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Pyridylcyclobutanes. The Acid-Catalyzed Cycloaddition of Enamines to Vinylpyridines

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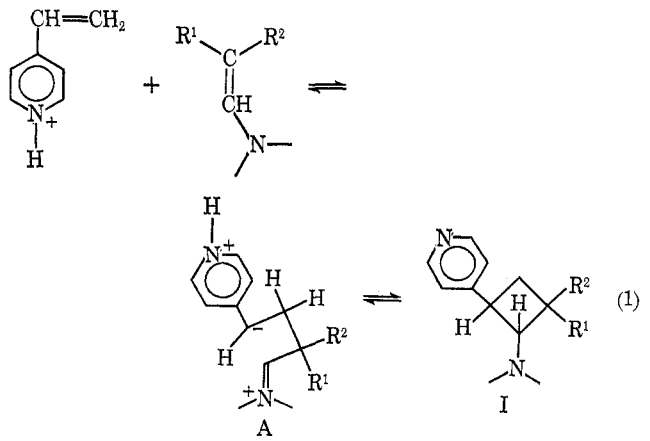
Cycloaddition of enamines of α-disubstituted aldehydes to 2- and 4-vinylpyridines proceeds only in the presence of an acid catalyst to give pyridylcyclobutane derivatives in moderate to good yields. The reaction fails with a 3-vinylpyridine and yields other ultimate products with enamines bearing β hydrogens. It is considered that the acid protonates the vinylpyridine and thus polarizes and activates the double bond to attack. The pyridylcyclobutanes suffered facile ring opening in acid solution but were stable to strong base, and the anion of 3-(4-pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1) could be alkylated to provide 3,3-disubstituted derivatives. 1 was selectively quaternized at the pyridine N but oxidized with a peracid at the morpholine N. Catalytic hydrogenation of 1 gave the piperidine derivative 19 which was much more stable to acid treatment.

As one outgrowth of our studies of pyridylcyclopropanes,[2] we were led to investigate compounds in which a substituted cyclobutane ring was directly attached to a pyridine nucleus. The present paper details our work on the synthesis of such compounds by the cycloaddition of enamines to 2- and 4- vinylpyridines, a reaction which was found to succeed only under conditions of acid catalysis and apparently only with enamines of α,α-disubstituted aldehydes (*i.e.*, enamines without β hydrogens). Subsequent reactions of the pyridylcyclobutane products are also discussed.

At first glance a direct approach to the pyridylcyclobutane system seemed eminently feasible, patterned after the cycloaddition of enamines to α,β-unsaturated carbonyl compounds and nitriles, *i.e.*, electrophilic olefins,[3-5] in which a vinylpyridine provided the electron-deficient double bond. Under a range of conditions as previously defined,[3-5] however, the morpholine and pyrrolidine enamines of isobutyraldehyde failed to add to 4-vinylpyridine, and only starting materials and polymeric resins were recovered from reaction mixtures.

4-Vinylpyridine apparently was not sufficiently reactive and it occurred to us that it might be possible to activate the double bond to attack by polarizing the molecule through protonation. Indeed, addition of a catalytic amount (*ca.* 2 mol %) of *p*-toluenesulfonic acid to reaction mixtures did promote facile cycloaddition with enamines of α,α-disubstituted aldehydes, providing the cyclobutane derivatives described in Table I in yields up to 80%. As long as a small amount of acid was present, the reaction could be carried out in polar or nonpolar solvents or without solvent at temperatures up to 150° but proceeded most smoothly under mildest conditions (even at room temperature) and with least contamination from polymeric by-products in a polar solvent, notably acetonitrile. This fact suggests, in keeping with conclusions drawn from studies of the parallel reactions with α,β-unsaturated carbonyl compounds,[3-6] that cycloaddition is not concerted but is a two-step process going through a charged transition state. Although only a small amount of protonated vinylpyridine can be present at equilibrium, the effect of acid must mean that a protonated vinylpyridine participates in the rate-determining step,[7] which should



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(2) A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966); A. P. Gray, H. Kraus, D. E. Heitmeier, and R. H. Shiley, *ibid.*, **33**, 3007 (1968).

(3) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelley, *ibid.*, **26**, 625 (1961); *ibid.*, **29**, 801 (1964).

(4) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **29**, 813 (1964).

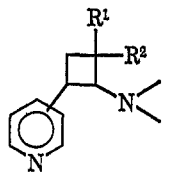
(5) I. Fleming and J. Harley-Mason, *J. Chem. Soc*, 2165 (1964).

(6) A. Risaliti, E. Valentin, and M. Forchiassin, *Chem. Commun.*, 233 (1969).

(7) A. P. Gray and W. L. Archer, *J. Amer. Chem. Soc.*, **79**, 3554 (1957).

TABLE I

PYRIDYLCYCLOBUTANES

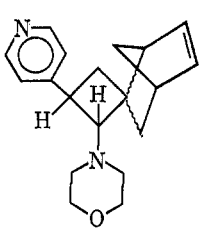


Compd[a]	Pyridyl isomer	R^1	R^2	−N<	Mp, °C	Yield, %
1	4	Methyl	Methyl	Morpholino	93–94	64
2	2	Methyl	Methyl	Morpholino	83–85	48
	Maleate salt				144–145	
3	2-(Maleate salt)	Methyl	Methyl	Pyrrolidino	127–128	13
4	4	Methyl	Methyl	Pyrrolidino	95–96	35
5	4	Methyl	Methyl	Dimethylamino	55–56	80
6	4	Methyl	Ethyl	Morpholino	99–100	40
7	4	Methyl	Phenyl	Morpholino	119–120	23
8	4	Ethyl	Ethyl	Morpholino	71–72	38
9	4	Methyl	*n*-Nonyl	Morpholino	61–62	39
10	4	R^1, R^2 = cyclohexylidene		Morpholino	152–153	61
11	4	R^1, R^2 = 3-cyclohexenylidene		Morpholino	166–167	60
12	4	R^1, R^2 = 5-norbornen-2-ylidene		Morpholino	Brown glass	48

[a] Satisfactory analytical values for C, H, and N (±0.35%) were obtained for all compounds except as follows. Calcd for **2**: N, 11.38. Found: N, 10.89. Calcd for **3** maleate salt: N, 8.09. Found: N, 7.72. Calcd for **12**: C, 76.98; mol wt, 296.4. Found: C, 76.58; mol wt (Rast), 300.0.

be the initial addition of the enamine to it. Without attempting a precise formulation of the transition state, we picture the reaction as proceeding somewhat as indicated for 4-vinylpyridine (eq 1).

