(50 mL) and then extracted with ethyl acetate. The aqueous solution acidified with concentrated HCl and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated to give **12** (7 g, 88%): mp 143–144 °C (benzene); IR (Nujol) 3400, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, m), 5.10 (1 H, m), 2.86 (2 H, d, J = 7 Hz), 1.42 (9 H, s); mass spectrum, m/z 209 (M^+). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.30; H, 7.21; N, 5.26.

4-(2-Acetoxyethyl)-2-[8-(*tert*-butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-1,2,3,4-tetrahydroisoquinolin-1-one (13). A solution of amine **10** (8.7 g, 30 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of acid **12** (7.95 g, 30 mmol), 1-methyl-2-chloropyridinum iodide (7.65 g, 30 mmol), and triethylamine (3.03 g, 30 mmol) in CH_2Cl_2 (100 mL) at room temperature for 2 h. This was followed by evaporation of the solvent and purification of the residue by column chromatography on a silica gel (150 g). Elution with ethyl acetate gave **13** (13.85 g, 86%) as colorless crystals: mp 94–95 °C (ether); IR (Nujol) 3350, 1730, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (1 H, dd, J = 7, 2 Hz), 7.0–7.6 (8 H, m), 5.1 (1 H, m), 2.1 (3 H, s), 1.4 (9 H, s); mass spectrum, m/z 537 (M^+). Anal. Calcd for $C_{30}H_{39}N_3O_6$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.90; H, 7.35; N, 7.86.

2-[8-(*tert*-Butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (14). A mixture of **13** (10.74 g, 20 mmol) and K_2CO_3 (13.8 g, 100 mmol) in methanol (100 mL) was stirred at room temperature for 2 h. The solvent was evaporated and the residue poured into iced water and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated. The remaining residue was purified by column chromatography on a silica gel (100 g). Elution with ethyl acetate gave **14** (8.9 g, 90%) as an oil: IR ($CHCl_3$) 3370, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (1 H, dd, J = 7, 2 Hz), 7.2–7.6 (8 H, m), 5.1 (1 H, m), 1.4 (9 H, s); mass spectrum, m/z 422 [(M − 73)$^+$].

2-[8-(*tert*-Butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-4-(formylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (15). A solution of pyridinum chlorochromate (4.3 g, 20 mmol) in CH_2Cl_2 (50 mL) was added dropwise to one of alcohol **14** (4.95 g, 10 mmol) in CH_2Cl_2 (50 mL) at room temperature for 2 h. The reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. The remaining residue was purified by column chromatographed on a silica gel (50 g). Elution was carried out with $CHCl_3$ and then ethyl acetate to give **15** (3.7 g, 75%) as an oil: IR ($CHCl_3$) 3370, 1720, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.9 (1 H, s), 8.1 (1 H, dd, J = 7, 2 Hz), 5.1 (1 H, m), 1.4 (9 H, s); mass spectrum, m/z 493 (M^+).

Isocyclocelabenzine (1). A mixture of aldehyde **15** (2 g, 4 mmol) and trifluoroacetic acid (20 mL) was stirred at room temperature for 0.5 h. The excess trifluoroacetic acid was removed, and the residue was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water, followed by drying ($MgSO_4$). TLC ($CHCl_3$/MeOH = 10:1 on silica gel plates) analysis of the reaction product indicated the conversion of **15** to **17**, which was used for the following reaction without purification. The product (1 g, 2.6 mmol) in MeOH (30 mL) was reduced with $NaBH_4$ (0.37 g, 10 mmol) at room temperature for 1 h. Following removal of the solvent, the residue was decomposed with aqueous NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated. The residue was purified by column chromatography on a silica gel (30 g). Elution with ethyl acetate gave isocyclocelabenzene (**1**) (450 mg, 46%) as colorless prisms: mp 224–225 °C (ethyl acetate) [lit.[1] mp 227–228 °C (ethyl acetate)]; IR ($CHCl_3$) 3300, 1630, 1600, 1580 cm^{-1}; ^1H NMR (400 Mz, $CDCl_3$) δ 8.11 (1 H, dd, J = 7.5, 1.5 Hz), 7.43 (1 H, td, J = 7.5, 1.5 Hz), 7.37 (1 H, td, J = 7.5, 1.5 Hz), 7.10–7.18 (4 H, m), 6.82 (2 H, m), 7.70 (1 H, dd, J = 8.0, 4.0 Hz), 3.98 (1 H, dd, J = 11.4, 3.1 Hz), 3.90–4.02 (3 H, m), 3.82 (1 H, dd, J = 13, 2.6 Hz), 3.78 (1 H, dd, J = 13, 4.9 Hz), 3.71 (1 H, m), 3.02 (1 H, m), 2.84 (1 H, m), 2.58 (2 H, ddd, J = 12.2, 6.2 and 3.0 Hz), 2.35 (1 H, dd, J = 13.4, 3.1 Hz), 2.22 (2 H, m), 2.18 (2 H, dd, J = 13.4, 11.4 Hz), 1.58–1.82 (3 H, m), 1.25 (1 H, s); mass spectrum, m/z 377 (M^+). Anal. Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7,21; N, 11.13. Found: C, 73.17; H, 7.20; N, 11.10.

