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Geometrical Isomerism of Phenylhydrazones of α-Keto Esters. II. *p*-Substituted Phenylhydrazones of Ethyl Pyruvate and 2,4-Dinitrophenylhydrazones of Some α-Keto Esters[1)]

Fumihide Ishibashi,* Takeo Nashima,* Junko Nishino, Ikuko Kobayashi, Yoshinori Ichihara,
Yoshimi Kitagawa, Shigeko Sasaki, Masako Yoshikawa, Atsuko Matsuoka,
and (late) Keiko Yamamoto
Department of Chemistry, Osaka Kyoiku University, Tennoji-ku, Osaka 543
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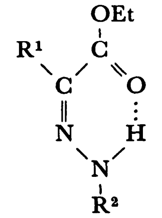
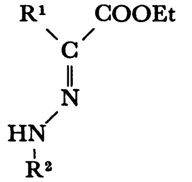
Each geometrical isomer of various substituted phenylhydrazones of ethyl pyruvate and 2,4-dinitrophenylhydrazones of some α-keto esters was isolated in a pure state. Partial isomerizations of the *E*-isomers of the former hydrazones to the *Z*-isomers took place by keeping solutions of the hydrazones in organic solvents containing C, H, and Cl in the dark. An *E*- or *Z*-structure was assigned to each molecule on the basis of IR and ^{1}H NMR spectra. In all cases, isomers with higher R_f-values on a silica gel TLC (using benzene as a developing solvent) involved an intramolecular hydrogen bonding between the imino hydrogen and the ester carbonyl oxygen. Thus, the *Z*-structure was assigned. An *E*-structure was assigned to other isomers with lower R_f-values. The present assignment is, thus, entirely the same as that proposed in a previous investigation.

Previously, we[1)] reported on the isolation of each geometrical isomer of 2,4-dinitrophenylhydrazones (DNPHs) of some pyruvic esters. *E*- and *Z*-configurations were assigned to the isomers on the basis of IR, visible, and ^{1}H NMR spectroscopy, thus correcting Van Duin's[2)] assignment.

This investigation stimulated us to reexamine the geometry of some of the hitherto-known substituted phenylhydrazones of the α-keto esters. With regard to the hydrazones reported in the present paper, their separation into individual isomers and the assignment of an *E*- or *Z*-structure to each of the isomers have scarcely been described in the literature. The reported melting points of the hydrazones, in most cases, are probably those either of a mixture of *E*- and *Z*-isomers, or of the more stable isomer of the two.[3,4)]

In the present work, we report on the preparation of some *p*-substituted phenylhydrazones of ethyl pyruvate and DNPHs of ethyl glyoxylate and ethyl benzoylformate, the fractional isolation of each geometrical isomer of the above hydrazones, and structural assignments of an *E*- or *Z*-configuration, by means of the previously mentioned method.[1)] In addition, the relative stability of each isomer compared to its geometrical counterpart is also discussed.


Z-form


E-form

R¹	R²	R¹	R²
1a=Me,	*p*-$CH_3C_6H_4$	**2a**=Me ,	2,4-$(NO_2)_2C_6H_3$
1b=Me,	C_6H_5	**2b**=H ,	2,4-$(NO_2)_2C_6H_3$
1c=Me,	*p*-ClC_6H_4	**2c**=C_6H_5,	2,4-$(NO_2)_2C_6H_3$
1d=Me,	*p*-$NO_2C_6H_4$		

Experimental

All the melting points are uncorrected. Visible and IR spectra were recorded on a Hitachi Recording Spectrophotometer ESP-3 and a Hitachi-Perkin-Elmer IR-Spectrometer-225, respectively. ^{1}H NMR spectra were recorded on a Hitachi-Perkin-Elmer R-20B operating at 60 MHz.

Geometrical isomers showing higher R_f-values on a silica gel TLC plate using benzene as the developing solvent are called α-isomers, and those with lower R_f-values are called β-ones for all the geometrical isomer pairs of hydrazones,[†] in common, studied in the present investigation.

Preparation of Ethyl 2-(*p*-Tolylhydrazono)propanoate (1a). **1a** was prepared from ethyl pyruvate, *p*-tolylhydrazine hydrochloride and sodium acetate in an aqueous ethanol solution according to the general procedure.

