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Synthesis of Ethanol-1-C14, Ethanol-2-C14, Ethyl Bromide-1-C14, Ethyl Bromide-2-C14 and C14-Labeled Methadon

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SYNTHESIS OF ETHANOL-1-C¹⁴, ETHANOL-2-C¹⁴, ETHYL BROMIDE-1-C¹⁴,
ETHYL BROMIDE-2-C¹⁴ AND C¹⁴-LABELED METHADON

by

B. M. Tolbert, Freda Christenson, Frances Nai-Hsuan Chang,
and Peter P. T. Sah

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June 22, 1948

ABSTRACT

Ethanol-1-C¹⁴, ethanol-2-C¹⁴, ethyl bromide-1-C¹⁴, and ethyl bromide-2-C¹⁴ have been prepared from labeled acetic acid by high yield synthetic procedures on a 10-20 mmole scale. DL-methadon (4,4-diphenyl-6-dimethylamino-3-heptanone) has been prepared labeled with C¹⁴ in either the 1 or 2 position.

This paper is based on work performed under Contract No. W-7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley, California.

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INTRODUCTION: - The important observations reported by Scott and Chen (1) (2) on the pharmacology of the new analgesic, methadon, has aroused considerable interest among workers in pharmacology. From the results of investigations reported later by a large number of clinics and research laboratories (3-18) it seems quite justified to say that in

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- (*) This paper is based on work performed under Contract #7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley, California
- (1) Scott & Chen, J. Pharm. & Exp. Therap., 87, 63 (1946).
 - (2) Scott, Robins, & Chen, Science, 104, 587 (1946).
 - (3) Elliott, Warrens & James, J. Pharmacol. Exp. Therap., 91, 98 (1947).
 - (4) Haag, Finnegan, & Larson, Fed. Proc., 6, 334 (1947).
 - (5) Isbell, et. al., Fed. Proc., 6, 340, (1947).
 - (6) Karr, Fed. Proc., 6, 343 (1947).
 - (7) Kirchof & Uchiyama, Fed. Proc., 6, 345 (1947).
 - (8) Kirchof & David, West J. Surg., 55, 183 (1947).
 - (9) Scott, Kohlstaedt, Robbins & Israel, Fed. Proc., 6, 370 (1947).
 - (10) Scott, et al., Anaesthesia & Analgesia, 26, 12, 18 (1947).
 - (11) Gentling & Lundy, Proc. Staff Meet. Mayo Clin., 22, 249 (1947).
 - (12) Shideman & Johnson, Fed. Proc., 6, 371 (1947).
 - (13) Troxil, Fed. Proc., 6, 378 (1947); J. Am. Med. Assoc., 136, 920 (1946).
 - (14) Thorp, Walton & Ofner, Nature, 159, 679 (1947).
 - (15) Wikler & Frank, Fed. Proc., 6, 384 (1947).
 - (16) Woods, Wyngaarden & Seevers, Proc. Soc. Exp. Biol. & Med., 65, 113 (1947).
 - (17) Bachelor & Elliott, Fed. Proc., 7, 203 (1948).
 - (18) Eadie, Bernheim & Fitzgerald, Fed. Proc., 7, 216 (1948).
-

methadon an efficient substitute for morphine has been found. Methadon is about twice as active as morphine and fifteen times more active than demerol as an analgesic. It has the great advantage over morphine and demerol in that it has much less tendency to cause addictions and no characteristic phenomena on withdrawal. The drug is also known under the trade names of "Amidone", "Dolophine", "Adanon", "Diaminon", and "10820".

