+42° after three minutes, +36° (constant) after two hours, in water, c 1.3; $\lambda_{max.}^{alc.}$ 260 mμ (log ε 3.68).

Anal. Calcd. for $C_{12}H_{19}O_8NS$: C, 42.72; H, 5.68; N, 4.15; S, 9.50. Found: C, 42.99; H, 5.90; N, 4.30; S, 9.79.

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BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH
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The Synthesis of Methylamine-C^{14} and Diazomethane-C^{14} [1]

BY R. D. H. HEARD, J. R. JAMIESON[2] AND S. SOLOMON[3]

In connection with the preparation of radioactive steroid hormones, a satisfactory micromethod was demanded for the conversion of $C^{14}O_2$, through methylamine, to diazomethane for use in Arndt–Eistert extensions. Isotopic methylamine has previously been prepared from $NaC^{13}N$ by chromous chloride reduction (Hershberg, *et al.*[4]), and from sodium acetate-1,2-C^{14}, bacteriologically prepared, or from methyl labeled acetic acid, obtainable from $C^{14}H_3I$ (Gal, *et al.*[5]).

In this instance it was desired to employ the readily available $NaC^{14}N$.[6] While many reductions of cyanide are described (reviewed by Migrdichian[7]), none was well suited to the present purpose either because of the formation of amine mixtures or difficulty of small scale adaptation. Hydrogenation of cyanide was re-examined *ab initio*, and found to proceed almost exclusively to the monoamine (85% yield) in the presence of a slight excess of hydrochloric acid which arrests reduction at this stage. It is essential however that pure hydrogen and freshly prepared Adams–Shriner platinum catalyst be employed for satisfactory reduction at N.T.P. Aged platinum oxide (approximately six months or more) and certain tank hydrogens (even scrubbed as described below) are unsuitable.

The conversion of methylamine to diazomethane was conducted in the usual manner[8] in apparatus scaled to size. In C^{14} runs, isotope dilution (usually about fivefold) was made with C^{12}-methylurea at this stage. To minimize loss of precipitated nitroso-C^{14}-methylurea without diminution of yield, the procedure of nitrosylation was reversed —*i.e.*, acid was added to the methylurea–nitrite solution. Nitroso-C^{14}-methylurea decomposes on thin plating with loss of 93% of the C^{14} as volatile product. In bulk it is reasonably stable and gives rise to diazomethane-C^{14} with the correct molar count. The over-all yield of diazomethane from cyanide is consistently 40% or slightly better and radioactive product with specific activity up to 15 million counts/min./mg. has been prepared.

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Experimental

Counts were ascertained from infinitely thin plates in the windowless flow gas chamber (Nuclear Instruments) operating at 40–50% efficiency, and are expressed below as disintegrations registered per minute per millimole.

Hydrogenation of $HC^{14}N$.—The sketch illustrates the vessels employed, the respective capacities of A and B being 125 and 30 ml. The vertical joint C was pivoted to allow rocking of the system by means of an arm driven from an eccentric and clipped to the neck of flask A. Flexible plastic tubing led from D to the usual vacuum line–hydrogen reservoir system. The reservoir was of the gas buret type (250-ml. capacity) which contained hydrogen generated (Kipp) from arsenic-free zinc and reagent grade hydrochloric acid, and scrubbed through solutions (20%) of potassium hydroxide, silver nitrate and saturated potassium permanganate.

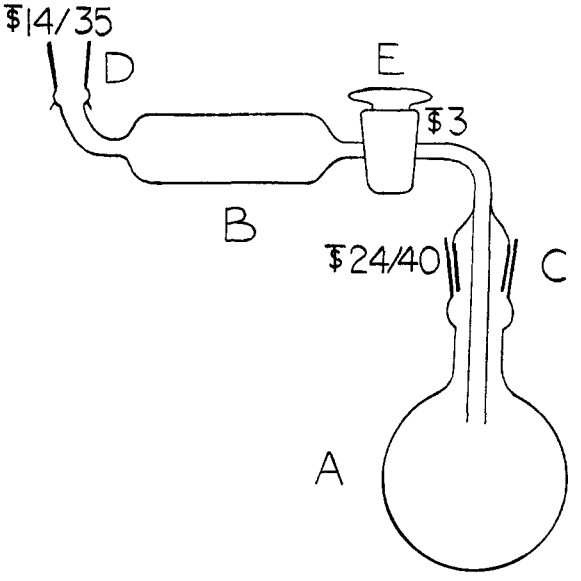

Fig. 1.