Only a single isomer of the cycloadduct I was isolated in each of the additions to enamines in which $R^1 = R^2$. This was clearly indicated by the nmr spectral data and by examination with tlc. In fact, surprisingly, even the cycloadducts (**6**, **7**, **9**, **11**) derived from enamines of asymmetrically substituted aldehydes, which involve three asymmetric centers in the cyclobutane ring, appeared to be (by tlc; nmr data were not helpful) uncontaminated by isomeric products, although here the evidence for homogeneity cannot be considered unequivocal. It was then reassuring in a negative way to find that at least **12**, derived from the enamine of



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norbornenecarboxaldehyde, was indeed a mixture of isomers presumably dependent on orientation of the norbornene system with respect to the cyclobutane ring. That the products are cyclobutane derivatives having the designated gross structures is clear from the nmr spectral data (see Experimental Section), which were consistent throughout the series.[8] In the absence of suitable models and more detailed analysis, the data do not permit establishment of stereochemistry. The unequivocal evidence that an analogous cycloaddition is a reversible process leading to the thermodynamically more stable cyclobutane product,[6] however, makes it reasonable to suppose that the present reaction is likewise thermodynamically controlled. If this be true, then it seems likely that the amine and pyridine substituents would be attached trans to each other on the cyclobutane ring as pictured in I. Little can be said with any degree of confidence about the stereochemical disposition of the R^1 and R^2 substituents where these are different.

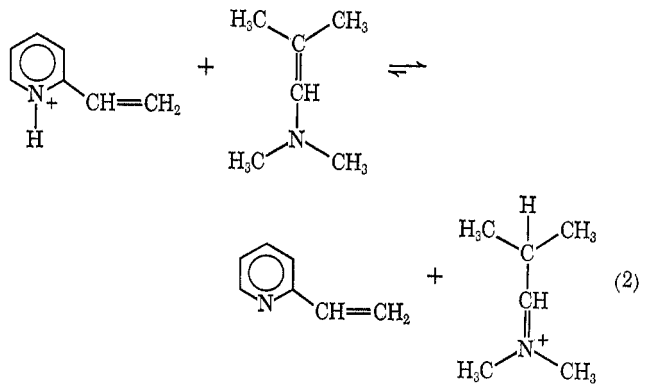
Cycloaddition proceeded less well with 2- than with 4-vinylpyridine. In this connection it is instructive to note that reaction of the morpholine enamine of isobutyraldehyde with 2-vinylpyridine gave **2** in reasonable yield (48%), the corresponding reaction with the pyrrolidine enamine provided **3** in very poor yield (13%), and reaction with the dimethylamine analog afforded no isolable product although reaction of the same enamine with 4-vinylpyridine had given **5** in 80% yield, the best realized in this series. Explanation may lie in the fact that 4-vinylpyridine is significantly more basic ($pK_a = 5.62$) than 2-vinylpyridine ($pK_a = 4.92$).[9] Thus, if the reactive species is the protonated form of the vinylpyridine as shown in eq 1, it may well be that the equilibrium for protonation of 2-vinylpyridine in the presence of the more basic enamines lies too far to the right (*e.g.*, eq 2).

In line with the idea that the vinylpyridine must be activated and that this is what is accomplished by addition of acid is the finding that a 3-vinylpyridine failed to undergo cycloaddition.[10] Under forcing conditions, reaction of 2-methyl-5-vinylpyridine with 1-morpholino-1-isobutene afforded, in addition to polymers and

(8) For a tabulation of nmr data for related cyclobutane derivatives, see I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

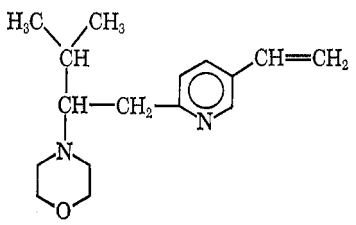
(9) A. Pietrzyk, R. Wiley, and D. McDaniel, *J. Org. Chem.*, **22**, 83 (1957).

(10) In unpublished work from this laboratory, 3-pyridyl analogs have been prepared by an alternative cycloaddition process.



(2)

recovered starting materials, a small amount of a product which ir and nmr spectral data suggest to be the aldol-type condensation product **26**. Also unresponsive to this cycloaddition were 4-vinylpyridines bearing terminal substituents such as methyl, phenyl, or even the electron-withdrawing carbomethoxy group. 2-Vinylquinoline did, however, give a cycloadduct **25** with 1-morpholino-1-isobutene, although the reaction went in poor yield.