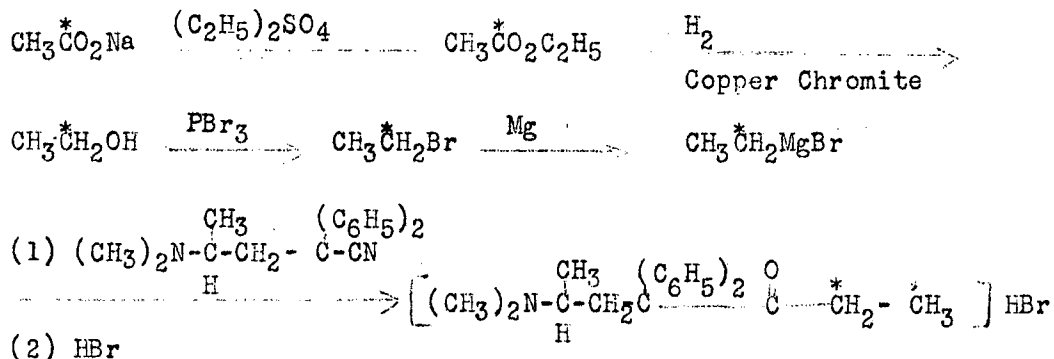
In order to know more exactly how this analgesic acts in the animal body we have prepared methadon (4,4-diphenyl-6-dimethylamino-3-heptanone) labeled with C¹⁴ in the 2-position by the condensation of the corresponding labeled ethyl magnesium bromide with 2,2-diphenyl-4-dimethylaminopentane-nitrile and subsequent hydrolysis (19) (20) (21). The ethanol was prepared by the reduction of the corresponding acetate-labeled ethyl acetate. The halide was prepared from the alcohol by the action of phosphorus tribromide. The preparations were carried out on a 10 mmole scale.

(19) Schultz, Robb & Sprague, J. Am. Chem. Soc., 69, 188, 2454 (1947).

(20) Easton, Gardener, Evanick, Stevens, J. Am. Chem. Soc., 70, 76 (1948).

(21) Kleiderer, et. al., Office of the Publication Board, Department of Commerce, Report PB981, p. 96.

The following series of reactions was used in the preparation of the 2-labeled methadon.



The carboxyl-labeled acetic acid was prepared from radioactive carbon dioxide by carbonating methyl magnesium iodide (22) (23) (24).

In a similar manner, 4,4-diphenyl-6-dimethylamino-3-heptanone-1-C¹⁴ (25) has been prepared using acetic acid-2-C¹⁴ as the starting material. This acetic acid was prepared by high pressure catalytic reduction of labeled carbon dioxide (26), iodination of the methanol thus produced, conversion of the methyl iodide to the Grignard reagent, and carbonation of this with inactive carbon dioxide (27).

(22) Dauben, W. G., Reid, J. C., and Yankwich, P.E., *Anal. Chem.*, 19, 828 (1947).

(23) R. Lemmon, unpublished experiments.

(24) Calvin, Heidelberger, Reid, Tolbert, and Yankwich, "Isotopic Carbon", John Wiley & Sons, 1948, in press.

(25) The nomenclature system for the labeled organic compounds is the same as that described in the book "Isotopic Carbon" by Calvin Heidelberger, Reid, Tolbert, and Yankwich, John Wiley & Sons, 1948, in press. For a similar scheme, see J. W. Otvos and C. D. Wagner, *Science*, 106, 409 (1947).

(26) Tolbert, B. M., *J. Am. Chem. Soc.*, 69, 1529 (1947).

(27) Tolbert, B. M., *J. Biol. Chem.*, 173, 205 (1948).

The methadon-2-C¹⁴ was prepared with a very high specific activity (0.5 μ c/mg.), whereas the activity of the 1-labeled compound was only a few hundred counts/min/mg. In Table I the yields, specific activities, and scale of reactions are summarized for these two preparations. Animal studies on the DL-methadon-2-C¹⁴ are in progress in the Division of Pharmacology, and results will be published in another journal in the future.

