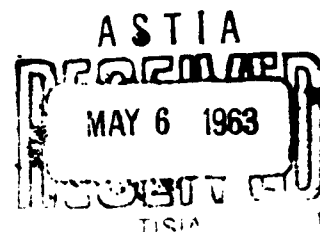63 3 3

TECHNICAL MEMORANDUM 1167

THE PREPARATION OF CARBON-14
LABELED TETRAMETHYLAMMONIUM BROMIDE

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PICATINNY ARSENAL

DOVER, NEW JERSEY

Picatinny Arsenal Technical Memorandum 1167

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LABELED TETRAMETHYLAMMONIUM BROMIDE

by

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ABSTRACT

Carbon-14 labeled tetramethylammonium bromide was prepared via the condensation of C-14 methyl bromide with trimethylamine using high vacuum techniques. Unrecrystallized product yields, in the range of 100% of theory (based on methyl bromide), are independent of variations in excess quantities of trimethylamine. C-14 methyl bromide is effectively derived from an intermixture of C-14 methyl iodide with methyl bromide in the ratio of 1:350. A series of preparations from aliquots of the stock CH_3^*I/CH_3Br mixture result in reproducible yields and specific activities of 1.8% average deviation.

INTRODUCTION

In the work on solution adsorption studies [1] trimethyl stearyl ammonium bromide (STAB), was shown to adsorb on HMX. The amount of STAB adsorbed from an aqueous solution at the leveling-off region of the isotherm is extremely small, 0.01 mg/g HMX. This amount is much too small to quantitatively evaluate the surface properties of HMX. In addition, the low solubility of STAB in the aqueous medium prevented the establishment of an extended plateau region. A need arose to investigate the possibility of developing an adsorbate-solvent system that would give a quantitative determination of the surface properties of HMX.

The affinity of an adsorbate molecule for an adsorbent surface in a solvent medium is governed by many factors and the isotherm produced can be subjected to variation. One of these factors is the chain length of the adsorbate molecule. It has been found that the surface activity of the fatty acids in aqueous solutions increases with the number of CH_2 groups in the chain [2]. The regularity of this increase was observed by Traube [3]. However, when solvents, other than water are used (eg. n-propyl alcohol, benzene and toluene), this order is found to be reversed[4]. By using a different solvent and selecting a smaller chain-length quaternary ammonium compound, it could be possible to work with a system giving higher adsorption values at equilibrium concentrations.

Tetramethyl ammonium bromide (TAB) was selected for this purpose for several reasons. The use of a solvent other than water might reverse the order of affinity of the homologous series of quaternary ammonium salts for HMX. From a structural consideration, TAB would appear to have a slightly greater basicity than is exhibited by STAB. TAB would, therefore, be expected to have a greater attraction than STAB for the electron dense centers at the surface of the HMX crystal lattice. If steric hindrance were another factor contributing to the low adsorption of STAB on HMX, TAB being a compact molecule, would more freely saturate the adsorbent surface. Still another factor to be considered in studying adsorption from solutions is micelle formation. Long chain molecules are known to form micelles as a function of concentration[5]. This not only complicates the problem of obtaining quantitative data but also could greatly alter the intrinsic affinity of an adsorbate molecule for an adsorbent surface. Obviously, TAB would not have the property of agglomerating in solution.

To pursue this investigation C-14-TAB was needed. This labeled compound is not listed in any of the catalogs, nor is a description of its preparation found in the open literature. It, therefore, became necessary to develop a method for the preparation of C-14-TAB having a desired specific activity of approximately 10 microcuries per millimole.