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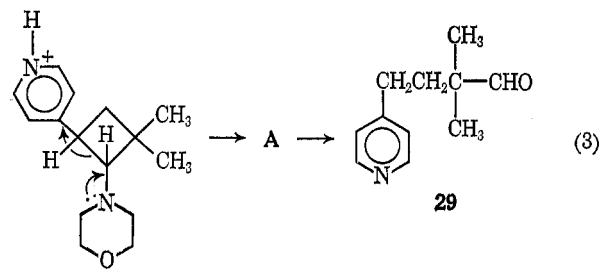
In contrast to experience with other electrophilic olefins,[3-6,11] only enamines derived from α-disubstituted aldehydes, and therefore enamines not possessing β hydrogens, appeared to undergo the acid-catalyzed cycloaddition to vinylpyridines. Reaction of the morpholine enamine of propionaldehyde with 4-vinylpyridine gave no isolable cycloadduct but only a 45% yield of 4-(morpholinoethyl)pyridine (**28**), identical with material prepared by the pyridylethylation of morpholine.[12] The obvious explanation for this result would be that the enamine had hydrolyzed in the course of reaction and the released morpholine had added to the 4-vinylpyridine. Although the reaction was carried out, and repeated, under optimum conditions for cycloaddition, under which no hydrolysis of β-disubstituted enamines was detected (a catalytic amount of *p*-toluenesulfonic acid monohydrate in undried acetonitrile at room temperature), the greater lability of enamines bearing β hydrogens[3] makes this rationalization perfectly plausible.[13] It is obviously important to learn if the cycloaddition could be effected under anhydrous conditions.

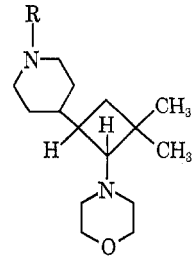
Although cyclohexanone enamines give cycloadducts in many cases,[4-6,11] in numerous others they are reported to give straightforward Michael adducts[14] and this has been ascribed to the lability and facile ring opening under the reaction conditions of cycloadducts derived from enamines bearing β hydrogens and/or to intramolecular proton transfer from the corresponding dipolar intermediates.[4-6,14] In the present work reaction of the morpholine enamine of cyclohexanone with 4-vinylpyridine did not proceed smoothly except under forcing conditions (catalytic amount of toluenesulfonic acid without solvent at 140°) and then yielded the Michael adduct, 2-(4-pyridylethyl)cyclohexanone (**27**), which is also produced by the reaction of the pyrrolidine enamine with vinylpyridine at higher temperatures without acid catalysis.[15] Either ring opening or proton transfer could account for this result. Hydrogens not present in products derived from enamines of α-disubstituted aldehydes could participate in both processes.

Although formed in the presence of a catalytic amount of acid, the pyridylcyclobutanes were found to be quite labile to acid treatment. Attempts to prepare hydrochloride salts or dissolution of the bases in dilute hydrochloric acid resulted in extensive breakdown. Allowing **1** to stand in glacial acetic acid at room temperature produced a 74% yield of 2,2-dimethyl-4-pyridinebutyraldehyde (**29**), the product which would have been expected if the initial reaction had proceeded by direct Michael-type addition. The acid-catalyzed conversion to the Michael adduct could result from electron withdrawal through the protonated pyridine ring (eq 3). Of course the morpholine N would also be protonated but reaction would occur only when it became free to participate.



29 (3)

Catalytic hydrogenation of **1** in solutions containing excess hydrochloric acid proceeded with opening of the cyclobutane ring and resulted in products derived from the hydrogenation of **29**.[16] When **1** was hydrogenated over Adams platinum oxide in ethanol solution containing just slightly more than 2 equiv of hydrochloric acid, however, ring opening did not occur and the piperidine derivative **19** was obtained in 88% yield. Acylation gave derivatives of **19** (R = acyl). Lithium aluminum hydride reduction of the *N*-benzoyl deriva-

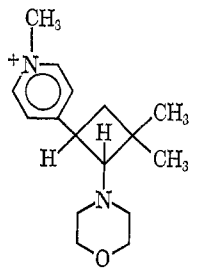


19, R = H
21, R = benzyl

(11) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, 1149 (1968).
(12) A. P. Phillips, *J. Amer. Chem. Soc.*, **78**, 4441 (1956).
(13) An alternate explanation would involve substitution of the enamine at N rather than C followed by degradation of the resultant dipolar intermediate *via* intramolecular proton transfer.
(14) *E.g.*, G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); A. Risaliti, M. Forichassin, and E. Valentin, *Tetrahedron Lett.*, 6331 (1966); A. Risaliti, M. Forchiassin, and E. Valentin, *Tetrahedron*, **24**, 1889 (1968); N. F. Firrell and P. W. Hickmott, *Chem. Commun.*, 544 (1969).
(15) G. Singerman and S. Danishefsky, *Tetrahedron Lett.*, 2249 (1964).
(16) Unpublished work from this laboratory.

tive gave 3-(1-benzyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (**21**). Supporting the thesis that cyclobutane ring opening involved electron transmission *via* the protonated pyridine ring was the finding that the corresponding piperidine derivatives were quite stable to acid, could be recovered without loss from acid solutions, and converted to stable hydrochloride salts. It may be noted that the influence of electron transmission through the pyridine ring here is opposite to that observed in the not really analogous pyridylcyclopropane series[2] where the pyridine substituent *stabilized* the carbocyclic ring to acid attack. In the earlier case ring opening is considered to be initiated by protonation of the α-hydroxyl group followed by electron flow away from rather than toward the pyridine ring. Electron withdrawal through a protonated pyridine would stabilize in the former and destablize in the latter situation. Thus, it appears that under the conditions used for the hydrogenation of **1** reduction of the pyridine ring precedes ring opening and provides a product stabilized to acid attack. Hydrogenation of **1** in the absence of acid over a rhodium catalyst also afforded **19**, but the yield was poor (35%).

Treated at room temperature with excess methyl iodide, **1** gave a dimethiodide salt **13**; treated carefully with 1 equiv, a monomethiodide **14** could be isolated, but the ease of diquaternization of **1** could be considered supportive of the postulated trans arrangement of the pyridine and morpholine groups. Both **13** and **14** retained the cyclobutane ring. The uv, ir, and nmr spectra of **14** showed unequivocally that the product was the pyridine–methiodide as shown. Although labile, **14** was sufficiently stable to be isolated and char-



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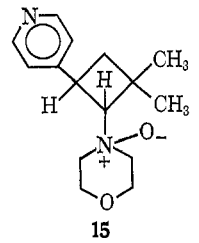
acterized (Table II). Careful treatment of **1** with benzyl bromide gave a crude monobenzyl quaternary salt which was also shown to be a pyridinium salt since catalytic hydrogenation afforded the same product (**21**) obtained by the lithium aluminum hydride reduction of the *N*-benzoyl derivative of **19** (Table III).

