tion of electrostatic potential, provided the spatial distribution of the reactive species is governed solely by long-range electrostatic forces. To date, the predicted catalytic effect has been observed only for reactions of bulky organic reagents,[5-9] and it has been demonstrated that, at least in some of these cases, hydrophobic bonding plays an important role in the interation of the reagent and the polyions.[8,9] We have therefore chosen to investigate the effect of two polyanions (polyvinylsulfonate (PVS) and polymethacryloxyethylsulfonate (PMES)) on the Hg^{2+}-catalyzed aquation of $Co(NH_3)_5Cl^{2+}$. This reaction has been studied extensively in the past in investigations of the kinetic salt effect, and it has the advantage that it may be followed by ultraviolet spectroscopy at extremely high dilution of the reagents. The nature of the reaction in the presence of polyelectrolyte was confirmed by (a) the absence of any spectral change of the cobalt complex over the time scale of the experiments reported in the absence of Hg^{2+} and (b) the identity of the ultraviolet spectrum observed at the end of the reaction with that obtained on addition of $Co(NH_3)_5 \cdot H_2O^{3+}$ to a solution containing the polymeric acid and Hg^{2+}.

The reactions were run at 5 ± 0.05° in solutions adjusted to pH 3 by perchloric acid, containing 5×10^{-6} *M* $Co(NH_3)_5Cl^{2+}$ and 5×10^{-5} *M* Hg^{2+}. Under these conditions, the disappearance of $Co(NH_3)_5Cl^{2+}$ is characterized by a pseudo-first-order rate constant of 2.38×10^{-7} sec^{-1} in the absence of polyelectrolyte. As expected, the catalytic effects produced by the two polyanions were enormous; in the absence of added simple electrolyte and with a polyanion concentration of 5×10^{-5} *N*, the reaction was accelerated by factors of 24,700 with PMES and 176,000 with PVS. The closer proximity of the fixed charges to the backbone of PVS accounts probably for its higher catalytic efficiency.

Addition of simple salts reduces the effect of the polyion on the reaction rate, since increasing counterion concentrations shield the fixed charges of the polyion and reduce its interaction with Hg^{2+} and $Co(NH_3)_5Cl^{2+}$. For instance, in the presence of 0.01, 0.03, and 0.05 *M* $NaClO_4$, the acceleration factors due to PVS fall off to 58,200, 13,000, and 4000.

Table I lists acceleration factors observed in the presence of 0.01 *M* $NaClO_4$. The data show that as the polyion concentration is increased, the reaction rate first increases, but then decreases sharply. This may be explained as follows. As long as the sum of the concentrations of the reagent ion is in large excess over the ionized sites of the polymer, only a small fraction of the reagent ions is held in the polyion domains and the distribution of the counterions in any one of these domains may be considered to be independent of the polyion concentration. The increase of the catalytic effect on polyion addition in the dilute concentration range reflects then the increasing fraction of bound $Co(NH_3)_5Cl^{2+}$. However, in more concentrated polymer solution the binding of both reagents is essentially complete, and further polymer addition distributes the reagents over more polymer domains, reducing the probability of their mutual collision.

Table I. Acceleration of the Hg^{2+}-Catalyzed Aquation of $Co(NH_3)_5Cl^{2+}$ by Polyanions[a]

Polyanion, *N*	Acceleration factor— PVS	PMES
1.5×10^{-5}	16,600	2,600
5×10^{-5}	58,200	5,300
1.5×10^{-4}	64,500	11,400
5×10^{-4}	44,100	9,300
1.5×10^{-3}	18,800	3,100

[a] 5×10^{-6} *M* $Co(NH_3)_5Cl^{2+}$, 5×10^{-5} *M* Hg^{2+}, 10^{-2} *M* $NaClO_4$, 5°.

A similar phenomenon is observed if the polyanion concentration is fixed and the Hg^{2+} concentration is varied. As long as only a fraction of the anionic sites of the polymer bind the reagent ions, an increase in Hg^{2+} concentration increases the local Hg^{2+} concentration in the polymer domains and thus accelerates the reaction of bound $Co(NH_3)_5Cl^{2+}$. However, once the polyanions are saturated with reagent ions, further Hg^{2+} addition displaces bound $Co(NH_3)_5Cl^{2+}$, and the reaction rate decreases.

