Synthesis of (*R*)-(–)-Carvone Derivatives

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(*R*)-(–)-Carvone, the main constituent of spearmint oil, has several synthetic applications and is used in cosmetics, food, and pharmaceutical preparations. In a recent study we demonstrated that (*R*)-(–)-carvone shows significant analgesic activity. In the present report, (*R*)-(–)-carvone derivatives which have pharmacological potential are described. These compounds can be used in studies of structure-activity relationship to develop novel drugs.

Key words: Terpenes, Essential Oils, *p*-Menthanes, Structure-Activity Relationship

Introduction

Carvone (*p*-mentha-6,8-dien-2-one) is a representative monoterpene ketone. The best-known source of (*R*)-(–)-carvone is spearmint oil (*Mentha spicata*), which is steam-distilled from the leaves of the plant, whereas the (*S*)-enantiomer of carvone is a constituent of dill and caraway oils [1 – 3]. Among terpene chirogens the carvones ((+)- and (–)-forms) are probably the most versatile. They have been used in the synthesis of diverse intermediates and natural compounds, principally other terpenoids [3 – 5].

Developing treatments for pain relief has been the motivating factor behind many studies carried out by academic investigators, and in the pharmaceutical industry, in response to the demand for powerful analgesics that exhibit pharmacological response through new mechanisms of action and lower side effects. It has been shown that monoterpene derivatives exhibit several types of pharmacological properties, such as antinociceptive [6, 7], sedative [8], and antidepressant [9] activity. The antinociceptive activity of (*R*)-(–)-carvone (**1**) and monoterpene analogs has also been demonstrated [10]. Recently, we investigated the analgesic potential of the *p*-toluenesulfonamide, a synthetic derivative of (*R*)-(–)-carvone (**1**). This sulfonamide shows a more potent pharmacological effect than (*R*)-(–)-carvone itself [11]. These facts led us to synthesize structurally related new (*R*)-(–)-carvone derivatives with pharmacological potential.

Results and Discussion

In this study we synthesized a series of *p*-menthane derivatives using (*R*)-(–)-carvone as starting material. In the first step, the reaction of (*R*)-(–)-carvone with potassium cyanide and acetic acid in ethanol under the published conditions [12] produced the ketonitrile **2** (Scheme 1). Reduction of compound **2** with sodium borohydride gave a 96 : 4 mixture of the cyanoalcohols **3a** and **3b** in 97 % yield. Dehydration of the secondary cyanoalcohols **3** using *p*-toluenesulfonyl chloride afforded the nitrile **4** in 48 % yield. Reduction of compound **4** with $LiAlH_4$ gave the free amine **5** in 91 % yield.

The synthesis of terpene derivatives often results in compounds with stereogenic centers and high stereoselectivity. The monoterpene starting materials are readily available, frequently in both enantiomeric forms, and contain the scaffolds of the desired mono-, sesqui-, and diterpene skeletons. The range of pharmacological activity that has been recorded for terpenes is remarkably wide. Terpene derivatives also exhibit several effects on the central nervous system (CNS), including analgesic activity [6, 7], apparently due to a variety of action mechanisms. Actually, terpene derivatives have shown pharmacological activity better than the terpene starting materials [6, 7, 11]. The best pharmacological profile arises upon addition of functional groups to the terpene chemical structure. The psychopharmacological activity of compounds of this group must originate

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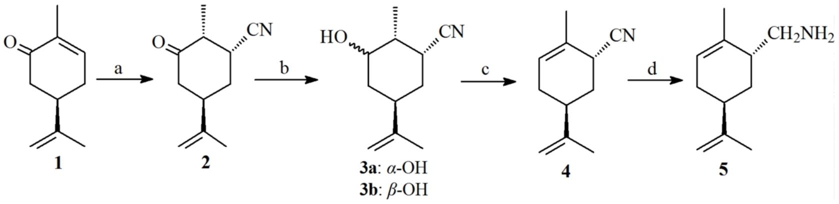

Scheme 1. Reagents and conditions: (a) KCN, EtOH, H_2O, acetic acid, 0 °C, 16 h, 90 %; (b) $NaBH_4$, MeOH, r. t., 5 min, 97 %; (c) TsCl, Py, 120 °C, 30 h, 48 %; (d) $LiAlH_4$, diethyl ether, 0 °C, 10 min, 91 %.

from the presence of a highly lipophilic bulky fragment which is capable of directly interacting with CNS membranes containing a lipid layer, as well as with hydrophobic fragments of proteins. Through appropriate structural modification of terpenes it should be possible to develop novel drugs with greater specificity in the pharmacological action. Therefore, the new compounds synthesized in this study have a high potential as psychoactive drugs that may have application in medical practice.