On the other hand, oxidation of **1** with 1 equiv of *m*-chloroperbenzoic acid yielded a mono *N*-oxide which was shown to be the morpholine *N*-oxide **15**. The uv



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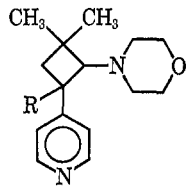
spectrum in acid and base was that of a typical pyridine, the ir spectrum showed no shift in the 1600-cm^{-1} band,[17]

TABLE II

4-PYRIDYLCYCLOBUTANE DERIVATIVES

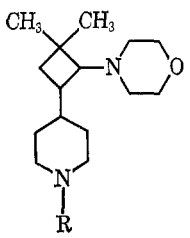


Compd	Derivative	R	Mp, °C	Analyses[a]
13	Dimethiodide	H	230–231	C, H, I[a]
14	Pyridine–methiodide	H	254–256	C, H, N
15	Morpholine *N*-oxide	H	163–164	C, H, O[a]
	Dimaleate salt		134–135	C, H, N
16		Benzyl	157–158	C,[a] H, N
17		Methyl	90–91	C, H, N
18		Phenyl	135–140	C, H, N

[a] Satisfactory analytical values for the indicated elements (±0.35%) were obtained for all compounds except as follows. Calcd for **13**: I, 47.88. Found: I, 48.24. Calcd for **15**: O, 12.20. Found: O, 12.82. Calcd for **16**: C, 78.54. Found: C, 77.97.

TABLE III

4-PIPERIDYLCYCLOBUTANE DERIVATIVES



Compd	R	Mp, °C	Analyses[a]
19	H	66–67	C, H, N
20	Benzoyl	104–107	C, H, N
	Hydrochloride salt	268–270	C, H, Cl
21	Benzyl	96–97	C, H, N
	Dihydrochloride salt	208–210	C, H, Cl[a]
22	Acetyl	121–122	C, H, N
	Hydrochloride salt	192–193	C,[a] H, Cl
23	3,4,5-Trimethoxybenzoyl	109–111	C, H, N
	Hydrochloride salt	259–260	C, H, Cl[a]
24	*n*-Butylcarbamoyl	105–106	C, H, N

[a] Satisfactory analytical values for the indicated elements (±0.35%) were obtained for all compounds except as follows. Calcd for **21** 2HCl: Cl, 17.08. Found: Cl, 16.72. Calcd for **22** HCl: C, 61.70. Found: C, 61.33. Calcd for **23** HCl: Cl, 7.34. Found: Cl, 7.71.

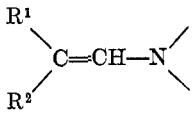
and in the nmr there was a marked alteration and displacement of the pattern of signals from the morpholine protons and a slight shift (compared to **1**) to lower rather than higher[18] fields for the pyridine proton signals. It would thus appear that relative basicity was the controlling factor in oxidation and directed initial reaction to the more basic morpholine N, whereas steric hindrance about the morpholine and, perhaps, polarizability of the pyridine directed alkylation first to the pyridine N.

The pyridylcyclobutanes were remarkably stable to harsh alkaline treatment. Subjection of **1**, **4**, and **5** to

(17) *Cf.* A. R. Katritzky, C. R. Palmer, F. J. Swinbourne, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, **91**, 636 (1969).

(18) A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, **43** (1961); unpublished results from this laboratory.

TABLE IV
ENAMINES OF DISUBSTITUTED ACETALDEHYDES

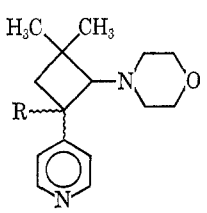


R¹	R²	Registry no.	−N<	Bp, °C (mm)	Ref bp, °C (mm)[a]	Ir,[b] ν_{max}, cm⁻¹, C=CN	Yield, %
Methyl	Methyl		Morpholino	65–70 (15)	56–57 (11)[c]		89
Methyl	Methyl		Dimethylamino	85–87	87–89 (760)[d]		35
Methyl	Methyl		Pyrrolidino	70–73 (40)	70–71 (38)[c]		84
Methyl	Ethyl	28478-25-3	Morpholino	86–89 (17)		1660	70
Ethyl	Ethyl	28478-26-4	Morpholino	90–93 (15)		1645	92
Methyl	Phenyl	28478-27-5	Morpholino	64–65[e]		1625	68
Methyl	*n*-Nonyl	28478-28-6	Morpholino	130–131 (0.05)		1665	61
Cyclohexylidene		16963-29-4	Morpholino	105–107 (6)		1650	79
3-Cyclohexenylidene		28487-14-1	Morpholino	90–94 (0.05)		1665	52
5-Norbornen-2-ylidene			Morpholino	128–133 (13)	132–135 (14)[f]		77

[a] Satisfactory analytical values for N (±0.2%) were obtained for all new compounds listed. [b] Spectra were obtained in chloroform solution. [c] Reference 20. [d] Reference 3. [e] Melting point. [f] L. A. Paquette, *J. Org. Chem.*, **29**, 2851 (1964).

conditions such as sodamide in boiling tetrahydrofuran, sodium ethoxide in boiling ethanol, or sodium hydride in hot dimethylformamide resulted only in recovery of starting material (75–90%). Although I can be viewed as a Mannich-type base, the amino group could neither be eliminated nor displaced by introduction of suitable nucleophiles. Since alkylation with Mannich bases undoubtedly proceeds through an elimination–addition mechanism, these results accord with the high energy of activation for introducing a double bond in a cyclobutane ring. Of course, if selective quaternization of the amino N had been possible, the difficulty might have been circumvented.[3] Experiments with the *N*-oxide **15** gave anomalous results.

