SYNTHESIS AND CYCLIZATION DIRECTION OF 2-DIAZOMALONDIAMIDE DERIVATIVES NEW REARRANGEMENT OF 5-HYDROXY-1,2,3-TRIAZOLE-4-CARBOXAMIDES

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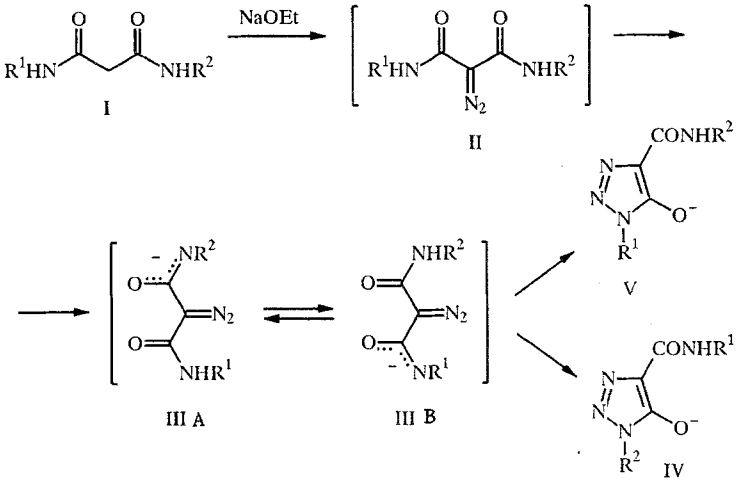
The thermal behavior of 5-hydroxy-1,2,3-triazole-4-carboxamides obtained on acidification of solutionns of triazol-5-olates has been investigated. A new rearrangement has been discovered in the 1,2,3-triazole series and the qualitative effect of the substituents in the initial triazole and of temperature have been clarified.

We showed previously that the reaction of malonic acid amides (I) with benzenesulfonyl azide (BSA) in the presence of sodium ethylate leads to the formation of highly reactive and unstable diazoimidolates (IIIA, B) which cyclize to 1,2,3-triazol-5-olates (IV) [1]. Cyclization of compounds (IIIA, B) occurs with the participation of the carboxamide group containing a substituent with higher electron-accepting properties (scheme 1).

Scheme 1



Isomer (IV) is formed if R^2 exceeds R^1 in electron-accepting properties (R^2 = Ar, R^1 = H, Alk) and a mixture of isomers (IV) and (V) is formed if R^1 and R^2 are close to one another in electronic properties.

It is suggested that the cyclization of diazo compound (II) in neutral media will occur by another mechanism and expand the synthetic possibilities of obtaining new derivatives of 5-hydroxy-1,2,3-triazoles, the 2-aza-analogues of the aglycone of the antibiotic bredenin, among the derivatives of which are found substances possessing high antitumor activity [2].

The present work is devoted to the development of methods of synthesis and to an investigation of the direction of cyclization of derivatives of 2-diazomalondiamide (II).

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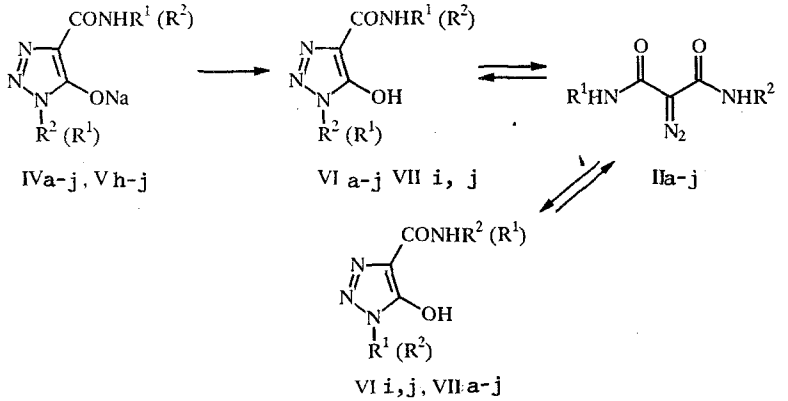
TABLE 1. IR and UV Spectra of Hydroxytriazoles (VIa-j), (VIIg i, j), and Diazomalondiamides (IIa-c)

