[Chem. Pharm. Bull. 14(3) 238~243 (1966)]

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35. Akira Takamizawa, Kentaro Hirai, and Shinzaburo Sumimoto : Studies on the Pyrimidine Derivatives and the Related Compounds. XXXVIII.*1 Investigation on 2-Alkoxymethylene-3-ethoxypropionitrile and Ethyl 2-Alkoxymethylene-3-ethoxypropionate.*2

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The reactions of 2-methoxymethylene-3-ethoxypropionitrile (I) and ethyl 2-methoxymethylene-3-ethoxypropionate (Ⅶ) with amidines to give the corresponding aminopyrimidine and pyrimidinol, respectively, have been reported in the previous papers.[1] It was also reported that the acid catalyzed condensations of I and Ⅶ with urea and thiourea derivatives yield tetrahydropyrimidine and thiazine derivatives, respectively.[2~4] Thus, these enol ether nitrile (I) and ester (Ⅶ) are very useful as three carbon sources for the syntheses of various kinds of heterocyclic compounds.

In the previous paper,[5] it has been suggested that I is a mixture of its geometric isomers from the infrared spectroscopic studies. However, the determination of *cis*- and *trans*-isomers has not yet been made completely.

The product prepared from 3-ethoxypropionitrile as cited in the previous paper[5] gives two peaks at the retention times of 9.6 and 11.7 minutes by gas chromatographic analysis (condition a*4). Further, the nuclear magnetic resonance (NMR) spectrum of this product showed two triplet signal peaks (J=0.8 c.p.s.) assigned to methylidyne proton at 3.10 and 3.22 τ, and the relative area was about 1:1.5. Thus, it becomes evident that this product is a mixture containing *cis*- and *trans*-isomers in a ratio of about 1.5:1. This mixture was purified by fractional distillation under reduced pressure. Each fraction was checked by NMR spectroscopy. The fraction of b.$p_{1.0}$ 91.0° (α-compound) showed only one signal for the methylidyne proton at 3.22 τ. Gas chromatography also shows this fraction has only one peak at a retention time of 16.5 minutes (condition b*4). The liquid of lower boiling point was not easily separated from the fraction of higher boiling point. However, after continuous distillation, the fraction of b.$p_{2.0}$ 91.5° (β-compound) which shows only one signal for the methylidyne proton at 3.10 τ was obtained. Gas chromatogram of this fraction also shows one peak at 14.8 minutes (condition b*4). Accordingly, it was recognized that the mixture was completely separated.

NMR studies of acrylonitrile and its derivatives[6] have shown that the signal of the *cis*-proton to the CN group appears at a lower field than that of the *trans*-proton. Therefore, also in the present case, the β-compound showing the signal of the

*1 Part XXXVII : A. Takamizawa, K. Hirai : J. Org. Chem., **30**, 2290 (1965).

*2 Preliminary communication of a part of this report was presented in This Bulletin, **11**, 1212 (1963). A part of this work was delivered at the XVIIIth Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

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*4 Gas chromatography was carried out under the conditions cited in the Experimental part (a, b, and c).

1) A. Takamizawa : Vitamins (Kyoto), **30**, 195 (1964), and the references cited therein.
2) A. Takamizawa, K. Hirai, Y. Sato, K. Tori : J. Org. Chem., **29**, 1740 (1964).
3) A. Takamizawa, K. Hirai : This Bulletin, **12**, 804, 1418 (1964); *Idem* : *Ibid.*, **13**, 681 (1965).
4) *Idem* : J. Org. Chem., **30**, 2290 (1965).
5) A. Takamizawa, K. Ikawa, M. Narisada : Yakugaku Zasshi, **78**, 622 (1958).
6) G. C. Reddy, J. H. Goldstein, C. Mandell : J. Am. Chem. Soc., **83**, 1300 (1961), and the references cited therein.

methylidyne proton at the lower field is believed to have the structure in which the CN group and the proton are at the same side (*trans*-isomer), and accordingly, the α-compound is the *cis*-isomer. This consideration was confirmed by measurements of the dipole moment of these two isomers. The dipole moments observed for the α- and β-compounds are 5.47D and 4.58D, respectively. Thus, the α-compound is evidently the *cis*-isomer, because the dipole moment expected for the *cis*-isomer, is considerably larger than that expected for the *trans*-isomer. The physical constants of these two isomers are listed in Table I.