Acknowledgment. We express our appreciation Professor H. Wagner of the University of Munich for kindly providing the sample of natural isocyclocelabenzene.

Registry No. **1**, 104595-98-4; (±)-**4**, 104465-74-9; (±)-**5**, 104465-75-0; (±)-**6**, 104465-76-1; (±)-**7**, 104465-77-2; (±)-**8**, 104465-78-3; (±)-**9**, 104465-79-4; (±)-**10**, 104465-80-7; (±)-**11**, 3646-50-2; (±)-**12**, 104465-81-8; **13**, 104465-82-9; **14**, 104465-83-0; **15**, 104465-84-1; **17**, 104487-52-7; 2-benzylhomophthalimide, 21640-31-3; ethyl bromoacetate, 105-36-2; acrylonitrile, 107-13-1.

Imidate Anions: *E*/*Z* Interconversion by Rotation vs. Nitrogen Inversion?

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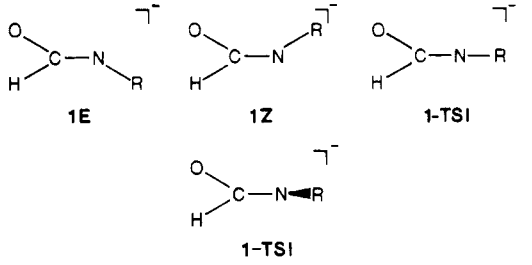
The preparation and characterization of some imidate anions, $HCONR^-$, the conjugate bases of amides, have recently been reported by Perrin, Lollo, and Hahn.[1] This study dealt with, among other things, the stereochemistry and *E*/*Z* isomerization of these new species. On the basis of NMR data, they concluded that in solution, the *E* stereoisomer is more stable than the *Z* and the anions undergo *nitrogen inversion* with a barrier of ca. 20 kcal/mol. With regard to the latter, the following was stated:[1] "The activation barriers for *E*/*Z* interconversion are only 19–23 kcal/mol. These are too low to be due to rotation about the C–N bond. For comparison, the barriers to rotation in the parent amide are 18–20 kcal/mol.... Therefore the mechanism for *E*/*Z* interconversion is not rotation, but nitrogen inversion." In what follows, we intend to show that this argument could be misleading.

Previously, Zielinski and co-workers[2] reported a conformational study of the imidate anion $HCONH^-$ (**1**, R = H) at the ab initio HF/3-21G level with complete geometry optimization. Local minima **1Z** and **1E** and structures **1-TSI** and **1-TSR** which repesent the transition states for the nitrogen inversion and rotation about carbon–nitrogen bond processes, respectively, were also considered. They



concluded that in the gas phase (a) the **1Z** (R = H) isomer is about 7 kcal/mol more stable than the **1E** (b) the inversion transition structure **1-TSI** lies *above* the rotational **1-TSR** by about 7 kcal/mol (**1-TSI** is in fact not a true transition state since it has two negative eigenvalues[2]), and (c) the barrier height of the rotation process is 30.6 kcal/mol; both findings are therefore at variance with the conclusions reached by Perrin et al.[1]