To vessel A was added a solution (50 ml.) of $NaC^{14}N$ (205 mg.; approximately 8.4 millicuries in 4.18 mmoles) in 2.24 molar proportions excess of sodium hydroxide. The $NaC^{14}N$ was prepared as previously described[6] from triphenylacetic acid-1-C^{14} which had 3.0×10^9 cts./min./mmole.

The solution was then taken to dryness *in vacuo* at 30°. After assembly to B, A was evacuated and sto co closed. Vessel B was then charged with 5 ml. of glacial acetic acid and 85 mg. of freshly prepared Adams–Shriner platinum oxide catalyst. After reduction of the latter, the apparatus was dismantled at D, and 0.96 ml. (11.5 mmoles) of concentrated hydrochloric acid in 5 ml. of acetic acid introduced to B. The system was refilled with hydrogen, and, after tilting B toward A, the contents of B were released to the evacuated vessel A on opening of the widebore stopcock E. Shaking was then commenced and hydrogenation continued until uptake of hydrogen ceased (4 to 7 hours) with the utilization of the theoretical two moles (210 ml.). Sodium chloride precipitates but is not detrimental to the reduction. After removal of catalyst by filtration (gravity), and washing with dilute hydrochloric acid, the filtrate was taken to dryness *in vacuo* to give a residue of monomethylamine hydrochloride and sodium chloride, which without further purification is suited to conversion[8] to methylurea and diazomethane.

For qualitative identification, the residue from an inactive run was triturated with hot butanol. The latter was concentrated to 3 ml. and, on refrigeration, gave mono-

methylamine hydrochloride, m.p. and admixture m.p. 222–224°. The recovery by extraction in this manner is only 33%. Calculated from the quantity of diazomethane eventually obtained (below) from the crude sodium chloride–methylamine hydrochloride mixture, however, the reduction proceeds to the monoamine to the extent of at least 85% (see also Hershberg, *et al.*[4]). Quantitative separation of pure methylamine at this stage requires distillation (gas rack) of the free amine liberated with alkali from the crude reduction residue and collection in hydrochloric acid.

Nitroso-C^{14}-methylurea.—The hydrogenation residue from 205 mg. (4.18 mmoles) of $NaC^{14}N$, in water (1 ml.), was refluxed (3 hours) with 711 mg. (11.85 mmoles) of urea. An aqueous solution (5.6 ml.) of carrier methylurea (790 mg., 10.7 mmoles), and sodium nitrate (1.3 g.), were added, and to this, sulfuric acid (0.65 ml. in 7.1 g. of ice–water mixture) was added dropwise and with stirring (15 minutes). The precipitated dried (vacuum) nitroso-C^{14}-methylurea (1.04 g., 10.0 mmoles) had m.p. and admixture m.p. 120–123°. The yield is 55%, calculated from cyanide and ascertained gravimetrically from trial runs from $NaC^{12}N$ without addition of methylurea.

Plated (1.0 μg./cm.^{2}), from methanol, the product showed 4.75×10^7 cts./min./mmole against 6.65×10^8 for the diazomethane-C^{14} generated (below) from the same material. Nitroso-methylurea thus decomposes with almost complete loss of methyl carbon on thin plating. Attempts to count under an end window G.M. tube led to contamination of the latter from volatile decomposition product(s).

Diazomethane-C^{14}.—The nitroso-C^{14}-methylurea (1.04 g.) was decomposed in the usual manner[3] with potassium hydroxide solution (3 ml. of 50%), and the liberated diazomethane-C^{14} (319 mg., 7.6 mmoles) distilled in ether (50 ml.).

For determination of specific activity, 50 mg. of 3-keto-Δ^4-etiocholenic acid was esterified with an aliquot (1.0 ml.) of the above ethereal solution of diazomethane-C^{14}. The corresponding C^{14}-methyl ester, separated and purified by alumina chromatography, had m.p. and admixture m.p. 132–133°, and 6.65×10^8 cts./min./mmole.

The over-all yield of diazomethane from cyanide is 41–42%, as determined in trial runs from $NaC^{12}N$ and estimated by back titration of excess standard benzoic acid solution.