Table I. Physical Constants of *cis*- and *trans*-2-Methoxymethylene-3-ethoxypropionitrile

Compound	$C_2H_5OCH_2$ \ C / $C\equiv N$ $I\alpha$ *cis* H / C \ OMe	$C_2H_5OCH_2$ \ C / $C\equiv N$ $I\beta$ *trans* MeO / C \ H
b.p. (°C/mm. Hg)	91.0/1.0	91.5/2.0
n_D^{23}	1.4591	1.4478
NMR (τ, in CCl_4)		
$=CH$	3.22 (triplet)	3.10 (triplet)
$=C-CH_2$	6.03 (doublet)	6.13 (doublet)
$=C-OCH_3$	6.12 (singlet)	6.12 (singlet)
J_{CH,CH_2} (c.p.s.)	0.8	0.8
Gas chromatography*4b (min.)	16.5	14.8
Dipole moment (D)	5.47	4.58
IR (Nujol) (cm^{-1}) characteristic	716	808
UV λ_{max}^{EtOH} mμ (log ε)	232 (4.17)	229 (4.12)

Next, the homologue, 2-ethoxymethylene-3-ethoxypropionitrile (II) was also investigated.

$C_2H_5OCH_2CCN$
 ‖
 $CHOCH_3$ I

$C_2H_5OCH_2CCN$
 ‖
 $CHOC_2H_5$ II

$C_2H_5OCH_2CHCN$
 |
 CH
 C_2H_5O OC_2H_5 III

$C_2H_5OCH_2CHCN$
 |
 CH
 C_2H_5O OCH_3 IV

This compound was prepared by the method cited in the previous paper.[5] The product obtained here showed three peaks at the retention times of 9.1, 17.2, and 21.6 minutes by gas chromatographic analysis (condition c*[4]).

Each fraction correspond to the respective peak was obtained by gas chromatographic separation. The fraction showing the peak at the retention time of 9.1 minutes had no conjugated CN band on its infrared (IR) spectrum, and the NMR spectrum exhibited no methylidyne proton. Elemental analysis also verified that this fraction is 2-diethoxymethyl-3-ethoxypropionitrile (III).[1]

The fractions showing the peaks at the retention times of 17.2 minutes (β-compound) and 21.6 minutes (α-compound), respectively, exhibited very similar IR spectra, but they could be distinguished by showing the characteristic bands at 810 and 710 cm^{-1}, respectively. The elemental analyses of these two fractions agreed with the value expected for II. Therefore, it was considered that α-compound and β-compound should be isomers of each other. NMR spectrum of the product before separation showed two triplet at 3.02 and 3.13 τ due to methylidyne protons, but these separated

fractions showed only one peak, respectively. Therefore, it was considered that the fraction showing the methylidyne proton signal at 3.02 τ (β-compound) should be *trans*-isomer and α-compound showing the signal at 3.13 τ should be *cis*-isomer by the reason described above. The result of the dipole moment measurements of these two fractions also supported this assignment. The physical constants of these two isomers are listed in Table II.

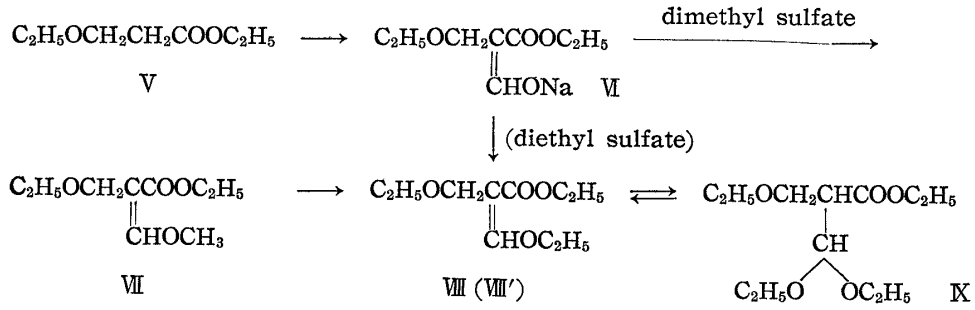
Table II. Physical Constants of *cis*- and *trans*-2-Ethoxymethylene-3-ethoxypropionitrile

