Notes

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Decarboxylation Reactions. I. Reaction of Enamines with Carboxylic Acids[1]

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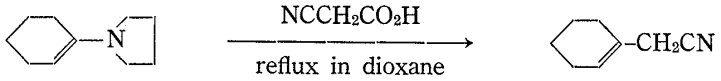
In recent years the reaction of enamines with certain carboxylic acids have been reported in several papers.[3-5] The reaction[3] with trichloroacetic acid yielding α-chloroacylamines, the reaction[4] with cyanoacetic acid yielding amine salts of α-cyanoalkylideneacetic acid and the reaction[5] of nitroacetic acid yielding β,γ-unsaturated nitro compounds have been reported. While the previously reported reaction[4] with cyanoacetic acid proceeds without decarboxylation, reactions of enamines with carboxylic acids such as cyanoacetic acid, malonic acid and acetoacetic acid, involving decarboxylation, have been investigated.

1-(1-Cyclohexene-1-yl)pyrrolidine, selected as a representative, was allowed to react with cyanoacetic acid in dioxane under refluxing. A reaction proceeded with considerable carbon dioxide evolution to give 1-cyclohexene-1-ylacetonitrile in 92% yield.

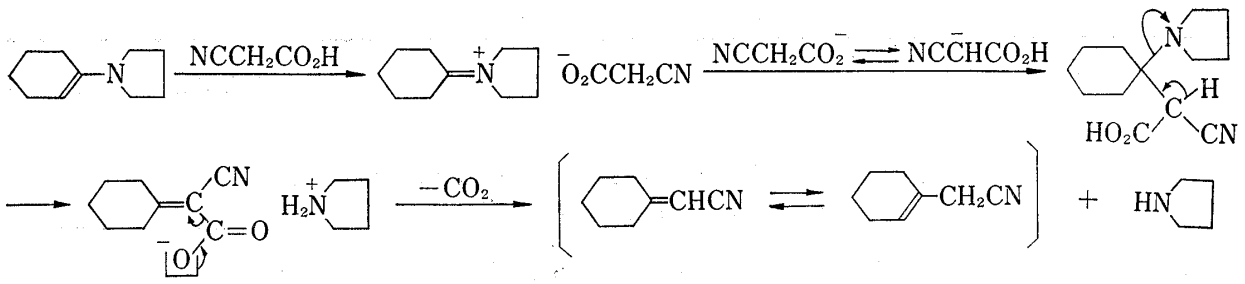


The structure was confirmed by following spectral data not to be cyclohexylideneacetonitrile, but 1-cyclohexene-1-ylacetonitrile. The ultraviolet (UV) spectrum of this compound does not exhibit the absorption of α,β-unsaturated nitrile at λ_{max}^{EtOH} 216 mμ,[6] and the infrared (IR) spectrum exhibits the absorption band of the unconjugated nitrile at $\nu_{max}^{CHCl_3}$ 2244 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum in deuterochloroform was also interpreted to fit the 1-cyclohexene-1-ylacetonitrile structure by the following assignment: the multiplet at τ 4.05—4.35 to the -C<u>H</u>=C<, the singlet at τ 7.02 to the -C<u>H</u>$_2$CN and the multiplet at τ 7.70—8.70 to the -(C<u>H</u>$_2$)$_4$-.

An analogous reaction has been reported by Armarego[5] in the reaction of the enamine with nitroacetic acid giving the β,γ-unsaturated nitro compound. Alt, *et al.*[4] have reported the reaction of 1-(cyclohexene-1-yl)morpholine with cyanoacetic acid in ethyl acetate giving the morpholinium salt of α-cyanocyclohexylideneacetic acid. We confirmed that this salt underwent decarboxylation in dioxane at elevated temperature to give 1-cyclohexene-1-ylacetonitrile. Consequently, the salt obtained by Alt, *et al.*[4] is inferred as an intermediate of the foregoing reaction.

