The Independent Isolation of a Primary Enamine and the Tautomeric Imine[1]

Chung-gi SHIN

Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama

and Mitsuo MASAKI,* and Masaki OHTA

Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

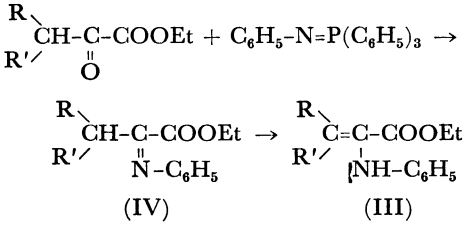
(Received October 30, 1970)

Isolation of a primary enamine and its tautomeric imine has been described and their dimerization discussed. Reduction of ethyl 3-methyl-2-nitro-2-butenoate with aluminum amalgam afforded ethyl 2-amino-3-methyl-2-butenoate (I) (enamine form), while treatment of ethyl 3-methyl-2-oxobutanoate with triphenylphosphinimine gave ethyl 2-imino-3-methylbutanoate (II) (imino form). The enamine and its tautomeric imine dimerized to give 3,6-diisopropylidene-2,5-dioxopiperazine (VII) and 2-ethoxycarbonyl-2,5-diisopropylimidazolid-4-one (IX), respectively. However, individual acylation of both the enamine and the imine gave the same acyl compound.

It has been postulated that α-imino acids are important intermediates in the transformation between α-amino acids and α-keto acids.[2] However, there has been no report on the tautomerism between imino acid and enamino acid. Previous investigations on the enamine had dealt almost exclusively with secondary and tertiary enamines.[3]

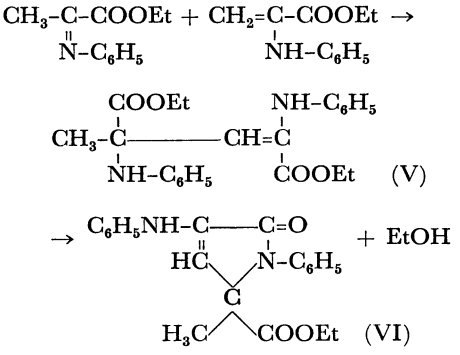
In a previous paper,[4] the authors reported briefly that a primary enamine (ethyl 2-amino-3-methyl-2-butenoate: I) could be isolated as a reduction product of the corresponding α,β-unsaturated α-nitrocarboxylic ester, and the tautomeric imine (ethyl 2-imino-3-methylbutanoate: II) from a reaction mixture of the corresponding α-oxocarboxylic ester with triphenylphosphinimine. The acylation of both I and II, however, gave the same acyl enamine derivative and the dimerization of I and II gave dioxopiperazine (VII) and imidazolidone derivative (IX), respectively. The isomerization between I and II, however, was unsuccessful.

On the other hand, in the case of the reaction of α-oxocarboxylic esters with *N*-phenyltriphenylphosphinimine, secondary enamine (III) and the tautomeric imine (IV) were obtained as an equilibrium mixture.



Scheme 1

On the basis of the IR and NMR data, it has been found that the isomerization of IV to III occurred and the composition of the reaction mixture was evaluated.[5] So far, however, a complete enamine-imine interconversion between III and IV has been unsuccessful.[5] In the case of ethyl pyruvate, the reaction mixture (III and IV; R=R′=H) dimerized to give 3-anilino-5-ethoxycarbonyl-5-methyl-1-phenyl-Δ^3-pyrrolin-2-one (VI) *via* ethyl 2,4-dianilino-4-ethoxycarbonyl-2-pentenoate (V) as an intermediate.[5]



Scheme 2

This paper reports the synthesis of ethyl 2-imino-3-methylbutanoate (II) through the reaction of ethyl 3-methyl-2-oxobutanoate with triphenylphosphinimine by the method of Appel and Hauss,[6] as well as the dimerization and chloroacetylation of I and II, respectively.

Results and Discussion

According to the method of Tatsuoka *et al.*[7] ethyl 2-amino-3-methyl-2-butenoate (I) was prepared in a 56% yield as a pale yellow oil from ethyl 3-methyl-2-nitro-2-butenoate with aluminum amalgam in ether under reflux.[8] Appel and Hauss reported the reaction of methyl pyruvate with triphenylphosphinimine to give methyl 2-iminopropionate, though the structure of the

1) A part of this paper was presented at the 21st Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1968.

