Decarboxylation of Schiff Bases[1]

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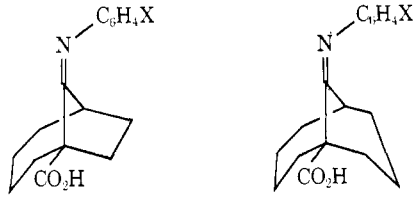
Abstract: Schiff bases of β-keto acids have not previously been isolated, presumably because they are thermally unstable. Because of the limitations on reactivity inherent in Bredt's rule, Schiff bases can, however, be prepared for β-keto acids where the carbonyl function is present on the bridgehead of a bicyclic system. In particular, the series of compounds below were synthesized, where X is a para substituent; the rates of decarboxylation of the

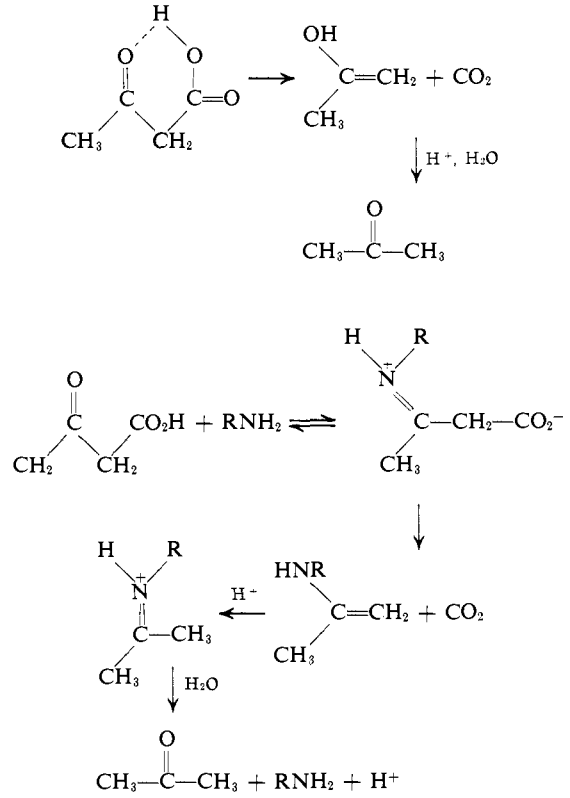


acids were measured. In nonpolar solvents (decalin, dioxane), the Schiff bases undergo decarboxylation about a million times as fast as do the corresponding keto acids. This finding is in accord with the accepted mechanism of enzymic and nonenzymic decarboxylation of β-keto acids.

The decarboxylation of β-keto acids normally occurs by way of the enol of the product as intermediate.[2] Amine-catalyzed decarboxylation has been postulated to take place by way of an imine, or Schiff base, which then loses carbon dioxide to form an enamine as intermediate.[3] Considerable evidence supporting this mechanism has been adduced both for the enzymic decarboxylation of acetoacetic acid catalyzed by the enzyme from Clostridium acetobutylicum[1,4] and for the corresponding nonenzymic process.[1,5,6] Inherent in these mechanistic constructions is the assumption that Schiff bases of β-keto acids decarboxylate much more rapidly than the corresponding β-keto acids themselves. This assumption is inherently reasonable, since the nitrogen atom of the Schiff base will protonate much more readily than the corrsponding ketonic oxygen atom, and will therefore provide a much better electron sink during the decarboxylation process. However, prior to the present work, this hypothesis could be verified only indirectly, since Schiff bases of β-keto acids proved too unstable to isolate. The accepted mechanisms for these decarboxylation processes are outlined in Scheme I.

However, bicyclic keto acids, where the carboxyl group is on a bridgehead,[2] undergo decarboxylation slowly if at all, since the enol, formed as an intermediate in the decarboxylation, necessarily contains a twisted and highly strained double bond. We have taken advantage of the restriction on decarboxylation imposed by bicyclic systems to prepare Schiff bases of a number of bicyclic β-keto acids.

Scheme I



The rates of decarboxylation in bicyclic systems depend upon the size of the ring; ketopinic acid does not undergo decarboxylation, whereas bicyclic β-keto acids where one ring contains more than eight atoms decarboxylate readily around 100°. Prelog and his coworkers,[7] in investigating the limits of Bredt's rule, prepared a series of unsaturated [*n*.3.1] β-keto acids

(1) (a) Preliminary announcements: F. W. Westheimer, *Proc. Int. Congr. Pure Appl. Chem.*, **23**, 5, 111 (1971); (b) F. H. Westheimer, XVth Robert A. Welch Foundation Conferences on Chemical Research, Nov 1–3, 1971, p 7.

(2) (a) J. Bredt, *Ann. Acad. Sci. Fenn., Ser. A2*, **29**, 3 (1927); *Chem. Z.*, **98**, II, 2298 (1927); (b) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

(3) K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934); *J. Amer. Chem. Soc.*, **58**, 240 (1936).

