# Chemical Transformation of 1,8-Cineole. Synthesis of *N*-Phenylimides from Cineolic Acid

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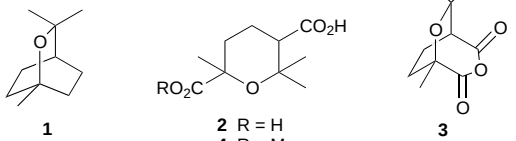
Chemical transformations of 1,8-cineole into cineolic acid derivatives, including *N*-phenylimides **6**, are reported; based on spectroscopic data the regioselectivity of some of the reactions and the heterocyclic ring conformation for each group of compounds have been established.

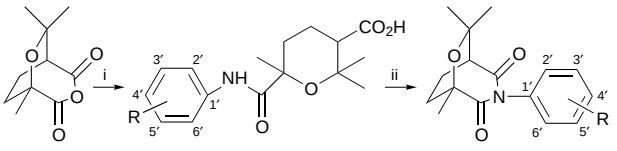
1,8-Cineole **1** is a very abundant component of the *Eucalyptus globulus* Labill. essential oil. It is a compound of very small economic significance and therefore any new application for it might contribute towards increasing its value.

Following previous work on the chemical modification of cineole[16,19] and on the synthesis of *N*-phenylimides[20] and taking into account that such compounds can be used as precursors in the synthesis of biologically active sulfonated imides,[21] studies on the synthesis of *N*-phenylimides from cineolic acid **2**, which can be obtained from 1,8-cineole, have now been undertaken.



**1** **2** R = H, **4** R = Me **3**

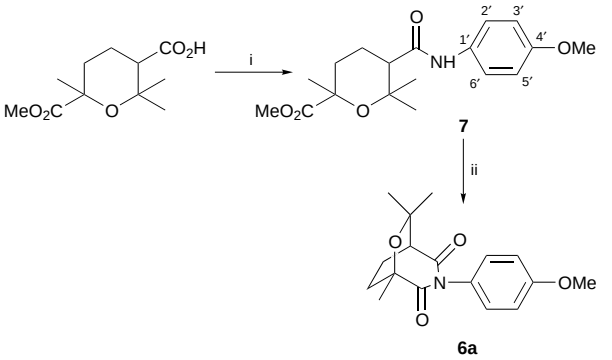
Cineolic acid **2** and the corresponding anhydride **3** and monomethyl ester **4** were prepared as described by Rae *et al*.[15] The synthetic route to the imides **6** was planned to follow the classical procedure shown in Scheme 2. 2,2,6-Trimethyl-6-phenylcarbamoyltetrahydro-2*H*-pyran-3-carboxylic acids **5** were regioselectively obtained in high yields, but their attempted cyclizations by refluxing in acetic anhydride were not successful and the carboxanilides **5** were quantitatively recovered after 24 h.



**3** **5** **a** R = 4′-OMe, **b** R = 4′-Br, **c** R = H, **d** R = 4′-Cl, **e** R = 3′-Cl, **f** R = 2′-Cl, **g** R = 4′-F **6**

**Scheme 2** *Reagents and conditions:* i, adequate aniline, $Et_2O$, room temp.; ii, $Ac_2O$, reflux

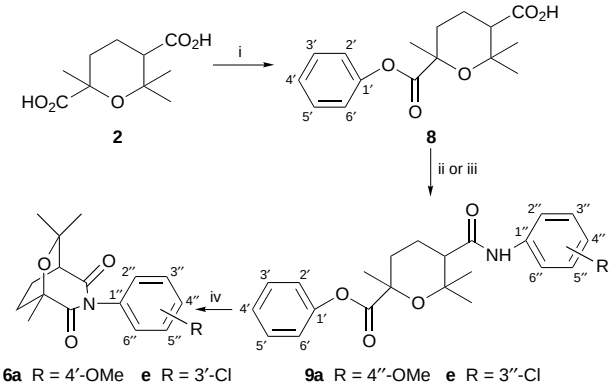
Enhancement of the nucleophilic character of the carboxanilide nitrogen, by abstraction of its proton, using sodium hydride, was expected to promote the cyclization. To proceed in such way, protection of the free carboxylic group was necessary. It was decided to use compound **4** with the 6-carboxylic group functionalized as an ester, and then to functionalize the 3-carboxylic group as a carboxanilide using a known procedure.[22] The desired imide **6a** was obtained, in very low yields, by refluxing **7** in dry tetrahydrofuran (THF), in the presence of sodium hydride (Scheme 3).



