rected. Analyses were performed by Clark, Means, and Perkins Microanalytical Laboratory, Urbana, Ill.

2-Benzyl-4,4-dimethyl-2-oxazoline (3). The method of Wehrmeister was used.[7] A mixture of 272 g (2.0 mol) of phenylacetic acid and 178 g (2.0 mol) of 2-amino-2-methyl-1-propanol in 500 ml of xylene was heated to maintain gentle reflux using a 35-cm Vigreux column and a Dean-Stark trap. After 30 h the calculated amount of water had been removed. The solution was cooled, washed with 10% $NaHCO_3$ and with brine, dried over K_2CO_3, and distilled. The product was 295 g (78%) of colorless liquid: bp 132–134 °C (19 Torr); NMR δ 7.22 (s, 5 H), 3.79 (s, 2 H), 3.52 (s, 2 H), 1.20 (s, 6 H); ir 1665 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.76; H, 7.72; N, 7.34.

2-Benzoyl-4,4-dimethyl-2-oxazoline (4). A solution of 69 g (0.37 mol) of **3** in 1000 ml of dry THF was cooled in dry ice–acetone to −77 °C and stirred under N_2 while 150 ml of *n*-butyllithium (2.45 M in hexane) (0.37 mol) was added over 60 min. The addition funnel was removed (*Caution:* if the funnel is left in place, residual butyllithium may cause detonation during introduction of oxygen) and replaced by a gas dispersion tube extending below the surface of the mixture. Dry oxygen was bubbled into the mixture at a rate such that the temperature remained below −70 °C, and the partially insoluble lithio derivative of **3** dissolved over 50 min. Introduction of oxygen was continued at −77 °C for an additional 3 h, then the solution was treated with 200 ml of 10% NH_4Cl and 1000 ml of ether. The organic layer was separated, washed with brine, and dried over K_2CO_3. The solvent was evaporated, and the residue was dissolved in 500 ml of hexane and allowed to stand for 2 days. A white solid precipitate, 14 g, was filtered off and washed with hexane. The combined filtrate and wash was evaporated, and the residue was distilled to give 44.8 g (60%) of a faintly yellow liquid, bp 104–108 °C (0.1 Torr). The analytical sample was further purified by chromatography on silica gel and distillation as a colorless liquid: bp 102–103 °C (0.1 Torr); NMR δ 7.1–8.3 (m, 5 H), 4.04 (s, 2 H), 1.38 (s, 6 H); ir 1670, 1630 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.54; N, 6.70.

Treatment of an ethanol solution of **4** with 1 equiv of phenylhydrazine gave, after cooling and recrystallization from ether–pentane, the phenylhydrazone as white needles, mp 90–91 °C.

Hydrolysis of **4** by method A (see below) gave 86% of phenylglyoxylic acid which was identical with an authentic sample.

Reduction of 4 with Sodium Borohydride. A solution of 10.15 g (0.05 mol) of **4** in 20 ml of 95% ethanol was added dropwise at 0–5 °C to a stirred solution of 1.9 g (0.05 mol) of $NaBH_4$ in 50 ml of 95% ethanol. After stirring for 2 h at 0 °C, the solution was diluted with an equal volume of water and extracted with three 50-ml portions of ether. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated to yield 10.02 g (98%) of the carbinol **5**. Recrystallization from acetone–hexane gave white crystals: mp 78–79.5 °C; NMR δ 7.1–7.6 (m, 5 H), 5.72 (br s, 1 H), 5.29 (s, 1 H), 3.82 (s, 2 H), 1.16 (s, 6 H); ir 3150, 1655 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.21; H, 7.40; N, 7.13.

Hydrolysis of **5** by method B (see below) gave 63% of mandelic acid identified by comparison with an authentic sample.

Reaction of 4 with Grignard Reagents. In a typical reaction, a solution of 30 mmol of the Grignard reagent in 25 ml of dry ether was prepared in the usual manner. To the stirred Grignard solution under N_2 was added, at a rate to maintain moderate reflux, a solution of 20 mmol of **4** in 40 ml of ether. When addition was complete the mixture was stirred under reflux for 1–2 h and was then treated carefully in the cold with 20 ml of 20% NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with three 50-ml portions of ether. The ether solutions were combined, washed with brine, dried (Na_2SO_4), and evaporated. The carbinols, **7**, could be isolated in yields of 85–95%, but usually the crude mixture was hydrolyzed without further purification using one of the methods below. In the case of *tert*-butylmagnesium chloride, the reagent was generated in THF, and the yield of **7f** was only 48%.

