product in reaction 2? A kinetic analysis of the proposed reaction scheme can be made as shown. The steady-state hypothesis is invoked for the reactive intermediate I. The ratio of rate constants k_c/k_b is

$$\begin{tikzcd}
\mathbf{5} + \mathbf{6} \arrow[r, "a"] \arrow[dr, "d"'] & {[\mathrm{I}]} \arrow[r, "b"] \arrow[d, "c"] & \mathbf{7} \\
 & \mathbf{8} &
\end{tikzcd}$$

$$\mathbf{8}/\mathbf{7} = (k_d/k_a)(k_c/k_b + 1) + (k_c/k_b)$$

given by the work in the previous paragraph, $k_c/k_b = \exp(0.0782\gamma/RT)$. The ratio of products **8**/**7** is known experimentally; the ratio of k_d/k_a can therefore be determined. The appropriate value of γ is that determined from the product distribution in the reaction of 1-cyanovinyl acetate with, perhaps, 1,1-dimethylbutadiene. Since these data are not available, an empirical value of γ determined from the results of reaction 1, $\gamma = 12.0$ kcal/mole, gives $k_d/k_a = 0.29$. So our answer to the second question is that we cannot exclude a simultaneous 4 + 2 cycloaddition reaction as a possibility in the formation of the Diels–Alder adduct. However, more experimental data may resolve this question.

In summary, within the framework of the PMO method, a two-step mechanism with a common intermediate can account for differing ratios of the two types of products in these anomalous Diels–Alder reactions, although some competing cycloaddition may be possible.

We recognize that we have taken a very simplified view of this whole problem. The observation of *cis–trans* isomers in reaction 2[2] and solvent effects have been ignored. The use of a simple Hückel method to compare energies of diverse systems is also difficult to justify theoretically. The justification for this approach must, as usual, be the comparison of the calculations with experimental results.

Acknowledgment.—We would like to thank the staff of the computer center of Texas Technological College for assistance in computing problems and generous gifts of computer time. Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (PRF No. 3069-A4). We also wish to thank Dr. K. E. Schueller and Dr. C. J. Dempster who very kindly made copies of their dissertations available to us.

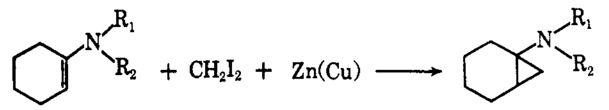
Synthesis and Nuclear Magnetic Resonance Analysis of Cyclopropyl- and 1-Bicyclo[*n*.1.0]alkylamines

D. L. MUCK AND E. R. WILSON

Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received July 27, 1967

In connection with other work in these laboratories, we have had a need for a series of 1-aminobicyclo[*n*.1.0]alkanes. A recent report by Blanchard, Simmons, and Taylor[1] described the synthesis of a few of these compounds, although generally in low yield, by methylene addition to enamines using methylene iodide and zinc–copper couple. An earlier report by Wittig and Wingler[2] described a similar addition to an enamine, but these workers used bis(iodomethyl)zinc as the methylene transfer agent. In this paper we would like to report a simple procedure for preparing cyclopropyl- and 1-bicyclo[*n*.1.0]alkylamines in good yields. We have found that enamines readily react with diazomethane in the presence of cuprous chloride to give the corresponding cyclopropyldialkylamines, with yields of 65–80% of distilled products. In the normal procedure, a twofold molar quantity of diazomethane in ether is dripped into a stirred ether solution of the enamine and suspended cuprous chloride at room temperature.



Cuprous salts have been well established in recent years as catalysts in the reaction of diazomethane with olefins to give cyclopropane derivatives[3] and earlier as polymerization catalysts for diazo compounds.[4] One early report by Bawn and Ledwith[4c] concerning new catalysts for polymerization reactions mentioned that an ether solution of cuprous iodide containing a little aliphatic amine gave an intense red color upon the addition of diazoethane, which disappeared as the diazoethane was exhausted by polymerization. It is interesting that in our reactions of cyclopropyl ring formation we also observe an intense red color which disappears with the removal of diazomethane.

In order to demonstrate the generality of the reaction, both the amine and the aldehyde or ketone used to prepare the enamines were varied to give a number of different starting materials. The results of methylene addition to the enamines prepared are shown in Table I. Although there may be a slight steric hindrance to addition in a trisubstituted enamine, the reaction in general was not affected by the nature of the alkyl substituents either on the double bond or on the nitrogen atom. However, when there were no alkyl groups substituted on the double bond, such as with vinylpyrrolidine, an apparent decrease in reactivity was observed and twice as much diazomethane was required as was generally needed.

