

THE SYNTHESIS OF ^{15}N LABELED ANILINE AND OTHER AMINES.

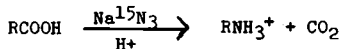
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INTRODUCTION.

In biological and pharmacological research it is sometimes necessary to trace the fate of the N moiety of many aryl and alkyl amines. By use of the Schmidt Reaction⁽¹⁻⁵⁾ employing Na^{15}N_3 and polyphosphoric acid or sulfuric acid various ^{15}N labeled aryl and alkyl amines were prepared in good yield. Among the compounds prepared by this method were: ^{15}N -aniline, ^{15}N - β -phenylethylamine, ^{15}N -amylamine, and ^{15}N -heptadecylamine.

DISCUSSION.

Starting with an aryl, arylalkyl or alkyl carboxylic acid containing the required carbon skeleton, the carboxylic group was readily substituted by an amine by use of the Schmidt Reaction. Better yields were obtained for aniline from trisubstituted carboxylic acid than from benzoic acid. After the Schmidt Reaction was completed the mixture was made alkaline and extracted with an organic solvent yielding the ^{15}N labeled amine. The recovered amines were further purified by gas-liquid chromatography and/or crystallization of the HCl salt. One example with full details is given:



EXPERIMENTAL.

Aniline from a Trisubstituted Carboxylic Acid: To a solution of 2.07 g (0.01 mole) of 2-phenyl-2-methylhexanoic acid⁽⁶⁾ in 40 g of polyphosphoric acid gently stirred at 50° was added to 0.650 g (0.01 mole) of Na^{15}N_3 ($^{15}\text{N} = 47.4$ atoms% excess, purchased from "Isotopes-A Teledyne Co." Westwood,

N.J.). The mixture was gently stirred for 8 hr. The flask was removed from the bath, filled with crushed ice, and stirred until the aqueous polyphosphoric acid solution could easily be poured into a separatory funnel. The mixture was extracted 3 times with 50 ml portions of methylene chloride. The methylene chloride extracts were combined, washed successively with 10% sodium hydroxide solution, and water to remove any unreacted acid (15%) and neutral products. The aqueous portion was made alkaline with solid sodium hydroxide while adding ice chips to maintain the temperature below 25°. The basic solution was extracted with methylene chloride. The extracts were washed with water, dried (MgSO_4), solvent stripped and evaporated in vacuo to give 0.594 g of a crude oil. Gas-liquid chromatography of the crude oil (silicone gum nitrile column) showed a single component, identified as aniline by comparison of its infrared spectrum, retention time and enhancement of the peak with an authentic sample. Derivatization of the crude oil by dissolution in anhydrous ether and treatment with hydrogen chloride yielded 0.694 g (57.5%) of aniline hydrochloride, mp 196-198° (lit 198°). Mixture mp determination gave no depression. The recovered aniline contained 46.8 atoms% excess. When benzoic acid was used instead of the trisubstituted carboxylic acid, the yield of aniline was unexplainably low (47.2%) based on the Na^{15}N_3 used⁽⁷⁾.

^{15}N - β -phenylaniline was prepared from β -phenylpropionic acid following the above described procedure. Yield 71% based on Na^{15}N_3 used⁽⁸⁾.

Caproic acid yielded by the above method 72% of ^{15}N -amylamine⁽⁹⁾.

^{15}N -heptadecylamine was prepared from stearic acid in 98% yield⁽¹⁰⁾.

REFERENCES

1. Schmidt - Z. angew. Chem. 36:511 (1923).
2. Schmidt - Ber. 58:2413 (1925).
3. Adams, R. - "Organic Reactions", Wiley, New York, 1946, Vol. 3, p. 307.

4. Phares, E.F. - Arch. Biochem. 33:173 (1951).
5. Rabinowitz, J.L. and Pritzker, B. - Anal. Chem. 36:403 (1964).
6. Palmere, R.M. and Conley, R.T. - J. Org. Chem. 35:2703 (1970).
7. Briggs and Lyttleton - J. Chem. Soc. 1943:421
8. Oesterlin - Z. angew. Chem. 45:536 (1932).
9. Adamson and Kenner - J. Chem. Soc. 1934:838
10. Briggs, DeAth and Ellis - J. Chem. Soc. 1942:61

Joseph L. Rabinowitz*, R.M. Palmere**, and R.T. Conley***

* Veterans Administration Hospital and Center for Oral Health Research,
University of Pennsylvania, Philadelphia, Pennsylvania 19104. To whom
reprint requests should be addressed.

** Seton Hall University, South Orange, N.J.

*** Wright State University, Dayton, Ohio