The ice bath was removed, and the solution was allowed to warm to room temperature. After 15 min, the solvent was removed in vacuo to obtain crystalline lithium hexamethyldisilazide. This material was dissolved in 1 mL of THF and cooled to −78 °C. A solution of 258 mg (1 mmol) of ketone **1**, 228 mg (1.5 mmol) of methyl bromoacetate, and 0.1 mL of hexamethylphosphoric triamide in 2 mL of THF was added over a 5-min period. After addition was complete, the mixture was stirred for 35 min and then allowed to warm to 0° C. At this point, 78 mg (1.3 mmol) of acetic acid was added, and the mixture was diluted with 30 mL of ether. The ether solution was washed with water, dried (Na_2SO_4), and immediately evaporated to provide 330 mg (100%) of orange oil, identical in all respects with a sample of hydroxy ester **3** prepared as described in part A.

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Registry No. **1**, 17974-57-1; **2**, 71987-70-7; **3**, 71987-71-8; **5**, 72016-48-9; **5** (*SS,RR*), 71987-72-9; **6**, 71987-73-0; **7**, 71987-74-1; Mesityl oxide, 141-79-7; methyl chloroacetate, 96-34-4; (β-ionylidineethyl)triphenylphosphonium bromide, 1180-79-6.

Marked Influence of Minute Amounts of Water on the Selectivity of Alkylation Site of Sodium 2-Naphtholate (Ambident Anion) in Aprotic Solvent

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It has been established that solvation is an integral part of most bimolecular reactions in solution. In particular, Parker[1] has demonstrated that the reactivities of anionic species are dramatically affected by the solvation through hydrogen bonding with protic solvent species. The marked activation of anionic species observed in dipolar aprotic solvents has since been attributed to the desolvation effect, that is, exclusion of hydrogen bond forming molecules from the reaction center.[1] On the other hand, the reaction rate in dipolar aprotic solvents has been believed to be affected little by small amounts (several millimolar) of remaining water,[2-4] since dipolar aprotic solvent molecules (i.e., hygroscopic molecules) can compete with reacting anions as acceptors for water molecules.[3] It was found, however, that the rate constants for the nucleophilic reactions of oxyanions are affected by a water concentration of less than 1 M, and the plots of rate constants vs. [H_2O] increased exponentially with decreasing water concentration.[5-7] The influence of small amounts of water on the reaction rate is an old but still controversial problem.

Table I. Effect of Water Concentration in THF on the Alkylation Site of Sodium 2-Naphthoate[a]

water concn, M			
initial	final	18-crown-6	P_0/P_c
0.006	0.033	0	2.08
0.08	0.22	0	1.12
0.51	0.69	0	0.99
0.94	1.19	0	0.79
2.00	2.66	0	0.41
0.02	0.05	1.43	51.7
0.08	0.09	1.43	46.5
0.16	0.16	1.43	40.6
0.69	0.70	1.43	40.1
1.09	1.11	1.43	37.6

[a] [Sodium 2-naphtholate] = [benzyl bromide] = 0.286 M.

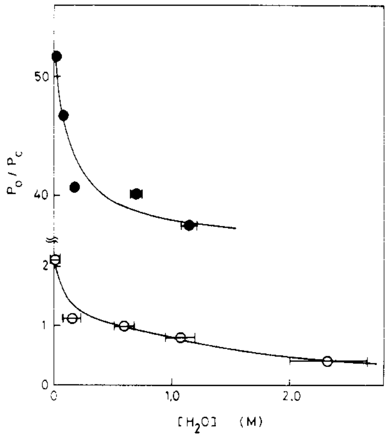
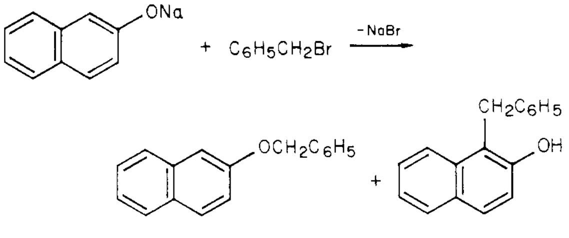


Figure 1. Plots of P_0/P_c as a function of water concentration in THF (○) and in THF/18-crown-6 (●).

