419. *Syntheses with Isotopic Tracer Elements. Part IV.* The Preparation of Methylamine and Diazomethane Labelled with Carbon Isotopes.*

By J. D. Cox and R. J. Warne.

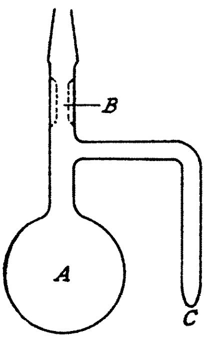
A technique for preparing carbon-labelled methylamine from labelled methyl iodide, utilising the Gabriel reaction, has been developed; the amine has been converted into carbon-labelled diazomethane with an overall isotopic yield (based on labelled barium carbonate) of 55%.

The work now described aimed at devising a satisfactory method of preparing labelled diazomethane by way of labelled methylamine. Although several syntheses of the latter have been described (Crompton and Woodruff, *Nucleonics*, 1950, **7**, No. 3, 49) only the modified Curtius degradation of acetic acid (Gal, Spenger, and Greenberg, *J. Org. Chem.*, 1950, **15**, 1261) avoids the use of labelled cyanide. We have found, however, that the Gabriel reaction provides a much simpler route to methylamine, and provided that both the labelled methyl iodide (Part I, *J.*, 1950, 3167) and potassium phthalimide used were anhydrous, a 98% yield of *N*-methylphthalimide was secured (cf. Graebe and Pictet, *Ber.*, 1884, **17**, 1173 : *Annalen*, 1888, **247**, 302); hydrolysis of *N*-methylphthalimide gave a quantitative yield of methylamine.

Methylamine was converted into diazomethane (*a*) through methylnitrosourea (Arndt, *Org. Synth.*, 1935, **15**, 3, 48; Hershberg, Schwenk, and Stahl, *Arch. Biochem.*, 1948, **19**, 300) and (*b*) through methyl 2-*N*-methyl-*N*-nitrosamino*iso*butyl ketone (Jones and Kenner, *J.*, 1933, 363; Adamson and Kenner, *J.*, 1935, 286; 1937, 1551; Berenbom and Fones, *J. Amer. Chem. Soc.*, 1949, **71**, 1629). By method (*a*) yields were 68% and 57% (from methylamine) on scales of 30 and 5 millimoles respectively, while by method (*b*) yields were 60% and 40% on the corresponding scales. Our overall yield of diazomethane from carbon dioxide was at best 55%.

Experimental.

Materials.—Potassium phthalimide was prepared as described in *Org. Synth.*, Coll. Vol. I, 1947, p. 119. Sodium cyanate was commercial material purified as described by Scattergood ("Inorganic Syntheses," Vol. II, McGraw-Hill, New York, 1946, p. 89). Dimethylformamide and mesityl oxide were also commercial materials and were redistilled before use; b. p.s were 152° and 131°, respectively. Samples of methylnitrosourea (purified by recrystallisation at −78° from ether) and methyl 2-*N*-methyl-*N*-nitrosamino*iso*butyl ketone (purified by distillation, b. p. 95°/0·5 mm.) had m. p.s 120° (decomp.) and 20°, respectively.



Preparation of N-*Methylphthalimide.*—(i) Potassium phthalimide (5·0 g., 27 millimoles) was weighed into bulb *A* of the vessel (a form of "Faraday tube") illustrated in the figure, then a constriction was made at *B*. With the vessel attached to a vacuum manifold, the potassium phthalimide was dried by heating it at 200°, *in vacuo*, for 1 hour. ^{13}C-Methyl iodide (2·84 g., 20·0 millimoles), which had previously been dried by milling (glass beads) with fresh phosphoric oxide in a closed tube, was condensed into *C* and the flask was sealed off at the constriction. *A* was heated to 180°, *C* being kept at room temperature, until no more liquid remained in it; the reaction time varied from 6 hours to 2 days. The flask was allowed to cool, then was cracked open. Trituration of the contents of *A* with the minimum quantity of ice-cold water, followed by cold 0·1N-potassium hydroxide and finally water again, left a crystalline mass of *N*-methylphthalimide, m. p. 133°, requiring no purification (Found: C, 66·5; H, 4·5; N, 8·5. Calc. for $C_9H_7O_2N$, containing 2·4 atoms % of ^{13}C: C, 67·1; H, 4·4; N, 8·7%). The product, which amounted to 3·19 g. (19·6 millimoles, 98%), could most readily be transferred by dissolution in chloroform, the solvent being subsequently removed by distillation under reduced pressure. A titration with standard silver nitrate solution showed that the aqueous extract of the reaction product contained 19·6 millimoles of I^- (98%).

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* Part III, preceding paper.

(ii) When methyl iodide, which had *not* been dried over phosphoric oxide was used, the yield of *N*-methylphthalimide fell to about 70%; 99% of the iodine, however, was found as I^- in the aqueous extract of the product.

(iii) Methyl iodide (0·755 g.; 5·32 millimoles) was allowed to react with potassium phthalimide (1·02 g.; 5·5 millimoles) in the presence of dimethylformamide (6 c.c.). After 16 hours at 100°, the reaction mixture was poured into water, and the product extracted with chloroform and isolated by evaporating the extract and adding water to the residue. The yield of *N*-methylphthalimide was 0·256 g. (30%), and I^- amounted to 5·06 millimoles (95%).

