The Reaction of Acetylenecarboxylic Acid with Amines. XV.[1] Reaffirmation of the Enamine Structure Facilitated by Intramolecular Hydrogen Bonding Common to the Reaction Products

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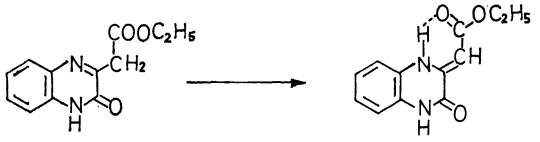
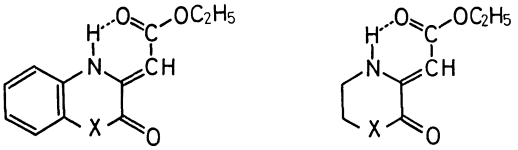
The reactions of dimethyl acetylenedicarboxylate (V) with *p*-chloroaniline, ethanolamine, ethylenediamine, *o*-aminophenol, and *o*-phenylenediamine gave dimethyl *N*-(*p*-chlorophenyl)aminofumarate(VI), 3-methoxycarbonylmethylene-3,4,5,6,-tetrahydro-2*H*-1,4-oxazin-2-one (VII), 3-methoxycarbonylmethylenepiperazin-2-one (VIII), 3-methoxycarbonylmethylene-3,4,-dihydro-2*H*-1,4-benzoxazine-2-one(IX), and 3-methoxycarbonylmethylene-3,4-dihydro-2(1*H*)-quinoxalinone(X), respectively. It has been shown that methoxycarbonylmethylene is a common structural element in all products, where the carbonyl is hydrogen-bonded with an amino group to form an enamine form. The spectra measured for crystals (IR) and for solutions in inert solvents (NMR) exhibited the fixation of the enamine form preferentially to the imine form, while NMR spectra for trifluoroacetic acid solutions indicated both forms in equilibrium. Tautomerization occurring in the acid is discussed.

In a preceding paper of this series,[2] we reported that the substance customarily called ethyl 2(1*H*)-quinoxalinone-3-acetate (I) should be named 3-ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (II) in consideration of IR spectral data, *viz.*, this compound exists in the enamine form as expressed by II which is facilitated by an intramolecular hydrogen bonding.



I II

The preceding report was the first to present evidence for the structural predomination common to a series of pyrazinone-type compounds (III and IV) having a β-carbonyl group in their side chain.[3,4] It was also reported that such a carbonylmethylene structure, facilitated by hydrogen bonding, predominates not only in these heterocycles but also commonly in β-iminopropionyl derivatives.[5]



X=NH, O and S (II: *X*=NH) III

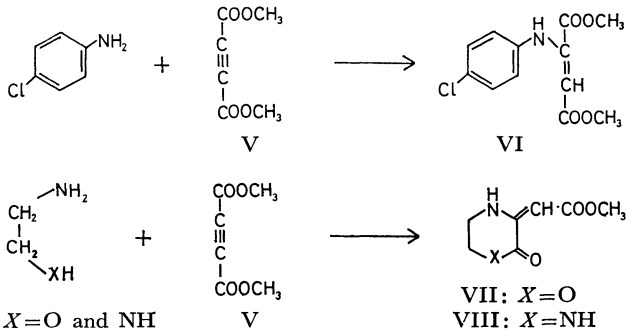
X=NH and O IV

Chapman[6] described the same enamine structure of I (*i.e.*,II) five years after. There is a contradiction[7] between his and our results, and our reports are inadequately cited in his paper. Some other workers also described simliar enamine forms[8–10] of heterocycles closely related to I or II, and they refer the enamine structure to imine-enamine tautomerism. In our papers, however, we refrained from explaining the enamine form by tautomerism, since we could not obtain any evidence for the presence of the corresponding imine form in our experiments carried out under ordinary conditions.

This paper deals with a reconfirmation of the enamine structure of several types of compounds with emphasis on the point that the imine form can not be detected in chloroform and methanol solutions.

