A GENERAL METHOD FOR THE SYNTHESIS OF LABELED ALKENES FOR THE PREPARATION OF LABELED STEROIDS. THE SYNTHESIS OF LABELED 1,10,11,11a-TETRAHYDRO-2-METHOXY-2H-NAPHTH[1,2-g]INDOLE AND 1,10,11,11a-TETRAHYDRO-11a-METHYL-2H-NAPHTH[1,2-g]-INDOL-7-OL[C-16,17-^{14}C].

K. Darrell Berlin,[1,2] John G. Morgan,[2]
Norman N. Durham,[3] and Robert W. Chesnut[3]

Department of Chemistry and Microbiology
Oklahoma State University
Stillwater, Oklahoma 74074

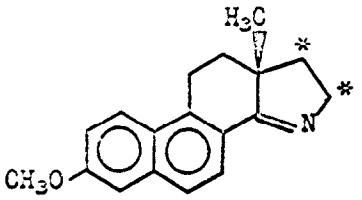
Received June , 1971

Received: June 7, 1971

ABSTRACT

A general technique of preparing labeled alkenes is described and demonstrated with the pyrolysis of $(C_6H_5)_2P(O)O^{14}CH_2-^{14}CH_2CN$ to give $^{14}CH_2=^{14}CHCN$. This method permits the rapid preparation of labeled acrylonitrile as needed on a wide scale range. The process is illustrated in the synthesis of the title azasteroids.

We recently described (4) preliminary results on growth inhibition of several microorganisms by the title azasteroids, 1 and 2, respectively. We wish now to describe a novel method for the rapid preparation of alkenes needed in the synthesis of steroids and to demonstrate



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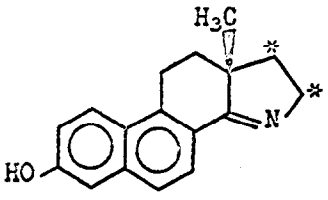

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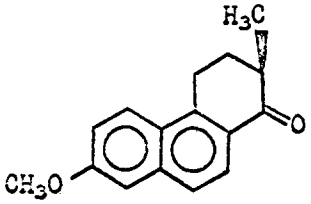
this approach in obtaining labeled 1 and 2. Labeling the D ring with ^{14}C seemed most feasible from ketoether 3 (5). Labeled acrylonitrile (4) like most unsaturated, labeled organic compounds, is expensive and has a propensity to polymerize upon shipment or storage. To avoid this problem and to be able to prepare 4 on demand, the following technique



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$^{14}CH_2=^{14}CHCN$

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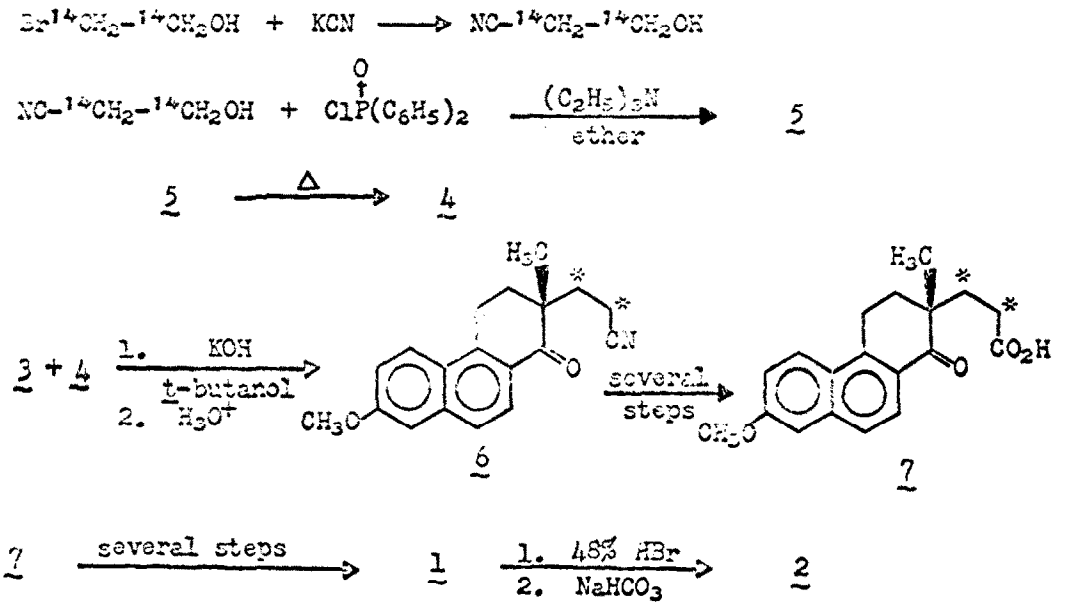
was developed. 2-Bromoethanol (containing 1 mC of $Br^{14}CH_2-^{14}CH_2OH$) was condensed with KCN in boiling ethanol:H_2O. The product, crude ethylene cyanohydrin, was esterified with diphenylphosphinic chloride. Decomposition of the reaction mixture with H_2O and extraction (H_2CCl_2) of same gave a yield (92%) of crude 5. Ester 5 can be stored and used when needed.

$$(C_6H_5)_2P(O)OCH_2CH_2CN \xrightarrow{\Delta} 4$$

The ester 5 was pyrolyzed in a N_2 stream in a simple system until the pyrolysis flask was full of solid [$(C_6H_5)_2P(O)OH$] (6). Collection of 4 in a solution of 3 in t-butyl alcohol containing 1 ml of 40% aq KOH provided immediate conditions for cyanoethylation of 3. The remainder of the procedure paralleled that reported for non-labeled 1 (5). The overall yield of labeled 1 based on the weight of labeled $Br-^{14}CH_2-^{14}CH_2OH$ was 21%.



