PHENYLHYDRAZONES OF α-KETO ACIDS, CONTAINING THE ISOXAZOLINE RING, AND THEIR ANOMALOUS BEHAVIOR IN THE FEOFILAKTOV REACTION

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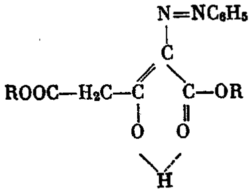
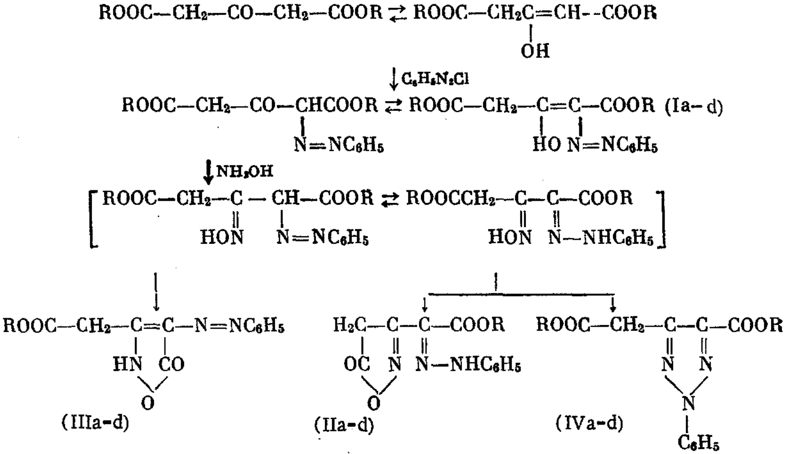
The Feofilaktov reduction of the arylhydrazones of α-keto acids is a convenient method for the synthesis of the simple α-amino acids, but its application to the synthesis of polyfunctional amino acids has received little study [1]. The preparation of β-hydroxyglutamic acid by the catalytic hydrogenation of phenylazoacetonedicarboxylic ester is known [2]. Glutamic acid derivatives with functional groups in the β-position are interesting as taste intensifiers [3]. Consequently, an attempt was made to synthesize α,β-diaminoglutaric acid from the phenylazoacetonedicarboxylic acid esters (Ia-d) via the oxime (Scheme 1).

The oximation gave two series of compounds: (IIa-d) and (IIIa-d), which belong to the substituted 5-isoxazolinones, and (IVb-d), compounds that belong to the triazole series. Their structure was proved, and a study was made of their reduction and also of some of their other properties (Table 1).

Structure of Obtained Compounds. In the starting esters (Ia, b) the keto-enol equilibrium is shifted toward the "azoenol" form, which is confirmed by their IR, UV, and NMR spectra. The IR spectrum of (Ib) in CCl_4 has the absorption band of the hydroxyl around 3300 cm^{-1}, in which connection the character of the absorption does not change when the solution is diluted from 0.2 to 0.01 M, which indicates the presence of an intramolecular hydrogen bond





$R = CH_3$ (a), C_2H_5 (b), $CH(CH_3)_2$ (c), $CH_2C_6H_5$ (d)

Scheme 1

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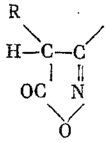
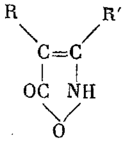
TABLE 1. Reaction Products of (Ia-d) with Hydroxylamine

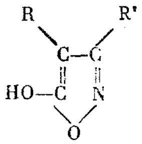
Compound	Found, %			Empirical formula	Calculated, %		
	C	H	N		C	H	N
(Ia)	56,44	5,01	10,12	$C_{13}H_{14}N_2O_5$	56,12	5,03	10,07
(IIa)	55,14	4,16	16,14	$C_{12}H_{11}N_3O_4$	55,17	4,22	16,09
(IIb)	56,73	4,65	15,27	$C_{13}H_{13}N_3O_4$	56,73	4,73	15,27
(IId)	63,50	4,34	12,40	$C_{18}H_{15}N_3O_4$	64,09	4,45	12,46
(IIIa)	55,53	4,31	16,37	$C_{12}H_{11}N_3O_4$	55,17	4,22	16,09
(IIIb)	56,63	4,74	15,37	$C_{13}H_{13}N_3O_4$	56,73	4,73	15,27
(IIIc)	57,89	5,38	14,22	$C_{14}H_{15}N_3O_4$	58,13	5,19	14,53
(IVc)	61,93	6,21	13,19	$C_{17}H_{21}N_3O_4$	61,63	6,35	12,69

The signal of an enol proton is present in the NMR spectrum (Table 2). The UV spectra of (Ia, b), which have λ_{max} 242-243 and 360 nm, are typical for compounds with an azo structure [4]. Compound (Ia) was isolated in two crystalline forms, which differ in color, solubility, and melting point; apparently they are geometrical isomers [5] (see Experimental part).

