

THE NEW "ONE-FLASK" SYNTHESIS OF  $^{14}\text{C}$  LABELLED  
1-BROMOALKANES - SYNTHESIS OF 1-BROMO  $[1-^{14}\text{C}]$  HEPTANE

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## ABSTRACT

Conditions were found for almost quantitative carboxylation of n-hexyllithium with  $^{14}\text{CO}_2$  to afford lithium  $[1-^{14}\text{C}]$  heptanoate. It was then possible to perform the reaction sequence lithium  $[1-^{14}\text{C}]$  heptanoate  $\rightarrow [1-^{14}\text{C}]$  heptan-1-ol  $\rightarrow$  1-bromo  $[1-^{14}\text{C}]$  heptane in one flask without isolation of intermediates. In the "hot" synthesis 12,8 GBq (346 mCi) of 1-bromo  $[1-^{14}\text{C}]$  heptane with radiochemical purity better than 97 % were prepared from  $\text{Ba}^{14}\text{CO}_3$  in 81 % yield.

Key words: 1-Bromo  $[1-^{14}\text{C}]$  heptane,  $[1-^{14}\text{C}]$  heptanoic acid,  $[1-^{14}\text{C}]$  heptan-1-ol, organolithium carboxylation.

## INTRODUCTION

At least 7,4 GBq (200 mCi) of 1-bromo  $[1-^{14}\text{C}]$  heptane (3) with molar radioactivity greater than  $1,7 \text{ GBq} \cdot \text{mmol}^{-1}$  ( $47 \text{ mCi} \cdot \text{mmol}^{-1}$ ) were required for the synthesis (1) of labelled new drugs Heptacaine and Carbizocaine for the purpose of their pharmacokinetic and pharmacodynamic studies.

The published (2) methods for synthesis of 3 start from  $[1-^{14}\text{C}]$  heptanoic acid, prepared either by carboxylation of n-hexylmagnesium bromide by  $^{14}\text{CO}_2$  or by hydrolysis of n-hexyl  $[^{14}\text{C}]$  cyanide. Upon acidification of the reaction mixture  $[1-^{14}\text{C}]$  heptanoic acid is extracted with diethyl ether and then reduced with lithium aluminium hydride as free acid or after esterification (3). Decomposition of alanate complex by diluted sulphuric acid or aqueous sodium hydroxide and diethyl ether extraction gives crude  $[1-^{14}\text{C}]$  heptan-1-ol (2) which is then purified by distillation. The conversion of 2 to bromide 3 is achieved by action of either hydrobromic

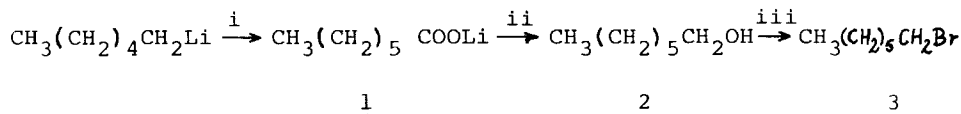
and sulphuric acid mixture or by the action of phosphorus tribromide. The overall radiochemical yield of this sequence does not exceed 50 % and manipulation with volatile intermediates having high molar radioactivities, required in our case, would be time consuming and not very safe.

Our aim was to eliminate throughout the whole synthesis as much of separation operations as possible and thus improve the yield and shorten the time needed. It follows, that carboxylation of n-hexyllithium producing lithium heptanoate (1) according to Scheme 1 would eliminate the need of free acid isolation, since the lithium salts of carboxylic acids are fairly soluble in tetrahydrofuran (THF) and can be reduced to corresponding alcohols by lithium aluminum hydride (4).

The usually adopted method for high yield carboxylation - to spray organolithium compounds in inert solvent over great excess of dry ice (5) - is obviously unsuitable. Soviet authors reported (6) 95 % yield of [ $^{14}\text{C}$ ]propionic acid by bubbling 223 mmol of gaseous [ $^{14}\text{C}$ ]carbon dioxide (3,6 MBq, 0,1 mCi) through a solution of ethyllithium (236 mmol) in n-hexane at  $-70^\circ\text{C}$  and at pressures 25 - 30 kPa.