The reaction path is then presumed as follows. The iminium ion formed from enamine suffers attack of the carbanion of cyanoacetic acid to give the adduct and this adduct under-

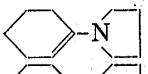
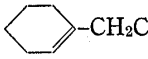
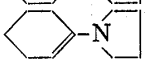
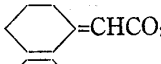
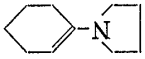
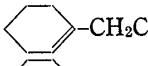
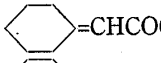
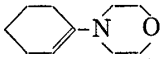
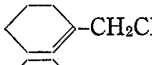
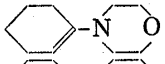
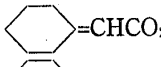
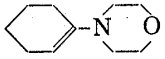
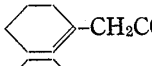
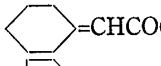
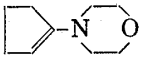
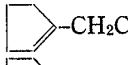
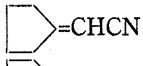
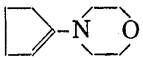
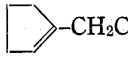
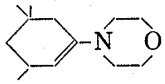
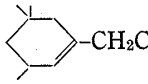
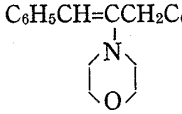
1) Presented in most part at the 16th Meeting of Tokai Branch, Pharmaceutical Society of Japan, Shizuoka, Sept. 25, 1971.
2) Location: *2-2-1, Oshika, Shizuoka.*
3) G.H. Alt and A.J. Speziale, *J. Org. Chem.*, **31**, 1340 (1966); A. Lukasiewicz and J. Lesinka, *Tetrahedron*, **24**, 7 (1968).
4) G.H. Alt and G.A. Gallegos, *J. Org. Chem.*, **36**, 1000 (1971).
5) W.L.F. Armarego, *J. Chem. Soc.* (*C*), **1969**, 986.
6) O.H. Wheeler, *J. Org. Chem.*, **26**, 4755 (1961).



goes deamination to give the salt intermediate, which is successively decarboxylated.

Some other enamines were then allowed to react not only with cyanoacetic acid but also with malonic acid and acetoacetic acid. Results are summarized in Table I. The reactions proceeded similarly with evolution of carbon dioxide to give the corresponding nitrile, carboxylic acid or methylketone derivatives possessing the α,β- or β,γ-carbon-carbon double bond. These structures were assigned from their IR, UV and NMR spectra. The compound,

Table I. Reaction[a] of Enamines with Carboxylic Acid

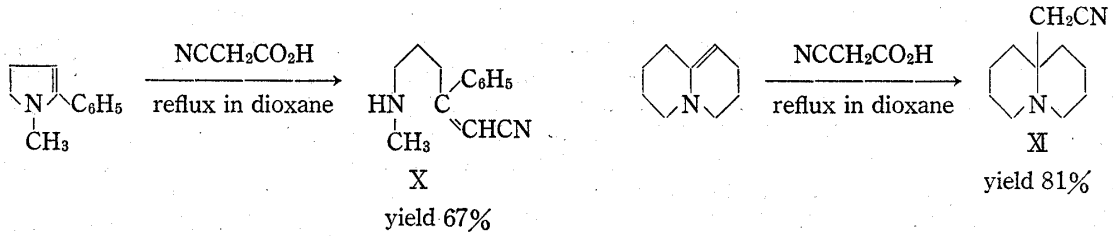
Run No.	Substrate	Carboxylic acid	Reaction temp.(°C)	Reaction time (hr)	Product	Compound No.	Yield (%)
1		$NCCH_2CO_2H$	reflux	5.5		I	92
2		$CH_2(CO_2H)_2$	reflux	3.0		II	17
3		$CH_3COCH_2CO_2H$	20—30	3.5	 	III IV	39
4		$NCCH_2CO_2H$	reflux	5.5		I	84
5		$CH_2(CO_2H)_2$	reflux	3.5		II	42
6		$CH_3COCH_2CO_2H$	12—20	7.0	 	III IV	56
7		$NCCH_2CO_2H$	reflux	8.5	 	V VI	72
8		$CH_2(CO_2H)_2$	reflux	3.5		VII	45
9		$NCCH_2CO_2H$	reflux	7.5		VIII	59
10		$NCCH_2CO_2H$	reflux	10.0	$(C_6H_5CH_2)_2C{=}CHCN$	IX	76

a) molar amount used: 0.03 mole of enamine, 0.05 mole of carboxylic acid, 40 ml of dioxane

