618. *Syntheses with Isotopic Tracer Elements. Part I. The Preparation of Methanol and Sodium Acetate Labelled with Carbon Isotopes.*

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A critical study of methods for the synthesis of methanol, methyl iodide, and acetic acid containing carbon isotopes has been carried out. Methods are described for the preparation of these intermediates in good yield and high purity from potassium cyanide or barium carbonate on the scale of 1—250 millimoles.

Carbon enriched in ^{13}C has for some time been available in potassium cyanide, obtained by the cyanide–hydrogen cyanide exchange reaction (cf. Urey *et al.*, *J. Chem. Physics*, 1939, **7**, 137; 1940, **8**, 532; Stewart, *Nucleonics*, 1947, **1**, No. 2, 25), but will shortly be available in barium carbonate from Harwell (cf. " Radioactive and Stable Tracers," A.E.R.E., M.O.S.; Amendment Sheet No. 1); ^{14}C is available only in barium carbonate. The basic requirements in the synthesis of isotopically labelled organic compounds for use in chemical and biological tracer investigations are suitable methods for the preparation of simple organic intermediates from these inorganic materials. Labelled methanol and the two theoretically possible labelled acetic acids are among the most needed intermediates, and their preparation by preferred routes from carbon dioxide and potassium cyanide has now been closely studied.

The criteria by which the suitability of preparative methods for ^{13}C- and ^{14}C-labelled materials are to be judged show some important differences. With the first mentioned it is most important to avoid dilution with carbon of natural isotopic ratio since the most highly enriched material normally available ($\sim$60 atoms % ^{13}C) can at best be diluted with less than 10^3 times the amount of natural carbon if the accuracy of mass-spectrometric assay is not to be too greatly reduced (cf. Nier, " Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, 1948, p. 29). ^{14}C is available in barium carbonate containing $\sim$6 atoms % of ^{14}C, and can be estimated in concentrations of 10^{-7} of this value with no loss of accuracy. Indeed the labelled material is for most tracer purposes too concentrated by a factor of at least 10^2, and often by 10^5, but it is often convenient to carry out the syntheses at the higher concentration and to dilute the products with pure normal carrier. This may greatly improve the chemical purity of the labelled material, but cannot affect the relative concentrations of the labelled compounds that may be present (*e.g.*, see p. 3168). For this reason it is important that the synthetic labelled material should be of high purity, and more especially that containing ^{13}C. In all preparations high yields are desirable, but are more important for ^{13}C-material since in general a given tracer investigation will involve a greater expense and expenditure of material when the stable isotope is used. Further, this high yield of pure material must often be obtained on a scale as low as, or lower than, 10 millimoles. Under these conditions it is advantageous to apply vacuum techniques to the syntheses.

Several methods have been used for the generation of carbon dioxide from barium carbonate in a closed evacuated system (cf. Calvin *et al.*, " Isotopic Carbon," Chapman and Hall, London, 1949; pp. 153—154). We have used 45% perchloric acid for generation by acidification (cf. Sakami, Evans, and Gurin, *J. Amer. Chem. Soc.*, 1947, **69**, 1110), and on the scale of a few millimoles the lead chloride fusion method of Zweibel, Turkevich, and Miller (*ibid.*, 1949, **71**, 376) is very satisfactory. Cyanide was oxidised to carbonate by alkaline permanganate, and the carbon dioxide recovered by acidification (cf. Weinhouse, Medes, and Floyd, *J. Biol. Chem.*, 1944, **155**, 143).

Three methods for the preparation of carbon-labelled methanol from carbon dioxide have been described. Melville, Rachele, and Keller (*ibid.*, 1947, **169**, 419) converted carbon dioxide into potassium hydrogen carbonate, which was reduced to potassium formate by hydrogen in the presence of palladium black (Bredig and Carter, *Ber.*, 1914, **47**, 541). The formate was esterified by heating it with methyl sulphate, and the ester converted into methanol by hydrogenolysis at atmospheric pressure over a copper chromite catalyst. The overall yield on the 3·5-millimole scale was better than 73%. A 100% dilution with unlabelled material is inherent in the method. Tolbert (*J. Amer. Chem. Soc.*, 1947, **69**, 1529) has described the catalytic reduction of carbon dioxide to methanol at high temperatures and pressures. On the 25-millimole scale yields of methanol of 81—86% were obtained. There was no dilution with unlabelled material, and water was apparently the only major impurity. An attractive method has been described by Nystrom, Yanko, and Brown (*J. Amer. Chem. Soc.*, 1948, **70**, 441),* whereby carbon dioxide is reduced to methanol by a solution of lithium aluminium hydride in an involatile solvent, the methanol being recovered after alcoholysis of the resulting complex by a high-boiling alcohol. The authors claim a yield of 81% of redistilled material of high purity (as judged by the refractive index).

This last method has been examined in detail. The solution of lithium aluminium hydride in diethylene glycol diethyl ether, prepared, filtered, and stored in a nitrogen atmosphere (the vapour pressure being $\sim$0·4 mm. Hg at 20°), was stirred or shaken in a closed evacuated system, to which the carbon dioxide was admitted; absorption was rapid and complete. On the small scale (below 20 millimoles) the subsequent alcoholysis of the complex and separation of the methanol by distillation were carried out at 100° in a current of inert gas at atmospheric pressure under patial reflux, but on a larger scale the fractional distillation was carried out under reduced pressure.

The first crude distillate was largely freed from the relatively involatile material by a single-plate distillation. This is fairly efficient since these involatile materials appear to consist only of solvent (v. p. at 0°, $\sim$0·1 mm. Hg), diethylene glycol monobutyl ether (v. p. at 0°, $\sim$0·01 mm. Hg), and involatile products formed by polymerisation of formaldehyde or by its reaction with the involatile alcohol to form acetals(?). In typical runs the yield of this distillate (on a weight basis, computed as pure methanol) varied between 84 and 113%, but in certain cases " yields " as high as 150% were obtained. The material, chemically, was rather impure : physical constants and impurities detected and estimated in some of the products obtained are given in Table I.* The most serious impurity was ethanol since this is not easily removed quantitatively on the small scale. It arises by scission of the diethylene glycol diethyl ether used as solvent during the reaction; the amount present (4—7%) agreed roughly with the extent of scission indicated by dilution of labelled ethanol in the reduction of acetyl chloride by diethylene glycol diethyl ether solutions of lithium aluminium hydride (Part II; succeeding paper).