TABLE I

PREPARATION OF METHADON-2-C¹⁴

	Weight Gm.	mMole	Sp. Act.	% Yield based on CO ₂
BaCO ₃	2.04	13.5	2.59 μ c/mg.	-----
Sodium Acetate-1-C ¹⁴	0.697	8.5	6.2 μ c/mg.	86 ¹
Ethyl Bromide-1-C ¹⁴	1.43	13.1	-----	66.2
Methadon-2-C ¹⁴	1.00	2.56	5.47 μ c/mg.	9.5

PREPARATION OF METHADON-1-C¹⁴

	Weight Gm.	mMole	Sp. Act.	% Yield based on CO ₂
Sodium Acetate-2-C ¹⁴	1.01	12.3	4.88 x 10 ³ cts/min/mg	63.7
Ethyl Bromide-2-C ¹⁴	2.05	18.8	-----	46.0
Methadon-1-C ¹⁴	1.20 ²	3.22 ²	4.08 x 10 ² cts/min/mg	12.5

1. This yield was low; other radioactive runs have given yields of 91.3, 93.0, and 94.2%.
2. Not all of the ethyl bromide was used in this condensation.

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EXPERIMENTAL: -

Preparation of labeled ethyl acetate: - Labeled sodium acetate (0.7-1.0 g.) was dried in vacuo to about 1 micron pressure and weighed into a 30 cc. acetylation flask fitted with a 14/20 standard joint. Five ml. redistilled diethyl sulfate was added to the flask, and a low temperature (dry ice) reflux condenser attached (see Fig. 1). The reaction mixture was heated on an oil bath at 150-170° for 1 to 1.5 hours. The unit was then connected to the vacuum line (see Fig. 2) and the ethyl acetate distilled in vacuo from the diethyl sulfate. All but a trace of high boiling impurities (mostly diethyl sulfate) were then removed by a second vacuum distillation. The yield of ethyl acetate by this method is 95-97% as determined by saponification of the ester. A small amount of diethyl ether is present in the ethyl acetate.

Preparation of labeled ethanol: - The ethyl acetate prepared as described was vacuum distilled into a 115 cc. hydrogenation bomb (28), charged with 5 g. of copper chromite catalyst (29), pumped to high vacuum and cooled with liquid nitrogen. It is necessary to have the bomb and the catalyst well degassed (by pumping and gentle flaming of the bomb) in order to get a satisfactory vacuum distillation transfer. When the distillation was completed, the bomb was closed, warmed to room temperature, and filled with hydrogen to 2500 psi, and heated, with shaking, for 10 hours at 250°.

After the bomb had cooled to room temperature, it was reconnected to the vacuum line and the hydrogen removed by discharging the bomb

(28) American Instrument Company, Micro bomb, 180 cc. capacity.

(29) Adkins, H., "Reactions of Hydrogen", University of Wisconsin Press, Madison Wisconsin, 1937.

contents through a special liquid nitrogen cooled trap (see Fig. 2). This trap consisted of a seven turn spiral of 8 mm. glass tubing and a 2 cm., medium porosity, sintered glass disc. The hydrogen coming from the bomb is first cooled in the spiral, and any condensed material not stopped in the spiral is then filtered out by the sintered glass disc. It was found that the usual liquid nitrogen cooled spiral traps are unsatisfactory, since at any appreciable rate of flow the volatile material in the hydrogen stream is condensed to a fog and is blown through the trap.

After the hydrogen was removed, the bomb was evacuated and the volatile contents of the bomb, as well as those in the warmed spiral-sintered glass trap, were vacuum distilled into the larger trap on the manifold. This product, a mixture of ethanol, water, and diethyl ether, was treated without purification with phosphorus tribromide to prepare the halide.

To identify and isolate the ethanol, the mixture was dried with anhydrous calcium sulfate and distilled in vacuo into a micro distilling column pot. The ethanol was identified by its boiling point, 76-78°, and index of refraction, $n_D^{17} = 1.3624$. The yield of ethanol was not determined due to difficulties in isolating the pure alcohol on a small scale. However, the yield of ethyl bromide served as a criterion of the yield of ethanol.