Experimental Section

General

GLC analyses were performed on a Shimadzu GC-17A instrument equipped with a flame-ionization detector, using a DB-1 (30 m × 0.25 mm) glass column. Column chromatography was performed on silica gel 60 (70 – 230 mesh ASTM Merck). Radial thin-layer chromatography was carried out on a Chromatotron model 8924 (silica gel 60PF274 Merck). Melting points were determined on a Microquimica MQWAPF-301 apparatus and are uncorrected. Infrared spectra were recorded with a Bomen Hartman & Braun MB-Series spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker ARX-200 spectrometer or at 400 and 100 MHz on a Bruker DRX-400 spectrometer, in $CDCl_3$ with TMS as internal standard. The mass spectra were recorded on a Micromass mass spectrometer Quattro LC, coupled with a chemical ionization source (reagent MeOH) under atmospheric pressure (APCI). Microanalyses were performed on a Fisons EA 1108 CHNS-O analyzer at the Chemistry Department, Universidade Federal de São Carlos. Solvents were purified prior to use: ethyl acetate and hexane were refluxed over P_2O_5, distilled and stored over molecular sieves; pyridine was stirred and refluxed over KOH, distilled and stored over KOH. Tetrahydrofuran (THF) was distilled from sodium under nitrogen.

*(–)-(1R,2R,5R)-2-Methyl-5-(1′-methylvinyl)-3-oxocyclohexanecarbonitrile (**2**)*

Reaction of (*R*)-(–)-carvone (**1**) (12.50 g) with hydrogen cyanide gave nitrile **2** in 90 % yield; m. p. 91.5 – 92.2 °C, $[\alpha]_D^{30}$ = –3.8 (*c* = 1.20 in $CHCl_3$) [lit. [12]: 93 – 94 °C, $[\alpha]_D^{18}$ = –4.0 (*c* = 1.04 in $CHCl_3$)]. ^{1}H and ^{13}C NMR data were in agreement with the literature [12].

*(1R, 2S, 4R, 6R)-6-Cyano-8-p-menthen-2-ol (**3a**) and (1R, 2R, 4R, 6R)-6-cyano-8-p-menthen-2-ol (**3b**)*

A 50 mL flask with a magnetic stirrer was charged with a solution of 0.50 g (2.82 mmol) of the carbonitrile **2** in methanol (6 mL). After addition of 0.15 g (3.95 mmol) of sodium borohydride the reaction mixture was stirred for 5 min at r. t. After addition of CH_2Cl_2 (40 mL), followed by a saturated solution of NaCl (15 mL), the mixture was washed with water (15 mL). Filtration yielded a clear solution which was dried over anhydrous sodium sulfate. The cyanoalcohols **3a** and **3b**, in a 96 : 4 ratio by gas chromatographic analysis, were isolated by removal of the solvent under reduced pressure (0.49 g, 2.73 mmol, 97 % yield). The **3a/3b** mixture was subjected to column chromatography on silica gel, eluting with hexane – EtOAc (1 : 1) to afford the cyanoalcohol **3a** (0.45 g, 89 % yield). Compound **3a**: $[\alpha]_D^{27}$ = +2.4 (*c* = 2.1, $CHCl_3$). – IR (film): ν = 3479, 2934, 2236, 1644, 993, 896 cm^{-1}. – ^{1}H NMR: δ = 4.80 – 4.77 (1H, m), 4.75 (1H, s), 2.95 – 2.99 (1H, m), 2.85 (1H, td, *J* = 4.8 Hz, 2.8 Hz), 2.69 (1H, tt, *J* = 12.5 Hz, 3.0 Hz), 2.13 – 2.05 (1H, m), 1.75 (3H, s), 1.72 – 1.65 (2H, m), 1.61 (1H, s), 1.53 – 1.42 (2H, m), 1.26 (3H, d, *J* = 12.2 Hz). – ^{13}C NMR: δ = 147.8, 121.6, 109.7, 69.9, 38.1, 36.3, 33.8, 33.5, 30.4, 20.9, 16.3. – MS: *m/z* = 180 [M+1]$^+$. – Anal. for $C_{11}H_{17}NO$: calcd. C 73.70, H 9.56, N 7.81; found C 73.62, H 9.58, N 7.79.