Treatment of **1** with sodamide in liquid ammonia did, however, produce the anion by removal of the proton α to the pyridine ring and subsequent alkylation with benzyl chloride and with methyl iodide afforded the 3,3-disubstituted cyclobutanes **16** and **17**, respectively.



16, R = benzyl
17, R = methyl
18, R = phenyl

Treatment with bromobenzene gave the phenyl derivative **18** in poor yield and even this required 2 equiv of sodamide in line with intervention of a benzyne intermediate. The nmr spectra of **16–18** clearly indicated their gross structure but nothing can be said about stereochemistry.

Many of the 4-pyridylcyclobutanes listed in Table I showed significant antidepressant and stimulant properties in rodents but were not pursued owing to their marked barbiturate-potentiating activity, probably mediated by inhibition of metabolism.

Experimental Section[19]

Materials. The enamines of disubstituted acetaldehydes used in this investigation are listed in Table IV and where indicated were prepared by methods described in the literature. New enamines were prepared by the method of Benzing[20] and were characterized by their infrared spectra and "basic" nitrogen analyses. 1-Morpholino-1-propene, bp 58–66° (10 mm), was prepared using method B of Brannock.[3] 1-Morpholino-1-cyclohexene showed bp 120–123° (20 mm) [lit.[21] bp 117–120 (10 mm)] and 2-vinylquinoline showed bp 116–119° (4 mm) [lit.[22] bp 120–125° (7 mm)]. All other materials were commercially available and were used without further purification.

Reaction of Enamines with Vinylpyridines. 3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1). Method A.—To a solution of 8 g of *p*-toluenesulfonic acid monohydrate in 500 ml of acetonitrile under nitrogen was added 157.6 g (1.5 mol) of 4-vinylpyridine followed by the dropwise addition of 217.4 g (1.54 mol) of 1-morpholino-1-isobutene. The mixture was heated for 2 hr on the steam bath and concentrated under reduced pressure to a red oil that solidified on cooling. The crude solid was recrystallized from hexane to give 237 g (64%) of **1** as colorless crystals: mp 93–94°; uv max (0.1 *N* HCl) 256.5 mμ (log ε 3.71); uv max (0.1 *N* NaOH) 258.0 mμ (log ε 3.36); ir ($CHCl_3$) 1600 (pyridine); nmr ($CDCl_3$) δ 8.40 (m, 2, α-pyridine protons), 7.05 (m, 2, β-pyridine protons), 3.50 (m, 4, morpholine OCH_2), 3.10 (q, 1, J = 9 Hz, proton on pyridine-attached cyclobutane carbon), 2.57 (d, 1, J = 9 Hz, proton on morpholine-attached cyclobutane carbon), 2.10 (m, 4, morpholine NCH_2), 1.88 and 1.48 (each, d, 1, J = 9 Hz, cyclobutane CH_2), 1.20 (s, 6, *gem*-dimethyl).

Method B.—A mixture of 45 g (0.43 mol) of 4-vinylpyridine, 64 g (0.45 mol) of 1-morpholino-1-isobutene, and 2 g of *p*-toluenesulfonic acid monohydrate in 125 ml of acetonitrile was allowed to stand at room temperature for 3 days. Concentration of the reaction mixture left a thick red oil that solidified on standing; recrystallization afforded 62.3 g (59%) of **1**, mp 92–93°.

3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane Dimethiodide (13).—A solution of 5.0 g of **1** in 25 ml of acetonitrile and 20 ml of methyl iodide, allowed to stand at room temperature for

(19) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded with a Beckman Model IR-5 spectrophotometer; peak positions are given in reciprocal centimeters. Nmr spectra were determined with a Varian Model A-60 spectrometer; pertinent chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants in cycles per second.

(20) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(21) S. Hunig, E. Benzing, and E. Lucke, *Chem. Ber.*, **90**, 2833 (1957).

(22) G. B. Bachman and D. D. Micucci, *J. Amer. Chem. Soc.*, **70**, 2381 (1948).

3 days, deposited 7.2 g of solid that crystallized from methanol to give 4.9 g of **13** as amber plates, mp 230–231°.

3-(4-Pyridyl)-2-pyrrolidino-1,1-dimethylcyclobutane (4).—A mixture of 103 g (0.98 mol) of 4-vinylpyridine, 123.6 g (0.98 mol) of 1-pyrrolidino-1-isobutene, and 4 g of *p*-toluenesulfonic acid monohydrate was heated for 6.5 hr on the steam bath in a nitrogen atmosphere. Dilution of the mixture with 25 ml of acetone afforded a crystalline precipitate which was recrystallized from acetone to give 77 g (35%) of **4** as large colorless crystals: mp 95–96° (no additional product could be isolated by further work-up of the mother liquors); ir ($CHCl_3$) 1600 (pyridine); nmr ($CDCl_3$) δ 8.42 (m, 2, α-pyridine protons), 7.13 (m, 2, β-pyridine protons), 3.15 (q, 1, J = 9 Hz, proton on pyridine-attached cyclobutane carbon), 2.50 (d, 1, J = 9 Hz, proton on pyrrolidine-attached cyclobutane carbon), 2.20 (m, 4, pyrrolidine NCH_2), 1.97–1.47 (complex m, 6, pyrrolidine CH_2CH_2 and cyclobutane CH_2), 1.21 and 1.17 (two s, 6, *gem*-dimethyl).