* Present address: Polymer Research Laboratory, Ube Industries, Ltd., Goi, Ichihara City, Chiba.

2) a) F. Knoop and H. Oesterlin, *Z. Phys. Chem.*, **148**, 294 (1925); *ibid.*, **170**, 186 (1927). b) E. F. Gale, *Chem. Ind.*, **1948**, 131. c) S. Sakurai, *J. Biochem.*, **43**, 851 (1956); *ibid.*, **44**, 47, 557 (1957); *ibid.*, **45**, 379 (1958).

3) A. G. Cook, "Enamines: Synthesis, Structure and Reactions," Marcel Dekker, New York and London (1969).

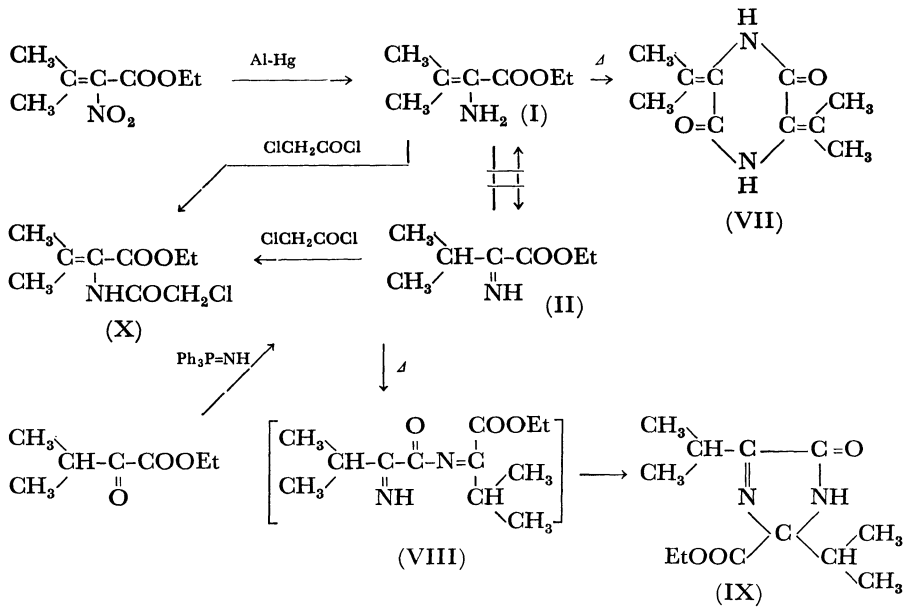
4) M. Masaki, C. Shin, H. Kurita, and M. Ohta, *Chem. Commun.*, **1968**, 1447.

5) C. Shin, H. Ando, and J. Yoshimura, This Bulletin, **44**, 474 (1971).

6) R. Appel and A. Hauss, *Z. Anorg. Chem.*, **311**, 290 (1961).

7) S. Tatsuoka, M. Murakami, and T. Tamura, *Yakugaku Zasshi*, **70**, 230 (1950).

8) C. Shin, M. Masaki, and M. Ohta, *J. Org. Chem.*, **32**, 1860 (1967).



Scheme 3

product was not clarified since the product could not be isolated and its characterization was deduced only by hydrogenation into (±)-alanine.[6] However, treatment of ethyl 3-methyl-2-oxobutanoate with triphenylphosphinimine in anhydrous acetonitrile for 2 hr under reflux afforded a pale yellow oil as an analytical pure product in a 40% yield, and the product was identified as ethyl 2-imino-3-methylbutanoate (II), the tautometric isomer of I. The infrared spectrum of II showed an intense ester carbonyl band at 1730 cm^{-1} and a medium band attributable to C=N stretching vibration at 1640 cm^{-1}, while that of I showed two intense absorption bands at 1730 cm^{-1} and 1690 cm^{-1} and medium bands at 1640 and 1600 cm^{-1} as shown in Figs. 1A and 1B.

