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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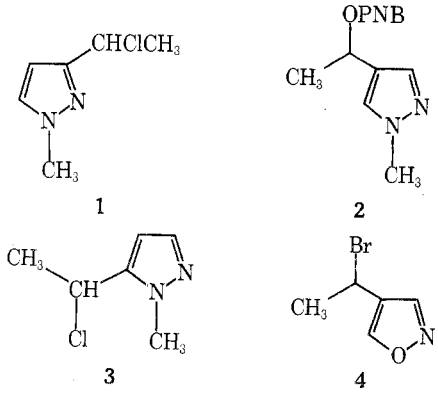
The solvolysis of α-arylethanol derivatives is a useful probe of aromatic reactivity.[2] Recent studies from this laboratory have extended this approach to thiazole[2] derivatives, isothiazole[3] derivatives, and imidazole[4] derivatives. The solvolysis reaction has several distinct advantages for the 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

Table I. Measured Rates of Solvolysis in 80% Ethanol

Compd solvolyzed	Temp, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
1	25.04	$1.21 \pm 0.02 \times 10^{-3}$	21.0	−1.7
	25.06	$1.196 \pm 0.004 \times 10^{-3}$		
	0.00	$4.27 \pm 0.06 \times 10^{-5}$		
	0.00	$4.28 \pm 0.03 \times 10^{-5}$		
2	25.00[a]	3.10×10^{-5}	22.0	−5.5
	44.57	$3.37 \pm 0.02 \times 10^{-4}$		
	45.00	$3.50 \pm 0.03 \times 10^{-4}$		
	60.0	$1.60 \pm 0.01 \times 10^{-3}$		
	60.0	$1.55 \pm 0.01 \times 10^{-3}$		
	75.0	$7.53 \pm 0.1 \times 10^{-3}$		
3	25.04	$3.38 \pm 0.03 \times 10^{-4}$	20.5	−5.7
	25.08	$3.45 \pm 0.01 \times 10^{-4}$		
	18.14	$1.41 \pm 0.01 \times 10^{-4}$		
	18.20	$1.46 \pm 0.01 \times 10^{-4}$		
	45.09	$3.15 \pm 0.01 \times 10^{-3}$		
	45.10	$3.16 \pm 0.01 \times 10^{-3}$		
4	24.98	$2.06 \pm 0.06 \times 10^{-4}$	18.84	−12.35
	24.98	$2.03 \pm 0.06 \times 10^{-4}$		
	44.50	$1.58 \pm 0.02 \times 10^{-3}$ [b]		
	57.60	$5.36 \pm 0.04 \times 10^{-3}$		
1-Phenylethyl bromide	25.00	$2.004 \pm 0.003 \times 10^{-4}$		
	57.68	$5.55 \pm 0.03 \times 10^{-3}$		

[a] Extrapolated from data at higher temperatures. [b] pH held constant at 4. Identical rate constants were obtained at pH 6, 8, and 10.

Table II. Reactivity Comparisons

Comparison for	Reactivity ratio, 25 °C	ρ[a]	σ_{Ar}^{+}
1:$C_6H_5CH(CH_3)Cl$	121	−5.12[b]	−0.41
2:$C_6H_5CH(CH_3)OPNB$	4×10^5	−5.8[c]	−0.99
3:$C_6H_5CH(CH_3)Cl$	34	−5.12[b]	−0.29
4:$C_6H_5CH(CH_3)Br$	1.02	−4.[d]	0.00

[a] Values of ρ used for determination of σ_{Ar}^{+}. [b] Reference 2. [c] Reference 4. [d] Approximate value, from rates of solvolysis of 1-phenylethyl chloride and 1-(1-*p*-chlorophenyl)ethyl bromide [cf. V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Am. Chem. Soc.*, **90**, 418 (1968)]. The value of σ_{Ar}^{+} for the isoxazolyl moiety is insensitive to the value of ρ.

necessary to compare pyrazoles with benzene would appear to vitiate the validity of Katritzky's partial rate factors. Different assumptions lead to different relative orders among the azoles.[11]

Our results reported here, in conjunction with the related results on isothiazoles,[3] should serve as a useful basis for making predictions for a wide range of heterocyclic reactions.

Experimental Section

Melting points were determined in a Büchi apparatus and are uncorrected. Boiling points are likewise uncorrected. Elemental analyses were obtained from the Analytical Services Laboratory, University of California, Berkeley.