Fractional Isolation of Each Geometrical Isomer of 1a. Crude **1a** (11.0 g), as it was prepared, was treated with petroleum ether and an insoluble precipitate was separated by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel using benzene as an eluting solvent. The α-isomer (1.3 g), obtained from the first eluting fraction, melted at 43.5—43.7 °C after recrystallization from aqueous methanol. The β-isomer was isolated from the second portion of the eluate which was combined with the precipitate obtained above (weight 9.3 g), and melted at 107.7—108 °C after recrystallization from petroleum ether containing a small volume of ethanol.

Partial Isomerization of the β-Isomer of 1a to the α-Isomer. A solution of 13.2 g of the β-isomer of **1a** in 55 ml of trichloroethylene was allowed to stand for 24 h in the dark. After removing the solvent, the residue was chromatographed on silica gel to yield 6.9 g and 5.6 g of the

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[†] An isomer with a smaller retention volume (higher R_f-value) was called an α-isomer by Van Duin[2)] and an A-isomer by Moriwaki et al.[5)] The other isomer was called a β-isomer and a *B*-isomer, respectively.

α- and β-isomers, respectively. Partial isomerizations were also carried out in 1,2-dichloroethane and chloroform.

Preparation of Ethyl 2-(Phenylhydrazono)propanoate (1b) and Ethyl 2-(*p*-Chlorophenylhydrazono)propanoate (1c), Fractional Isolation of Each Geometrical Isomer of the Above Hydrazones, and Partial Isomerization of the β-Isomers of 1b and 1c to the Corresponding α-Isomers.
The above operations were all carried out in essentially the same way as described for **1a**.

Preparation of Ethyl 2-(*p*-Nitrophenylhydrazono)propanoate (1d). **1d** was prepared in a yield of 70% by the reaction of ethyl pyruvate with *p*-nitrophenylhydrazine in 50% acetic acid according to the usual procedure. The product consisted exclusively of the β-isomer.

Table 1. Yields for the Synthesis of **1**

Compd	Yield/%	
	α	β
1a	12	86
1b	15	80
1c	9	81
1d	Trace	70

Table 2. Partial Isomerization of β-Isomers of **1** to the Corresponding α-Isomers

Compd	Conditions			Ratio
	Solvent	Dark/Light	Hour	α : β
1a	$CHCl_3$	In the dark	24	1 : 1.2[b]
	$CHCl_3 : C_6H_6$[a]	In the dark	72	1 : 6
	$CHBr_3$	In the dark	36	1 : 5
	$CH_2Cl\text{-}CH_2Cl$	In the dark	24	1 : 0.6
	$CHCl{=}CCl_2$	In the dark	24	1 : 0.5
	$CHCl_3$	Sunlight	3	1 : 2.6[b]
	$CHCl{=}CCl_2$	Sunlight	3	1 : 1.3[b]
1b	$CHCl_3$	In the dark	2	1 : 0.4
	$CHCl_3 : C_6H_6$[a]	In the dark	72	No isomerization
	$CHBr_3$	In the dark	48	1 : 9
	$CH_2Cl\text{-}CH_2Cl$	In the dark	48	1 : 0.9
	$CHCl{=}CCl_2$	In the dark	36	1 : 1.4
	$CHCl_3$	Sunlight	2	1 : 1.8[b]
	$CHCl{=}CCl_2$	Sunlight	3	1 : 2.3[b]
1c	$CHCl_3$	In the dark	24	1 : 1.4
	$CHCl_3 : C_6H_6$[a]	In the dark	72	1 : 0.4
	$CHBr_3$	In the dark	48	1 : 3
	$CH_2Cl\text{-}CH_2Cl$	In the dark	72	1 : 1
	$CHCl{=}CCl_2$	In the dark	48	1 : 4
	$CHCl_3$	Sunlight	2	1 : 2.5[b]
	$CHCl{=}CCl_2$	Sunlight	2	1 : 1.7[b]
1d	$CHCl_3$	In the dark	72	No isomerization
	$CHBr_3$	In the dark	48	1 : 6
	$CH_2Cl\text{-}CH_2Cl$	In the dark	72	No isomerization
	$CHCl{=}CCl_2$	In the dark	72	No isomerization
	$CHCl_3$	Sunlight	36	1 : 1
	$CHCl_3 : C_6H_6$[a]	Sunlight	48	1 : 4
	$CHBr_3$	Sunlight	6	1 : 1
	$CH_2Cl\text{-}CH_2Cl$	Sunlight	24	1 : 0.5
	$CHCl{=}CCl_2$	Sunlight	48	1 : 0.7

a) Chloroform : benzene = 1 : 9 (v/v). b) Significant degradation occurred.

