CINEOLIC ACID DERIVATIVES: REGIOSELECTIVE SYNTHESIS, NMR AND MS STUDIES

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Abstract

The synthesis of several derivatives of cineolic acid is reported. Based on NMR and MS studies the regioselectivity of some reactions is demonstrated.

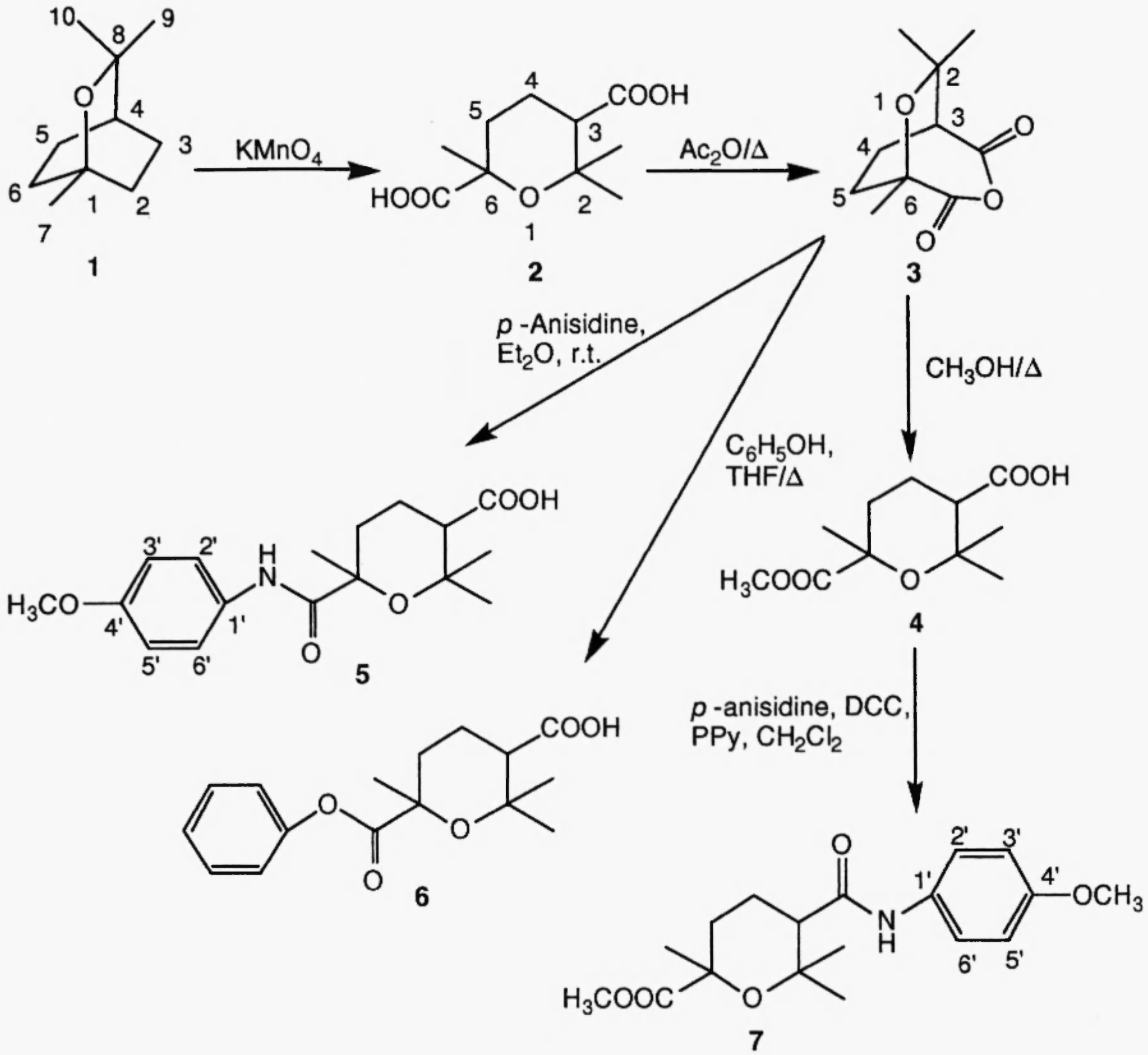
INTRODUCTION

Cineolic acid, (2,2,6-trimethyltetrahydropyran-3,6-dicarboxylic acid) **2**, can be obtained by oxidation of 1,8-cineole **1** with potassium permanganate in alkaline aqueous solution (1). This acid can be converted into cineolic anhydride **3** by its heating in acetic anhydride. The transformation of **3** into the monomethyl ester **4** has been considered to be regioselective, although no spectroscopic evidence was put forward (2).

As part of a program aiming to obtain new products from cheap and abundant natural compounds, the synthesis of several new derivatives of cineolic acid **2** has been undertaken; based on NMR and MS studies, it has also been possible to demonstrate unequivocally the regioselectivity of the reactions involved.

RESULTS AND DISCUSSION

Reaction of **3** with *p*-anisidine or phenol gave, respectively, the amide **5** or the ester **6**. The 3-carboxanilide **7** was synthesised from acid **4** with *p*-anisidine, using dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-pyrrolidinopyridine (PPy) (3,4). Products **5**, **6** and **7** were purified by thin layer chromatography on silica gel eluting with mixtures of ethyl acetate:petroleum ether, and crystallised from petroleum ether:dichloromethane.