3-(2-Quinolyl)-2-morpholino-1,1-dimethylcyclobutane (25).—A solution of 10.0 g (0.07 mol) of 1-morpholino-1-isobutene, 11.0 g (0.07 mol) of 2-vinylquinoline, and 0.4 g of *p*-toluenesulfonic acid monohydrate in 25 ml of acetonitrile was allowed to stand under nitrogen for 3 days. The red solution was concentrated to dryness and the residue crystallized from pentane to give 2.4 g (11.6%) of **25** as colorless needles: mp 123–124°; nmr ($CDCl_3$) δ 8.10 (d, 2, quinoline 3,4 protons), 7.53 (m, 4, quinoline 5,6,7,8-protons), 3.62 (m, 4, morpholine OCH_2), 3.32 (m, 1, proton on quinoline-attached cyclobutane carbon), 2.90 (d, 1, J = 9 Hz, proton on morpholine-attached cyclobutane carbon), 2.24 (m, 4, morpholine NCH_2), 1.98 and 1.60 (each, d, 1, poorly resolved cyclobutane CH_2), 1.28 (s, 6, *gem*-dimethyl).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.98; H, 8.16; N, 9.45. Found: C, 77.01; H, 8.24; N, 9.41.

Other pyridylcyclobutanes, prepared similarly (usually as described for **1**, method B) from the appropriate enamine (Table IV), *p*-toluenesulfonic acid monohydrate, and 2- or 4-vinylpyridine, are listed in Table I. The reactions could also be carried out in other polar solvents such as isopropyl alcohol or dimethylformamide although acetonitrile was generally used since less resinous by-product formed in this solvent.

2-(2-Morpholino-3-methyl-1-butyl)-5-vinylpyridine (26).—A mixture of 60 g (0.5 mol) of 2-methyl-5-vinylpyridine, 71 g (0.5 mol) of 1-morpholino-1-isobutene, and 2.0 g of *p*-toluenesulfonic acid monohydrate was heated in a nitrogen atmosphere at 140° for 8 hr. The mixture was cooled to room temperature and diluted with hexane to precipitate polymeric material. The hexane solution was decanted, concentrated, and vacuum distilled to give 60 g of material, bp 60–75° (16 mm), which from the infrared spectrum was a mixture of enamine and vinylpyridine. Distillation of the residue yielded 9.8 g (7.5%) of what is presumed to be **26**: bp 118–121° (0.1 mm); ir (neat) 1630 (vinyl), 1595 (pyridine); nmr (CCl_4) δ 8.43 (broad s, 1, α-pyridine proton), 7.52 (d, 1, γ-pyridine proton), 7.03 (m, 1, β-pyridine proton), 6.58 (m, 1, vinyl CH), 5.50 (broad q, 2, vinyl CH_2), 3.48 (m, 4, morpholine OCH_2), 2.82 (broad s, 3), 2.42 (m, 4, morpholine NCH_2), 1.7 (broad band, 1), 1.0 (q, 6, *gem*-dimethyl).

Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.80; H, 9.29; N, 10.76. Found: C, 73.85; H, 9.37; N, 10.53.

2-(4-Pyridylethyl)cyclohexanone (27).—A mixture of 25.5 g (0.15 mol) of 1-morpholino-1-cyclohexene, 17.0 g (0.16 mol) of 4-vinylpyridine, and 1 g of *p*-toluenesulfonic acid monohydrate was heated at 140° for 9 hr under nitrogen and vacuum distilled to give 22.0 g (72%) of **27**: bp 134–148° (0.5 mm); ir ($CHCl_3$) 1700 (ketone C=O), 1600 (pyridine); picrate, mp 127–130° [lit.[15,23] bp 134–139° (0.3 mm); ir 1705, 1590; picrate, mp 129.5–131°].

4-(Morpholinoethyl)pyridine (28).—A solution of 30.0 g (0.23 mol) of 1-morpholino-1-propene, 24 g (0.23 mol) of 4-vinylpyridine, and 1 g of *p*-toluenesulfonic acid monohydrate in 75 ml of acetonitrile was allowed to stand in a stoppered flask for 7 days. The dark red solution was concentrated *in vacuo* and the residue was distilled through a molecular still to give 20 g (45%) of **28**, which solidified on standing, mp 49–50° unchanged on recrystallization from pentane. The mixture melting point with material (49–50°) prepared by the pyridylethylation of morpholine[12] was not depressed.

Anal. Calcd for $C_{11}H_{16}N_2O$: N, 14.57. Found: N (basic), 14.31.

Reactions of 3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1). Ring Opening. 2,2-Dimethyl-4-pyridinebutyraldehyde (29).—A solution of 32.0 g (0.13 mol) of **1** in 375 ml of glacial acetic acid was allowed to stand at room temperature for 2 days. Concentration *in vacuo* at 50° left a yellow oil which was dissolved in ice water. The aqueous solution was made basic with 20% sodium hydroxide and extracted with ether. Drying and removal of the ether followed by distillation of the residue gave 17.0 g (74%) of **29** as a pale yellow oil: bp 104–107° (0.1 mm); $n^{20}D$ 1.5048; ir (neat) 1710 (C=O) and 1590 (pyridine); nmr ($CDCl_3$) δ 9.58 (s, 1, aldehyde proton), 8.46 (m, 2, α-pyridine protons, 7.08 (m, 2, β-pyridine protons), 2.50 (m, 2), 1.75 (m, 2), 1.15 (s, 6, *gem*-dimethyl).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.53; H, 8.53; N, 7.91. Found: C, 74.77; H, 8.81; N (basic), 7.82.

Stability of 1 and Other Cyclobutanes to Base.—To a solution of 12.5 g (0.05 mol) of **1** in 50 ml of dimethylformamide was added 2.2 g (0.05 mol of NaH) of a 56% sodium hydride–oil dispersion and the mixture was heated on the steam bath for 3 hr. Cautious addition of 250 ml of water with cooling precipitated 11.5 g (92% recovery) of **1** as a white solid, mp 90–93°. The mixture melting point with pure **1** (93–94°) was not depressed. **1** was also perfectly stable to boiling for 15 min with 10% aqueous sodium hydroxide.

Similar results obtained when cyclobutane **4** was treated with sodium amide in liquid ammonia followed by boiling in tetrahydrofuran (80% recovery of **4**) or when **5** was heated at reflux with sodium ethoxide in ethanol (73% recovery of **5**).

