The Behaviour of Some Acylthiosemicarbazides in the Reaction with α-Halogenated Esters

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*New six unexpected 1,3,4-oxadiazoles were obtained starting from acylthiosemicarbazides. N^1-[4-(4-X-phenylsulfonyl)benzoyl]-N^4-(2/3-methoxyphenyl)-thiosemicarbazides **2**,**3a-c** were treated with ethyl chloro- or bromoacetate in presence of anhydrous sodium acetate in order to obtain new thiazolidin-4-ones compounds. However, formation of desired thiazolidin-4-ones from these acylthiosemicarbazides failed and instead 1,3,4-oxadiazoles were obtained. For confirmation presence of these compounds, 5-[4-(phenylsulfonyl)phenyl]-2-(3-methoxyphenylamino)-1,3,4-oxadiazole **5a** was synthetized by cyclodesulfurization of acylthiosemicarbazide **3a** with mercury (II) acetate. The structures of these compounds were elucidated by FTIR, UV, ^{1}H-NMR and ^{13}C-NMR, MS spectra and elemental analysis.*

Keywords: 1,3-thiazolidin-4-one, 1,3,4-oxadiazole, acylthiosemicarbazide, cyclodesulfurization

The literature presents that the thiosemicarbazides form 1,3-thiazolidin-4-one through the reaction α-halogenated organic compounds (α-halogeno esters, α-halogeno acids, α-halogeno acid chlorides) [1-7]. Thiazolidin-4-ones are compounds with varied biological action: antibacterial, anticonvulsivante, anti-inflammatory, anti-HIV [6-13] etc. Therefore, as a sequel of the study in the heterocycles chemistry obtained through the cyclization of the thiosemicarbazides [14,15], our group of research has proposed the obtainment of heterocyclic compounds from the 1,3-thiazolidin-4-one class through the reaction of N^1-[4-(4-X-phenylsulfonyl)benzoyl]-N^4-(2/3-methoxyphenyl)-thiosemicarbazides **2**,**3a-c** with esters α-halogenated in the presence of sodium acetate.

The spectral data and the elemental analysis for the products obtained disproved the obtainment of thiazolidin-4-ones, pleading for the formation of some compounds by the 2-aminosubstituted 1,3,4-oxadiazoles class.

Experimental part

The melting points of the obtained compounds were determined with a Böetius apparatus and are not corrected. The IR spectra were registered in a KBr pallets with a spectrophotometer with Fourier transform FTS-135 BIORAD, at 4000-400 cm^{-1}, and the UV spectra with a spectrophotometer SPECORD 40 Analytik Jena, within the range 200-600 nm. The NMR spectra were registered with a Varian Gemini 300BB apparatus, at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. DMSO-d_6 was used as a solvent with a minimum grade of deuteration of 99% and tetramethylsilane (TMS) as an internal standard. The mass spectra were registered with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS coupled with a high performance liquid chromatograph with Varian ProStar 240 pump and a Varian ProStar 410 automatic injector. For the obtainment of ions was used an electrospray interface (ESI) or a atmospheric pressure chemical ionization (APCI). The solvent used was DMSO; the liquid chromatography was performed on a Hypersil Gold (Thermo) column with pre-column, and the mobile phase was 30% water and 70% methanol.

N^1-[4-(4-X-Phenylsulfonyl)benzoyl]-N^4-(2/3-methoxyphenyl)-thiosemicarbazides **2**,**3a-c**, known in the literature [16-17], was synthesized through the refluxing of an echimolecular mixture formed by the hydrazide of the 4-(4-X-phenylsulfonyl)-benzoic acid **1** (X=H, Cl, Br) and the 2- or 3- methoxyphenyl izothiocyanates in anhydrous ethanol.

Through the reaction of acylthiosemicarbazides **2**,**3a-c** with ethyl chloro- or bromoacetate and of anhydrous sodium acetate, in the alcoholic medium at reflux, instead of the expected 1,3-thiazolidin-4-ones, there were obtained the compounds of 1,3,4-oxadiazoles class **4,5a-c** (fig. 1).

*Synthesis of 5-[4-(4-X-phenylsulfonyl)phenyl]-2-(2/3-methoxyphenylamino)-1,3,4-oxadiazoles **4,5a-c***

1 Mmol of appropriate thiosemicarbazide **2** or **3** and 1.1 mmols ethyl chloro- or bromoacetate were refluxed in 50 mL of absolute ethanol in presence of 4 mmols anhydrous sodium acetate for 11 h. The reaction mixture was cooled, diluted with water and allowed to stand overnight. The resulted precipitate was filtered, washed with water and, finally, with ethyl ether. Obtained compounds were recrystallized from ethanol.

