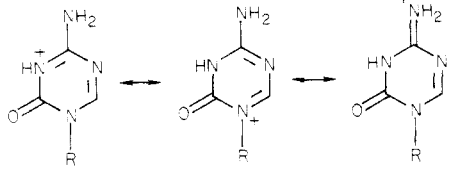
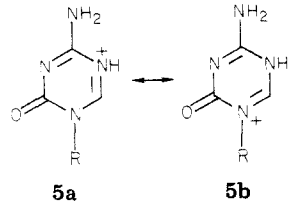
rotational rates have been estimated[10] and the influence of solvent on hindrance of rotation has also been examined.[19]

The $\Delta G^{\ddagger}$ value estimated from the ^{15}N spectra for the exchange process which averages the N3,N5 $^{3}J_{^{15}N-H}$ couplings in 1 is 17 kcal/mol. This value falls in the range of the values observed for rotation of the dimethylamino group of 1,4′,4′-trimethylcytosine and 4,4′-dimethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-D-glucopyranosyl)cytosine in other solvents,[19] and this fact supports the interpretation of exchange being the result of speeding up of restricted rotation about the C4-N4′ bond. In any case, at 25 °C, the proton-coupled ^{15}N resonance of N4′ is not expected to be a precise 1:2:1 triplet if the protons attached to N4′ are magnetically nonequivalent, unless the difference between their one-bond couplings to N4′ is small. This appears to be the case with **1**, but in many similar situations, as with primary amides, such differences in one-bond couplings are well-known.[23]

Protonation of cytosine and 1-methylcytosine has been shown to occur on N3 by means of ^{1}H NMR spectroscopy.[17,22,25] The locus of protonation of cytidine (**2**) was shown in the ^{15}N NMR spectrum by the shift of the N3 resonance (166.1 ppm) upfield by 64.8 ppm on the addition of acid to **2** in Me_2SO.[7] Titration of 5-azacytidine (**1**) with trifluoroethanoic acid in (methylsulfinyl)methane and determination of the associated ^{15}N shift changes showed a striking parallelism to the changes for the corresponding nitrogens of **2**. Thus, for addition of 1.5 mol of trifluoroethanoic acid to 1 mol of ribonucleoside, the changes in parts per million for **1** are −1.8, N3, +64.5, and N4′, −10, and for **2** are N1, −1.1, N3, +64.8, and N4′, −12.0. The chemical shift of N5 of **1** moves by +5.6 ppm, which has the direction and magnitude expected for, at most, about 10% protonation on N5. Therefore, we conclude that N3 is the favored nitrogen for the protonation of **1**. This is consistent with expectations based on the relative favorableness of the contributing resonance structures of the possible conjugate acids of **1** by addition of a proton to N3 (**4a–e**), similar to **2** protonated, vs. N5 (**5a** and **5b**).



4a **4b** **4c**



5a **5b**

Registry No. 1, 320-67-2.

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Three-Membered Rings. 8. Reaction of 1-Halocyclopropane 1,2-Diesters with 1,8-Diazabicyclo[5.4.0]undec-7-ene. Unexpected Products

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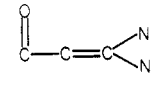
A general method for the preparation of substituted cyclopropane-1,2-dicarboxylic acids has been described.[1] A limitation of that method is that all cis-1,2,3-trisubstituted cyclopropanes and similar tetrasubstituted cyclopropanes with three substituents cis cannot be prepared. Potentially, there are several possible solutions to this problem. One of these would be the catalytic reduction of 1,2,3- or 1,2,3,3-substituted cyclopropenes. It was felt that dehydrohalogenation of the readily available 1-halocyclopropane 1,2-diesters[1] would provide the requisite cyclopropenes for the 1,2,3 case. Dehydrohalogenation of halocyclopropanes has been attempted before and has led commonly to isomerization or simple adduct formation with the basic reagent.[2] In spite of this, several bases not previously used in such dehydrohalogenations have been examined. The results with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are reported here.