Compound	Mp, °C	IR spectrum (KBr), ν, cm^{-1}	UV spectrum (in ethanol), λ_{max}, nm	Yield, %
VIa	196...197	3365, 3275 (NH), 3190, 3100, 2970 (CH), 1635 (C=O)	218 (4,12), 270 (4,00)	92
VIb	175...177	3350, 3275 (NH), 3190, 3080 sh., 3035, 2905, 2850 (CH), 1635 (C=O)	220 (4,12), 270 (4,05)	91
VIc	172...173	3370, 3270 (NH), 3200, 3080, 3030, 2900, 2835 (CH), 1650 (C=O)	222 (4,20), 270 (4,08)	93
VId	188...190	3350, 3270 (NH), 3180, 3100 (CH), 1655 (C=O)	220 (4,12), 270 (4,06)	91
VIe	156...157* 182...183	3355, 3280, 3180 (NH), 3115, 2980, 2935, 2900 (CH), 1720, 1680 (C=O)	220 (4,18), 270 (4,08)	95
VIf	172...173* 205...207	3440, 3320, 3180 (NH), 2130 (N=N), 1680 (C=O)	265 (4,02)	94
VIg	171...172	3290 (NH), 3150, 3100, 3035, 2920 (CH), 1635 (C=O)	225 (4,20), 270 (4,08)	93
VIIg	220...222	3270 (NH), 3140, 3110, 3025, 2915, 1630 (C=O)	220 (4,15), 262 (4,00)	60
Vh	213...214	3340 (NH), 3160, 3000 (CH), 1650 (C=O)	262 (4,10)	94
VIi + VIIi	162...163	3330, 3300 (NH), 3150, 3010, 2990 (CH), 1655, 1640 (C=O)	265 (3,85)	81
VIj + VIIj	154...156	3290 (NH), 3080, 3060, 2950 (CH), 1650, 1635 (C=O)	268 (3,85)	83
IIa	—	3335, 3240 (NH), 3155, 3060 (CH), 2110 (N=N), 1660, 1640 (C=O)	268 (4,05)	—
IIb	—	3340, 3250 (NH), 3180, 3140, 3100, 2900, 2850 (CH), 2100 (N=N), 1675, 1635 (C=O)	269 (4,06)	—
IIc	—	3340, 3250 (NH), 3185, 3135, 2910, 2840 (CH), 2100 (N=N), 1670, 1635 (C=O)	272 (4,08)	—

*Temperature of transition to diazo compound.

The initial $NHR^1(R^2)$-amides of 1-$R^2(R^1)$-5-hydroxy-1,2,3-triazole-4-carboxylic acid were obtained by treating with hydrochloric acid aqueous solutions of sodium 4-[$NHR^1(R^2)$-carbamoyl]-1-$R^2(R^1)$-1,2,3-triazol-5-olates (IVa-j) and (Vh-j) the synthesis of which has been described in [1] (scheme 2).

Scheme 2



II, IV, VI, VII R^1=H, a R^2=Ph, b R^2=C_6H_4Me-4, c R^2=C_6H_4OMe-4, d R^2=C_6H_4Br-4, e R^2=C_6H_4COOEt-4, f R^2=$C_6H_4NO_2$-4; R^1=Me, g R^2=C_6H_4Me-4; R^1=H, h R^2=Me, i R^2=Bzl; R^1=Me, j R^2=Bzl.
V, VI, VII (R^1) = H, h (R^2)=Me; i (R^2)=Bzl; (R^1)=Me, j (R^2)=Bzl

A single amide of 1-methyl-5-hydroxy-1,2,3-triazole-4-carboxylic acid (VIh) is precipitated from an aqueous solution of a mixture of the isomers (IVh) and (Vh) on adding acid. The isomeric hydroxytriazole (VIIh) remains in solution. However the analogous operation with mixtures of 1,2,3-triazol-5-olates (IVi) + (Vi) and (IVj) + (Vj) leads to mixtures of the two isomeric hydroxytriazoles (VIi) + (VIIi) and (VIj) + (VIIj).

Analysis of the spectral data of the hydroxytriazoles (VIa-e, g-j) and (VIIi, j) showed that opening and recyclization of the triazole ring does not occur on isolating them from the sodium salts of (IV) and (V). The main argument in favor of this

TABLE 2. Ratio of Isomers (VI), (II), and (VII) in DMSO-d_6 at Various Temperatures Depending on Time

