



SYNTHESIS OF NATURAL PRODUCT INTERMEDIATES 5-METHYL-7-METHOXY-1-TETRALONE AND 5-METHOXY-7-METHYL-1-TETRALONE

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Abstract

Acylation of m-cresyl methyl ether with succinic anhydride in presence of anhydrous aluminium chloride gave β -(2-methyl-4-methoxy) benzoyl propionic acid as a major product which on Clemmensen reduction furnish 4-(2-methyl-4-methoxyphenyl) butyric acid. Polyphosphoric acid cyclization of above acids yielded 5-methyl-7-methoxy-1-tetralone and 5-methoxy-7-methyl-1-tetralone which are useful as intermediates in the synthesis of many natural products such as terpenes, sesquiterpenes etc.

Keywords: Acylation, m-cresyl methyl ether, tetralone.

Introduction

Among various compounds of natural occurrence, terpenes constitute the largest group having plant origin. Most of the natural terpene hydrocarbons have the molecular formula $(C_5H_8)_n$. Depending on the value of n, terpenes have been classified into mono($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$), triterpenes ($C_{30}H_{48}$), tetraterpenes ($C_{40}H_{64}$) and polyterpenes. Mono and sesquiterpenes are the main constituents of volatile essential oils which are obtained from sap and tissues of plants while di and tri terpenes are not steam volatile and are obtained from gums and resins of the plants. Besides terpene hydrocarbons, there occur their oxygenated derivatives such as alcohols, ketones and aldehydes also. All the classes of terpenes have one common feature that, most of them obey a well known isoprene rule.

On thermal decomposition, almost all the terpenes form isoprene as one of the products which lead to the suggestion that the skeleton structures of all naturally occurring terpenes can be built up of isoprene units. This is known as isoprene rule and was first time pointed out by Wallach. Thus, divisibility into isoprene units may be regarded as an essential condition to be satisfied by the structure of any plant synthesized terpene. However, there exists a class of sesquiterpenes viz. eremophilanes which do not obey isoprene rule. Thus 'eremophilane' is the first naturally occurring non-isoterpenoid compound. The detailed investigation of this class of compounds has earlier been made by Pinder [1] and Sorm [2].

Present work reports the synthesis of 5-methyl-7-methoxy-1-tetralone and 5-methoxy-7-methyl-1-tetralone using m-cresyl methyl ether and succinic anhydride as starting compounds.

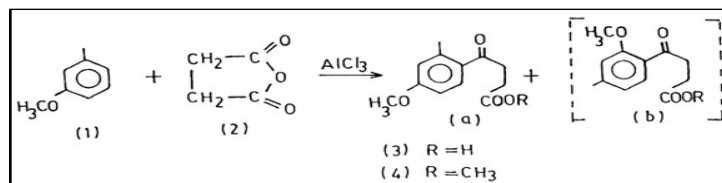
The synthesized tetralones may form the basis of the syntheses of various natural compounds such as cacalol, cacalone pyrocurenone etc.

Experimental

All the chemicals used were of analytical grade and used without further purification. The products synthesized were characterized by infrared (IR) and proton magnetic resonance (PMR) spectroscopic techniques.

(a) Synthesis of β -(2-methyl-4-methoxy)-benzoylpropionic acid

Friedal-Crafts acylation of stoichiometric amounts of succinic anhydride (100 g, 1 mole) (2) in nitrobenzene (450 mL), 86 g, (0.7 mole) m-cresyl methyl ether (1) along with anhydrous aluminium chloride (200 g, 1.49 M) was stirred for about 4 hours and the reaction mixture was allowed stand overnight. Usual work-up yields two isomers of acids (3a, 3b) named β -(2-methyl-4-methoxy)- benzoylpropionic acid as a major product and a small amount of *ortho* acylated product viz. β -(2-methoxy-4-methyl)-benzoylpropionic acid. The yield of acids is found to be 140 g having melting points (m. p.) in the range of 127-128°C. With a view to check the purity of acid, small amount of acids (1 g) was converted in to their methyl esters (4a, 4b) using methanol (15 mL) and sulfuric acid, the m. p. range of which is 48-50°C. Examination of thin layer chromatography (TLC) of the esters showed two close spots, one (nearly 10%) with higher R_f value appeared like a cap over the other spot of major component (nearly 90%) with lower R_f value. The methyl esters were separated on preparative TLC plates and the isomers were identified to be the methyl esters of *ortho* and *para* acylated products on the basis of spectral evidences.



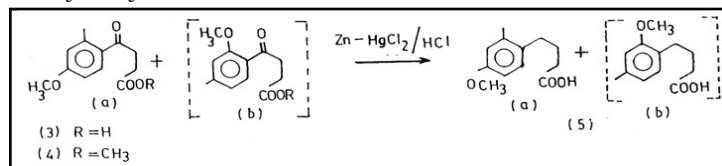
IR spectrum of ester (Fig. 1) showed a strong carbonyl peak at 1725 cm^{-1} and a ketone carbonyl peak at 1680 cm^{-1} .