Results

We synthesized methyl ester homologues of the compounds,[2–5] in order to extend our study on their enamine structures by means of IR and NMR spectroscopy. The syntheses were carried out by the reactions of dimethyl acetylenedicarboxylate (V) with *p*-chloroaniline, ethanolamine, ethylenediamine, *o*-aminophenol and *o*-phenylenediamine, as follows:



X=O and NH V VII: *X*=O VIII: *X*=NH

1) Part XIII: This Bulletin, **37**, 1745 (1964), and Part XIV: *Nippon Kagaku Zasshi*, **85**, 704 (1964). Presented in part at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

2) Y. Iwanami, *Nippon Kagaku Zasshi*, **82**, 778, 780 (1961).

3) Y. Iwanami, *ibid.*, **83**, 100, 161, 316, 593, 597 (1962); H. Sasaki, H. Sakata, and Y. Iwanami, *ibid.*, **85**, 704 (1964).

4) Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura, and S. Isoyama, This Bulletin, **37**, 1740 (1964); Y. Iwanami, S. Isoyama, and Y. Kenjo, *ibid.*, **37**, 1745 (1964).

5) Y. Iwanami, *Nippon Kagaku Zasshi*, **82**, 632, 634 (1961); **83**, 600 (1962).

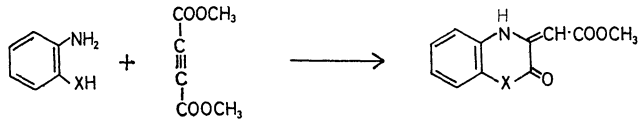
6) D. D. Chapman, *J. Chem. Soc.*, **1966**, 806.

7) If not a contradiction, it could be a serious misprint.

8) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).

9) W. von Philipsborn, H. Stierlin, and W. Traber, *Helv. Chim. Acta*, **46**, 2592 (1963).

10) L. Merlini, W. von Philipsborn, and M. Viscontini, *ibid.*, **46**, 2597 (1963).



X=O and NH V IX: X=O X: X=NH

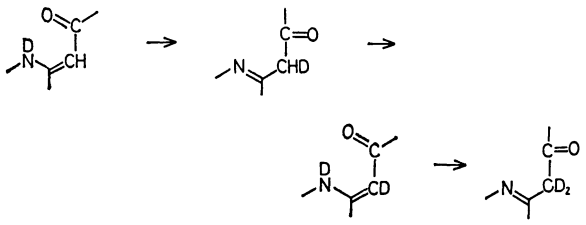
The IR spectra of these reaction products (VI—X) were measured for potassium bromide disks. All ester carbonyl bands exhibit marked lower frequency shifts compared to those of normal esters. Since absorption bands of the carbon-carbon double bond are observed in all cases, a double bond adjacent to the carbonyl (α, β-unsaturated) probably contributes to the shifts. Every carbonyl band, however, is not in the expected range[11] of 1730—1717 cm^{-1} for an α, β-unsaturated ester carbonyl, but in a less wave number region of 1696—1659 cm^{-1}. This can be explained by the intramolecular hydrogen bonding of the carbonyl with the amino group displacing its band toward much lower frequency side.[11] These results show that all the products are in enamine structure but not in imine form.

The products are thus to be named dimethyl *N*-(*p*-chlorophenyl)aminofumarate (VI), 3-methoxycarbonylmethylene-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (VII), 3-methoxycarbonylmethylenepiperazin-2-one (VIII), 3-methoxycarbonylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (IX), 3-methoxycarbonylmethylene-3,4-dihydro-2(1*H*)-quinoxalinone (X).

The NMR spectra of VI, VII, VIII, and IX in deuteriochloroform commonly show singlets due to an olefinic (methine) proton instead of expected methylene if they exist in imine forms. Moreover, each spectrum shows at least one amino proton signal, the integration of which represents a single proton on nitrogen (two signals appear in the case of VIII). Its position in a lower field suggests hydrogen bonding involving the amino proton.