#### RESULTS AND DISCUSSION

When we tried to reproduce the results of the aforementioned Soviet authors (Ref. 6) on 5 mmol scale by letting carbon dioxide (starting pressure 12 kPa) to absorb in the vigorously stirred solution of n-hexyllithium in hexane cooled to  $-78^\circ\text{C}$ , the yield of lithium heptanoate (1) was only 67 %, 31 % of theoretical yield of di-n-hexylketone



- i      $^{14}\text{CO}_2$
- ii     $\text{LiAlH}_4$  - THF
- iii    $\text{HBr} - \text{H}_2\text{SO}_4$

SCHEME 1

were isolated. Di-n-hexylketone was characterized by its melting point, IR and  $^1\text{H}$  NMR spectra. The high ketone formation by n-hexyllithium attack on primarily formed lithium heptanoate (1) was most probably caused by greater solubility of 1 in reaction media in comparison with lithium propionate<sup>x</sup>. We tried to improve acid salt yield by modifying reaction conditions and the results are summarized in Table 1.

TABLE 1

## YIELDS OF HEPTANOIC ACID UNDER VARIOUS REACTION CONDITIONS

No	The reaction conditions	Yield of heptanoic acid
I.	$\text{CO}_2$ absorbed in cooled n-hexyllithium <sup>a</sup>	67 %
II.	n-hexyllithium added to frozen <sup>b</sup> $\text{CO}_2$	12 %
III.	n-hexyllithium dropped to cooled <sup>a</sup> $\text{CO}_2$ and n-hexane	56 %
IV.	precooled n-hexyllithium dropped to cooled <sup>a</sup> $\text{CO}_2$ and n-hexane	76 %
V.	precooled n-hexyllithium introduced beneath <sup>a</sup> the level of cooled n-hexane and $\text{CO}_2$	95 %

<sup>a</sup> ethanol - dry ice bath

<sup>b</sup> liquid nitrogen bath

<sup>x</sup> In fact no distinct precipitate was formed (cf. ref. 6) during carboxylation, but a thickgel.

Two important conditions were deduced from the results I-IV; the first one - the carbon dioxide must be in excess throughout the reaction - and the second one - the reaction temperature must be kept as close to  $-78^{\circ}\text{C}$  as possible (when n-hexyllithium is dropped into the reaction flask, it reacts with gaseous  $\text{CO}_2$  during fall and the drop overheates). Both conditions were fulfilled in experiment No. V. and thus the high yield of 1 was obtained by reaction of equimolar amounts of n-hexyllithium and carbon dioxide. For doing this we devised apparatus represented on Figure 1. Apparatus consists from reaction flask A with magnetic stirr bar equipped with adapter consisting from screw cap B with silicone rubber septum and ground glass stopcock<sup>x</sup> C. Solution of n-hexyllithium is pushed from PE syringe D via PE capillary E through ethanol - dry ice bath F and eventually via stainless steel needle G under the level of n-hexane -  $\text{CO}_2$  mixture in flask A (magnetic stirr bar, cooling bath of A and cotton wool insulation of PE capillary E are not shown for simplicity).

After evaporation of n-hexane from the reaction mixture we thus obtained very pure 1; its direct reduction with lithium aluminum hydride in THF under reflux gave heptane-1-ol (2) in almost quantitative yield, as shown by g.l.c.. This prompted us to omit the isolation procedure for 2 as well and to decompose the alanate complex, after thorough evaporation of THF, directly with sufficient amounts of hydrobromic and sulphuric acid. The reaction mixture was then heated on  $120^{\circ}\text{C}$  and 1-bromoheptane was isolated by extraction with diethyl ether. The yield of this last step in "cold" experiments was 92 %. The identity of prepared 1-bromoheptane was confirmed by its boiling point and comparison with authentic specimen by g.l.c. on two different columns.

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<sup>x</sup> Stopcock C is closed during cryotransfer of  $\text{CO}_2$  since the silicone rubber septum alone is not sufficiently leak-proof to maintain high vacuum.

