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Tetrahydro-2H-1,3,4-oxadiazines. I. Ring–Chain Tautomerism of 2-Alkyl-4,5-dimethyl-6-phenyltetrahydro-2H-1,3,4-oxadiazines

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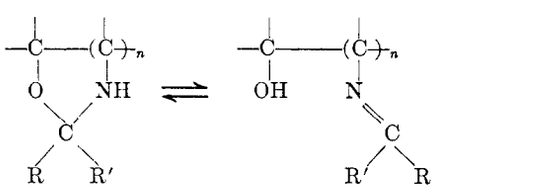
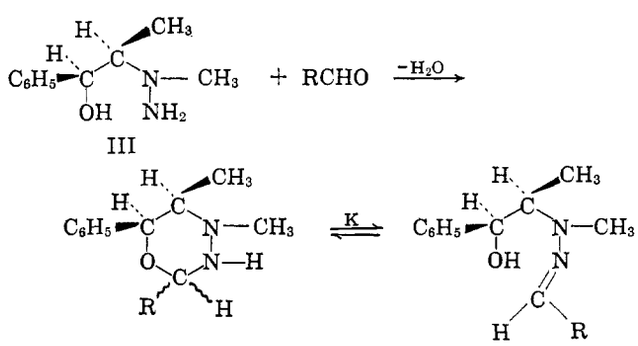
N-Amino-*l*-ephedrine condenses with formaldehyde and other aliphatic aldehydes (RCHO) to form 4,5-dimethyl-6-phenyltetrahydro-2H-1,3,4-oxadiazine and its 2-alkyl- (R-) substituted derivatives, respectively; these ring compounds exist in tautomeric equilibrium with their chain analogs, γ-hydroxyhydrazones. A quantitative study of this ring–chain tautomerism in solution shows that the extent of ring formation at equilibrium varies inversely with increases in temperature, the size of R, and the polarity of the solvent. Enthalpy effects appear to contribute more than entropy effects to the influence of the substituent R in altering the position of the equilibrium.

Ring–chain tautomerism[1] involving hydroxyl and imine functions is well established as demonstrated by oxazolidines (IA)[2] and tetrahydro-1,3-oxazines (IIA)[3] (*i.e.*, structures having a secondary nitrogen atom) in equilibrium with their corresponding acyclic Schiff bases IB and IIB. On the other hand, there appears to be no account of ring–chain tautomerism involving



IA, $n = 1$ IIB, $n = 2$; R and R′ = H or alkyl

hydroxyl and hydrazone functions. The condensation product of N-β-hydroxyethyl-N-methylhydrazine[4] and benzaldehyde appears to exist solely as the hydrazone tautomer on the basis of its ultraviolet spectrum. This result is not unexpected since considerable stability is imparted to the hydrazone form by virtue of the conjugation of the aromatic ring with the hydrazone double bond. Such stability would be absent if the aromatic ring were replaced with an alkyl group. Formation of the chain tautomer, *via* addition of the OH across the hydrazone double bond, might be expected to result, at least to some extent. That this, indeed, would occur was demonstrated by the condensation products of N-amino-*l*-ephedrine[5] (III) and aliphatic aldehydes, the presence of a tautomeric mixture of the tetrahydro-2H-1,3,4-oxadiazine (IVA) and γ-hydroxyhydrazone (IVB) being clearly indicated by nmr and infrared spectra (*cf.* Experimental Section and tables referred to therein). Thus, having shown the interaction of hydroxyl and hydrazone functions in ring–chain tautomerism, we directed our efforts toward the quantitative determination of various parameters (size of R, temperature, and solvent polarity) on the equilibrium constant, K, with the anticipation that this information



III

IVA IVB

R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$,

might enhance the general knowledge of ring–chain phenomena in saturated heterocyclic systems, par-

(1) For the most recent comprehensive review on this subject, see P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(2) (a) E. D. Bergmann, *ibid.*, **53**, 309 (1953); (b) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 358 (1953); (c) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. Chim.*, **71**, 168 (1952); (d) J. Metzger, *ibid.*, **71**, 243 (1952); (e) E. D. Bergmann, Y. Hirshberg, S. Pinchas, and E. Zimkin, *ibid.*, **71**, 192 (1952); (f) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951); (g) E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright, and A. C. Cope, *ibid.*, **66**, 1747 (1944); (h) A. C. Cope and E. M. Hancock, *ibid.*, **64**, 1503 (1942).