II, possessing α,β-carbon-carbon double bond exhibited the UV absorption maximum at 222.5 mμ characteristic of the conjugated system, whereas the compounds I, VII and VIII possessing β,γ-carbon-carbon double bond exhibited no absorption in ultraviolet region. In the spectrum of the compound, IX, the UV absorption of α,β-unsaturated nitrile was overlapped with the absorption of the benzene ring, but the nitrile absorption at the lower frequency ($\nu_{max}^{CHCl_3}$ 2214 cm^{-1}) in its IR spectrum corresponded to that of α,β-unsaturated nitrile. In the runs 3,6 and 7 in Table I, the products were obtained as mixtures of isomers as shown in Table I. Gas chromatogrums of these showed two peaks and they exhibited the UV absor-

ptions characteristic of α,β-carbon-carbon double bonds. In the IR spectrum of the mixture of the compound V and VI both α,β- and β,γ-unsaturated nitriles were clearly observed.

Cyclic enamines such as 1-methyl-2-phenyl-2-pyrroline and $\Delta^{1,(10)}$-dehydroquinolizidine were also allowed to react with cyanoacetic acid under the same conditions to give 6-methylamino-3-phenyl-2-hexenenitrile (X) and 10-cyanomethylquinolizidine (XI), respectively.



The free amine, X and its perchlorate exhibit the IR and UV absorption corresponding to α,β-unsaturated nitrile. NMR spectrum of the perchlorate is well interpreted to fit the structure. The structure of XI was also confirmed by IR and NMR spectral data.

Experimental[7]

Materials——The following seven enamines were prepared according to the previously reported methods. 1-(1-Cyclohexene-1-yl)pyrrolidine,[8] bp 127—129° (31 mmHg), n_D^{18} 1.5140; 1-(1-cyclohexene-1-yl)morpholine,[8] bp 124—125° (18 mmHg), n_D^{15} 1.5140; 1-(1-cyclopentene-1-yl)morpholine,[3] bp 106—107° (14 mmHg), n_D^{28} 1.5091; 1-(3,5,5-trimethyl-1-cyclohexene-1-yl)morpholine,[9] bp 97—98° (2 mmHg), n_D^{16} 1.4960; 1-(1,3-diphenyl-2-propene-2-yl)morpholine,[10] bp 162—163° (0.4 mmHg), mp 58—60°; 1-methyl-2-phenyl-2-pyrroline,[11] bp 117—119° (20 mmHg), n_D^{17} 1.5782; $\Delta^{1,(10)}$-dehydroquinolizidine,[12] bp 93° (24 mmHg), n_D^{20} 1.5120.

Acetoacetic acid was prepared by the following method. To 75 ml of 16% KOH solution 26 g of ethylacetoacetate was added on cool. The mixture was stirred in an ice-water bath for 24 hr. After addition of 40 g of Amberlite IR-120-B, stirring was continued for additional 15 min and followed by filtration. The same treatment with the Amberlite was repeated twice. Lyophilization of the filtrate gave crystals of acetoacetic acid which decomposed at about 50° with evolution of carbon dioxide.

Reaction of Enamines with Cyanoacetic Acid——General Procedure: The seven enamines were allowed to react with cyanoacetic acid by the following general procedure.

A solution of 0.03 mole of enamine and 4.5 g (0.05 mole) of cyanoacetic acid in 40 ml of dioxane was refluxed with stirring. Dry air free from carbon dioxide was passed through the reaction vessel in order to check the evolution of carbon dioxide by $Ba(OH)_2$ solution. After the evolution of carbon dioxide was almost ceased, the reaction solution was concentrated under reduced pressure. Distillation of the resulting residue gave the product as oily or solid distillate. Yield of the product obtained in each run is shown in Table I. The following is physical, spectral and analytical data of the products.

