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THE PREPARATION OF ^{18}O, ^{15}N, and ^{14}C ENRICHED N-METHYL-2-(4-NITROPHENOXY)-ETHANAMINE HYDROCHLORIDES and N-METHYL-N-(2-HYDROXYETHYL)-4-NITROANILINES

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ABSTRACT

Preparations are described of the hydrochloride of partially enriched N-methyl-2-(4-nitrophen[^{18}O]oxy)ethanamine, N-methyl-2-(4-nitrophenoxy)-ethan[^{15}N]amine, and N-methyl-2-(4-nitro[1-^{14}C]phenoxy)ethanamine, designated herein as [^{18}O]-2, [^{15}N]-2, and [^{14}C]-2, respectively. By base-catalyzed rearrangement these enriched ethanamine derivatives were converted, respectively, into N-methyl-N-(2-[^{18}O]hydroxyethyl)-4-nitroaniline, N-methyl-N-(2-hydroxyethyl)-4-nitro[^{15}N]aniline, and N-methyl-(2-hydroxyethyl)-4-nitro[1-^{14}C]aniline, designated as [^{18}O]-3, [^{15}N]-3, and [^{14}C]-3.

INTRODUCTION

Our preparations were confined only to partially-enriched 2, although in principle, by dispensing with dilutions with unenriched intermediates, the fully enriched ^{15}N and ^{18}O isomers could be prepared in the same way.

Preparation of [^{15}N]-2 and [^{18}O]-2 called for the preparation of appropriately enriched N-methylethanolamine, while preparation of [^{14}C]-2, required the preparation of 4-nitro[1-^{14}C]benzenesulfonyl chloride.

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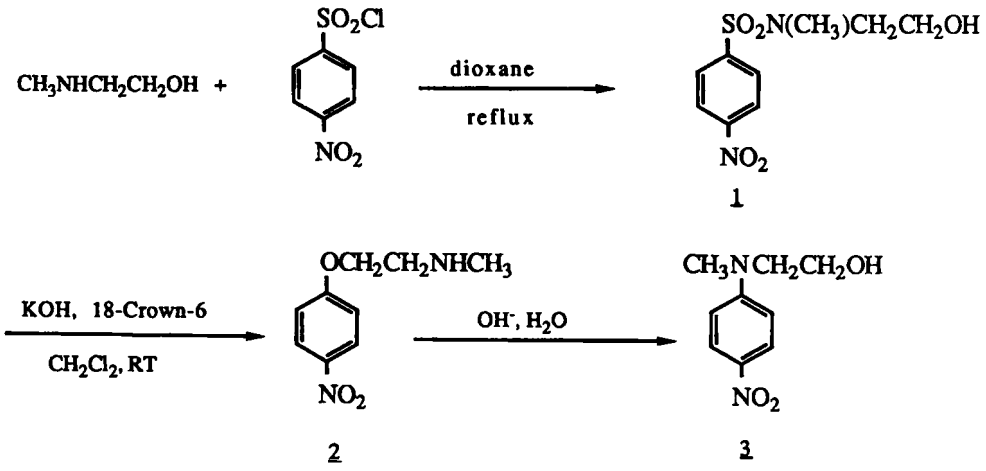
[^{15}N]- and [^{18}O]ethanolamine were prepared by the diborane reduction of [^{15}N]- and [^{18}O]sarcosine, by a modification of the method of Brown and coworkers (2). The isolation of pure N-methylethanolamine from this procedure was found to be unachievable, probably because of the difficulty of hydrolyzing the aminoalcohol-borane complex. A lengthy procedure for the purification of ethanolamine obtained by the diborane reduction of cyanomethyl pivalate has been described (3). On the other hand, Papanastassiou and Bruni (4) have reported that 2-chloro-2'-fluorodiethylamine, prepared by the diborane reduction of N-(2-chloroethyl)-fluoroacetamide, and still containing boron after isolation, was converted by p-toluensulfonation into the p-toluenesulfonamide-p-toluenesulfonate. We adopted this procedure to convert our boron-containing N-methylethanolamine into the 4-nitrobenzenesulfonamide (1), which was needed on the route to 2. Compound 2 is highly sensitive to base-catalyzed Smiles rearrangement (into 3), but, nevertheless, can be prepared by the controlled concomitant base-catalyzed rearrangement and loss of SO_2 from 1. The method for doing this, described by Knipe and coworkers (5-7), was modified so as to obtain 2 as its hydrochloride, which can be purified very easily by crystallization and can be stored. Therefore, purification of products in the steps of Scheme 1 was delayed until the stage of 2·HCl.