(4) (a) G. Hamilton and F. H. Westheimer, *J. Amer. Chem. Soc.*, **81**, 2277 (1959); (b) I. Fridovich and F. H. Westheimer, *ibid.*, **84**, 3208 (1962); (c) F. H. Westheimer, *Proc. Chem. Soc., London*, 253 (1963); (d) P. A. Frey, F. C. Kokesh, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **93**, 7266 (1971); F. C. Kokesh and F. H. Westheimer, *ibid.*, **93**, 7270 (1971).

(5) J. P. Guthrie and F. H. Westheimer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 562 (1967).

(6) J. P. Guthrie, *J. Amer. Chem. Soc.*, **94**, 7024 (1972); J. P. Guthrie and F. Jordan, *ibid.*, **94**, 9132, 9136 (1972).

(7) V. Prelog, P. Braman, and M. Zimmerman, *Helv. Chim. Acta*, **32**, 1284 (1949).

where the keto group was on the 1-carbon atom bridge and the carboxyl group was attached at a bridgehead. The keto acids with n larger than 4 undergo decarboxylation at high temperature. Although these bicyclic β-keto acids might then seem ideal for the present purposes, unfortunately (as Prelog also noted), those with n equal to or larger than 5 are inactive toward carbonyl reagents such as semicarbazide or Girard's reagent. Our efforts were therefore directed toward searching for bicyclic β-keto acids that not only decarboxylate at reasonable temperatures, but also react with carbonyl reagents. The needs for the present study were finally satisfied by 9-ketobicyclo[4.2.1]nonane-1-carboxylic acid and 10-ketobicyclo[4.3.1]decane-1-carboxylic acid. Although the phenylimines of these compounds decarboxylate much more rapidly than do the corresponding β-keto acids, they can be prepared, and their rates of decarboxylation can be measured. Unfortunately, since they undergo hydrolysis or alcoholysis readily, the rates had to be measured in nonaqueous solvents.

Experimental Section

Materials. 9-Ketobicyclo[3.3.1]nonane-1-carboxylic Acid. Ethyl 9-ketobicyclo[3.3.1]nonane-1-carboxylate[8] was prepared *via* β-(1-carboethoxy-2-ketocyclohexyl)propionaldehyde. The product, after recrystallization from chloroform–*n*-pentane, melted at 41.5–42.5° (lit.[8] 26–32°); ir (KBr) $\lambda_{C=O}$ 5.75–5.85 μ. Hydrolysis yielded 9-ketobicyclo[3.3.1]nonane-1-carboxylic acid, which, after recrystallization from methylcyclohexane, melted at 137–138° (lit.[8] 136–137°): ir (KBr) λ_{CO_2H} 5.8, $\lambda_{C=O}$ 5.9 μ; nmr ($CDCl_3$) δ 12.0 (s, CO_2H).

10-Ketobicyclo[4.3.1]decane-1-carboxylic acid[9] was prepared by the same general method as that used for its [3.3.1] analog above. The acid sublimed at 90° (0.02 mm) and melted at 103–104.5° (lit.[9] 102–104°): ir, λ_{CO_2H} 2.4–4.0, $\lambda_{C=O}$ 5.8–5.9 μ; nmr δ 12.03 (s, CO_2H).

11-Ketobicyclo[5.3.1]undecane-1-carboxylic acid was prepared by the method of Warnhoff,[9] *et al.* The essential step consists in closing β-(1-carboethoxy-2-ketocyclooctyl)propionaldehyde to the bicyclic system with dimethylbenzylamine–oxalic acid as catalyst. The corresponding ester melted at 40–42.2° (lit.[9] 43–45°); ir (KBr), $\lambda_{C=O,CO_2H}$ 5.75, 5.89 μ. The acid, after recrystallization from ethyl acetate–petroleum ether, melted at 129.5–131.8° (lit.[9] 130–132°): ir (KBr) λ_{CO_2H} 3–4, $\lambda_{C=O}$ 5.85, 5.90 μ; nmr δ 11.50 (s, CO_2H).

2-Ketobicyclo[3.3.1]nonane-1-carboxylic acid,[10] after sublimation, melted at 108.5–109.5° dec (lit.[10] 105–106°): ir (KBr) $\lambda_{C=O}$ 5.8–5.9 μ; nmr ($CDCl_3$) δ 11.5 (s, CO_2H).

9-Ketobicyclo[4.2.1]nonane-1-carboxylic Acid. The bicyclic keto-acid was first reported by Wiseman, *et al.*,[11] but without detailed procedures or melting point. The following simple preparation is serviceable, although yields are poor.

Twelve grams of a 50% dispersion of sodium hydride in mineral oil was washed with toluene and the metal hydride suspended in 500 ml of dimethylformamide. 2-Carbethoxycyclopentanone (67 g) was added drop by drop with stirring to the cooled solution, followed by the slow addition of 100 g of tetramethylene dibromide. After 15 additional hours of stirring, the reaction mixture was neutral, and the dimethylformamide was removed under vacuum to leave a viscous residue which was diluted with water and extracted with ether. The ethereal solution was concentrated and the residue vacuum distilled (145–149° (0.3 mm)) to give 77.5 g of 2-carbethoxy-2-(4-bromobutyl)cyclopentanone: ir (film) $\lambda_{C=O}$ 5.70, 5.80 μ; nmr (CCl_4) δ 1.25 (t, J = 7 Hz), 3.40 (t, J = 7 Hz), 4.15 (q, J = 7 Hz).