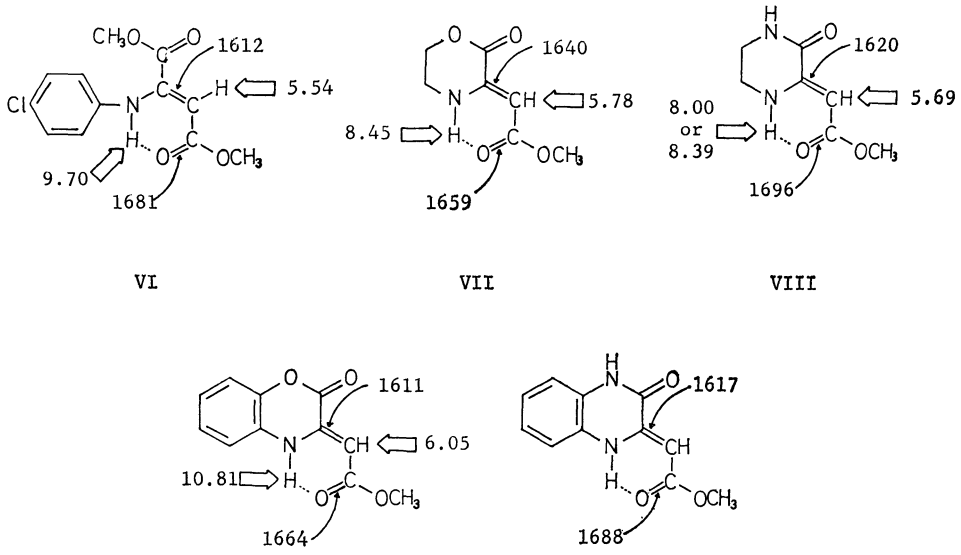
Main IR absorption bands and NMR signals of these compounds are shown in Fig. 1, together with the structural formulas which illustrate the actual forms of enamine type (the ring amide structures of VIII and X are also supported by both spectral data). Since IR spectra were measured for potassium bromide disks and NMR spectra for solutions, all these compounds can be satisfactorily expressed by the formulas shown in Fig. 1 both in solution and crystalline states.

If interconversion of imine and enamine (tautomerism) takes place, the hydrogen of side chain methine or methylene should be exchangeable with deuterium in the presence of deuterium oxide. One of the possible exchange mechanisms would be as follows:



When the NMR spectra of these compounds were measured in deuteriomethanol (CD_3OD), exchange with deuterium oxide removed the amino proton signal(s) (Table 1). Nevertheless, the signal of the methine proton did not disappear. Its relative intensity remained unchanged to afford 1:3 ratio to the integration of methyl singlet in every case. Hence it appears that tautomerism never occurs in deuteriomethanol and probably in deuteriochloroform.

On the other hand, some different results were



VI VII VIII

IX X

Fig. 1. Structural formulas of the products. Large arrow ⇨ shows the position of the NMR signal (δ) in deuteriochloroform, and small arrow → indicates the IR absorption (cm^{-1}) for potassium bromide disk. Compound X was insoluble in deuteriochloroform.

11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., London (1958), p. 179.

Table 1. Chemical shifts of the products

Compound	CD_3OD			CF_3COOH		
	CH_3	CH_2	=CH	CH_3	CH_2	=CH
VI	3.42	—	5.11	3.36 3.49	3.46	4.48
VII	3.39	—	5.18	3.52	3.55	5.62
VIII	3.37	—	5.14	3.42	3.54	5.52
IX	3.49	—	6.92	3.52	3.52	5.62

The values are in ppm (δ) relative to internal tetramethylsilane. The mark—: no indication of the signal (side chain) at all. Compound was sparingly soluble in CD_3OD. The signals of X in CF_3COOH were already reported.[8]

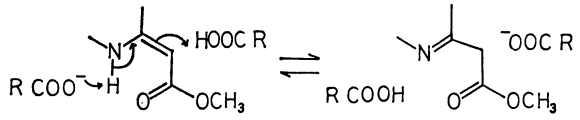
obtained from the measurement using trifluoroacetic acid. Both methine and methylene proton signals are exhibited in this acid as listed in Table 1. Methylene proton signals can be interpreted as due to the side chain methylene of each compound existing in the imine form. The enamine and imine forms are, therefore, equilibrated in the acid.

A variety of the existing ratios of enamine to imine in the acid are shown by calculation based upon the relative intensities of methine singlets, as follows: approximately 1:2, 1:0.5, 1:8, and 1:>10 for VI, VII, VIII, and IX, respectively.

In deuteriotrifluoroacetic acid, either methine or methylene proton signal disappears by replacement with deuterium. It can therefore be said that tautomerization becomes possible under certain conditions caused by trifluoroacetic acid.