In order to ensure that the calculated relative energies reported[2] are not an artifact of the geometry optimization procedure using a rather small basis set (3-21G), we have first reconsidered the four stationary points of interest at higher level of accuracy. The energy difference between

(1) Perrin, C. L.; Lollo, C. P.; Hahn, C.-S., *J. Org. Chem.* **1985**, *50*, 1405.
(2) Zielinski, T. J.; Poirier, R. A.; Peterson, M. R.; Csizmadia, I. G. *J. Comput. Chem.* **1982**, *3*, 477.

0022-3263/86/1951-4703$01.50/0

Table I. Total and Relative Energies of $HCONH^-$ and $HCONCH_3^-$ Species Considered at Different Levels of Calculations

	total energies, au				relative energies, kcal/mol		
method[a]	1Z	1E	1-TSR	1-TSI	$E(Z-E)$ (rotation)	$\Delta E^{\ddagger}$ (rotation)	$\Delta E^{\ddagger}$ (inversion)
			A. $HCONH^-$ (1, R = H)				
HF/4-31G	−168.06300	−168.05201	−168.01473	−168.00600	6.9	30.3	35.8
HF/6-31G**	−168.32291	−168.31494	−168.27448	−168.25623	5.0	30.4	41.8
HF/6-31++G	−168.26430	−168.25455	−168.21904	−168.21178	6.1	28.4	33.0
MP2/6-31++G	−168.60977	−168.60147	−168.56631	−168.55614	5.2	27.3	33.7
MP3/6-31++G	−168.59945	−168.59096	−168.55448	−168.54475	5.3	28.2	34.3
MP4SDQ/6-31++G	−168.61837	−168.60983	−168.57451	−168.56421	5.4	27.5	34.0
CISD/6-31++G	−168.57318	−168.56415	−168.52819	−168.51902	5.7	28.2	34.0
			B. $HCONCH_3^-$ (1, R = CH_3)				
HF/4-31G	−207.03192	−207.02126	−206.98153	−206.97666	6.7	31.6	34.8
HF/6-31G**	−207.35239	−207.34493	−206.30284	−207.29084	4.7	31.1	38.6

[a] Using the HF/4-31G-optimized geometries given in Figures 1 and 2.

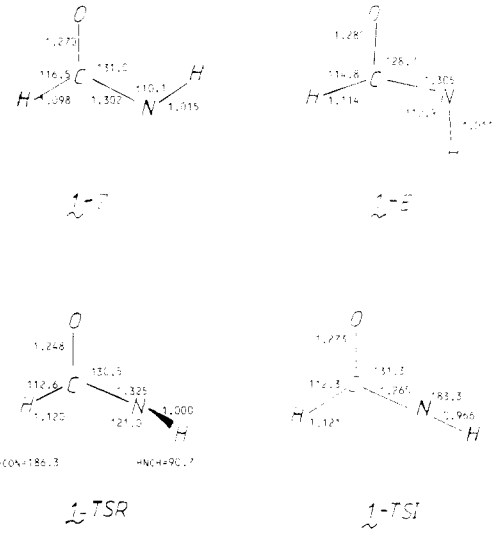


Figure 1. HF/4-31G-optimized geometries of $HCONH^-$ (1, R = H) species. Bond lengths in Å and bond angles in degrees.

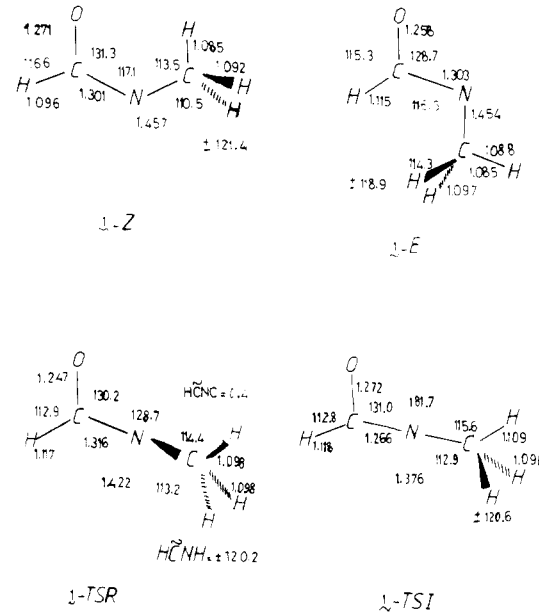
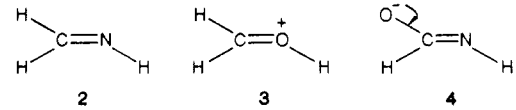