Details of several typical runs are given in Table II. The total excess of isotope recovered as methoxyl in the crude methanol was 69—77%. In general, the higher the overall recovery of isotope, the higher the concomitant impurity; for example, in runs with ^{14}C-compounds the greatest weight " yield " of crude material was 150% and the recovery of methoxyl activity was then 77%. In this case the total activity in the crude methanol was 91% of that in the carbon dioxide reduced, and some 85% of this total activity was present in methoxyl. The remaining activity was probably present in formaldehyde, formals, and, possibly, methyl formate.

Another unsatisfactory feature of the reduction was the dilution with inactive material which always took place.* The percentage dilution of isotope at a particular labelled atom over a reaction stage or series of stages was calculated by means of the expression $100M_1(A_1 - A_2)/M_2A_2$, where M_1 and M_2 are the molecular weights of the normal and the

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* [*Note added in proof.*] Since submitting this paper we have received a report, entitled " Production of Methanol-^{14}C by the Lithium Aluminium Hydride Process " (ORNL 395, U.S.A.E.C.), by Nystrom, Skraba, and Mansfield. Working with diethylene glycol diethyl and monobutyl ethers, these authors also found that alcoholysis of solutions of the hydride liberates small amounts of methanol, but found no positive evidence for the presence of ethanol; they state that traces of ethyl ether are present in methanol prepared by this method. We cannot confirm the presence of ethyl ether, but very small traces cannot be excluded. We have shown that ethyl iodide present in methyl iodide prepared from the crude methanol is present in quantity ($\sim$4—6%) considerably greater than could arise (*i.e.*, <2%) from the diethylene glycol diethyl ether originally present. Nystrom *et al.* describe a useful method for the separation of methanol and diethylene glycol diethyl ether in which the crude product is distilled in a high vacuum between vessels at −25° to −45°, and −196°.

labelled final compound respectively, and A_1 and A_2 are the concentrations of excess isotope in the relevant atom of the initial and the final compound respectively. For ^{14}C labelling $M_1/M_2 \simeq 1$ in the great majority of cases. The dilution thus calculated was variable, values over the range 7—10% having been observed. This may be attributed to the absorption of atmospheric carbon dioxide by the lithium aluminium hydride during its preparation and storage in solid form. It has been demonstrated that when solutions of the hydride in diethylene glycol diethyl ether are submitted to a blank decomposition, alcoholysis, and distillation (using ethylene glycol monophenyl ether as the alcohol) mixtures of methanol and ethanol are obtained. Further, methanol was detected in ethanol prepared by lithium aluminium hydride reduction of acetyl chloride (see Part II; succeeding paper). The dilution observed was greater if the solution of the hydride was not filtered until absolutely clear before use.

TABLE I.

	Product.					Impurities in the product.		
Reaction.	Crude wt. yield, %.	Overall wt. yield, %.	n_D^{20}.	d_4^{20}.	V. p./0°, mm. Hg.	H_2O, %.	CH_2O, %.	Others.
$CO_2 \longrightarrow$ MeOH [a]	113	113	1·339	0·827	24	7·5	2·1	(*a*, *c*, *d*)
$CO_2 \longrightarrow$ MeOH [a]	84	84	1·337	0·818	28	2·5	(*f*)	(*a*, *d*, *e*)
$CO_2 \longrightarrow$ MeOH [b]	100	100	1·3345	0·803	29	4·5	0·4	(*b*, *g*)
$CO_2 \longrightarrow$ MeOH [b]	105	105	1·3384	0·823	30	6·5	0·7	(*b*)
MeOH $\longrightarrow$ MeI	60	68	1·522 [h]	2·22	—	Trace	—	EtI, 4—5%
MeOH $\longrightarrow$ MeI	84	71	1·524 [h]	2·20	—	,,	—	EtI
MeOH $\longrightarrow$ MeI	83	83	1·5308	2·24	—	,,	—	—
MeOH $\longrightarrow$ MeI	81	85	1·531	2·26	—	,,	—	—
Pure MeOH $\longrightarrow$ MeI	93	—	1·530	2·28	—	—	—	—

[a] Solvent, diethylene glycol diethyl ether; decomposer, diethylene glycol monobutyl ether. Each less than 3% in the product. [b] Solvent, tetrahydrofurfuryloxytetrahydropyran; decomposer, tetrahydrofurfuryl alcohol. Each less than 4% in the product. [c] EtOH, 4—6·5%; lower limit set by isolation (see p. 3175). [d] Butanol, presumed present; see Part II (succeeding paper). [e] EtOH, detected by the CHI_3 test. [f] Detected by the chromotropic acid test. [g] Formals, 0·4% (as CH_2O). [h] At 25°.

TABLE II.

Starting material.	$K^{13}CN$.[1]	$K^{13}CN$.[1]	$Ba^{14}CO_3$.[1]	$K^{13}CN$.[2]	$CH_3{\cdot}OH$.[12]
Millimoles	221	197	3·02	69	—
Excess isotope, concn.	15·24 [3]	43·05 [3]	209 [4]	52·4 [3]	—
,, quantity	33·7 [5]	84·9 [5]	630 [6]	36·1 [5]	—
Methanol.					
Crude wt. yield, %	92	92	150	125	—
Recovery of excess isotope, as OMe, %	75 [7]	69 [7]	77 [7]	89 [7]	—
,, ,, all forms, %	—	—	91 [8]	—	—
Methyl iodide.					
Overall wt. yield, %	74	68	— [9]	86	93
Millimoles	164·5	134	24·6	59	—
Excess isotope, concn.	14·3 [3]	40·3 [3]	17·9 [4]	50·7 [3]	—
,, quantity	23·5 [5]	54·0 [5]	443 [6]	30·1 [5]	—
,, recovery, %	70	63·5	70·5	83	—
Dilution with inactive material, %	7·1 [10]	6·8 [10]	— [11]	3·4 [10]	—
Wt. yield from crude MeOH, %	87	74	92	71·5	93
Sodium acetate.					
Overall wt. yield, %	70·5	65	— [9]	84	—
Millimoles	156	126·5	24·4	58·0	—
Excess isotope, concn.	7·13 [3]	20·13 [3]	9·0 [4]	25·36 [3]	—
,, quantity	22·1 [5]	50·9 [5]	440 [6]	29·4 [5]	—
,, recovery, %	66	60	70	81·5	—
Wt. yield from MeI, %	95	94·5	99	98·5	98