Reaction with 1-(1-Cyclohexene-1-yl)pyrrolidine (Run No. 1): and 1-(1-Cyclohexene-1-yl)morpholine (Run No. 4): In these two runs 1-cyclohexene-1-ylacetonitrile (I) was obtained as a liquid, bp 98—100° (16 mmHg) [lit.,[13] bp 105° (22 mmHg)]. n_D^{25} 1.4750. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN), 1674 (C=C). NMR ($CDCl_3$) τ: 4.05—4.35 (1H, m, CH=C), 7.02 (2H, s, CH_2CN), 7.70—8.70 [8H, m, $-(CH_2)_4$]. *Anal.* Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.51; N, 11.56. Found: C, 79.11; H, 8.95; N, 11.65.

Reaction with 1-(1-Cyclopentene-1-yl)morpholine (Run No. 7): In this run an oily product, bp 104—105° (43 mmHg) was shown to be a mixture of 1-cyclopentene-1-ylacetonitrile (V) and cyclopentylideneacetonitrile (VI). A gas chromatogrum (column: 15% diethyleneglycol succinate on chromosorb P) of this material showed two peaks. In this IR spectrum (in $CHCl_3$) the two bands at 2248 cm^{-1} to the unconju-

7) Spectra reported herein were determined with a Hitachi EPS-3T UV spectrophotometer, a Hitachi EPI-G2 IR spectrophotometer and a JEOL-JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, m=multiplet, s=singlet.

8) G. Stork, A. Brizzolara, H. Landesman, J. Simuskovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 208 (1963).
9) G. Opitz and W. Merz, *Ann.*, **652**, 117 (1962).
10) D. Pocar, G. Bianchetti and P.D. Croce, *Gazz. Chem. Ital.*, **95**, 1220 (1965).
11) L.C. Craig, *J. Am. Chem. Soc.*, **55**, 295 (1933).
12) N.J. Leonard, A.S. Hay, R.W. Fulmer and V.W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).
13) A. Kandiah and R.P. Linsted, *J. Chem. Soc.*, **1929**, 2139.

gated nitrile and at 2214 cm^{-1} to the conjugated nitrile is indicative of the mixture of the two compounds. The presence of the carbon-carbon double bond conjugated with nitrile also allows the UV absorption (in hexane) at 218 mμ. *Anal.* Calcd. for C_7H_9N: C, 78.46; H, 8.47; N, 9.12. Found: C, 77.98; H, 8.21; N, 9.18.

Reaction with 1-(3,5,5-Trimethyl-1-cyclohexene-1-yl)morpholine (Run No. 9): 3,5,5-Trimethyl-1-cyclohexene-1-ylacetonitrile (VIII) was obtained as a liquid, bp 106—107° (10 mmHg), n_D^{25} 1.4637. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2242 (CN), 1664 (C=C). NMR ($CDCl_3$) τ: 6.47 (1H, d, J=7.0 Hz, CH=C), 7.05 (2H, s, CH_2CN), 7.08—8.68 (3H, m, $-CH_2CH\langle$), 8.96 (2H, s, CH_2), 9.02 [6H, s, $(CH_3)_2C$], 9.08 (3H, d, J=6.0 Hz, CH_3). *Anal.* Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.64; H, 10.47; N, 8.75.

Reaction with 1-(1,3-Diphenyl-2-propene-2-yl)morpholine (Run No. 10): 3-Benzyl-4-phenyl-2-butenenitrile (IX) was obtained as a liquid, bp 143—146° (0.2 mmHg). n_D^{25} 1.5799. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2214 (CN), 1628 (C=C). NMR ($CDCl_3$) τ: 2.60—3.20 (10H, m, C_6H_5), 4.98 (1H, s, CH=C), 6.34 (2H, s, $-CH_2-$), 6.70 (2H, s, $-CH_2-$). *Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 86.75; H, 6.60; N, 6.11.

