Syntheses of \( \alpha \)-Propylamino-2-methyl-[\( \text{carbonyl}^{14}\text{C} \)] propioanilide

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In studies on the behaviour of drugs in biological systems it is often necessary to be able to trace such compounds in low concentrations. To study the metabolism and distribution of the local anesthetic, \( \alpha \)-propylamino-2-methylpropioanilide \(^1\) (Citanest \( ^\text{\textregistered} \)), it was necessary to use a radioactive product, hence we prepared a \([\text{\textsuperscript{14}}\text{C}]\)labelled anilide.

The preparation of diethylamino-2,6-dimethyl-[\( \text{carbonyl}^{14}\text{C} \)]acetanilide in a 20 \% yield, based on sodium \([\text{\textsuperscript{14}}\text{C}]\)acetate, has been outlined by Geddes and Douglas \(^2\) and Geddes \(^3\) but only few experimental details have been published. This synthesis was carried out \(^4\) partly by use of the vacuum line technique. Several synthetic methods have been given \(^5\) for the preparation of similar derivatives, but they involve the use of either elaborate apparatus or of special arrangements such as the vacuum line technique.

This communication describes the preparation of \( \alpha \)-propylamino-2-methyl-[\( \text{carbonyl}^{14}\text{C} \)]propioanilide using standard laboratory technique and apparatus. Ethyl magnesium bromide was treated with \([\text{\textsuperscript{14}}\text{C}]\)carbon dioxide, the propionic acid liberated and heated with red phosphorus and bromine to yield \( \alpha \)-bromopropionyl bromide. This was allowed to react with \( o \)-toluidine and the bromo-2-methylpropioanilide formed was then heated with propyamine, giving the hydrochloride of \( \alpha \)-propylamino-2-methyl-[\( \text{carbonyl}^{14}\text{C} \)]propioanilide in an overall yield of 62 \%. The purity of the product was ascertained by chromatography by which it was also shown that all radioactivity was located in one spot.

Ethyl magnesium bromide was prepared by adding 125 mmoles (13.6 g) of ethyl bromide (dried over anhydrous sodium sulphate) in 50 ml of dry ether to 125 mmoles (3.20 g) of magnesium filings suspended in 65 ml of dry ether at such a rate as to cause gentle reflux. The mixture was refluxed for a further 15 min to complete the reaction and then cooled, giving 125 ml of an approximately molar solution, from which 100 ml could be pipetted off without contamination from the deposit at the bottom of the flask.

Carbonation of the ethylmagnesium bromide was performed in the apparatus shown in Fig. 1. Into flask A (100 ml), containing about fifty 6 mm \( \text{O} \) glass beads, was introduced 50.0 mmoles (9.87 g) of barium \([\text{\textsuperscript{14}}\text{C}]\)carbonate (radioactivity: 0.2 mC/mmmole). The apparatus was evacuated to 10 mm Hg and then filled with nitrogen. The flask B (500 ml) was removed, 100 mmoles of freshly prepared ethyl magnesium bromide (100 ml of the ethereal solution prepared as described above) was quickly introduced and the flask again connected to the apparatus and immersed into an ethanol-dry ice bath of \(-50^\circ\text{C} \). (A lower temperature of the cooling-bath or a higher concentration of the Grignard reagent will cause crystallization.) After 5 min, the apparatus was alternately evacuated to 25 mm Hg with a water pump via stopcock E and filled with nitrogen via stopcock F three times. Finally, the apparatus was evacuated to 25 mm Hg and the stopcock C of the funnel D was closed. The T-tube carrying the cooks E and F was removed and 70 ml of conc. sulfuric acid (p.a.) was introduced into the funnel D (100 ml capacity). With the flask B still in the ethanol-dry ice bath, the apparatus was tilted slightly so as to cause the sulfuric acid to run into flask A (containing the barium \([\text{\textsuperscript{14}}\text{C}]\)carbonate).
The addition was made dropwise during 20 min while carefully agitating the flask at intervals. Finally, the flask A was heated in an oil bath of 70°C for 5 min. The apparatus was then removed from the baths and allowed to attain room temperature. After frequent shakings during 10 min, flask B was again immersed in the ethanol-dry ice cooling bath (−50°C) and 50 ml of molar sulfuric acid was slowly added during half an hour. The flask was then allowed to warm to room temperature and swirled at intervals, stopcock C being opened to avoid overpressure. The content of flask B was transferred to a separatory funnel, the ethereal layer separated and combined with the ether solution obtained from extracting the water phase five times with 50 ml portions of ether. After drying overnight over 8 g of magnesium sulfate, the ethereal solution was transferred together with the drying agent to a separatory funnel (500 ml) into which a sintered glass disk had been fused. The separatory funnel was connected to a distillation flask (100 ml), containing ~10 mg of phosphorus pentoxide, and the ether solution was carefully evaporated until about 40 ml was left, whereupon a further ~10 mg of phosphorus pentoxide was introduced. Evaporation was then completed at a bath temperature of 70°C until the temperature at the distillation head was 40–42°C.