The NMR spectrum of I showed peaks at τ 5.72 (q, $-C\underline{H}_2CH_3$, 2H), 6.82 (broad s, $-NH_2$, 2H), 7.91 (s, $-CH_3$, 3H), 8.22 (s, $-CH_3$, 3H), and 8.67 (t, $-CH_2C\underline{H}_3$, 3H), while that of II showed peaks at τ 0.00 (broad s,

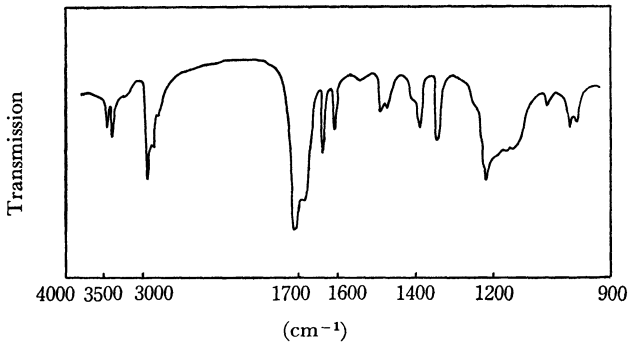


Fig. 1A. Infrared spectrum of I in NaCl.

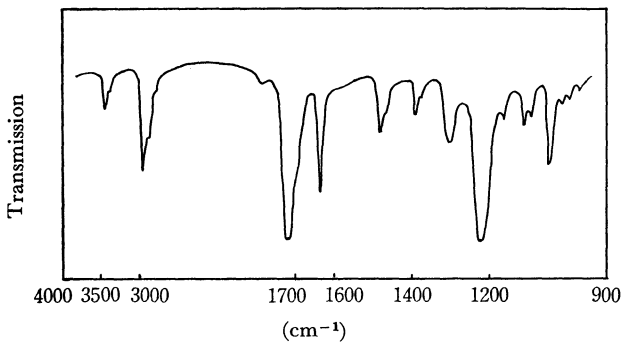


Fig. 1B. Infrared spectrum of II in NaCl.

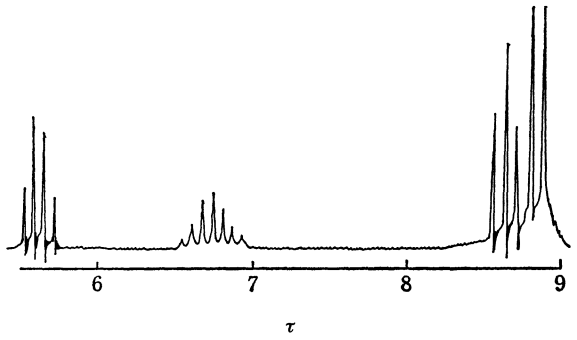


Fig. 2A. NMR spectrum of ethyl 3-methyl-2-oxobutanoate in $CDCl_3$.

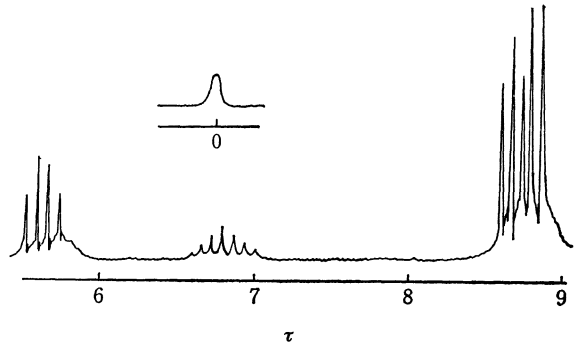


Fig. 2B. NMR spectrum of II in $CDCl_3$.

