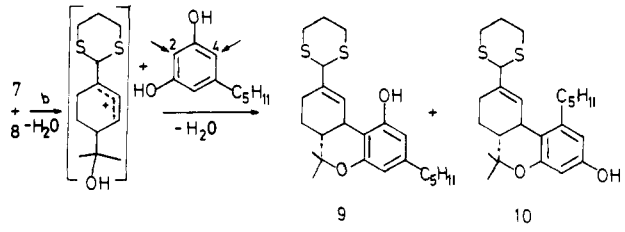
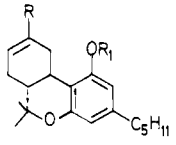
Scheme II[a]

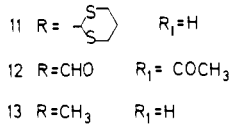


[a] All compounds are racemic. [b] p-TSA, refluxing benzene.

mixtures).[12] The reaction probably proceeds via a common terpenic intermediate that condenses at either the 2 or 4 position of olivetol.[13]

No evidence was found for the formation of Δ^6 analogues of compounds **9** and **10**, even after prolonged treatment with *p*-TSA (benzene, 70 °C).[14] Furthermore, when THC **11**,[15] the Δ^6 counterpart of **9**, was treated in the same way, it was recovered unchanged. These findings contrast with the fact[3,17]





11 R= R_1=H

12 R=CHO R_1= $COCH_3$

13 R=CH_3 R_1=H

that under identical conditions Δ^1- and Δ^6-THC (**1** and **13**, respectively) rapidly equilibrate, with only 3% of the Δ^1 isomer remaining at equilibrium. The Δ^1 unsaturation in THCs **9** and **10** may derive its remarkable stability to acid from electronic effects such as (i) competitive formation of a sulfonium ion adjacent to C_1, or (ii)[18] diminution of hyperconjugative stabilization (a result of the substitution of sulfur for hydrogen at C_7). Either effect would destabilize an incipient carbonium ion at C_1.

As a demonstration of the flexibility afforded cannabinoid synthesis by the dithiane masking group,[19] compound **9** (0.10 mmol) was treated with mercuric oxide (0.21 mmol) and boron trifluoride etherate (0.50 mmol) in 15% aqueous THF[20] to form Δ^1-aldehyde **14** (65%, identified as its acetate).[21] Oxidation of this acetate to the corresponding acid has been reported.[21] Reduction of **14** with $LiAlH_4$ proceeded smoothly and furnished the allylic alcohol **15** (66%), the optically active form of which[22] is a major metabolite of Δ^1-THC in man.

The implications of the ability to inhibit the isomerization of normally labile double bonds to general synthesis are being investigated further.