Barry Vogel, Herbert Morawetz
Polymer Research Institute, Polytechnic Institute of Brooklyn
Brooklyn, New York 11201
Received December 8, 1967

Heterocyclic Studies. XXVII. Tautomerism in the Dihydro-1,2-diazepin-4-one System[1]

Sir:

In the course of rather extensive studies of rearrangements and substitution reactions of the 2,3-dihydrodiazepinone **1**,[2] enolization involving both the N-2 and C-3 protons, leading to the deuterium exchange at C-7 and C-3, respectively, has been observed,[3,4] but no other tautomeric forms were detected. We now report the isolation of a second tautomer of this system and the interconversion of these compounds.

The bicyclic ketone **2** is readily obtained by photocyclization of **1** and reverts to the seven-membered valence isomer in the dark.[5] However, treatment of **2** with base at room temperature gives a third isomer, isolated in about 50% yield. This compound,[6] mp 167–168°, ν_{CO}^{KBr} 1630 cm^{-1}, λ_{max}^{MeOH} 241 (ε 12,700), 304 (ε 8000), and 386 mμ (ε 5100), has been found to be the 1,5-dihydrodiazepinone **4**. The spectral values suggest a multiply unsaturated carbonyl system; a semicarbazone,[6] mp 217°, was obtained. Distinctive evidence for structure **4** was provided by the nmr spectrum, which contained a doublet methyl peak; the H-5 peak was split by both H-3 and H-7 [δ^{CDCl_3} 1.08 (d, J = 7 Hz; 3), 3.78 (m; 1), 6.77 (dd, J = 4 and 1.6 Hz, in D_2O → d, 1.6 Hz; 1), and 7.33 ppm (s; 6); $\delta^{DMSO\text{-}d_6}$ 0.89 (d, J = 7; 3), 3.67 (ddq, J = 7, 1.6, and 1.6 Hz; 1), 6.97 (d, J = 1.6 Hz; 1) 7.25 (d, J = 1.6 Hz; 1), and 7.37

(5) W. Kern, W. Harold, and B. Scherlag, *Makromol. Chem.*, **17**, 231 (1956).
(6) T. J. Painter, *J. Chem. Soc.*, 3932 (1962).
(7) C. L. Arcus, T. L. Howard, and D. S. South, *Chem. Ind.* (London), 1756 (1964).
(8) I. Sakurada, Y. Sakaguchi, T. Ono, and T. Ueda, *Makromol. Chem.*, **91**, 243 (1966).
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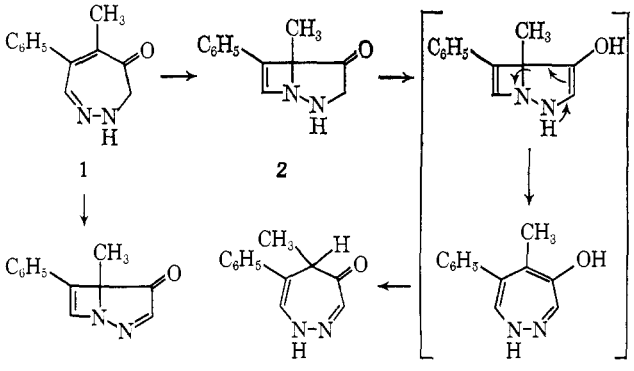
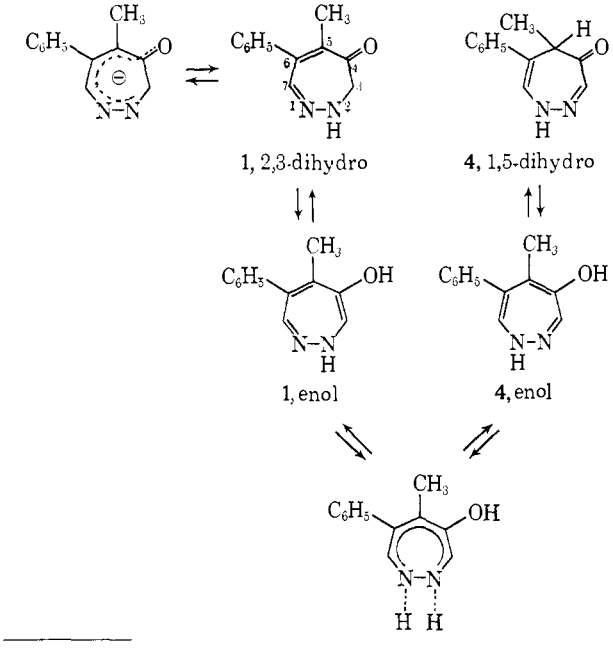
(1) Supported by Grant GP-5219 from the National Science Foundation.
(2) J. A. Moore, *Trans. N. Y. Acad. Sci.*, 27, 591 (1965).
(3) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).
(4) J. A. Moore, H. Kwart, G. Wheeler, and H. Bruner, *ibid.*, 32, 1342 (1967).
(5) W. J. Theuer and J. A. Moore, *Chem. Commun.*, 468 (1965).
(6) Satisfactory analytical values were obtained for all compounds reported.