Isomers	Proportion of isomers, %, time							
	8-10 min after solution	1 d (24°C)	10 d (24°C)	15 min (100°C)	30 min (100°C)	60 min (100°C)	180 min (100°C)	150-300 h (100°C)
VIb	75			12	10	6	6	
IIb	25	*	*	85	85	85	84	*
VIIb	0			3	5	9	10	
VIc	80			20	15	13	13	25
IIc	20	*	*	78	82	83	83	65
VIIc	0			2	3	4	4	10
VIe	50	0	0	0	0	0	0	0
IIe	50	100	100	95	70	45	35	35
VIIe	0	0	0	5	30	55	65	65
VIg	80	10	5	10	7	5	5	
IIg	20	25	10	25	23	15	15	*
VIIg	0	65	85	65	70	80	80	
VIIg	100	90	85	85		80	80	
IIg	0	10	10	10	—	15	15	*
VIg	0	0	5	5		5	5	
VIh	90			70	55	50	50	55
IIh	10	*	*	20	30	30	30	25
VIIh	0			10	15	20	20	20
VIi	85			40	40	40	40	45
IIi	10	*	*	50	45	45	45	35
VIIi	5			10	15	15	15	20
VIj	85			35	30	30	30	35
IIj	10	*	*	30	30	25	25	20
VIIj	5			35	40	45	45	45

*The isomer mixture was not kept for this time interval.

is the absence from the IR spectra of these hydroxytriazoles of absorption bands in the region characteristic for the stretching vibrations of the diazo group (Table 1). Signals at 8.5-11.0 ppm typical of the resonance of methyl and arylamide group protons are absent from the ^{1}H NMR spectra of compounds (VIa-e, h) which confirms the presence of the R^2 substituent in position 1 of the triazole ring. The methyl group protons of compound (VIg) resonate at 2.85 and 2.38 ppm. The first signal corresponds to the proton resonance of the methyl group at position 4 of the benzene ring and confirms the structure of compound (VIg).

The hydroxytriazole (VIf) is an exception since there is an intense band in the 2130 cm^{-1} region of the IR spectrum of the product obtained after acidification of an aqueous solution of triazolate (IVf) indicating the presence of the diazomelondiamide (IIf).

Unlike hydroxytriazoles which have the same substituent at position 1 of the triazole ring and in the carboxamide group, thermal fission of the triazole ring of which leads to a 2-diazomalonnndiamide ($R^1 = R^2$), it is possible to form three isomers by heating triazoles (VIa-j) and (VIIi, j) under analogous conditions (DMSO-d_6), 100°C). It is possible that the appearance of the triazole isomer is the product of a rearrangement through the intermediate 2-diazomalondiamide (IIa-j).

We have studied this rearrangement using ^{1}H NMR and synthetic methods. The data obtained by ^{1}H NMR are shown in Tables 2 and 3.

The isomer ratios were determined from the integrated signals of the methyl group protons and of the methylene protons of the benzyl groups, which have different chemical shifts and multiplicity, at position 1 of the triazole ring and in the carboxamide group. In addition the integrated signal of the NH protons of the N-arylcarboxamide groupings were used since these protons do not participate in deuterium exchange. On adding CD_3COOD, the integrated signal of these protons was unchanged.

TABLE 3. ^{1}H NMR Spectra of Hydroxytriazoles (VI) and (VIIa-j) and of the Diazomalondiamides (IIa-j)