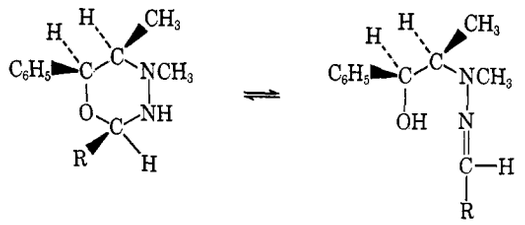
(3) (a) E. D. Bergmann and A. Kaluszner, *Rec. Trav. Chim.* **78**, 315 (1959); (b) *cf.* with footnote beginning on p 2180 of R. Lukes, J. Kovar, and K. Blaha, *Collection Czech. Chem. Commun.*, **25**, 2179 (1960).

(4) G. Benoit, *Bull. Soc. Chim. France*, 242 (1947).

(5) D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.* **29**, 668 (1964).

TABLE I

N-AMINO-*l*-EPHEDRINE ALDEHYDE CONDENSATION PRODUCTS



IV

R[a]	Formula	C Calcd, %	C Found, %	H Calcd, %	H Found, %	N Calcd, %	N Found, %	Mol wt Calcd	Mol wt Found
H[b]	$C_{11}H_{16}N_2O$	68.72	68.79	8.39	8.45	14.57	14.78	192	198
CH_3[c]	$C_{12}H_{18}N_2O$	69.87	69.70	8.79	8.90	13.58	13.60	206	210
CH_3CH_2[c]	$C_{13}H_{20}N_2O$	70.87	70.80	9.15	9.11	12.72	12.90	220	222
$(CH_3)_2CH$[c]	$C_{14}H_{22}N_2O$	71.75	72.06	9.46	9.19	11.96	12.43	234	237
$(CH_3)_3C$[c]	$C_{15}H_{24}N_2O$	72.54	72.55	9.74	9.60	11.28	11.36	248	244

[a] These products evaporately distilled in the range of *ca.* 60–82° at 1–4 × 10^{-4} mm. [b] Infrared spectrum (film), ν 3375 (OH), 1620, and 1635 (doublet, >C=NN) cm^{-1}. [c] Infrared spectrum (10% CCl_4), ν 3400 (OH) and 1620 (>C=NN) cm^{-1}; possibly the low intensity, moderately sharp absorption at 3175 cm^{-1} is due to NH, clearly observable in R = CH_3 but faintly perceptible in R = $C(CH_3)_3$.

ticularly the tetrahydro-2H-1,3,4-oxadiazines, a comparatively new ring system.[6]

Experimental Section

General.—Boiling points are uncorrected. The aldehydes were reagent grade, either freshly opened bottles were used, or these were distilled just before use. All solvents used were spectral grade. Computation of equilibrium data was performed by the Dow Computations Laboratory as indicated.

Condensation Products IV.—All of the products, except the formaldehyde derivative, were prepared according to the general procedure described here for the acetaldehyde derivative. To a stirred, externally cooled solution of 15 g (0.084 mole) of N-amino-*l*-ephedrine in 75 ml of benzene was added a cold solution of 4.1 g (0.093 mole) of acetaldehyde in 10 ml of benzene, the addition rate being such that the reaction temperature was maintained between 6 and 10°. About 25 min was required for the addition. Stirring was continued as the reaction temperature was allowed to rise slowly to room temperature during 2 hr. Anhydrous magnesium sulfate (2 g) was added to the mixture to absorb water formed in the reaction; stirring was continued for *ca.* 4 hr. The reaction mixture was filtered and benzene was removed from the filtrate *in vacuo* with the aid of a rotary evaporator. The residue, a light yellow oil of 17.2 g, was distilled at 2 × 10^{-4} mm in a high vacuum system consisting of a single unit, distillation flask head condenser, three collection receivers, a liquid nitrogen trap, and an oil diffusion pump. Two fractions were obtained, *ca.* 60° (2.8 g) and 68° (6.2 g); both were light yellow. The second fraction was used in the study.