ppm (s; 5)].[7] The formation of **4** is considered to proceed by enolization and cyclic elimination in the five-membered ring, in contrast to the reverse cycloaddition in the four-membered ring which leads to **1**.

In the presence of air, a compound with two less hydrogens was obtained in small amounts as a by-product with **4**. This compound,[6] isolated by sublimation from the mother liquor of **4**, had mp 70° [$\nu_{CO}^{CCl_4}$ 1730 cm^{-1}; λ_{max}^{MeOH} 265 (ϵ 17,000) and 342 mμ (ϵ 370); δ^{CDCl_3} 1.69 (s; 3), 7.20 (s; 1), 7.37 (s; 5), and 7.78 ppm (s; 1)].[4] Reduction with sodium borohydride gave the same bicyclic carbinol, mp 220°, obtained by reduction of **2**.[5] These properties clearly define the diazabicyclo[3.2.0]heptadienone structure **3**. The synthesis of **3** was effected in 87% yield by treatment of the N-2-tosyl derivative of **2** in toluene solution at 25° with sodium methoxide.

The isolation of the 1,5-dihydro tautomer **4** has permitted us to examine the possible interconversion and relative stabilities of these diazepinones. The relationship between the enols of **1** and **4** is formally analogous to that existing in unsymmetrical N-unsubstituted pyrazoles, in which separate tautomers have never been isolated, but with the important difference that the eight π-electron systems in these enols can be expected to be separated by a significant energy barrier in the attainment of a planar transition state.

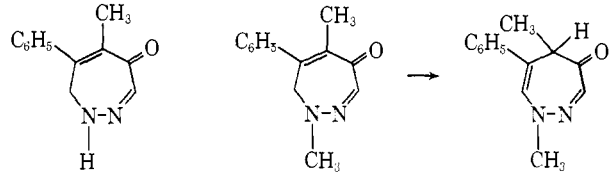


(7) In nmr descriptions, s = singlet, d = doublet, q = quartet; the final numeral is whole number of protons from integral.

In DMSO-d_6 solution containing NaOD, the methyl doublet at 0.89 ppm in the nmr spectrum of **4** rapidly collapsed to a singlet, corresponding to enolization and deuterium exchange at C-5, but there was no measurable exchange of the C-3 or C-7 protons due to formation of an anion at N-1. At 40°, with 0.12 equiv of NaOH/mole of **4**, a peak at 1.67 ppm due to the methyl group of **1** appeared, and increased to a height corresponding to about 10–11% of the total methyl resonance in 30 hr. Under the same conditions, isomerization of the 2,3-dihydro isomer had progressed to give 54% of the 1,5-dihydro compound in 13 days. After 7 weeks the two spectra, including impurity peaks, were essentially identical, with the ratio **4**:**1** ~8.