Interpretation of Nmr Spectra.—Nmr spectra were obtained on all of the compounds prepared and analyzed as much as possible in order to support the proposed structures. The data obtained are listed in Table II, where the *endo* protons are designated as "A"

---

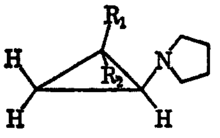
[1] E. P. Blanchard, H. E. Simmons, and J. S. Taylor, *J. Org. Chem.*, **30**, 4321 (1965).

[2] G. Wittig and F. Wingler, *Chem. Ber.*, **97**, 2146 (1964).

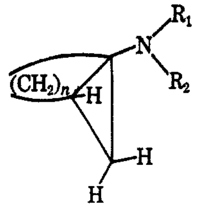
[3] (a) P. Yates and J. Fugger, *Chem. Ind.* (London), 1511 (1957); (b) M. F. Dull and P. G. Abend, *J. Am. Chem. Soc.*, **81**, 2588 (1959); (c) G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961); (d) W. v. E. Doering and W. Roth, *Tetrahedron*, **19**, 715 (1963); (e) E. Vogel, W. Wiedemann, H. Kiefer, and W. F. Harrison, *Tetrahedron Letters*, 673 (1963); (f) W. R. Roth, *Ann.*, **671**, 10 (1964); (g) R. E. Pincock and J. I. Wells, *J. Org. Chem.*, **29**, 965 (1964).

[4] (a) G. D. Buckley, L. H. Cross, and N. H. Ray, *J. Chem. Soc.*, 2714 (1950); (b) L. C. Leitch, P. E. Gagnon, and A. Cambron, *Can. J. Res.*, **28b**, 256 (1950); (c) C. E. H. Bawn and A. Ledwith, *Chem. Ind.* (London), 1180 (1957).

TABLE I
PHYSICAL CONSTANTS OF AMINES



A

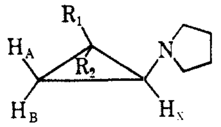


B

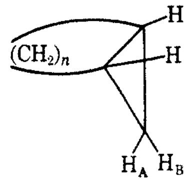
No.	Type	R_1	R_2	n	Bp, °C (mm)	$n^{25}D$	Yield,[a] %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	A	H	H	...	[b]	1.4465[c]	73[d]	$C_7H_{13}N$	75.68	11.71	12.61	75.88	11.46	12.56
2	A	Me	Me	...	50 (15)	1.4421	69	$C_9H_{17}N$	77.70	12.23	10.07	77.46	12.39	9.98
3[e]	A	Et	H	...	55 (15)	1.4435[c]	80	$C_9H_{17}N$	77.70	12.23	10.07	77.80	12.11	10.10
5	B	$(CH_2)_4$	...	4	48 (1)	1.4865	72	$C_{11}H_{19}N$	80.00	11.52	8.48	79.84	11.70	8.24
7	B	$(CH_2)_4$	...	3	81 (12)	1.4820	75	$C_{10}H_{17}N$	79.47	11.26	9.27	79.51	11.28	9.30
8	B	Et	Et	3	74 (28)	1.4544	72	$C_{10}H_{19}N$	78.43	12.42	9.15	78.55	12.47	9.07
9	B	Me	Me	3	67 (55)	1.4470[a]	65	$C_8H_{15}N$	76.80	12.00	11.20	76.72	12.27	11.04

[a] Based on pure isolated amine; yields measured by vpc were normally quantitative. [b] This compound appeared to decompose on distillation. [c] Corrected to 25°. [d] Crude yield. [e] Stereochemistry unknown.

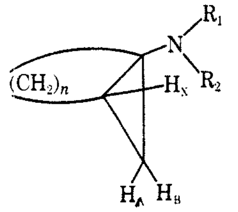
TABLE II
NMR SPECTRAL DATA[a]



A



B



C

No.[e]	Type	R_1	R_2	n	H_A	H_B	J_{AX}	J_{BX}	J_{AB}[b]
1	A	H	H	...	9.58	9.58	5.0[c]	5.0[c]	...
2	A	Me	Me	...	9.78	9.66	4.0	7.0	−4.3
3[d]	A	Et	H	...	9.75	9.37	...	...	...
4	B	...	...	4	10.04	9.53	4.5	9.3	−4.5
5	C	$(CH_2)_4$	...	4	9.81	9.30	...	9.8	−4.0
6	B	...	...	3	9.83	9.47	4.0	7.5	−5.0
7	C	$(CH_2)_4$	...	3	9.66	9.44	4.0	8.2	−4.5
8	C	Et	Et	3	9.51	9.42	...	8.1	−4.5
9	C	Me	Me	3	9.60	9.48	4.7	8.1	−4.4