Initial studies showed that an equimolar mixture of DBU with dimethyl 1-chloro-3-methylcyclopropane-1,2-dicarboxylate (**1**)[1] in ethyl acetate at room temperature resulted in the slow formation of DBU hydrochloride. No cyclopropene could be detected, but a small amount of crystalline product (**2**) was obtained. Elemental and spectral analysis showed **2** to be an adduct of DBU and the diester **1** minus the elements of hydrogen chloride *and* methanol. Subsequent work showed that this "adduct" could be obtained in moderate yield (47%) by using a threefold excess of DBU over diester **1**. A trapping experiment using furan as a solvent gave the same results as in ethyl acetate—**2** was produced, but no adduct of a presumed cyclopropene intermediate and furan was observed.

Compound **2** shows an infrared band at 1715 cm^{-1} expected for an ester. An even stronger, considerably broader band appears at 1550 cm^{-1}; in conjunction with a medium-strength band at 1615 cm^{-1}, this is suggestive of a highly polarized conjugated system and is consistent with a vinylogous urea-type structure (I). A shoulder at 3010



I

cm^{-1} is suggestive of a tertiary C–H in a cyclopropane. The remaining spectrum is rich in bands, but correlation with specific structural features is uncertain.

The ^{1}H NMR spectrum is a mess at 60 MHz and is not completely resolved at 200 MHz. However, the singlet (3 H) at δ 3.73 clearly belongs to a methyl ester, and the doublet (3 H) at δ 1.54 is a CH_3CH grouping. A doublet

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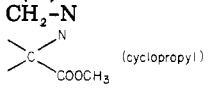
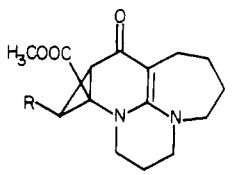
Table I. ^{13}C NMR Spectral Results

^{13}C NMR (decoupled) δ ($CDCl_3$, Me_4Si)		mult	
2	3	(undecoupled)	struct assignt
185.36	185.13	s	C(O)C=C
167.67	167.67	s	$COOCH_3$
166.19	166.25	s	
94.54	93.06	s	C(O)C=C
52.95	52.65	t	CH_2-N
52.53	51.23	s	 (cyclopropyl)
50.76	50.88	q	OCH_3
47.92	47.74	t	CH_2-N
35.67	35.73	t	CH_2-N
27.98	27.62	t	$=CCH_2$
26.08		d	C(O)CH (cyclopropyl)
25.20	24.90	t	CCH_2C
	22.95	d	C(O)CH (cyclopropyl)
20.88	20.64	t	CH_2C
20.17	19.99	t	CH_2C
18.98		d	CH (cyclopropyl)
	11.12	t	CH_2 (cyclopropyl)
5.79		q	CH_3

(1 H) at δ 2.27 is reasonable for a cyclopropyl H adjacent to a carbonyl group; with J = 10 Hz, this H probably is coupled trans to a second cyclopropyl H.[3] A triplet (2 H) at δ 2.84 and a multiplet (4 H) at δ 3.25–3.36 fit nicely for H_2C–N systems; this multiplet in part (2 H) and the triplet are coupled to a multiplet (2 H; possibly two overlapping very similar quintets) at δ 2.07–2.15, suggesting the combination $NCH_2CH_2CH_2N$. A multiplet (2 H; possibly two overlapping triplets) at δ 2.42–2.48 indicates an allylic methylene. The region from δ 1.73 to 1.88 is a very complex multiplet (5 H) which has resisted resolution and structural correlation.

The ^{13}C NMR spectral results are shown in Table I.

With all 16 carbons and 17 of the 22 hydrogens accounted for, and on the basis of the combined spectral data, structures **2** and **3** are proposed.