Figure 2. HF/4-31G optimized geometries of $HCONCH_3^-$ (1, R = CH_3) species. Bond lengths in Å and bond angles in degrees.

species are thus determined by single point calculations with basis sets including polarization functions (6-31G**)[3] and diffuse functions (6-31++G)[4] making use of the optimized geometries with the 4-31G[5] basis set. Correlation energies have also been evaluated via the Møller–Plesset perturbation theory to second through fourth order[6] as well as by configuration interaction calculation.[7] In addition, we have also examined four stationary points of the *N*-methyl imidate anion 1 (R = CH_3) but only at the HF/4-31G and HF/6-31G** levels. The optimized geometries for stationary points of $HCONH^-$ and $HCONCH_3^-$ are shown in Figures 1 and 2, respectively.

As seen in Table I, the relative energies are not oversensitive to basis set or correlation effects. For both species considered (1, R = H and R = CH_3), the *Z* forms are calculated to be more stable by ~5 kcal/mol than the *E*. Replacing H by CH_3 slightly reduces the inversion barrier and marginally enlarges the rotational ones. Overall, our calculations also suggest that the gas-phase stereomutation pathway of imidate anions $HCONR^-$ (1 with R = H or alkyl group) by rotation around C–N bond is favored over that by nitrogen inversion even though that the energy difference between two barrier heights is rather small (≤6 kcal/mol). This is of course opposite to what occurs in the usual C=N double bond in methylenimine **2** where the inversion barrier is appreciably smaller than the rotational one (≥30 kcal/mol).[8] This is not quite surprising since for imidate anions, we are dealing with a carbon–nitrogen bond exhibiting a partial double bond character.[9] The HF/4-31G optimized geometries indicate in fact that the C–N bond lengths in **1E** (1.305 Å) and **1Z** (1.302 Å) are longer than that in methylenimine **2** (1.26 Å) but shorter than that in formamide (~1.35 Å). For this type of bond, the stereoisomerization could take place either by rotation or inversion depending upon the nature of bonding atoms. However, the barrier heights of both processes are rather close each to other. For example, in the case of the methoxycarbenium cation **3**, the barrier to inversion and rotation were recently calculated as 22.9 and 25.9 kcal/mol (at HF/6-31G**),[10] respectively.



(3) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(4) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.
(5) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.
(6) Krishnan, R.; Pople, J. A. *Int. J. Quantum Chem.* **1978**, *14*, 91.
(7) Pople, J. A.; Seeger, R.; Krishnan, R. *Int. J. Quantum Chem.* **1977**, *11*, 149.
(8) Leroy, G.; Nguyen, M. T.; Sana, M.; Villaveces, J. L. *Bull. Soc. Chim. BeLg.* **1980**, *89*, 1023.
(9) Veillard, A. In *Quantum Mechanics of Molecular Conformations*; Pullmann B., Ed.; Wiley: New York, 1975; Chaper 1.

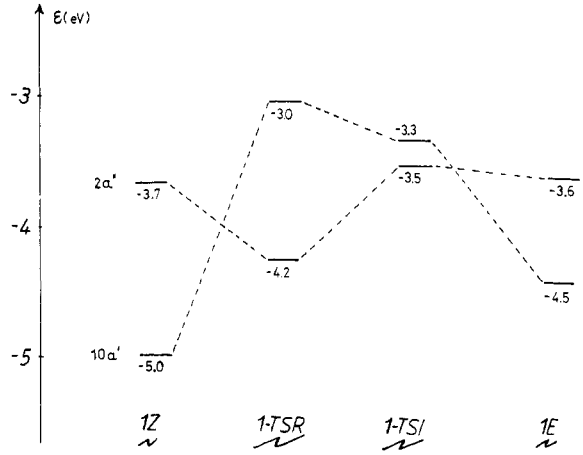


Figure 3. MO energies correlation diagram for imidate anion species 1 (R = H) calculated at HF/6-31++G.