Discussion

The phenomenon observed on the compounds in trifluoroacetic acid is noteworthy. However, there is an essential difference between the compounds and β-diketones such as acetylacetone or ethyl acetoacetate, which ordinarily exist as an equilibrium mixture of keto and enol tautomers, while all the compounds in the present study shut themselves much more firmly in the enamine form in crystals and chloroform or methanol solution (at least the imine form is extremely minimized). The imine formation and tautomerization therewith in trifluoroacetic acid may be caused by a concerted reaction[12] which proceeds by simultaneous attack of the acid and the base as illustrated below.



Generally, imine form is predominant[13,14] in imine-enamine tautomerism:

Enamines are stable only when there is no hydrogen on the nitrogen ($-\overset{|}{C}=\overset{|}{C}-NRR'$).[13,14] It is interesting that all our products possess a hydrogen on the nitrogen atom but the enamine forms remain stable.

This series represents a special case of proton-shift isomerization or tautemerization. However, we recently encountered a perfectly converse predominance of the imine form observed on the same side-chain derivative of a more complicated heterocycle, which will be reported in the following paper.

Experimental

IR spectra were measured for KBr disks with a Nippon Bunko DS-301 spectrophotometer, and NMR spectra were determined on a Hitachi H-60 model.

The synthetic procedures of the all compounds were essentially the same as the corresponding ethyl derivatives[2-5] except that diethyl acetylenedicarboxylate was replaced by dimethyl acetylenedicarboxylate (V) and methanol was used as the solvent instead of ethanol. Only their melting points (uncorr.), yields in percent, and data of elementary analyses are described.

Dimethyl N-(p-Chlorophenyl)aminofumarate (*VI*). This was prepared by the reported procedure.[5] Yield 83%; mp 75—76°C.

Found: C, 53.59; H, 4.82; N, 5.06%. Calcd for $C_{12}H_{12}O_4NCl$: C, 53.44; H, 4.49; N, 5.19%.

3-Methoxycarbonylmethylene-3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one (*VII*). This was prepared by the reported procedure.[2] Yield 69%; mp 81—82°C.

Found: C, 49.36; H, 5.52; N, 7.97%. Calcd for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18%.

3-Methoxycarbonylmethylenepiperazin-2-one (*VIII*). This was prepared by the reported procedure.[4] Yield 88%; mp 173—174°C.

Found: C, 49.55; H, 6.14; N, 16.61%. Calcd for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46%.

3-Methoxycarbonylmethylene-3,4-dihydro-2H-1,4-benzoxazine-2-one (*IX*).[15] This was prepared by the reported procedure.[2] Yield 67%; mp 170°C (lit.[15,16] mp 170°C).

Found: C, 60.49; H, 4.33; N, 6.45%.

3-Methoxycarbonylmethylene-3,4-dihydro-2(1H)quinoxalinone (*X*). This was prepared by the reported procedure.[2] Yield 75%; mp 227°C (lit.[17,18] mp 225°C).

Found; C, 60.67; H, 4.43; N, 12.78%.

Grateful acknowledgement is made to Miss Masako Asahina, and Dr. Yutaka Fujise, Tohoku University, for NMR spectroscopy, to Dr. Tomohisa Takita, Institute of Microbial Chemistry, for helpful discussion on NMR data, and to Prof. Hiro-oki Sasaki of this institute for his interest and encouragement.

12) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., London (1960), p. 385.

13) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Co., New York (1968), p. 62.

14) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York (1964), p. 486.

15) A compound probably identical with this product has been reported to be its isomer, 2-methoxycarbonylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-3-one.[16] Chemical shifts and melting point of the compound described in the paper supports its identity. The structure allocated as IX is more satisfactory for interpretation of its IR absorption bands in comparison with those of the oxazinone derivatives[2-4] including VII of the present report.

16) R. M. Acheson, M.W. Foxton, and G. R. Miller, *J. Chem. Soc.*, **1965**, 3200.

17) F. Weygand, W. Steglich, and H. Tanner, *Ann, Chem.*, **658**, 128 (1962).

18) Reported as methyl 2-hydroxyquinoxaline-3-acetate.