[1] Solvent, diethylene glycol diethyl ether; decomposer, diethylene glycol monobutyl ether. [2] Solvent, tetrahydrofurfuryloxytetrahydropyran; decomposer, tetrahydrofurfuryl alcohol. [3] Atoms % excess ^{13}C. [4] μc. of ^{14}C per mg.-atom of carbon. [5] Mg.-atoms of excess ^{13}C. [6] μc. of ^{14}C. [7] Calc. from MeI results, on assumption of 93% conversion of OMe into MeI. [8] By oxidation and radioactive assay of crude MeOH. [9] Not available; the crude $^{14}CH_3{\cdot}OH$ was diluted with excess pure MeOH before conversion into MeI. [10] Calc. from excess isotope concn. [11] Not available (see note 9). [12] Typical run with pure material.

When the crude methanol samples were converted into methyl iodide by reaction with hydriodic acid, apparent weight yields of 60—87% were obtained (Tables I and II). Under identical conditions pure methanol gave 93 ± 0·5% of methyl iodide. Much of the impurity was eliminated; the methyl iodide appeared to have a purity of greater than 95%, the only important contaminant being ethyl iodide (Table I). In the subsequent conversion into sodium acetate this also was largely eliminated. The recovery of excess isotope in the overall conversion of carbon dioxide into methyl iodide was 63—71%.

The reduction residue was examined in one instance, this being the ^{14}C run mentioned above. The results are set out in Table III. The recovered solvents, which contained only ~5% of the total activity present in the residue, were carefully fractionated, and pure samples of diethylene glycol diethyl and monobutyl ethers recovered. These had no measurable activity; hence it may be assumed that there was no exchange with the alkoxy-groups of the solvents, and that the ethanol present in the methanol arose solely by scission of the ether linkages. The steam-volatile acid was not identified in this instance, but was probably formic acid (see below).

Since the materials used by Nystrom *et al.* were unsatisfactory, a search was made for more suitable hydride solvents and alcohols for the decomposition. Benzyl alcohol, ethylene glycol monophenyl ether, and tetrahydrofurfuryl alcohol are all satisfactory alcoholytic agents.

Of a number of materials examined as solvent for lithium aluminium hydride, diethylene glycol dimethyl ether, potentially attractive because scission would dilute but not contaminate the labelled methanol, proved to be a poor solvent. Tetrahydropyran, however, dissolves the hydride readily but its comparatively high vapour pressure at 0° makes difficult its use in a closed evacuated system; the "bubbling" procedure of Nystrom *et al.* would probably be more satisfactory. In a trial experiment, carbon dioxide (50 mM.) was reduced and methanol recovered by alcoholysis and distillation. The resulting distillate (containing some 50% of tetrahydropyran) was treated with hydriodic acid and the product distilled to give methyl iodide in 66% overall yield. This method was not examined further but it showed obvious promise for large-scale experiments (say 1 mole) where losses in distillation by normal laboratory technique become negligible.

The most suitable solvent we used was tetrahydrofurfuryloxytetrahydropyran. This semi-cyclic acetal is stable in alkaline conditions, is a good solvent for lithium aluminium hydride (solutions up to M. at room temperature may be made), and has low volatility. When it was used in conjunction with tetrahydrofurfuryl alcohol for the decomposition in the reduction of carbon dioxide, the yields of methanol (crude product after single-plate distillation, by weight) were 90—120%. The recovery of excess isotope was ~89%. Physical constants and chemical purity of this product were comparatively good. The only impurities detected were water, formaldehyde, and small amounts of tetrahydrofurfuryl alcohol. Conversion into methyl iodide by reaction with hydriodic acid gave methyl iodide of excellent purity, in weight yields (on carbon dioxide) of 77—86% (see Tables I and II). The recovery of excess isotope was ~83%. This methyl iodide reacted completely with potassium cyanide solution. Dilution with inactive material to the extent of some 3·5% was observed at the reduction stage. This is much less than in cases where diethylene glycol diethyl ether is the solvent. In one instance the residue from a reduction using tetrahydrofurfuryloxytetrahydropyran was examined (see Experimental part). Formic acid was recovered and identified as the *S*-benzylthiuronium derivative.

No detailed investigation of the course of the reduction of carbon dioxide by lithium aluminium hydride has been published. Schlesinger and Finholt (unpublished work, quoted by Nystrom *et al.*, *loc. cit.*), working presumably with carbon dioxide in excess, found that two moles of carbon dioxide were absorbed per mole of hydride and that under these conditions a complex was formed which liberated formaldehyde on acidification, in yields up to 25%. Nystrom *et al.*, working with excess of hydride, noted reduction to the methanol stage (*i.e.*, to a complex giving methanol when acidified or alcoholysed) with the consumption of 0·75 mole of hydride per mole of carbon dioxide. We have demonstrated that even when the hydride is in 100% excess appreciable amounts of the carbon dioxide are reduced no further than to formate, and that formaldehyde is always present in the methanol liberated by alcoholysis of the complex. Thus it is likely that the reduction proceeds *via* formate and formaldehyde and that the latter is present as metallic (most probably aluminium) derivatives of methanediol, which undergo a nucleophilic displacement reaction with aluminohydride ions, giving a methoxide (cf. Trevoy and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675). That the methanol formed on alcoholysis is originally present as methoxide has not been proved, but in view of the stoicheiometry of the overall reaction this is very probable. It is worthy of note that we have been unable to detect any carbon monoxide or methane in the gaseous products of alcoholysis, whereas in the analogous reduction of carbon monoxide preliminary experiments have shown that not only methanol but substantial quantities of methane are liberated on alcoholysis (for example, yields of methane of from 6 to 37%, depending upon the temperature of the reaction, have been recorded). This suggests that the methanol-giving intermediates in the two reductions have different structures, that from carbon monoxide probably involving $Al{-}O{-}CH_2{-}Al$ groupings, susceptible to further attack by aluminohydride ions with the formation of methylaluminium. Further work is in progress on the detailed mechanism of the reaction; a full account of the reduction of carbon monoxide will be published later.