Table II. Total (au) and Relative (kcal/mol) Energy of the Complexes between the Imidate Anion $HCONH^-$ and One Water Molecule Calculated at HF/4-31G.

species[a]	total energy	relative energy	ΔE(complexation)[b]
1E·H_2O	−244.00360	2.7	−27.0
1Z·H_2O	−244.00803	0.0	−22.8
1-TSR·H_2O	−243.96089	29.6	−23.5
1-TSI·H_2O	−243.93982	42.8	−15.8

[a] Using the HF/4-31G-optimized geometries given in Figure 4. [b] ΔE(complexation) = $E(HCONH{\cdot}H_2O^-) - E(HCONH^-) - E(H_2O)$. The HF/4-31G energy of H_2O is −75.90864 au.

The E/Z interconversion processes in imidates anions 1 can be understood in a simple way by considering the MO-correlation diagram of relevant structures. Figure 3 indicates that although both converting processes destabilize the 10a′-orbitals (π-character) of the anions, the rotation around C–N via **1-TSR** significantly stabilizes the 2a″-orbitals (HOMO's, lone pair character). Conversely, such a stabilization does not occur in the inversion via **1-TSI**. The global effect is obviously in favor of the rotational motion.

In ref 1, the following was stated: "... our results show that even the strong π donor, $-O^-$, does not change the inversion barrier substantially, relative to imines (e.g., $Me_2C{=}NPh$, $\Delta G^{\ddagger} = 20.3$) or imidate esters (e.g., MeC(O-*p*-tol)=NMe, $\Delta G^{\ddagger} = 20.2$)" (ref 1, p 1409). We observe that if we consider the imidate anions 1 as an imine substituted at carbon by the ($-O^-$) moiety (structure 4), the latter should on the contrary strongly affect the stereomutation pathway. As a matter of fact, although a π-donor substituent at carbon has been shown to exert a small effect on the inversion barrier in imines,[8,11] conversely it reduces their rotational barriers quantitatively.[8] It has been predicted that a strong π-donor group (along with a strong donor inverting group) could bring both barriers closer or even reverse the process.[8] Apparently, the extremely strong π-donor group ($-O^-$) has changed the situation in imidate anions 1. Thus it becomes clear that the "zero effect" of ($-O^-$) group on the barrier height mentioned[1] arises from the fact that these authors compared rather the rotational barrier in imidate anions to the inversion barrier in imines.

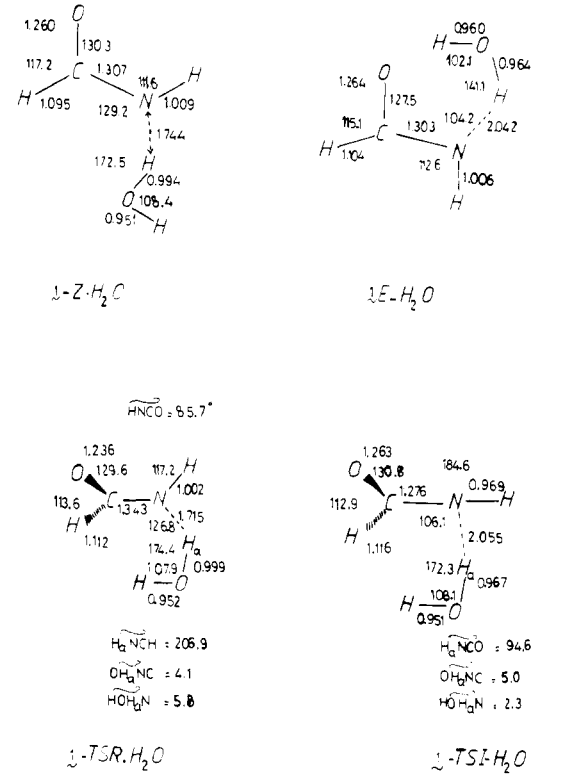


Figure 4. HF/4-31G-optimized geometries of complexes between four $HCONH^-$ species and H_2O. Bond lengths in Å and bond angles in degrees.