Partial Isomerization of the β-Isomer of 1d to the Corresponding α-Isomer. A solution of the β-isomer of **1d** in 1,2-dichloroethane was irradiated with sunlight for 24 h to yield a mixture of the isomers in an α to β ratio of 1:0.4.

Yields of the α- and β-isomers of **1** in the syntheses and results of partial isomerization of the β-isomers of **1** to the α-ones are summarized in Tables 1 and 2, respectively.

Preparation of Ethyl 2-(2,4-Dinitrophenylhydrazono)acetate (2b). **2b** was synthesized according to the method described by Copé et al.[3] After a separation of the crude product into the α- and β-isomers by means of chromatography, the ratio of the yields of the α-isomer to the β-one was ca. 3:1.

Preparation of Ethyl 2-Phenyl-2-(2,4-dinitrophenylhydrazono)acetate (2c). Ethyl benzoylformate, synthesized by the oxidation of mandelic acid with potassium permanganate and subsequent esterification, was treated with 2,4-dinitrophenylhydrazine either in an ethanol-sulfuric acid solution or in an aqueous hydrochloric acid solution. The ratios of the yield of the α-isomer to that of the β-one were 3.7:1 under the former reaction conditions and 1.8:1 under the latter ones, as determined after chromatographic separation of the crude products.

Results and Discussion

Isolation of Geometrical Isomers. Since each of the *p*-substituted phenylhydrazones (**1a—d**) studied, when formed from the reactants, consisted overwhelmingly of the β-isomer (as seen in Table 1), the corresponding α-isomer was obtained as follows. In the case of **1a**, **1b**, or **1c**, the β-isomer was dissolved in organic solvents consisting of C, H, and halogen such as chloroform, 1,2-dichloroethane, trichloroethylene, bromoform, or chloroform–benzene, and left in the dark at room temperature. At a higher temperature (or with sunlight) the reaction was accompanied by a significant degradation of the hydrazones. A conversion of the β-isomer to α-one occurred so extensively that the isolation of the latter became facile by means of chromatography. It is quite interesting that when a sample of the β-isomer was dissolved in ethanol, benzene, carbon tetrachloride, or tetrachloroethylene and kept in the dark, no appreciable isomerization to the α-isomer was observed.

On the other hand, even if a solution of the β-isomer of **1d** in any one of the above solvents consisting of C, H, and halogen was left in the dark, no appreciable amount of the α-isomer was observed in the resulting equilibrium mixture. However, the irradiation of a 1,2-dichloroethane or trichloroethylene solution of **1d** with sunlight or UV light caused the equilibrium to shift toward the formation of the α-isomer.

In the preparation of **2c**, the ratio of the yield of

Table 3-a. Melting Points, Elementary Analyses, Crystalline Forms, and R_f-Values of *p*-Substituted Phenylhydrazones of Ethyl Pyruvate

Compd	Mp(θ_m/°C)[a]	Analysis(%) Found(Calcd)			Formula	Crystalline form	R_f-value[b]
		C	H	N			
α	43.5— 43.7	65.14	7.41	12.41		Needles	0.87
1a,		(65.43	7.32	12.72)	$C_{12}H_{16}N_2O_2$		
β	107.7—108.0	65.15	7.70	12.66		Needles	0.19
α	31.7— 32.2[c]	64.32	6.61	14.08		Prisms	0.79
1b,		(64.06	6.84	13.58)	$C_{11}H_{14}N_2O_2$		
β	117.9—118.4[d]	64.19	7.08	13.34		Prisms	0.14
α	60.0— 61.0	54.79	5.54	11.45		Needles	0.86
1c,		(54.89	5.44	11.64)	$C_{11}H_{13}N_2O_2Cl$		
β	137.5—138.5	54.89	5.36	11.47		Needles	0.23
α	110.5—110.9	52.34	5.05	16.95		Prisms	0.41
1d,		(52.59	5.22	16.73)	$C_{11}H_{13}N_3O_4$		
β	191.8—192.7	52.68	4.85	16.74		Prisms	0.02

a) Uncorrected. b) TLC on silica gel using benzene as the developing solvent. c) Elguero et al.[6] reported 33—34 °C for the *Z*-isomer. d) Elguero et al.[6] reported 117—118 °C for the *E*-isomer.