Formaldehyde Derivative IV (R = H).—A mixture of 12 g (0.056 mole) of N-amino-*l*-ephedrine (1.7 g, 0.056 mole) of paraformaldehyde and 75 ml of benzene was refluxed for 15 min; the room temperature mixture was treated with 2.3 g of anhydrous magnesium sulfate, stirred for 2 hr, and allowed to stand overnight. The reaction was worked up and distilled as before. The products are summarized in Table I.

Analytical Procedure.—For the temperature study, equilibrations were conducted in *sym*-tetrachloroethylene containing 0.1% (w/v) trifluoroacetic acid. Sample solutions of IV were made up accurately to 20% (w/v) and placed in nmr sample tubes containing a trace of tetramethylsilane (internal standard). Equilibrations were conducted at 22.5, 35, 50, and 82°, fresh sample solutions being used for each temperature study. For each temperature equilibration, except at 22.5°, the sample tubes were heated in an oil bath at a designated temperature (maximum fluctuation ±0.3°) for 6–7 hr, whereupon the nmr spectra of the samples were recorded using a Varian A-60 spectrometer equipped with an integrator and sample thermostat held at the designated temperature of the equilibration. Temperature control and measurement in the nmr probe was accomplished by a Varian V-6057 variable-temperature system which utilized relative changes in the chemical shifts of the hydroxyl functions of methanol and ethylene glycol for temperature calibration. The 22.5° equilibration was approached from a lower and a higher temperature. Thus, samples were chilled at −10° for 1 day, then let stand at 22.5 ± 0.5° for 6–7 hr, and their spectra were recorded as before; similarly, samples were heated at 82° for 3 hr, then let stand at 22.5 ± 0.5° for 20 hr, and their spectra were recorded. The propionaldehyde derivative IV (R = CH_3CH_2) was used as subject for determining the effect on solvent on the equilibrium IV (A ⇌ B). Sample solutions, 20% (w/v), containing trifluoroacetic acid (1 μl/ml of solution) were made up in carbon tetrachloride, methanol, acetonitrile, and dimethyl sulfoxide; these were allowed to stand at 22.5 ± 0.5° for 7 hr and their spectra were recorded at this temperature. At least duplicate runs were made for all determinations; longer periods of equilibration at various temperatures showed equilibrium to to have been established during the prescribed time intervals except for the formaldehyde derivative. Integration of spectra was performed in the usual manner. Preliminary studies were made on the nmr spectra of each derivative to determine the best peaks to be used for the determination of each tautomer. This was achieved by cross-checking characteristic peaks of each tautomeric form in the mixture before and after deuteration. The specific peaks used for the determination of each tautomer are noted in Table II. The best fit to plots, ln K *vs.* $1/T$, of the data for the temperature equilibrium study of IV (A ⇌ B) was obtained by the method of least squares by computer analysis using the stepwise regression method.[7] Parameters N and C of the resulting equation ln $K = N(1/T) + C$ and their standard deviations were obtained from which thermodynamic quantities $\Delta H°$ and $\Delta S°$ for IV (A ⇌ B) were calculated using the relationships $N = -\Delta H°/R$ and $C = \Delta S°/R$. These data are summarized in Table III.

Results and Discussion

There are a number of possible species associated with both the ring and chain tautomers of the tetrahydrooxadiazines (IV) that may be involved in the equilibrium and should be considered. Associated with the ring tautomer are *cis–trans* isomers originating at the 2 position by virtue of the direction of ring closure and the dominant ring conformers associated with each geometric isomer. The chain tautomer can exist in two geometric forms, *syn* or *anti*. These species and their possible interrelations are outlined in Scheme I.

(6) The only account of this ring system that could be found in the literature was the preparation of substituted 5-methyl-6-phenyltetrahydro-1,3,4-oxadiazines by M. J. Kalm, U. S. Patent 3,251,838 (1966).

(7) A. Ralston and H. S. Wilf, "Mathematical Methods for Digital Computers," John Wiley and Sons, Inc., New York, N. Y., 1960, pp 191–203.