Proton magnetic resonance spectra were obtained using a Varian T-60. Reported chemical shift values are in parts per million downfield from internal tetramethylsilane. The multiplicity of the signals is reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad.

1-(1-Methyl-4-pyrazolyl)ethanol. 1-Methylpyrazole was converted to 4-formyl-1-methylpyrazole by the procedure of Finar and Lord.[12] A solution of 6.0 g (0.055 mol) of 4-formyl-1-methylpyrazole in 100 ml of anhydrous ether was added dropwise with stirring to 36 ml of 3 M methylmagnesium bromide in ether. The reaction mixture was stirred overnight. Saturated ammonium chloride solution (100 ml) was added, the layers were separated, and the aqueous layer was washed with chloroform (4 × 25 ml). The organic layers were combined and dried ($MgSO_4$), and the solvents were evaporated. The yellow residue was distilled under vacuum to yield 3.2 g (36%) of 1-(1-methyl-4-pyrazolyl)ethanol: bp 89–91 °C (0.3 Torr); NMR ($CDCl_3$) δ 1.48 (d, J = 6 Hz, 3, CH_3CHOH–), 3.77 (s, 3, NCH_3), 4.03 (bs, 1, OH), 4.83 (q, J = 6 Hz, 1, CH_3CHOH), 7.29 (s, 1, 3-H), 7.35 (s, 1, 5-H).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 57.13; H, 7.87; N, 22.28.

1-(1-Methyl-4-pyrazolyl)ethyl *p*-nitrobenzoate (2) was prepared in the usual manner[4] for use in kinetic studies: NMR (CCl_4) δ 1.65 (d, J = 7 Hz, 3, CH_3CHOH–), 3.78 (s, 3, NCH_3), 6.00 (q, J = 7 Hz, 1, CH_3CHOH–), 7.08 (s, 2, 3-H and 5-H), 8.10 (s, 4, ArH).

1-(1-Methyl-5-pyrazolyl)ethyl chloride (3) was reported previously.[13]

1-(1-Methyl-3-pyrazolyl)ethanol. 1-Methyl-3-formylpyrazole was prepared following the procedure of Shrapranova and Somin[14] from 1,1-diethoxy-3-buten-2-one[15] and methylhydrazine, followed by oxidation with lead tetraacetate and hydrolysis. Addition of methylmagnesium bromide in ether to the aldehyde in ether gave, after quenching with ammonium chloride and extraction with methylene chloride, a solution of the alcohol. After drying the solvents were evaporated and the residue was distilled to yield 68% of 1-(1-methyl-3-pyrazolyl)ethanol: bp 110–112 °C (2.5 Torr); NMR ($CDCl_3$) δ 1.48 (d, J = 6 Hz, 3, CH_3CHOH–), 3.10 (bs, 1, OH), 3.80 (s, 3, NCH_3), 4.92 (q, J = 6 Hz, 1, CH_3CHOH–), 6.13 (d, J = 2 Hz, 1, 4-H), 7.23 (d, J = 2 Hz, 1, 5-H).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 57.19; H, 7.84; N, 22.12.

1-(1-Methyl-3-pyrazolyl)ethyl Chloride (1). To a solution of 0.6 g (0.005 mol) of thionyl chloride in 10 ml of 1,2-dichloroethane was added 0.63 g (0.005 mol) of 1-(1-methyl-3-pyrazolyl)ethanol in 3 ml of the solvent. The mixture was stirred and heated under reflux for 30 min. The solution was cooled in an ice bath, and then 0.5 g (0.005 mol) of triethylamine was added dropwise. The solution was cooled thoroughly, and the precipitated triethylamine hydrochloride was removed by filtration and rinsed with a few milliliters of solvent. The solvent was evaporated and the resulting yellow oil (0.7 g, 97%) was shown to be free of alcohol by NMR. The chloride was used in the kinetic determinations without further purification: NMR ($CDCl_3$) δ 1.85 (d, J = 6.5 Hz, 3, CH_3CHCl–), 3.82 (s, 3, NCH_3), 5.10 (q, J = 6.5 Hz, 1, CH_3CHCl–), 6.22 (d, J = 2 Hz, 1, 4-H), 7.32 (d, J = 2 Hz, 1, 5-H).