Hydrolysis Method A. The oxazoline (20 mmol) or the crude product from the Grignard reaction above was dissolved in 20 ml of HCl (6 N) and heated under reflux. Times required for complete hydrolysis varied from 1 to 4 h. The mixture was cooled and extracted with 50 ml of ether, and the ether solution was washed with brine, dried (Na_2SO_4), and evaporated. The products were recrystallized from cyclohexane.

Hydrolysis Method B. The oxazoline (20 mmol) or the crude product from the Grignard reaction was treated with 6 ml of 6 N HCl and warmed to 50–60 °C for 15–30 min. The resulting mixture was treated with a solution of 10 g of NaOH in 50 ml of methanol–water (1:1) and heated under reflux for 1–2 h. The methanol was evaporated and the aqueous solution was acidified to Congo red with HCl (concentrated). The mixture was extracted with three 50-ml portions of ether, and the ether solution was washed with brine, dried, and evaporated. The products were recrystallized from cyclohexane.

Acknowledgment. This work was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society. Helpful discussions and encouragement by Professor A. I. Meyers are appreciated.

Registry No.—**3**, 1569-08-0; **3** lithio derivative, 60031-36-9; **4**, 60031-37-0; **4** phenylhydrazone, 60031-38-1; **5**, 611-73-4; MeI, 74-88-4; EtBr, 74-96-4; *i*-PrBr, 75-26-3; PhBr, 108-86-1; PhC≡CBr, 932-87-6; *t*-BuCl, 507-20-0.

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Oximation of 3,5-Dimethyl-4-piperidones. Configurations and Conformations of the Adducts

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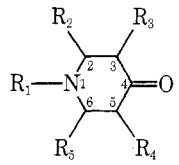
Isolated examples of changes of configuration and conformation during oximation of hexacyclic ketones substituted α,α' to the carbonyl group have been observed and according to Johnson[1a,b,c] attributed to the $A^{(1-3)}$ interaction due to introduction of the hydroximino group. *cis*-2,6-Dimethylcyclohexanone, for example, gives predominantly the oxime conformation with the two methyl groups in an axial orientation[2] signifying that reaction occurs on a ketone which although less stable conformationally is less crowded sterically; previously[1c] this oxime has been shown to epimerize very slowly to trans compound. 1-Methyl-*cis*-3,5-diphenyl-4-piperidone, on the other hand, gives only the oxime where the phenyl groups are in an orientation trans to each other.[3] The Mannich base character of piperidones makes them able to epimerize their α,α' positions through a keto–enol equilibrium more easily than other ketones or their β,β' positions through a reverse Mannich reaction.[4,5] In the latter example[3] oximation occurs on 1-methyl-*trans*-3,5-diphenyl-4-piperidone formed by prior epimerization of the cis ketone in the reaction medium.

It would seem then that for piperidones configurational rather than conformational changes would be more facile. However, in a single instance, that of 1-methyl-*cis*-2,6-diphenyl-*cis*-3,5-dimethyl-4-piperidone, it has been reported that the product of reaction has a twist-boat conformation with no suggestion of epimerization.[6]

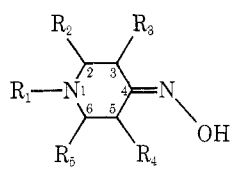
With a view to clarifying the situation, we have made a more detailed examination of the oximation of *cis*-3,5-dimethyl-

