Journal of Labelled Compounds — July-September 1965 — Vol. I, No. 3.

Synthesis of ^{14}C-labelled isopropyl, diisopropyl and methyldiisopropyl amine *

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SUMMARY

Isopropyl, diisopropyl and methyldiisopropyl amines, specifically labeled with ^{14}C in the isopropyl moiety, have readily been prepared at a good yield, starting from Acetone-2-^{14}C. Isopropylamine-2-^{14}C [III] at 10 mC/mM was obtained by a two step synthesis with a 75 % overall yield based on Acetone-2-^{14}C. Diisopropylamine-2-^{14}C [VI] at 3 mC/mM was prepared in a two step synthesis in 61 % overall yield. From [VI], methyldiisopropylamine-2-^{14}C [VII] at 1 mC/mM was obtained in one step at a 93 % yield.

Starting with various ketones, it is possible to carry out radiosynteses of homologous primary, secondary and tertiary amines according to the described reaction schemes.

INTRODUCTION.

It is well known that N-carboxyanhydrides readily undergo polymerization in the presence of suitable initiators such as primary, secondary and tertiary amines, as well as strong bases [1]. Since the mechanism involved in this polymerization when initiated by a strong base is still rather uncertain, a possible explanation could be furnished by recognizing the initiator's role during the process.

According to BAMFORD [2], polymerizations catalyzed by tertiary amines or strong bases yield polymer chains without incorporating the initiator in the molecule. On the contrary, when a primary amine initiates the polymerization, one initiator molecule should be linked to each molecule of polymer formed [1]. Labeled initiators have been used in an attempt to clarify these hypotheses. For instance, polymerizations of N-carboxyanhydrides have

* Received on 16 July 1965.

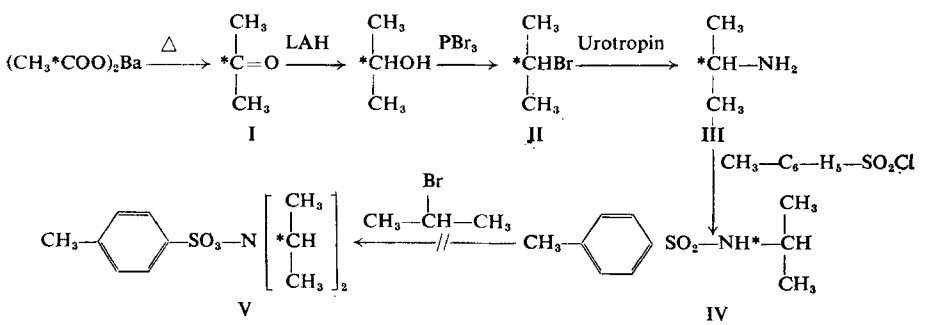
been studied using ^{14}C-labeled CH_3ONa [3] as well as a deuterated primary amine [4] as initiators.

Recently, we have carried out kinetic studies on polymerizations and determinations of molecular weight distribution for polymers initiated by isopropyl, diisopropyl and methyldiisopropyl amines. When diisopropyl amine was employed, the resulting kinetic data were similar to those obtained from either a tertiary amine or CH_3ONa [5]. In view of this and in order to further investigate our findings we synthesized ^{14}C-labeled isopropyl [III], diisopropyl [VI] and methyldiisopropyl amine [VII]. Herein, we report the radiosyntheses of these compounds. Their application in studies on polymerization mechanisms will be reported elsewhere.

For the preparation of III, VI and VII, we found it convenient to formulate a sequence of reactions that would employ a simple labeled intermediate, common to all three amines. Thus, acetone-2-^{14}C was chosen, as shown in Reactions Schemes 1 and 2. It was prepared in good yield according to the method described by LOGAN and MURRAY [6]. Although this method presents the disadvantage of converting half of the activity into Ba or Ca carbonate-^{14}C, the product obtained is pure and the labeled carbonate can be recovered and reutilized. Further, since III, VI and VII contain one or two secondary alkyl groups linked to nitrogen, we thought it desirable to devise a general method for the preparation of homologous primary, secondary and tertiary amines of this type through a sequence of simple reactions.

