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Registry No. (±)-3, 103564-29-0; (±)-4, 69100-18-1; **5**, 89589-68-4; **6**, 31608-22-7; **7**, 103564-32-5; (±)-**8**, 103564-30-3; (±)-**9**, 103564-31-4; dihydropyran, 110-87-2; 4-bromobutanol, 33036-62-3.

Cation–Anion Combination Reactions. 25.[1] Reactivity of Carbonate Ion

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Carbonate–bicarbonate buffers are frequently used for the pH range around 10. Neither the carbonate nor bicarbonate ions are considered to be very reactive twoard organic electrophiles, although Swain[2] has reported a nucleophilicity parameter for bicarbonate ion in water.

In the course of other work, we have observed a reaction of carbonate ion with (*p*-methoxyphenyl)tropylium cation in water and have been able to measure both rate and equilibrium constants for this reaction.

Experimental Section

The (*p*-methoxyphenyl)tropylium perchlorate was available from an earlier study.[3] The stop–flow spectrophotometer used for the entire study was the single wavelength instrument described previously[4] and was thermostatted at 25.0 °C. Absorbance was measured at the wavelength of maximum absorbance of the cation, 425 nm.

A master solution of the (*p*-methoxyphenyl)tropylium perchlorate in acetonitrile, ca. 10^{-2} M, was diluted into very dilute aqueous acid to give a reaction solution having a cation concentration of ca. 6×10^{-5} M. This solution was mixed with the carbonate/bicarbonate buffer solutions in the stop–flow apparatus.

Two series of experiments, one with a buffer ratio, $(\mathrm{HCO_3^-})/(\mathrm{CO})_3{}^{2-})$, of 1.34 (pH 10.0), and the other with a buffer ratio of 4.0 (pH 9.5), were carried out.

Results

Upon mixing the solution of the cation with the carbonate buffer solution, the absorbance of the cation disappears in two clearly distinguishable stages, each following good first-order kinetics. The rate and extent of the first stage of reaction depends on the concentration of carbonate ion, but is independent of the buffer ratio. The second, slow, stage of reaction shows a dependence on the extent of the first stage as expected for the reaction scheme

$$\mathrm{R^+ + CO_3{}^{2-}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ROCO_2{}^-} \tag{1}$$

$$\mathrm{R^+ + OH^-\ or\ H_2O} \xrightarrow{k_2} \mathrm{ROH} \tag{2}$$

where the first reaction reaches equilibrium faster than the second reaction.

Table I. Reaction of Carbonate Ion with (*p*-Methoxyphenyl)tropylium Ion in Water at 25.0 °C

$10^2 I$,[a] M	$10^3 a_{\mathrm{CO_3}}$[b]	$(A_0 - A_\infty)/A_\infty$[c]	$10^{-2} k_{\mathrm{fast}}$[d]	$10^{-3} K_{\mathrm{eq}}$[e]	$10^{-4} k_1$[f]
		at pH 10.0			
0.93	1.44	1.37	0.68	0.95	2.7
1.40	2.00	2.01	0.77	1.00	2.6
1.86	2.53	2.33	0.93	0.92	2.6
2.32	2.98	2.72	1.04	0.91	2.6
2.78	3.42	2.90	1.09	0.85	2.4
3.25	3.83	3.62	1.23	0.95	2.5
3.70	4.23	4.09	1.34	0.97	2.5
		at pH 9.5			
0.70	0.70	0.66	0.38	0.93	2.1
1.75	1.49	1.20	0.70	0.80	2.6
3.50	2.51	2.10	0.97	0.84	2.6
5.25	3.35	2.76	1.11	0.82	2.4
7.00	4.08	3.43	1.22	0.84	2.3
			avg	0.90	2.5

[a] Ionic strength. [b] Activity of carbonate ion, calculated using the activity coefficient given by: $-\log \gamma = 2.046 I^{1/2}/(1 + 1.481 I^{1/2})$. [c] A_0 is the absorbance at zero time, and A_∞ is the absorbance when the fast stage of reaction has reached equilibrium. [d] Pseudo-first-order rate constant for fast stage. [e] Calculated from $(A_0 - A_\infty)/(A_\infty \times a_{\mathrm{CO_3{}^{2-}}})$. [f] Second-order rate constant in units of $\mathrm{M^{-1}\ s^{-1}}$ for reaction 1.

The experimental data allowing the evaluation of the rate and equilibrium constants for reaction 1 are shown in Table I.