Table I. NMR Data for Ketones



	Compd	Structural assignments						
		H_2	H_3	H_5	H_6	Me-3	Me-5	*N*-Me
1	R_1 = H R_2 = R_5 = Ph (eq) R_3 = R_4 = CH_3 (eq)	3.55 J = 10.5	2.67 J_1 = 10.5 J_2 = 6.5	2.67 J_1 = 10.5 J_2 = 6.5	3.55 J = 10.5	0.78 J = 6.5	0.78 J = 6.5	
2	R_1 = H R_2 = R_5 = Ph (eq) R_3 = CH_3 (eq) R_4 = CH_3 (ax)	3.56 J = 10.5	≃2.77	≃2.77	4.27 J = 3.5	0.81 J = 6.5	1.07 J = 7	
3	R_1 = R_3 = R_4 = CH_3 (eq) R_2 = R_5 = Ph (eq)	≃3.0 J = 10.5	≃3.0 J_1 = 10.5 J_2 = 6.0	≃3.0 J_1 = 10.5 J_2 = 6.0	≃3.0 J_1 = 10.5	0.84 J = 6.0	0.84 J = 6.0	1.73
4	R_1 = R_3 = R_4 = CH_3 (eq) R_2 = R_5 = H	3.02 eq J_1 = 10.5 J_2 = 2.0 2.11_{ax} J_1 = 10.5 J_2 = 10.5	2.70 J_1 = 10.5 J_2 = 2.0 J_3 = 6.5	2.70 J_1 = 10.5 J_2 = 2.0 J_3 = 6.5	3.02 eq J_1 = 10.5 J_2 = 2.0 2.11_{ax} J_1 = 10.5 J_2 = 10.5	0.98 J = 6.5	0.98 J = 6.5	2.38
5	R_1 = R_3 = CH_3 (eq) R_4 = CH_3 (ax) R_2 = R_5 = H					0.98 J = 6.5	1.15 J = 7	2.33

Table II. NMR Data for Oximes



	Compd	Structural assignments						
		H_2	H_3	H_5	H_6	Me-3	Me-5	*N*-Me
6	R_1 = H R_2 = R_5 = Ph R_3 = R_4 = CH_3 twist 2,5	3.89 J = 5.8	3.04 J_1 = 5.8 J_2 = 7.4	3.75 J_1 = 9.2 J_2 = 6.7	3.85 J = 9.2	1.38 J = 7.4	1.46 J = 6.7	
7	R_1 = H R_2 = R_5 = Ph (eq) R_3 = CH_3 (eq) R_4 = CH_3 (ax)	3.57 J = 10.5	2.86 J_1 = 10.5 J_2 = 6.5	4.28 J_1 = 3.5 J_2 = 7.0	4.16 J = 3.5	1.12 J = 6.5	1.16 J = 7.0	
8	R_1 = R_3 = R_4 = CH_3 R_2 = R_5 = Ph twist 2,5	3.31 J = 4.0	2.98 J_1 = 4 J_2 = 7	3.88 J_1 = 9 J_2 = 6.5	3.46 J = 9	1.36 J = 7.0	1.38 J = 6.5	1.85
9	R_1 = R_3 = CH_3 (eq) R_2 = R_5 = H R_4 = CH_3 (ax)	2.55 to 2.90	2.55 to 2.90	3.89 J_1 = 7.5 J_2 = J_3 = 4	ax 2.05 J_1 = 11 J_2 = 4 eq 2.55 to 2.90	1.16 J = 6.5	1.35 J = 7.5	2.15
10	R_1 = CH_3 (eq) R_2 = R_5 = H R_3 = R_4 = CH_3 (ax)	ax 2.11 J_1 = 11.5 J_2 = 4.5 eq ≃ 2.59	2.77 J_1 = 7.5 J_2 = J_3 = 4.5	3.72 J_1 = 7.5 J_2 = J_3 = 4.5	ax 2.03 J_1 = 11.5 J_2 = 4.5 eq ≃2.59	1.40 J= 7.5	1.44 J = 7.5	2.17

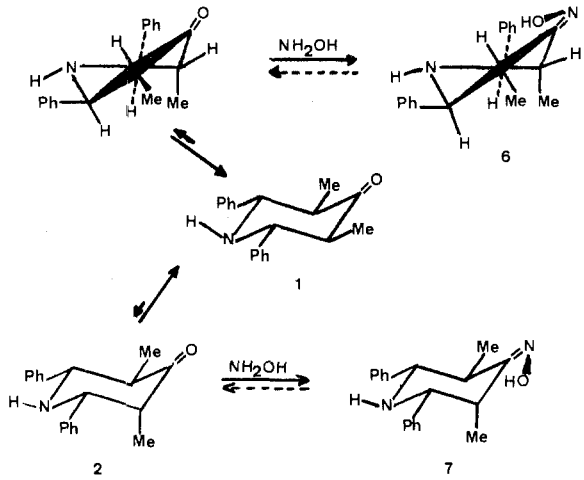
4-piperidones in a weakly acidic medium (pH 5.5). For this purpose we have made use of chemical and NMR methods.