3,3-Disubstituted Cyclobutanes.—To a slurry of 4.3 g (0.11 mol) of sodium amide in 200 ml of liquid ammonia was added in portions 25.0 g (0.1 mol) of **1**. The red mixture was stirred for 30 min and treated, dropwise (5 min), with 17.2 g (0.12 mol) of methyl iodide in 25 ml of dry tetrahydrofuran, which treatment discharged the red color. As the ammonia evaporated it was replaced with 200 ml of tetrahydrofuran and the mixture was finally heated at reflux for 3 hr. The filtered tetrahydrofuran solution was evaporated to a solid residue that was twice recrystallized from hexane to give 10.8 g (40%) of **3-(4-pyridyl)-3-methyl-2-morpholino-1,1-dimethylcyclobutane (17)** as colorless crystals: mp 90–91°; nmr ($CDCl_3$) δ 8.58 (m, 2, α-pyridine protons), 7.26 (m, 2, β-pyridine protons), 3.68 (m, 4, morpholine OCH_2), 2.77 (s, 1, proton on morpholine-attached cyclobutane carbon), 2.26 (m, 4, morpholine NCH_2), 1.83 (s, 2, cyclobutane CH_2), 1.60 (s, 3, CH_3 attached to 3 carbon of cyclobutane), 1.37 and 1.18 (each, s, 3, *gem*-dimethyl).

Compounds **16** (46%) and **18** (10%, using 2 equiv of sodium amide) were similarly prepared by reaction with benzyl chloride and bromobenzene, respectively.

Morpholine N-Oxide.—To a solution of 25.0 g (0.1 mol) of **1** in 100 ml of methylene chloride was added, dropwise, a solution of 24.0 g (0.12 mol) of 87% *m*-chloroperbenzoic acid in 500 ml of methylene chloride. After being allowed to stand for 20 hr at room temperature the mixture was washed with a nearly saturated solution of potassium carbonate, dried, and concentrated to leave a tan solid. Two recrystallizations from acetone yielded 9.2 g (35%) of **3-(4-pyridyl)-2-morpholino-1,1-dimethylcyclobutane morpholine *N*-oxide (15)** as colorless crystals: mp 163–164°; uv max (0.1 *N* HCl) 254.5 mμ (log ϵ 3.68); uv max (0.1 *N* NaOH) 257.5 mμ (log ϵ 3.23); ir ($CHCl_3$) 1600 (pyridine); nmr ($CDCl_3$) δ 8.58 (m, 2, α-pyridine protons), 7.36 (m, 2, β-pyridine protons), 4.3–2.1 (complex m, 12, morpholine and cyclobutane protons), 1.61 and 1.40 (each, s, 3, *gem*-dimethyl).

The dimaleate salt of **15**, prepared in chloroform and recrystallized from isopropyl alcohol, melted at 134–135°.

Selective Pyridine Quaternization.—To a solution of 24.6 g (0.1 mol) of **1** in 200 ml of benzene at room temperature was added, dropwise over a 2-hr period, a solution of 15.6 g (0.11 mol) of methyl iodide in 30 ml of benzene. The mixture was stirred for 16 hr to give 15 g of tan crystals, mp 234–238°. Recrystallization from methanol yielded 9.0 g (23%) of **3-(4-pyridyl-2-morpholino-1,1-dimethylcyclobutane pyridine methiodide (14)**: mp 254–256°; uv max (0.1 *N* HCl) 258.0 mμ (log ϵ 3.63); uv max (0.1 *N* NaOH) 257.5 mμ (log ϵ 3.72); ir ($CHCl_3$) 1638 (pyridinium); nmr ($CDCl_3$) δ 9.37 (m, 2, α-pyridine protons), 8.05 (m, 2, β-pyridine protons), 4.70 (s, 3, pyridinium NCH_3), 3.60 (m, 4, morpholine OCH_2), 2.15 (m, 4, morpholine NCH_2), 1.25 (s, 6, *gem*-dimethyl). Other cyclobutane protons are accounted for in the integration but absorptions are not resolved.

3-(1-Benzyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (21). A. *Via* Hydrogenation of the Benzyl Quaternary Salt of 1.—To 24.6 g (0.1 mol) of **1** in 100 ml of benzene was added, dropwise over a 5-hr period, 19.0 g (0.11 mol) of benzyl bromide

(23) G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

in 25 ml of benzene. The mixture was stirred for 16 hr and the precipitate collected and dried to give 49 g of an uncrystallizable solid melting at 80–82° with foaming.

A solution of 21.0 g of the solid in 200 ml of ethanol was shaken with 2 g of a 5% rhodium-on-carbon catalyst for 20 hr at room temperature in an Adams–Parr apparatus under 50 psi of hydrogen. The filtered solution was concentrated to an oil that was dissolved in water; the aqueous solution was treated with solid potassium carbonate and extracted with ether. Evaporation of the ether left 6 g of oil that solidified, mp 91–93°; mixture melting point with pure (mp 96–97°) **21** (see below) was not depressed.

B. *Via* **Hydrogenation of 1.**—To a solution of 40.0 g (0.16 mol) of **1** in 200 ml of ice-cold ethanol was slowly added 37 ml of concentrated hydrochloric acid and the mixture was shaken at room temperature with 1.5 g of platinum oxide catalyst at an initial pressure of 50 psi of hydrogen. Reduction was complete in 10 hr after which the catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residual oil was dissolved in 200 ml of water. The aqueous solution was made strongly basic with 50% sodium hydroxide and extracted with benzene. Drying and removal of the benzene left an oil that solidified on standing. Recrystallization from pentane gave 36 g (88%) of **3-(4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane** (**19**) as colorless crystals: mp 66–67°; ir ($CHCl_3$) 3220 (NH), pyridine absorption absent; nmr ($CDCl_3$) δ 3.68 (m, 4, morpholine OCH_2), 2.30 (m, 4, morpholine NCH_2), 1.65 (s, 1, NH), 1.07 and 1.05 (two s, 6, *gem*-dimethyl). Other absorptions were unresolved between 3.2 and 1.3 but all protons are accounted for in the total integration.