The pseudo-first-order rate constants for the slow stage of reaction allow the evaluation[5] of the pseudo-first-order rate constants for reaction 2. At pH of 10.0, we obtain $k_2 = 6.1\ \mathrm{s^{-1}}$, and, at pH 9.5, we find $k_2 = 2.1\ \mathrm{s^{-1}}$. Neither constant varies significantly with buffer concentration. The values are slightly higher than those we calculate (k_2 = 4.3 and 1.7, respectively) from the rate constants for reactions of water and hydroxide ion at 23 °C which were reported earlier.[3]

Discussion

The rate constant for reaction of hydroxide ion with (*p*-methoxyphenyl)tropylium cation, at 23 °C, is only slightly greater than that for reaction of carbonate ion: $k_{\mathrm{OH}}/k_{\mathrm{CO_3}} = 4.0 \times 10^4/2.5 \times 10^4 = 1.7$. The ratio of equilibrium constants is much greater, $K_{\mathrm{OH}}/K_{\mathrm{CO_3}} = 2.0 \times 10^5$. In terms of the exchange equilibrium

$$\mathrm{ROH + HCO_3{}^- \rightleftharpoons RCO_3{}^- + HOH} \tag{3}$$

of the type suggested by Hine[6] and recently discussed by us for a variety of nucleophiles and cations,[7] we can evaluate $K = 1.3$ using pK_a of 15.7 for water and 10.3 for $\mathrm{HCO_3^-}$. This value is much closer to unity than those for most nucleophiles and cations. For reactions in which $\mathrm{R^+}$ is the Pyronin-Y cation (3,6-bis(dimethylamino)xanthylium cation) or (*p*-(dimethylamino)phenyl)tropylium cation, all nucleophiles studied, with the exception of the one alkoxide ion studied, give equilibrium constants much greater than unity for the exchange reactions analogous to eq 3. Even peroxide ion, an oxygen nucleophile, has $K \approx 10^4$ for the exchange reaction.

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Registry No. carbonate, 3812-32-6; *p*-methoxyphenyltropylium cation, 29631-26-3.

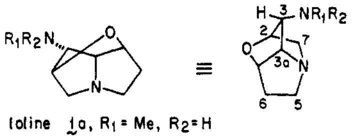
Communications

Synthesis of the Lolium Alkaloids

Summary: The total synthesis of loline and norloline using a nitrone-based methodology is reported herein.

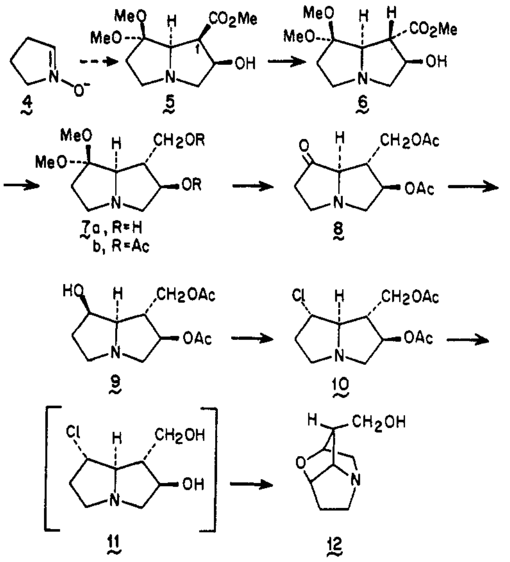
Sir: Tall fescue (*Festica arundinacea*) is a cool-season, perennial bunch grass which is important as a pasture grass because it grows well in poor soil, withstands drought and conditions of inadequate drainage, and affords a good yield of dry matter per acre.[1-3] Cattle grazing on this grass have been known to develop a lameness known as "fescue foot".[4,5] In addition, there have been reports of increased respiration[6] and abdominal fat necrosis[7] in cattle feeding on this grass.

As a result of investigations into the alkaloidal content of tall fescue, a small array of norpyrrolizidine alkaloids have been isolated, all incorporating a unique oxygen bridge.[8] From *L. cuneatum* and *F. arundinacea*, a total of seven closely related lolium alkaloids were discovered. They have all been interconverted.[8-13] The structure of loline (**1a**) was confirmed by an X-ray crystallographic analysis of loline dihydrochloride.[14-16] The pharmacological activity of loline (**1a**) and related compounds has been reviewed.[11] When the crude alkaloidal extract is fed to cattle, fescue toxicity is not produced,[17] thereby suggesting that the toxicity of *L. cuneatum* is associated with nonalkaloid[21] constituents. Loline has been shown to possess weak antitumor activity,[18] and derivatives of this ring system can produce muscle relaxation.[19]



loline **1a**, R_1 = Me, R_2 = H
norloline **1b**, R_1 = H, R_2 = H
1c, R_1 = Me, R_2 = Ac

Scheme I



These alkaloids have not yielded to the thrusts of several synthetic attempts,[16,20-22] although the skeleton has been assembled.[16,22] The syn relationship between the 3-substituent, in proposed synthetic intermediates, and the skeletal nitrogen has remained elusive.

Since a nitrone-based methodology has been successful in the synthesis of several pyrrolizidine alkaloids (e.g., supinidine,[23] retronecine,[24] croalbinecine[25]), we chose to explore its potential for the construction of the unique skeleton of the loline alkaloids and for the controlled introduction of the syn-3-amino functionality (cf., **1a**).

A tempting means of constructing the skeletal architecture of loline involves a Michael closure of the penultimate precursor (i.e., **2**) in our earlier synthesis of *dl*-retronecine;[24] however, this approach suffers from a poor trajectory of approach of the hydroxyl group to the β-

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