Results

***cis*-2,6-Diphenyl-*cis*-3,5-dimethyl-4-piperidone (1).** Under the reaction conditions this ketone gives two oximes, **6** (mp 138 °C) and **7** (mp 205 °C), separated by preparative thin layer chromatography; this result does not seem to have been noticed before (Scheme I). The ratio is 80% for **6** and 20% for **7**.

Deoximation, by heating with sodium metabisulfite,[7] gives 100% of **1** starting from **6** and a mixture of 80% of **1** and 20% of **2** starting from **7**. At room temperature, on the other hand, **7** gives **2** exclusively, and reoximates rapidly under these conditions returning to **7** only. When oximation of **1** is carried on in the presence of D_2O, positions 3 and 5 are deuterated by

Scheme I



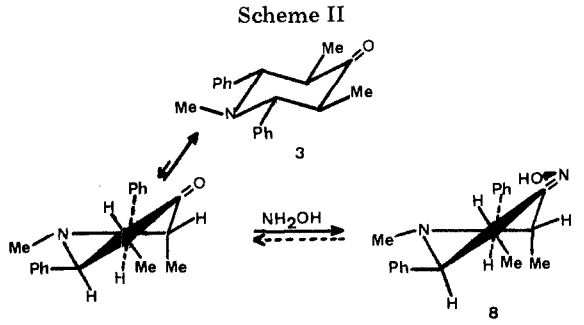
exchange.

The NMR data (Table I) indicate that **1** and **2** are ketones epimeric at the 5 position (**2** has two different methyl signals with different coupling; $J_{H_5H_6}$ = 3.5 Hz corresponding to axial–equatorial coupling constant). They appear to correspond to the compounds isolated by Theil and Deissner but whose configurations were not determined;[8] **2** has been isolated by Haller and Ziriakus starting from the semicarbazone of **1**.[6]

The chemical and spectral results we obtained (Table II) show that oxime **7** possesses an axial 5-methyl group derived by epimerization of **1** in the reaction medium (two different methyl signals; $J_{H_5H_6}$ = 3.5 Hz). The oxime **6** appears to have a 2,5-twist-boat conformation (two different methyl signals with different coupling, $J_{H_2H_3}$ = 5.8, $J_{H_5H_6}$ = 9.2 Hz, differing from normal J_{a-a} or J_{a-e}).[12,13] We have excluded the possibility that epimerization of a phenyl group has occurred in this instance not only for steric reasons but also on the basis of the NMR results.

1-Methyl-*cis*-2,6-diphenyl-*cis*-3,5-dimethyl-4-piperidone (3). Ketone **3** gives only the oxime **8** which on deoximation at elevated temperature yields the starting ketone exclusively (Scheme II). Epimerization of this ketone either

Scheme II

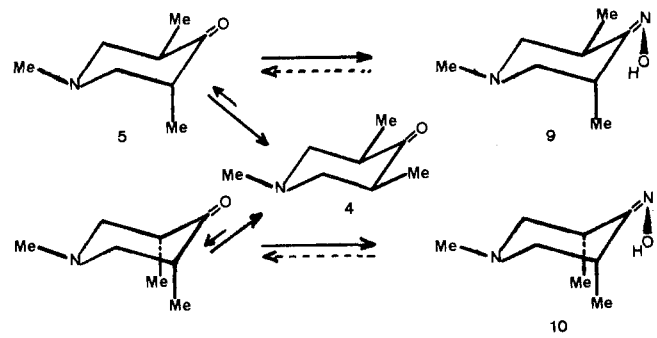


in acidic or basic media, as has already been observed,[8] appears not to be possible. The NMR data confirm the conformational similarity between **6** and **8**: both of them have a 2,5-twist-boat conformation (see above).

1-Methyl-*cis*-3,5-dimethyl-4-piperidone (4). In order to confirm the generality of the α,α' epimerization, it was considered important to study ketone **4** since the easy epimerization of the corresponding 1-methyl-*cis*-3,5-diphenyl-4-piperidone[3] might have been uniquely due to the presence of the phenyl substituent.

The oximation of **4**, at elevated temperatures, leads to oximes **9** (mp 98 °C) and **10** (oil) in a ratio of 65 and 35%, respectively (Scheme III). At room temperature **10** alone is

Scheme III



formed in 15 min. Deoximation of the two oximes gives back the starting ketone under all conditions.