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Phenylquinolines[1]

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Several phenylquinolines were prepared for the purpose of studying orientation in nitration. 6-Phenylquinoline (I) and 8-phenylquinoline (II) have been prepared previously[3] by the Skraup reaction on *o*- and *p*-aminobiphenyl. The decomposition of benzenediazonium hydroxide in quinoline has also been used to prepare 8-phenylquinoline.[4] The Conrad–Limpach reaction has been used to obtain 8-phenyl-4-hydroxyquinaldine.[5]

The yield of I by the Skraup reaction on the acetyl derivative[6] of *p*-aminobiphenyl was considerably greater than from the free amine. In the case of II, there seemed to be little difference in the yield. However, in both instances the use of *o*-nitrophenol as the oxidizing agent gave a better yield than did arsenic acid. 8-Phenyl-4-hydroxyquinaldine (V) was obtained by the Conrad–Limpach reaction but unlike most ring closures of this type the crude methyl β-(*o*-biphenylamino)-crotonate underwent ring closure by merely heating in vacuum at 180–190°. The melting point of V however was 207–209°, much lower than the 280° reported by Hughes and Lions.[5] A product of the same melting point (207–209°) was obtained when some of the crude aminocrotonate, which had not previously been subjected to a high temperature, was added to boiling phenyl ether. This melting point, however, is lower than one would predict.

The ring closure of *p*-phenylacetoacetanilide by the customary reagent, concentrated sulfuric acid, always produced either a sulfur containing substance or did not cause ring closure. Phosphoric acid did not give satisfactory results either, only small amounts of a material believed to be 6-phenyl-4-methylcarbostyril was obtained. Rather unexpectedly, the addition of *p*-phenylacetoacetanilide to mineral oil at 275° gave a 70% yield of a substance (m.p. 213–214°) which did not depress the melting point of the compound obtained by the phosphoric acid ring closure. As in the case of V, melting point of 6-phenyl-4-methylcarbostyril is much lower than expected. Attempts at ring closure of *o*-phenylacetoacetanilide gave only oils and other intractable material.

o-Aminobiphenyl and *p*-aminobiphenyl were condensed with ethyl sodioethoxalylacetate according to the procedure of Lisk and Stacy[7] then ring closure to the 8- and 6-phenyl-4-hydroxy-2-carbethoxyquinoline was brought about in boiling phenyl ether. Saponification and decarboxylation proceeded without difficulty.

Experimental

6-Phenylquinoline (I).—A solution of 67.3 g. (0.4 mole) of 4-aminobiphenyl in 200 ml. of methanol was treated at room temperature with 46.6 ml. (0.48 mole) of acetic anhydride. After precipitation seemed to be complete, the *p*-phenylacetanilide was removed by filtration, washed with 50-ml. portions of ethyl alcohol and dried at 100°. The yield was 72 g. (88%), m.p. 168–172°. Recrystallization from methyl alcohol gave a substance which melted at 171–172°. The melting point recorded in literature is 171°.[8]

A mixture of 21.1 g. (0.10 mole) of crude *p*-phenylacetanilide, 8.3 g. (0.06 mole) of *o*-nitrophenol, 6.5 g. of boric acid and 37.5 g. (0.40 mole) of anhydrous glycerol was heated in an oil-bath to about 110° and 18 ml. of concentrated sulfuric acid was added in small portions while the solution was stirred mechanically. The rate of addition was regulated so as to keep the temperature of the reaction mixture at 125–130°. After the addition of sulfuric acid, the solution was maintained at 130–133° for two hours and finally refluxed for five hours. After cooling, ice was added, then the reaction mixture was neutralized with concentrated sodium hydroxide and the solid removed by filtration. The dark colored substance was dissolved in 30 ml. of ethyl alcohol, treated with Norite, filtered and the boiling alcohol solution diluted with water to the cloud point. The yield of gray colored solid was 8.6 g. (42%); the substance melted at 103–106°. Recrystallization from 50% ethyl alcohol raised the melting point 109–110°. The melting point recorded for 6-phenylquinoline is 110–111°.[3]

8-Phenylquinoline (II).—This substance was prepared from *o*-aminobiphenyl, instead of its acetyl derivative, by essentially the same method as was used for 6-phenylquinoline, except that the substance was extracted with benzene

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(2) Abstracted from a thesis submitted by Mason Hayek to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University, June, 1947.

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