SCHEME 1



4-Nitro[1-^{14}C]benzenesulfonyl chloride was prepared from commercially-available 4-nitro[1-^{14}C]aniline by a modification of the Sandmeyer reaction as described by Meerwein and coworkers (8). The isotopic enrichments of our 2 were, finally, 8% for ^{18}O, 10% for ^{15}N, and 8.8 mCi/mol for ^{14}C. Each of our samples of enriched 2 had spectroscopic characteristics agreeing with those in the literature.

Base-catalyzed Smiles rearrangement of enriched 2 gave the correspondingly enriched 3.

EXPERIMENTAL

[^{18}O]SARCOSINE HYDROCHLORIDE

A mixture of 25.5 g of sarcosine hydrochloride and 12.2 g of water containing 11% of $H_2{}^{18}O$ was heated at 100-102 °C under a nitrogen atmosphere for 70 h. Water was removed quantitatively at 0.7 mm Hg and 25-40 °C to give ^{18}O enriched sarcosine hydrochloride.

N-METHYLETHANOL[^{15}N]AMINE and N-METHYLETHAN[^{18}O]OLAMINE

In these preparations commercially available [^{15}N]sarcosine hydrochloride, 99% enriched, was diluted to 10% enrichment with sarcosine hydrochloride, while the [^{18}O]sarcosine hydrochloride contained approx. 8% ^{18}O, as calculated from the randomisation of oxygen exchange described above.

Sarcosine hydrochloride, 6.3 g (50 mmol), was neutralized with 100 mL of 0.5 M methanolic sodium methoxide under nitrogen. After removal of methanol, 25 mL of anhydrous tetrahydrofuran (THF) was added, and was followed by the dropwise addition of 150 mL of 1 M BH_3·THF complex (150 mmol) in THF. The mixture was stirred at room temperature for 4 h and then refluxed for one h. The solution was cooled in an ice-water bath and the excess of diborane and adduct was decomposed by careful addition of 50 mL of 6 N HCl. The acidified mixture was refluxed for 12 h, cooled in an ice-water bath, and to it was carefully added a solution of 40 g of NaOH in 80 mL of water. The resulting mixture was refluxed for 2 h, cooled to room temperature, and saturated with K_2CO_3. The organic layer was separated and the aqueous layer was extracted successively with 3 x 100 mL and 4 x 50 mL of diethyl ether. The organic

layers were combined, dried over anhydrous K_2CO_3, and the solvent was removed to give the crude product, N-methylethanolamine 5.4 g. The excess of weight was due to the presence of complexed borane.

4-NITRO[1-^{14}C]BENZENESULFONYL CHLORIDE

Glacial acetic acid, 40 mL, was saturated with SO_2 (g). To this solution was added a solution of 2 g of $CuCl_2 \cdot 2H_2O$ in 5 mL of water and SO_2 (g) was passed into the mixture for an additional 20 min.

A mixture of 9.94 mg of 4-nitro[1-^{14}C]aniline (44.2 mCi/g) and 6.9 g of 4-nitroaniline was suspended in 18 mL of concentrated HCl and diazotized at 3-5 °C with a solution of 3.8 g of $NaNO_2$ in 6 mL of water. The diazonium solution was added in small portions to the mixture of SO_2 and $CuCl_2$ in acetic acid while keeping the temperature at approx -10 °C. Vigorous foaming was observed. After the addition was complete the mixture was allowed to warm to room temperature and was stirred at this temperature for 20 min. The mixture was transferred to a beaker with a help of 200 mL of water, stirred for 15 min, and filtered, The solid was washed with 4 x 50 mL of water, giving 7.5 g of crude product after vacuum drying.

