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UTILIZATION OF LIMONENE FRACTION OF THE CITRUS ESSENTIAL OILS

Part I. Production of Carvacrol from Orange Oil

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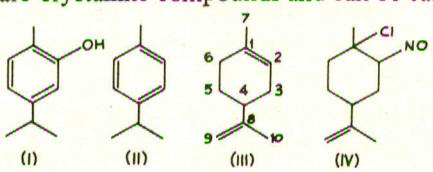
Limonene – a predominant component of the citrus essential oils has been utilised to produce carvacrol. The synthesis involves the preparation of limonene nitrosochloride and carvoxime which are obtained in 90 and 92% yields respectively. Overall yield of carvacrol, starting from limonene was up to 60%.

INTRODUCTION

Carvacrol (I) has powerful antiseptic and germicidal properties and is used extensively in many medicinal and oral preparations, room sprays, disinfecting liquids and antiseptic toilet soaps. Chlorinated carvacrol is also similarly used and is compounded in haemorrhoidal creams such as 'Hadensa cream' for local use. Carvacrol (2-methyl-5-isopropyl phenol), has chemical properties similar to those of other phenols. It is volatile with steam and occurs naturally as one of the major components of the essential oil of origanum, savory and marjoram.

The synthesis of carvacrol can be attempted through a number of routes. *p*-Cymene (II) and limonene (III) which are structurally related to carvacrol have been utilized as the starting materials. *p*-Cymene which is already in the aromatised form, on sulphonation gives mainly 2-sulphonic acid; the sodium salt of which on caustic fusion yields the sodium salt of carvacrol [1]. Thymol invariably accompanies carvacrol, as the sulphonation of *p*-cymene gives 3-sulphonic acid as well.

Limonene is an alicyclic compound which is functionalized first at the 2-position and is then aromatised. Allylic oxidation of limonene with t-but - chromate [2] and chromium trioxide–pyridine complex [3] gives a mixture of 3- and 6-carbonyl derivatives and their hydroxy compounds which are difficult to separate. Aerial oxidation also yields a complex mixture [2]. On the other hand limonene gives an addition compound with nitrosyl chloride which on dehydrohalogenation and subsequent treatment with strong acids gives pure carvacrol. All the intermediates in this route are crystalline compounds and can be easily purified.



(I) (II) (III) (IV)

The preparation of limonene nitrosochloride (IV) has been carried out by the addition of nitrosyl chloride [4,9] and by the action of ethyl nitrite, amyl nitrite [5] or nitrogen trioxide [6] in the presence of hydrochloric acid. The conversion of the nitrosochloride to carvoxime [V] has been affected through the use of alcoholic alkali [7], sodium methoxide [8], urea [9] and pyridine [10] in acetone.

The present studies are a part of the project [11] to utilise limonene which will be available to the extent of 250,000 kg annually from the deterpenation of the orange oil alone.

The method for the production of carvacrol has been improved upon and much simplified resulting in higher yields with greater purity of the product as well. Instead of below zero temperatures for the production of limonene nitrosochloride, comparatively moderate temperatures (0 – 4°) can be employed in the process reported here.

EXPERIMENTAL

Materials. Limonene was obtained from the orange oil which contains 85–90% of this terpene. It was a by-product of the deterpenation of orange oil. The deterpenation was carried out by fractional distillation and the fraction boiling between 172 –180° was collected and redistilled to obtain a fraction boiling at 176–178°. The IR and GLC of this fraction were identical with those of a pure limonene sample. Commercial ethanol was kept over calcium oxide overnight, refluxed for 4 hr and then distilled from calcium oxide. Commercial sodium nitrite, urea and purified hydrochloric acid (free from dissolved chlorine and other impurities) were used in the present studies.

Procedure

Limonene nitrosochloride (IV). Limonene (136 g, 1 mole), sodium nitrite (72 g, 1.04 mole), ethanol (175 ml)

and water (100 ml) were placed in a three-necked flask equipped with a dropping funnel, a mechanical stirrer and a thermometer to record the temperature of the reaction mixture. A mixture of ethanol (175 ml) and purified hydrochloric acid (250 ml; ~ 2.5 mole) was placed in the dropping funnel. The reaction flask was cooled (ice-salt freezing mixture) and the addition of alcoholic hydrochloric acid was so regulated as to maintain a temperature of 0°–5° of the reaction mixture. It took 3 hr to add the required quantity of the acid. After the addition has been made, stirring was continued for another hour and the mixture was then allowed to stand and crystallise at low temperature. The solid material was filtered and a crude product weighing 195 g was obtained. It was stirred with 350 ml of chilled ethanol and filtered to obtain 181 g (90%) of white crystalline limonene nitrosochloride; m.p. 102–103°. (lit [12] m.p. 103–104°); IR (nujol) ν_{max} 2850, 1645 (>C = CH_2) 1450, 1375, 1205, 1185, 1155, 887 (>C = CH_2) cm^{-1}.