The PMR spectrum (Fig. 2) of β -(2-methoxy-4-methyl) benzoyl propionic ester exhibited the signals due to the aromatic methyl protons, ester methyl protons and methoxy group 2.26, 3.72 and 3.85 δ respectively. The keto-methylene appeared as a triplet at 3.26 δ while methylene group adjacent to ester also appeared as a triplet at 2.76 δ . Two aromatic protons *ortho* to methoxy group appeared as a multiplet at 6.78 δ and the protons *meta* to methoxy group appeared as doublet at 7.78 δ . The downfield shift for aromatic methyl (2.6 δ) is indicative of *ortho* ketonic group. No attempt was made to separate *ortho* and *para* succinolyted products at this stage.

(b) Clemmensen reduction of β -(2-methyl-4-methoxy) benzoyl propionic acid to 4-(2-methyl-4-methoxyphenyl) butyric acid 4-(2-methoxy-4-methylphenyl) butyric acid

Clemmensen's reduction [3] is the important reaction to reduce aryl-alkyl ketones formed

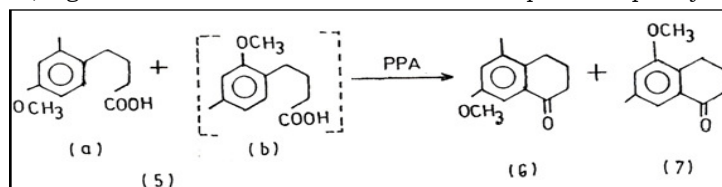
during Friedel-Crafts acylation group to the methylene group. A mixture of zinc wool (170 g), mercuric chloride (19 g), water (300 mL) and conc. hydrochloric acid (8 mL) was shaken together in 2 litre round bottom flask for 20 minutes. The clear solution was decanted and to this water (75 mL), conc. HCl (175 mL) toluene (260 mL) and the keto acid 4.3 (50 g) were added slowly with stirring. The mixture was refluxed for 40 hours. During heating after every eight hours, conc. HCl (25 mL) was added. After heating, organic layer was separated and aqueous layer was extracted with the ether. The combined organic layer was washed with water, dried over anhydrous calcium chloride and solvent was removed to yield 39 g desired reduced acids (5a, 5b) named as 4-(2-methyl-4-methoxyphenyl) butyric acid and small amount of 4-(2-methoxy-4-methylphenyl) butyric acid having m p. 73-74°C. The m. p. of reduced acid was in close agreement with that reported earlier (75-76°C) [4].



(c) Cyclization of 4-(2-methyl-4-methoxyphenyl) butyric acid and 4-(2-methoxy-4-methylphenyl) butyric acid to give 5-methyl-7-methoxy-1-tetralone and 5-methoxy-7-methyl-1-tetralone

Polyphosphoric acid (PPA) was prepared by using *ortho*phosphoric acid (25 mL) and phosphorus pentoxide (40 g) at room temperature. To this, 6 g above mixture of acid

(5a, 5b) was added slowly with constant stirring for 45 minutes at 95°C to obtain cyclized isomers (6 and 7) viz. 5-methyl-7-methoxy-1-tetralone as a major product and 5-methoxy-7-methyl-1-tetralone in minor amount (3.8 g) [5]. The two tetralones were separated effectively by column chromatography and their structures were confirmed spectroscopically.



IR spectrum of 5-methyl-7-methoxy-1-tetralone (Fig. 3) showed a strong peak at 1680 cm^{-1} for aromatic ketone.

PMR spectrum of 5-methyl-7-methoxy-1-tetralone (Fig. 4) showed a multiplet for homobenzylic methylene group at 2.2 δ , a singlet

for aromatic methyl group at 2.3 δ , a multiplet for ketomethylene group and benzylic methylene group at 2.7 δ , a singlet at 3.9 δ for aromatic methoxy group, two broad singlets for aromatic protons *ortho* and *para* to methyl groups at 7.0 and 7.5 δ respectively. The proton appearing at

7.5 δ must have been deshielded due to the presence of peri carbonyl group. The enlargement of aromatic signals in pmr spectrum showed them to be sharp doublets with a small coupling constant of 2 Hz which is in perfect agreement with the *meta* position.

The IR spectrum (Fig. 5) and PMR spectrum (Fig. 6) of 5-methoxy-7-methyl-1-

tetralone were very much similar to that of the 5-methyl-7-methoxy-1-tetralone. This is in agreement with the fact that, during succinolyzation *ortho* acylated product was present but to a minor extent, though literature [6] reports the formation of single isomer that is *para* acylated product.