This report describes the high vacuum line procedure developed for the preparation of C-14-TAB.
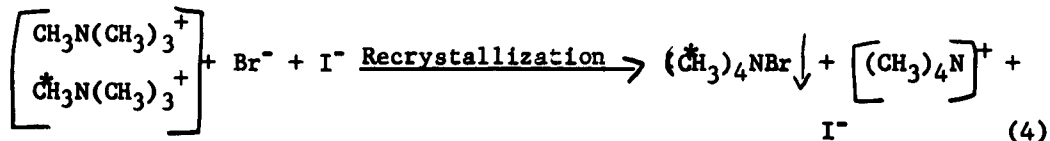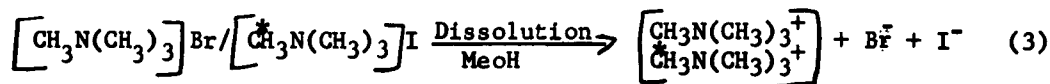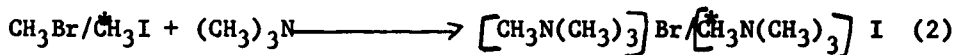

RESULTS AND DISCUSSION

The synthesis of C-14-TAB was based on the reaction described in Houblen-Wehl[6], i.e.

$$CH_3Cl + (CH_3)_3N \longrightarrow (CH_3)_4NCl \qquad (1)$$
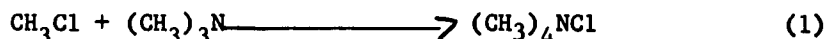
Based on the increasing order of reactivity of the alkyl halides in going from F to I, methyl iodide was selected for the synthesis of the C-14-labeled compound. It was reasoned that the methyl iodide would drive the reaction to product formation to a greater degree than would the chloride or even bromide. In this manner a maximum incorporation of the C-14-methyl group in the adduct molecule could be effected. Since cost is an important consideration in the syntheses of C-14-labeled compounds, the minimum loss of activity is most desirable. Consistent with this economy consideration is the fact that the price of C-14-CH_3I is 35% lower than that of the C-14-CH_3Br.

Although the desired labeled compound is the bromide salt of tetra-methylamine, the use of C-14-CH_3I when intermixed in trace quantities with CH_3Br was considered to behave as C-14-CH_3Br. The actual molar ratio of C-14-CH_3I to CH_3Br used in this synthesis was 1:350 as indicated in Table 2. The effectiveness of this equivalence can best be illustrated by the following set of equations:

$$CH_3Br/\overset{*}{C}H_3I + (CH_3)_3N \longrightarrow \left[CH_3N(CH_3)_3\right]Br/\left[\overset{*}{C}H_3N(CH_3)_3\right]I \quad (2)$$

$$\left[CH_3N(CH_3)_3\right]Br/\left[\overset{*}{C}H_3N(CH_3)_3\right]I \xrightarrow[\text{MeOH}]{\text{Dissolution}} \begin{bmatrix} CH_3N(CH_3)_3^+ \\ \overset{*}{C}H_3N(CH_3)_3^+ \end{bmatrix} + B\bar{r} + I^- \quad (3)$$

$$\begin{bmatrix} CH_3N(CH_3)_3^+ \\ \overset{*}{C}H_3N(CH_3)_3^+ \end{bmatrix} + Br^- + I^- \xrightarrow{\text{Recrystallization}} (\overset{*}{C}H_3)_4NBr\downarrow + \left[(CH_3)_4N\right]^+ + I^- \quad (4)$$

Assuming the reaction product in equation (2) to be a mixture, subsequent dissolution converts the tagged and untagged quaternary ammonium ions into a pool that becomes common to both halide ions. Since the iodide ion exists in trace quantities, it remains in solution in equilibrium with the quaternary cation after recrystallization and is removed by filtration together with a relatively larger fraction of dissolved $(\overset{*}{C}H_3)_4NBr$ (this is indicated in equation

(4)). The process of recrystallization hence, not only equilibrates the tagged with the untagged quaternary species, but equally as important, removes the iodide as an impurity. The removal of the iodide is most critical since its behavior in tracer studies, being different than that of the bromide, would seriously interfere with interpretations attributed solely to the bromide.