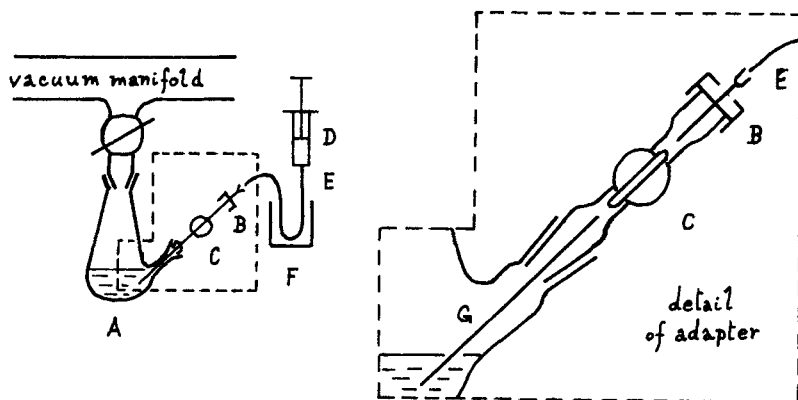


FIGURE 1

The possibility of "one-flask" synthesis of 3 starting from *n*-hexyllithium and carbon dioxide with high yield on starting  $\text{CO}_2$  was thus demonstrated. In the "hot" synthesis 15,7 GBq (424 mCi) of  $^{14}\text{CO}_2$  were converted using by us invented procedure without isolation of intermediates to 12,8 GBq (346 mCi, 81 %) of 1-bromo [ $1-^{14}\text{C}$ ] heptane with molar radioactivity  $1,73 \text{ GBq} \cdot \text{mmol}^{-1}$  ( $47 \text{ mCi} \cdot \text{mmol}^{-1}$ ) and radiochemical purity greater than 97 %.

The described method is suitable also for preparation of other 1-bromoalkanes labelled at C-1 by radioisotope  $^{14}\text{C}$  or stable isotope  $^{13}\text{C}$ .

#### EXPERIMENTAL

G.l.c. radiochromatography was performed on Packard apparatus equipped either by FID or radioactivity detector consisting from proportional counter (volume  $2 \text{ cm}^3$ ) with methane as a counting gas; hydrogenation cracking method was utilized (catalyst obtained from Berthold). Samples of heptanoic acid and di-*n*-hexylketone were analyzed on 5 % FFAP on Inerton ( $0,16-0,20 \mu$ ) column ( $0,3 \times 200 \text{ cm}$ ) argon flow  $40 \text{ cm}^3 \cdot \text{min}^{-1}$ , column temperature  $170^\circ \text{C}$ ; when also heptane-1-ol and 1-bromoheptane were present the temperature programme  $5^\circ \text{C} \cdot \text{min}^{-1}$  starting from  $80^\circ \text{C}$  was used. 1-Bromoheptane samples were also analyzed on 10 % Apiezon L on Chromaton N Super ( $0,16 - 0,20 \mu$ ) column ( $0,4 \times 200 \text{ cm}$ ), argon flow  $35 \text{ cm}^3 \cdot \text{min}^{-1}$  and column temperature  $120^\circ \text{C}$ .

Radioactivity was measured on Packard 2660 apparatus in liquid scintillator SLD-31 (Lachema Czechoslovakia; dioxane based). Corrections for quenching were done by channel ratio method after preliminary gauging with standard set made by Dept. of Dosimetry of our institute. Two counting solutions of each sample were prepared and five one minute counts were taken for each solution. IR spectra was measured on Zeiss-Jena IR-20 apparatus in chloroform.  $^1\text{H}$  NMR spectra was measured on Tesla B 467 (60 MHz) apparatus in deuteriochloroform with TMS as internal standard. T.l.c. was performed on Silufol plates (Kavalier - Sázava, Czechoslovakia) in dioxane - propan-2-ol 1 : 1 mixture, heptanoic acid was detected by spraying with 0.05% solution of bromothymol blue in 0.1 M lithium methanolate as yellow spots on blue-green background ( $R_f$  0.7).

n-Hexyllithium was prepared from 21,1 cm<sup>3</sup> (150 mmol) of 1-bromohexane and lithium (2,6 g, 375 mmol) by the method described for the synthesis of n-butyllithium (7), the resulting ethereal solution of n-hexyllithium was filtered, evaporated on vacuum rotary evaporator and the residue was extracted with 120 cm<sup>3</sup> of n-hexane<sup>x</sup>. The molarity of thus obtained solution and the total yield were estimated by titration of an aliquot with butan-2-ol i xylene with o-phenatrolin as indicator (8). The yield of n-hexyllithium on 1-bromo-hexane was 86 %.