A 77-g sample of the bromo ester in 600 ml of toluene and 300 ml of dimethylformamide was stirred at 70° for 48 hr with 6.5 g of sodium hydride. The cooled mixture was acidified with acetic acid and the solvent removed under reduced pressure. The viscous residue was diluted with water and extracted with ether. The dried ethereal solution was concentrated and the residue vacuum distilled to give 11 g (20% yield) of ethyl 9-ketobicyclo[4.2.1]nonane-1-carboxylate, boiling at 103–108° (0.75 mm): ir (film) $\lambda_{C=O}$ 5.7, 5.8 μ; nmr (CCl_4) δ 1.2 (t, J = 7 Hz), 4.1 (q, J = 7 Hz).

A 10.5-g sample of the above ester was stirred for 30 hr with 100 ml of 10% potassium hydroxide. After the aqueous solution was washed with ether, it was acidified and the product extracted into methylene chloride. The solvent was removed from the filtered methylene chloride solution by rotary evaporation and the residue was sublimed (100° (0.02 mm)). The product was recrystallized from toluene–petroleum ether to give 6.8 g (74%) of 9-ketobicyclo-[4.2.1]nonane-1-carboxylic acid: mp 105–106.5°; ir (KBr) $\lambda_{C=O}$ 5.8, 5.9 μ; nmr ($CDCl_3$) δ 11.7 (s, CO_2H). *Anal.* Calcd for $C_{10}H_{14}O_3$ (mol wt, 182.2): C, 65.92; H, 7.74. Found: C, 65.96; H, 7.59.

Ketopinic acid, prepared according to Bartlett and Knox,[12] melted at 235.5–238° (lit.[12] 233–234°).

Bicyclo[3.3.1]nonan-2-one. A solution of 1.82 g of bicyclo[3.3.1]-nonane-1-carboxylic acid in 1 ml of chloroform and 1 ml of aniline was allowed to stand at room temperature for 12 hr, and then extracted with *n*-pentane. The *n*-pentane solution was washed with aqueous hydrochloric acid, the pentane evaporated and the residue steam distilled to yield 1.2 g of bicyclo[3.3.1]nonan-2-one, identified by comparison of its ir spectrum with that of an authentic sample.[13]

Bicyclo[5.3.1]undecan-11-one. A solution of 2.1 g of 11-keto-bicyclo[5.3.1]undecane-1-carboxylic acid and 1 g of aniline in 10 ml of chloroform was refluxed for 48 hr. Work-up as above yielded 1.3 g of ketone, bp 56.5–58° (0.01 mm) (lit.[9] 90–90.5° (1.5 mm)).

Schiff Bases (Ketimines). 10-Phenyliminobicyclo[4.3.1]decane, 2-phenylimino-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid, 9-phenyliminobicyclo[4.2.1]nonane-1-carboxylic acid, and 9-phenyliminobicyclo[3.3.1]nonane-1-carboxylic acid were prepared by published procedures.[14]

9-(*p*-Methoxyphenylimino)bicyclo[4.2.1]nonane-1-carboxylic acid was prepared by the same general procedure[14] as for the compounds listed above, utilizing Linde 5A molecular sieves as catalyst and chloroform as solvent. After filtration of the sieves and evaporation of the solvent, the solid was twice recrystallized from toluene–petroleum ether to yield 0.47 g (33% yield) of anil acid: mp 105.0–106.0° dec; ir (KBr) $\lambda_{C=O}$ 5.78, $\lambda_{C=N}$ 6.02 μ; nmr ($CDCl_3$) δ 3.10 (br, 1 H, bridgehead) 3.82 (s, 3 H, OCH_3), 6.92 (s, 4 H, phenyl), 15.2 (s, 1 H, CO_2H). *Anal.* Calcd for $C_{17}H_{21}NO_3$ (mol wt, 287.4): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.70; H, 7.38; N, 4.86.

9-(*p*-Chlorophenylimino)bicyclo[4.2.1]nonane-1-carboxylic Acid. A similar preparation to that above, but substituting *p*-chloroaniline for anisidine, gave a 40% yield of anil acid: mp 121.0–122.0° dec; ir (KBr) $\lambda_{C=O}$ 5.75, $\lambda_{C=N}$ 6.00 μ; nmr ($CDCl_3$) δ 3.10 (br, 1 H, bridgehead), 6.7–7.5 (mult, 4 H, phenyl), 14.7 (br, 1 H, CO_2H). *Anal.* Calcd for $C_{16}H_{18}NO_2Cl$ (mol wt, 291.8): C, 65.86; H, 6.22; N, 4.80. Found: C, 66.19; H, 6.32; N, 4.73.