Table 3-b. Melting Points, Elementary Analyses, Crystalline Forms, and R_f-Values of DNPHs of α-Keto Acid Ethyl Esters

Compd	Mp(θ_m/°C)[a]	Analysis(%) Found(Calcd)			Formula	Crystalline form	R_f-value[b]
		C	H	N			
α	124.0—124.5[c]	42.27	3.39	19.66		Plates	0.51
2b,		(42.56	3.57	19.85)	$C_{10}H_{10}N_4O_6$		
β	134.0—135.0	42.40	3.44	19.61		Prisms	0.12
α	159.5—160.0[d]	53.80	4.03	15.64		Prisms	0.57
2c,		(53.63	3.94	15.64)	$C_{16}H_{14}N_4O_6$		
β	149.5—150.5	53.66	4.16	15.71		Scales	0.18

a) Uncorrected. b) TLC on silica gel using benzene as the developing solvent. c) Cope et al.[3] reported 125.0—125.5 °C for the sample of an unseparated isomer mixture. d) Stuart et al.[4] reported 151.5—152.0 °C for the sample of an unseparated isomer mixture.

the α-isomer to β-one was larger during a reaction in an ethanol–sulfuric acid solution than in an aqueous hydrochloric acid solution. The observation was similar to that seen in the case of **2a** reported in the previous investigation.[1]

In a solution of **2a**—**c** in methanol, ethanol or chloroform, no interconversion between the α- and β-isomers occurred in the dark.

Melting points, analytical data, crystalline forms and R_f-values for compounds **1** and **2** are listed in Tables 3-a and 3-b, respectively.

Assignment of *E*, *Z*-Structure. Data regarding visible, IR, and ^{1}H NMR spectra for **1** and **2** are listed in Table 4. Several points are seen from the Table. (1) Visible spectra for all the hydrazones, except for **2b**, show absorption maxima for the α-isomers at longer wavelengths than those for the corresponding β-isomers. In the case of **2b**, the absorption maximum for the α-isomer lies at a wavelength that is slightly shorter than that for β-one. (2) The extinction coefficient at the absorption maximum is greater for α-isomers of **1a**, **1b**, **1c**, and **2b** than for the corresponding β-one; the reverse is true for the remaining hydrazones. (3) The ester carbonyl stretching bands in the IR spectra in Nujol mulls appear at smaller wavenumbers for α-isomers of **1b**, **1d**, **2a**, and **2b** than for the corresponding β-ones. This is in agreement with results obtained in the previous study.[1] On the other hand, the reverse is true in the case of **1a**, **1c**, and **2c**. Those observations have not yet been consistently explained. (4) However, the imino stretching bands in Nujol mulls appear at smaller wavenumbers for α-isomers for all the hydrazones studied than those for the corresponding β-ones. (5) Furthermore, the IR spectra in 0.01 M (1 M=1 mol dm^{-3}) carbon tetrachloride solutions for all hydrazones without exception reveal both carbonyl and imino stretching absorptions at smaller wavenumbers for α-isomers than for the corresponding β-ones. The same results are obtained even at dilutions of 10 times. (6) Finally, chemical shifts (in ppm) shown by imino protons in the ^{1}H NMR spectroscopy are larger by about δ 1.9 to 4.4 for α-isomers for all the hydrazones studied than those for the corresponding β-isomers.

From all of the above observations, it can be said

Table 4. Visible, IR, and ^{1}H NMR Spectra for **1** and **2**

Compd		Visible in EtOH		IR						^{1}H NMR δ_{NH}	
				Nujol mull cm^{-1}		0.01 M[a] cm^{-1}		0.001 M[a] cm^{-1}			
		λ_{max} nm	ε $\times 10^{-4}$	ν_{N-H}	$\nu_{C=O}$	ν_{N-H}	$\nu_{C=O}$	ν_{N-H}	$\nu_{C=O}$		
1a,	α(*Z*)	355	1.83	3250	1685	3260	1680	3261	1680	12.1[b]	12.1[c]
	β(*E*)	332	2.16	3260	1674	3359	1705	3360	1704	7.7[b]	9.3[c]
1b,	α(*Z*)	349	1.83	3250	1687	3268	1682[d]	3261	1679	12.1[b,e]	12.1[c]
	β(*E*)	325	2.15	3310	1698	3364	1704[d]	3362	1706	7.7[b,e]	9.5[c]
1c,	α(*Z*)	349	1.97	3270	1690	3256	1678	3261	1681	12.1[b]	12.1[c]
	β(*E*)	329	2.30	3290	1680	3360	1704	3365	1706	9.0[b]	9.5[c]
1d,	α(*Z*)	381	3.13	3250	1684	3260	1687	3261	1687	12.2[b]	12.4[c]
	β(*E*)	373	2.95	3300	1690	—	—	3361[f]	1712[f]	10.3[b]	10.2[c]
2a,	α(*Z*)[g]	360	2.62	3200	1697	3206	1700	3205	1701	14.1[h]	
	β(*E*)[g]	348	2.37	3320	1723	3316	1714	3315	1714	11.1[h]	
2b,	α(*Z*)	349	2.57	3205	1694	3208	1702	3210	1701	14.4[h]	
	β(*E*)	350	2.58	3290	1712	3298	1725	3294	1710	11.4[h]	
2c,	α(*Z*)	389	2.87	3180	1728	3210	1697	3210	1695	13.8[h]	
	β(*E*)	354	2.60	3275	1694	3280	1722	3280	1720	11.3[h]	