Acetic acid labelled with tracer carbon in the carboxyl group has been prepared by treatment of methylmagnesium iodide with labelled carbon dioxide by many investigators (cf. " Isotopic Carbon," pp. 172—179). We have found the procedure of Lemmon (*op. cit.*, p. 178) to be satisfactory.

Where the starting material is labelled potassium cyanide, methylation followed by hydrolysis is more suitable. Methylation by means of methyl sulphate (Walden, *Ber.*, 1907, **40**, 3215) followed by hydrolysis is claimed to give an overall yield of sodium acetate of 83% (Weinhouse, Medes, and Floyd, *J. Biol Chem.*, 1945, **158**, 411). Methyl iodide is more satisfactory (Auger, *Compt. rend.*, 1907, **145**, 1287); it is best used in the cold, with concentrated aqueous solutions of cyanide. After recovery of the acetonitrile, acidification, and steam-distillation, yields of very pure anhydrous sodium acetate of 98—100% are readily obtained on scales as low as 1 millimole. There is no dilution with unlabelled material.

Methyl-labelled acetic acid has been obtained from methyl iodide by way of the Grignard compound (Tolbert, *J. Biol. Chem.*, 1948, **173**, 205, reports yields of 70—75%), or from cyanide by the reactions $Na{*}CN \longrightarrow Zn({*}CN)_2 \longrightarrow HO{\cdot}C_6H_4{\cdot}{*}CH{:}NH,HCl \longrightarrow HO{\cdot}C_6H_5{\cdot}{*}CH_3 \longrightarrow$ ${*}CH_3{\cdot}CO_2Na$ (Anker, *ibid.*, 1946, **166**, 219; the overall yield was " greater than 50% "). On the basis of results quoted by Anker the dilution with inactive material appears to have been 7·5%. We have converted labelled methyl iodide into methyl-labelled sodium acetate by reaction with excess of cold aqueous potassium cyanide (cf. Auger, *loc. cit.*) followed by hydrolysis. Yields of 97—100% of very pure material are easily obtained, and there is no dilution with inactive material. When the methyl iodide is converted into acetonitrile by boiling aqueous cyanide the yield is much lower (Little and Bloch, *J. Biol. Chem.*, 1950, **183**, 42, quote an overall yield of 66% from methanol). Methyl iodide made from ethanol-containing methanol reacted only partly, some of the ethyl iodide present remaining unchanged; some propionate was probably present in the acetate, but its amount was shown to be less than 2%.

EXPERIMENTAL.

Micro-analyses are by Miss M. Corner and Drs. Weiler and Strauss; mass-spectrometric analyses are by Drs. R. Bentley and J. F. Martin. M. p.s are not corrected.

General.—High-vacuum apparatus. A vacuum manifold of the type illustrated in Fig. 2 was used throughout the work. The pumping system consisted of a rotary oil pump, with protective cold trap, and a mercury diffusion pump which was connected through cold traps to the manifold. The pressure within the system was measured by mercury manometers and " Vacustat " McLeod type gauges. The system had a volume of some 500 c.c. between T_2 and T_{14} (with T_{11} closed) and could be evacuated to a pressure of 10^{-4} mm. Hg in about three minutes; bulbs of 1-l. and 4-l. capacities were attached to T_{11}. The plug of T_2 was grooved so that it could be opened very slowly. Unless otherwise stated, all joints and taps were lubricated with Apiezon M grease.

Combustion of samples for isotopic analysis. Samples were converted into carbon dioxide either by conventional " dry " combustion (mixed with pure lead chromate in the case of sodium salts) or by an adaptation of the " wet " method of Van Slyke and Folch (*J. Biol. Chem.*, 1940, **136**, 509). The carbon dioxide was normally absorbed in barium hydroxide solution, and barium carbonate separated and washed by centrifugation.

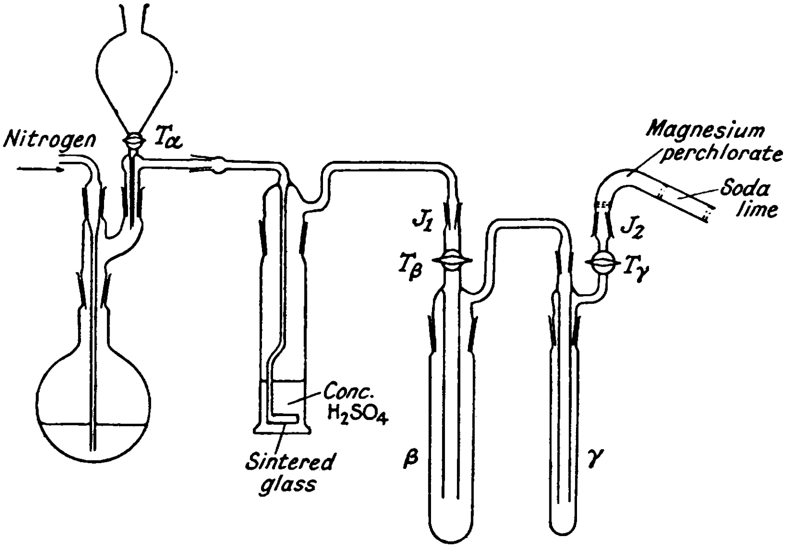
Assay of samples for ^{14}C. The method of gas (CO_2) counting was employed. A detailed description of the technique will be given by Audric and Long in Part III (to be published).