We tried to establish the existence of the epimer of **4** by NMR. The ketone under weakly acidic conditions (HCl) gives no indication of the signals due to the ketone **5**, even at 70 °C; nevertheless, in D_2O and especially at higher temperatures (70 °C), a slow exchange, made particularly apparent by decoupling the methyl signals, is observed. The same study made in $CDCl_3$, under basic conditions (NaOH added), indicates the presence of ketone **5** to the extent of 30% at 70 °C; the ratio drops to 15–20% at room temperature. With added D_2O, the exchange occurs on both ketones in the 3 and 5 positions, also made evident from the decoupling of the methyl signals.

Unfortunately it appears impossible to isolate **5** from the mixture of the two ketones obtained in basic medium: during attempted separation **5** is invariably converted to the more stable isomer **4**.

Thus, the results clearly show that enolization through a keto–enol equilibrium may occur, even in a weakly acidic medium, yielding the ketone **5** precursor of **9**. The spectral properties of this latter oxime support this further in that its spectrum is very similar to that of oxime **7** (Table II) whose methyl groups are known to be in a trans configuration. The chemical shifts and coupling constants of **10** are in accordance with that already found for a compound with two axial methyl groups: the difference in the chemical shifts $\Delta\delta = \delta H_{5_{syn}} - \delta H_{3_{anti}}$ = 0.95 ppm is in good agreement with the difference of 0.92 ppm[2] which we observed previously for the oxime of *cis*-2,6-dimethylcyclohexanone, $J_{H_2H_3} = J_{H_5H_6}$ = 4.5 Hz, showing H_3 and H_5 to be equatorially coupled (7.5 Hz) with axial methyls.

Discussion

Our results, together with those already reported in the literature, indicate that for the oximation of α,α'-substituted 4-piperidones the following rules are applicable.

(1) The reaction will proceed under the mildest conditions via the syn-axial isomer, if such is possible (conformational inversion).

(2) Where enolization is facile, such as with the 4-piperidones, epimerization can occur and the reaction may give the α,α' trans-substituted oxime (different configuration).

(3) When both conformational inversion and epimerization are hindered, the reaction may occur mainly (if not entirely) via a distorted (i.e., twist-boat) cis conformation.

The latter point, which corresponds to the behavior of **1** and **3**, requires further elaboration. In these two cases an additional inhibition factor exists, i.e., the steric factor due to the phenyl groups. Examination of models of **1** and **3** suggests that the conformation in which the planes of the phenyl ring lie perpendicular to the cyclohexane ring is most favored. If epimerization occurs and a methyl group becomes axial, the neighboring phenyl is forced to rotate.[14] This new configuration is thermodynamically less stable because of two new interactions, one arising from the nitrogen substituent, the

other from the equatorial 3 or 5 proton. For **1** such a configuration may just be possible and would account for the presence of the minor oxime **7** but with **3** where strong interactions between the phenyl and the *N*-methyl develop, epimerization would be prevented.

Conclusion

The conformations or configurations of the oximes prepared from α,α'-substituted 4-piperidone in a weakly acidic medium are those that minimize the $A^{(1-3)}$ strain due to the hydroximino group.

Depending upon thermodynamic stability, crowding in the β,β' positions of the ketones, and reaction temperature, oximes of different structure are obtained whose proportions are determined by the ease of formation of the reactive species and their relative reactivity.

Experimental Section

The ketones **1**, **3**, and **4** prepared by known methods,[9-11] were oximated in a sodium acetate medium.[6] Oximes **6** and **7** were separated by preparative thin layer chromatography on silica gel F 254 (Merck); elution was with a mixture of ether–petroleum ether (50:50). **9** was crystallized from the crude mixture of **9** and **10** in petroleum ether.

The NMR spectra were recorded either on a Varian A-60, Varian HA-100, or Cameca 250. For the ketones $CDCl_3$ was used as solvent, and pyridine-d_5 for the oximes. The chemical shifts are given in parts per million (δ) from Me_4Si and coupling constants in hertz. In some cases $Eu(DPM)_3$ or double resonance were used.

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Registry No.—**1**, 18699-96-2; **2**, 37418-41-0; **3**, 18700-01-1; **4**, 29804-19-1; **5**, 31499-19-1; **6**, 59953-67-2; **7**, 59953-68-3; **8**, 37418-39-6; **9**, 59953-69-4; **10**, 59953-70-7.