These esters, called phosphinates, of primarily alcohols appear to be excellent precursors of labeled alkenes needed in the synthesis of labeled steroids. Optimization of conditions and isolation of all intermediates would likely result in higher yields in long syntheses. This must be weighed against increased handling of ^{14}C and additional workup time. It is even possible to recover $(C_6H_5)_2P(O)OH$ and convert it back to $(C_6H_5)_2P(O)Cl$.(7). Many primary, non-labeled alcohols have been so converted to alkenes (6,8). The method is useful on a small scale if isolation of the pure ester is desired since nearly all of the pure esters are solids.

MATERIALS AND METHODS

The ketoether 3 was prepared previously (5). Ethylenebromohydrin-1,2-^{14}C[1mC] was obtained from Mallinckrodt nuclear. Diphenylphosphinic chloride was obtained from Columbia Organic Chemicals.

Synthesis the Nitrile 6. 2-Bromoethanol (6.38 g, 0.05 mole) containing 1mC of $Br-^{14}CH_2-^{14}CH_2OH$ was dissolved in 25 ml of ethanol and

the solution was heated to boiling. To the boiling solution was added dropwise 3.31 g (0.05 mole) of KCN dissolved in 15 ml of H_2O. Boiling was continued overnight. The solution was cooled, filtered, and flash evaporated to yield 2.15 g (ca. 60%) of $NC-^{14}CH_2-^{14}CH_2OH$.

This crude ethylene cyanohydrin was dissolved in ca. 100 ml of anhydrous ether containing 8.0 g (0.08 mole) of reagent triethylamine. Diphenylphosphinic chloride (9.0 g, 0.04 mole) in 40 ml of anhydrous ether was added dropwise with stirring to the above solution. When the addition was complete, the mixture was boiled for 1 hr and poured into ca. 150 ml of distilled H_2O. An inhomogeneous mixture of liquid and semi-solid formed. Methylene chloride dissolved the solid and converted the mixture to a two-phase system. The organic phase was separated, washed (0.1 NH_4Cl, satd. NaCl) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 7.67 g (0.028 mole, ca. 50% based on $Br-^{14}CH_2-^{14}CH_2OH$) of ester 5 as a yellow oil. No attempt was made to purify it.

Crude ester 5 was pyrolyzed by the simple technique reported (6) (below 250°) with the exception that the effluent (containing 4) was directed into 200 ml of warm (60°) t-butyl alcohol containing 6.79 g (0.028 mole) of the ketoether 3 and 1 ml of 40% aq. KOH. The solution was kept at 60° (to effect complete solution of 3 which is sparingly soluble) with stirring overnight. Solvent was removed at aspirator pressure and the residue was boiled 36 hr with 50 ml of 20% KOH. The solution was diluted (H_2O), extracted (ether) and neutralized (0.1 NH_4Cl). After the extract was dried ($MgSO_4$), it was evaporated to give acid 7 as a hard crystalline solid; yield of crude 7 was 4.91 g.

The rest of the procedure was essentially the same as reported for the synthesis of non-labeled 1 and 2 (5). The quantities used of $(C_2H_5)_3N$ and C_2H_5OCCl were 2.59 g (0.025 mole) and 3.13 g (0.028 mole), respectively, along with 2.19 g (0.033 mole) of NaN_3. Hydrolysis of the isocyanate required only 6 hr. Chromatography over neutral alumina gave 3.90 g (52.5%—based on 5) of 1. A sublimed (150°/0.04 mm) sample of 1 (1.25 g) was colorless and crystalline (mp 180-181°, s.t., vac.) and had an activity of 47,180 counts/minute/mg (0.021 μC/mg).

A sample (1.95 g) of 1, unrecrystallized, was boiled with 30 ml of 48% HBr for 14 hr under N_2. The inhomogeneous mixture was diluted (H_2O) to ca. 1 liter and dissolved in 2% aq. NaOH. The resulting solution was filtered and completely neutralized with 10% aq. $NaHCO_3$. The precipitate was filtered, vacuum dried, and sublimed (250°/0.04 mm) to give 1.51 g of 2 [mp 290-3° (s.t., vac.)] identical in all respects to the non-labeled compound (5). The activity was 41,000 counts/min/mg (0.019 μC/mg).

ACKNOWLEDGMENT

We are grateful for partial financial assistance by a grant to Oklahoma State University from the American Cancer Society, Grant IN-91A.

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