As stated above, the present calculated results are mainly related to species in gas phase. Therefore, the foregoing discussion raises the question concerning the solvent effect on the relative stabilities between stationary points on the energy surface. In a recent paper, Cremer and co-workers[10] showed that the barrier to rotation of methoxycarbenium cation **3** is lowered by solvation while conversely the inversion barrier is raised. The overall effect is that the lowest pathway to isomerization of **3** in solution involves rotation unlike the case in the gas phase (see above). In order to qualitatively assess the trends in solvation energies (SE) they[10] employed the relationship[12-13] in eq 1, where A is a proportionality constant, C_{iL}

$$SE = A\frac{\sum_i C_{iL}^2}{E_L - E_H} \qquad (1)$$

are the coefficients of the LUMO components, E_L and E_H are the energies of LUMO and HOMO, respectively. In the present case, this results from the stabilizing charge-transfer interaction between the HOMO's of the anions 1 and the LUMO of an electron-captor solvent molecule. According to the HOMO's energies displayed in Figure 1, eq 1 predicts an increasing order of the SE's: **1-TSR** > **1-TSI** and **1E** > **1Z**. This implies that the *Z*-*E* energy differences will be diminished in solution while the rotational transition structure **1-TSR** is still favored in solution at the expense of the inversion **1-TSI**.

A more quantitative attempt to estimate the SE's can be achieved by calculating the complexation energies between 1 and one water molecule. The 4-31G-optimized geometries of four relevant complexes are displayed in Figure 4; note that if a more flexible basis set were used

(10) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.
(11) Hegarty, A. F.; Brady, K.; Mullane, M. *J. Chem. Soc., Perkin Trans. 2* **1980**, 535.
(12) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975.
(13) Jorgensen, W. L. *J. Am. Chem. Soc.* **1977**, *99*, 280.

a larger HOH_aN angle could be expected in the complex. Table II emphasizes that with both isomers **1E** and **1Z** (R = H) and with both transition structures **1-TSR** and **1-TSI**, the **1E** and the **1-TSR** are found to be more stabilized by interaction with water molecule, respectively. As a consequence, it can be expected that when the solvation energy could be more fully taken into account, the solvated *E* isomer could become more stable than the solvated *Z* isomer as observed in solution[1] but the solvated rotational transition structure is still of lower energy than the solvated inversion. The nature of the counterion could also be important in determing the mechanism of interconversion, particularly in aprotic solvents. This may have been an important factor in the smaller barrier seen in solution.[1] Under these conditions experiments in the presence and absence of a complexing agent such as a crown ether would be of interest.

In conclusion, the imidate anions, $HCONR^-$ (with R = H or alkyl group) undergo *E*/*Z* interconversion by a rotation about the carbon–nitrogen partial double bond both in the gas phase and in protic solution and not by nitrogen inversion as previously claimed by Perrin, Lollo, and Hahn.[1]

Acknowledgment. We are indebted to the Department of Education (Irish Government) for financial support and the UCD computer center for computer time grant.

Registry No. $OHCNH^-$, 67131-48-0; $OHCNCH_3^-$, 58272-35-8.