Reaction with 1-Methyl-2-phenyl-2-pyrroline: 6-Methylamino-3-phenyl-2-hexenenitrile (X) was obtained as a liquid, bp 134—138° (1 mmHg). Perchlorate: colorless prisms (EtOH), mp 157—158°. IR ν_{max}^{KBr} cm^{-1}: 2212 (CN). UV λ_{max}^{EtOH} mμ (ε): 256.5 (16200). NMR (CF_3CO_2H) τ: 2.15 (5H, s, C_6H_5), 2.60—3.98 (2H, b, NH), 4.24 (1H, s, CH=C), 6.40—7.12 [4H, m, $-(CH_2)_2-$], 7.01 (3H, s, NCH_3), 7.49—8.32 (2H, m, $-CH_2-$). *Anal.* Calcd. for $C_{13}H_{17}O_4N_2Cl$: C, 51.92; H, 5.69; N, 9.31. Found: C, 52.15; H, 5.66; N, 9.32.

Reaction with $\Delta^{1,(10)}$-Dehydroquinolizidine: 10-Cyanomethylquinolizidine (XI) was obtained as a solid, bp 150—152° (20 mmHg), colorless prisms (petr. ether), mp 60—61°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2234 (CN). NMR ($CDCl_3$) τ: 7.35 (2H, s, CH_2CN), 7.40—7.80, 7.80—8.87 [16H, m, $-(CH_2)_4-$, $-(CH_2)_4-$]. *Anal.* Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.98; H, 10.06; N, 15.66.

Reaction of Enamines with Malonic Acid——A mixture of 0.03 mole of enamine and 5.2 g (0.05 mole) of malonic acid in 40 ml of dioxane was refluxed until evolution of carbon dioxide was almost ceased. The reaction solution was concentrated under reduced pressure.

In the runs with 1-(1-cyclohexene-1-yl)pyrrolidine (Run No. 2) and 1-(1-cyclohexene-1-yl)morpholine (Run No. 5), washing of the residue with 10% HCl gave fine crystals which were recrystallized from petr. ether to give needles of cyclohexylideneacetic acid (II). mp 86—87° (lit.[14] mp 91°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1692 (C=O), 1640 (C=C). UV λ_{max}^{hexane} mμ (ε): 222.5 (14100) [lit.[15] UV λ_{max}^{EtOH} mμ (ε): 220 (14000)]. NMR ($CDCl_3$) τ: −2.81 (1H, s, OH), 4.40 (1H, s, C=CH), 7.00—7.35, 7.55—7.95 and 8.15—8.55 [10H, m, $-(CH_2)_5-$]. *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.51; H, 8.64.

In the run with 1-(1-cyclopentene-1-yl)morpholine (Run No. 8), the residue was dissolved in ether. The ethereal solution was washed with 10% HCl and dried over $MgSO_4$. After removal of ether distillation of the residue under reduced pressure gave 1-cyclopentene-1-ylacetic acid (VII) as a solid distillate, bp 102—103° (5 mmHg). Plates (petr. ether), mp 49—50°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712 (C=O), 1640 (C=C). NMR ($CDCl_3$) τ: −1.42 (1H, s, OH), 4.32—4.53 (1H, m, CH=C), 6.83 (2H, s, CH_2COO), 7.37—8.35 [6H, m, $-(CH_2)_3-$)] *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.70; H, 7.70.

Reaction of Enamines with Acetoacetic Acid——1-(1-Cyclohexene-1-yl)morpholine (Run No. 3) and 1-(1-cyclohexene-1-yl)pyrrolidine (Run No. 6) were allowed to react by the following procedure.

A solution of 0.03 mole of enamine and 5.1 g (0.05 mole) of acetoacetic acid in 40 ml of dioxane was stirred at room temperature until the evolution of carbon dioxide ceased. The reaction solution was concentrated under reduced pressure. Distillation of the residue gave an oily product, bp 48—52° (4 mmHg). This product was shown to be a mixture of 1-cyclohexene-1-ylacetone (III) and 1-cyclohexylideneacetone (IV). A gas chromatogram of this material showed two peaks. The UV absorption maximum at 215 mμ (in hexane) proved the presence of conjugated carbon-carbon double bond. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1712 (C=O), 1618 (C=C). *Anal.* Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.57; H, 10.09.

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