Non radioactive carboxylation experiments.

I. In 250 cm<sup>3</sup> flask equipped with magnetic stirr bar (teflon coated) 5,4 cm<sup>3</sup> of 0,92 M solution of n-hexyllithium in n-hexane and 20 cm<sup>3</sup> of dry n-hexane were placed and the solution was degassed by repeated freezing and evacuation on vacuum manifold. The flask was then cooled by ethanol - dry ice bath and connected with vacuum manifold containing 5 mmol of CO<sub>2</sub> while stirring the solution vigorously. The pressure of CO<sub>2</sub> drops from initial 12 kPa to 1,3 kPa in 15 minutes and during another hour of stirring to 0,26 kPa. The reaction mixture was then left to warm to laboratory temperature, evaporated to dryness, residue was dissolved in water; mixture was extracted with 3x10 cm<sup>3</sup> of chloroform.

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<sup>x</sup> The work with n-hexyllithium was done under argon atmosphere, vacuum in rotary evaporator was abolished, after cutting off the water pump, by argone.

The remaining water solution, containing lithium heptanoate and lithium carbonate, was evaporated to dryness, residue was dissolved in dilute sulphuric acid and heptanoic acid was extracted with three 20 cm<sup>3</sup> portions of chloroform<sup>xx</sup>. Identity of heptanoic acid was confirmed by g.l.c. and t.l.c. ( $R_f$  0,7) comparison with authentic sample. The yield of heptanoic acid was 67 % (g.l.c.).

The aforementioned chloroform extracts were dried with  $\text{Na}_2\text{SO}_4$  (aliquot of the solution was saved for g.l.c. estimation of the yield), evaporated and crystallization of the residue from small volume of ice cold ethanol afforded 185 mg of di-n-hexylketone m.p. 29 - 30 °C (Lit. 9 gives m. p. 30 °C, ethanol). The total yield estimated by g.l.c. was 31,2 % of theory.

IR ( $\text{CHCl}_3$ ):  $\nu_{\text{C}=\text{O}}$  1715 cm<sup>-1</sup>, fingerprint in accordance with Collection spectrum CA 23 719.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0,68 - 1,05 (m, 6 H,  $\text{CH}_3$ -), 1,05 - 1,83 (m, 16 H,  $-\text{CH}_2$ ), 2,38 (t, 4 H,  $-\text{CH}_2\text{CO}-$ ).

II. Carbon dioxide was frozen in a 250 cm<sup>3</sup> flask by liquid nitrogen bath, pressure in the flask adjusted to 66,5 kPa (500 torr) and through the rubber septum 5,4 cm<sup>3</sup> of the solution of n-hexyllithium were slowly added, the frozen mixture was overlaid with 10 cm<sup>3</sup> of n-hexane and then the cooling bath was removed. The mixture was left to warm to laboratory temperature and then was evaporated to dryness. The residue was dissolved in dilute sulphuric acid and the mixture was extracted with 3 x 20 cm<sup>3</sup> of chloroform. G.l.c. analysis of the chloroform extract indicated 11,5 % yield of heptanoic acid and 87 % yield of di-n-hexylketone.

III. To 5 mmols of  $\text{CO}_2$ , frozen in flask by liquid nitrogen bath, 15 cm<sup>3</sup> of n-hexane were added, the nitrogen bath was replaced by ethanol - dry ice bath and 5,6 cm<sup>3</sup> of 0,92 M n-hexyllithium in n-hexane were added dropwise during 10 minutes by syringe via septum cap. The mixture was then stirred for another hour while still cooled. Reaction mixture was then processed as described for II. The yields of heptanoic acid and di-n-hexylketone were 54 % and 53 %, respectively.