Two reaction schemes were taken into consideration. Preliminary work to test the validity of the method for the preparation of III, VI and VII according to Reaction Scheme 1, showed that III can be readily obtained and in

REACTION SCHEME 1

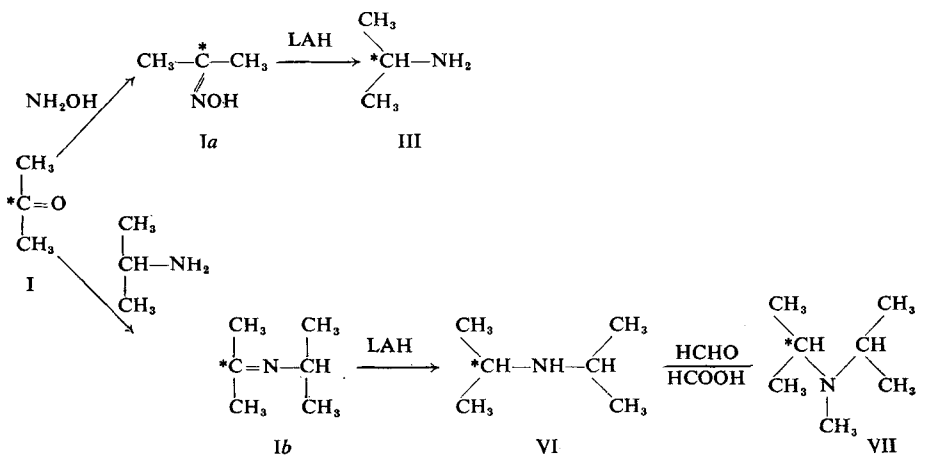


good yield. On the contrary, the attempted preparation of VI according to SEARLE and CUPERY for the synthesis of dimethylamine [7], failed to yield the desired compound. The condensation of III with p-toluensulfonyl chloride gave an almost quantitative yield of p-toluen-N-isopropyl-sulfonamide [IV].

However, when IV was made to react with 2-bromo-propane, not only as described by these AA, but also under varied drastic conditions, no p-toluen-N-diisopropylsulfonamide [V] was obtained. It is reasonable to assume that unfavorable steric factors hinder this reaction.

Thus, Reaction Scheme 1 was abandoned in favor of Reaction Scheme 2 :

REACTION SCHEME 2



The reactions shown in this scheme have previously been described in the literature, in a non-labeled form, sometimes for these same compounds and sometimes for analogous ones. For these latter, it was necessary to modify the methods according to the physico-chemical characteristics of the desired compounds. Further, since radioactive compounds were required, the procedures reported below represent, in all cases, technical adaptations of previously reported reactions.

Isopropylamine-2-^{14}C was obtained in an overall 75 % yield by $LiAlH_4$ reduction of the oxime [*Ia*] which was formed when 2-^{14}C-labeled acetone was made to react with hydroxylamine [8]. VI was prepared by the condensation of acetone-2-^{14}C with unlabeled isopropylamine [9], followed by $LiAlH_4$ reduction [10] of the resulting ketimine [*Ib*]. The overall yield was 61 %. The labeled tertiary amine, VII, was obtained in an almost quantitative yield by alkylation of VI with formaldehyde and formic acid [11].

EXPERIMENTAL.

Isopropylamine-2-^{14}C [III].

Acetone-2-^{14}C-oxime [*Ia*]. Two mM of hydroxylamine.HCl, 80 mg of carbonate-free NaOH, 0.8 ml of H_2O, and a micro magnetic stirring bar were

introduced into a 10 ml round bottom, long necked flask. After the flask was connected to the vacuum line, frozen by liquid N_2 and evacuated, 2 mM of acetone-2-^{14}C at 10 mC/mM were vacuum transferred into the flask which was then sealed by a flame at the constriction of its neck. The reaction mixture was allowed to stir at room temperature for 24 hrs. Then, the neck was broken open and the contents of the flask extracted twice with 5 ml portions of ethyl ether. This solution was used in the next step without further drying. During the trial runs, instead, the combined ether extracts were dried over $MgSO_4$, followed by filtration and evaporation of the solvent. The yield in this case was 95 %; m.p. 59-60° C (Lit. 59-60° C [8]).

Isopropylamine-2-^{14}C·HCl [III]. To a stirred solution of 9 mM of $LiAlH_4$ (a large excess in respect to I*a*) in 10 ml of dry ethyl ether, kept at 0° C in a 50 ml two-necked round bottom flask fitted with an addition funnel and a dry ice-acetone cold finger condenser, the previously obtained acetone-2-^{14}C-oxime ethereal solution was slowly added. After the addition was completed, the reaction mixture was refluxed for 3 hrs. The excess $LiAlH_4$ was carefully decomposed by the addition of wet ether and a few drops of water, and the resulting slurry was acidified with dil. HCl until two clear layers were obtained. The ether layer did not contain any activity and was discarded; the remaining phase was attached to the vacuum line for the removal of the last traces of ether. The pressure was brought to 600 mm Hg, and an excess of 10 % NaOH solution was added at once through the addition funnel. The freed isopropylamine-2-^{14}C was collected by vacuum distillation over a frozen solution of dil. HCl which was connected to the manifold. The solution of amine.HCl thus obtained was evaporated and dried to constant weight affording 143 mg of product. Overall yield (based on acetone-2-^{14}C) : 75 %; m.p. (picrate) 151° C (Lit. 150° C [12]).