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(12) It must be emphasized that only the 2,5 twist-boat conformation is in agreement with H_6 simultaneously more deshielded and more coupled than H_3 with respect to anisotropy of C=NOH and the Karplus rule.
(13) In such twist-boat conformations, models show a possible p,Π overlapping through space between the orbital of the electronic pair of nitrogen and the one of the carbonyl group contributing to the stabilization of the unfavored conformation.
(14) This change in orientation of one phenyl is in fact reflected in the chemical shifts of ketones **1** and **2** and oximes **7** and **9**.

Solvolytic Reactivity of Pyrazolylethanol and Isoxazolylethanol Derivatives

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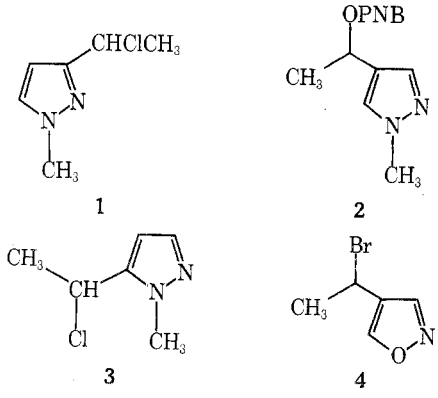
The solvolysis of α-arylethanol derivatives is a useful probe of aromatic reactivity.[2] Recent studies from this laboratory have extended this approach to thiazole[2] derivatives, isothiazole[3] derivatives, and imidazole[4] derivatives. The solvolysis reaction has several distinct advantages for the investigation of basic heterocyclic systems, as it may be carried out under neutral conditions, and thus avoid extrapolations and uncertainties in making a choice between the free base or its protonated form as the reactive species, when working in strongly acidic media.[5]

In the present report we present briefly our results on the pyrazole system and the isoxazole system. These may then be compared with earlier results for furan,[6a] pyrrole,[6b] and other aromatic derivatives.

We prepared and measured the rates of solvolysis for 1-(1-methyl-3-pyrazolyl)ethyl chloride (**1**), 1-(1-methyl-4-pyrazolyl)ethyl *p*-nitrobenzoate (**2**), 1-(1-methyl-5-pyrazolyl)ethyl chloride (**3**), and 1-(4-isoxazolyl)ethyl bromide (**4**).



Rates were measured in 80% ethanol, the solvent used in our previous studies, and the results are thus directly comparable. The choice of leaving group was dictated by the general level of reactivity of the systems. Pertinent rate data are accumulated in Table I.

The reactivity of each of these systems may be compared with appropriately analogous benzene derivatives, and then the effective replacement substituent constants,[2] σ_{Ar}^+, derived, using the ρ value determined by substituted 1-phenylethyl derivatives. These comparisons are presented in Table II.

Each of these ring systems shows markedly reduced reactivity compared to the heterocyclic system without the additional aza nitrogen. Thus, the change from the 3-furyl moiety to the 4-isoxazolyl moiety results in a change in the σ_{Ar}^+ value from −0.46 to 0.00. This change is reminiscent of the reduced reactivity of pyridine analogues of cumyl chloride,[7] noting the shift in the σ^+ value on changing from phenyl ($\sigma^+ \equiv 0.00$) to 3-pyridyl ($\sigma_{Ar}^+ = +0.54$). Additional comparisons of this sort, using the value of Hill et al.,[6b] for pyrrole show a change of σ_{Ar}^+ from −1.8 to the values reported in Table II of −0.41, −0.99, and −0.29 for the 3, 4, and 5 positions of the pyrazole nucleus, respectively. In each case, the shift in the σ_{Ar}^+ values is larger than the analogous 2, 3, or 4 positions of the pyridine system[7] (as a model for the introduction of the aza nitrogen).

There have been only a limited number of other investigations seeking to evaluate the quantitative electrophilic reactivity of pyrazoles and isoxazoles. The bromination of pyrazoles was investigated by Boulton and Coller.[8] Their rate of reaction is very close to that reported by Bell and Rawlinson[9] for the bromination of phenol, and thus σ_{Ar}^+ is very close to σ^+ for *p*-OH, e.g., −0.97 ± 0.08. Our results agree with this comparison.

On the other hand our results are at variance with the partial rate factors determined by Clementi, Forsythe, Johnson, and Katritzky[10] for the hydrogen–deuterium exchange reaction in sulfuric acid. The long range of the extrapolations