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<sup>xx</sup> In repeated runs we disclosed, that the solutions of heptanoic acid in commercially available p.a. chloroform are not stable and always fresh standard solution for g.l.c. had to be prepared.

IV. To the stirred mixture of 5 mmols of  $\text{CO}_2$  and  $20 \text{ cm}^3$  of n-hexane in flask cooled with ethanol - dry ice bath  $5,6 \text{ cm}^3$  of 0,92 M n-hexyllithium solution precooled to  $-78^\circ\text{C}$  were added dropwise during 20 minutes. The mixture was stirred for another one hour at  $-78^\circ\text{C}$  and then was processed as in II. The yields of heptanoic acid and di-n-hexylketone were 76 % and 17,4 %, respectively.

V. The solution of 10 mmols of n-hexyllithium in n-hexane (0,92 M solution) precooled to  $-78^\circ\text{C}$  was introduced during 30 minutes beneath the level of stirred and to  $-78^\circ\text{C}$  cooled mixture of 10 mmols  $\text{CO}_2$  and  $50 \text{ cm}^3$  of n-hexane using apparatus represented on Figure 1. The pressure in the apparatus was adjusted to 85 kPa by nitrogen. The mixture was stirred another hour at  $-78^\circ\text{C}$ , then  $3 \text{ cm}^3$  of methanol were added to destroy any accidental excess of organometallic and the mixture was processed as II. According to g.l.c. of chloroform extract heptanoic acid was prepared in 95 % yield, contaminated with only 4 % of di-n-hexylketone.

Synthesis of 1-bromo [ $1\text{-}^{14}\text{C}$ ]heptane (3).

[ $^{14}\text{C}$ ]Carbon dioxide, freed from 15,7 GBq (424 mCi, 9,08 mmol) of  $\text{Ba}^{14}\text{CO}_3$  by conc.  $\text{H}_2\text{SO}_4$  had been transferred via vacuum manifold to the  $250 \text{ cm}^3$  flask, represented on Fig. 1, containing  $60 \text{ cm}^3$  of dry degassed n-hexane, using liquid nitrogen. When the cryotransfer was complete the pressure in the flask was adjusted to 85 kPa (640 torr) by dry nitrogen. The liquid nitrogen bath was replaced by ethanol - dry ice bath and the  $9,5 \text{ cm}^3$  of n-hexyllithium (8,8 mmol) solution were added as described for V. Mixture was cooled and stirred for one hour, then  $3 \text{ cm}^3$  of methanol were injected by syringe and n-hexane was evaporated on the vacuum manifold. The residue was thoroughly desiccated over phosphorus pentoxide at 13 Pa (0,1 torr) overnight. Flask A was disconnected from vacuum manifold, the adapter with C and D was replaced by stopper and the 700 mg (18,4 mmol) of lithium aluminum hydride were added followed with  $20 \text{ cm}^3$  of freshly distilled THF. The mixture was refluxed and stirred for one hour with occasional shaking in hand to rinse the residue from flask walls. The cooler was closed with calcium chloride tube. THF was evaporated using vacuum manifold, flask A was cooled to  $-78^\circ\text{C}$  and  $10 \text{ cm}^3$  of 48 % hydrobromic acid were added via



reflux cooler. The mixture was then heated to 110 - 120 °C and once again cooled to -78 °C; 4 cm<sup>3</sup> of conc. H<sub>2</sub>SO<sub>4</sub> were added and the mixture was stirred and heated to 110 - 120 °C for 3 hours. When cooled down, water (20 cm<sup>3</sup>) and diethyl ether (10 cm<sup>3</sup>) were added, the mixture was transferred to the extractor and was continuously extracted with diethyl ether 3 hours. Ethereal extract was dried with anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered and for storing replenished to 100 cm<sup>3</sup>.

According to radio-g.l.c. 12,8 GBq (346 mCi, 81 %) of 1-bromo [ $1-^{14}\text{C}$ ] heptane (3) were prepared with molar radioactivity 1,73 GBq.mmol<sup>-1</sup> (47 mCi.mmol<sup>-1</sup>) and radiochemical purity better than 97 %.

#### ACKNOWLEDGEMENT

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