**7** **6a**

**Scheme 3** *Reagents and conditions:* i, *p*-anisidine, DCC, PPy, $CH_2Cl_2$, room temp.; ii, NaH, THF, reflux

To improve the yield of this reaction, protection of the 6-carboxylic group as a phenyl ester was considered. The phenyl ester **8** was synthesized regioselectively. This compound was then converted into the anilides **9** using two different procedures[22,23] as shown in Scheme 4; however, procedure iii gave better yields. Subsequently, the desired imides **6** were obtained in fairly good yields by refluxing **9** in dry THF in the presence of NaH.



**2** **8**

**6a** R = 4′-OMe, **b** R = 4′-Br, **c** R = H, **d** R = 4′-Cl, **e** R = 3′-Cl, **f** R = 2′-Cl, **g** R = 4′-F **9a** R = 4″-OMe, **b** R = 4″-Br, **c** R = H, **d** R = 4″-Cl, **e** R = 3″-Cl, **f** R = 2″-Cl, **g** R = 4″-F

**Scheme 4** *Reagents and conditions:* i, phenol, DDC, PPy, THF, room temp.; ii, adequate aniline, DCC, PPy, $CH_2Cl_2$, room temp.; iii, adequate aniline, cyanuric chloride, triethylamine, acetone, room temp.; iv, NaH, THF, reflux

The imides **6** were unstable: they completely hydrolysed on standing in solution in contact with moisture during 3 days, as was demonstrated with a test carried out with imide **6a**. Mass spectrometric studies on compound **10** showed that the hydrolysis was also regioselective (Scheme 5).

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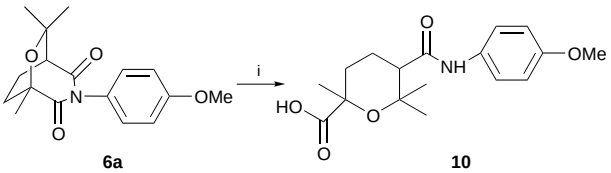


**6a** **10**

**Scheme 5** *Reagents and conditions:* $CHCl_3$, room temp., 3 days

The structures of all the products were unambiguously established by using several 1D and 2D NMR techniques and also by mass spectrometry. The regioselectivity observed[15,16] in the functionalization of **2** and **3** was further confirmed through NOESY experiments with compound **7**.

The conformation of the tetrahydropyran ring of compounds **2**, **4**, **5** and **7–10** was established on the basis of NMR data. Proton-coupled $^{13}C$ NMR of 6-*C*O and the multiplicity of the resonance of 3-H suggest that the tetrahydropyran ring is in a chair conformation. However, NOESY experiments carried out with compound **7**, as well as the one-dimensional selective INEPT spectrum of compound **8**, strongly suggest that in these compounds the tetrahydropyran ring is present in a distorted chair conformation.

Analysis of the mass spectra of compounds **2**, **4**, **5**, **7**, **8** and **9** revealed the possibility of determining the substitution pattern of the carboxylic acid groups and therefore of confirming the regioselectivity of some of the reactions previously described. Two important fragmentations were observed.

**Table 2** Most important fragmentations of compounds **2–10**

| Compound | 1st frag. (loss of) | 2nd frag. (loss of) |
|---|---|---|
| **2** | $\cdot CO_2H$ | $H_2O$ |
| **3** | CO | $H_2O$ |
| **4** | $\cdot CO_2Me$ | $H_2O$ |
| **5** | $\cdot CONHC_6H_4R$ | $H_2O$ |
| **6** | CO | $\cdot(RC_6H_4NH)$ |
| **7** | $\cdot CO_2Me$ | $MeOC_6H_4NH_2$ |
| **8** | $\cdot CO_2Ph$ | $H_2O$ |
| **9** | $\cdot CO_2Ph$ | $R\text{-}C_6H_4NH_2$ |
| **10** | $\cdot CO_2H$ | $MeOC_6H_4NH_2$ |

The first one corresponds to the loss of 6-$COR^1$. The second fragmentation corresponds to the loss of $R^2H$ from the 3-carboxylic acid group or derivatives, leading in all cases to the formation of an intense peak at *m*/*z* 153. The identity of the group $R^1$ can be determined based on the difference between the mass of the molecular ion and the mass of the first fragment; based on the difference between the masses of the first and the second fragment the group $R^2$ can be identified.

Techniques used; NMR [$^1H$, $^{13}C$, HETCOR ($^1H/^{13}C$), COSY ($^1H/^1H$), selective INEPT, NOESY and HMBC], mass spectrometry (low- and high-resolution), elemental analysis

References: 25

Schemes: 5

Table 1: Connectivities found in the HMBC spectrum of **2**

Figures: 2

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