The reaction of compounds (Ia-d) with NH_2OH can proceed in an ambiguous manner: with the formation of the oxime as the intermediate product, the cyclization of which should give either the 3- or the 3,4-substituted 5-isoxazolinones [6, 7], or with the formation of hydroxamic acids and their conversion to two series of 3-isoxazolinones [8]. It is also known that the 5-isoxazolinones, depending on the solvent and the substituents in the ring, can exist in three tautomeric forms [7, 9].


(CH)


(NH)


(OH)

In addition, a transition of the azo group of the starting compounds to the hydrazone group could be expected [10].

The chief reaction products, the two series of isomeric 5-isoxazolinones (IIa, b, d) and (IIIa, b, c), and also (IVc), belong to the triazole series (see Scheme 1). The structure of the obtained compounds was confirmed by the UV, IR, and NMR spectra. The UV spectra of (IIIa-c), respectively with λ_{max} 378, 400, and 396 nm, are characteristic for compounds that have an azo structure. The UV absorption of (IIa, b, d), with λ_{max} 277-280 nm, indicates their hydrazone structure [4]. The IR spectra of the (III) compounds have an absorption band in the 3200-3225 cm^{-1} region, which is characteristic for the NH group; this band is absent in the (II) compounds.

The NMR spectra (see Table 2) have the signals of the protons of the ester, $>CH_2$ and phenyl groups. The signal of the proton of the $>CH-N=NC_6H_5$ group is absent for (IIIa-c), which indicates the different structure of the isoxazoline ring of (II) and (III). In addition, the signals of the protons of the phenyl ring in the compounds, which contain the azo and the hydrazone group, are different.

As a result, the (II) compounds have the structure of 5-isoxazolines with a 3-substituted ring in the CH form and a hydrazone structure of the substituent. The (III) compounds are 3,4-disubstituted

TABLE 2. NMR Spectra (δ, ppm) in CF_3COOH*

Group	(Ia)	(Ib)	(IIa)	(IIb)	(IIb)	(IId)	(IIIa)	(IIIb)	(IIIc)	(IV)	(V)	(VI)
CH_2	3,80	3,76	3,97	4,17	4,00	3,90	3,75	3,73	3,70	3,9	3,7	4,0
C_6H_6	7,17	7,33	7,20m 7,63m	7,60m 8,16m	7,25m 7,68m	7,12m 7,56m	7,15	7,20	7,15	7,03m 7,43m	6,95m 7,6m	— —
OH	13,27	12,84	—	—	—	—	—	—	—	—	—	—
Others	—	—	—	6,4 м- =N—NH	—	—	—	—	—	—	—	1,0—2,0m (11H)

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*The chemical shifts of the ester groups are not given; m = multiplet; the other signals are singlets. Compound (Ib) in CCl_4, and (IIb) in D_3CCOCD_3. Compounds (IVa), (V), and (VI) were taken relative to TMS (external standard), while the others were taken relative to TMDS (internal standard).

TABLE 3. Yields and Ratios of Reaction Products

Starting compound	Yield of reaction products, %			
	total	(II)	(III)	(IV)
(Ia)	94,5 *	85	9,5	—
(Ib)	80†	57,5	22,5	Traces
(Ic)	69†	Traces	45	24
(Id)	7†	7	—	Traces

*When based on (Ia).

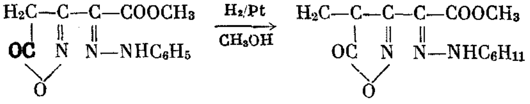
†When based on the acetonedicarboxylic acid ester.