In addition to the above set of conditions that would promote the indirect equilibration of the $CH_3Br/\overset{*}{C}H_3I$ mixture, there is a highly favorable possibility of equilibration via exchange taking place directly in the gas mixture before condensation with trimethylamine $(CH_3)_3N$. Schmied and Fink[7] report the thermal exchange of I_2 with CH_3I and HI in the gas phase to be catalyzed by the glass surface of the container. It is implied that the alkyl halide is sufficiently labile to dissociate into free radicals:

$$\overset{*}{C}H_3I \rightleftharpoons \overset{*}{C}H_3\cdot + I\cdot \qquad (5)$$

This is considered the initiating step in the mechanism of exchange. Since this is true for CH_3I, CH_3Br would be expected to dissociate in like manner,

$$CH_3Br \rightleftharpoons CH_3\cdot + Br\cdot \qquad (6)$$
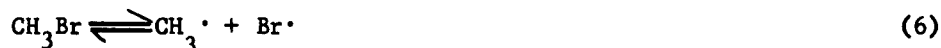
For a $\overset{*}{C}H_3I/CH_3Br$ gas mixture, the combined dissociations as indicated in equations (5) and (6) would result in equilibration, thusly:

$$\overset{*}{C}H_3I + CH_3Br \rightleftharpoons \overset{*}{C}H_3\cdot + I\cdot + CH_3\cdot + Br\cdot \rightleftharpoons CH_3I + \overset{*}{C}H_3Br \qquad (7)$$
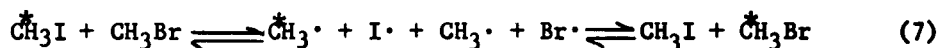
More specifically, Moelwyn-Hughes[8] made an exhaustive kinetic study of the exchange between methyl halides and halogen ions in polar and non polar solvents. The mechanism for exchange in solution is necessarily ionic:

$$CH_3Br + I^- \rightleftharpoons CH_3I + Br^- \qquad (8)$$

With equation (8) being true, certainly the exchange:

$$CH_3Br + \overset{*}{C}H_3I \rightleftharpoons CH_3I + \overset{*}{C}H_3Br \qquad (9)$$
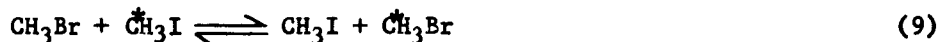
in methyl alcohol should also take place. It was, therefore, quite apparent that the C-14 labeled methyl group would be incorporated in the TAB molecule either by $\overset{*}{C}H_3I/CH_3Br$ exchange prior to condensation with trimethylamine, or by formation of a common quaternary cation, or both.

The C-14-CH_3I supplied by New England Nuclear weighed 14.2 mg (0.1 mM) and had a total activity of 0.50 millicuries. It was evident that the

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procedure for the preparation of C-14-TAB could not be of the conventional type as cited in Houblin-Wehl[6]. The reaction reported with the methyl chloride was run by using appropriate refrigerants and drying tubes at crucial points in the apparatus exposed to the atmosphere. The vacuum line shown in Figure 1 was especially designed and fabricated for the synthesis involving trace quantities of high specific activity CH_2I. The degassing of materials was done at liquid N_2 temperature and all additions of reactants were performed in a closed system at reduced pressures in the micron range. The mixture of CH_3I/CH_3Br gases was allowed to remain in the storage flask for one week before drawing off aliquots. Then the gas mixture was transferred to ampoules containing methyl alcohol and kept sealed from 1 to 3 days prior to its condensation with $(CH_3)_3N$. After combining the reactants, the reaction flask was sealed and allowed to stand a minimum of one day before isolating and recrystallizing the reaction product. In this manner ample opportunity was given for the complete equilibration of the tagged with the untagged constituents.