[a] All spectra were obtained in deuterated chloroform. [b] Sign assumed to be negative. [c] $^1/_2|J_{AX} + J_{BX}|$. [d] Stereochemistry unknown. [e] Registry no.: **1**, 14924-55-1; **2**, 14924-56-2; **3**, 14924-57-3; **4**, 286-08-8; **5**, 14924-59-5; **6**, 285-58-5; **7**, 15043-70-6; **8**, 14924-61-9; **9**, 4779-18-4.

and the *exo* as "B." The bridgehead proton "X" could not be assigned in most cases because of overlapping absorption by the neighboring methylene protons. With all but two of the compounds, the absorptions observed for the cyclopropane methylene protons were generally characteristic of the AB portion of an ABX pattern. However, since J_{AX} was approximately equal to J_{AB}, only a seven-line pattern was obtained with proton "A" lines present in an unsymmetrical triplet upfield from the pair of doublets due to proton "B." With compounds **2**, **4**, and **5**, the coupling constants were calculated from the experimental line positions of the cyclopropyl methylene protons and shown to agree well with the experimental values. This was not possible with compounds **6** and **7** due to a slight overlapping of these absorptions. The geminal coupling constants J_{AB} were assumed to be negative in accord with the results of earlier workers.[5] The methylene protons of the cyclopropane ring were assigned on the basis that the *cis* coupling constant, J_{BX}, should be larger than the *trans* coupling constant, J_{AX}. This assignment has been reported to be generally valid for cyclopropane hydrogens by Dauben and Wipke,[6] who calculated values for vicinal couplings in bicyclo[*n*.1.0]alkane systems using the Karplus equations and obtained good agreement with 35 compounds for the values of 8.2 and 3.8–4.3 Hz for the *cis* and *trans* couplings, respectively.

With compounds **1** and **3**, where more than three cyclopropane protons were present, the results obtained were necessarily different. Compound **3**, with four nonequivalent cyclopropyl protons, gave a very complex spectrum with considerable overlapping of lines. The spectrum obtained from compound **1** in deuterated chloroform was deceivingly simple. The two pairs of methylene cyclopropane protons appeared at τ 9.58 as a doublet, a surprising result since the geminal ring protons of both cyclopropylamine[7] and 1-pyrrolidino-2,2-dimethylcyclopropane (compound **2**) exhibit different chemical shifts. However, in solvents other than deuterated chloroform, such as acetone or benzene, the doublet observed for the methylene cyclopropane protons was transformed into the expected complex multiplet. There appears to be no obvious explanation for this rather drastic solvent effect.

In an effort to obtain more evidence for the structure of pyrrolidinocyclopropane, a series of decoupling experiments in deuterated chloroform were conducted.

---

(5) (a) K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **85**, 2788 (1963); (b) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, **85**, 3218 (1963); (c) C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962); (d) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 684, 1623 (1963).

(6) W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967).

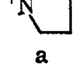
(7) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, p 37.

When the cyclopropyl proton α to the pyrrolidine nitrogen was decoupled, the peak due to the methylene cyclopropane protons was transformed from the doublet into a singlet. Similarly, the α-proton peak was converted from an apparent pentuplet (one line covered by overlapping absorptions) into a singlet when the doublet in question was irradiated. As a follow-up, the two absorptions due to the pyrrolidine ring protons were separately irradiated, with the result that the respective multiplets were converted into singlets; with no change in the cyclopropyl proton absorptions. These results are certainly consistent with the proposed structure for pyrrolidinocyclopropane.

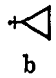
Considering now the chemical shifts for the bicyclo[*n*.1.0]alkane derivatives **4**–**9**, we see that the *endo* proton H_A always resonates at higher field than the *exo* proton H_B. This relationship is consistent with the prediction that the *endo* proton would be subjected to the diamagnetic anisotropic shielding of the carbon–carbon bonds directly over it, thereby resulting in a shift to higher field. This explanation has been used to account for the upfield position of *axial* protons in cyclohexane relative to the equatorial protons[8] and of *endo* protons in bicyclo[2.2.1] derivatives.[9,10] Dauben and Wipke[6] observed a similar effect in their study on the bicyclo[*n*.1.0]alkanes, but noted reversals in positions of the *endo–exo* protons of some derivatives having alkyl groups at the bridgehead positions.