5-isoxazolinones with a ring in the NH form, in which connection the substituent in the 4 position has an azo structure. Geometrical isomerism is apparently possible for the (III) compounds [see Experimental part, (IIIa)]. The structure of the (IV) compounds is discussed below. Both the yields and the ratio of products (II), (III), and (IV) depend on the structure of the radical in the ester groups (Table 3).

Properties of (II) and (III) Compounds. A characteristic of the obtained 5-isoxazolinones is their resistance toward reduction; the (II) compounds remain unchanged when treated with Zn/CH_3COOH, $NaBH_4$, or $LiAlH_4$. Compound (IIa) is converted to the triazole ester (IVa) under the conditions of the Feofilaktov reaction (Zn and an alcohol solution of HCl gas), from which the dibasic acid (V) is obtained by hydrolysis. The same acid is formed by refluxing (IIa, b) with either aqueous acid or alkali solutions, and also by the acid hydrolysis of (IVc), which is obtained directly by the reaction of (Ic) with hydroxylamine.

A conjugated system of bonds, characteristic for the hydrazone structure of (II), is retained in the triazole derivatives (IV) and (V), which finds its reflection in the similarity of the UV, IR, and NMR spectra of (IV) and (V) with those of (II).

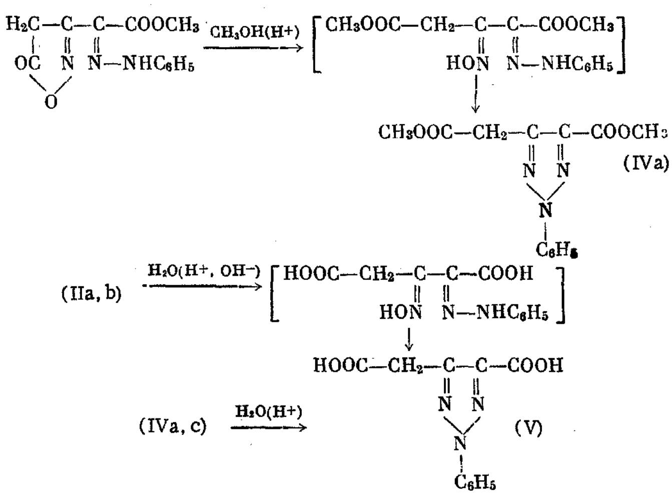
The catalytic hydrogenation of (IIa) and (IIb) (skeletal Ni, 80 atm, 80°C, alcohol) fails to lead to the expected cleavage of aniline and an opening of the isoxazoline ring [2]. The molecule is destroyed under more drastic conditions; we were able to detect trace amounts of the diaminoglutaric acid. Only the phenyl ring is hydrogenated in neutral medium in the presence of platinum (see Tables 2-4)



(IIa) (VI)

The acid properties of the (II) compounds are due to the lability of the protons of the CH_2 group, which was shown by the deuterium exchange method (NMR). The pK_a values of (IIa, b) differ somewhat from the literature data, as can be seen from Table 5, for the 4-unsubstituted 5-isoxazolinones. The difference is caused by the effect of the conjugated system of double bonds in (IIa, b), when compared with the effect of Br in the 4 position of the isoxazolinone ring [7].

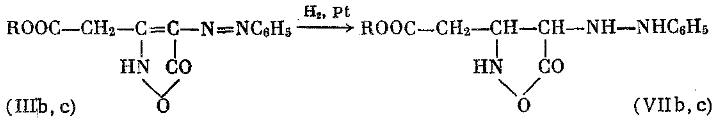
The properties of the 3, 4-substituted isoxazolinones (III) differ from the properties of the 3-substituted (II). Thus, triazole derivatives are not formed when the (III) compounds are treated with alcoholic HCl solution. In the presence of Pt all of the double bonds in (IIIb, c) are hydrogenated, but again the cleavage of aniline and an opening of the isoxazolinone ring fail to occur



Scheme 2

TABLE 4. Transformation Products of (II) and (III)

Compound	Found, %			Empirical formula	Calculated, %		
	C	H	N		C	H	N
(V)	52,89	3,69	16,62	$C_{11}H_9N_3O_4$	53,44	3,64	17,00
(IVa)	56,65	4,82	15,37	$C_{13}H_{13}N_3O_4$	56,73	4,73	15,27
(VI)	53,88	6,08	15,74	$C_{12}H_{17}N_3O_4$	53,93	6,37	15,73
(VIIb)	55,90	6,06	15,03	$C_{13}H_{17}N_3O_4$	55,91	6,09	15,05
(VIIc)	57,43	6,88	14,03	$C_{14}H_{19}N_3O_4$	57,31	6,49	14,33



$R = C_2H_5$(b), i-C_3H_7(c).