Compound	$C_2H_5OCH_2$(C=C(CN)H)OC_2H_5 IIα *cis* Fr-3	$C_2H_5OCH_2$(C=C(CN)OC_2H_5)H IIβ *trans* Fr-2
Gas chromatography*4c (min.)	21.6	17.2
NMR (τ, in CCl_4)		
=CH	3.13 (triplet)	3.02 (triplet)
=C-CH_2	6.12 (doublet)	6.17 (doublet)
J_{CH,CH_2} (c.p.s.)	0.8	0.8
n_D^{23}	1.4570	1.4567
Dipole moment (D)	5.57	5.17
UV λ_{max}^{EtOH} mμ (log ε)	233 (4.17)	230 (4.20)
IR (Nujol) (cm^{-1}) characteristic	710	810
Anal. Calcd. for $C_8H_{13}O_2N$		
C 61.91	61.88	61.38
H 8.44	8.39	8.36
N 9.03	8.99	8.43

Interconversion between IIα and IIβ by standing for a long time at room temperature was not observed.

The conversion of 2-ethoxymethoxymethyl-3-ethoxypropionitrile (IV) into the enol ether nitrile (I) was previously reportred.[7] Acetal III was heated with concentrated sulfuric acid under mild reduced pressure to eliminate ethyl alcohol and the product obtained here was found to be a mixture of IIα and IIβ by gas chromatographic analysis. The NMR spectrum of this product also showed that it was a mixture of IIα and IIβ in a ratio of about 4:5.

To obtain ethyl 2-methoxymethylene-3-ethoxypropionate (VII),[8] 2-sodioformyl compound (VI) derived from ethyl β-ethoxypropionate (V) was methylated with dimethyl sulfate, and the oil of $b.p_5$ 114° was obtained. Gas chromatogram of this oil showed two peaks at the retention times of 17.9 and 21.5 minutes (condition c*[4]). Corresponding



7) A. Takamizawa, K. Ikawa, M. Narisada: Yakugaku Zasshi, **78**, 643 (1958).
8) A. Takamizawa, K. Tokuyama, H. Sato: *Ibid.*, **79**, 664 (1959).

fractions (Ⅶ and Ⅷ) to respective peaks were separately obtained by gas chromatography. These two fractions have conjugated C=O, C=C, and =C-O-C- bands in their IR spectra. UV spectra of these fractions are very similar. These results suggest the presence of conjugated ester groups. By elemental analyses, Ⅷ was found to have one more methylene group than Ⅶ.

These facts suggest that the structure of Ⅷ should be formulated as ethyl 2-ethoxymethylene-3-ethoxypropionate. Then, Ⅵ was ethylated with diethyl sulfate. But this reaction did not proceed easily and after the addition of more diethyl sulfate, acetal Ⅸ and the compound (Ⅷ′) were obtained. Gas chromatographic analysis of these products showed the peaks at 5.0 and 11.5 minutes (condition c*[4]) respectively, and the identity with the separated fraction (Ⅷ) obtained in methylation reaction of Ⅵ was verified by retention time analysis in gas chromatography. It was considered that in the course of reaction the methoxymethylene compound (Ⅶ) formed first would partially suffer from the transetherification by the reaction of ethanol in the reaction mixture to give the ethoxymethylene compound (Ⅷ).

NMR spectrum of Ⅶ showed two methylidyne protons at 2.58 and 2.68 τ in a ratio of about 1:1, which suggests that Ⅶ should be a mixture of *cis*- and *trans*-isomers. However, NMR spectrum of Ⅷ obtained by gas chromatographic separation showed only one methylidyne proton signal at 2.64 τ, which suggests that *cis*- or *trans*-isomer would be exclusively yielded.

