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IMPROVED METHOD OF OBTAINING PIPERITONE

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UDC 542.941/942+547.596.7

A new convenient variant of the reduction of thymol methyl ether by lithium and isopropanol in the presence of ethylenediamine at 80-85°C and a molar equivalent ratio of ether to alcohol to amine to metal of 1:(8-12):(2.5-3):(4-6) has been developed. The proposed method permits the yield of piperitone to be doubled in comparison with known methods.

One of the main components of essential oils from medicinal raw material is p-menth-1-en-3-one (piperitone) (I) [1], which is also used in fine organic synthesis [2].

In natural sources, piperitone is present in admixture with terpene alcohols and its isolation is associated with considerable experimental difficulties. Of synthetic methods, the most convenient are the reduction of thymol ethers with alkali metals in liquid ammonia and ethanol [3] and with calcium hexaammoniate in the presence of isopropanol and isobutanol [4] followed by isomerization and acid hydrolysis of the dihydro derivatives obtain A disadvantage of these methods is the use of large amounts of carefully purified liqu m-monia and of a pyrophoric metal ammoniate. The reduction of thymol ethers with alka tals and alkaline-earth metals and a mixture of amines requires large amounts of the latt p to 47 moles per mole of the ether) [5-7], and in all the cases described the yield o iperitone does not exceed 23%.

We have recently established that on the reduction of anisole and its methyl-substituted derivatives with lithium and isopropanol in the presence of 0.25-1.0 mole of ethylenediamine the yield of 1,4-dihydro derivatives reaches 70-72% [8].

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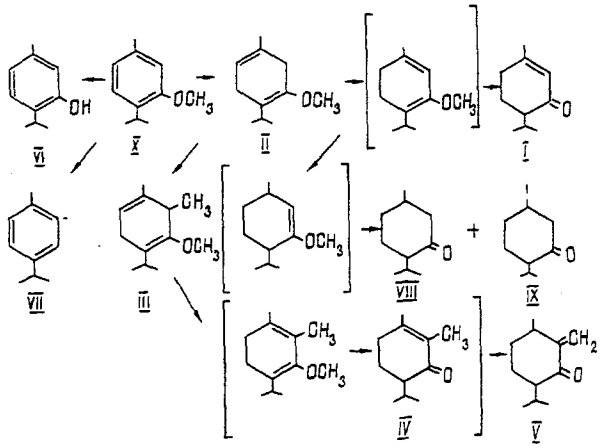
TABLE 1. Preparation of Piperitone

Amounts of reagent, moles or g-equiv. per 1 mole of thymol ether			Yield of oil, wt.-%	Conversion, %	Composition of the reaction products, wt. %					Yield piperitone, wt. %
lithium	isopropanol	ethylenediamine			piperitone (I)	mixture of methone and isomenthone (VIII) and (IX)	6-isopropyl-3-methyl-2-methylenecyclohexanone (V)	thymol (VI)	p-cymene (VII)	
2	4	1	84*	38	63	6	31	—	—	19
4	8	2	86	60	67	9	24	—	—	32
6	12	2,5	87	75	74	6	20	—	—	49
6	13	3	85	73	67	6	20	7	—	42
4	4	29 [6]	58	65	25	13	—	60	2	9
Birch's method [3]			78	39	38	28	—	27	7	12
Calcium hexaammonate—mixture of isopropanol and isobutanol [4]			79	44	64	7	—	25	5	23

*On reduction with the lithium—isopropanol—ethylenediamine system the reaction products contained 1-2% of high-molecular-mass compounds, and by methods [3] and [4] 10 and 8%, respectively.

In the present work we have shown that a 3-3.3-fold increase in the amount of isopropanol and a decrease in the amount of ethylenediamine from 29 to 2.5-5.0 moles doubles the yield of piperitone in comparison with the known method [9] (Table 1).

The capacity for the alkylation by alcohols of compounds containing activated methylene groups [10] means that C-2 of the ether (II) is alkylated by the methanol formed as the result of hydrolysis. The methyl-substituted ether (III) obtained is converted by the usual scheme into 6-isopropyl-2,3-dimethylcyclohex-2-enone (IV), which isomerizes into 6-isopropyl-3-methyl-2-methylenecyclohexanone (V).



It can be seen from Table 1 that in the proposed variant the hydrogenolysis of the initial ether with the formation of thymol (VI) and p-cymene (VII), the separation of which from piperitone even by precision rectification, is not a simple task, takes place to a considerably smaller degree than in the other methods described.