TABLE II

EQUILIBRATION DATA. PERCHLOROETHYLENE SOLUTION

R	22.5°			35°			50°			82°			Peak[a] absorptions used to determine A and B
	B/A, %	Av B/A, %	K/log K	B/A, %	Av B/A, %	K/log K	B/A	Av B/A, %	K/log K	B/A, %	Av B/A, %	K/log K	
H	54/46	...	...	...	...	...	...	...	...	...	...	...	(c); (a', b')
	66/34												
CH_3	39.7/60.3	38.3/61.7	0.620/−0.208	41.4/58.6	41.8/48.2	0.718/−0.144	47.6/52.4	47.0/53.0	0.887/−0.052	59.2/40.8	58.8/41.2	1.43/0.155	(a, d);
	37.0/63.0			42.2/57.8			46.3/53.7			58.3/41.7			(a', d')
CH_3CH_2	44.4/55.6	44.8/55.2	0.812/−0.090	50.6/49.4	50.1/49.9	1.00/0.00	56.7/43.3	56.7/43.3	1.31/0.117	63.7/36.3	64.7/35.3	1.83/0.262	(d); (b')
	45.1/54.9			49.7/50.3			56.7/43.3			65.7/34.3			
$(CH_3)_2CH$	62.5/37.5	62.8/37.2	1.09/0.228	65.2/34.8	65.3/34.7	1.88/0.274	76.4/23.6	70.0/30.0	2.33/0.367	76.4/23.6	76.8/23.2	3.31/0.520	(d); (b')
	63.2/36.8			65.4/34.6			70.2/29.8			77.3/22.7			
$(CH_3)_3C$	79.9/20.1	79.6/20.4	3.90/0.591	80.5/19.5	81.0/19.0	4.26/0.629	84.0/16.0	84.4/15.6	5.41/0.733	87.4/12.6	87.3/12.7	6.87/0.837	(c, d); (b')
	79.3/20.7			81.4/18.6			84.7/15.3			87.1/12.9			

[a] See Table IV, p 259, for chemical shifts relative to internal standard tetramethylsilane.

TABLE III

COMPUTER ANALYSIS–THERMODYNAMIC CALCULATIONS.[a]

EQUILIBRIA OF IV

$$A \underset{}{\overset{K}{\rightleftharpoons}} B$$

$$\ln K = N(1/T) + C$$

R	$\Delta H°$, kcal/mole[b]	$\Delta S°$, eu[c]
CH_3	2.93 ± 0.18	8.94 ± 0.56
CH_3CH_2	2.88 ± 0.14	9.31 ± 0.44
$(CH_3)_2CH$	2.41 ± 0.11	9.15 ± 0.35
$(CH_3)_3C$	2.05 ± 0.15	9.62 ± 0.46

[a] Based on data in Table II in which K and T were fitted to equation $\ln K = N(1/T) + C$. [b] $\Delta H° = -NR$. [c] $\Delta S° = CR$.

To our knowledge no conformational analysis studies have been made on tetrahydro-2H-1,3,4-oxadiazines; in fact, relatively few studies have been made on heterocyclic rings containing more than one heteroatom, and fewer still on systems containing more than two heteroatoms.[8] It might be anticipated, however, from systems studied that the tetrahydrooxadiazines exist predominantly in the chain form as do simple piperazine[8,9] and dioxane[8] derivatives. Considering conformations a-1 to a-4, Scheme I (conformers depicting an axial N-methyl group were not considered because of the relatively large free energy required[9] and because of the high inversion rate about the nitrogen atom[10]; NH appears to have a slight preference for the equatorial position[9]), form a-2 may be ruled out as a substantial participant because of the 1,3-diaxial interaction between the 6-phenyl and 2-R group. Less severe 1,3-diaxial interactions are present in the three remaining cyclic forms, at least to some extent, assuming the NH to be in the axial position about one-third[11] of the time. Taking a-1 as having the lowest free energy, an estimate of the populations of a-3 and a-4 relative to a-1 might be achieved by considering the 1,3-diaxial interactions and the relative energies associated with each. For a-3, the relative energy above a-1 should range approximately from 0.9 kcal/mole for R = CH_3 to 2.7 kcal/mole for R = t-C_4H_9.[12] The 1,3-diaxial phenyl–hydrogen interaction of a-4 should raise its energy about 1.3 kcal/mole above that of a-1;[12] some of this energy difference is lessened, however, by the change of the 5-methyl group from axial in a-1 to equatorial in a-4. This energy difference is difficult to estimate since the only nonbonded 1,3-diaxial interactions the 5-methyl group can experience in a-1 involves one of the lone electron pairs on the 1-oxygen and, because of nitrogen inversion, alternately, the lone electron pair and hydrogen on the 3-nitrogen. No data could be found that would permit an estimate of the energy associated

(8) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. B. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 248–251.