Materials. Reagents were normally of AnalaR grade. The solvents mentioned in the ensuing sections were dried and fractionally distilled before use, the following fractions being used: tetrahydropyran, b. p. 87—88°, n_D^{24} 1·4180; diethylene glycol diethyl ether, b. p. 88°/23·5 mm., n_D^{25} 1·4098 (v. p. equation: $\log_{10} p = -2700/T + 8{\cdot}7$); diethylene glycol monobutyl ether, b. p. 130°/28 mm., n_D^{25} 1·4304; ethylene glycol monophenyl ether, b. p. 123°/14 mm., n_D^{25} 1·5342; tetrahydrofurfuryl alcohol, b. p. 80°/20 mm., n_D^{20} 1·4520; and *tetrahydrofurfuryloxytetrahydropyran*, b. p. 135°/25 mm., n_D^{20} 1·4617, d_D^{20} 1·045 (v. p. equation: $\log_{10} p = -2950/T + 8{\cdot}6$). The last solvent was prepared in 75% yield by the acid-catalysed reaction of tetrahydrofurfuryl alcohol with 2 : 3-dihydropyran according to the general method of Woods and Kramer (*J. Amer. Chem. Soc.*, 1947, **69**, 2246) (Found: C, 64·5; H, 9·8. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%).

Lithium aluminium hydride solutions were prepared by stirring the coarsely crushed material with the pure solvent. The suspension was filtered through sintered glass and the resulting solution was analysed by decomposing aliquots with ethylene glycol monophenyl ether and measuring the evolved hydrogen. All manipulations with solutions of the hydride were carried out in a nitrogen atmosphere. Solutions in tetrahydrofurfuryloxytetrahydropyran up to $\sim$1·0M. have been prepared. The hydride is more soluble in diethylene glycol diethyl ether, but it is convenient to use solutions more concentrated than $\sim$1·5M.

Preparation of Carbon Dioxide.—(a) *Preparation from potassium cyanide enriched with* ^{13}C. The commercial material was a mixture, the main constituents of which were potassium cyanide (78—90%), carbonate (22—10% containing only a very slight enrichment of ^{13}C) and formate (normally less than 2%). The material was not homogeneous and was best analysed by taking micro-samples from a solution containing at least 0·5 g. Cyanide was determined by titrating aliquots, containing 50 mg. of crude material, with N/50-silver nitrate in the presence of ammonia and potassium iodide (Vogel, "Quantitative Inorganic Analysis," Longmans Green, London, 1939, p. 327). Formate was determined by titration of an aliquot with N/50-permanganate (Vogel, *op. cit.*, p. 361) after quantitative displacement of hydrogen cyanide with a stream of pure carbon dioxide (6 hours' bubbling was required). Material not accounted for as cyanide or formate was assumed to be carbonate for the purpose of this preparation.

FIG. 1.



Potassium cyanide containing 50 millimoles of KCN was weighedi nto a flask and dissolved in carbon dioxide-free water (25 c.c.). To the solution was added 120% of the amount of 0·25N-barium hydroxide needed to precipitate all the carbonate. The barium carbonate was filtered off and washed with water (50 c.c.), and the filtrate was transferred quantitatively to a 500 c.c. flask. Potassium permanganate (16 g.) and 6N-sodium hydroxide (45 c.c.; carbonate-free) were added, sufficient wash-water being used to bring the volume of solution to about 200 c.c. A stream of carbon dioxide-free nitrogen was bubbled through the reaction mixture which was heated slowly to the boil under a reflux condenser fitted with a soda-lime guard-tube. Boiling was maintained for 4 hours.

The reflux condenser was then replaced by a dropping funnel with side-arm and the apparatus illustrated in Fig. 1 was assembled. When the air had been swept from the apparatus by the nitrogen stream, Dewar vessels around β and γ were filled with liquid nitrogen. 10N-Sulphuric acid (35 c.c.) was added dropwise through T_α to the reaction mixture during ½ hour, then a further 75 c.c. were added rapidly. Expulsion of carbon dioxide was completed by warming the reaction mixture at 50° for 2 hours. T_β and T_γ were shut; the traps were detached at J_1, re-attached to a vacuum manifold (Fig. 2) through J_2, and evacuated. During these operations the traps were kept immersed in liquid nitrogen. With T_2 shut, the carbon dioxide in β and γ was allowed to expand into the system (including a 1-l. bulb); the gas was condensed into trap *G* by liquid nitrogen cooling and was dried by sublimation at $-78°$ (with a solid carbon dioxide–methanol bath around *G*) into trap *H*, cooled in liquid nitrogen. Finally, the carbon dioxide was allowed to evaporate into an evacuated system of known volume and the pressure measured. The preparation has been carried through on scales of 3 to 220 millimoles.

(b) *Preparation from barium carbonate.* Barium carbonate (3·90 g.) was weighed into the 100-c.c. flask *F* (Fig. 2), and water (5 c.c.) was added. 60% Perchloric acid (15 c.c.) was charged into *E*. The apparatus was assembled and, with baths of solid carbon dioxide–methanol around trap *C* and flask *F*, the whole system was evacuated (the bore of the plug of T_{17} had previously been evacuated). T_2 was closed, trap *G* cooled to $-196°$, and the bath around *F* removed. The perchloric acid was immediately added and reaction began as soon as the water in *F* began to melt; the flask *F* was rotated about its joint to ensure complete mixing and then the solution was warmed to 30°. After a few minutes T_{12} was closed and the carbon dioxide condensed in trap *G* was dried by sublimation at $-78°$ as described in (*a*).

The yield from pressure measurement was 100%. The procedure has been used on scales of 0·5 to 35 millimoles.

For experiments on the scale of 1 millimole or less, it proved convenient to generate carbon dioxide from barium carbonate by the lead chloride method of Zweibel, Turkevich, and Miller (*J. Amer. Chem. Soc.*, 1949, **71**, 376). It should be noted however, that most commercial lead chloride evolves carbon dioxide on fusion.

FIG. 2.