*5-[4-(phenylsulfonyl)phenyl]-2-(2-methoxyphenylamino)-1,3,4-oxadiazole **4a***

m.p.=208-210°C; yield 56%

Elemental analysis: found: C:61.97; H:4.17; S:7.84; N:10.36%; calc. for $C_{21}H_{17}N_3O_4S$ (407.44): C:61.90; H:4.21; S:7.87; N:10.31%

IR(KBr; cm^{-1}): 3410 (νNH), 3061; 3018s (νCH_{aril}); 2933 ($\nu_{as} CH_3$); 2837 ($\nu_{sim} CH_3$); 1626 (νC=N); 1579; 1554 ($\nu C=C_{aril}$); 1322; 1294 ($\nu_{as} SO_2$); 1159 ($\nu_{sim} SO_2$);

UV(methanol, λ_{max} (nm), logε): 205 (4.64); 254 (4.46); 329 (4.43)

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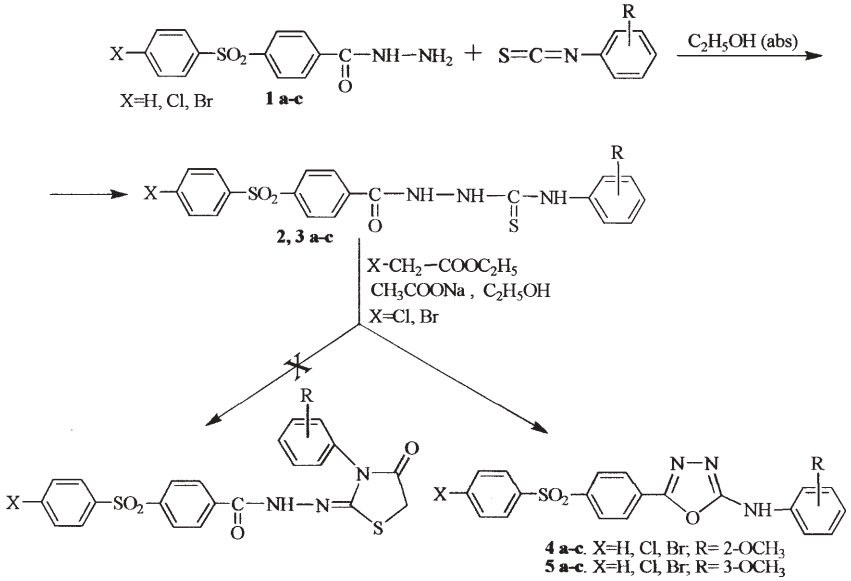

Fig. 1

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

5-[4-(4-chlorophenylsulfonyl)phenyl]-2-(2-methoxyphenylamino)-1,3,4-oxadiazole ***4b***

m.p.=226-228°C; yield 66%

Elemental analysis: found: C:57.13; H:3.60; S:7.23; N:9.60%; calculated for $C_{21}H_{16}ClN_3O_4S$ (441.89): C:57.08; H:3.65; S:7.26; N:9.51%

IR(KBr; cm^{-1}): 3415 (νNH); 3089 (νCH_{aril}); 2945 (ν$_{as}CH_3$); 2841 (ν$_{sim}CH_3$); 1626 (νC=N); 1578; 1553 (νC=C_{aril}); 1323; 1290 (ν$_{as}SO_2$); 1159 (ν$_{sim}SO_2$); 765 (νC-Cl)

UV(methanol, λ_{max} (nm), logε): 206 (4.64); 255 (4.46); 330 (4.42)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

ESI-MS: *m/z* (%) $[M+H]^+$ 442 (100, isotopic contribution ^{35}Cl), $[M+H]^+$ 444 (33, isotopic contribution ^{37}Cl), [2M+Na] 905 (20, isotopic contribution ^{35}Cl), 907 (19, isotopic contribution ^{37}Cl)

5-[4-(4-bromophenylsulfonyl)phenyl]-2-(2-methoxyphenylamino)-1,3,4-oxadiazole ***4c***

m.p.=235-237°C; yield 67%

Elemental analysis: found: C:51.95; H:3.27; S:6.63; N:8.58%; calculated for $C_{21}H_{16}BrN_3O_4S$ (486.34): C:51.86; H:3.32; S:6.59; N:8.64%

IR(KBr; cm^{-1}): 3416 (νNH); 3087 (νCH_{aril}); 2944 (ν$_{asim}CH_3$); 2841 (ν$_{sim}CH_3$); 1626 (νC=N); 1576; 1551 (νC=C_{aril}); 1322; 1291 (ν$_{asim}SO_2$); 1159 (ν$_{sim}SO_2$); 575 (νC-Br)

UV(methanol, λ_{max} (nm), logε): 205 (4.65); 255.5 (4.47); 332 (4.33)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

APCI-MS: *m/z* (%) $[M+H]^+$ 486 (78, isotopic contribution ^{79}Br), $[M+H]^+$ 488 (100, isotopic contribution ^{81}Br)