10-(*p*-Methoxyphenylimino)bicyclo[4.3.1]decane-1-carboxylic acid was prepared by the same method[14] from 10-ketobicyclo[4.3.1]-decane-1-carboxylate and anisidine; the product melted at 118–119.0° dec: ir (KBr) $\lambda_{C=O}$ 5.78, $\lambda_{C=N}$ 6.10 μ; nmr ($CDCl_3$) δ 3.2 (br, 1 H, bridgehead), 3.82 (s, 3 H, OCH_3), 6.7–7.1 (mult, 4 H, phenyl), 15.3 (br, 1 H, CO_2H). *Anal.* Calcd for $C_{18}H_{23}NO_3$ (mol wt, 301.4): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.44; H, 8.10; N, 4.44.

10-(*p*-Chlorophenylimino)bicyclo[4.3.1]decane-1-carboxylic acid, prepared as above, but substituting *p*-chloroaniline for *p*-anisidine, melted at 133.0–134.5° dec: ir (KBr) $\lambda_{C=O}$ 5.78, $\lambda_{C=N}$ 6.10 μ; nmr ($CDCl_3$) δ 3.00 (br, 2 H, bridgehead), 6.7–7.5 (mult, 4 H, phenyl), 14.2 (br, 1 H, CO_2H). *Anal.* Calcd for $C_{17}H_{20}NO_2Cl$ (mol wt, 305.8): C, 66.77; H, 6.59; N, 4.58. Found: C, 66.67; H, 6.71; N, 4.38.

9-Phenyliminobicyclo[4.2.1]nonane. 9-Keto[4.2.1]nonane-1-carboxylic acid (0.91 g) and aniline (0.55 g) were refluxed with 2 g of

(8) (a) A. C. Cope and M. E. Synerhold, *J. Amer. Chem. Soc.*, **72**, 5228 (1950); (b) E. W. Colvin and W. Parker, *J. Chem. Soc.*, 5764 (1965).

(9) E. W. Warnhoff, C. M. Won, and W. T. Tai, *J. Org. Chem.*, **32**, 2664 (1967).

(10) (a) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, **85**, 1325 (1963); (b) J. A. Marshall and H. Faubl, *ibid.*, **92**, 948 (1970).

(11) (a) J. R. Wiseman, H. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1969); (b) J. R. Wiseman and W. A. Fletcher, *ibid.*, **92**, 956 (1970).

(12) P. D. Bartlett and L. H. Knox, *Org. Syn.*, **45**, 14, 55 (1940).

(13) M. Hartman, *Z. Chem.*, 6, 182 (1966).

(14) K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1570 (1971).

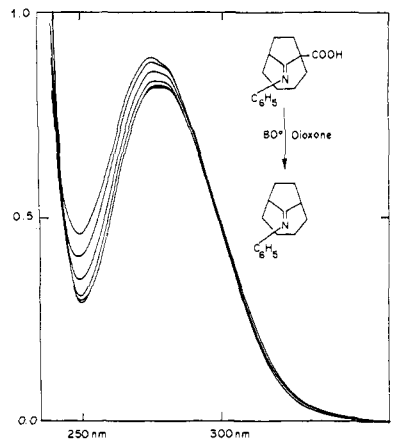


Figure 1. The ultraviolet absorption spectra for successive scans during the decarboxylation of 9-phenyliminobicyclo[4.2.1]nonane-1-carboxylic acid to 9-phenyliminobicyclo[4.2.1]nonane at 80° in dioxane. The rate was determined from the data at 250 nm; the absorption diminishes as the reaction proceeds.

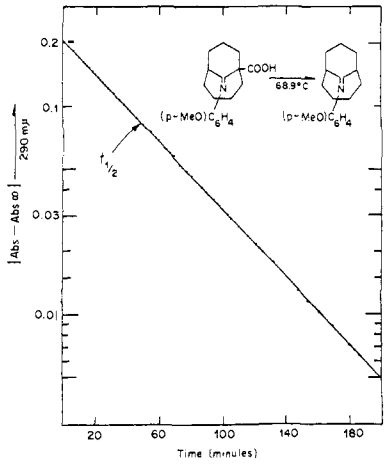


Figure 2. Plot of the spectrophotometric data, as a first-order reaction, for the decarboxylation of 10-*p*-methoxyphenyliminobicyclo[4.3.1]decane-1-carboxylic acid in decalin plus 4.3 vol % of dioxane at 70°.

molecular sieves in 10 ml of benzene for 5 hr. Vacuum distillation yielded 0.76 g of semisolid anil acid, ir (film) $\lambda_{C=N}$ 5.95 μ. *Anal.* Calcd for $C_{15}H_{19}N$ (mol wt, 213.3): C, 84.46; H, 8.98; N, 6.57. Found: C, 84.28; H, 9.15; N, 6.65.

Deuterated bicyclic phenylimino acids were prepared by an exchange reaction. About 0.1 g of the protic acids was dissolved at room temperature in 0.5 ml of CH_3CO_2D, and the solutions were lyophilized; the process was then repeated, and the products were recrystallized from toluene–petroleum ether. The melting points of these acids were the same as those of the corresponding protic acids, but the proton signal at low field in the nmr spectra was no longer present.

The solvent decalin was the mixture of cis and trans isomers present in Eastman's spectral grade solvent; dioxane was purchased from Analabs, Inc. Other materials were of reagent grade.