An interesting effect of ring size on the chemical shifts of the *endo*- and *exo*-cyclopropyl methylene protons of some of the bicyclo[*n*.1.0]alkane derivatives studied is noteworthy. A comparison of compound **4** with **6**, and of **5** with **7**, shows a large downfield shift of the *endo* proton H_A as the ring changes from six to five carbon atoms. A similar effect was previously observed by Dauben and Wipke[6] and they attributed the shifts to a steric nonbonded interaction of the *endo* proton with *cis* proton on carbon atom 3 of the five-membered ring.

Discussion of Mass Spectral Data.—To provide additional evidence for the proposed structure of pyrrolidinocyclopropane, a mass spectral analysis was made. The molecular weight of 111 ($C_7H_{12}N$) expected for the monomer was confirmed by the absence of any peak higher than 111 amu. The splitting pattern was also consistent with the proposed structure, as a strong peak at 110 amu along with peaks at 70 and 41 amu (structures a and b, respectively) were obtained. Added proof of the structure was obtained when the empirical formulas of the molecular ion and four fragments were obtained by peak-matching techniques, using perfluorokerosene as a standard. The results are shown in Table III.

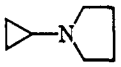


a



b

TABLE III

MASS SPECTRAL DATA FOR 

m/e	Empirical formula	Mass: Calcd	Mass: Measured
111	$C_7H_{13}N^+$	111.1048	111.1027
110	$C_7H_{12}N^+$	110.0970	110.0960
96	$C_6H_{10}N^+$	96.0813	96.0810
70	$C_4H_8N^+$	70.0657	70.0660
68	$C_4H_6N^+$	68.0500	68.0499

Experimental Section[11]

Preparation of Enamines. Method A.—In all but two cases described in methods B and C the enamines used were prepared by refluxing a benzene solution of the reactants through a column of 4A Molecular Sieves for 3 hr.[12] The enamines were then distilled under reduced pressure and used immediately.

1-Dimethylaminocyclopentene. Method B.—1-Dimethylaminocyclopentene was prepared by diluting 8.40 g (0.10 mole) of cyclopentanone with 100 ml of anhydrous ether at 0° and adding 4.95 g (0.11 mole) of condensed dimethylamine in one portion. The resulting solution was stored over 10 g of 4A Molecular Sieves in a freezer overnight and then distilled to give 7.02 g (63%) of clear liquid, bp 68° (45 mm), which exhibited a strong infrared absorption at 1648 cm^{-1}.

Vinylpyrrolidine. Method C.—To 2.56 g (0.036 mole) of pyrrolidine in 15 ml of anhydrous ether, stirred at 0° with about 4 g of anhydrous magnesium sulfate,[13] was added dropwise 1.54 g (0.035 mole) of acetaldehyde during 10 min. This mixture was allowed to stand in a freezer overnight, filtered, and then used without further purification. A small portion was removed and evaporated on a rotary evaporator to give a clear liquid which showed a strong infrared absorption for the enamine double bond at 1642 cm^{-1}. The product darkened rapidly when exposed to air.

Preparation of Cyclopropylamines.—The preparation of 1-pyrrolidinobicyclo[3.1.0]hexane is described as a typical example of this procedure. 1-Pyrrolidinocyclopentene (6.85 g, 0.05 mole) was diluted with 30 ml of dry ether and 1.0 g (0.01 mole) of finely powdered cuprous chloride was added. While stirring magnetically, an ether solution of diazomethane[14] (5.0 g, 0.12 mole) was slowly added during 1 hr. An initial deep red color developed as the evolution of nitrogen began, but this later changed to brown, and finally back to green soon after the addition was complete. Filtration with suction of the resulting mixture gave a light green solution which was evaporated to an oil on a rotary evaporator. Vacuum distillation gave 5.6 g (75%) of a clear colorless liquid, bp 81° (12 mm). The infrared spectrum showed complete loss of the enamine double bond absorption (1645 cm^{-1}) and the nmr spectrum

---

[8] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959.

[9] (a) T. J. Flautt and W. F. Erman, *J. Am. Chem. Soc.*, **85**, 3212 (1963); (b) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

[10] One apparent exception recently reported by D. E. Minnikin, *Chem. Ind.* (London), 2167 (1966), describes the chemical shifts of the methylene protons of a 1,2-dialkylcyclopropane as being opposite to this generality. However, Minnikin apparently did not have coupling constant data available and was therefore hampered in his attempt to assign the respective chemical shifts.