Scheme 1

The products obtained were characterised by ^{1}H and ^{13}C NMR, HETCOR (^{1}H/^{13}C), DEPT, INEPT, HMBC (in the case of compounds 2 and 7) and also by e.i.-MS. Carbon resonance assignments of the carboxylic acid groups of compound 2 were based on the proton-coupled ^{13}C NMR spectra: signal at δ 175.9 ppm is due to the 3-COOH carbon atom resonance and appears as a doublet ($^2J_{CH}$ 6.9 Hz), due to the coupling with H_3. At δ 178.2 ppm a double quartet ($^3J_{CH}$ 7.9 Hz, $^3J_{CH}$ 3.4 Hz) is assigned to the 6-COOH carbon resonance, which couples with 6-CH$_3$ and H-5 *equatorial* protons. These assignments were made in an unequivocal way, using HMBC experiments (5). Correlation due to long-range couplings was found between H-3 proton and the carbon atom resonances at δ 75.4 and 175.9 ppm. The first signal was then attributed to the resonance of C-2 carbon atom, and the second one to 3-CO in agreement with our previous assignment. It was also possible to found the connectivity between the resonance of the 6-CH$_3$ protons and the signals at δ 32.5, 74.6 and 178.2 ppm. These resonances are due respectively to C-5, C-6 and 6-CO carbon atoms.

The assignments of the 6-CO and 3-CO carbon resonances became the key to confirm the regioselective synthesis of compounds 4-6 (6): for these, due to their functionalizations, shifts to lower frequencies (-1.5 to -3.2 ppm) in the carbon resonances of the 6-CO-substituents were observed, while 3-COOH remained as free carboxylic acid groups. For these groups the doublet resonances of the carbon atoms are not significantly affected (+0.1 to -0.2 ppm). Regioselectivity was also confirmed by one-dimensional selective INEPT measurements (7). These give the connectivity of a selected proton, by irradiation of the corresponding resonance, to the carbon atoms to which it is coupled and can be optimized for different long-range J (C/H) coupling. In the case of compound 4, on irradiation of the methoxyl proton resonance optimised for 7 Hz long-range J (C/H) coupling, enhancement of the signal at δ 176.7 ppm was observed; this signal was then assigned to the 6-CO carbon resonance. Similarly, on irradiation of the NH proton resonance of compound **5**, enhancements of the signals at δ 175.0 and 122.8 ppm were observed; the former signal was attributed to the resonance of 6-CO carbon, and the latter to the C-2',6' carbon atom resonances.

With compound 7, due to the 3-amide and 6-ester functionalizations, it was possible to assign the 3-CO and 6-CO carbon atom resonances: on irradiation of both the methoxyl groups' resonances the enhancements of the signals at δ 176.8 and 156.4 ppm were observed; these signals were attributed to 6-CO and C-4' carbon resonances. On irradiation of the NH proton resonance, enhancements on the signals at δ 172.3 and 122.6 ppm were observed, and such signals were attributed to 3-CO and C-2',6' carbon resonances.

The assignments of 3-CO and 6-CO carbon resonances of compound 7 were also confirmed using an HMBC experiment (5); the relevant connectivities are the following:

H-3 ----------> C-2, 2-CH$_3$ and 3-CO
H-5$_{eq}$ ----------> C-6 and 6-CO
6-CH$_3$ ----------> C-5, C-6 and 6-CO
N-H ----------> 6-CO and C-2',6'

For the diacid 2 the molecular ion, m/z 216, was not found in its mass spectrum, but there were two strong peaks at m/z 171 and m/z 153, corresponding to successive losses of CO$_2$H and

H_2O. In the mass spectra of compounds 4-6 similar intense peaks were also observed, suggesting that the first fragmentation corresponds to the loss of the 6-substituent, and the second fragmentation to the loss of a water molecule (Table 1). Finally, the fragmentation of 7 was characterised by a low intensity molecular ion at m/z 335, and strong peaks at m/z 276 and 153; in this way it is proposed that such peaks correspond to successive losses of groups $COOCH_3$ and $CH_3OC_6H_4NH_2$ being present in positions 6 and 3 respectively. Such MS fragmentation behaviour is then related with the substitution patterns of cineolic acid derivatives.

Table 1: Most Important Fragmentations of Compounds **2**, 4-7.

Compound	Mol. Ion	First Fragmentation		Second Fragmentation	
	m/z	m/z	loss of	m/z	loss of
2	-	171	$\cdot CO_2H$	153	H_2O
4	-	171	$\cdot CO_2CH_3$	153	H_2O
5	321	171	$\cdot CONHC_6H_4OCH_3$	153	H_2O
6	-	171	$CO_2C_6H_5$	153	H_2O
7	335	276	$\cdot CO_2CH_3$	153	$CH_3OC_6H_4NH_2$

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5. The long-range couplings in the HMBC experiments were optimized for 10 Hz. In this communication it is only considered the relevant information for the assignments of the 3-CO and 6-CO carbon resonances.
6. ^{13}C NMR spectra were determined at 75 MHz, in DMSO-d_6. For compounds 4,5 and 6 the chemical shifts (δ, ppm from TMS) of 3-CO and 6-CO are the following: 4 175.7 and 176.7; 5 176.0 and 175.0; 6 175.5 and 175.0.
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