Kinetics. The reaction rates were determined spectrophotometrically, with a Gilford Model 240 spectrophotometer. The changes in absorption spectrum during decarboxylation of one of the imino acids are illustrated in Figure 1 for the reaction of 9-phenyliminobicyclo[4.2.1]nonane-1-carboxylic acid. In this series, the changes in absorbance generally amounted to about 0.2 OD units out of a total optical density of 1–1.5; this change, although small, was adequate to obtain good first-order rate constants, as illustrated in Figure 2. Similar but somewhat larger changes in uv spectra permitted a determination of the rates of decarboxylation of the β-keto acids as well.

In order to obtain good spectrophotometric data, particularly for the solutions of keto acids that were heated above 150°, it was necessary to avoid autoxidation of the reactants. The kinetics were therefore conducted in a special cell, constructed by connecting a square fused quartz cuvette through a graded seal to a Pyrex–Teflon needle valve. Solutions of keto acids in decalin were introduced into this cell, and degassed by the standard freezing–evacuating–thawing procedure. Since the concentration of keto acid (or imino acid) was low (*e.g.*, about 10^{-4} *M*), the total amount of CO_2 generated during the reaction was negligible (only a few cubic millimeters), and bubbles did not interfere with the spectrophotometric measurements. This procedure was successful, as is shown by the good isosbestic points for the spectral curves for the decarboxylation of the β-keto acids; *cf.* Figure 3. The reactions were followed over as much as 4 half-lives, and the final absorbance reading was determined by calculation. A computer program determined its value by a least-squares method so as to minimize deviations from a first-order plot. Some measure of the success of this procedure is evident from Figure 2.

The decarboxylations of the β-imino acids were followed in thermostated cells in the Gilford spectrophotometer. The decarboxylation of the β-keto acids at high temperatures could not be followed in this way, and it was therefore necessary to heat solutions in the evacuated cuvette for a stated interval in a high temperature thermostat, and then remove the cell, cool it quickly, and make the spectrophotometric reading at room temperature where the reaction rate is essentially nil. The cell was then reintroduced into the thermostat. The heating and cooling times were generally negligible compared to reactions times. For those experiments conducted at the highest temperatures, however, some correction was needed.[15] After measuring the rate of heating of the cell, and determining the activation energies for the decarboxylations, a semiempirical correction was applied by subtracting 2 min from the time interval of each measurement. The error remaining after this correction cannot be large, and the rate constants so determined yielded smooth Arrhenius plots.[16]

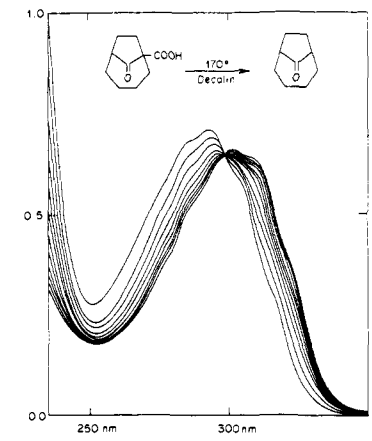
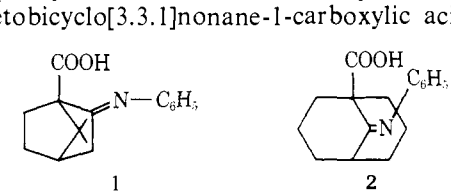


Figure 3. The ultraviolet absorption spectra for successive scans during the decarboxylation of 9-ketobicyclo[4.2.1]nonane-1-carboxylic acid in decalin at 170°. The rate was determined from the data at 315 nm; the absorption increases as the reaction proceeds.

Absolute temperatures were determined with calibrated National Bureau of Standards thermometers.

Results

The phenylimino derivatives of ketopinic acid (**1**) and of 9-ketobicyclo[3.3.1]nonane-1-carboxylic acid (**2**) do



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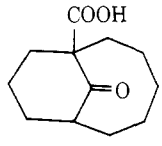
not undergo decarboxylation even at 300°. We were unable to prepare the Schiff base of 11-ketobicyclo[5.3.1]undecane-1-carboxylic acid (**3**) even using the new

(15) R. C. Fay, A. Y. Girgis, and U. Klabunde, *J. Amer. Chem. Soc.*, **92**, 7056 (1970).

(16) K. Taguchi, Ph.D. Thesis, Harvard University, 1972.

methods we had previously developed;[14] this finding is in accord with the general lack of reactivity of the carbonyl group in such compounds.[7] The decarboxylation of 2-ketobicyclo[3.3.1]nonane-1-carboxylic acid (**4**)



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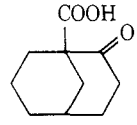

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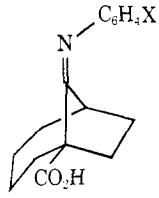
is catalyzed by aniline at room temperature; we have been unsuccessful in isolating the Schiff base, but obviously its rate of decarboxylation must be enormous relative to that of the corresponding keto acid.