[11] All reactions were carried out under argon. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., Spang Microanalytical Laboratories, Ann Arbor, Mich., and by the analytical group of these laboratories. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. All of the liquid reagents used were purchased from Matheson Coleman and Bell while the dimethylamine came from the Matheson Gas Co. N-Nitroso-N-methylurea was purchased from the Aldrich Co. Nmr spectra were obtained with a Varian HA-100 nmr high-resolution spectrometer. In all cases, tetramethylsilane (TMS) was used as an internal standard and shifts in τ units are referred to it. A number of the amines prepared were purified for elemental analysis by collection from an F & M Model 700 gas chromatograph equipped with a 6 ft × 0.25 in. column packed with 10% Apiezon H on 60–80 mesh Chromosorb W, acid washed, dimethyldichlorosilane treated. Mass spectra were obtained with an Atlas SM-1 double-focusing high-resolution instrument. Peak matching was accomplished at about 8000 resolution (based on the 10% valley definition).

[12] J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

[13] Molecular sieves caused considerable darkening and apparent decomposition. We are indebted to Professor L. A. Paquette for suggesting the use of maganesium sulfate.

[14] F. G. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1940, p 165.

exhibited multiplets centered at τ 7.42, 8.35, 8.82, and 9.50 (relative areas 4:9:2:2).

Registry No.—1-Dimethylaminocyclopentene, 4840-12-4; vinylpyrrolidine, 4540-16-3.

Acknowledgments.—The authors gratefully acknowledge the assistance of L. H. Sickman, Jr., and H. C. Kowollik, and the comments of Dr. T. J. Flautt and Professors E. C. Taylor and W. M. Jones.

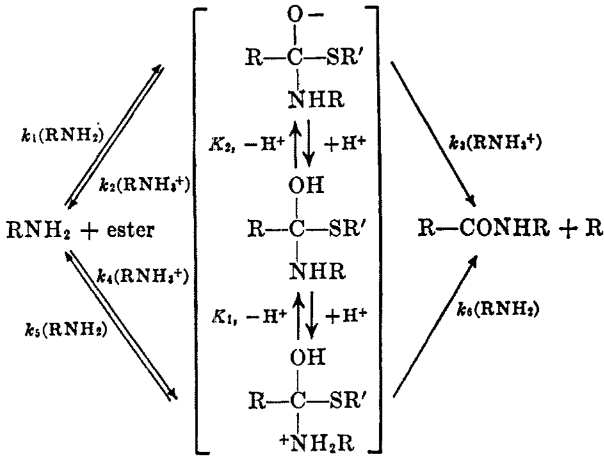
A Reinvestigation of the Reaction of Piperidine with 2,2,2-Trifluoroethyl Thiolacetate[1]

NITYA G. KUNDU[2] AND THOMAS C. BRUICE[3]

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106

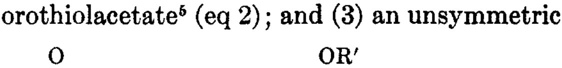
Received June 28, 1967

Previous papers from this laboratory have reported three cases of kinetic evidence for the formation of tetrahedral intermediates in displacement reactions on thiol esters: (1) tetrahedral intermediates in acid–base equilibrium during simultaneous general acid and general base catalyzed hydroxylaminolysis and methoxylaminolysis of δ-thiolvalerolactone, γ-thiolbutyrolactone, n-butyl thiolacetate, isopropyl thiolacetate, and t-butyl thiolacetate[4] (eq 1, the so-called "cross-



(1)

over mechanism" between parallel reactions paths); (2) an unsymmetrical hydrolytic pathway for ethyl trifluorothiolacetate[5] (eq 2); and (3) an unsymmetrical



$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OR' + H_2O \underset{k_2\,H_3^+O}{\overset{k_1\,H_2O}{\rightleftarrows}} R{-}\underset{\displaystyle OH}{\overset{\displaystyle OR'}{C}}{-}O^- \xrightarrow{k_3} product} \quad (2)$$

general base–general acid (by piperidine) catalyzed hydrolysis of 2,2,2-trifluoroethyl thiolacetate[1] (eq 3). Of these three cases (1) appears well documented and the kinetic scheme, required to fit the data, is unique among the large number of schemes considered. Case 2 appears to be certain since the rate constants are not only calculable from the appropriate kinetic equations but by O[18] exchange as well.[6] Following the report of