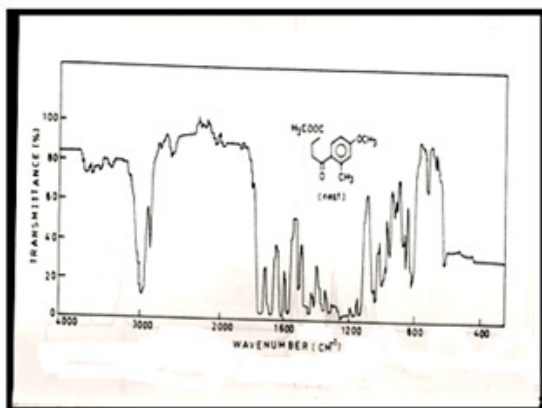


Fig. 1 IR Spectrum

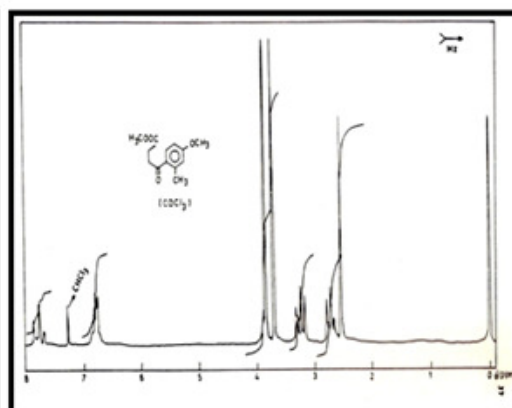


Fig. 2 PMR Spectrum

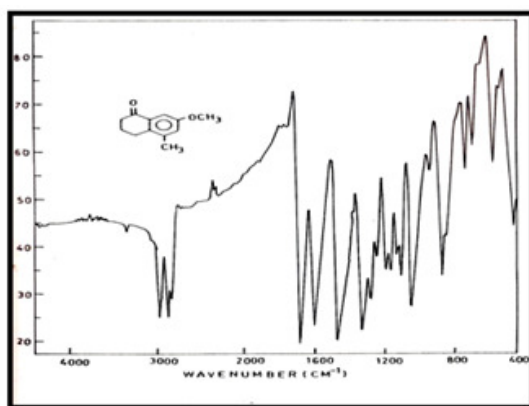


Fig. 3 IR Spectrum

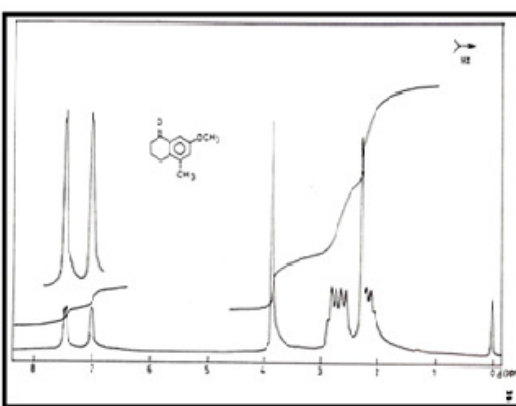


Fig. 4 PMR Spectrum

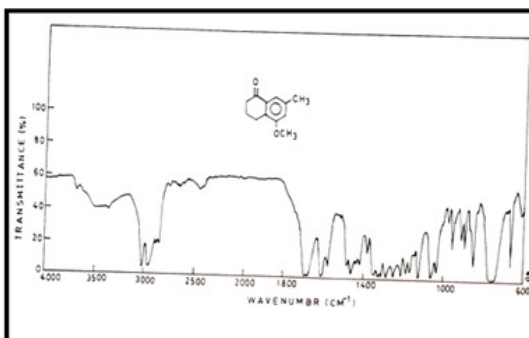


Fig. 5 IR Spectrum

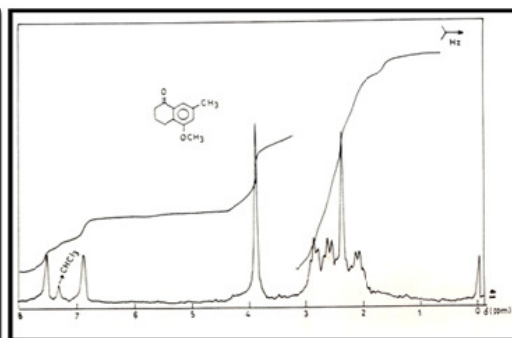


Fig. 6 PMR Spectrum

Conclusions

Synthesis of natural product intermediates 5-methyl-7-methoxy-1-tetralone and 5-methoxy-7-methyl-1-tetralone was carried successfully by acylation of m-cresyl methyl ether with succinic anhydride in presence of anhydrous aluminium chloride. These tetralones can be used as the substrates for the synthesis of many natural products such as cacalol, cacalone, pyrocurzerenone etc.

References

- [1] A. R. Pinder., *Ess. Oil Rec.* 59, 645 (1968)
- [2] F. Sorm, *Pure and Applied Chem*; 21, 263 (1970)
- [3] *Organic Synthesis, Coll*; Vol. II, 499 (1963), Ed. A. H. Blatt (J. Wiley and Sons, New York).
- [4] *Dictionary of Organic compounds*, 5th Ed. (1982) Ed. J. Buckingham (Chapmann and Hall).
- [5] R. C. Gilmore and W. J. Horton, *J. Am. Chem. Soc*; 73, 1411 (1951).
- [6] *Friedal-Crafts acylation and related reactions*, Vol III A G. A. Olah, 1964 (J. Wiley and Sons New York).