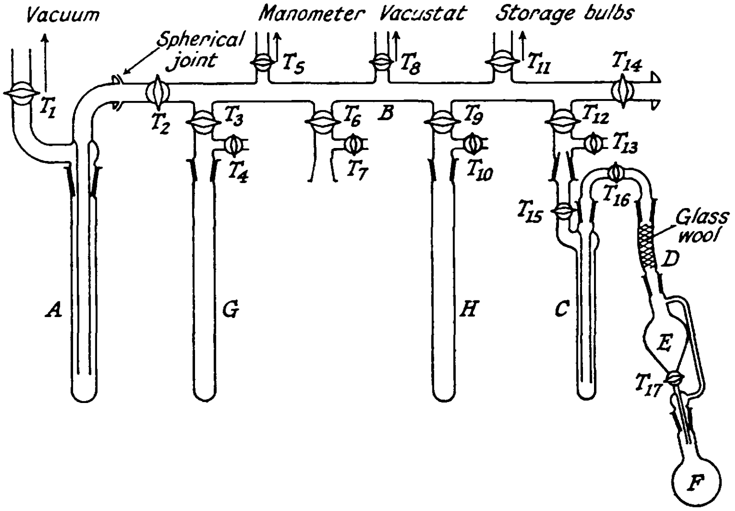
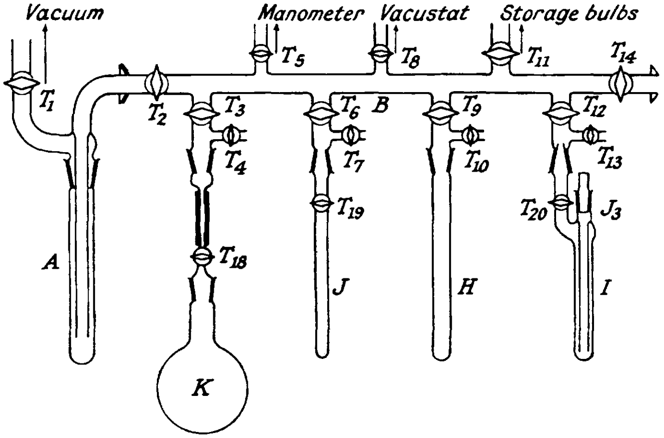


FIG. 3.



Preparation of Methanol.—(i) *Method for scale greater than* 30 *millimoles.* A solution of lithium aluminium hydride (1·5 moles of $LiAlH_4$ per mole of carbon dioxide to be reduced) was poured into a round-bottomed flask *K* which was connected to the vacuum manifold by means of a short length of rubber pressure tubing with suitable adaptors (Fig. 3). The flask was cooled in an ice-bath and evacuated. With T_2 shut, carbon dioxide from *H* was expanded into the manifold (with a 1-l. bulb in the system) and allowed to come in contact with the hydride solution. When the reaction flask was gently shaken, the gas was steadily adsorbed, only $\sim$1% remaining after 1 hour.

The flask was removed from the vacuum line and the apparatus illustrated in Fig. 4 assembled; a liquid nitrogen bath was placed around trap *I*, and a solid carbon dioxide–methanol bath around trap *L*. The decomposing alcohol (12 moles per mole of carbon dioxide taken) was slowly added through the dropping-funnel, the flask being gently shaken. The dropping-funnel was next removed and replaced by a capillary leak attached to a supply of dry nitrogen. The apparatus was connected to a water-pump, and the flask was heated in an oil-bath at 110°. At 70 mm. pressure (maintained by means of a manostat) this bath-temperature was just sufficient to keep the high-boiling solvent or alcohol refluxing from the cold-finger while methanol distilled into *I*. After 4 hours' heating, nitrogen was admitted to the apparatus, T_{20} shut, trap *I* detached and a stopper quickly inserted at J_3.

The distillate was purified by the following procedure. Trap *I* and a second trap *J* (previously weighed) were attached to the vacuum line (Fig. 3). *J* carried an A cone, engaging with the B socket of the manifold, which permitted quantitative removal of grease; weighings of *J* were reproducible to better than 1 mg. The system (including a 1-l. bulb) was evacuated, after which T_2 was closed; the liquid nitrogen was removed from around trap *I*, and the distillate allowed to warm to room temperature. When the pressure in the system had become constant, T_{20} was shut and the vapour condensed into trap *J* by liquid-nitrogen cooling. T_{19} was shut, T_{20} opened, and the process repeated until the vapour pressure was less than 1 mm. The following series of vapour pressure readings (liquid " reservoir " at 23°) was typical: 93, 86, 82, 80, 42, 7, 1 mm. Hg. The vapour pressure of the combined distillates was then taken at 0°. The residue in trap *I* gave a strong formaldehyde reaction (chromotropic acid test).

The method has been used on scales of 30 to 220 millimoles.

(ii) *Method for scale less than* 30 *millimoles*. The method was similar to that described in Part II (succeeding paper) for the reduction of acetyl chloride to ethanol. A stopper was inserted at J_9 (Part II, Fig. 2) and carbon dioxide was admitted to the hydride solution (in vessel *U*) through T_{12}. Addition of the decomposing alcohol and isolation of the volatile product were carried out as described for ethanol. This method has been used on scales 3 to 15 millimoles.

FIG. 4.

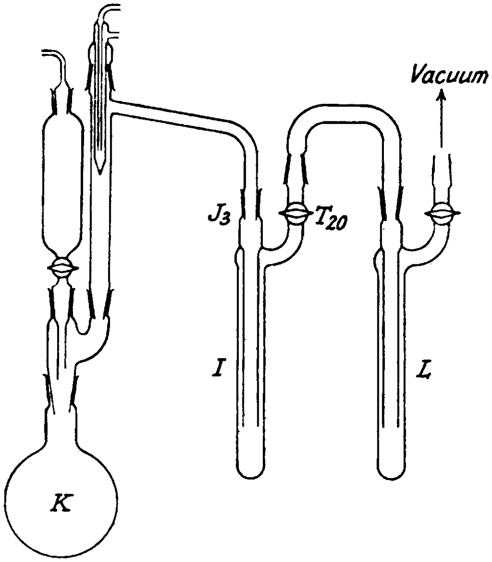
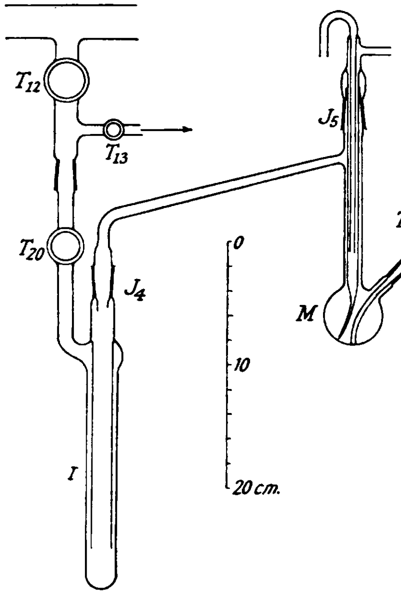


FIG. 5.