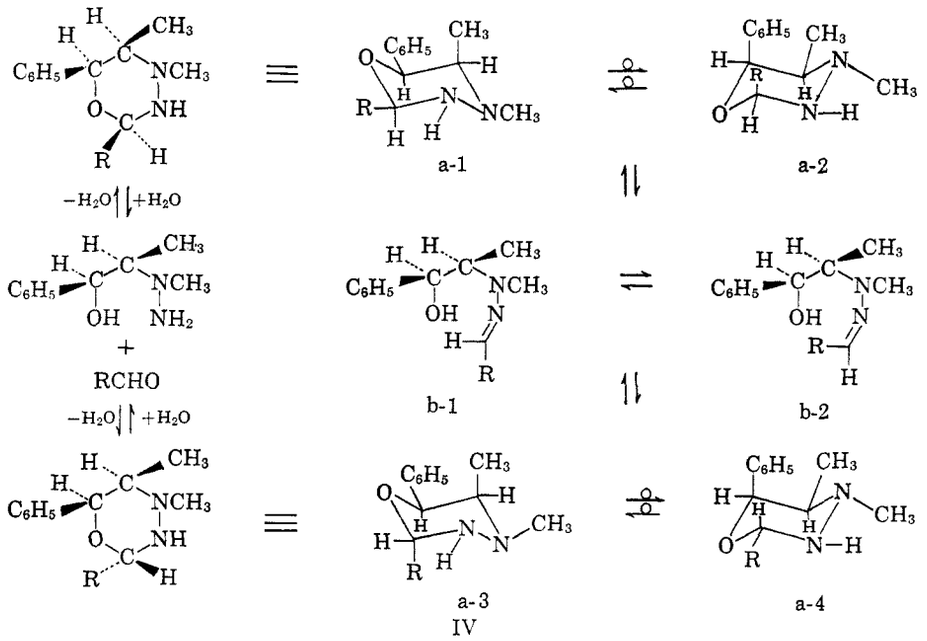
(9) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).

(10) L. W. Reeves and K. O. Stromme, *J. Chem. Phys.*, **34**, 1711 (1961).

(11) Assuming the preference of the hydrogen on nitrogen for the equatorial position to be about 0.4 kcal as found for piperidine in benzene solution.[9] G. B. Lambert and R. G. Keske [*J. Am. Chem. Soc.*, **88**, 620 (1966)] have recently presented qualitative evidence contrary to this finding for piperidine; *i.e.*, the lone pair of electrons in piperidine appear to have a greater preference for equatorial position than does the NH. Their conclusion was based on nmr data recorded in methanol solution.

(12) E. L. Eliel, "Sterochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 236.

SCHEME I



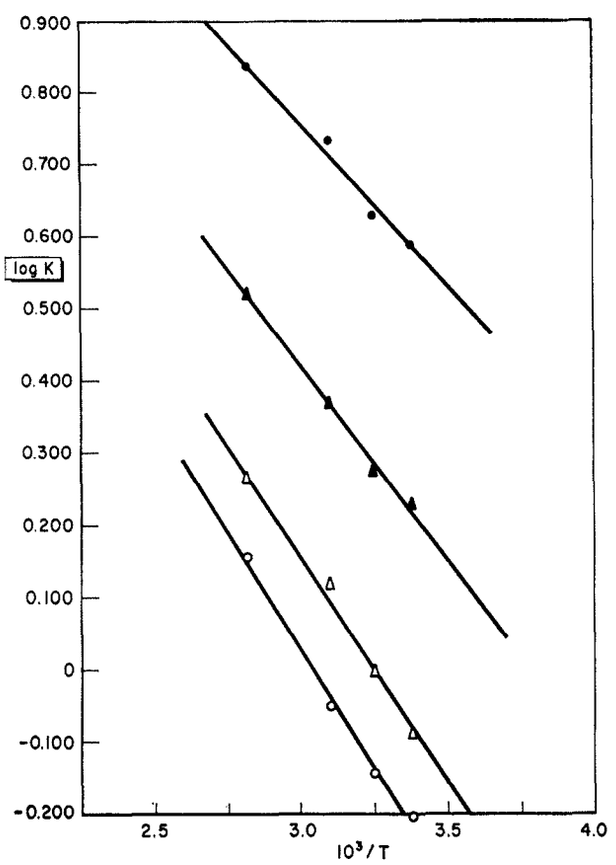
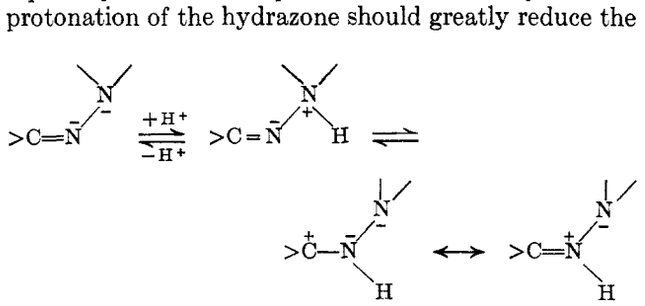


