughout the reaction. To the cooled solution is added three-quarters of a solution of 24.2 g. (0.35 mole) of sodium nitrite in 75 ml. of water, followed by 32 ml. of concentrated hydrochloric acid. During the diazotization the temperature of the solution is maintained below 5° by the addition of ice in small pieces. After a few minutes another 32 ml. of acid is added. Further additions of the sodium nitrite solution are made slowly until a positive test for excess nitrous acid is observed (Note 6). The diazonium solution is buffered to pH ~6 by the addition of a cooled solution of 50 g. of sodium acetate in 125 ml. of water. A solution of 52 g. (0.20 mole) of 4-dimethylamino-2′-methoxybenzhydrol in 500 ml. of acetone is added rapidly, followed by an additional 500 ml. of acetone. The reaction mixture becomes red almost immediately, and stirring is continued for 30 minutes at 0–5°. The cooling bath is replaced by a warm water bath (50–60°), and stirring is continued for an additional 30 minutes. The reaction mixture is diluted with an equal volume of water and extracted with three 750-ml. portions of ether. The combined ethereal extracts are washed with water until all the dissolved methyl orange is removed, then dried over calcium sulfate. The ether is removed under reduced pressure, and the residue is distilled to yield 19–20.5 g. (69–75%) of colorless liquid, b.p. 79–80° (1.5 mm.), n^{25}D 1.5586 (Note 7).

2. Notes

1. *o*-Bromoanisole obtained from Eastman Kodak Company was used without further purification.

2. A good commercial grade (Matheson, Coleman and Bell) of *p*-dimethylaminobenzaldehyde was used without further purification.

3. In one run the checkers cooled the reaction mixture in an ice bath throughout the addition. In another run only initial cooling was used. There was no difference in yield.

4. The checkers found that separation of the aqueous and organic phases is very difficult if the mixture is shaken. In one run shaking and washing were omitted without affecting the yield or purity of the product.

5. Eastman white label sulfanilic acid was used without purification.

6. Excess nitrous acid causes an *immediate* blue color at the point of contact with starch-iodide test paper. At all times there must be an excess of mineral acid (Congo red test paper).

7. The submitters found for the 2,4-dinitrophenylhydrazone m.p. 252–254° (lit.[2] m.p. 249–250°). The checkers found m.p. 34–36° for *o*-anisaldehyde (lit.[3] m.p. 37°) and m.p. 249–251° for the 2,4-dinitrophenylhydrazone.

3. Methods and Merits of Preparation

o-Anisaldehyde is commercially available. However, this procedure illustrates a method of general applicability [4,5] for the preparation of aromatic, aliphatic, and unsaturated aldehydes.

1. Department of Chemistry, Adelphi College, Garden City, Long Island, New York.

2. E. K. Harvill and R. M. Herbst, *J. Org. Chem.*, **9**, 21 (1944).
3. F. B. Garner and S. Sugden, *J. Chem. Soc.*, 2877 (1927).
4. M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).
5. A. Sisti, J. Burgmaster, and M. Fudim, *J. Org. Chem.*, **27**, 279 (1962).

N-(2-BROMOALLYL)ETHYLAMINE

(Allylamine, 2-bromo-N-ethyl-)

$$CH_2{=}\underset{\displaystyle Br}{\underset{|}{C}}CH_2Br + 2C_2H_5NH_2 \rightarrow CH_2{=}\underset{\displaystyle Br}{\underset{|}{C}}CH_2NHC_2H_5 + C_2H_5\overset{+}{N}H_3\ \ Br^-$$

Submitted by ALBERT T. BOTTINI and ROBERT E. OLSEN[1]
Checked by THOMAS H. LOWRY and E. J. COREY

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ethylamine, 2,3-dibromopropene, and the product. 2,3-Dibromopropene is a strong lachrymator. The operator should wear rubber gloves and protective goggles because some 2-haloallylamines have caused severe skin and eye irritation.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, a dropping funnel, and a dry ice condenser charged with an ice-salt mixture (Note 1). Three hundred milliliters (240 g., 3.7 moles) of aqueous 70% ethylamine solution (Note 2) is placed in the flask, the stirrer is started, and 200 g. (1.00 mole) of 2,3-dibromopropene (Note 3) is added dropwise over a period of 1 hour. After the addition is complete, the reaction mixture is stirred for 3 hours. Ether (300 ml.) is added, and the mixture is cooled in an ice bath. Sodium hydroxide (100 g.) is added with stirring and cooling. The cold mixture is transferred to a separatory funnel, and the phases are separated. The organic layer is dried in two stages over 25-g. portions of sodium hydroxide. The organic layer and the small amount of water that separates during the second stage of drying are decanted into a separatory funnel, and the phases are separated. Most of the ether and unreacted ethylamine are removed from the organic layer by distillation through a 250-mm. x 13-mm. column packed with glass helices, and the residue is distilled through the same column at

reduced pressure under nitrogen to give 115–128 g. (70–78%) of N-(2-bromoallyl)ethylamine; b.p. 53–55° (27 mm.), 79–81° (75 mm.) (Note 4); n^{25}D 1.4765–1.4770.

2. Notes

1. The checkers used an inner-spiral water condenser. The cooling water was chilled to about 0° by prior passage through a short copper coil immersed in ice.

2. The aqueous 70% ethylamine solution used was the practical grade obtained from Eastman Organic Chemicals.

3. The 2,3-dibromopropene used was obtained from Columbia Organic Chemicals Co., Columbia, South Carolina, and was redistilled before use. The preparation of 2,3-dibromopropene is described in an earlier volume of this series.[2]

4. The reported boiling point of N-(2-bromoallyl)ethylamine is 148–153°.[3] It is strongly recommended that the product and other 2-haloallylamines be distilled at reduced pressure under nitrogen, for the submitters have noted two instances when a 2-haloallylamine polymerized with considerable evolution of heat during slow distillation at atmospheric pressure.