On the other hand, the product (Ⅷ′) obtained by ethylation of Ⅵ showed two methylidyne proton signals in its NMR spectrum, but the intensity of the signal at lower field (2.67 τ) was very large compared with that of the signal at higher field (2.75 τ) (the integrated ratio was about 5:1). These facts show that *trans*-isomer was predominantly yielded by ethylation reaction, and the product formed as the result of transetherification of Ⅶ is considered to be the pure *trans*-isomer. Because, it was also known that the *cis*-proton is more deshielded than the *trans*-proton in α,β-unsaturated esters.[9] However, separative detection of *cis*-isomer in gas chromatography failed in various conditions.

The elimination of ethyl alcohol from acetal ester (Ⅸ) was achieved by heating with catalytic amounts of concentrated sulfuric acid. The product obtained showed the peak identical with that of enol ether ester (Ⅷ) in gas chromatogram. NMR spectrum of this product showed single methylidyne proton signal at 2.67 τ. Therefore, this product consists of pure *trans*-2-ethoxymethylene compound.

From these results, it may be assumed that the cyano group which has small steric requirement does not effect the ratio of *cis/trans* enol ether formation, but steric interference of ethoxycarbonyl group produces predominant formation of *trans*-isomer. Further work on this problem is in progress.

Experimental*[5]

Nuclear Magnetic Resonance——Spectra were taken with a Varian A-60 analytical spectrometer system on about 10% solutions in carbon tetrachloride containing about 1% tetramethylsilane as an internal reference. Chemical shifts are expressed in τ-units and coupling constants are in c.p.s. Accuracy limits are about $\pm 0.02\,\tau$ and ± 0.3 c.p.s. Effect of solvents and concentrations in the NMR spectrum of I were ascertained. For example, in pyridine or in pure liquid, the positions of two signal peaks for the methylidyne protons of each isomer are almost coincided.

*[5] Boiling points are uncorrected.

9) T. Hayashi, I. Hori, H. Baba, H. Midorikawa: J. Org. Chem., **30**, 695 (1965), and the references cited therein.

Gas Chromatographic Analysis——It was carried out under the following conditions: Apparatus, Shimadzu GC-1B. a)*6 Column, 4 mm.×1.5 m; 0.75% neopentyl glycol succinate on Anackrom A; column temp., 106°; N_2 23 ml./min. b) Column, 6 mm.×3 m.; 5% KF-54[10] on Chromosorb W; column temp., 120.5°; H_2 100 ml./min. c) Column, 6 mm.×3 m.; 5% diethylene glycol succinate on Chromosorb W; column temp., 160°; He 100 ml./min.

***cis*- and *trans*-2-Methoxymethylene-3-ethoxypropionitrile (Iα and Iβ)**——I was prepared by the same procedure as described previously,[5] and the product, b.p_2 87~105°(15 g.), NMR: =CH; 3.10, 3.22 τ (triplet, J=0.8 c.p.s.) with relative area of 1:1.5, was fractionated through the distilling column packed with a stainless nets, and the purity of each fraction was checked by gas chromatography and NMR spectroscopy. *cis*-2-Methoxymethylene-3-ethoxypropionitrile (Iα) was obtained as the fraction, b.$p_{1.0}$ 91.0°(3.2 g.). *trans*-2-Methoxymethylene-3-ethoxypropionitrile (Iβ) was obtained as the fraction, b.$p_{2.0}$ 91.5°(1.2 g.). The physical constants of these two isomers are listed in Table I.

2-Diethoxymethyl-3-ethoxypropionitrile (III) and *cis*- and *trans*-2-Ethoxymethylene-3-ethoxypropionitrile (IIα and IIβ)——The product obtained by formylation of β-ethoxypropionitrile with subsequent ethylation,[5] b.$p_{2.0}$ 108~114°, showed three peaks at the retention times of 9.1, 17.2 and 21.6 min. in gas chromatogram (condition c*4). This product was subjected to gas chromatographic separation under the following conditions. Apparatus, Yanagimoto GCG-3D; Column, 14 mm.×5 m.; 5% diethylene glycol succinate on Chromosorb W (30~60 mesh; washed with conc. HCl and siliconized); Column temp., 170°, Injection temp., 230~235°; He 200 ml./min. The product (3.363 g.) was injected onto the column (0.1 ml.×34 times) and three fractions were separated.