Bromination was carried out in the same 100 ml distillation flask after it had been equipped with a reflux condenser carrying a CaCl2-drying tube, and a dropping funnel. 20.0 mmoloes (0.620 g) of red phosphorus (purified as described by Vogel 4) and 5 drops of propionic acid anhydride were introduced into the flask, followed by the dropwise addition at room temperature of 120 mmoloes (19.2 g = 6.10 ml) of bromine (purified as described by Vogel 4) at such a rate as to obtain a vigorous reaction. The reaction mixture was then refluxed for one hour. The bromopropionyl bromide thus obtained was distilled under nitrogen at 10 mm Hg into an ice water cooled receiver. (The stem of the receiving adapter extended to the bottom of the receiver.) A maximum bath temperature of 150°C was allowed. When no more distillate was obtained, the distillation flask was removed and the distillation head and condenser were rinsed into the receiver with 75 ml of dry benzene.

The receiver containing the benzeno bromopropionyl bromide was equipped with a separatory funnel, a reflux condenser and a stirrer, and 130 mmoloes (13.9 g) of freshly distilled o-toluidine in 30 ml of dry benzene were added during 5 min with stirring. The hydrobromide of the o-toluidine separated immediately and the mixture was heated to 70°C for 15 min to complete the reaction. While still hot, the benzene solution was filtered through a glass filter and the filtrate washed three times with 15 ml portions of hot benzene. To the combined benzene solutions were added 176 mmoloes (10.0 g) of propylamine and the solution refluxed for 4 h. The hydrobromide of propylamine separated as colourless crystals and was filtered off on a glass filter and washed with 10 ml of dry benzene. The combined benzene solutions were extracted 4 times with 40 ml of 2 N hydrochloric acid. The extracts were combined and the acidity of the solution was adjusted first with 30 % sodium hydroxide and then with a 2 N solution to pH = 5.7. The solution was then extracted 4 times with 25 ml of ether to remove the excess o-toluidine. The ether extracts were discarded and the aqueous solution was made alkaline (pH 10) with 2 N sodium hydroxide. The liberated base was extracted 4 times with 40 ml of ether and the combined extracts evaporated in vacuo to dryness using a final bath temperature of 100°C and a pressure of 10 mm Hg. The residue was dissolved in absolute ether and the hydrochloride of the aminomethylamino-1,4-naphthoquinol and the precipitate formed was filtered off and after one crystallization from ethanol-ether (1:6) it melted at 165–167°C. Yield 8.0 g (62 %). The radioactivity of the product was 0.85 μC/mg.

The procedure described above is also applicable to smaller scale synthesis. Thus, a 5 mmol synthesis gave a 36 % yield of 2-propylamino-2,6-dimethylacetanilide hydrochloride. In this smaller scale, the flasks A and B and the funnel D were of 25 ml capacities and the volumes of the solvents used in the reactions and extractions were proportionally reduced. A 5 mmole synthesis of diethylamino-2,6-dimethylacetanilide hydrochloride from methyl iodide yielded 24 % of final product, applying the above procedure with minor modifications.

4. Geddes, I. C. Personal communication.
7. Ref. 4, p. 185.

Received April 17, 1962.

Acta Chem. Scand. 16 (1962) No. 4