Scheme 2. (Continued)

The structure of (VIIb, c) was confirmed by the NMR spectra. In harmony with the structure characteristics, the (III) compounds are weaker acids than the (II) compounds (see Table 5).

EXPERIMENTAL

The acetonedicarboxylic acid (ACDA) esters were obtained as described in [11]. The IR spectra were taken as Nujol mulls on a Hitachi EPI-S2 spectrometer, the UV spectra were taken in absolute alcohol (Hitachi EPS-3), and the NMR spectra were taken on a Hitachi–Perkin–Elmer R-12 spectrometer at 60 MHz; the pKa were determined potentiometrically. The TLC was run on DSF-5 silica gel (Schuchardt) and Silufol UV-254 (Kavalir). For the column chromatography we used either DS-O (15 μ) (Schuchardt) or KSK silica gel.

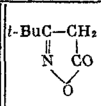
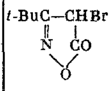
Dimethyl Ester of Phenylazoacetonedicarboxylic Acid (Ia). The coupling of 9.0 g of the methyl ester of acetonedicarboxylic acid (ACDA) with phenyldiazonium chloride gave 12.3 g of the crystalline phenylazo derivative with mp 88-90° (from methanol). Extraction of the mother liquor with ether gave an additional 0.7 g of product with mp 92-96°, from which two crystalline forms of the product were isolated: lemon yellow crystals with mp 88-90°, which were less soluble in methanol, and yellow crystals with mp 85-87°, which were more soluble in methanol. The mixed melting point was 92-95°. The compounds have the same elemental composition, and the same UV, IR, and NMR spectra. Infrared spectrum (ν, cm^{-1}): 3150 m, 1725 s, 1690-1675 s, 1600 m, 1525 s. Ultraviolet spectrum: λ_{max} 243 nm (ε 15,000), 3600 nm (ε 25,000).

Diethyl, Diisopropyl, and Dibenzyl Esters of Phenylazoacetonedicarboxylic Acid (Ib, c, d). The coupling of the appropriate ACDA ester with phenyldiazonium chloride gave the (Ib, c, d) directly, which were used in the crude form for the subsequent transformations.

Crystalline (Ib) had mp 45-47° (cf. 48.5° [5]; 61-64° [2]). Infrared spectrum (ν, cm^{-1}): 3150 m, 1725 s, 1690-1670 s, 1600 m, 1525 s. Ultraviolet spectrum: λ_{max} 242 nm (ε 15,900), 360 nm (ε 24,800).

Reaction of (Ia) with Hydroxylamine. A methanol solution of NH_2OH composed of 1.875 g of $NH_2OH \cdot HCl$ and an equivalent amount of KOH was mixed with 5 g of (Ia), and the mixture was either refluxed for

TABLE 5. Acid Properties

Compound	pK_a	Equiv. wt. Found/Calculated	Compound	pK_a	Equiv. wt. Found/Calculated
(IIa)	3,8	267/261	 t-BuC—CH₂ N CO O	5,25±0,02	129/141
(IIb)	3,9	270/275			
(VI)	3,7	266/267	 t-BuC—CHBr N CO O	3,17±0,02	242/220
(V)	3,2; 4,6	123/123,5			
(IIIb)	6,6	281/275			

2 h or let stand at 20° for 2 days (a purer product is obtained in the latter case). The methanol was distilled off to give 4.54 g (96.5%) of a mixture of (IIa) and (IIIa). The mixture was dissolved in chloroform, transferred to a column of silica gel, which was filled by the wet method in chloroform, and eluted with a $CHCl_3-CH_3COOH$ (99 : 1) mixture. Two fractions were collected: I was collected visually as two very close yellow bands, while II was collected as a colorless band that was checked by TLC. The eluate that had a sky-blue fluorescence in UV light was collected. The solvent was evaporated, and the compound was dried in vacuo at 50°.