Anal. (picrate) : $C_9H_{12}O_7N_4$

Calc. :	C = 37.45	H = 4.17	N = 19.40
Found :	C = 37.05	H = 4.10	N = 19.62

Diisopropylamine-2-^{14}C.HCl [VI].

N-Isopropylideneisopropylamine-2-^{14}C [Ib]. To 15 mM of isopropylamine, 3g of freshly dehydrated $MgSO_4$ and 15µl of conc. HCl placed in a 10 ml round bottom flask fitted with a stopcock and cooled by liquid N_2, 5 mM of acetone-2-^{14}C at 3 mC/mM were added by vacuum distillation. The stopcock was closed, the liquid N_2 removed, and the contents stirred overnight at room temperature. The reaction flask was connected to the vacuum manifold and its contents transferred to a 50 ml round bottom, long necked flask containing a micro magnetic stirring bar from which the excess isopropylamine was distilled off. This was carried out by immerging the flask and part of its neck into a freezing bath at −60° C and, under vacuum, condensing

isopropylamine which evaporated into a spiral trap cooled at liquid N_2 temperature. The residue, consisting of pure *Ib*, was dissolved in 10 ml of dry ether and used in the next step. Because *Ib* sublimes readily even at low temperatures, it was impossible to avoid a certain loss of this product during the evaporation of isopropylamine.

Diisopropylamine-2-^{14}C·HCl [VI]. The previously obtained ethereal solution of *Ib* was added over a 15 minute period to a stirred slurry of 20 mM $LiAlH_4$ in 20 ml of dry ether contained in a 100 ml two-necked flask, fitted with an addition funnel and a finger condenser, which was cooled with a dry ice-acetone mixture. When the addition was completed, the dry ice-acetone mixture was substituted with ice and water and the reaction mixture was allowed to reflux for 5 hrs., after which the excess $LiAlH_4$ was carefully decomposed with wet ether and water. Diisopropylamine-2-^{14}C and ether were then vacuum distilled into a flask containing an excess of dil. HCl which was attached to the vacuum line and frozen by liquid N_2. When the mixture thawed, the flask was shaken until all the amine was found in the water phase as the hydrochloride salt. This occurred after several minutes of shaking and was followed by the disappearance of radioactivity in the ether phase. After removal of the ether, evaporation of the water solution afforded a white salt which was dried to constant weight. Overall yield (based on acetone-2-^{14}C) : 418 mg or 61 %; m.p. (picrate) 146-147° C (Lit. 147.5° C [12]); m.p. (picrate, made from Fluka diisopropylamine) 146-147.5° C; mixed m.p. (picrates obtained from VI and unlabeled isopropylamine) 125° C.

Anal. (picrate) : $C_{12}H_{18}O_7N_4$

Calc. :	C = 43.60	H = 5.45	N = 16.95
Found :	C = 43.21	H = 5.67	N = 17.20

Methyldiisopropylamine-2-^{14}C·HCl [VII].

Methyldiisopropylamine-2-^{14}C·HCl [VII]. To 3 mM of VI at 1 mC/mM dissolved in 1 ml of water contained in a 50 ml round bottom flask which was connected to a vacuum manifold, 10 mM of solid NaOH were added. The free amine was vacuum distilled into an evacuated flask in which 2 ml of HCOOH (98-99 %) had been placed and frozen by liquid N_2. Nitrogen gas was introduced, and the reaction flask was disconnected from the vacuum line. After addition of 0.5 ml of a 36 % formaldehyde solution, the reaction mixture was heated at 80° C for 45 minutes and then refluxed for 4 hrs. When cooled, 1.5 ml of conc. HCl were added to the mixture that was then concentrated at a rotating evaporator. The thick oily residue was crystallized by adding 3 ml of ethanol and 6 ml of dry ethyl ether. The filtered product was dried over P_2O_5 in a vacuum desiccator. Yield : 93 %; m. p. (picrate) 203° C (Lit. 202-203° C [13]).

Anal. (picrate) : $C_{13}H_{20}O_7N_4$

Calc. :	C = 48.80	H = 5.83	N = 16.27
Found :	C = 48.52	H = 5.71	N = 16.44

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