Fraction 1 (0.506 g.) was determined as 2-diethoxymethyl-3-ethoxypropionitrile (III). *Anal.* Calcd. for $C_{10}H_{19}O_3N$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.88; H, 9.50; N, 7.24.

Fraction 2 (0.398 g.) was determined as *trans*-2-ethoxymethylene-3-ethoxypropionitrile (IIβ) and fraction 3 was determined as *cis*-isomer (IIα). The physical constants of two isomers were listed in Table II.

Elimination of Ethyl Alcohol from Acetal Nitrile (III)——One drop of conc. H_2SO_4 was added to III and distilled under the mild reduced pressure (<20 mm. Hg). Colorless oil of b.$p_{20>}$ 52~56°(0.34 g.) was treated with 3,5-dinitrobenzoyl chloride to give 0.11 g. of ethyl 3,5-dinitrobenzoate. Residue was dissolved in ether, washed with dil. K_2CO_3, dried and concentrated. Residual oil was distilled in reduced pressure to give the colorless oil of b.$p_{0.9}$ 70~127°(0.7 g.). This oil showed three peaks at the retention times of 9.7, 17 and 22 min. in gas chromatogram (condition c*4). These three peaks were determined as IV, IIβ, and IIα, respectively, by retention time analysis with the sample obtained above in gas chromatography.

NMR spectrum of the oil of b.$p_{0.9}$ 70~127° showed two methylidyne proton signals at 3.03 and 3.12 τ with the relative area of about 5:4.

Ethyl 2-Methoxymethylene-3-ethoxypropionate (VII) and Ethyl 2-Ethoxymethylene-3-ethoxypropionate (VIII)——a) The oil of b.p_5 114° obtained by the formylation of ethyl β-ethoxypropionate with subsequent methylation with dimethyl sulfate as described in the previous paper[7] showed the gas chromatographic peaks at the retention times of 17.9 and 21.5 min. (condition b*4). This product was subjected to the gas chromatographic separation under the following conditions: Apparatus, Yanagimoto GCG-3D; Column, 14 mm.×6 m.; 5% KF-54 on Chromosorb W (30~60 mesh, siliconized); Column temp., 170°, Injection temp., 230~240°; He 300 ml./min. The product (2.697 g., 0.15 ml.×18 times) was injected onto the column and separately obtained fraction 1 (0.17 g.), fraction 2 (0.99 g.) and fraction 3 (0.80 g.). Fractions 2 and 3 showed single peak at 18.0 and 21.5 min., respectively (condition b*4). Fraction 2, VII, is a colorless oil. n_D^{23} 1.4528. UV λ_{max}^{EtOH} mμ (log ε): 239 (4.07). IR ν_{max} cm^{-1}: 1705 (C=O), 1645 (conj. C=C), 1250 (=C-O-C), 1115 (C-O-C). NMR τ: 2.58, 2.68 (=CH-O-) (1:1 ratio). *Anal.* Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.20; H, 8.72.

Fraction 3, VIII, is colorless oil. n_D^{23} 1.4531. UV λ_{max}^{EtOH} mμ (log ε): 239 (4.10). IR ν_{max} cm^{-1}: 1710 (C=O), 1645 (conj. C=C), 1222 (=C-O-C), 1105 (C-O-C). NMR τ: 2.64 (=CH-O). *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 58.96; H, 9.03.