Carvoxime (V). Limonene nitrosochloride (150 g, 0.74 mole) in absolute ethanol (300 ml) was refluxed with urea (60 g; 1 mole) on a water-bath for 1 hr. The reaction mixture at the end was poured on broken ice and the product was filtered after the ice had melted. The solid carvoxime was washed thoroughly with cold water and spread over a filter sheet to let it dry at room temperature. The dry product weighed 113 g; yield 92%; m.p. 67–70° (lit [9] m.p. 65–72°); IR (nujol) ν_{max} 2830, 1645, (>C = CH_2), 1450, 1370 (nujol), 965, 945, 907, 887 (>C = CH_2) cm^{-1}.

Carvacrol (I). Carvoxime (55 g; 0.33 mole) was added to 15% aqueous sulphuric acid (300 ml) and the mixture was stirred on a water-bath for 1 hr. The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 ml). The combined organic layer was washed with brine once and dried (Na_2SO_4). It was fractionally distilled to obtain 36 g of pure carvacrol (yield 72%); b.p. 235–237° (lit [12] b.p. 236–237); IR (film) ν_{max}, 3350 (–OH), 3030, 2990, 1630, 1575, 1425, 1250, 995, 935, 865, 810, 715 cm^{-1}; UV (EtOH) λ_{max} 234 nm (ϵ 22000). The product was completely soluble in 5 per cent aqueous sodium hydroxide.

Table 1. Effect of temperature and hydrochloric acid on the percentage yield of limonene nitrosochloride.

HCl (ml)	Yield (%)		
	–7°	0°	15°
150	31	32	21
200	82	81	60
250	90	91	40
400	72	54	20

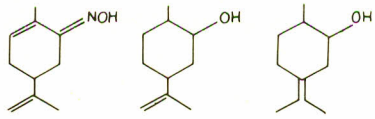
Conversion of Carvone to Carvacrol. (i) Synthetic carvone (10 g) was stirred with 1*N* aqueous sulphuric acid (50 ml) on a water-bath for 3 hr. The organic layer on GLC showed it to be a mixture of carvone (60%) and carvacrol (40%).

(ii) Carvone (10 g) was heated at 200° with 5% palladium on charcoal for 3 hr. Nitrogen was bubbled through the reaction mixture. At the end, the product was filtered and the GLC analysis showed it be almost pure carvacrol with no trace of carvone left in it.

RESULTS AND DISCUSSION

Limonene (III) has two double-bonds; one is endocyclic and the other is part of an isopropyl side-chain. The reactivity of the two double-bonds towards an approaching reagent is different because of the substitution pattern. The trisubstituted endocyclic double bond is more electrophilic and can, therefore, be preferentially attacked on this site to produce valuable chemicals from limonene.

The synthesis of carvacrol involved (a) the production of limonene nitrosochloride, (b) dehydrochlorination of the nitrosochloride to carvoxime, and (c) hydrolysis alongwith isomerisation of carvoxime to carvacrol. The limonene nitrosochloride was produced by the addition of concd hydrochloric acid to a cooled and stirred mixture of limonene, sodium nitrite, ethanol and water. It was a one-pot reaction in which the production of nitrosyl chloride and its addition to limonene was carried out simultaneously. Hydrochloric acid reacted with sodium nitrite in the flask to produce nitrous acid which with ethanol yielded ethyl nitrite *in situ*. Another moel of concentrated hydrochloric acid acted upon ethyl nitrite to yield the required nitrosyl chloride in the same mixture. The nitrosyl chloride preferentially attacked 1:2-double bond of limonene and a white product (m.p. 102–103) was thus obtained.



(V) (VI) (VII)

Addition of HCl (concd) and stirring was so regulated as to maintain the temperature of the reaction mixture around 0°. Rapid addition of the acid with poor stirring of the reaction contents resulted in poor yields of the nitrosochloride because of the localised heating. Temperature had a marked influence on the yield of the product (Table 1). As the temperature of the reaction pot was allowed to rise above 5°, the yield dropped down drastically and the major product was a resinous material which did not crystallise. Probably at higher temperatures, the

addition of nitrosyl chloride took place unscrupously at the 1:2 and 8:9 double bonds to give a mixture or the addition compound. The compound so formed decomposed in the presence of excess of strong acid and nitrosyl chloride to yield a resinous product. An excess of the required two moles of HCl (concd; ~ 2.5 moles) was used to obtain the optimum yield of the limonene nitrosochloride. Large excess of the acid had a deterimental effect on the yield (Table 1). Excess of sodium nitrite, however, had no influence on the course of the reaction.

The dehydrochlorination of the limonene nitrosochloride was affected with urea which was used as a mild base. Absolute ethanol and isopropanol were employed as solvents. The dryness of the alchols was essential as the aqueous alcohols drastically lowered the yield of the carvoxime 80, 95 and 99% ethanol yielded 20, 50 and 92% of carvoxime respectively. Potassium hydroxide (0.1%) in absolute ethanol also gave similar yields of the oxime. Carvoxime on stirring with 15% sulphuric acid for 1 hr on a steam-bath gave carvacrol which was separated and distilled to remove the impurities. Carvacrol could also be produced by the isomerisation and dehydrogenation of carvone with 5% Pd/C at 200°. The reaction probably goes through an intermediate triene-ols (VI) anc (VII). Heating and stirring of carvone with sulphuric acid (1*N*) yielded a mixture.

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