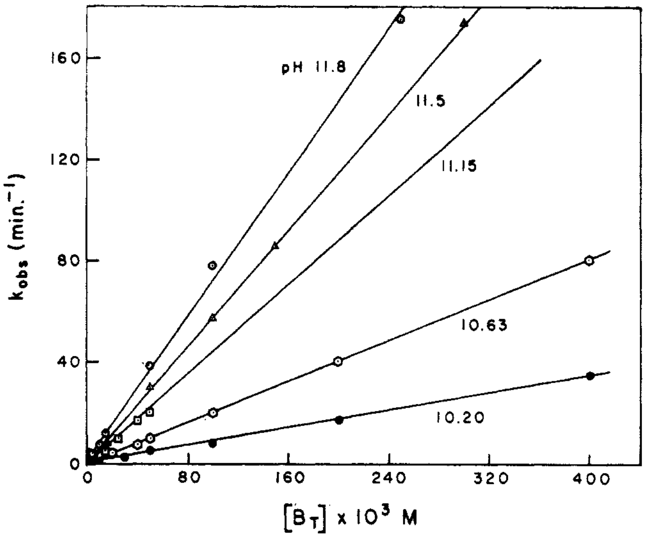


Figure 1.—The linear dependence of the pseudo-first-order rate constants for the reaction of piperidine with 2,2,2-trifluoroethyl thiolacetate on the total piperidine concentration.

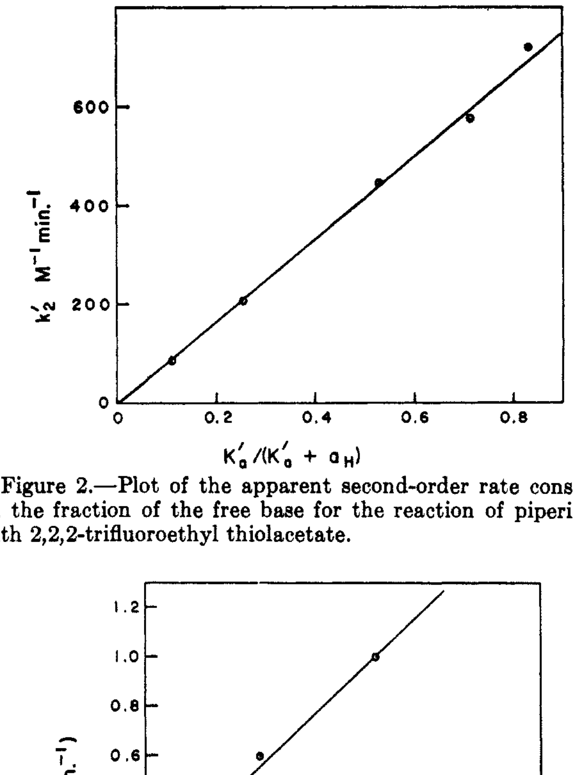


Figure 2.—Plot of the apparent second-order rate constant *vs.* the fraction of the free base for the reaction of piperidine with 2,2,2-trifluoroethyl thiolacetate.

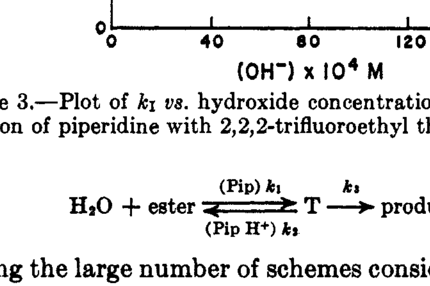


Figure 3.—Plot of k_I *vs.* hydroxide concentration for the reaction of piperidine with 2,2,2-trifluoroethyl thiolacetate.

$$\mathrm{H_2O + ester \underset{(Pip\,H^+)\,k_2}{\overset{(Pip)\,k_1}{\rightleftarrows}} T \xrightarrow{k_3} product} \quad (3)$$

---

[1] A correction of that portion of the paper by M. J. Gregory and T. C. Bruice [*J. Am. Chem. Soc.*, **89**, 2121 (1967)] deals with the nucleophile piperidine.

[2] Postdoctoral Fellow, University of California at Santa Barbara, Santa Barbara, Calif.

[3] To whom correspondence should be addressed.

[4] T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 738, 739, 4886 (1964).

[5] L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 5697 (1964); **87**, 4138 (1965).

[6] M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).