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(5) *cis*-**4**: NMR (CCl_4) δ 4.93 (d, 1, $J_{2,3}$ = 6 Hz, C_3 H), 3.87 (dd, 1, $J_{1,2}$ = 3, $J_{2,3}$ = 6 Hz, C_2 H). *trans*-**5**: NMR (CCl_4) δ 4.67 (m, 1, $J_{2,3}$ = 2 Hz, C_3 H), 3.95 (m, 1, $J_{1,2}$ = 6 Hz, C_2 H). The mixture had satisfactory C, H analysis.
(6) Ketone **6**: IR (CCl_4) 3460 (OH), 1670 (C=O) cm^{-1}; NMR (CCl_4) δ 7.18 (dt, 1, J_d = 10, J_t = 2 Hz, C_3 H), 5.98 (dd, 1, J = 10, 3 Hz, C_2 H), 3.13 (s, 1, OH, exchangeable), 2.6–1.3 (m, 5), 1.25, 1.15 (2s, 6, $-C(CH_3)_2$). For related compounds displaying similar transannular coupling, see W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).
(7) Pure samples of **4** and **5** gave ketone **6** under these conditions, albeit at different rates.
(8) A second compound isolated (11%) was tentatively identified as 4-(1-hydroxy-1-methylethyl)-3-methoxycyclohexanone: NMR (CCl_4) δ 3.33 (s, 3, OCH_3), 4.16 (m, 1, C_3 H); IR (neat) 1720 (C=O) cm^{-1}.
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(11) (a) First isomer eluted: NMR ($CDCl_3$) δ 6.06, 5.98 (AB, 2, J = 11 Hz, olefinics), 4.30 (s, 1, SCHS), 2.93 (m, 4, methylene protons α to sulfur), 2.38 (s, 1, OH, exchangeable), 2.33–1.67 (m, 5), 1.25, 1.22 (2s, 6, $-C(CH_3)_2$); mol wt (high resolution mass spectrometry) 274.10456 (calcd for $C_{13}H_{22}O_2S_2$, 274.10613). (b) Identical results were observed with the second isomer eluted (9%): NMR ($CDCl_3$) δ 6.10, 5.93 (AB, 2, J = 11 Hz, olefinics), 4.25 (s, 1, SCHS), 2.93 (m, 4, methylene protons α to sulfur), 2.33–1.67 (m, 5), 1.25, 1.18 (2s, 6, $-C(CH_3)_2$).
(12) Compound **9**: NMR (CCl_4) δ 6.97 (br, 1, olefinic), 6.11, 6.03 (2, aromatics), 4.53 (s, 1, C_7 H), 3.22 (br, 1, C_3 H), 2.77 (m, 4, methylene protons α to sulfur), 2.37 (m, C_1'' H_2), 1.37, 1.03 (2s, 6, C_8 $(CH_3)_2$), 0.88 (t, 3, C_5'' H_3). **10**: NMR (CCl_4) δ 6.23 (br, 1, olefinic), 6.22, 6.02 (2, aromatics), 4.38 (s, 1, C_7 H), 3.12 (br, 1, C_3 H), 2.77 (m, 4, methylene protons α to sulfur), 2.37 (m, C_1'' H_2), 1.33, 1.00 (2s, 6, C_8 $(CH_3)_2$), 0.90 (t, 3, C_5'' H_3).
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(14) Compound **9** suffers partial decomposition after 1 h, which can be forestalled by acetylating the phenolic hydroxyl group.
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A Failure of the Reactivity–Selectivity Principle for the Quaternization of Pyridines

Sir:

Figure 1 shows linear free-energy relationships between logarithms of second-order rate constants for the nucleophilic attack of a series of 3- and 4-substituted pyridines on four alkylating agents of widely varied reactivity. The results are of interest because the unit slope of each line shows that *there is no variation in selectivity* among the nucleophiles in response to the the changing reactivity of the alkylating agent. The behavior is exactly equivalent to that observed by Ritchie and his students[1-10] for the reactivity of a series of resonance-stabilized carbonium ions with (mostly anionic) nucleophiles in water. Ritchie found that his kinetic data followed the one-parameter equation $\log k/\log k_0 = N+$ where $N+$ is characteristic of the nucleophile and is insensitive to variation of the attacking electrophile over a wide range of carbonium stability.

Pross,[11] Giese,[12] and Johnson[13] have reviewed the present status of the reactivity-selectivity principle (RSP) and the

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known exceptions to it, especially the Ritchie equation. Pross[11] considers that the RSP applies primarily to very simple reactions which obey rate-equilibrium relationships. One source of violations of the RSP are those in which variable solvation factors are important.

The present case cannot be elucidated in these terms. Like most other reactions of pyridines,[14,15,16] log k_2 values for the reactions plotted on Figure 1 all correlate cleanly with the pK_a's of the pyridines in water[17] or even in the gas phase.[16] Since both reactants are neutral and the solvents (nitrobenzene or 2-nitropropane) are nonhydroxylic, solvent reorganization should be nearly constant across the series.

In a previous report[14] we noted the remarkably close relationship between the free energies of activation for some Menschutkin reactions of pyridines and their heats of reaction, even though the transition states and the final states were separated by 40–60 kcal/mol. We find this again for several of the reactions in Figure 1. Thus, the effect of substitution on the pyridine in the transition state is reflected faithfully in the product with virtually no perturbation from changing the substrate reactivity. Also, the variation of the heats of reaction for methyl fluorosulfonate with the series of pyridines gives a linear correlation with unit slope against the corresponding heats of reaction with ethyl fluorosulfonate.