Compound	^{1}H NMR spectrum (in DMSO-D_6), δ, ppm
VIa	8,0...6,95 (7H, m, Ph + NH_2)
IIa	10,64 (1H,s, NH), 8,0...6,95 (5H,m, Ph)
VII[a]	9,70 (1H,s, NH), 8,00...6,95 (5H,m, Ph)
VIb	7,77...7,33 (4H,m, C_6H_4), 7,42 (2H,s, NH_2), 2,37 (3H,s, Me)
IIb	10,52 (1H,s, NH), 7,77 (2H,s, NH_2), 7,48...7,00 (4H,m, C_6H_4), 2,25 (3H,s, Me)
VIIb	9,63 (1H,s, NH), 7,48...7,00 (4H,m, C_6H_4), 2,25 (3H, s, Me)
VIc	7,76...6,95 (4H, m, C_6H_4), 7,45 (2H,s NH_2), 3,79 (3H, s, OMe)
IIc	10,40 (1H, s, NH), 7,75 (2H, s, NH_2), 7,49...6,75 (4H, m, C_6H_4), 3,70 (3H, s, OMe)
VIIc	9,55 (1H, s, NH), 7,49...6,75 (4H, m, C_6H_4), 3,70 (3H,s, OMe)
VIId	7,45 (6H,s, C_6H_4 + NH_2)
IId	10,70 (1H,s, NH), 7,80 (2H,s, NH_2), 7,48 (4H, s, C_6H_4)
VIId	9,85 (1H,s, NH), 7,48 (4H, s, C_6H_4)
VIIIe	7,93 (4H,s, C_6H_4), 4,3 (2H, q, J = 6,8 Hz, CH_2), 1,32 (3H,t, J = 6,8 Hz, Me)
IIe	10,97 (1H,s, NH), 8,20...7,40 (4H, m, C_6H_4), 4,29 (2H,q, J = 6,8 Hz, CH_2), 1,32 (3H, t, J = 6,8 Hz, Me)
VIIe	9,86 (1H,s, NH), 8,00...7,60 (4H,m, C_6H_4), 4,31 (2H,q, J = 6,8 Hz, CH_2), 1,33 (3H, t, J = 6,8 Hz, Me)
VIf	8,40...7,40 (6H, m C_6H_4 + NH_2)
IIf	11,20 (1H, s NH), 8,50...7,50 (4H, m, C_6H_4)
VIIf	10,56 (1H,s, NH), 8,50...7,50 (4H,m, C_6H_4)
VIg	8,14 (1H,s, NH), 7,77...7,29 (4H,m, C6H4), 2,82 (3H, s, Me), 2,39 (3H, s Me)
IIg	10,45 (1H, s, NH), 7,66...7,03 (4H,m, C_6H_4), 2,84 (3H,s, Me), 2,30 (3H,s, Me)
VIIg	9,95 (1H, s, NH), 7,66...7,03 (4H, m, C_6H_4), 3,72 (3H,s, Me), 2,30 (3H, s, Me)
VIh	7,45 (2H, s, NH_2), 3,74 (3H, s Me)
VIh	7,65 (1H,s, NH), 6,50 (2H,s, NH_2), 2,78 (3H,s+d, J = 5,5Hz, Me)
VIIh	7,65 (1H,s, NH), 2,78 (3H,s+d, J = 5,5 Hz Me)
VIi	7,65 (2H,s NH_2), 7,30 (5H, s, Ph), 5,27 (2H,s, CH_2)
IIi	8,87 (1H,m, NH), 7,63 (2H, br,s NH_2), 7,30 (5H,s, Ph), 4,41 (2H, s+d J = 5,5Hz, CH_2)
VIIi	8,87 (1H,m, NH), 7,30 (5H, s Ph), 4,48 (2H,s t,d J = 5,5 Hz, CH_2)
VIj	8,14 (1H, m, NH), 7,31 (5H,s, Ph), 5,31 (2H, s, CH_2), 2,82 (3H,s + d J = 5,5Hz, Me)
IIj	8,88 (1H,m, NH), 8,80 (1H, m, NH), 7,31 (5H,s, Ph), 4,40 (2H,s+d, J = 5,5 Hz, CH_2)
VIIj	8,55 (1H,m, NH), 7,31 (5H,s, Ph), 4,50 (2H,s+d, J = 5,5 Hz CH_2), 3,70 (3H,s, Me)

The determination of the ratio of the isomers (VI):(II):(VII) for a, d, and f at the required precision was unsuccessful by ^{1}H NMR spectra since the region of the carboxamide proton signals overlaps the region where the multiplet of the aromatic protons appears. However it may be concluded that, as for compounds (VIb, c, e, g-j), fission of the triazole ring begins under these conditions and the diazo compounds (IIa, d, f) are formed to a significant degree. On increasing the temperature to 100°C the diazo compounds (IIa, d, f) are partially cyclized to the isomeric hydroxytriazoles (VIIa, d, f). Fission of the triazole ring of compounds (VIa, d, f) is confirmed by the appearance at low field at 10.6 (IIa), 10.7 (IId), and 11.18 ppm (IIf) of signals characteristic of the resonance of NH-arylamide protons in the N-arylamides of 2-diazocyanoacetic acid [3] and a significant displacement of the multiplets [compounds (IIa, f)] and singlet (IId) of the aromatic protons towards high field.

Arguments in favor of the cyclization of diazo compounds (IIa, d, f) into triazoles (VIIa, d, f) are the reduction with time (at 100°C) of the relative integrated value of the signal of the NH-arylamide protons of the diazo compounds (IIa, d, f) and the increase of the signal at higher field at 9.7 (VIIa), 9.9 (VIId), and 10.93 ppm (VIIf) which is assigned to the signal of the NH proton of the N-arylcarboxamide group at position 4 of the triazole ring.

Since the cyclization of diazo compounds (IIa-f) to triazoles (VIIa-f) was discovered by us when using elevated temperatures it seemed of interest to investigate this process at lower temperatures. Compound (VIe) was therefore maintained at 30°C for 10 d. However, according to ^{1}H NMR data, triazole ring fission had completely stopped after this time which indicates the need for significant heating to cyclize the diazo compound (IIe).

This enabled us to synthesize diazo compounds (IIa-c) by boiling triazoles (VIa-c) in ethanol solution for 3 h with subsequent slow crystallization.