Figure 1.—Arrhenius plot of the equilibria of IV in perchloroethylene solution: O, CH_3; △, CH_3CH_2; ▲, $(CH_3)_2CH$; ●, $(CH_3)_3$.

with this particular interaction.[13] It has been stated that the lone pair on a heteroatom may be disregarded unless there is a polar substituent on a neighboring carbon,[14] and since this is not the case here it would appear that the difference in the energy of the axial and equatorial 5-methyl group would be slight; therefore, the energy of a-4 would still be expected to lie about 1.3 kcal/mole above that of a-1. If these estimated free-energy differences are translated to relative populations by utilizing the relationship $\Delta G^\circ = -RT \ln K$, then, at equilibrium at 25° with R = CH_3, the estimated proportions of a-1, a-3, and a-4 would be roughly 75, 17, and 8%, respectively.

Inspection of the nmr spectra of all the tetrahydrooxadiazines IV showed only single absorptions, where discernable, for the various proton groups of the cyclic tautomer. The spectrum of the methyl derivative, which should have the most varied composition, shows four split methyl doublets, two for the ring and two for the chain tautomers. From the spectra it may be concluded that either the respective proton groups of a-1, a-3, and a-4 have about the same chemical shifts or that the equilibrium between them is sufficiently fast such that only a single weight-average absorption is observed. The latter presumption seems to be the more tenable.

The chain form of IV can exist in two geometric isomeric forms, *syn* and *anti* or b-2 and b-1, respectively. Interconversion of *syn* and *anti* isomers of simple hydrazones can generally be induced with heat or light with relative ease. Interconversion should be especially facile in the presence of acid catalysts since protonation of the hydrazone should greatly reduce the

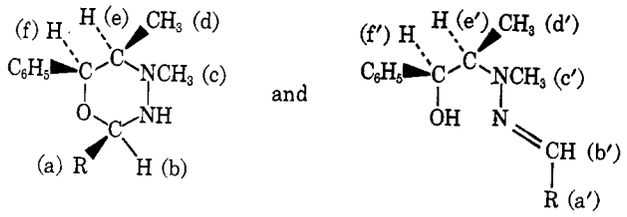


(13) To estimate the energy of such an interaction based on the "size" of the lone pair would be nebulous because the lone pair does not have "size" in the usual macroscopic sense, but may be taken to indicate the energy of a system in terms of the location of neighboring groups or atoms, and in this sense will depend on how it is measured (*cf.* footnote 7 in ref 9). *Cf.* also with the discussion on this subject by T. A. Claxton, *Chem. Ind.* (London), 1713 (1964).

(14) Reference 8, p 245.