4-Ethylisoxazole. The procedure of Bredereck et al.[16] yielded 4-ethylisoxazole: bp 44–48 °C (ca. 15 Torr) [lit. 48 °C[16b] (16 Torr)]; NMR (CCl_4) δ 1.20 (t, J = 8 Hz, 3, $-CH_2CH_3$), 2.48 (q, J = 8 Hz, 2, CH_2CH_3), 8.07 (s, 1, 3-H), 8.18 (s, 1, 5-H).

1-(4-Isoxazolyl)ethyl Bromide (4). To a solution of 4-ethylisoxazole (8.64 g, 0.089 mol) in carbon tetrachloride (87 ml) were added *N*-bromosuccinimide (16.2 g, 0.091 mol) and ca. 0.5 g of benzoyl peroxide. The reaction mixture was irradiated and heated under reflux for 3 h. The initial heating was cautious. The solution was cooled and filtered. The solvent was removed to yield a slightly yellow product in yields varying from 82% to (most often) >95%. NMR (CCl_4) δ 2.00 (d, J = 6 Hz, 3, CH_3CHBr–), 5.08 (q, J = 6 Hz, 1, CH_3CHBr–), 8.20 (s, 1,3-H), 8.35 (s, 1,5-H). This compound was utilized without further purification for kinetic studies; however, hydrolysis to 1-(4-isoxazolyl)ethanol and elemental analysis of the alcohol were performed.

1-(4-Isoxazolyl)ethanol. A sample of 1-(4-isoxazolyl)ethyl bromide in tetrahydrofuran was diluted with an equal volume of water. The solution was kept slightly acidic. Stirring was continued for 2.5 h and periodically small portions of Na_2CO_3 were added. The solution was extracted with methylene chloride and the organic extract was dried ($MgSO_4$). Distillation gave a 4-g fraction (60%) boiling at 65–90 °C (0.5 Torr). Chromatography of this fraction on a neutral alumina column eluting with hexane–ethyl acetate solutions yielded pure 1-(4-isoxazolyl)ethanol: bp 65 °C (0.5 Torr); NMR ($CDCl_3$) δ 1.46 (d, J = 6 Hz, 3, CH_3CHOH–), 3.0 (s, 1, OH), 4.85 (q, J = 6 Hz, 1, CH_3CHOH–), 8.15 (s, 1, 3-H), 8.23 (s, 1, 5-H).

Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.89; H, 6.45; N, 12.46.

Kinetic methods have been described previously.[13]

Registry No.—**1**, 60031-44-9; **2**, 60031-45-0; **2** free alcohol, 40534-33-6; **3**, 57527-84-1; **4**, 60031-46-1; 4-formyl-1-methylpyrazole, 25016-11-9; methyl bromide, 74-83-9; 1-(1-methyl-3-pyrazolyl)ethanol, 60031-47-2; 1-methyl-3-formylpyrazole, 27258-32-8; 4-ethylisoxazole, 60031-48-3; *N*-bromosuccinimide, 128-08-5; 1-(4-isoxazolyl)ethanol, 21169-70-0.

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Reaction of 1-Azirine with Diphenyldiazomethane. On the 1:2 Adducts of 1-Azirine and Diphenylcarbene