Before committing the radioactivity, an extensive series of cold runs was made to check out the vacuum line techniques involved and determine the optimum conditions for maximum product yields. Table 1 shows the yields of TAB corresponding to the respective quantities of CH_3Br used. The $(CH_3)_3N$ was always kept in excess of the CH_3Br and varied widely to observe if there was a critical amount necessary for attaining maximum product yields. As can be seen in Table 1, the excess $(CH_3)_3N$ was not critical and with the exception of the first two runs, the yields were in the range of 100% of theory. The yields reported in the literature[6] were in the order of 90-95%. The high vacuum technique is thus shown to optimize product formation to theoretical proportions and hence beyond those obtained by the conventional method of preparation. Assuming that the activity is incorporated via the separate reaction of CH_3I (as outlined in the common pool mechanism in equations (2) - (4)), CH_3I being more reactive would be taken up quantitatively even though small amounts of CH_3Br are lost. In the case of exchange taking place between CH_3I and CH_3Br before condensation with $(CH_3)_3N$, then whatever amount of activity that may be lost as CH_3Br is greatly reduced by the dilution factor of 1/350 (See Table 2). In any event, having obtained theoretical yields, it would appear that the activity would be quantitatively introduced by this method of synthesis.

Methyl iodide normally exists as a liquid with a vapor pressure of 760 mm at $42.5^\circ C$. However, the small quantity of 14.2 mg in a 957 cc volume storage flask had a corresponding partial pressure of only 1.88 mm at STP. The partial pressure of CH_3Br in the same storage flask was less than one atmosphere, as indicated in Table 2. Both constituents were therefore, in the gas phase from the start, when the first aliquot was drawn from the expanded gas mixture. In the event exchange did not take place in the gas phase, it was considered

Table 1

INDEPENDENCE OF TAB YIELD WITH VARYING
AMOUNTS OF $(CH_3)_3N$ IN EXCESS OF METHYL BROMIDE

mm (Pres) CH_3Br	Temp. ^oC	Wt. (g) CH_3Br	Wt. (g) $(CH_3)_3N$[1]	Percent Excess $(CH_3)_3N$	Wt. (g) Crude[2] TAB	Percent Yield TAB
1098	23	1.13	0.77	10	1.65	90
580	23	0.60	0,44	19	0.86	89
551	24	0.57	0.44	26	0.94	102
1052	20	1.09	0.88	29	1.80	102
398	20	0.41	0.43	65	0.67	100
557	19.5	0.58	0.43	19	0.96	102

(1) Dissolved in methyl alcohol
(2) Product freed of excess $(CH_3)_3N$

Table 2

PARTIAL PRESSURES OF C-14 CH_3I AND
CH_3Br IN STORAGE FLASK AT STP

Gas	Wt (g)	No. Moles (x 10^4)	B. P. °C	Gas Temp °K	(Part. Press)[2] STP (mm)
$\overset{*}{C}H_3I$[1]	0.014	1	42.5	292.5	1.88
CH_3Br	3.35	350	4.5	292.5	563

(1) 0.5 millicurie/14.2 mg CH_3I
(2) In 957 cc Storage Flask

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important to keep both constituents in the gas phase, thereby precluding the possibility of fractionating the mixture. If one of the constituents were initially in a partial liquid phase, successive expansions would have resulted in varying ratios of CH_3I to CH_3Br in the aliquots drawn off; therefore, correspondingly varying specific activities of C-14-TAB would have been obtained. Table 3 shows the specific activities to remain constant with each successive aliquot preparation. The average specific activity of 2.29×10^5 d/m/mg TAB actually obtained is shown by calculation (See Experimental Procedure) to correspond to 5.42 millicurie/mM CH_3I as against 5.0 mM. CH_3I shown on the ampoule label. It is specified in the supplier's catalog that the specific activity is given as an approximation in millicuries per mM. Since the calculation showed more activity in the CH_3I than was indicated on the label, the only conclusion to be drawn is that the method of synthesis effectively incorporated the original activity quantitatively into the TAB molecule. The yields are also shown to be constantly theoretical and in agreement with those obtained in the cold runs. It may be argued that the specific activities of successive sample preparations need not necessarily be of constant value and that the different activities could be made uniform by dissolution followed by precipition. For the adsorption study such an argument does indeed apply. However, as a general application of the method of synthesis, constant specific activities may be of utmost importance. It was in this vein that the refinement in the procedure was included.