Unlike compounds (VIa-c), the compounds (IIa-c) are yellow and readily soluble in ethanol. Absorption bands are present in the IR spectra of compounds (IIa-c) in the 2100-2110 cm^{-1} region which are characteristic of the stretching

vibrations of the diazo group and in the 1625-1670 cm^{-1} region characteristic of the stretching vibrations of a C=O bond. Twin absorption bands develop indicating the presence of two carbonyl groups.

Heating diazo compound (IIe) at 100°C for 2 h already leads to the formation of a thermodynamically equilibrated mixture of compounds (IIe) and (VIIe), the ratio of which is 1:2 according to ^1H NMR data and remains unchanged for a further 10 h.

Unlike compounds (VIa-f), the hydroxytriazole (VIg) readily undergoes rearrangement to the isomeric triazole (VIIg) which even precipitates from DMSO-d_6 solution because of poor solubility. Compound (VIIg) was also isolated in pure form after recyclization of compound (VIg) in boiling ethanol solution for 3 h.

In order to confirm that this rearrangement occurs conditions of thermodynamic control we investigated the ratio of isomers ([VI:II:VII]g) and ([VII:II:VI]g) after 2 d at 24°C and 3 h at 100°C. The equality of these ratios, 1:2:17 at 24°C and 1:3:6 at 100°C, confirmed the thermodynamic control of this rearrangement.

The data shown in Table 2 indicate that the substituents R^1 or R^2 may be arranged in the following sequence of ability to stabilize the hydroxytriazoles (VI) under conditions of thermodynamic control; Bz > Me > 4-$MeOC_6H_4$ > 4-MeC_6H_4, Ph > H > 4-EtC_6H_4COO, 4-$NO_2C_6H_4$. Among the isomers (II) and (VII) the chain isomers (II) are thermodynamically more stable in the absence of a methyl or benzyl substituent.

We have therefore predicted and detected a new rearrangement in the 1,2,3-triazoles. The effect of the substituents in the initial triazole and of temperature on the course of the rearrangement has been clarified. It was shown that the presence of electron-accepting substituents at position 1 of the triazole ring and electron-donating substituents in the carboxamide group in the initial isomer facilitate the course of the rearrangement. The possibility of selectively preparing N-arylamides of 2-carbamoyl-2-diazoacetic acid has been established.

EXPERIMENTAL

IR spectra were recorded in KBr disks on a Specord IR-75 spectrometer. UV spectra were taken on a Beckman M 26 instrument in ethanol. The ^1H NMR spectra were obtained on Bruker WR-80 spectrometers (80.13 MHz) in DMSO-d_6. Chemical shifts for ^1H were measured relative to TMS as internal standard (δ_{TMS} = 0.00 ppm). The resolution when plotting ^1H NMR spectra was 0.1-0.15 Hz. A check on reactions, the composition of reaction mixtures, and the purity of the compounds synthesized was carried out by TLC on Silufol UV 254 plates in various solvent systems. The properties of the compounds synthesized are summarized in Tables 1 and 3.

Data of elemental analysis for C, H, N, and Br corresponded to calculated values.

The sodium 4-[N-R^1(R^2)-carbamoyl]-1-R^2(R^1)-1,2,3-triazol-5-olates (IVa-j) and (Vh-h) were synthesized as described in [1].

5-Hydroxy-1-R^1(R^2)-4-[N-R^1(R^2)-carbamoyl]-1,2,3-triazoles (VIa-j), (VIIi, j). These were obtained from the triazolates (IVa-j) and (Vh-j) in a similar manner to the amide of 5-hydroxy-1,2,3-triazole-4-carboxylic acid [4].

5-Hydroxy-1-methyl-1,2,3-triazole-4-(N-tolylcarboxamide) (VIIg). A. A solution of trizole (VIg) (1.0 g: 4.3 mmole) was heated at 100°C in DMSO (1 ml) for 1 h, cooled to 0°C, and kept at this temperature for 24 h. The crystals which had precipitated were filtered off and washed with ethanol and ether. The crystals were colorless and rhombic.

B. A suspension of triazole (VIg) (1.0 g: 4.3 mmole) in ethanol (30 ml) was heated until completely dissolved and then 3 h further. The reaction mixture was cooled to room temperature and left for 24 h. The solid was filtered off and washed with ether. The product obtained corresponded in melting point and IR spectrum to triazole (VIIg) obtained by method A.

2-Carbamoyl-2-diazo-N-R-acetamides (IIa-c). A solution of compound (IVa) or (IVb) (5 mmole) in ethanol (15 ml) was boiled for 3 h. Water (5 ml) was then added and the mixture cooled. The solid (fine yellow crystals) was filtered off and washed with water.

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