Fraction I represented 0.45 g (9.5%) of (IIIa), which was obtained as yellow needles with mp 134-141° (from MeOH). Infrared spectrum (ν, cm^{-1}): 3225 m, 1750-1660 b (max 1720 s), 1605 m, 1575-1520 s. Ultraviolet spectrum: λ_{max} 249 nm (ε 12,000), 378 nm (ε 23,700). On rechromatographing we isolated a compound with mp 138-141° (first yellow band), which has the same elemental composition, and identical IR and NMR spectra. Fraction II represented 4.00 g (85%) of (IIa), which was obtained as colorless plates with mp 148-149° (from either C_6H_6 or $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1750-1655 (max 1725, 1715 s), 1600 m, 1530 s. Ultraviolet spectrum: λ_{max} 277 nm (ε 20,000). Deuterium exchange: (IIa) in D_2O /NaOD solution exchanges both protons of the CH_2 group. NMR spectrum*: singlet at 3.28 ppm, which disappears completely in 1 h.

Reaction of (Ib) with Hydroxylamine. Compound (Ib), obtained from 13.2 g of the diethyl ester of ACDA, was treated with a solution of 0.097 M of NH_2OH in ethanol. The reaction and separation of the products were run the same as in the case of (IIa) and (IIIa). Fraction I represented 4.04 g (22.5%) of (IIIb), which was obtained as yellow needles with mp 104-106° (from ethanol). Infrared spectrum (ν, cm^{-1}): 3225 m, 1735 s, 1690 sh, m, 1605 m, 1585-1535 s. Ultraviolet spectrum: λ_{max} 249 nm (ε 10,600), 400 nm (ε 26,500). Fraction II represented 10.31 g (57.5%) of (IIb), which was obtained as colorless needles with mp 140-141° (from either C_6H_6 or $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1760-1640 b (max 1740, 1700 s), 1595 m, 1515 m. Ultraviolet spectrum: λ_{max} 280 nm (ε 20,100). Traces of (IVb) were detected by TLC.

Reaction of (Ic) with Hydroxylamine. The starting diisopropyl ester of ACDA had bp 154-154.5° (16 mm); n_D^{25} 1.4330. Compound (Ic), obtained from 13.5 g of the ester, was treated with 0.06 M of NH_2OH in isopropanol. After distilling off the alcohol the residue was diluted with a double amount of ether and cooled. We isolated 2.7 g (21.5%) of (IIIc) as yellow scales, mp 119-120° (from isopropanol). The mother liquor was separated on a silica gel column. Fraction I represented 3 g (24%) of (IIIc). Infrared spectrum (ν, cm^{-1}): 3200 m, 1720 s, 1605 m, 1570-1530 s. Ultraviolet spectrum: λ_{max} 249 nm (ε 9800), 396 nm (ε 19,000). Fraction II represented 3 g (24%) of (IVc), which was obtained as colorless plates with mp 102-104° (from C_6H_6). Infrared spectrum (ν, cm^{-1}): 1740-1650 b (max 1735, 1715 s), 1605 m, 1515 m. Traces of (IIc) were detected by TLC.

Reaction of (Id) with Hydroxylamine. In a similar manner, from 10 g of the dibenzyl ester of ACDA was obtained 0.7 g of (IId), mp 139-141° (from CCl_4). Infrared spectrum (ν, cm^{-1}): 1670-1730 b (max 1710, 1725 sh, s), 1600 m, 1530 m. Ultraviolet spectrum: λ_{max} 278 nm (ε 19,000). Compound (IIId) was not detected by TLC, while traces of (IVd) were detected.

Reaction of (IIa) with Methanolic HCl Solution. Compound (IIa) (0.5 g) was allowed to stand for 3 days in methanolic HCl solution at 20° (or it was refluxed for 1 h). The product was dissolved in chloroform and separated on a silica gel column as described above. Two fractions of the eluate were collected, each of which has one fluorescent spot under UV light (TLC). Fraction I represented 0.17 g of (IVa), mp 103-105° (from methanol). Infrared spectrum (ν, cm^{-1}): 1740-1670 b (max 1740, 1715 s), 1590 m, 1525 m. Ultraviolet spectrum: λ_{max} 276 nm (ε 20,200). Fraction II represented 0.25 g of the starting (IIa).