Kinetic measurements could, however, be made with 9-phenyliminobicyclo[4.2.1]nonane-1-carboxylic acid and 10-phenyliminobicyclo[4.3.1]decane-1-carboxylic acid, compounds **5** and **6**, with their substituted analogs,



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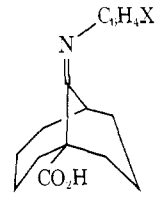

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and with the corresponding β-keto acids. The rates of decarboxylation of the various imines are shown in Table I; the rates of decarboxylation of the unsubstituted β-phenylimino acids and of the corresponding β-keto acids are shown as a function of temperature in Tables II and III.

Table I. Rate Constants for the Decarboxylation[a] of Bicyclo-β-phenylimino Acids at 78.5°

Compd	Series	Para substituent	$10^4 k$, sec^{-1} Decalin	Dioxane
5, X = H	4.2.1	OCH_3	14.4	6.20
		H	12.7	4.98
		Cl	9.6	3.64
6, X = H	4.3.1	OCH_3	8.44	2.40
		H	5.15	1.35
		Cl	3.60	0.92

[a] Some of these rates were determined at temperatures a fraction of a degree from 78.5°; the figures here have been corrected, using Arrhenius parameters [K. Taguchi, Ph.D. Thesis, Harvard University, 1972] to 78.5°.

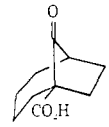
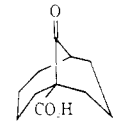
The rates of decarboxylation of the unsubstituted phenylimino acids were confirmed, in a highly approximate way, by following the course of the reaction in dioxane at 80° by thin-layer chromatography. For the [3.2.1] series, the thin-layer plates were developed with benzene–acetonitrile at 2:1; the R_f of the acid is 0.45 and that of the product imine is 0.71; the progress of the reaction could then be followed, and the results, although of course crude, substantiate those determined spectrophotometrically. Similarly, in the [4.3.1] series, the R_f values, using benzene–THF at ~7:1 are 0.42 and 0.52 for acid and product, respectively, and again the decarboxylation gave a rate in agreement with that determined spectrophotometrically.

Since the β-imino acids decarboxylate so much more rapidly than the corresponding β-keto acids, we were unable to measure the rates for the two series at the same temperatures; the decarboxylation of the imino acids was conducted in the range from 70 to 95°, whereas the decarboxylation of the keto acids required from 130 to 170°. A comparison of the reaction rates therefore involves a large extrapolation, with consequent opportunities for error. Further, since the temperature coefficient for the slow decarboxylation of the β-keto acids is so much larger than that for the more rapid decarboxylation of the imino acids, the rate ratio depends on the temperature for which it is calculated.

Table II. Temperature Dependence of the Rate Constants of the Decarboxylation of Bicyclo-β-phenylimino Acids

Compd	Series	Decalin Temp, °C	Decalin $10^4 k$, sec^{-1}	Dioxane Temp, °C	Dioxane $10^4 k$, sec^{-1}
5, X = H	4.2.1	69.0	4.31	71.7	2.27
		78.6	12.7	78.5	4.98
		86.2	27.9	89.1	15.2
ΔH = 26.5 ± 2 kcal/mol					
6, X = H	4.3.1	78.7	5.27	79.6	1.50
		86.5	12.0	87.8	3.70
		93.0	23.1	93.0	6.30
ΔH = 26.4 ± 2 kcal/mol					

Table III. Temperature Dependence of the Rate Constants for the Decarboxylation of Bicyclo-β-keto Acids in Decalin

Structure	Series	Temp, °C	$10^5 k$, sec^{-1}
	4.2.1	145.0	1.46
		154.0	3.73
		161.0	7.64
		169.0	19.0
		170.0	20.2
ΔH = 38.7 ± 2 kcal/mol			
	4.3.1	129.0	2.43
		133.0	3.82
		140.0	9.30
		150.0	23.8
ΔH = 36.7 ± 2 kcal/mol			

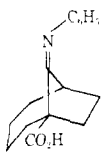
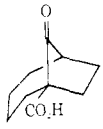
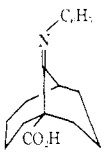
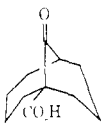
It should be noted parenthetically that, although the more highly strained [4.2.1] bicyclic keto acid decarboxylates more slowly than its [4.3.1] analog, the reverse is true for the β-imino acids, and this fact has not yet been satisfactorily explained. The value of k_H/k_D obtained with various acids fell around 1.01 ± 0.01.

The data for rate comparisons are gathered in Table IV. The measured rates of decarboxylation of the bicyclo β-imino acids at around 80° are compared with the rates for the keto acids, extrapolated to that same temperature. Further, rates for both compounds have been extrapolated to 30°, where the ratios are of course still larger, in order to have data at temperatures comparable to those for enzymic processes.