(iii) *Characterisation of the methanol product*. Successful preparations of methanol were carried through with the following solvents.

(*a*) Diethylene glycol diethyl ether (solvent for $LiAlH_4$) was used with benzyl alcohol, diethylene glycol monobutyl ether, or ethylene glycol monophenyl ether for alcoholysis. Apparent weight yields in 8 experiments were 84—113%; in 1 experiment the " yield " was 150%. The true yields of methanol (determined by conversion into methyl iodide) were 68—77%. The methanol was contaminated by formaldehyde (2% in one sample, identified by the chromotropic acid test and determined by the hydroxylamine hydrochloride method), ethanol (about 5% in one sample, identified by isolation of ethyl iodide from the Zeisel product and determined by the iodoform reaction), water (up to 8%, determined by the Karl Fischer method), and traces of the high-boiling solvents (calculations based on the vapour pressure indicated the presence of less than 3%). The presence of other volatile products, *e.g.*, methylal was not excluded. The physical properties of the products are given in Table I.

The " methanol " gave a *p*-nitrophenylurethane, m. p. 175°.

(*b*) Tetrahydropyran was used as a solvent for lithium aluminium hydride; a 1·2M-solution at 0° readily absorbs carbon dioxide. Alcoholysis by diethylene glycol monobutyl ether followed by fractional distillation gives a mixture of methanol and tetrahydropyran. Methanol–tetrahydropyran mixtures are very non-ideal: when such mixtures containing a large excess of the latter are distilled, the bulk of the former comes over as a mixture of almost constant composition (~50% methanol by volume, b. p. 66°, n_D^{26} 1·372). In this way the methanol may be separated from the bulk of the reaction mixture, and by treatment with hydriodic acid followed by fractional distillation methyl iodide of high purity is obtained. In a preliminary run, methyl iodide, b. p. 42—43°, n_D^{25} 1·526, was obtained in a 66% yield from carbon dioxide.

(*c*) When tetrahydrofurfuryloxytetrahydropyran was used as solvent, tetrahydrofurfuryl alcohol and diethylene glycol monobutyl ether were suitable for alcoholysis. Apparent yields in 5 experiments were 90—125%. with true yields of 85—92%. Impurities in the methanol were formaldehyde (0·4—0·7%, determined gravimetrically as the dimedone derivative, m. p. 189°), water (up to 6·5%), and traces of the high-boiling solvents (less than 4% by vapour-pressure calculations); further amounts of formaldehyde–

dimedone derivative, obtained after the " methanol " had been subjected to acid hydrolysis, indicated the presence of about 0·5% of methylal. The physical properties of the products are given in Table I.

The methanol gave a *p*-nitrophenylurethane, m. p. 176·5°, and an α-naphthylurethane, m. p. 122°.

(iv) *Miscellaneous experiments.* (*a*) An examination was made of the gas (mainly hydrogen) evolved when a solution of lithium aluminium hydride which had absorbed carbon dioxide was treated with a high-boiling alcohol. The gas contained no carbon dioxide, carbon monoxide, or hydrocarbon.

(*b*) When solutions of lithium aluminium hydride were decomposed with a high-boiling alcohol, varying amounts of volatile products containing methanol (determined by Simmonds's method, *Analyst*, 1912, **37**, 16) were obtained.

(*c*) A residual reaction mixture from the preparation of ^{14}C-methanol was examined. The total volatile product was removed by vacuum-distillation and was fractionally distilled to separate diethylene glycol diethyl and monobutyl ethers; the fractions were burnt to carbon dioxide for counting. The dry residue of lithium and aluminium compounds was acidified with dilute sulphuric acid in a stream of nitrogen, and the gas was passed through a barium hydroxide solution bubbler. The precipitate was removed for ^{14}C assay. The solution of lithium and aluminium salts was next steam-distilled and the distillate neutralised with sodium hydroxide; this solution was evaporated to dryness, and the residue oxidised to carbon dioxide. The steam-distillation residue was likewise oxidised. Radioactivity results are summarised in Table III.

TABLE III.

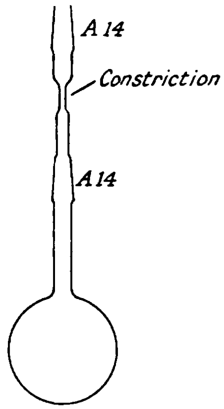
	Activity, μc.	% of total initial activity.
Barium carbonate	630	100
* Crude methanol	572	91
Methoxyl activity	484	77
Non-methoxyl activity (by diff.)	88	14
Reaction residue	41	6·5
Recovered solvents	2·0	0·3
,, CO_2	0·4	0·06
Steam volatile acid	12·8	2·4
,, distn. residue	5·9	0·9

* The residue from the single-plate distillation was not examined in this case.

(*d*) The reaction residue from a preparation of ^{14}C-methanol (using tetrahydrofurfuryloxytetrahydropyran and tetrahydrofurfuryl alcohol) which gave an abnormally low yield was distilled *in vacuo* to remove the solvent and excess of alcohol. The residue was acidified with dilute sulphuric acid and steam-distilled until acid was no longer present in the distillate. The latter was titrated with N-sodium hydroxide (pH-meter) to pH 7·5, and evaporated to dryness. The acid present (titration) amounted to 13·5 millimoles (13% of the carbon dioxide reduced); it was identified as formic acid by conversion into the *S*-benzylthiuronium derivative, m. p. and mixed m. p. with an authentic sample 152° (Found: C, 51·0; H, 6·0; N, 13·3; S, 15·1. Calc. for $C_9H_{12}O_2N_2S$: C, 51·0; H, 5·7; N, 13·2; S, 15·1%).