EXPERIMENTAL PROCEDURE

Preparation of C-14-Tetramethylammonium Bromide

After placing the metal hammer in position, the ampoule containing the C-14-CH_3I was flame-sealed onto the vacuum line (Figure 1). The storage flask was calibrated with water (957 cc) prior to affixing it to the apparatus. Knowing the volume of the storage flask, the vacuum line above the manifold stopcocks and to the right of the line stopcock was calibrated by the usual gas expansion method, $P_1 V_1/T_1 = P_2 V_2/T_2$ and found to be 200 cc. The connection to the CH_3Br tank was made at the manifold stopcock indicated in Figure 1, keeping the tank needle-valve closed. All stopcocks were opened except the last two, to the far right. A liquid nitrogen, $(N_2)_1$, bath was placed at the trap to the far left and the system was pumped on with an oil diffusion pump containing 703 Dow Corning silicone oil. When the thermionic guage gave a reading of zero micron pressure, the line stopcock was closed to check for leaks in the vacuum line. With the line stopcock closed at zero pressure holding, the needle-valve to the CH_3Br tank was slowly opened. The CH_3Br was introduced into the line at an equilibrium pressure of 563 mm (read on the manometer), after which the stopcock to the storage flask was closed.

Table 3

REPRODUCIBILITY OF YIELD AND SPECIFIC
ACTIVITY IN THE PREPARATION OF C-14 TAB

mm (Pres)[1] CH_3I/CH_3Br	Temp °C	Wt. (g) $CH_3{}^*I/CH_3Br$	Percent Yield[2] C-14 TAB (crude)[4]	Spec. Act[3] C-14 TAB $d/m/mg$ ($\times 10^{-4}$)
557	19.5	0.58	102	22.5
467	20	0.49	98	22.2
985	24	1.01	101	21.7
1312	23	1.35	100	23.0

(1) 200 cc volume
(2) Based on CH_3Br
(3) Purified by dissolution in methanol and precipitation with ether
(4) Product freed of excess $(CH_3)_3N$

The CH_3Br in the manifold line, including the connection to the closed tank needle-valve, was frozen out with $(N_2)_l$ at one of the stopcocks to the far right of the line. With all stopcocks closed, the line stopcock was opened and the manifold line was degassed to zero pressure. The CH_3Br was then degassed by freezing it at -196°C and pumping on it for 10 minutes or until zero pressure was indicated on the gauge. After closing the line stopcock the seal to the C-14-CH_3I was broken. The $(N_2)_l$ bath was then removed from the storage flask, thereby, allowing both gases to equilibrate into an homogeneous mixture. The mixture was then recondensed into the storage flask with (N_2), reading zero pressure on the gauge prior to closing the stopcock to the storage flask. The gas mixture was allowed to remain in the storage flask one week before drawing off aliquots for product formation.

With the line stopcock closed, a 30 cc ampoule containing approximately 5 cc methyl alcohol was placed on the vacuum line (as indicated in Figure 1) and degassed twice at -196°C. The stopcocks to the ampoule and the line were closed and the storage flask stopcock opened. At equilibrium the pressure reading (common to the storage flask and manifold line) was then recorded and the stopcock to the storage flask closed. Knowing the pressure in the 200 cc manifold volume, the quantity of $\overset{*}{C}H_3I/CH_3Br$ (hereafter referred to as CH_3Br) was calculated at STP in the usual manner:

$$\frac{200 \text{ cc-mole } CH_3Br}{2.24 \times 10^4 \text{ cc}} \times \frac{273°K}{Obsd \ °K} \times \frac{95 \text{ g } CH_3Br}{\text{mole } CH_3Br} \times \frac{Obsd \ Pres}{760 \text{ mm}} = g\overset{*}{C}H_3Br$$