Preparation of Methylamine Sulphate.—^{13}C-Methylphthalimide (3·19 g., 19·6 millimoles) was heated under reflux with constant-boiling hydrochloric acid (7 ml., 100% excess) for 4 hours, the crystals deposited in the condenser being washed down with more acid from time to time. The reaction mixture was cooled to 0°, made alkaline with sodium hydroxide, and distilled in a Kjeldahl ammonia-distillation apparatus; the distillate was collected under 1·038N-sulphuric acid (19·00 ml.). 0·18 Ml. of 1·00N-methylamine solution was required to neutralise the excess of acid, so that 19·6 millimoles (100%) of methylamine had distilled. ^{13}C-Methylamine sulphate was obtained by evaporating the solution to dryness.

Generation of Diazomethane from the Nitroso-compounds.—(*a*) To an ethereal solution of methyl 2-methylnitrosamino*iso*butyl ketone (5 g.) was added the wax-like material obtained by dissolving sodium (0·2 g.) in *cyclo*hexanol (6·5 c.c.). After an induction period, the ether became yellow, and the ethereal solution of diazomethane was distilled off, being condensed in a trap at −78°. The yield of diazomethane, 90%, was determined by reaction with excess of benzoic acid, followed by alkali titration of the remaining acid.

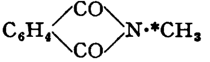
(*b*) Methylnitrosourea (3 g.), dissolved in ether (50 c.c.), was allowed to react with 10N-sodium hydroxide solution (10 c.c.), and the resulting ethereal solution of diazomethane distilled off. The yield of diazomethane, 91%, was determined as described in (*a*).

Preparation of Diazomethane from Methylamine Sulphate.—(*a*) To a 3·55M-solution of methylamine sulphate (5·00 c.c., 17·75 millimoles) was added 10N-potassium hydroxide solution (3·55 c.c.). Mesityl oxide (4·5 c.c.) was run dropwise into the magnetically stirred solution at 0°, then the reaction mixture was allowed to warm to room temperature during 2 hours. The solution was cooled to 0° again, and acetic acid (4·5 c.c.) added dropwise followed by a solution of sodium nitrite (5 g. in 7 c.c. of water). Finally, the nitroso-compound was extracted (continuously) with ether from the reaction product, and diazomethane generated from the extract as described above; 20·9 millimoles of diazomethane (59%) were thereby obtained. In two experiments on the 5-millimoles scale, the yield was 40%.

(*b*) Sodium cyanate (0·6 g.) and a few drops of 0·1N-sulphuric acid were added to a solution of ^{13}C-methylamine sulphate (3·1 millimoles in 2 c.c. of water); the solution was heated under reflux for 15 minutes, then cooled to −5°. After 2·75N-sulphuric acid (3·5 c.c.) had been run in, sodium nitrite (0·5 g.) was added portionwise during 1 hour, the reaction mixture being kept at −5° and stirred magnetically for 1 hour more. Ether was added. The resulting mixture was transferred to a separating funnel, and the aqueous phase extracted with three portions of cold ether; diazomethane was liberated from the combined extracts as previously described.

The resulting ethereal solution of diazomethane was treated with weighed small portions of *meso*-dibromosuccinic acid (m. p., in a sealed tube, 255°) until the yellow colour was just discharged; 0·51 g. (1·78 milliequivs. ≡ 3·56 millimoles of diazomethane, 57%) were required. The ethereal solution was washed in turn with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was crystallised from light petroleum (b. p. 40—60°) to give prisms of methyl *meso*-dibromosuccinate, m. p. 63° (Found: C, 23·5; H, 2·3. Calc. for $C_6H_8O_4Br_2$ containing 4·4 atoms % of ^{13}C: C, 23·8; H, 2·65%). Finally, a specimen of the dimethyl ester was oxidised to carbon dioxide for mass-spectrometric assay (see table). Experiments on the 30-millimoles scale gave diazomethane yields (from methylamine) of 65—68%.

Analyses for ^{13}C in the intermediates in a preparation of ^{13}C-diazomethane are recorded in the table. The agreement between " calculated " and " found " values shows that no appareciable dilution occurs during the preparation.

	Atoms % of ^{13}C.	
^{13}C-Labelled species.	Calc.[a]	Found.
(1) $^*CH_3I$ ………………	—	13·85
(2)  $C_6H_4(CO)_2N{\cdot}{}^*CH_3$	2·39 [b]	2·47
(3) $^*CH_3{\cdot}NH_2,\frac{1}{2}H_2SO_4$ [c]	10·6 [d]	11·0
(4) $(CHBr{\cdot}CO_2{}^*CH_3)_2$ [e]	4·38 [f]	4·37

[a] All calculations assume the natural abundance of ^{13}C to be 1·07%. [b] Calculated from the " found " value for (1). [c] The labelled product (1 millimole) obtained by hydrolysis of (2) was diluted with unlabelled methylamine (0·325 millimole) before assay. [d] Calculated from the " found " value for (2). [e] The ethereal solution of diazomethane obtained from (3) was caused to react with *meso*-dibromosuccinic acid, and the resulting dimethyl ester was assayed. [f] Calculated from the " found " value for (3).

We are grateful to Dr. S. L. Thomas for his advice and thank Miss M. Corner for microanalyses and Dr. R. Bentley (N.I.M.R.) for mass-spectrographic determinations. The work described above formed part of the programme of the Chemical Research Laboratory and this paper is published by permission of the Director.

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[*Received, March 1st,* 1951.]