Preparation of methyl iodide. The apparatus illustrated in Fig. 5 was used. Joints J_4 and J_5 were lubricated with silicone grease, and J_6 with hydriodic acid. In a typical experiment ^{14}C-methanol (0·6465 g.) was distilled through the manifold into flask *M*. Air was admitted through T_{13} and hydriodic acid (25 c.c.; *d* 1·7) was run through J_5. The reaction vessel was detached at J_4 and connected to a train which consisted of a bubbler containing a suspension of red phosphorus in dilute sodium carbonate solution, a U-tube packed with magnesium perchlorate and thence through J_4 to trap *I*. The latter was surrounded by a bath of liquid nitrogen. A slow stream of nitrogen was passed through T_{21}, and flask *M* was heated in an oil bath to 80° during ¼ hour; the bath-temperature was raised to 90° during the next ¼ hour, by which time a vigorous reaction had begun (methyl iodide refluxed rapidly from the cold finger). The bath temperature was then kept at 90—100° for a further 2 hours. T_{20} was shut and a stopper inserted at J_4. The distillate in trap *I* was distilled *in vacuo* into a weighed trap (*J* in Fig. 3). The above procedure has been used (with apparatus of the appropriate size) on scales between 5 and 200 millimoles.

FIG. 6.



In a series of experiments the weight yields of methyl iodide from methanol prepared by method (*a*) (see above) were 60—87% (from carbon dioxide). The overall isotopic yields in three experiments were 63—71%.

The weight yields of methyl iodide in four experiments with methanol prepared by method (*c*) (see above) were 77—86% (based on carbon dioxide). An overall isotopic conversion was 83%; n_D^{20} was 1·5301—1·5308, and d_D^{20} 2·24—2·26 (Found: I, 88·9. Calc. for CH_3I: I, 89·4%).

Preparation of Sodium Acetate.—(i) *Preparation of* $^*CH_3{\cdot}CO_2Na$. ^{14}C-Methyl iodide (2·634 g.) was distilled *in vacuo* into a flask of the type shown in Fig. 6; the flask contained potassium cyanide (1·7 g.; 25% excess) and water (3 c.c.). When all the methyl iodide had distilled in, the flask was sealed off at the constriction. The flask was shaken at room temperature overnight, whereafter the reaction was complete. If the methyl iodide contained ethyl iodide, as was the case with method (*a*), the ethyl iodide was left largely unchanged at this stage; the amount of unchanged iodide in one experiment gave a lower limit, 4·5%, for the amount of ethanol in the crude methanol. Where no ethyl iodide was present the liquid became homogeneous. The contents of the flask were then cooled to $-78°$ and the neck cracked open. Water, acetonitrile, and unchanged methyl iodide were next distilled through the manifold into a flask (capacity 60 c.c.) containing carbonate-free 20N-sodium hydroxide (2·0 c.c.; 100% excess); the flask was sealed at a constriction which had been previously made in the neck and was heated at 80° for 4 hours. The neck of the flask was then cracked open and the hydrolysate rinsed with water into a 100-c.c. flask; steam was blown through the alkaline solution for 5 minutes to remove traces of methanol [see (ii) below]. The reaction mixture was made strongly acid with sulphuric acid, and silver sulphate (0·4 g.) was added. Acetic acid was removed by steam-distillation, 1 l. of distillate being collected. 18·44 C.c. of N-sodium hydroxide were required to bring the solution to pH 8·8 (glass electrode and pH-meter). Finally, the solution was evaporated to dryness, anhydrous sodium acetate being obtained by drying the residue *in vacuo* at 250°. 1·515 G. of sodium acetate were thereby obtained (corresponding to 18·49 c.c. of N-alkali). The yield from methyl iodide was 99%, and the overall isotopic yield from carbon dioxide 70%. In two ^{13}C experiments [with methanol prepared by method (*a*)] the overall isotopic yields were 60 and 66% (see Table II). The above method was suitable for the scales of 5 to 50 millimoles. On scales greater than 50 millimoles, it was necessary to cool the flask during the methylation, and advantageous to carry out distillation and alkaline hydrolysis by ordinary laboratory methods.

Sodium acetate prepared as described above meets the following specifications: cyanide, halide, sulphate, and formate not detectable; carbonate less than 0·2% (Found: C, 28·9; H, 4·2; Na, 27·9. Calc. for $C_2H_3O_2Na$ containing 7 atoms % excess ^{13}C: C, 29·35; H, 3·7; Na, 28·0%). The semi-distillation value S (Virtanen and Pulkki, *J. Amer. Chem. Soc.*, 1928, **50**, 3138) for the acid derived from sodium acetate, made from methanol prepared by method (*a*), was 35·2. S for pure acetic acid determined in the same apparatus, 35·1. Molecular-weight determination, micro-analyses, and S values all indicated that less than 2% of sodium propionate was present.

A preparation of sodium ^{13}C-methyl-labelled acetate, from methanol prepared by method (*c*), gave an isotopic yield of 81% (based on carbon dioxide).

(ii) *Preparation of* $CH_3\cdot{}^*CO_2Na$ *from* K^*CN. The preparation was similar to that described in (i), with the following modifications. x Millimoles of potassium cyanide were treated with 1·5 x millimoles of methyl iodide; after hydrolysis the alkaline solution of sodium acetate was steam-distilled for $\frac{1}{4}$ hour since much greater amounts of methanol than in (i) were present (if methanol was not removed, up to 50% of the acetic acid distilled as methyl acetate). 0·4x Millimoles of silver sulphate was used.

The weight and isotopic yields in 8 experiments were 97—100% and the purities of the products were similar to those given in (i). The method has been used on scales of 3—250 millimoles.

(iii) *Preparation of* $CH_3\cdot{}^*CO_2Na$ *from* $^*CO_2$. Carbon dioxide was allowed to react with a solution of methylmagnesium iodide in ether at $-20°$ (Lemmon's method, quoted in " Isotopic Carbon," p. 178—179). 80—90% of the carbon dioxide taken was absorbed by the Grignard solution during 20 minutes; the reaction mixture was then immediately worked up, the remaining carbon dioxide being recovered by absorption in aqueous barium hydroxide. Yields of sodium acetate up to 96% (based on carbon dioxide absorbed) were thereby obtained.

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