Discussion

First and foremost, the β-imino acids decarboxylate 10^5–10^7 times as fast as the corresponding β-keto acids. This is consistent with the thesis originally advanced by Pedersen[3] to explain the aniline-catalyzed decarboxylation of dimethylacetoacetic acid, and is in accordance with the Schiff base mechanism that has been established for the enzymic decarboxylation of acetoacetic acid.[1,4] Although the temperature coefficients for the

Table IV. Comparison of the Rates of the Decarboxylation of Bicyclo-β-phenylimino Acids with Those of the Corresponding β-Keto Acids in Decalin, Extrapolated to a Common Temperature

Acid	Temp, °C	Rate constant k, sec^{-1}	Comment	Ratio
	78.6	12.7×10^{-4}	Measured	
	30.0	2.86×10^{-6}	Extrapolated	
	78.6	2.23×10^{-9}	Extrapolated	5×10^{5}
	30.0	3.13×10^{-13}	Extrapolated	1×10^{7}
	78.7	5.27×10^{-4}	Measured	
	30.0	1.22×10^{-6}	Extrapolated	
	78.7	3.40×10^{-8}	Extrapolated	2×10^{4}
	30.0	7.37×10^{-12}	Extrapolated	2×10^{5}

decarboxylation processes are not precise, and although extrapolations over long temperature ranges leave a considerable margin for error, the rate differences are so large that they cannot be obscured; even if the ratios in Table IV are substantially in error, which is unlikely, they cannot be in error by an amount anywhere near that which would be required to compromise the statements above.

The most important qualification that must be made with respect to these data is that they were determined in nonpolar solvents (decalin and dioxane), whereas many of the reactions of interest, and in particular enzymic decarboxylations, take place in water. Since the phenylimines here formed hydrolyze in water, and alcoholize in alcohol, comparisons in polar solvents cannot easily be made with these systems. However, the transfer of a proton from a carboxyl group to an imine nitrogen atom would be expected to be more nearly complete in water than in a nonpolar solvent like dioxane or decalin. Furthermore, the transfer must be reasonably complete in the transition state, since the reactions show essentially no deuterium isotope effect. Solvent effects on decarboxylations can be negligible or huge. The rate of decarboxylation of acetoacetic acid is insensitive to change in solvent,[17] presumably because the reaction proceeds from the un-ionized acid through a cyclic, hydrogen-bonded transition state of relatively low polarity. On the other hand, decarboxylations where the polarity of the transition state is substantially less than that of the starting material show a large enhancement of the rate in nonpolar as opposed to polar solvents.[18] In particular, Crosby and Lienhard[18] observed an increase in rate of about 10^4-fold for the decarboxylation of 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride in ethanol as compared to the same reaction in water; here the transition state is very much less polar than the zwitterionic reactant. In the present example, however, the starting material is almost certainly the imino acid, and not the zwitterion, and therefore no great change in polarity on decarboxylation is anticipated. Evidence that the carboxyl group is present in the imines comes from both ir and nmr spectra; further, the low pK anticipated for the conjugate acids of the Schiff bases of aniline and the high pK's for carboxylic acids in solvents other than water essentially preclude the possibility that the starting material is a dipolar ion. Presumably the imino acids, like the corresponding keto acids, decarboxylate by way of a hydrogen-bonded structure, and this in turn implies that the aryl groups on the nitrogen atoms in the Schiff bases are directed away from the carboxyl function.

The rate of the decarboxylation of the β-phenylimino acids is not strongly dependent on the structure of the aniline used in the preparation of the Schiff base (Table I). For example, the rates are only slightly greater for the *p*-methoxy- than for the *p*-chloro-substituted compounds. This observation is consistent with a mechanism where the proton is transferred from the carboxyl group to the imino nitrogen atom; the transfer will be more nearly complete to the nitrogen atom of the more strongly basic anisidine (pK = 5.34) than to that of the less strongly basic *p*-chloroaniline (pK = 3.84).[19] But the Hammett ρ factor for these two decarboxylations is only about -0.5 ± 0.2, and this suggests that the transition state is not highly polar.

Another major difference between these data and those that might obtain for simple systems (*e.g.*, for the enzymic or nonenzymic decarboxylation of acetoacetic acid) concerns the bicyclic structures here used. They were needed in order to impart requisite stability to the β-imino acids. But the rate ratio for decarboxylation as between a β-imino acid and a β-keto acid need not be independent of structure. The strain introduced into the product enol from the decarboxylation of the keto acids, and the strain introduced into an enamine from the decarboxylation of an imino acid may not be equal, and extrapolation from the bicyclic system to a simple one is not straightforward.

The rate of decarboxylation of acetoacetic acid, in model systems, is subject to amine catalysis.[3,5,6] The rate-limiting step in the model system depends on experimental conditions in such a way as to suggest that the formation of the Schiff base and the decarboxylation step proceed at comparable rates, and are perhaps a million times as fast as the simple decarboxylation of acetoacetic acid. This is about the same factor as that observed in the present research; however, in view of the large uncertainties introduced both by the difference in solvent and by the unusual structures that have been employed in this study, the approximate agreement in rate factor is probably only coincidental.

Similarly, the enzymic process is one where decarboxylation is only partially rate limiting.[20] The catalytic

(17) F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, **63**, 3238 (1941).

(18) (a) J. V. Rund and R. A. Plane, *ibid.*, **86**, 367 (1964); (b) G. R. Jurch, Jr., and K. C. Ramey, *Chem. Commun.*, 1211 (1968); (c) J. Crosby and G. E. Lienhard, *J. Amer. Chem. Soc.*, **92**, 2891, 5707 (1970).

(19) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 323 (1964).