TABLE IV

DATA FOR IV[a] AND CHEMICAL SHIFTS[b]



R	a	b	c	d[c]	e[d]	f[c]
H	4.53	4.53	2.37	0.61 (6.5)	3.32	4.88 (3.0)
CH_3	1.32 (6.0)[c]	4.63 (6.0)[e]	2.42	0.59 (6.5)	*Ca.* 3.0	4.97 (2.5)
CH_3CH_2	...	4.43 (6.0)[f]	2.38	0.56 (6.5)	*Ca.* 3.1	4.94 (2.8)
$(CH_3)_2CH$	...	4.25 (5.5)[c]	2.38	0.56 (6.5)	*Ca.* 3.1	4.93 (2.8)
$(CH_3)_3C$	*Ca.* 1.11	4.14	2.38	0.58 (7.0)	*Ca.* 3.14	4.96 (*ca.* 2.8)
R	a'	b'	c'	d'[c]	e'[d]	f'[c]
H	5.98	5.98	2.59	0.98 (6.8)	3.32	5.10 (3.3)
CH_3	1.86 (5.0)[c]	6.51 (5.0)[e]	2.58	0.89 (6.5)	*Ca.* 3.0	5.24 (2.0)
CH_3CH_2	...	6.52 (5.0)[f]	2.56	...	*Ca.* 3.1	5.24 (2.3)
$(CH_3)_2CH$	...	6.49 (4.7)[c]	2.56	...	*Ca.* 3.1	5.23 (2.0)
$(CH_3)_3C$	1.11	6.51	2.59	0.86 (6.5)	*Ca.* 3.14	5.27 (2.2)

[a] Ambient instrument temperature, deuteriochloroform solution. [b] Downfield from tetramethylsilane; coupling constant, J, in cycles per second is indicated in parentheses. [c] Doublet. [d] Multiplet. [e] Quartet. [f] Triplet.

double-bond character of the C=N bond and thereby facilitate rotation about the C=N bond.[15]

At equilibrium the *anti* form, b-1, of IV should predominate because of steric hindrance experienced by the *syn* form b-2. As with the ring tautomer, the nmr spectra of IV shows only one chain form as anticipated because of the facile equilibrium between the *syn* and *anti* isomers.

The data presented in tabular form in Tables I–IV and graphically in Figures 1 and 2 show the quantitative effects of temperature, bulk of substituent R, and solvent polarity of the equilibria of IV. Evident by these data is the displacement of the equilibrium toward the chain tautomer with an increase in temperature. A greater degree of freedom in the chain form is indicated and this is substantiated by the rather large positive entropy value of about 9+ eu for the series (variation of R). The relative change in enthalpy values for the series, however, was larger, $\Delta H^\circ = 2.93 \pm 0.18$ kcal for R = Me and 2.05 ± 0.15 kcal for R = *t*-Bu; therefore enthalpy effects appear to contribute more to the effect of R in changing the position of the equilibrium of IV. Similar effects have been observed for oxazolidine–Schiff base (I) equilibria.[2b,d]

The size of substituent R has a similar effect on the equilibrium of IV; for example, at 22.5° the extent of the chain form for the methyl and *t*-butyl derivatives is 38 and 80%, respectively, corresponding to a free-energy difference ($\Delta F^\circ_{22.5°(t\text{-Bu})} - \Delta F^\circ_{22.5°(\text{Me})}$) of about 1 kcal/mole. There appears to be no obvious reason why an increase in the size of R of IV should lower the free energy of the chain form, probably the contrary. Therefore, the net increase in the free-energy difference between the ring and chain forms with increasing size of R must be due to a relatively large increase in the free energy of the ring form. It is not immediately apparent, however, from sketches of the probable ring forms (Scheme I) of the tetrahydrooxadiazines why an increase in the size of R should shift the direction of the equilibrium toward the chain form since it is possible for the tetrahydrooxadiazines to exist in form a-1 in which R is equatorial and hence free from apparent steric interactions. When a-1 is depicted by a Newman projection the *gauche* interaction between R and the hydrogen on N-3 (in structure IV

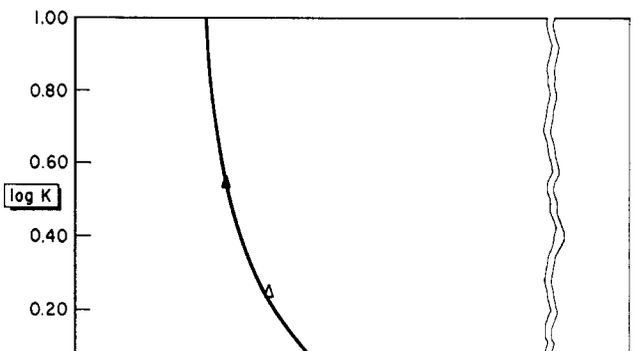
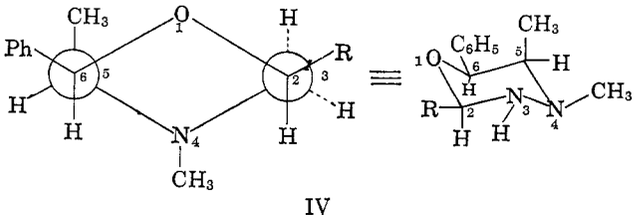