The reactivity of ambident anions is highly solvent dependent;[8-11] therefore, it is expected that it is influenced by small amounts of water remaining in solvents in the order of 10^{-3} M concentration. However, there is no precedent for this type of investigation. In this paper, we wish to report that the ratio of O- vs. C-alkylation products (P_0/P_c) in the reaction of sodium 2-naphtholate (**1**) with benzyl bromide (**2**) (eq 1), which is known to change from 97/0 in *N,N*-dimethylformamide to 10/84 in water,[8] is markedly affected by a several millimolar concentration of water remaining in tetrahydrofuran (THF) and that, without accurate determination of the water concentration, the quantitative estimation of the reactivity of the ambident anion becomes meaningless.



(1)

The results of the P_0/P_c determination as a function of the water concentration is summarized in Table I. THF was chosen as solvent because it provides the convenient

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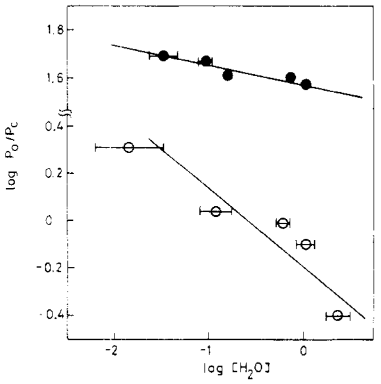

Figure 2. Plots of log P_o/P_c as a function of log $[H_2O]$ in THF (○) and in THF/18-crown-6 (●).

P_o/P_c value (60/36)[8] for the examination of the influence of water, and, in addition, the water concentration in it is readily controllable. The maximum P_o/P_c value of 2.08 was attained at $[H_2O]$ = 6 (at the initial stage of the reaction)–33 (at the final stage of the reaction) mM. It was difficult to prepare THF drier than this with the present experimental apparatus (see Experimental Section). As shown in Figure 1, the ratio decreased with increasing water concentrations and finally reached an equilibrium value of 0.40. Previously, the P_o/P_c value in THF was reported to be 1.67 by Kornblum et al.[8] and 1.70 by Akabori and Tsuji.[12] It is presumed, therefore, that THF used in these experiments would have contained about 40 mM of water.

Akabori and Tsuji[12] reported that the P_o/P_c value in THF is enhanced to 32–73 by the addition of macrocyclic polyethers. In the present study the P_o/P_c value was similarly enhanced by the addition of 18-crown-6 (fivefold excess), and the maximum P_o/P_c value of 51.7 resulted at $[H_2O]$ = 20–50 mM. The P_o/P_c value was again sensitive to the water concentration, and the final ratio at high water concentrations was about 30.

One may summarize on the basis of the foregoing results that (1) the ratio is so sensitive to the water concentration that the P_o/P_c value without indication of the water concentration seems almost meaningless, (2) added water molecules suppress preferentially the formation of the O-alkylation product, and (3) added crown ether which would decrease the tightness of ion pairs[13,14] results in a remarkable activation of the oxyanionic nucleophilicity in preference to the carbanionic nucleophilicity.

The exponential curves in Figure 1 can be approximated by eq 2, in which k_o and k_c denote the overall rate con-

$$\frac{P_o}{P_c} = \frac{k_o[1][2][H_2O]^{-n_o}}{k_c[1][2][H_2O]^{-n_c}} = \frac{k_o}{k_c}[H_2O]^{n_c-n_o} \qquad (2)$$

stants for the O- and C-alkylation reactions and $-n_o$ and $-n_c$ are the apparent reaction orders for the O- and C-alkylations with respect to water, respectively. The $-n_o$ and $-n_c$ are introduced in order to evaluate the extent of the water inhibition.[15] Equation 2 can be rewritten as eq 3 which features a linear relation between log $[H_2O]$ and log P_o/P_c.

$$\log \frac{P_o}{P_c} = \log \frac{k_o}{k_c} + (n_c - n_o) \log [H_2O] \qquad (3)$$

The k_o/k_c term in eq 3 corresponds to the P_o/P_c value at $[H_2O]$ = 1.0 M. The plots of log $[H_2O]$ vs. log P_o/P_c (Figure 2) showed approximately linear relationships with correlation coefficients better than 0.98 (Figure 2). On the basis of the least-squares computation, the following values were obtained: $n_c - n_o = -0.27$, $k_o/k_c = 0.68$ in THF; $n_c - n_o = -0.08$, $k_o/k_c = 37.7$ in THF/18-crown-6. If the influence of small amounts of water reported herein belongs to a class of general medium effects, the values extrapolated to an aqueous solution (i.e., $[H_2O]$ = 55.5 M) should be identical with the P_o/P_c value in an aqueous system (i.e., 0.12).[8] However, the aqueous P_o/P_c values estimated from eq 3 were somethat greater than this: 0.23 for the THF system and 27.1 for the THF/18-crown-6 system. The result clearly endorses the fact that the water problem reported herein belongs to a class of novel specific solvations.