(20) M. H. O'Leary and R. Baughn, *J. Amer. Chem. Soc.*, **94**, 626 (1972).

rate constant for the enzymic reaction is about 10^9 times as fast as that for the simple decarboxylation of acetoacetate ion (both constants are first order), and the data therefore suggest that the decarboxylation of the ketimine is 10^9 as fast as that for the uncatalyzed decarboxylation of acetoacetate ion.[1,4,5]

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Asymmetric Syntheses Using Optically Active Oxosulfonium Alkylides[1]

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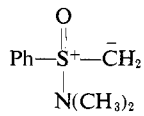
Abstract: Asymmetric inductions in the reactions of chiral (dialkylamino)aryloxosulfonium alkylides with aldehydes and ketones to give oxiranes and with electrophilic alkenes to give cyclopropanes are reported; optical yields were found to be in the range of 7–43%. The ylides were generated from optically active (dialkylamino)-alkylaryloxosulfonium fluoroborates which were prepared from resolved sulfoximines.

A convenient and stable reagent for the synthesis of oxiranes and cyclopropanes has been shown to be (dimethylamino)phenyloxosulfonium methylide (**1**).[2] The sulfur center of this ylide is chiral; if resolved into one enantiomeric form, the ylide should be capable of transferring its methylene in an asymmetric manner. Thus, optically active oxiranes and cyclopropanes would be obtained. In this paper we describe the synthesis of opically active (dialkylamino)-aryloxosulfonium alkylides and the asymmetric inductions in their reactions.[3]



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Optically active ylides derived from trialkyl- and diarylmethylsulfonium salts have been prepared, but racemize too quickly to be capable of significant asymmetric synthesis.[4] The proposed mechanism of their racemization is one of pyramidal inversion. The quaternary sulfur of the oxosulfonium ylide, *e.g.*, **1**, cannot become planar so readily and should be configurationally stable.

The preparation of optically active oxiranes by asymmetric epoxidations, and the production of optically active cyclopropanes by a variety of asymmetric syntheses is well documented.[5] Many chiral peracids have been reacted with alkenes to give optically active epoxides;[6] asymmetric induction is usually less than 2%.

A number of the chiral cyclopropane syntheses cited[5a] involve methylene or alkylidene transfer to an optically active substrate, *e.g.*, the addition of dimethyloxosulfonium methylide to (−)-menthyl cinnamates gave the enantiomer, (1*R*,2*R*)-*trans*-2-arylcyclopropanecarboxylic acids, in 3–4% excess, upon hydrolysis of the esters.[7]

For simple methylene transfer reactions, there are few asymmetric syntheses of cyclopropanes where the optical activity is introduced by the chirality of the reagent. One in which the reagent is presumed to be chiral is a Simmons–Smith reaction in the presence of (−)-menthol; for example, *trans*-methyl crotonate reacted with methylene iodide and zinc–copper couple to give *trans*-methyl 2-methylcyclopropanecarboxylate in 1.9% optical purity.[8]

An example of chiral catalyst for asymmetric methylene transfer is also known. The chelate, prepared from (−)-(*S*)-α-methylbenzylamine, salicylaldehyde, and cupric ion, has been used to effect additions of diazoalkyl compounds to alkenes in optical yields of 6–8%.[9]

Results and Discussion

Optically active (dialkylamino)alkylaryloxosulfo-

(1) Part XLV in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623).

(2) C. R. Johnson, M. Haake, and C. W. Schroeck, *J. Amer. Chem. Soc.*, **92**, 6594 (1970).

(3) For a preliminary report of this work, see C. R. Johnson and C. W. Schroeck, *ibid.*, **90**, 6852 (1968).

(4) D. Darwish and R. L. Tomilson, *ibid.*, **90**, 5938 (1968); B. M. Trost and R. F. Hammen, *ibid.*, **95**, 962 (1973).

(5) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," 1st ed, Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 219–296. (b) For asymmetric epoxidations, see also the following F. Montanari, I. Moretti, and G. Torre, *Boll. Sci. Fac. Chim. Ind. Bologna*, **26**, 113 (1968); J. L. Pierre, P. Chautemps, and P. Afnaud, *Bull. Soc. Chim. Fr.*, 1317 (1969). (c) For asymmetric syntheses of cyclopropanes, see also the following R. Noyori, H. Takaya, Y. Nakanisi, and H. Nozaki, *Can. J. Chem.*, **47**, 1242 (1969); S. Inamasu, N. Horiiki, and Y. Inouye, *Bull. Chem. Soc. Jap.*, **42**, 1393 (1969); S. Sawada and Y. Inouye, *ibid.*, **42**, 2669 (1969).

(6) (a) H. B. Henbesti, *Chem. Soc., Spec. Publ.*, **No. 19**, 83 (1965); (b) R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Commun.*, 1085 (1967).

(7) H. Nozaki, H. Ito, D. Tunemato, and K. Kondo, *Tetrahedron*, **22**, 441 (1966).

(8) S. Sawada, J. Oda, and Y. Inouye, *J. Org. Chem.*, **33**, 2141 (1968).

(9) H. Nozaki, H. Takawa, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968).