Figure 2.—Plot of log K of IV (R = CH_2CH_3) *vs.* $1/D$ (dielectric constant) and effect of solvent polarity on K: ●, CCl_4; ○, CH_3OH; △, CH_3CN; ▲, DMSO.



the dotted lines indicate the positions of the hydrogen resulting from nitrogen inversion) becomes apparent. An increase in the size of R should increase the energy

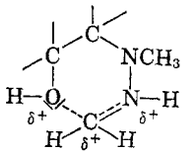
(15) *Cf.* the discussion on the *syn–anti* isomerism of simple imines by R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

of this *gauche* interaction. On the other hand, models show that the chain form can be so arranged that an increase in the size of R can be accommodated without serious concomitant steric interactions. Where semiquantitative data have been available this same general trend appears to exist for oxazolidine[2a]– and tetrahydro-1,3-oxazine[3a]– Schiff base equilibria, specifically for those compounds derived from aliphatic ketones; *i.e.*, an increase in the size of R and/or R′ (I and II) favors formation of the chain form. Alkylation of the carbon skeleton, however, increases the tendency of ring formation in both cases.[3a]

Generally in ring–chain tautomerism, ring stability increases with increasing substitution.[1] In addition, ring formation is further enhanced by an increase in the size of the substituents.[1] This phenomenon is particularly striking for geminal disubstitution. It appears that the effect of the size of the substituent on the equilibrium of IV, as well as that for oxazolidine– and tetrahydro-1,3-oxazine–Schiff base equilibria, stands in contrast to this general rule *if* the substituent(s) in question is attached to the carbon atom involved in ring opening and closure; *i.e.*, an increase in the size of R (and/or R′ for I and II) decreases ring stability. It should, however, be noted for these systems that the ring skeletal atom bearing the substituent, R and/or R′, undergoes a change in hybridization on passing from the ring to the chain form, *i.e* from sp^3 to sp^2, and *vice versa*.

As might be anticipated, solvent polarity also has an effect on the equilibrium of the tetrahydrooxadiazines. The more polar the solvent, in terms of its dielectric constant, the greater is the tendency for the chain form which is more polar than the ring form. The plot (Figure 2) of log K *vs.* $1/D$ for the ethyl derivative (IV, R = CH_3CH_2) clearly demonstrates this point.

Unlike the previously discussed derivatives of IV, the derivative derived from formaldehyde (R = H) displayed anomalous behavior in the equilibrium study. In the first place, the tendency to favor the chain form was substantially larger than would be predicted from the other derivatives on the basis of the size of R; for example, the apparent composition of R = H in perchloroethylene solution at 22.5° was about 47% ring and 53% chain, whereas the composition for R = CH_3 under the same conditions was 62 and 38%, respectively. The second anomaly was the difficulty in obtaining reproducible equilibration results, particularly when attempting to approach equilibrium for a designated temperature from opposite temperature directions; for example, the equilibrium composition at 22.5° was 46:54 (ring–chain) when approached from −10° and 34:66 when approached from 82°. The composition at 82° is 31:69 when heated from room temperature for about 6 hr, and, at −10°, 46:54 when cooled from room temperature for 2 days, but 33:67 when first heated to 82° for 1.5 hr and then cooled at −10° for 11 days. These data appear to indicate that the rate of equilibration is quite slow. The other derivatives of IV experienced no difficulty in reaching equilibrium under the same conditions. Perhaps the slow rate of the acid-catalyzed equilibration for this derivative may be attributed to a lack of stabilization, by an alkyl group, of the positive charge developed in the transition state at the carbon atom involved in ring closure (and ring opening). The



presence of an alkyl group at this carbon atom, as in the case with the other derivatives of IV, would help stabilize this charge and thereby lower the energy of activation for the process. No ready explanation is at hand to account for the greater preference of formaldehyde derivative to exist in the chain form, if indeed this is the case.

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