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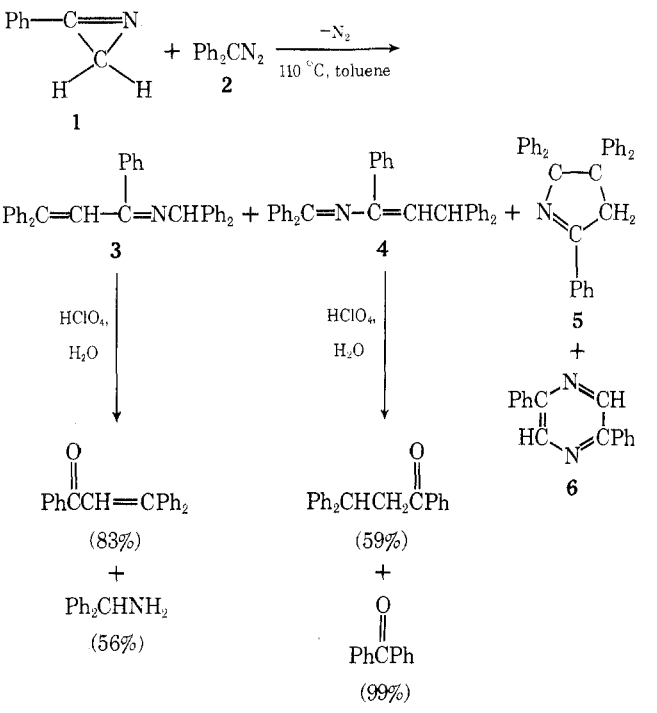
In this paper, we present studies on the reaction of 2-phenyl-1-azirine (1) with diphenylcarbene giving rise to 1:2 adducts. In this reaction, diphenyldiazomethane (**2**) was employed as the carbene source and thermolysis of the diazomethane **2** was carried out in refluxing toluene in the presence of the azirine **1** under an atmosphere of nitrogen. The reaction mixture was column chromatographed (aluminum oxide) to give 4-azapenta-1,3-diene **3** (20%), 2-azapenta-1,3-diene **4** (12%), pentaphenylpyrroline **5** (19%), and diphenylpyrazine **6** (17%). The compounds **3, 4,** and **5** had the same molecular formula of $C_{34}H_{27}N$ and, hence, are 1:2 adducts of the 1-azirine and diphenylcarbene. The structural assignment of these compounds was performed by means of spectrometry. The azadiene structures of **3** and **4** were further ascertained by the chemical evidences, as shown in Scheme I.

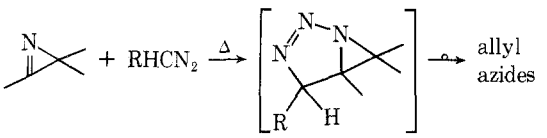
The product **5,** on the other hand, resisted hydrolysis under acidic conditions and gave **4** (31%) and tetraphenylethylene (16%) upon heating at 200 °C under reductive conditions (H_2 100 atm in the presence of platinum oxide). Oxidation of the compound **5** with *m*-chloroperbenzoic acid gave the *N*-oxide of **5.** The ir spectrum of the *N*-oxide showed the shift of C=N absorption toward a lower frequency. The pyrazine **6,** which often appears in the reactions of the azirine, was surely formed by the dimerization of **1** followed by dehydrogenation.

The above results are quite different from those of the reactions of simple diazomethane and phenyldiazomethane. These two diazomethanes have been reported to react with the azirines as 1,3-dipoles giving allyl azides.[1a,b] The azides were presumably formed via a five-membered intermediate

Scheme I



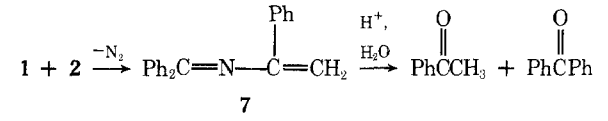
given by cycloaddition of the 1,3-dipoles across the C=N bond.



R = H or Ph

It is clear that the 1:2 adducts cannot be produced by such a reaction as above and, therefore, we should assume the reaction of diphenylcarbene. Regarding the reactions of 1-azirines with carbenelike reagents, several reports have been made.[1] Hassner and his co-workers observed the formation of a 1:1 adduct in the reaction with dichlorocarbene.[1d] They gave little consideration to the structure of the minor 1:2 adduct and suggested the structure containing an aziridine ring. However, under the conditions we employed, neither the 1:2 adducts which contain an aziridine linkage nor 1:1 adducts were isolated. Even when the mole ratio of **1** to **2** was greater than a unit, no 1:1 adduct was observed but the 1:2 adducts **3, 4,** and **5** were obtained.

It is reasonable to consider that the above three 1:2 adducts arose from the single 1:1 adduct **7,** which was isolated from the reaction mixture at a lower temperature. We obtained 2-azabutadiene **7** in 71% yield by treating the azirine **1** with the



diazomethane **2** in refluxing ether for 40 h. An increase in the amount of **2** relative to that of **1** caused a decrease in the yield of **7** and the formation of **5.** The structure of the compound **7** was determined by analytical data and also by the acidic hydrolysis giving acetophenone (67%) and benzophenone (87%).

Although it is uncertain whether the carbene is formed in refluxing ether or not, the structure of **7** corresponds to the 1:1 adduct of an azirine and dichlorocarbene.[1d] Furthermore,