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The synthesis and purification of ^{14}C-labeled menthol

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Summary

The synthesis of ^{14}C-labeled menthol was accomplished by preparation of ^{14}C-labeled (±) pulegone. Catalytic hydrogenation and chemical reduction converted (±) pulegone to the isomeric menthols possessing 1.10 mCi total activity. Gas chromatographic separation of this material gave the relative abundance of each isomer.

Introduction and results

Mechanistic studies in this laboratory required the preparation of specifically labeled (±) menthol. The general procedure of Black, Buchanan, and Jarvie [1] was adopted to prepare specifically labeled (±) pulegone which was used to obtain the radioactive isomeric menthols.

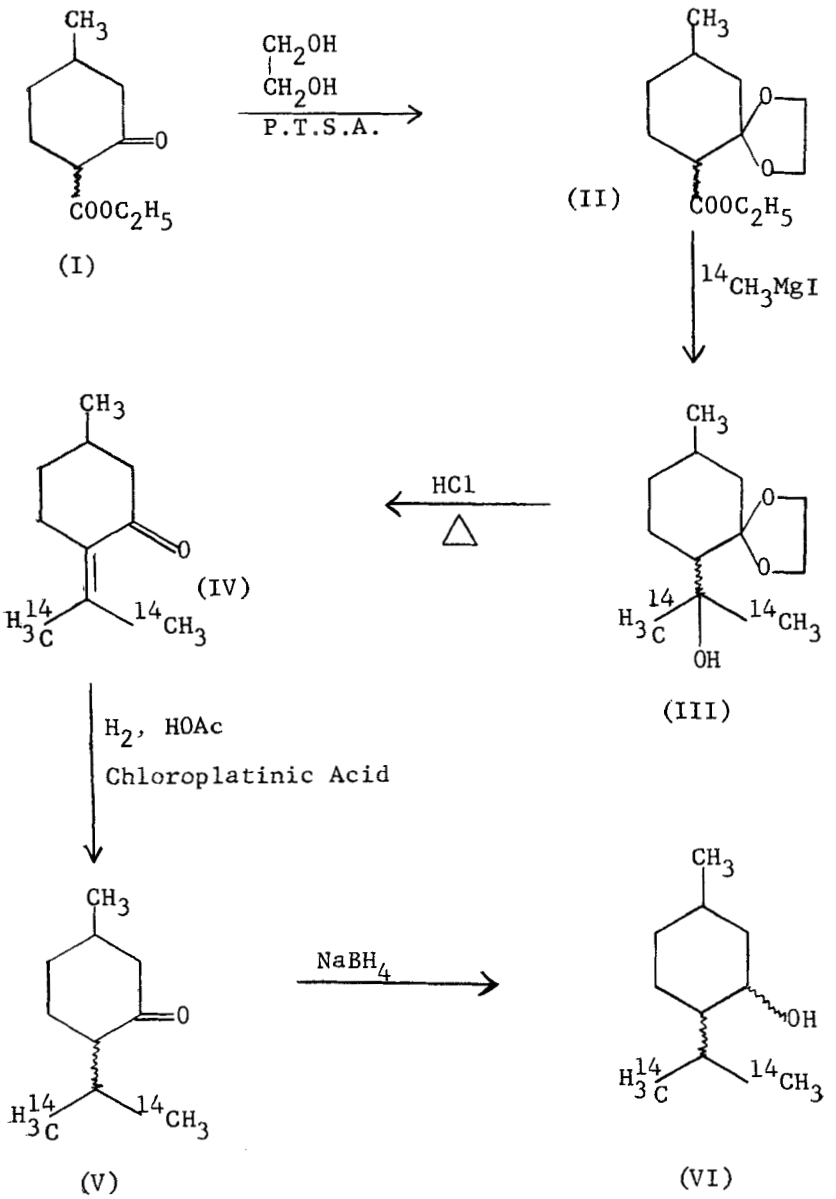
Ethyl 4-methyl-2-oxocyclohexanecarboxylate (I), prepared from ethyl oxalate and (±) 3-methylcyclohexanone, was converted to the cyclic ketal (II). The Grignard reagent from magnesium and ^{14}C-methyl iodide (specific activity 5 mCi/mmole) [2] was reacted with II and after mild hydrolysis gave the alcohol (III). Dehydration of the alcohol produced specifically labeled (±) pulegone (IV). Hydrogenation in glacial acetic acid yielded the isomeric menthones (V). Sodium borohydride converted the menthones to the ^{14}C-labeled menthols (VI).

The general reaction scheme was as follows (see page 262) :

Separation of the ^{14}C-menthol isomers (neomenthol, neoisomenthol, isomenthol, and d,l-menthol) was accomplished using vapor phase chromatography.[3a, 3b] The isomeric weight ratios are shown in Table 1.