This known amount of $\overset{*}{C}H_3Br$ was then transferred to the ampoule containing methyl alcohol by means of a $(N_2)_l$ bath. At zero pressure reading, the ampoule was flame-sealed and the $\overset{*}{C}H_3Br/MeOH$ mixture was allowed to stand 2-3 days. A metal hammer was inserted into the break-seal end of the ampoule which was then secured to the vacuum line and evacuated above the break-seal. A reaction flask containing a methanol solution of $(CH_3)_3N$, in excess of the CH_3Br was placed on the vacuum line as indicated in Figure 1, and degassed twice at -196°C. The preparation of $(CH_3)_3N$ was based on the procedure given in Org Syn[9] with the exception that the starting material was $(CH_3)_3N \cdot HCl$. With the two stopcocks opened and all the others closed, the break-seal was broken and the contents transferred to the reaction flask at -196°C. At zero pressure the reaction flask was sealed and the reaction mixture allowed to stand overnight prior to isolation of the product, TAB. The above procedure was followed for repeated preparations of TAB from successive aliquots of $\overset{*}{C}H_3Br$ drawn off.

After purification by dissolution in methanol and precipitation with ether, the sublimation point was determined by placing the specimen on the Kofler hot stage twenty degrees below the reported value, (386°C), and found to be 374-6°C. The purity of the product was established by the gravimetric determination of the bromine content as silver bromide. The average bromine content of two determinations was 51.58% as compared to the theoretical of 51.90%. The TAB was thus shown to be of 99.4% purity.

Determination of Liquid Scintillation Counter Efficiency

For this determination correction is made for the quenching of the solvent system by counting the standard in the same solvent mixture used for the C-14 TAB. The solvent system consisted of 2 ml methyl alcohol, 20 ml toluene containing 4.00 g 2,5 diphenyloxazole (PPO)/l. and 100 mg $2,2^1$-p-phenylene-bis-(5-phenyloxazole) (POPOP)/l. The quenching due to the standard benzoic acid and TAB was eliminated by counting 1-2 mg sample weights. The specific activity of the Bureau of Standards Benzoic Acid is listed as, 5,500 d/m-mg. The average weight of benzoic acid for three determinations was 2.138 mg. The total d/m was: 2.138 x 5,500 = 11,760 d/m. The actual average d/m obtained with the TRI-CARB liquid scintillation counter was 7460 d/m (at 1200 volts and discriminator settings of 10-100 v). Therefore the calculated percent efficiency is given by:

$$\% \text{ Eff} = 7460/11,760 \times 100 = 63.4$$

The mc/mM CH_3I Calculated from the Activity of C-14-TAB

The c/m-mg TAB is first converted to d/m-mg TAB by dividing the average c/m of 1 mg C-14-TAB by the efficiency calculated above:

$$140,200/.634 = 224,000 \text{ d/m-mg TAB}$$

The d/m-mg TAB is then converted to millicuries (mc) per mM CH_3I by correcting for the dilution of CH_3I with CH_3Br (1:350); and for the difference in the specific activity of one mg TAB as compared to one mg CH_3I, as follows,

$$2.24 \times 10^5 \frac{d}{\text{m-mg TAB}} \times \frac{154 \text{ mg TAB}}{141.9 \text{ mg } CH_3I} \times 350 = 8.5 \times 10^7 \text{ d/m/mg } CH_3I$$

and finally:

$$8.5 \times 10^7 \frac{d}{\text{m-mg } CH_3I} \times \frac{142 \text{ mg } CH_3I}{\text{mM } CH_3I} \times \frac{\text{sec-mc}}{3.7 \times 10^7 \text{ d}} \times \frac{m}{60 \text{ sec}} = 5.42$$

mc/mM CH_3I

The specific activity shown on the supplier's label is:

$$5.0 \text{ mc/mM } CH_3I$$

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CONCLUSIONS

The high vacuum line method developed for the synthesis of C-14 TAB produces theoretical yields. The yields, based on methyl bromide, are not dependent upon any critical excess concentration of $(CH_3)_3N$.

The specific activity of C-14 TAB remains constant with successive aliquot preparations. The total amount of activity originally present in the CH_3I is incorporated in the final reaction product, TAB.

The mechanism(s) by which the TAB molecule is labeled with Carbon-14 is either by the exchange of $\overset{*}{C}H_3I$ with CH_3Br in the gas phase as well as in methanol solution, or by the complete equilibration of the tagged with the untagged quaternary ammonium cations in methanol solution or both.