EXPERIMENTAL

GLC analysis was conducted on an LKhM 8 MD chromatograph with a thermal conductivity detector in a 3 × 3000 mm column filled with Inerton N-AW-DMCS (0.20-0.25 mm) impregnated with 10% of 1,2,3-Tris-(2-cyanoethoxy)propane. The column temperature was 160°C and the carrier gas nitrogen at the rate of 40 ml/min. The menthone and isomenthone were identified by the addition of authentic compounds. The relative retention times of the substances were: (I) – 2.77; (V) – 1.50; (X) – 1.00; (II) – 0.62; and (VIII and IX) – 0.44. The IR spectra of the compounds obtained were recorded in thin layers on a UR-20 spectrometer, the UV spectra of ethanolic solutions of the substances on an SF-4D spectrophotometer, and the PMR spectra on a Varian HA-100 spectrometer with a working frequency of 100 MHz using solutions

(c ~ 5 vol. %) in $CDCl_3$, with TMS as internal standard. ^{13}C NMR spectra were taken on a Bruker WH-90 spectrometer with a working frequency of 90 MHz. To obtain the carbon spectra we used 30% (by volume) solutions of the compounds in $CDCl_3$ with TMS as internal standard, the duration of a pulse being 8 μsec with a delay of 5 sec.

Reduction of 1-Isopropyl-2-methoxy-4-methylbenzene (X). At 85-90°C, with stirring, 41 g of lithium was added in finely cut pieces to a mixture of 164 g of 1-isopropyl 2-methoxy-4-methylbenzene, 754 g of isopropanol, and 180 g of ethylenediamine. The reaction mixture was stirred until the lithium had dissolved completely (~30 min) and it was then separated off, and 1000 ml of water was added. The organic layer was separated off and was washed with water (5 × 200 ml) and dried with Na_2SO_4. This gave 139 g (85% of theoretical) of an oily product with n_D^{20} 1.4825, from which, by rectification in a column with an efficiency of 70 t.p. we isolated 1-isopropyl-2-methoxy-4-methylcyclohexa-1,4-diene (II). Purity 98%, bp 109-110°C (18 mm Hg), d_4^{20} 0.9268, n_D^{20} 1.4865, MR_D 51.5. Calc. 51.5. Found, %: C 79.1; H 10.8. $C_{11}H_{18}OF_2$. Calculated, %: C 79.5; H 10.9. The compound was characterized by the absence of an absorption maximum in the UV spectrum at 225-300 nm. IR spectrum (ν, cm^{-1}): 3030, 1660, 825 (C=CH), 1375, 1365 [$CH(CH_3)_2$], 1150, 1055 (C–O–C). PMR spectrum (δ, ppm): 0.95 d [6H, J 6.9, $CH(CH_3)_2$], 1.66 s (3H, CH_3–C=C), 2.70 m (4H, $2CH_2$), 2.93 sept (1H, CH), 3.56 s (3H, CH_3O), 4.67 m (1H, C=CH). ^{13}C NMR spectrum (δ, ppm): C-1 133.2, C-2 36.1, C-3 153.3, C-4 122.0, C-5 25.3, C-6 91.3, C-7 18.6, C-8 29.4, C-9, 10, 21.3, C-11 54.3.

Piperitone (I). A mixture of 8.5 g of 1-isopropyl-2-methoxy-4-methylcyclohexa-1,4-diene and 210 ml of 5% HCl was heated at 90°C for 2 h and was then cooled to room temperature. The organic layer was separated off and was washed with water (3 × 50 ml) and dried with Na_2SO_4. Distillation of the oil obtained (7.4 g) gave piperitone with a yield of 98%, bp 110-111°C (15 mm Hg), d_4^{20} 0.9529, n_D^{20} 1.4920, MR_D 46.3. $C_{10}H_{16}OF$. Calc. 45.7. UV spectrum [C_2H_5OH, λ_{max}, nm (log ε)]: 238 (4.01). Calc. λ_{max} 239 nm. IR spectrum (ν, cm^{-1}): 3020, 1620, 865 (C=CH), 1675 (C=O), 1510 (C=C–C=O), 1380, 1345 [$CH(CH_3)_2$]. PMR spectrum (δ, ppm): 0.83 d and 1.03 d (6H, J 6.4, $2CH_3$), 1.97 s (3H, CH_3–C=C), 1.75-2.55 m (6H, 2CH, $2CH_2$), 5.95 m (narrow multiplet due to long-range constants, 1 H, C=CH). ^{13}C NMR spectrum (δ, ppm): C-1 196.6, C-2 129.6, C-3 162.3, C-4 36.5, C-5 23.9, C-6 46.3, C-7 18.9, C-8 29.6, C-9, 10 22.4 and 23.3. According to the literature [6]: purity 92%, d_4^{20} 0.9327, n_D^{20} 1.4842. IR spectrum (ν, cm^{-1}): 1660 (C=O), 1385, 1365 [$CH(CH_3)_2$]. ^{13}C NMR spectrum (δ, ppm) [11]: C-1 200.0, C-2 126.8, C-3 160.5, C-4 30.5, C-5 23.2, C-6 51.6, C-7 23.9, C-8 25.9, C-9, 10 18.5 and 20.6.