3. Methods of Preparation

This method is essentially that described by Pollard and Parcell.[3] No other procedure appears to have been used to prepare N-(2-bromoallyl)ethylamine. A number of N-(2-haloallyl)alkylamines have been prepared by treatment of a 2,3-dihalopropene with a primary alkylamine in water,[3,4] ether,[3,4] or benzene.[5]

4. Merits of the Preparation

The method described here has been used for the preparation of a number of N-(2-haloallyl)alkylamines from a water-soluble amine and the corresponding 2,3-dihalopropene.[3,4]

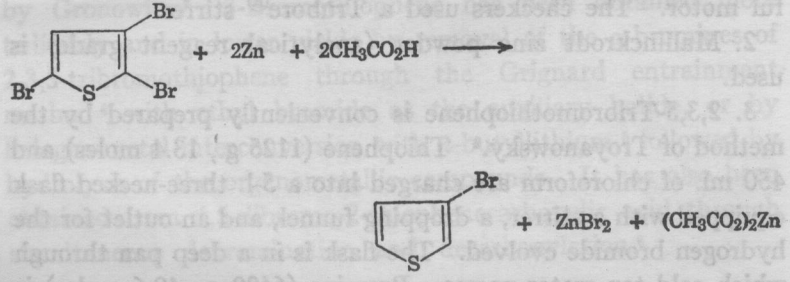
Treatment of an N-(2-bromoallyl)alkylamine with sodium amide in liquid ammonia yields the N-alkylallenimine together with a small amount of the N-alkylpropargylamine.[3–7] Similar

treatment of an N-(2-chloroallyl)alkylamine yields only the N-alkylpropargylamine.[4,6]

1. Department of Chemistry, University of California, Davis, California.
2. R. Lespieau and M. Bourguel, *Org. Syntheses*, Coll. Vol. 1, 209 (1941).
3. C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, 73, 2925 (1951).
4. A. T. Bottini, B. J. King, and R. E. Olsen, *J. Org. Chem.*, 28, 3241 (1963).
5. J. V. Braun, M. Kuhn, and J. Weismantel, *Ann.*, 449, 254 (1926).
6. A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 79, 1462 (1957).
7. A. T. Bottini and R. E. Olsen, this volume, p. 53.

3-BROMOTHIOPHENE

(Thiophene, 3-bromo-)



Submitted by S. Gronowitz and T. Raznikiewicz [1]
Checked by Max Tishler, Arthur J. Zambito, and Ronald B. Jobson

1. Procedure

A 5-l., three-necked, round-bottomed flask is equipped with an efficient stirrer (Note 1), a reflux condenser, and a dropping funnel. Water (1850 ml.) is added, stirring is begun and continued throughout the procedure, and 783 g. (12.0 moles) of zinc dust (Note 2) and 700 ml. of acetic acid are added. The mixture is heated to reflux, the heating mantle is removed, and 1283 g. (4.00 moles) of 2,3,5-tribromothiophene (Note 3) is added dropwise at such a rate that the mixture continues to reflux. The addition is complete in about 70 minutes. Heat is applied, and the mixture is refluxed for 3 hours. A condenser is arranged for downward distillation, and the mixture is distilled until no more or-

ganic substance distills with the water (Note 4). The heavier organic layer is separated, washed successively with 50 ml. of 10% sodium carbonate solution and 100 ml. of water, dried over calcium chloride (Note 5), and fractionated through a vacuum-mantled Dufton column (Note 6). A 19-g. fore-run, b.p. 78–159°, consists mainly of thiophene and 3-bromothiophene. 3-Bromothiophene is collected at 159–160°; n^{20}D 1.5919–1.5928; weight 580–585 g. (89–90%) (Notes 7 and 8).

2. Notes

1. The submitters used a Teflon® paddle-type stirrer sealed with rubber tubing lubricated by glycerol and driven by a powerful motor. The checkers used a Trubore® stirrer.

2. Mallinckrodt zinc powder (analytical reagent grade) is used.

3. 2,3,5-Tribromothiophene is conveniently prepared by the method of Troyanowsky.[2] Thiophene (1125 g., 13.4 moles) and 450 ml. of chloroform are charged into a 5-l. three-necked flask equipped with a stirrer, a dropping funnel, and an outlet for the hydrogen bromide evolved. The flask is in a deep pan through which cold tap water passes. Bromine (6480 g., 40.6 moles) is added dropwise to the stirred mixture over a period of 10 hours. After the mixture has stood overnight, it is heated at 50° for several hours, washed with 2*N* sodium hydroxide solution, refluxed for 7 hours with a solution of 800 g. of potassium hydroxide in 1.5 l. of 95% ethanol, and poured into water. The organic layer is separated, washed with water, dried over calcium chloride, and fractionated to give 3200–3650 g. (75–85%) of 2,3,5-tribromothiophene; b.p. 123–124° (9 mm.); m.p. 25–27°.

4. About half of the volume is distilled over. The temperature of the vapor rises during the distillation from 95° to 101°.

5. The checkers washed the drying agent with ether and combined the wash with the filtrate.

6. A Dufton column was not available to the checkers. In its place a 2.5-cm. x 38-cm. column packed with glass helices was used. This column was heated by a 4.5-cm. concentric glass jacket wrapped with Nichrome ribbon. A 6.5-cm. concentric