The catalytic hydrogenation of **1** was also carried out in ethanol solution without any added hydrochloric acid using a 5% rhodium-on-carbon catalyst (8 g of catalyst for 15 g of **1**) at 50° to give a 35% yield of **19**, mp 66–67° undepressed on admixture with **19** prepared with added hyrochloric acid.

An ice-cooled solution of 11.0 g (0.04 mol) of **19** in 150 ml of benzene and 20 ml of triethylamine was treated, dropwise, with 8.5 g (0.06 mol) of benzoyl chloride in 15 ml of benzene. The mixture was stirred for 5 hr at room temperature, washed twice with water, dried, and concentrated to an oil that solidified. Recrystallization from hexane provided 14.5 g (92%) of colorless crystals of **3-(1-benzoyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane** (**20**): mp 102–104°; mp 104–107° after one additional recrystallization; ir ($CHCl_3$) 1625 (amide —C=O), 1585 (phenyl).

The hydrochloride salt of **20**, prepared in ethyl acetate and recrystallized from isopropyl alcohol–hexane, showed mp 268–270°.

The acetyl (**22**) and the 3,4,5-trimethoxybenzoyl (**23**) derivatives (Table III) were similarly prepared.

To a slurry of 2.0 g (0.05 mol) of lithium aluminum hydride in 200 ml of dry tetrahydrofuran was added, dropwise, a solution of 10.0 g (0.03 mol) of **20** in 100 ml of dry tetrahydrofuran. The mixture was stirred for 2 hr at room temperature and then heated at reflux for 2 hr. The cooled mixture was treated with 5 ml of water followed by 25 ml of 20% sodium hydroxide. The coagulated aluminum hydroxide was filtered off and the filtrate was dried and concentrated leaving a solid that was crystallized from pentane to give 5.6 g (58%) of **21**: mp 93–95°; mp 96–97° after further recrystallization; nmr ($CDCl_3$) δ 7.33 (s, 5, phenyl protons), 3.68 (m, 4, morpholine OCH_2), 3.51 (s, 2, benzyl CH_2), 2.35 (m, 4, morpholine NCH_2), 1.08 and 1.05 (two s, 6, *gem*-dimethyl). All other protons were unresolved between 3.1 and 1.3 and accounted for in total integration.

The dihydrochloride salt of **21** was recrystallized from isopropyl alcohol and showed mp 208–210°.

3-[1-(*n*-Butylcarbamoyl)-4-piperidyl]-2-morpholino-1,1-dimethylcyclobutane (**24**).—To a cold solution of 12.6 g (0.05 mol) of **19** in 25 ml of benzene was added 10.0 g (0.1 mol) of *n*-butyl isocyanate in 15 ml of benzene. The solution was allowed to stand for 16 hr at room temperature and concentrated *in vacuo* and the residual oil was crystallized from hexane to give 16 g (91%) of **24** as glistening plates: mp 105–106°; ir ($CHCl_3$) 3390 (NH), 1635 (urea C=O).

Registry No.—**1**, 28487-22-1; **2**, 28487-23-2; **2** maleate, 28487-20-9; **3**, 28487-24-3; **4**, 28487-25-4; **5**, 28487-26-5; **6**, 28487-27-6; **7**, 28487-28-7; **8**, 28487-29-8; **9**, 28487-30-1; **10**, 28487-31-2; **11**, 28487-32-3; **12**, 28487-33-4; **13**, 28487-34-5; **14**, 28487-35-6; **15**, 28487-36-7; **15** dimaleate, 28487-21-0; **16**, 28487-37-8; **17**, 28487-38-9; **18**, 28487-39-0; **19**, 28487-40-3; **20**, 28487-41-4; **20** HCl, 28487-42-5; **21**, 28487-43-6; **21** 2HCl, 28487-44-7; **22**, 28487-45-8; **22** HCl, 28487-46-9; **23**, 28487-47-0; **23** HCl, 28487-48-1; **24**, 28537-46-4; **25**, 28487-15-2; **26**, 28487-16-3; **27**, 28487-17-4; **28**, 28487-18-5; **29**, 28487-19-6.

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Hydrolysis of Halopyridines at 250–350°. Formation of a Rearranged Product from 3-Halopyridines

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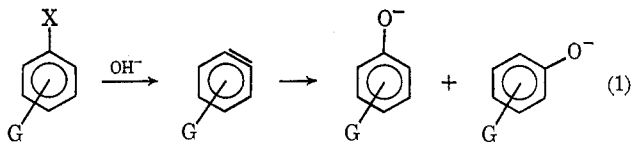
3-Chloro-, 3-bromo-, or 3-iodopyridine when heated with 4 *M* aqueous potassium hydroxide at 250–350° gives mixtures of 3-hydroxypyridine and 4-pyridone. The ratio of the yields of these products as indicated by nmr analysis of the reaction mixtures decreases in the order Cl > Br > I. 3-Iodopyridine gives more rearranged than unrearranged product; it also gives pyridine. Under the same conditions 2- or 4-chloro-, bromo-, and iodopyridines give 2- or 4-pyridone, respectively. 3-Hydroxypyridine is stable under the hydrolysis conditions but 2- and 4-pyridone degrade at the higher temperatures; nonaromatic products were characterized. It is suggested that the hydrolysis reactions of 3-halopyridines may involve competing direct substitution and elimination-addition reactions. The latter involves the formation of 3,4-pyridyne as an intermediate.

It has been known for many years that halobenzenes undergo alkaline hydrolysis at 250–350° to give phenols.[1,2] The mechanisms for this reaction are said to include direct substitution and aryne (elimination–addition) pathways, the aryne route being favored at higher temperatures.[3] The formation of structurally rearranged hydrolysis products is cited as evidence for the aryne route (eq 1). When only aryne formation



(1)

takes place, the ratio of rearranged to unrearranged products is independent of the identity of the leaving

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