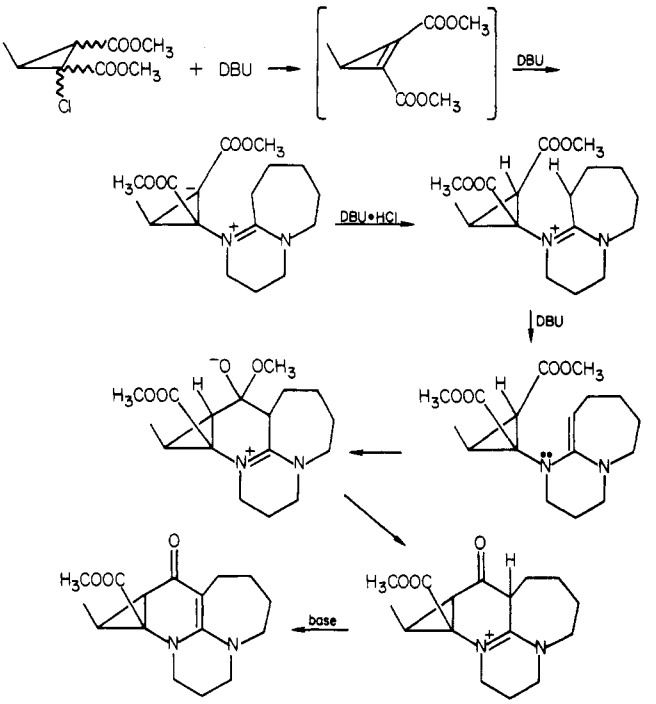


2, R = CH_3
3, R = H

Treatment of dimethyl 1-bromocyclopropane-1,2-dicarboxylate with 3 mol of DBU in ethyl acetate also produced an "adduct", **3**, in 63% yield. This material has spectral properties very similar to those for **2**. Thus, its IR spectrum has a strong band at 1720 cm^{-1} (ester), a stronger, broader band at 1550 cm^{-1} with a weaker band at 1640 cm^{-1} (O=C—C=C(N<)N), and a shoulder at 3025 cm^{-1} (cyclopropyl).

(3) (a) It should be noted that although cyclopropyl H's are commonly cited as appearing upfield (δ 0.2–1.0) relative to most hydrogens, this is not true when two or more electronegative groups (carbonyls, halogens, nitro, etc.) are attached to the cyclopropane ring. In these cases, the cyclopropyl H's are shifted downfield into the more normal region (δ 1.0–5.0). Many such examples can be found in the Sadtler collection of spectra. (b) Although the examples are much fewer, a similar type of shift arising from electronegative groups can be observed in ^{13}C NMR spectra of cyclopropanes. For example, see: H. Fauduet and R. Burgada, *Synthesis*, 642 (1980).

Scheme I



The ^1H NMR spectrum (200 MHz) is very similar in chemical shift groups to those observed for **2**. Thus, a singlet (3 H) at δ 3.68 is a methyl ester, and multiplets at δ 3.2–3.5 (4 H; appears as a triplet superimposed on a complex multiplet), δ 2.80–2.99 (2 H), and δ 2.11 (2 H; appears like a quintet of doublets) match the groups in **2** arising from a $NCH_2CH_2CH_2N$ system. Also, a triplet (2 H) at δ 2.44 matches the multiplet in the spectrum of **2** for an allylic CH_2. An ill-defined multiplet (4 H) at δ 1.6–1.9 is not resolved. In contrast to the spectrum of **2**, the spectrum of **3** shows a well-defined set of three doublets at δ 1.45 (1 H), 1.95 (1 H), and 2.28 (1 H); this system as part of a cyclopropyl group shows couplings of J_{trans} = 11 Hz, J_{cis} = 13 Hz, and J_{gem} = 8 Hz and the chemical shifts characteristic of a dicarbonyl-substituted cyclopropane.[3]

The ^{13}C NMR spectral results for **3** are shown in Table I. Structure **3** clearly is consistent with this spectral data.

We have not explored the reaction further, but it appears to be of a general nature. As proposed in Scheme I, the β ester appears to be unnecessary for the addition step to the α,β-unsaturated ester.[4] Consequently, it might be expected that this reaction could occur to some extent with any α,β-unsaturated ester initially present or formed during a reaction involving DBU. Also, although we have not examined the possibility, similar results might be expected with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).