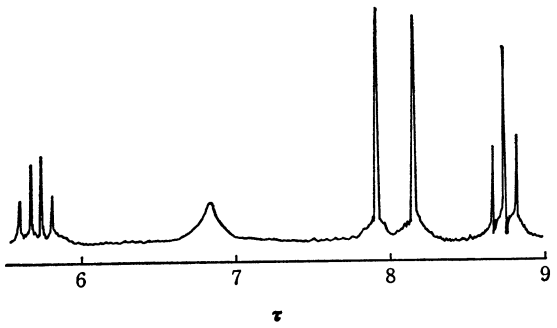
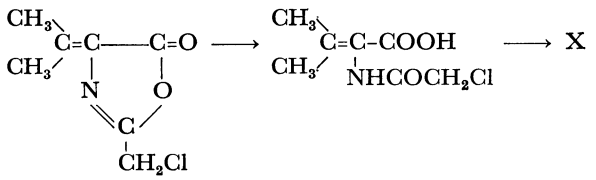


Fig. 2C. NMR spectrum of I in $CDCl_3$.

one imino proton), 5.67 (q, $-C\underline{H}_2CH_3$, 2H), 6.87 (m, methine proton, 1H), 8.65 (t, $-CH_2C\underline{H}_3$, 3H), and 8.80 (d, two $-CH_3$, 6H) as shown in Figs. 2B and 2C. The pattern is essentially the same as that of parent α-keto ester except that, in the latter, no signal lower than 5.0 was observed and the one proton multiplet shifted to τ6.72 (Fig 2A). The NMR spectrum of I showed no signal lower than τ5.0 (Fig 2C).

When enamine (I) was treated with chloroacetyl chloride in aqueous sodium hydrogencarbonate with vigorous stirring at room temperature, ethyl 2-(2-chloroacetamido)-3-methyl-2-butenoate (X) was obtained in a 47% yield, which was also obtained in a 30% yield from II by reaction with chloroacetyl chloride in ether in the presence of triethylamine. The ester (X) was synthesized by the hydrolysis of 2-chloromethyl-4-isopropylideneoxazol-5-one followed by the esterification of the resulting *N*-(chloroacetyl) dehydrovaline, and the acetyl enamine structure (X) was confirmed with NMR spectrum by Kurita *et al.*[9]



When α-imino ester (II) was allowed to stand for a week at room temperature and then redistilled, 2-ethoxycarbonyl-2,5-diisopropylimidazolid-4-one (IX) was obtained in a 79% yield. α-Amino ester (I) was heated in a sealed tube at 180—190°C for 48 hr to give the dioxopiperazine (VII). The structure of X was derived from its elemental and spectroscopic analyses (see Experimental). It has been found that the above three dimerization courses (Schemes 2 and 3) were different. Thus it seems that the interconversion between I and II can not be carried out under the experimental conditions mentioned above, although the conversion of III to IV occurred at room temperature. Attempt to isomerize enamine or imine conversely by alkali was unsuccessful.

Experimental

All boiling and melting points are uncorrected. The IR spectrum was recorded with a Hitachi EPI-S2 Spectrometer. The NMR spectrum was measured with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 100 MHz.

Materials. Triphenylphosphinimine hydrobromide was prepared by the reaction of triphenylphosphine dibromide with ammonia in the presence of triethylamine by the method of Horner and Oediger[10] Mp 240—242°C (decomp.). The acetonitrile used was distilled from phosphorous pentoxide and dried over calcium hydride.

Ethyl 2-Amino-3-methyl-2-butenoate (I). The procedure was modified from the method of Tatsuoka *et al.*[7] A solution of ethyl 3-methyl-2-nitro-2-butenoate (22 g) in ether (150 m*l*) was added drop by drop to aluminum amalgam (from 13 g of aluminum) placed in ether (300 m*l*) with vigorous stirring at room temperature. After a few minutes, the ether began to reflux. During the addition of the above solution, a few drops of water was added at 10-min intervals to maintain refluxing. After addition of the solution was completed, the stirring was continued for 2 hr. The mixture was extracted thoroughly several times with ether. The combined ethereal extract was dried over anhydrous sodium sulfate and then evaporated. Distillation of the residual oil afforded a pale yellow oil (6.9 g, 56%), bp 65—72°C/9 mmHg.

Found: C, 58.51; H, 9.03; N, 9.79%. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78%.