Finally, we note the important disparity between our results and those from two closely related reactions reported recently in this journal. Berg, Gallo, and Metzger[18,19] found that a series of 2-substituted pyridines obey the RSP in their quaternization both with methyl iodide and methyl fluorosulfonate. Because of the great difference in reactivity of methyl iodide compared with methyl fluorosulfonate they were forced (as we have been) to use different kinetic methods to study rates with the two alkylating agents. However, they also used different solvents for the two series.

The fact that our results for the 3- and 4-substituted pyridines in 2-nitropropane as solvent do not fit the RSP which was established for 2-substituted pyridines[18,19] is probably due to factors resulting from the difference in substitution pattern. That the discrepancy is probably *not due* to the difference in techniques or conditions between our work and that of Berg, Gallo, and Metzger is suggested by the point on Figure 1 for methylation of 2-chloropyridine. We were unable to measure this directly for the alkylation with methyl iodide because the low solubility and instability of *N*-methyl-2-chloropyridinium iodide in 2-nitropropane precluded use of the conductance technique (see below) used for the other methylations. However, a clean linear free-energy plot, with unit slope, of the logarithms of our rate constants in 2-nitropropane vs. those of Coppens, Declerck, Gillet, and Nasielski[20] in nitrobenzene gave the estimated value shown in Figure 1. This agrees closely with that found by Berg, Gallo, and Metzger[18,19] using their competitive method.

Another closely related study is that of Lewis and Vanderpool who get RSP behavior for the reaction of phenoxides with a series of methylating agents[21] of greatly varied reactivities.

We are not prepared to speculate at this time on the reasons why the RSP shows such capricious behavior, but believe that these results provide a warning against reliance on this popular mechanistic tool. Johnson[13] and Bordwell[24] have also advised that it is dangerous to infer information about transition-state structure from such "ingenuous" [13] principles.

The kinetics were followed by a calorimetric technique[22] for the alkylation of the substituted pyridines with methyl and ethyl fluorosulfonate by monitoring the heat of reaction as a function of time. A conductance technique[23] was used to monitor the production of *N*-alkylpyridinium iodide salt for the reactions of the substituted pyridines with methyl and ethyl iodide. A concentration vs. specific resistance plot for each pyridinium salt was constructed and rates were then measured by following the specific resistance of the reaction solution as a function of time.

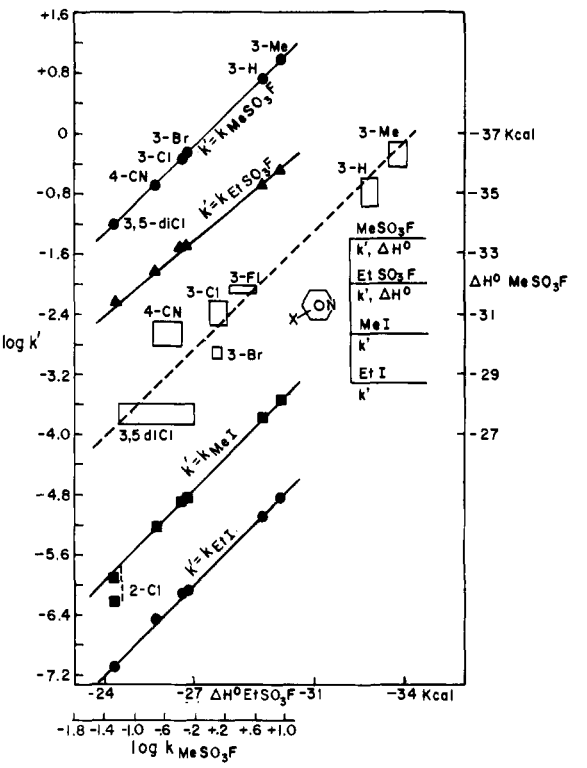

Figure 1. Comparison of rate data (log k_{RX} vs. log k_{MeSO_3F}) and heats of alkylation ($\Delta H°_{EtSO_3F}$ vs. $\Delta H°_{MeSO_3F}$) for quaternization of a series of substituted pyridines in 2-nitropropane as solvent. All slopes are unity within experimental error. See text regarding estimation of the point for 2-chloropyridine.

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