The fact that n_c is smaller than n_o both in the presence and in the absence of crown ether is rationalized in terms of the Parker's proposition that a negative charge on relatively large atoms (i.e., "soft bases") is solvated less strongly by protic solvent species. On the other hand, it is not easy to rationalize why the $n_c - n_o$ value in THF is greater (negatively) than that in the presence of crown ether. This implicates that the reactivity ratio of O^- vs. C^- alkylations is more sensitive to water concentration in the ion-paired form than in the free-ion form. A most likely explanation is that the countercation (Na^+) of the ion pair may assist (or facilitate) the solvation of the anionic nucleophiles (X^-) (in particular, that of the oxyanionic nucleophile) through the interaction $X^- \cdots H_2O \cdots Na^+$ more efficiently than that complexed with 18-crown-6. The association between sodium 2-naphtholate and water would be thus enhanced in the ion-paired form.

In conclusion, the present study suggests that the reactivity of sodium 2-naphtholate in THF (and probably other ambident anions in aprotic solvents in general) is affected by a several millimolar concentration of remaining water, and, in some cases, the rate constants become meaningless without accurate indication of the water concentration. This conclusion would be informative to the quantitative estimation of the reactivity of anions in aprotic solvents.

Experimental Section

Analysis. The products were analyzed by a Shimadzu GC Mini I gas chromatograph equipped with a Shimadzu Chromatopac EIA integrator with a 2.4 m × 3 mm column packed with silicon GE SE-30. The calibration lines were depicted by using diphenyl as internal standard, the correlative coefficients being better than 0.99. Each product was measured in triplicate, and the average value was recorded in the figures. The relative error arising from the measurements was less than 4%.

General Procedures. The reaction of benzyl bromide and sodium 2-naphtholate was carried out according to the method of Kornblum et al.[8] The typical procedure is as follows. Sodium 2-naphtholate (0.02 mol) prepared according to the Kornblum's method[8] was placed in a 100-mL four-necked flask and dissolved in 50 mL of THF (distilled from sodium metal and then dried over molecular sieve 5A) under a nitrogen stream by stirring with a Teflon-coated magnetic bar. If desired, aliquots of water were added at this time. The solution was equilibrated to 30 °C, and 20 mL of THF containing 0.02 mol of freshly distilled benzyl bromide was added from a dropping funnel within 5 min. The reaction was continued at 30 °C for 24 h. Under a continuous nitrogen stream, aliquots (e.g., 100 μL) of the solution were withdrawn to determine the water concentration, and then the reaction was stopped by adding aqueous dilute HCl solution. The

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variation of the water concentration during the reaction is expressed by the bar in figures. Further workup of the reaction products was carried out according to the method of Kornblum et al.[8]

Determination of Water Concentration. The water content of THF was determined by a coulometric Karl–Fischer apparatus (Kyoto Electronic Co. Ltd., Type MK-AII). Its sensitivity was better than 20 μL of water for 1-mL solutions (i.e., ca. 1 mM). When the same THF solution was measured in triplicate, the relative error was less than 8%.

Acknowledgment. We are indebted to Professor J. Sunamoto for the use of a coulometric Karl–Fischer apparatus. We also thank Miss M. Sadauchi for technical assistance.

Registry No. 1, 3019-88-3; **2**, 100-39-0; 2-benzyloxynaphthalene, 613-62-7; 1-benzylnaphth-2-ol, 36441-31-3.

New Clerodane Diterpenoid from *Teucrium eriocephalum*

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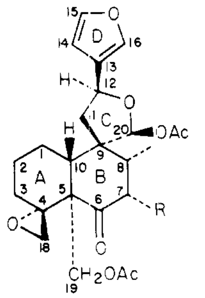
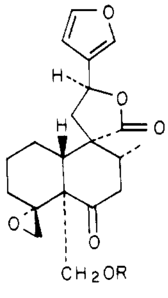
Continuing our studies on diterpenic compounds from the *Teucrium* species (family Labiatae),[2,3] we have now investigated *T. eriocephalum* Wk.,[4] a species which grows only in limited areas of northeast Spain. From aerial parts of this plant a new diterpenoid, eriocephalin (1), has been isolated.

Eriocephalin (1) is the 7α-hydroxy derivative of gnaphalidin (2), a diterpene recently isolated[3] from *Teucrium gnaphalodes* L'Her. together with related products.

The present paper deals with the structure determination of eriocephalin and with a comparative study of ^{13}C NMR spectra of 1, 2, gnaphalin (4), and 19-acetylgnaphalin (5).