Preparation of ethyl bromide: - The mixture of alcohol and water from the hydrogenation was distilled in vacuo into the bromination unit shown in Fig. 3. This unit was then removed from the vacuum line and a second low-temperature condenser of the type shown in Fig. 1 connected to the

ground joint. Both condensers were then cooled with dry ice-isopropyl alcohol, and phosphorus tribromide was added dropwise to the alcohol-water mixture. A large excess of phosphorus tribromide (2-3 ml.) was added, and the mixture refluxed for 3 hours on a steam bath. The entire bromination assembly was then connected to the vacuum line, and the ethyl bromide, together with some volatile impurities, distilled into the large trap on the manifold.

The product mixture was then vacuum distilled into a reaction tube containing 10 ml. of 1 N sodium hydroxide solution (see Fig. 2-D). The vessel was removed from the line and shaken for several minutes to remove acid impurities. To dry the ethyl bromide, it was then distilled in vacuo (together with some water) into a second reaction tube containing an excess of phosphorus pentoxide (Fig. 2-C). This mixture was also warmed and shaken several minutes. The ethyl bromide was vacuum distilled into yet a third reaction vessel and shaken with 5 ml. concentrated sulfuric acid for several minutes to remove ether and olefins. The purified ethyl bromide was distilled into a storage vessel (Fig. 2-E). The halide was identified on an inactive run by its boiling point, 34-39°, and its index of refraction, $n_D^{18} = 1.4326$. The yield of ethyl bromide was 67-77% based on acetic acid.

Purification of 2,2-diphenyl-4-dimethylaminopentanenitrile: - The nitrile, donated by Eli Lilly & Company, was decolorized with Norite A and recrystallized three times from 80% ethanol. The product, consisting of large white prisms, was dried with calcium chloride in vacuo, m. p. 91-91.2°. Anal. calc. for $C_{19}H_{22}N_2 = C, 81.97; H, 7.97; N, 10.06$.

Found: C, 81.98, 81.97; H, 7.95, 7.80; N, 10.26, 10.28

Preparation of the labeled ethyl Grignard and condensation with the nitrile: - The ethyl Grignard was prepared on the vacuum line and the nitrile added in benzene solution. The apparatus for the reaction is shown in Fig. 4. Nitrogen was admitted to the dried, well-evacuated system containing 0.35 g. magnesium turnings. Ten ml. dry ethyl ether was then pipetted into the reaction flask through the stirrer opening. After the stirrer was replaced, the ether was frozen in liquid nitrogen and the system re-evacuated. Labeled ethyl bromide (approximately 1 ml.) was vacuum distilled into the flask which was then closed from the manifold. With ice-acetone mixture in the condenser the ether solution was refluxed, with stirring, for 1 hour. Through the dropping funnel was then added 2.35 g. of the nitrile dissolved in 6 ml. dry benzene. The dropping funnel was washed twice with 1 ml. dry benzene; during this addition, the pressure in the reaction flask was about three-quarters atmosphere (mostly ether vapor) and the benzene solution was added slowly enough that no air was drawn into the reaction vessel. The solution was then refluxed for 3 hours; a white precipitate formed. The Grignard flask was transferred to the hood, cooled to 0° C, opened, and 24.4 ml. 20% hydrobromic acid solution added dropwise to decompose the Grignard complex.

Purification of the methadon: - The impure methadon solution was transferred to an Erlenmeyer flask and heated on the steam bath. After the ether and benzene were boiled off, the acid solution was cooled and extracted with ether. The water layer was made alkaline with 20 ml. of 3 N sodium hydroxide and extracted with ether.

The ether extract from alkaline solution was evaporated to a small volume, and 2 ml. of 20% hydrobromic acid was added. The acid solution was heated on a steam bath again to expel ether. Then a few cc. of absolute ethanol were added. The ethanol solution was concentrated on the steam bath, and the methadon crystallized out, filtered, and re-crystallized from 80% ethanol. M.P. - 224°. Anal. calc. for $C_{21}H_{28}NOBr$: C, 64.61; H, 7.23; Found: C, 65.23; 65.22; H, 7.27, 7.40.