Hypochlorite-Promoted Transformations of Trichothecenes. 2. Fragmentation-Rearrangement of the Primary Product from Verrucarol[1]

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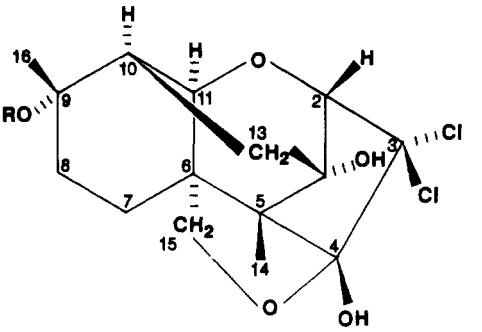
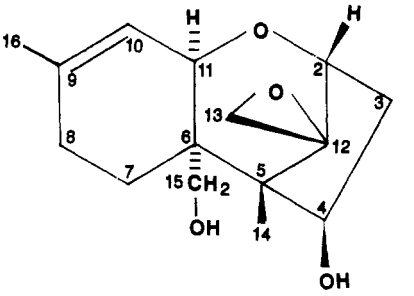
Recently we reported the isolation of two unusual pentacyclic dichlorohemiketals (**1a,b**), formed in nearly quantitative yield on treatment of verrucarol (**2**) with alkaline hypochlorite at room temperature.[2] The overall reaction involved several different processes: nucleophilic attack at C-9 resulting in opening of the epoxide and formation of the C-10,C-13 bond,[3] preferential oxidation at C-4[4] followed by α-chlorination in the manner of a haloform reaction, and cyclization to the hemiketal. These haloform/rearrangement products were thermally stable and resistant to further transformation by hypochlorite at room temperature. Since α-halo carbonyl compounds generally undergo base-promoted cleavage at elevated temperatures,[5] we sought to investigate the effect of hot



1a R=H
1b R= CH_3



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alkali on these products (**1**).

Accordingly, the predominant dichloro hemiketal **1a** ($C_{15}H_{20}Cl_2O_5$) was heated 4 h at 95 °C with 1 N aqueous sodium hydroxide containing 5–10% methanol. After neutralization, direct GC/MS analysis of the resulting mixture without derivatization showed a mixture of three products in relative ratio 1:2:1. Column chromatography on silica gel resulted in complex mixtures of secondary transformation products, in addition to the predominant primary product as a pure solid, and one of the other primary products in sufficient purity for spectral characterization. The molecular formulas of the latter two products, determined by electron impact and chemical ionization mass spectrometry (EI and CIMS), are $C_{14}H_{21}ClO_4$ and $C_{14}H_{20}O_4$, respectively. Their structures were established by ^{13}C–^1H heteronuclear and ^1H–^1H homonuclear NMR chemical shift correlation experiments. The results are summarized in Tables I and II.

Comparison of these data with the assignments documented previously for **1**[2] showed some significant differences. For the monochloro compound **3**, the signals for the two C-15 protons are not significantly changed, while the signals for the pair attached to C-13 are shifted downfield by ca. 1 ppm, to δ 2.31 and 2.85. Carbon 5 is no longer quaternary; the signal for its attached proton (a quartet due to the C-14 methyl group attached to C-5) is observed at δ 3.15. Thus, the ^{13}C singlet at δ 212.9 is assigned to a ketone carbonyl at C-12. Both the signals for C-2 (δ 100.6) and its attached proton (δ 4.99) are shifted significantly downfield in comparison to those of **1a**, and the proton is observed as a triplet. Finally, an additional methylene carbon signal appears (δ 44.4) with its attached protons as a doublet at δ 3.59. From these data, the chlorine-containing product can be assigned one of two tricyclic structures **3a,b**. The configurational assignment at C-5 was based on the observation that no long-range coupling was apparent between H-5 and H-13 under conditions where couplings smaller than 1 Hz are readily observed.[6]

(1) Portions of this material were presented at the 20th American Chemical Society Middle Atlantic Regional Meeting, Baltimore, MD, Sept 1986.
(2) Burrows, E. P.; Szafraniec, L. L. *J. Org. Chem.* **1986**, *51*, 1494.
(3) Sigg, H. P.; Mauli, R.; Flury, E.; Hauser, D. *Helv. Chim. Acta* **1965**, *48*, 962.
(4) Muller, B.; Tamm, Ch. *Helv. Chim. Acta* **1975**, *58*, 541.
(5) Chakrabartty, S. K. In *Oxidation in Organic Chemistry, Part C*; Trahanovski, W. S., Ed; Academic Press, Inc.; New York, 1978; pp 343–370.
(6) Burrows, E. P.; Szafraniec, L. L., unpublished data.