6-Isopropyl-3-methyl-2-methylenecyclohexanone (V). To 42.4 g of the product of the reduction of ether (I) was added 1050 ml of 5% HCl. The mixture was heated at 90°C for 2 h and was then cooled to room temperature and the organic layer was separated off and was washed with water (3 × 100 ml) and dried with Na_2SO_4. The resulting oil (36 g) was rectified in a column with an efficiency of 70 t.p., giving 6-isopropyl-3-methyl-2-methylenecyclohexanone (V). Purity 80%. Subsequent chromatography on alumina (activity grade II) (with hexane as eluent) yielded a sample with a purity of 98%, d_4^{20} 0.9471, n_D^{20} 1.4835, MR_D 50.1. $C_{11}H_{18}OF$. Calc. 50.1. Semicarbazone, mp 185-186°C. Found, %: C 63.8, H 9.7, N 19.3. $C_{12}H_{21}N_3O$. Calculated, %: C 63.3, H 9.8, N 19.7. UV spectra of compound (V) [C_2H_5OH, λ_{max}, nm (log ε)]: 228 (4.05). Calc. λ_{max} 230 nm. IR spectrum (ν, cm^{-1}): 3045, 1620, 895 (C=CH_2), 1690 (C=O), 1505 (C=C–C=O), 1380, 1370 [$CH(CH_3)_2$]. PMR spectrum (δ, ppm): 0.72 d, 0.90 d (9H, J 6.8, 4.4, 6.5, $3CH_3$), 1.24-2.39 m (7H, 3CH, $2CH_2$), 5.88-6.60 m (2H, C=CH_2). According to the literature [12]: UV spectrum [CH_3OH, λ_{max}, nm (log ε)]: 230 (3.79). IR spectrum (ν, cm^{-1}): 1695 (C=O), 1613 (C=CH_2).

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MODIFIED OXIDATION OF (+)-3-CARENE BY POTASSIUM PERMANGANATE

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UDC 547.313+542.943

The oxidation of (+)-3-carene under the conditions of phase-transfer catalysis has been studied. It has been shown that when the reaction is performed in acetic acid the keto acids (IIa) and (IIIa) and (−)-3α-hydroxycaran-4-one (IV) are formed.

The synthesis of optically active pyrethroids from (+)-3-carene, which is a readily available product of wood chemistry is fairly urgent. In the development of our investigations in this direction we have studied the oxidative cleavage of (+)-3-carene under the action of $KMnO_4$ using phase-transfer catalysis.

It has been shown previously that the oxidation of (+)-3-carene by the action of $KMnO_4$ forms mainly neutral products [1], while the yield of caronic and homocaronic acids is insignificant [2, 3], while on the oxidation of (+)-3-carene with $KMnO_4$ in H_2O—AcOH keto acids are formed [4]. In recent years, definite advances have been achieved in the use of phase-transfer catalysis (PTC) for the oxidation of unsaturated compounds by $KMnO_4$ [5]. It appeared desirable to investigate the oxidation of (+)-3-carene by $KMnO_4$ under PTC conditions with the aim of obtaining the acids (II) and (III).

(+)-3-Carene was oxidized with $KMnO_4$ at room temperature under PTC conditions. In the benzene/Bu_4NBr, benzene/DB18C6, acetone/DB18C6, and water/DB18C6 systems the yield of acids was 8%, and of these caronic and homocaronic acids amounted to not more than 2%. The composition of the neutral fraction was practically the same as in the results published previously [1].

The oxidation of (+)-3-carene in the $KMnO_4$/AcOH/H_2O/Bu_4NBr system gave us 31% of neutral products and 50% of an acid fraction, the GLC analysis of which after esterification with CH_2N_2 showed the presence of 22.8% of the keto ester (IIb) and 23.3% of the keto ester (IIIb). When the Bu_4NBr was replaced by TEBAC, the yield of neutral products amounted to 48% and that of acid products to 38%. The amount of the keto ester (IIb) after the esterification of the acid fraction with CH_2N_2 was 3%, and that of the keto ester (IIIb) 36.6%. The oxidation of (+)-3-carene with $KMnO_4$/AcOH/H_2O gave 38.5% of neutral products of 35% of a mixture of acids the GLC analysis of which after esterification with CH_2N_2 showed the presence of 20.5% of the keto ester (IIb) and 60% of the keto ester (IIIb).

Thus, the use of phase-transfer catalysis substantially increases the yield of the acids (II) and (III) (see top of following page).

The products of neutral character also consisted of a mixture of substances in which the amount of the main substance (IV) was 76.5% on oxidation in the presence of Bu_4NBr, 40%

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