*(6R, 4S)-6-Cyano-p-mentha-1,8-diene (**4**)*

To a solution of the cyanoalcohols **3a**, **b** (4.00 g, 22.34 mmol) in dry pyridine (6.5 mL, 80.42 mmol) stirred under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (4.69 g, 24.58 mmol) at r. t. The solution was heated to 120 °C for 30 h, and then cooled to r. t. Hexane (15 mL) and HCl 1M solution (1.0 M solution, 20 mL) were then added. The reaction mixture was extracted with hexane, washed with saturated copper sulfate, water, and sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane – EtOAc, 90 : 10) on silica gel to yield the pure product **4** (1.74 g, 10.80 mmol, 48 % yield). Compound **4**: $[\alpha]_D^{27}$ = +233.0 (*c* = 1.5, $CHCl_3$). – IR (film): ν = 2922, 2237, 1645, 892 cm^{-1}. – ^{1}H NMR:

δ = 5.68 – 5.64 (1H, m), 4.80 (1H, quin, J = 1.4 Hz), 4.74 (1H, quin, J = 0.8 Hz), 3.15 – 3.10 (1H, m), 2.54 – 2.35 (1H, m), 2.23 – 2.07 (2H, m), 1.84 – 1.82 (3H, m), 1.79 – 1.72 (2H, m), 1.76 (3H, s). – ^{13}C NMR: δ = 147.5, 126.9, 126.1, 120.9, 109.7, 37.1, 31.6, 30.8, 30.1, 21.7, 20.7. – MS: *m/z* = 162 [M+1]$^+$. – Anal. for $C_{11}H_{15}N$: calcd. C 81.94, H 9.38, N 8.69; found C 82.01, H 9.40, N 8.66.

*(6R, 4S)-6-Aminomethylene-p-mentha-1,8-diene (**5**)*

A dry, nitrogen-purged, 50 mL three-necked flask with a magnetic stirrer was charged with a suspension of lithium aluminum hydride (0.19 g, 5.15 mmol) in anhydrous ether (6.2 mL). A solution of 0.41 g (2.57 mmol) of nitrile **4** in ether (6.2 mL) was added dropwise over 10 min to this suspension maintained at 0 °C, and the stirring was continued for further 10 min. Destruction of the excess lithium aluminum hydride was completed by cautious dropwise addition of water (6 mL), 15 % NaOH (6 mL) and again water (18 mL). Stirring was continued until a granular colorless precipitate was formed. Filtration yielded a clear ether solution which was washed with water (20 mL) and dried over anhydrous sodium sulfate. The free amine was isolated by removal of the ether under reduced pressure (0.38 g, 2.32 mmol, 91 % yield). Compound **5**: $[\alpha]$ = +88.3 (c = 1.2, $CHCl_3$). – IR (film): ν = 3376, 2922, 1644, 1037, 887 cm^{-1}. – ^{1}H NMR: δ = 5.48 – 5.44 (1H, m), 4.72 (2H, t, J = 0.9 Hz), 2.88 (1H, dd, J = 13.0 Hz, 3.4 Hz), 2.61 (1H, dd, J =12.7 Hz, 9.2 Hz), 2.25 – 2.13 (1H, m), 2.24 – 2.13 (1H, m), 2.04 (2H, s), 1.94 – 1.82 (2H, m), 1.74 (3H, s), 1.48 (3H, s), 1.45 – 1.37 (2H, m). – ^{13}C NMR: δ = 149.7, 134.2, 122.9, 108.5, 43.9, 43.0, 36.0, 30.9, 29.3, 22.0, 20.7. – MS: *m/z* = 166 [M+1]$^+$. – Anal. for $C_{11}H_{19}N$: calcd. C 79.94, H 11.59, N 8.47; found C 79.88, H 11.62, N 8.49.

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