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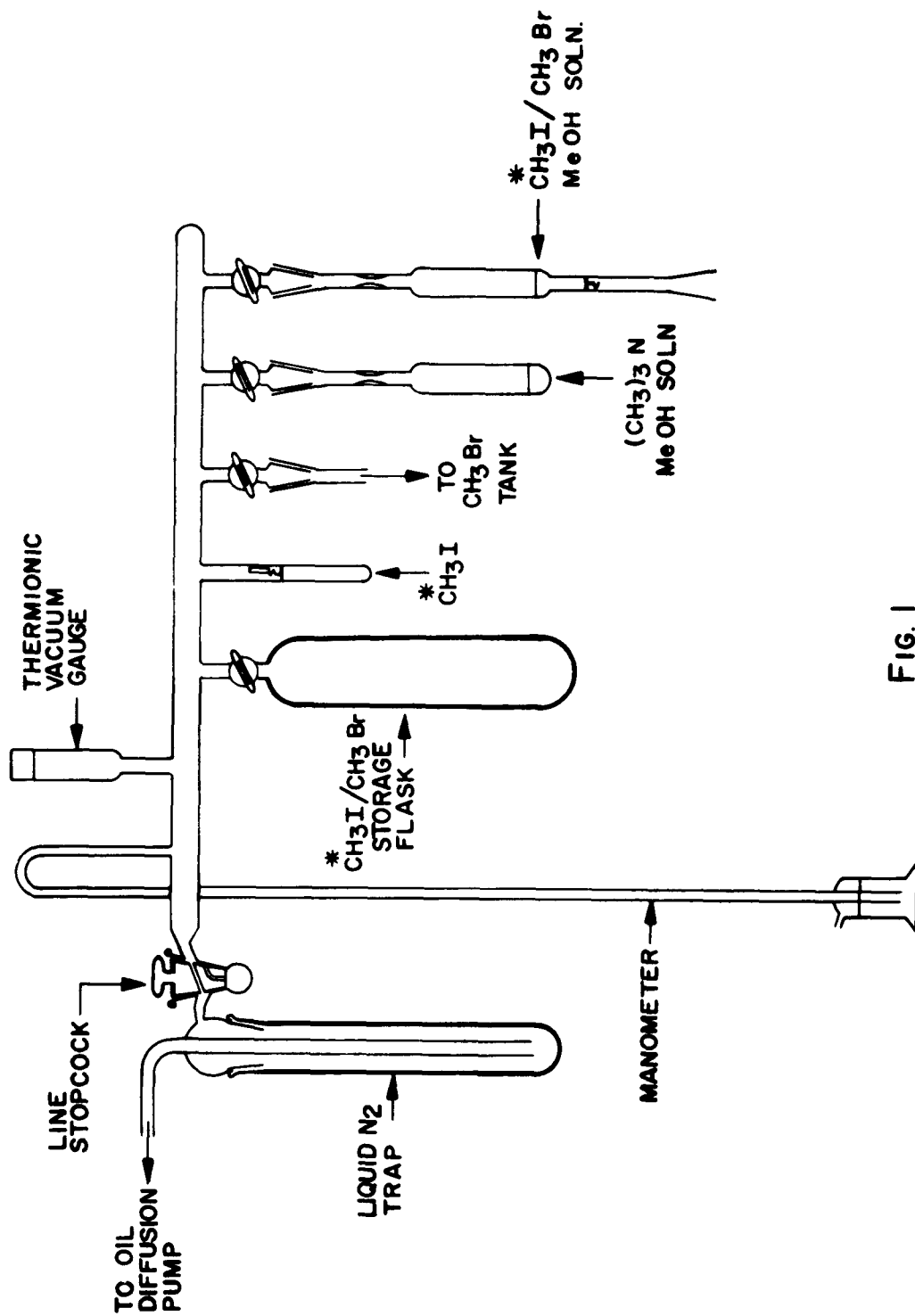# VACUUM LINE APPARATUS USED FOR THE PREPARATION OF C-14 TETRAMETHYL AMMONIUM BROMIDE

FIG. 1

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