a) In CCl_4. b) In CCl_4. c) In MeOH. d) Elguero et al.[6] reported 1675 and 1696 cm^{-1} in $CHCl_3$ solution for *Z*- and *E*-isomer, respectively. e) Elguero et al.[6] reported 14.03 and 7.8 ppm in $CDCl_3$ solution for *Z*- and *E*-isomer, respectively. f) Saturated solution (below 0.001 M). g) Previous data.[1] h) In $CDCl_3$.

that each α-isomer involves an intramolecular hydrogen bonding between the imino hydrogen and the ester carbonyl oxygen. Accordingly, it can be concluded that the *Z*-structure should be assigned to the α-isomer and the *E*-structure to the β-one. This conclusion is the same as that shown in the previous paper.

Recently, using our assignment method, Cracknell et al.[7] reported structural assignments of an *E*- or *Z*-structure to geometrical isomers of phenylhydrazones of benzocyclobutene-1,2-dione.

We also examined the behavior of ^{1}H NMR signals of an imino proton for **1** in a polar solvent such as methanol (**2** was insufficiently soluble in methanol). This was compared with that in a nonpolar solvent such as carbon tetrachloride (Table 4). By changing the solvent from carbon tetrachloride to methanol, the imino proton signal flattened somewhat as a result of an exchange of protons between the hydrazone and the solvent molecule. Also, the signal appeared at a lower magnetic field in methanol than in carbon tetrachloride. It is noted from this comparison that the imino proton signals exhibited almost the same tendency in a methanol solution as in a carbon tetrachloride solution. Thus, in the first place, the imino proton signals of all the *Z*-isomers appeared in either solution at a lower magnetic field than those of the corresponding *E*-isomer. This suggests that an intramolecular hydrogen bonding exists in the *Z*-isomer, but not in the *E*-isomer, even in a polar solvent. Secondly, in the case of *E*-isomers, as the electronegativity of the *p*-substituent in the phenyl group becomes larger, the imino proton signal appears at a lower magnetic field in both solvents. This observation might be rationally interpreted in terms of the normal effect of electronegativity on the chemical shift of a proton.

Stability to Isomerization. Each of the individual geometrical isomers studied in the present investigation did not isomerize as it was kept in a pure state either upon irradiation with UV light or upon heating the sample to cause melting. The latter observation is contrary to that made by Katsuki et al.[8] regarding the behavior of the DNPHs of a few of α-keto acids. Also, during recrystallization from methanol or ethanol in the dark (or under dim light) isomerization took place to such a slight extent that samples were obtained practically in pure states. Only for cases **1a**, **1b**, and **1c** did isomerization take place to an ultimate equilibrium in several organic solvents consisting of C, H, and halogen even in the dark.

References

1) Part I: T. Nashima, F. Ishibashi, M. Iwamoto, Y. Aihara, S. Anzai, and G. Yamano, *Bull. Chem. Soc. Jpn.*, **50**, 539 (1977).

2) H. Van Duin, *Recl. Trav. Chim. Pays-Bas*, **73**, 78 (1954).

3) A. C. Cope and D. L. Ross, *J. Am. Chem. Soc.*, **83**, 3854 (1961).

4) D. B. Stuart and R. M. Herbst, *J. Org. Chem.*, **6**, 867 (1941).

5) T. Moriwaki, H. Katsuki, and S. Tanaka, *Nippon Kagaku Zasshi*, **76**, 1367 (1955).

6) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, **1966**, 2981.

7) M. E. Cracknell, M. C. Goodland, and J. F. W. McOmie, *Bull. Chem. Soc. Jpn.*, **56**, 965 (1983).

8) H. Katsuki, C. Tanegashima, M. Tokushige, and S. Tanaka, *Bull. Chem. Soc. Jpn.*, **45**, 813 (1972).