Experimental Section

Melting points were obtained on a Thomas-Hoover melting apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 710 B spectrometer as KBr pellets. The ^1H NMR spectra were obtained at 200 MHz on a Bruker Spectrospin instrument by Dr. Raja Khalifah, and the ^{13}C NMR spectra were obtained at 50.32 MHz on the same instrument by Dr. T. S. Viswanathan both at the Veterans Administration Hospital in Kansas City. Microanalyses were performed at Galbraith Laboratories Inc. Ethyl acetate was dried over mo-

(4) A similar addition of DBU to a strained α,β-unsaturated ketone has been reported recently: H. O. House, M. B. Detar, and D. Van Derveer, *J. Org. Chem.*, **44**, 3793 (1979).

lecular sieves (4 Å), and DBU (Aldrich Chemical Co.) was used as received.

Reaction of Dimethyl 1-Chloro-3-methylcyclopropane-1,2-dicarboxylate (1) with DBU. The chloro diester 1[1] (4.13 g, 0.02 mol) in 50 mL of ethyl acetate was treated with DBU (9.15 g, 0.06 mol) in 20 mL of ethyl acetate with stirring. Progress of the reaction was examined by TLC (silica gel, iodine developer). After 7 days, no 1 could be observed. The white solid (2.10 g) that had formed was removed by filtration and identified as essentially pure DBU hydrochloride by its infrared spectrum (comparison with a known sample). The filtrate was concentrated by removal of ethyl acetate, and the residue was redissolved in a small volume of ethyl acetate. This solution was chromatographed on silica gel and eluted with ethyl acetate. A crystalline product (2.75 g, 47% assumed as 2) was obtained. An analytical sample recrystallized from ethyl acetate had the following: mp 150–151 °C dec; IR 3010 (sh), 2958 (sh), 2930, 2855, 1715, 1615, 1550, 1510, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, 3 H), 1.73–1.88 (m, 5 H), 2.07–2.15 (m, 2 H), 2.27 (d, 1 H), 2.42–2.48 (m, 2 H), 2.84 (t, 2 H), 3.25–3.36 (m, 4 H), 3.73 (s, 3 H); mass spectrum, m/e 290 (M^+), 259 ($M^+ - OCH_3$), 231 ($M^+ - CO_2CH_3$), 217, 203, 189, 175, 161, 147.

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.56; H, 7.92; N, 9.45.

Repetition of the experiment with furan as a solvent and equimolar quantities of the chloro diester 1 and DBU showed no materials by TLC not previously observed, i.e., no adduct of furan and a cyclopropene.

Reaction of Dimethyl 1-Bromocyclopropane-1,2-dicarboxylate with DBU. Reaction of the bromo diester[2c] with DBU in ethyl acetate was carried out and worked up as in the chloro diester case above to give 3.51 g (63% assumed as 3) of crystalline solid. An analytical sample recrystallized from ethyl acetate had the following: mp 139–140 °C; IR 3025 (sh), 2945, 2855, 1720, 1640, 1540–1560 (br), 1510, 1440, 1385, 1320, 1270, 1210, 1155, 1130, 1060, 1030, 980, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (dd, 1 H), 1.6–1.9 (m, 4 H), 1.95 (dd, 1 H), 2.11 (m, 2 H), 2.28 (dd, 1 H), 2.44 (t, 2 H), 2.80–2.99 (m, 2 H), 3.2–3.5 (m, 4 H), 3.68 (s, 3 H); mass spectrum, m/e 276 (M^+), 245 ($M^+ - OCH_3$), 244 ($M^+ - HOCH_3$), 217 ($M^+ - CO_2CH_3$), 203, 189, 161, 80, 66.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.23; H, 7.22; N, 10.04.

Registry No. 1, 76010-95-2; 2, 76010-96-3; 3, 76010-97-4; dimethyl 1-bromocyclopropane-1,2-dicarboxylate, 76010-98-5; DBU, 6674-22-2.