LABELED N-METHYL-N-(2-HYDROXYETHYL)-4-NITROBENZENESULFONANAMIDE (1). ([^{15}N]-1, [^{18}O]-1 and [^{14}C]-1)

N-methylethanolamine labeled with ^{15}N and ^{18}O was used for preparing [^{15}N]-1 and [^{18}O]-1, while 4-nitro[1-^{14}C]benzenesulfonyl chloride was used for preparing [^{14}C]-1. The general method was as follows:

A solution of 5.1 g (68 mmol) of N-methylethanolamine and 7.5 g (34 mmol) of 4-nitro[1-^{14}C]benzenesulfonyl chloride in 60 mL dioxane was refluxed for 5 h. The mixture was cooled to room temperature and kept overnight, after which the dioxane layer was decanted. The oily residue was extracted twice with 60 mL of CH_2Cl_2. The organic layers were combined, diluted with 200 mL of CH_2Cl_2, and the solution was washed with 25 mL of water. After drying the solution over $MgSO_4$ and decolorizing with activated charcoal the solvent was removed by rotary evaporator under vacuum. The residue was trituated with n-pentane to give the crude sulfonamide, [^{14}C]-1, 10.9 g.

LABELED N-METHYL-2-(4-NITROPHENOXY)-ETHANAMINE HYDROCHLORIDE (2·HCl) ([^{15}N]-2, [^{18}O]-2, [^{14}C]-2)

To a solution of 10.9 g of isotopically enriched, crude [^{14}C]-1 in 250 mL of CH_2Cl_2 containing 3.5 g of 18-Crown-6 was added 26 pellets of KOH. The mixture was stirred mechanically and the rearrangement of [^{14}C]-1 to [^{14}C]-2 was followed by uv at 310 nm (the maximum for 2). When absorbance at 310 nm reached its maximum the mixture was filtered and the solid KOH was washed with 3 x 50 mL of CH_2Cl_2. The organic layers were combined and washed once with 20 mL of water. The CH_2Cl_2 solution was dried over $MgSO_4$ after which HCl(g) was passed through it to precipitate 2·HCl. The product was collected by filtration and was recrystallized from a mixture of absolute ethanol-diethyl ether (10:1) to give 5.0 g of [^{14}C]-2·HCl (43%, based on 4-nitroaniline), mp 153-153.5 °C. Obtained also were [^{15}N]-2, 40%, and [^{18}O]-2, 47% (based on sarcosine hydrochloride).

LABELED N-METHYL-N-(2-HYDROXYETHYL)-4-NITROANILINE (3). ([^{15}N]-3, [^{18}O]-3, and [^{14}C]-3)

A solution of 100 mg of labeled 2·HCl in 25 mL of 1 M aqueous NaOH was stirred at room temperature for 9 h. The product (3) precipitated. The mixture was extracted with 5 x 50 mL of CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and the solvent was removed to give 3 in quantitative yield. Purification was accomplished both by sublimation and recrystallization from toluene, mp 104 °C. Lit mp 104 °C (9).

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REFERENCES

1. On leave of absence from Bogazici University, Istanbul, Turkey.
2. Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; and Stock, T. P. — J. Org. Chem. 38: 2786 (1973).
3. Ott, D. G. — Synthesis with Stable Isotopes. Wiley-Interscience, New York, 1981, p. 197; the preparation of 2-amino[2-^{13}C]ethanol.

4. Papanastassiou, Z. B. and Bruni, R. J. — J. Org. Chem. 29: 2870 (1964).

5. Knipe, A. C.; Sridhar, N.; and Loughran, A. — J. Chem. Soc., Chem Comm. 630 (1976).

6. Knipe, A. C.; Sridhar, N.; and Lound-Keast, Jr. — J. Chem. Soc., Perkin I, 581 (1977).

7. Knipe, A. C. and Lound-Keast, J. — J. Chem. Soc., Perkin II 1741 (1976).

8. Meerwein, H.; Dittmar, G.; Goellner, R.; Hafner, K.; Mensch, R.; and Steinfort, O. — Chem. Ber. 90: 841 (1957).

9. Kleb, K. G. — Angew. Chem. Int. Ed. 7: 291 (1968).