DISCUSSION: - Almost any operation which involves transfer and storage of small quantities of volatile materials can be carried out with efficiency and safety in a closed, evacuated system. The advantages are particularly worthwhile in the case of radioactive compounds where the material itself is both valuable and dangerous. Thus, the handling and transfer of the ethyl acetate, ethanol, and ethyl bromide were carried out in the standard vacuum manifold shown in Fig. 1. The reaction vessel, reflux condensers, and other equipment used in the synthesis were fitted with ground joints so that they could be connected to the vacuum line and in vacuo transfer of the labeled compounds was used.

Small amounts of radioactive compounds are often very difficult to purify without excessive loss. Therefore, synthetic procedures have been chosen that will give (1) a relatively pure product, (2) an easily purified product, or (3) one with impurities which will not interfere with succeeding reactions. Thus, the sodium acetate was esterified with diethyl sulfate, since the ethyl acetate can be easily separated from the less volatile diethyl sulfate. Although there is some ether produced during this reaction, this does not harm the succeeding chemical steps, and the ether can ultimately be removed by washing the ethyl bromide with

sulfuric acid. Other esterification procedures either gave relatively poor yields (i.e., 90% or less) or impure or diluted products. By reducing the ethyl ester of acetic acid, only one alcohol is produced, and the need of separating a mixture of alcohols is eliminated. Although the specific activity is diluted one-half in this step, this is not particularly undesirable since very active acetic acid can be easily prepared.

In the preparation of the radioactive methadon, several modifications of the published synthetic procedure were tried. In the previous work, the nitrile was considered the most expensive of the reagents, and the condensation condition and purification scheme was established with this in mind. Thus, Easton et. al (20) used a two-fold excess of ethyl Grignard over the nitrile. This resulted in practically complete utilization of the nitrile and an easily purified product.

The results of a series of experiments in which the ratio of the nitrile to the ethyl bromide are compared with the yield of methadon are summarized in Table II. As the relative amounts of these two reagents did not seem very critical under the conditions of the experiment, the radioactive preparations were made with a two-fold excess of the ethyl bromide in order to simplify the purification of the methadon.

TABLE II

EFFECT OF RELATIVE AMOUNTS OF REAGENTS ON THE GRIGNARD
CONDENSATION

<u>Quantity of Ethyl Bromide</u> <u>Quantity of Methadon Nitrile</u>	Yield, %
1.0	19.3
1.55	22.5
2.0	21.7
2.3-2.4	21.5

In order to maintain an appreciable amount of solvent in the preparation, it was necessary to use a more dilute Grignard solution than described in the literature; experiments showed that this concentration was not critical within the limit of 0.1 to 3.0 mmole Grignard per ml. ether. Initial experiments on the synthesis of the methadon were carried out using ethyl iodide instead of ethyl bromide. It was found that when ethyl iodide was used, a non-crystalline product was obtained after hydrolysis of the Grignard complex. Since the conversion of the ethyl alcohol to the bromide or the iodide is about equally easy, it was decided to use the ethyl bromide in the condensation. It is probable that with adequate purification procedures, either halide would have given satisfactory yields. The yield of ethyl magnesium bromide from the ethyl bromide was determined by titration to be about 82% based on the halide.

The absorption spectra of the active and inactive samples of methadon produced were checked with samples prepared by Eli Lilly & Company and found to be identical, both in shape and molar absorption coefficient.

ACKNOWLEDGMENTS: - The authors wish to thank Philip F. Kirk for his technical assistance in the Grignard reactions, Dr. Louis Strait for his aid in identifying and analyzing the methadon by absorption spectra measurements, Dr. H.W. Elliott for the determination of the analgesic potency of the sample, and the help and encouragement of Professors Hamilton Anderson and M. Calvin.