Table 1. Relative Amounts [4]

Neomenthol	*Neoisomenthol*	*Menthol*	*Isomenthol*
1.15	1.75	1	0.01


CH3
CH2OH
CH2OH
P.T.S.A.
O
COOC2H5
(I)
(II)
14CH3MgI
HCl
(III)
(IV)
H2, HOAc
Chloroplatinic Acid
NaBH4
OH
(V)
(VI)

EXPERIMENTAL.

Ethyl 2-ethylenedioxy-4-methylcyclohexanecarboxylate (II).

The cyclic ketal (II) was prepared by the method of Black, Buchanan, and Jarvie [1] in 82 % yield, b.p. 86-87° C/2 mm from the 2-oxoester (I). The ultraviolet and infrared spectra were in good agreement with that reported.

^{14}C-Labeled (±) Pulegone (IV).

The Grignard reagent was prepared by the addition over a 45 minute period of ^{14}C-methyl iodide (5 mCi/mmole) [2] to a stirred solution of 2.13 gm of magnesium turnings in 25-ml of dry ether. The mixture was refluxed for 1.5 hours and then 7.5 gm of the ketal (II) in 45-ml of dry ether was added over a period of 30 minutes. After stirring for two additional hours, the reaction was cooled to room temperature and decomposed by the slow addition of 100-ml of 20 % aqueous ammonium chloride. The ether phase was separated and the aqueous layer extracted with three 50-ml portions of ether. The combined ether extracts were washed with water, dried over sodium sulfate, and stripped to dryness *in vacuo* at 30° C. The oily residue, 6.3 gms, was assumed to be the ketal-ol (III). This material was refluxed for two hours with 60-ml of 60 % aqueous methanol containing one-half ml of concentrated hydrochloric acid. After cooling to room temperature 10-ml of 10 % sodium bicarbonate was gradually added and the methanol removed *in vacuo* at 30° C. The residue was extracted with three 25-ml portions of ether. The combined ether extracts were dried over sodium sulfate and evaporated to dryness to yield 3.9 gm of crude ^{14}C-pulegone. Distillation at 132-134° C/60 mm gave 3.2 gms of ^{14}C-labeled (±) pulegone (IV).

^{14}C-Labeled (±) Menthones (V) and Menthols (VI).

Radioactive (±) pulegone (IV) was catalytically hydrogenated for two hours at 45 p.s.i. in 25-ml of glacial acetic acid. The hydrogenation catalyst was prepared from 0.2 gm of chloroplatinic acid and 1.0 gm of sodium borohydride in 15-ml of 10 % aqueous sodium bicarbonate. The ^{14}C-labeled (±) menthones (V, 2.5 gm) were obtained by filtration and after solvent removal under reduced pressure were used in the next step without further purification.

The isomeric menthone mixture was dissolved in 7.5-ml of methanol and a solution containing 0.8 gm of sodium borohydride in 30-ml of 75 % aqueous methanol was gradually added over 30 minutes. After refluxing for four hours, the reaction was cooled to room temperature and decomposed by the addition of 25-ml of 2.5 N sodium hydroxide. The resulting mixture was stirred for one hour and extracted with three 15-ml portions of benzene.

The combined benzene extracts were washed with water until neutral, dried over sodium sulfate and allowed to evaporate at room temperature. The residual oil, 2.3 gm, 1.10 mCi total activity, was shown to be composed

of 26.4 % d,l-menthol-^{14}C, 45 % neoisomenthol-^{14}C, 29.5 % neomenthol, and a trace of isomenthol-^{14}C by vapor phase chromatography [4] on Hyprose S.P.-80. The retention times of these isomers compared exactly with authentic samples of non-labeled material. The purified d,l-menthol-^{14}C had a specific activity of 0.5 mCi/mmole and was suitable for our mechanism studies.

REFERENCES

1. BLACK, C., BUCHANAN, G. L., and JARVIE, H. W. — *J. Chem. Soc.*, 2971-73 (1956).
2. Obtained from New England Nuclear Corporation.
3*a*. MOORE, D. R. and KOSSOY, A. D. — *Anal. Chem.*, **33**, 1437 (1961).
3*b*. The Hyprose SP-80 was coated 20 % by weight on Chromosorb W-HMDS, 60-80 mesh. The column was a quarter-inch O.D. copper tubing, 15 feet long. The column was maintained at 150° C with a helium flow rate of 50 cc per minute.
4. The mass calculations were performed using a CRS-100T Infotronics integrator.
5. Radioactivity measurements were conducted by liquid scintillation counting in a Packard Tri-Carb Scintillator. Instagel was the scintillator solution and toluene-^{14}C(U) was used as the internal standard.