Hydration Constants of Pyridinecarboxaldehyde *N*-Oxides

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The knowledge of hydration constants is important in studies of reactions of carbonyl compounds, particularly those involving acid–base and metal ion catalysis.[1-6] In systems such as the pyridinecarboxaldehydes, the activation of the carbonyl group can be influenced by direct interactions at the oxygen atom or by remote effects of substituents and Lewis acids acting on the aromatic nitrogen. Both kinds of influence may be involved in the hydration of these compounds by metalloenzymes.[7,8] In order to evaluate the role of remote interactions in the hydration of pyridinecarboxaldehydes, we have determined the hydration constants of a series of N-substituted derivatives in aqueous solution.

Most studies of hydration equilibrium have been made by using nuclear magnetic resonance spectroscopy (NMR). The ultraviolet (UV) spectrophotometry has been considered less convenient for the determination of hydration constants because of the disadvantage that the extinction coefficients should be previously known.[9] To circumvent the problem, values obtained in nonaqueous solvents, or from extrapolation of kinetics plots to zero time, have been used for these parameters. In some cases, when the absorption spectra of the carbonyl and the hydrated species differ appreciably, a simple spectrophotometric method can be applied, without requiring the previous knowledge of extinction coefficients, or the use of any reagent. Such a method is based on the systematic variation of the equilibrium constants with the temperature,[10] and, therefore, it requires that $\Delta H \neq 0$. One can start by choosing two wavelengths (here referred to as 1 and 2) where the absorption of the carbonyl (C) and of the hydrated (H) species has little overlap. The total concentration (C_T) of the compound should be kept constant during the experiment. Then, by measuring the absorbances of the hydrated form ($A_{H,1}$) and of the carbonyl ($A_{C,2}$) compound at several temperatures, it is possible to calculate the ratio of the extinction coefficients ($\epsilon_{H,1}/\epsilon_{C,2}$) from a plot of $A_{H,1}$ vs. $A_{C,2}$ according to eq 1. The hydration constant is given by eq 2.

$$A_{H,1} = C_T\epsilon_{H,1} - \frac{\epsilon_{H,1}}{\epsilon_{C,2}}(A_{C,2}) \quad (1)$$

$$K_{hydr} = \frac{A_{H,1}/A_{C,2}}{\epsilon_{H,1}/\epsilon_{C,2}} \quad (2)$$

The method can also be extended to the situation where the absorption band of the carbonyl compound has some overlap with that of the hydrated form. In this case a Gaussian or log-normal analysis of the spectra provides a better estimate of the absorbance of the pure species. The alternative is to use eq 3 to obtain the ratio R ($R = (\epsilon_{H,1} - \epsilon_{C,2})/\epsilon_{C,2}$). Now, the expression of the hydration constant can be shown by eq 4.

$$A_{H,1} = C_T\epsilon_{H,1} - \frac{(\epsilon_{H,1} - \epsilon_{C,1})}{\epsilon_{C,2}}(A_{C,2}) \quad (3)$$

$$K_{hydr} = \frac{(A_{H,1}/A_{C,2})\epsilon_{C,2} - \epsilon_{C,1}}{R\epsilon_{C,2} + \epsilon_{C,1}} = \frac{(A_{H,1}/A_{C,2})\epsilon_{C,2} - \epsilon_{C,1}}{\epsilon_{H,1}} \quad (4)$$

If the $\epsilon_{C,1}$ term in eq 4 were neglected, then the calculated value of K_{hydr} would be artificially increased. Therefore, by working at several wavelengths, one can test for the several experimental values of R which minimize K_{hydr}. Such a procedure is essentially the same as varying the wavelength in order to locate the region of minimum overlap. Under these circumstances, if $\epsilon_{C,1}$ is negligible, eq 4 becomes equivalent to eq 1.

We have tested the temperature variation method for 4-pyridinecarboxaldehyde, since in this case the hydration constants have been previously determined by Pocker et al.[11] The spectral changes with temperature, as shown

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