SUMMARY: -

1. Ethanol-1-C¹⁴, ethanol-2-C¹⁴, ethyl bromide-1-C¹⁴, and ethyl bromide-2-C¹⁴ have been prepared from labeled acetic acid by high yield synthetic procedures on a 10-20 mmole scale.
2. DL-methadon (4,4-diphenyl-6-dimethylamino-3-heptanone) has been prepared labeled with C¹⁴ in either the 1 or 2 position.

CAPTIONS FOR FIGURES

- Fig. 1. - Reflux condenser and flask used with vacuum line synthesis of ethyl acetate.
- Fig. 2. - Vacuum manifold used in synthesis of ethyl bromide: A, large trap; B, spiral-sintered glass disc trap; C, D, reaction vessels; E, storage vessel; F, connection for hydrogenation bomb. The connections on the upper side of the line are for gas storage bulbs and pressure measuring units.
- Fig. 3. - Bromination flask.
- Fig. 4. - Vacuum line Grignard vessel: A, flask; B, enclosed induction motor stirrer with external stator; C, brass bourdon vacuum gauge; d, reflux condenser; E, dropping funnel.

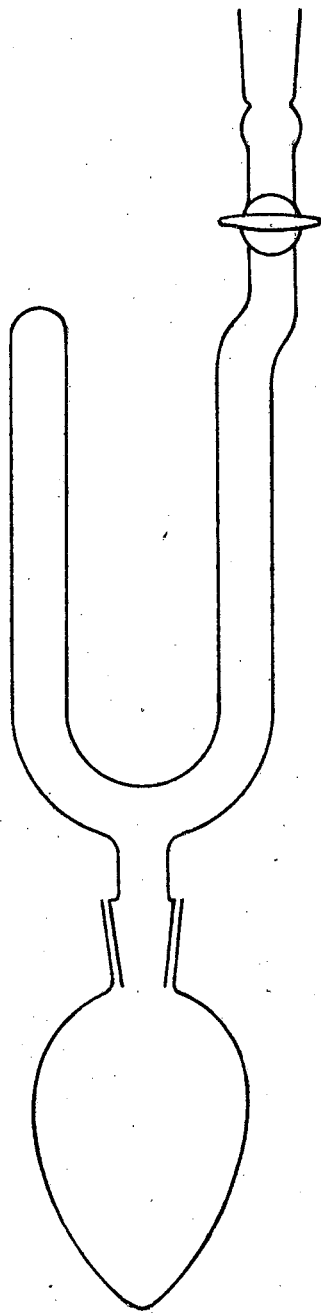


FIG. 1

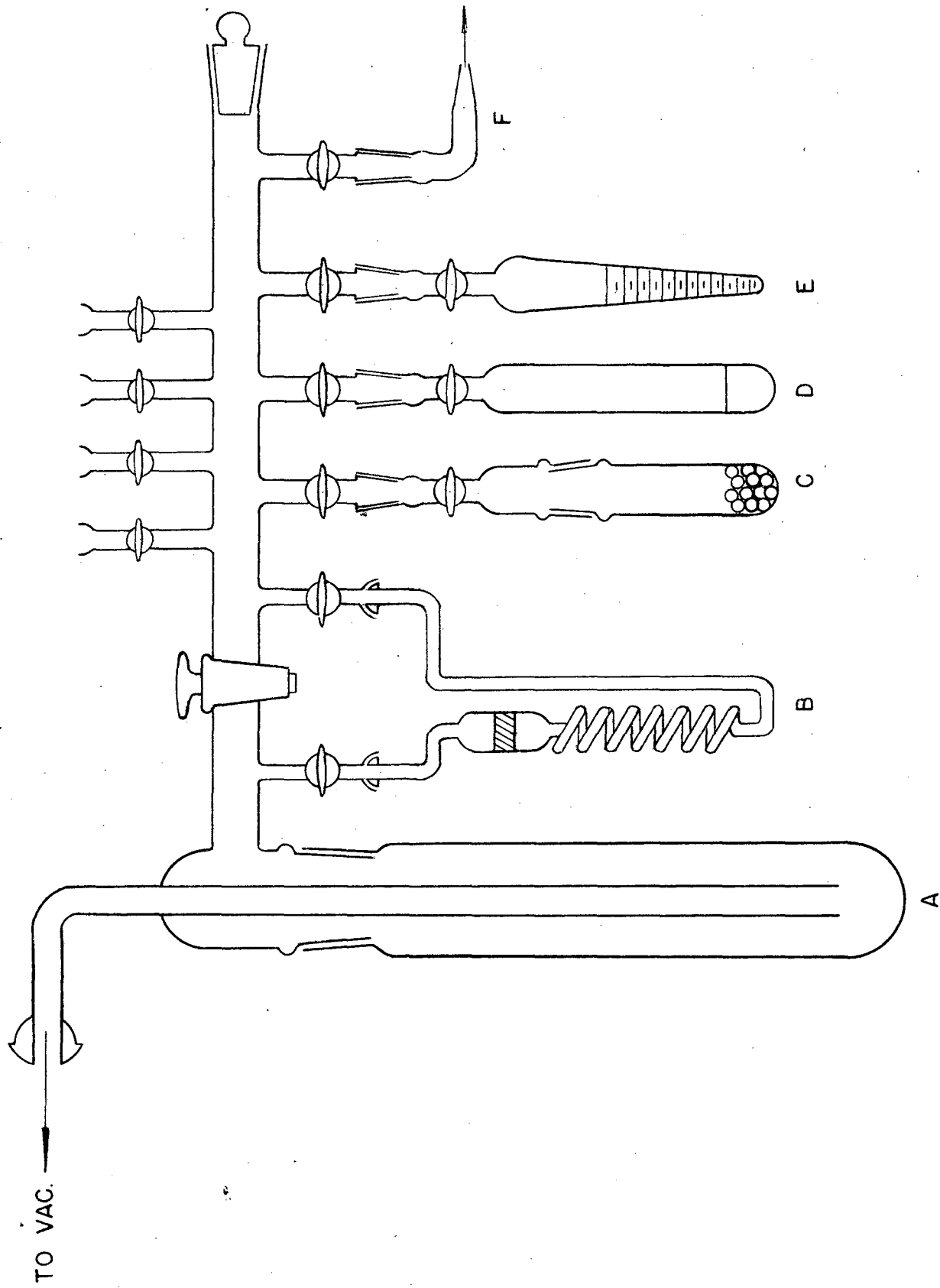


FIG. 2

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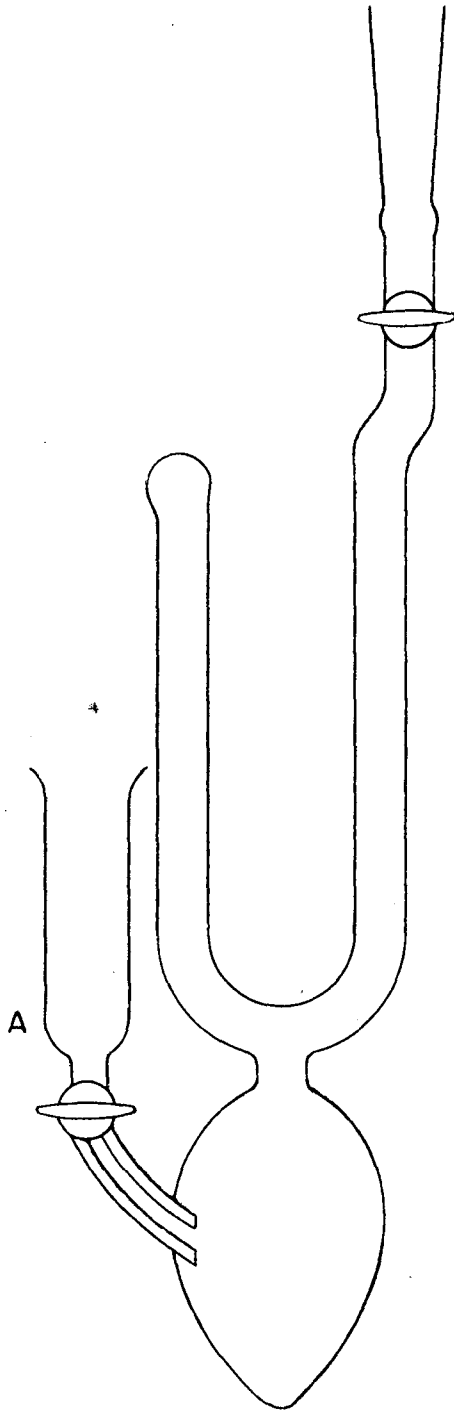