Ethyl 2-Imino-3-methylbutanoate (II). To a solution of triphenylphosphinimine (from triphenylphosphinimine hydrobromide (10.74 g) and sodium hydride (1.3 g)) in acetonitrile (150 m*l*), ethyl 3-methyl-2-oxobutanoate (4 g) was added and heated on a steam bath with stirring. After 30 min, the solution began to reflux. After stirring was continued for more 5—10 min, the solution was allowed to stand at room temperature with stirring and then acetonitrile was evaporated. Dry ether was added to the residual oil and then substance precipitated was filtered off. The ethereal solution was concentrated again, and then the residual oil was extracted with dry petroleum ether three times (each 50 m*l*). After concentrating the solution, the resulting oil was distilled under reduced pressure to afford a pale yellow oil (1.6 g, 40%), bp 65—67°C/15 mmHg.

Found: C, 58.68; H, 9.37; N, 9.56%. Calcd for $C_7H_{13}NO_2$; C, 58.72; H, 9.15; N, 9.78%.

3,6-Diisopropylidene-2,5-piperazinedione (VII). The reaction was carried out using the technique of Fischer for 3,6-dialkyl-2,5-piperazinedione.[11] Compound I (0.5 g) was heated in a sealed tube at 180—190°C for 48 hr. Into the reaction mixture was added a small quantity of ethanol. The crystalline product was collected and recrystallized from ethanol to afford colorless needles (0.14 g, 20.5%), mp 264—265°C (decomp.), undepressed on admixture with the authentic sample.[8]

2-Ethoxycarbonyl-2,5-diisopropylimidazolid-4-one(IX). Compound II (1.2 g) was allowed to stand for a week at room temperature. Distillation under reduced pressure, was unsuccessful. The residual syrup gradually crystallized at room temperature. Redistillation of the crystalline syrup gave a pale yellow oil (0.8 g, 80%), bp 116—117°C/0.07 mmHg (mp 48—49°C). NMR ($CDCl_3$): τ 0.77 (broad s, NH), 5.71 (q, $-C\underline{H}_2CH_3$, 2H), 6.94 (m, methine proton, 1H), 7.22 (m, methine proton, 1H), 8.71 (t, $-CH_2C\underline{H}_3$, 3H), 8.72 (d, two $-CH_3$, 6H), 8.96 (d, $-CH_3$, 3H), 9.26 (d, $-CH_3$, 3H). IR (KBr): 3107, 1750, 1630, 1275, 1200 cm^{-1}.

9) H. Kurita, Y. Chigira, M. Masaki, and M. Ohta, This Bulletin, **41**, 2759 (1968).

10) L. Horner and H. Oediger, *Ann. Chem.*, **627**, 142 (1959).

11) E. Fischer, *Ber.*, **34**, 433 (1901).

Found: C, 59.85; H, 8.21; N, 11.76%. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66%.

Ethyl 2-(2-Chloroacetamido)-3-methyl-2-butenoate (X).

A) From I: Chloroacetyl chloride (0.8 g) was added drop by drop, with vigorous stirring, to I (1 g) suspended in a solution of sodium hydrogencarbonate (0.6 g) in water (15 m*l*) at room temperature. After stirring for 30 min, a crystalline product precipitated. The crystals were collected, washed well with water, and recrystallized from 50% ethanol to afford colorless needles (0.7 g, 47%), mp 117—118°C, undepressed on admixture with the authentic sample.[9] NMR ($CDCl_3$): τ 2.07 (broad s, NH), 5.77 (q, $-C\underline{H}_2CH_3$, 2H), 5.86 (s, $-COCH_2-$, 2H), 7.80 (s, $-CH_3$, 3H), 8.15 (s, $-CH_3$, 3H), 8.72 (t, $-CH_2C\underline{H}_3$, 3H). IR (KBr): 3200, 1720, 1665, 1535 cm^{-1}.

B) From II: A solution of chloroacetyl chloride (0.58 g) in dry ether (30 m*l*) was added drop by drop, with stirring, to a solution of II (0.7 g) in dry ether (30 m*l*) in the presence of triethylamine (0.5 g) in an ice-salt bath. After stirring overnight at room temperature, triethylamine hydrochloride precipitated was filtered off, and then the ethereal solution was concentrated to give residual oil. Heated at 70°C under reduced pressure (2 mmHg), the oil immediately converted into crystals. Recrystallization from di-*n*-butyl ether afforded colorless needles (0.32 g, 30%), mp 118.5—119°C, undepressed on admixture with the sample obtained by procedure *A*.