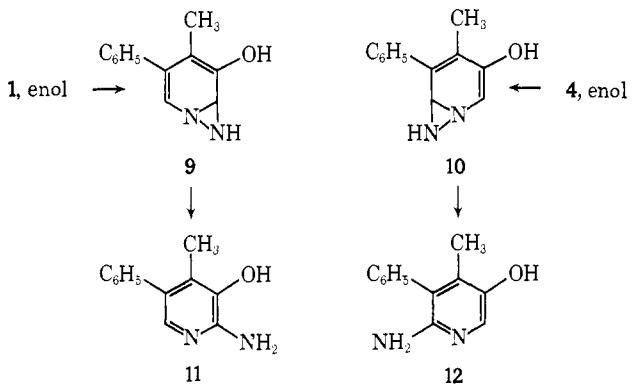
These data demonstrate clearly that the two diazepinones are interconvertible and that **4** is the more stable tautomeric form under these conditions. The isomerization of **1** at 60° in DMSO with 0.1 equiv of base for 4 days provides a convenient preparative method for **4**, which can be isolated in 50–60% yield. With 0.25 equiv of NaOD/mole the ratio **4**:**1** drops to ~3, and with excess base none of the 1,5-dihydro isomer **4** is observed.[3] The predominance of the 2,3-dihydro form at higher base concentration reflects formation of the anion **5** by ionization of the N-2 H of **1**.[3]

A third ketonic tautomer, the 1,7-dihydrodiazepinone **6**, must also be considered in these equilibria; the 1-methyl derivative **7** was previously isolated and characterized.[8] No evidence of **6** was detected in these experiments, however, in keeping with the failure of **4** to undergo deuterium exchange at C-7. The greater stability of the 1,5-dihydro system could be demonstrated directly in the 1-methyl series; treatment of **7** with 0.12 equiv of NaOD in DMSO at 40° caused disappearance of 90% of **7** in 6 hr and formation of 75% of the 1-methyl-1,5-dihydro compound **8**.[6] In a preparative experiment, **8** was isolated in 40% yield after 1.75 hr, mp 93°, ν^{KBr} 1640 cm^{-1}, δ^{CDCl_3} 1.04 (d, J = 7.3 Hz; 3), 3.67 (s; 3), 3.6–3.8 (m; 1), 6.63 (d, J = 1.6 Hz; 1), 7.21 (d, J = 1.3 Hz; 1), and 7.30 ppm (s; 5).



At higher temperature and/or higher base concentration, the interconversion of the diazepinones **1** and **4** is accompanied by rearrangement to the 2- and 6-aminopyridines **11** and **12**. The 2,3-dihydro tautomer **1** has been shown to give rise to approximately equal amounts of **11** and **12** in aqueous or methanolic alkali.[3] It was of considerable interest to discover that the 1,5-dihydrodiazepinone **4**, in 2.5 N $NaOCD_3$ in CD_3OD at 25°, was converted to a mixture containing 40% of the 2,3-dihydrodiazepinone, 51% of the 6-aminopyridine **12**, and 7% of the 2-aminopyridine **11**. The small amount of **11** formed corresponds to that expected from the slower rearrangement of the 2,3-dihydro tautomer. This result reveals that the 6-aminopyridine **12** can arise from **4** by a pathway independent of the 2,3-dihydrodiazepine. A likely intermediate in this transformation, contrary to our earlier view,[3] is the valence

(8) J. A. Moore and W. J. Theuer, *J. Org. Chem.*, **30**, 1887 (1965).



tautomeric 1,7-diazabicyclo[4.1.0]heptadienol **10**. It was previously suggested that the pyridine mixture observed in the reaction of the 2,3-dihydro tautomer **1** arose by cleavage of the diazepine ring and recyclization of an acyclic intermediate to **11** and **12**.[3,4] In view of the interconvertibility of **1** and **4** and the findings with the 1,5-dihydro compound, however, it is possible that the formation of **11** and **12** from the 2,3-dihydro isomer does not involve a common precursor and that the 2-aminopyridine is generated from the bicyclic valence tautomer **9**.

Melvin G. Pleiss, James A. Moore
Department of Chemistry, University of Delaware
Newark, Delaware 19711
Received December 4, 1967

Stable Enol Esters from N-*t*-Butyl-5-methylisoxazolium Perchlorate

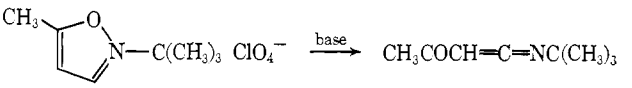
Sir:

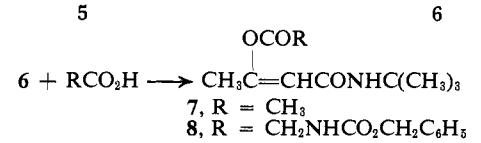
We wish to report that the intramolecular O,N-acyl migration of enol esters derived from isoxazolium salts can be prevented by the bulky N-*t*-butyl substituent.