FIG. 3

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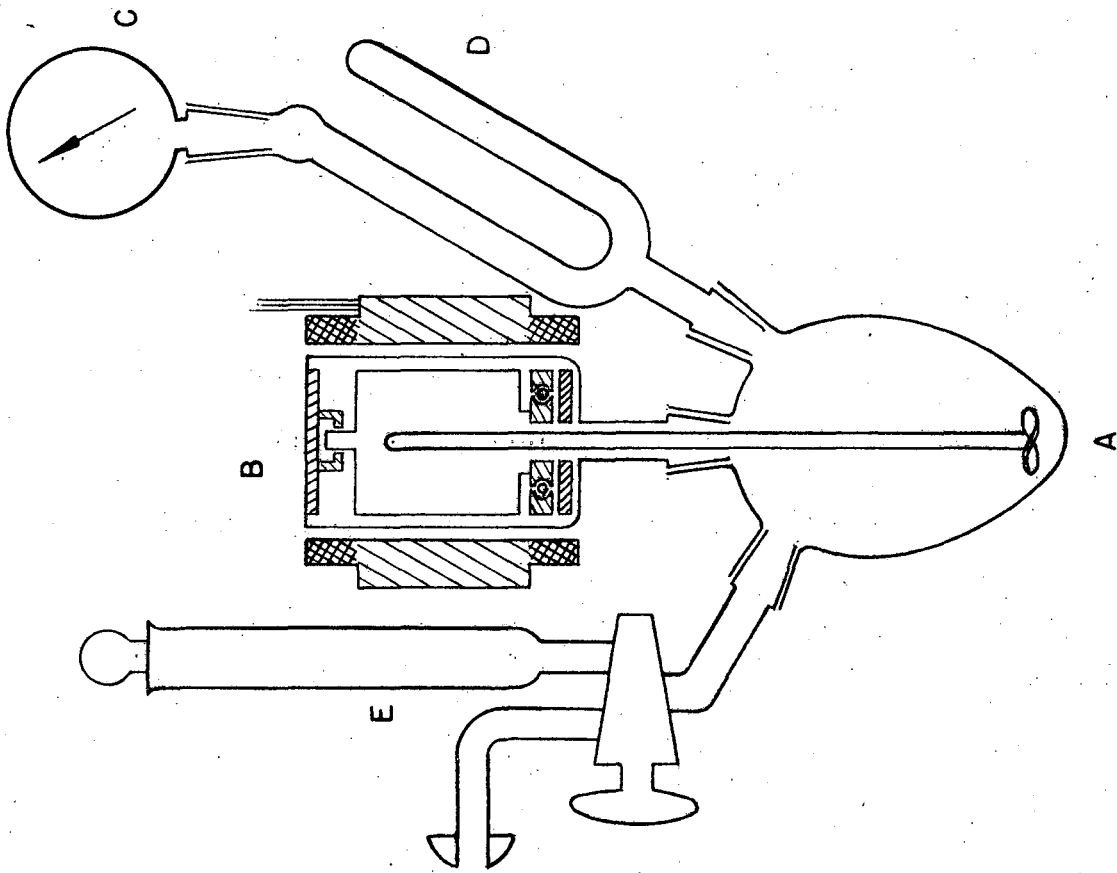


FIG. 4