Hydrolysis of (IIa, b) and (IVa, c). A mixture of 0.5 g of (IIa) and 10% HCl solution was refluxed for 2 h and then evaporated. We obtained (IV) in quantitative yield, mp 245-246° (from water). Ultraviolet spectrum: λ_{max} 277 nm (ε 20,300). Compound (V) was obtained in a similar manner by the hydrolysis of (IIb), (IVa), and (IVc). A mixture of 0.5 g of (IIa) and 10% NaOH solution was refluxed for 2 h, the mixture was acidified, and the precipitate was filtered and washed with ice water. The yield of (V) was 0.32 g.

Hydrogenation of (IIa). A solution of 0.5 g of (IIa) in 20 ml of methanol was hydrogenated in the presence of 0.08 g of PtO_2 for 4 days (40 atm, 20-25°). The clear colorless solution, devoid of the starting (IIa) (TLC), was decanted, evaporated, and the residue was diluted with benzene and cooled. We obtained

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*Tetramethylsilane was used as the external standard.

0.2 g of (VI), mp 63-66°. Infrared spectrum (ν, cm^{-1}): 2800-2650 m, 1730-1670 (max 1705 s), 1605 m, 1535 m. Ultraviolet spectrum: λ_{max} 238 nm (ε 9200).

Hydrogenation of (IIIb) and (IIIc). A solution of 0.65 g of (IIIb) in 20 ml of ethanol was hydrogenated for 3 days in the presence of 0.08 g of PtO_2 (30 atm, 20-25°). The mixture was treated with 30 ml of ethanol, heated up to the boil, the catalyst was filtered, and the filtrate was evaporated. We obtained 0.5 g of crude (VIIb). A double recrystallization from ethanol gave 0.26 g of (VIIb) with mp 171-173°. Infrared spectrum (ν, cm^{-1}): 3100-2500 s (diffuse), 1725 s, 1605 s, 1585-1560 s. NMR spectrum* (δ, ppm): 0.99 (triplet, $J_{CH_3-CH_2}$ = 7.0 Hz, CH_3); 2.98 (doublet, J_{CH_2-CH} = 6.0 Hz, CH_2); 4.02 (quadruplet, $J_{CH_2-CH_3}$ = 7.0 Hz, CH_2); 4.75 (multiplet, CH); 7.02 (singlet, C_6H_5); 7.2 (multiplet, 4H). Ultraviolet spectrum: λ_{max} 220 nm (ε 9800), 296 nm (ε 11,000), 327 nm (ε 20,000).

A solution of 0.5 g of (IIIc) in 20 ml of isopropanol was hydrogenated for 5 h in the presence of 0.08 g of PtO (50 atm, 50°). After the above described treatment we obtained 0.23 g of (VIIc), mp 166-167° (from isopropanol). Infrared spectrum (ν, cm^{-1}): 3150-2600 s (diffuse), 1725 s, 1605 s, 1560-1550 s. NMR spectrum (δ, ppm): 0.98 (doublet, J_{CH_3-CH} = 6.2 Hz, $2CH_3$); 2.96 (doublet, J_{CH_2-CH} = 6.0 Hz, CH_2); 4.73 (multiplet, 2H); 6.94 (singlet, C_6H_5); 7.2 (multiplet, 4H).

CONCLUSIONS

1. The reaction of the esters of phenylazoacetonedicarboxylic acid with hydroxylamine gave three products in ratios that depended on the structure of the radical of the ester group: the esters of the phenylhydrazone of 2-isoxazolin-5-on-3-ylglyoxylic acid (IIa), the esters of 4-phenylazo-3-isoxazolin-5-on-3-ylacetic acid (III), and 2-phenyl-4-carbalkoxymethyl-5-carbalkoxytriazoles (IV).

2. The phenylhydrazones (II) and phenylazo compounds (III), which contain an isoxazoline ring, are resistant to chemical reduction in neutral medium; aniline is not cleaved and the isoxazoline ring is not opened during catalytic hydrogenation.

3. The phenylazoacetonedicarboxylic acid esters have an azoenol structure.

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*The NMR spectrum was taken in CF_3COOH, using HMDS as internal standard.