The acyl migration rearrangement is a possible side reaction in the synthesis of peptides using N-ethyl-5-phenylisoxazolium-3′-sulfonate (**1**). Although high yields are obtained in peptide syntheses with **1** under optimum conditions, lower yields result if the addition of the amine component to the solution of the enol ester **2** is delayed.[1] Slow rearrangement, which has been observed in studies of model unsulfonated enol esters,[2] presumably gives the less useful acylating agent **3** under these conditions.[1] Therefore, isoxazolium salts which give stable enol esters are of special interest because they might be still more efficient than **1** in peptide synthesis and would allow isolation, rigorous purification, and storage of the intermediate acylating agents.

One approach[3] to the design of improved isoxazolium salt peptide reagents was suggested by the superiority of **1** compared to the N-methylisoxazolium zwitterion in test preparations, which indicated that the esters from **1** were less susceptible to rearrangement, owing to the increased bulk of the N-ethyl group.[1] Enol esters with still bulkier N-alkyl substituents would then be expected to be even more resistant to the side reaction.[7] A test of the simple steric approach was made possible by the discovery of a convenient method for the *t*-butylation of isoxazoles.[9] Our preliminary investigation has revealed that the enol esters from the new reagent N-*t*-butyl-5-methylisoxazolium perchlorate (**5**)[10] are stable compounds which have synthetic utility as acylating agents.

Since the intermediate ketoketenimine **6** can be isolated from **5**,[10] it was hoped that direct combination of carboxylic acids with **6** would provide an elegant method of preparing the enol esters, and an initial preparation with acetic acid and **6** gave very promising results. Exact equivalents of the reactants were dissolved in carbon tetrachloride, and the solvent was removed under reduced pressure at room temperature to force the reaction to completion.[11] The crystalline residue consisted of the nearly pure ester **7**,[12] and, after recrystallization from carbon tetrachloride–petroleum ether (bp 20–40°), the yield of pure material was 95%. However, attempts to extend this procedure to more polar solvents, which were desired for use in the conversion of N-protected amino acids to enol ester acylating agents, resulted in the isolation of less pure products. With nitromethane as the solvent, the ester **8** of carbobenzoxyglycine could be obtained in 91% yield on precipitation with petroleum ether, but several recrystallizations were required for complete purification. Studies are in progress to elucidate the nature of the side reactions responsible for the formation of the impurities in the enol ester preparation.[13]





The enol esters are sufficiently stable for storage and use as synthetic intermediates. In contrast to the previously isolated, unsulfonated N-methyl enol ester of acetic acid, which decomposes within a few days,[2] the pure crystals of **7** and **8** were unchanged after months of storage in a desiccator over phosphorus pentoxide. Spectral tests further revealed no rearrangement or other

(1) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).
(2) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, 7, 415 (1966).
(3) It has recently been found that enol esters from the N-ethylbenzisoxazolium cation (**4**) are stable,[4] and acylating agents have been isolated also from derivatives of **4**.[5,6]
(4) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).
(5) S. Rajappa and A. S. Akerkar, *Chem. Commun.*, 826 (1966).
(6) D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2743 (1967).
(7) The esters from N-arylisoxazolium salts were found to be especially susceptible to intramolecular acyl migration *via* the anion.[8]
(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).
(9) R. B. Woodward and D. J. Woodman, *ibid.*, 31, 2039 (1966).
(10) R. B. Woodward and D. J. Woodman, *J. Am. Chem. Soc.*, **88**, 3169 (1966).
(11) The N-*t*-butylketoketenimine **7** does not react as rapidly with carboxylic acids as do those from previously studied isoxazolium salts.
(12) Elemental analyses and spectral data are in accord with the expected structures **7** and **8**.
(13) It is unlikely that the source of the difficulty is the presence of nucleophilic contaminants in the solvents. The water product **9** is detectable with undried solvents, but purification to remove basic impurities and drying of solvents do not improve the results. Moreover, nmr spectral tests show similar peaks from unidentified side products with both nitromethane and acetonitrile as solvents for acetic acid. The possibility that these contaminants arose from rearrangement or other decomposition of the product ester was ruled out by control experiments which established that the product was stable to the reaction conditions alone or in combination with either starting material.