b) To the suspension of 55.2 g. of sand state sodium in 300 ml. of abs. toluene, 108 g. of abs. EtOH was added dropwise in ice cooling. After stirring at room temperature for 2 hr. the mixture of 180 g. of $HCOOC_2H_5$ and 176 g. of ethyl β-ethoxypropionate was added dropwise in ice cooling. After standing the reaction mixture at room temperature overnight, 400 ml. of abs. toluene was added and stirred at room temperature for 6 hr. Diethyl sulfate 367 g. was added dropwise in ice cooling, the reaction mixture allowed to stand in an ice bath overnight, stirred for 2 hr. at room temperature and for 4 hr. at 50°. Fifty five gram of diethyl sulfate was added and stirred for 3 hr. at 50°. The reaction mixture washed with H_2O, the organic layer was dried over anhyd. $MgSO_4$ and concentrated. The residual oil was distilled in reduced pressure to give 65.5 g. of IX and 47 g. of the oil of b.p_4 115~122°.

*6 This run was kindly carried out by Dr. N. Ikekawa of Institute of Physical and Chemical Research, to whom the authors are grateful.

10) I. Ishizuka, K. Okuno: Ann. Rept. Shionogi Research Lab., **12**, 122 (1962).

Gas chromatographic peak of the latter was identical with that of Ⅷ obtained above a). NMR τ : 2.75, 2.82 (liquid) (integrated ratio 5:1), 2.67, 2.75 (in CCl_4) (integrated ratio 5:1) (=CH-O-). *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97; O, 31.64. Found : C, 59.21; H, 8.65; O, 31.98.

Elimination of Ethyl Alcohol from IX——One drop of conc. H_2SO_4 was added to 2.0 g. of Ⅸ and distilled under the mild reduced pressure (<30 mm. Hg) to distilled off EtOH. The residue was dissolved in benzene and washed with dil. K_2CO_3. Benzene solution was dried and concentrated to give the oil, which was distilled at $b.p_{0.6}$ 64~78° (0.6 g.). This oil exhibited the peaks at the retention time of 4.3 min. due to Ⅸ and that of 9.2 min. (condition c[*4]), which was found to be identical with that of Ⅷ. NMR τ : 2.67 (=CH-O-).

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Summary

cis- and *trans*-2-Methoxymethylene-3-ethoxypropionitrile and 2-ethoxymethylene compounds are successfully separated and their structures were determined. Corresponding ester derivatives were not able to separate, however, the ratio of *cis/trans*-formation was made clear by elimination of ethyl alcohol from corresponding acetal compounds.

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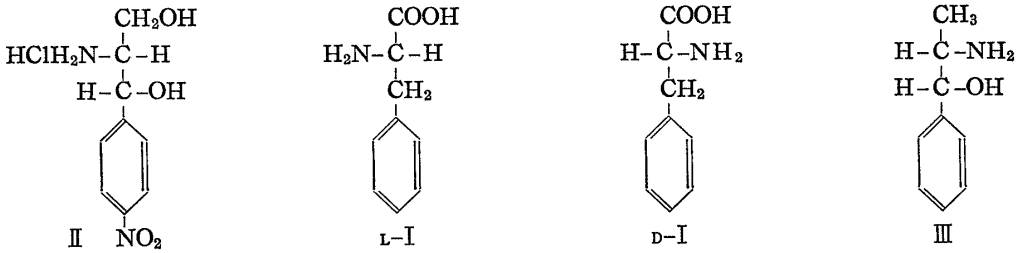
36. Kenji Koga,[*1] Hisayuki Matsuo,[*2] and Shun-ichi Yamada[*1] : Studies on Optically Active Amino Acids. VII.[*3] Stereoselective Synthesis of *l*-Norephedrine Hydrochloride from D-Phenylalanine.[*4]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

In Part Ⅳ[1] of this series, the present authors reported the synthesis of chloramphenicol base hydrochloride (Ⅱ) from L-phenylalanine (L-I), by making use of the comparable configuration at the α-carbon in L-I with the asymmetric center bearing the



Ⅱ L-I D-I Ⅲ

Chart 1.

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[*3] Part Ⅵ : This Bulletin, **13**, 1399 (1965).

[*4] Presented at the 84th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1964.

1) S. Yamada, K. Koga, H. Matsuo : This Bulletin, **11**, 1140 (1963).