1, R = OH
2, R = H
3, R = OAc



4, R = H
5, R = Ac

Table I. ^{13}C Chemical Shifts of Compounds 1, 2, 4, and 5[c]

	compd			
carbon no.	1	2	4	5
1	22.6 t	23.3 t	23.5 t	23.5 t
2	25.7 t	24.9 t	24.8 t	24.8 t
3	30.4 t	33.0 t	32.9 t	32.8 t
4	60.8 s	61.1 s	61.9 s	61.2 s
5	53.6 s[a]	54.3 s	55.5 s	54.2 s
6	206.7 s	205.6 s	207.6 s	206.5 s
7	74.6 d[b]	45.0 t[a]	44.1 t[a]	43.5 t[a]
8	43.0 d	41.7 d	40.8 d	41.6 d
9	53.2 s[a]	51.6 s	51.6 s	51.6 s
10	51.2 d	55.1 d	54.5 d	55.6 d
11	49.6 t	45.7 t[a]	43.7 t[a]	43.7 t[a]
12	73.2 d[b]	71.1 d	71.9 d	71.9 d
13	127.6 s	125.7 s	124.9 s	124.8 s
14	108.5 d	108.4 d	107.8 d	107.8 d
15	139.3 d	139.4 d	139.3 d	139.4 d
16	143.4 d	143.4 d	144.2 d	144.2 d
17	10.6 q	18.0 q	17.1 q	17.1 q
18	51.9 t	49.2 t	50.0 t	48.5 t
19	62.5 t	61.8 t	62.4 t	62.1 t
20	98.8 d	97.8 d	176.5 s	176.8 s
OCOMe	170.1 s 169.3 s	170.4 s 169.3 s		170.5 s
OCOMe	21.4 q 20.9 q	21.3 q 20.7 q		20.8 q

[a,b] These assignments may be reversed, but those given here are considered to be the most likely. [c] In ppm relative to Me_4Si.

Eriocephalin had a $C_{24}H_{30}O_9$ molecular formula, and its IR spectrum showed characteristic absorptions for a furan ring (3145, 3130, 1505, 880 cm^{-1}), a ketone (1715 cm^{-1}), one or more ester groups (1732 cm^{-1}, br), and a hydroxyl group [3500 (KBr), 3610 (CCl_4) cm^{-1}]. The presence of this last function was confirmed because Ac_2O–pyridine treatment of compound 1 yielded a monoacetyl derivative (3, $C_{26}H_{32}O_{10}$) of the natural product.

The ^1H NMR spectrum of eriocephalin (1) showed signals for a secondary methyl group at δ 0.89 (d, $J = 7$ Hz), a β-substituted furan ring (two α-furan protons at δ 7.36 and one β-furan proton at δ 6.37), and two acetates (δ 2.08 and 1.97), one of which was placed on a methylene group attached to a fully substituted carbon atom (a two-proton singlet at δ 4.69) and the other one on an hemiacetalic carbon atom without vicinal protons (one-proton singlet at δ 6.33). The closure of this hemiacetal group was revealed by a one-proton triplet at δ 5.20 ($J = 8$ Hz) which must be allylic to the furan ring and vicinal to a methylene group. All these signals are also encountered in the ^1H NMR spectrum of gnaphalidin (2). In addition, the ^1H NMR spectrum of 1 showed a doublet signal (1 H, $J = 6$ Hz) at δ 4.77 assigned to the geminal proton of a secondary hydroxyl group, because it was shifted at lower field (δ 5.60) in the ^1H NMR spectrum of the acetyl derivative. On the other hand, the ^1H NMR spectrum of compound 3 showed a typical pattern (which is not clear in the spectrum of 1) for an α,α-disubstituted oxirane ring [δ 2.92 (1 H, dd, $J_1 = 4$ Hz, $J_2 = 2$ Hz) and 2.40 (1 H, d, $J = 4$ Hz)] identical with those found in gnaphalidin (2) and related diterpenoids.[3]

All the above data were in agreement with structure 1 for eriocephalin, in which the secondary hydroxyl group was placed on C-7 by double-resonance experiments. When the signal of the secondary methyl group, or also the doublet at δ 4.77, was irradiated, a clear modification was observed at δ 2.44 (H-8), and the signals at δ 0.89 (secondary methyl group) and 4.77 (geminal proton of the alcohol) collapsed to singlets on irradiation at H-8. The same effects were observed between the signals at δ 1.03 (3 H-17), 2.50 (H-8), and 5.60 (H-7) in the ^1H NMR

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