APCI-MS: *m/z* (%) fragments through collision with Ar: 337 (100) $[M+H\text{-}CH_3OC_6H_4NH]^+$ isotopic contribution ^{79}Br, 339 (100) $[M+H\text{-}CH_3OC_6H_4NH]^+$ isotopic contribution ^{81}Br

5-[4-(phenylsulfonyl)phenyl]-2-(3-methoxyphenylamino)-1,3,4-oxadiazole ***5a***

m.p.=239-240°C; yield 52%

Elemental analysis: found: C:61,98; H:4.15; S:7.81; N:10.38%; calculated for $C_{21}H_{17}N_3O_4S$ (407.44): C:61.90; H:4.21; S:7.87; N:10.31%

IR(KBr; cm^{-1}): 3308 (νNH); 3086, 3007 (νCH_{aril}); 2972 (ν$_{asim}CH_3$); 2841 (ν$_{sim}CH_3$); 1627 (νC=N); 1578; 1552 (νC=C_{aril}); 1317; 1290 (ν$_{asim}SO_2$); 1159 (ν$_{sim}SO_2$)

UV(methanol, λ_{max} (nm), logε): 204 (4.55); 253 (4.39); 327 (4.35)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in the tables 1 and 2.

APCI-MS: *m/z* (%) $[M+H]^+$ 408 (100)

APCI-MS: *m/z* (%) fragments through collision with Ar: 141 (100) $[C_6H_5SO_2]^+$,

259 (38) $[C_6H_5SO_2C_6H_4NCO]^+$

5-[4-(4-chlorophenylsulfonyl)phenyl]-2-(3-methoxyphenylamino)-1,3,4-oxadiazole ***5b***

m.p.=277-279°C; yield 58%

Elemental analysis: found: C:57.03; H:3.59; S:7,20; N:9.59%; calculated for $C_{21}H_{16}ClN_3O_4S$ (441.89): C:57.08; H:3.65; S:7.26; N:9.51%

IR(KBr; cm^{-1}): 3305 (νNH); 3089; 3030 (νCH_{aril}); 2964 (ν$_{asim}CH_3$); 2841 (ν$_{sim}CH_3$); 1627 (νC=N); 1579; 1553 (νC=C_{aril}); 1321; 1287 (ν$_{asim}SO_2$); 1159 (ν$_{sim}SO_2$); 764 (νC-Cl)

UV(methanol, λ_{max} (nm), logε): 204 (4.58); 253 (4.44); 330 (4.35)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

5-[4-(4-bromophenylsulfonyl)phenyl]-2-(3-methoxyphenylamino)-1,3,4-oxadiazole ***5c***

m.p.=284-286°C; yield 65.5%

Elemental analysis: found: C:51.98; H:3.25; S:6.50; N:8.73%; calculated for $C_{21}H_{16}BrN_3O_4S$ (486.34): C:51.86; H:3.32; S:6.59; N:8.64%

IR(KBr; cm^{-1}): 3438 (νNH); 3067 (νCH_{aril}); 2958 (ν$_{asim}CH_3$); 2857 (ν$_{sim}CH_3$); 1624 (νC=N); 157i; 1550 (νC=C_{aril}); 1325; 1291 (ν$_{asim}SO_2$); 1157 (ν$_{sim}SO_2$); 570 (νC-Br)

UV(methanol, λ_{max} (nm), logε): 204 (4.58); 254 (4.43); 330 (4.36)

The spectral data ^{1}H-RMN and ^{13}C-NMR are presented in tables 1 and 2.

For the confirmation of these compounds structure, the 1,3,4-oxadiazole **5a** was synthesized and, through the reaction of cyclodesulfurization of acylthiosemicarbazide **3a** with mercury (II) acetate, according to the reaction:

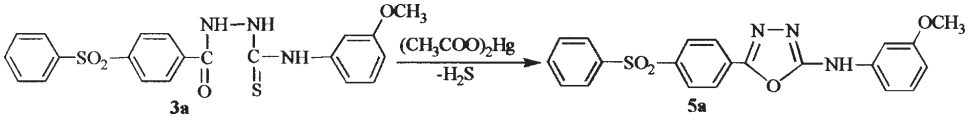

Table 1

THE ^{1}H-NMR SPECTRA OF 5-[4-(4-X-PHENYLSULFONYL)PHENYL]-2-(2/3-METHOXYPHENYLAMINO)-1,3,4-OXADIAZOLES 4,5 a-c (DMSO-d_6; δ PPM, JHz)

No	X	R	H-7, H-11	H-8, H-10	H-13, H-17	H-14, H-16	H-15	H-19	H-20	H-21	H-22	H-23	NH
4a.	H	19-OCH_3 3.85s	8.08d (8.5)	8.15d (8.5)	8.00dd (7.2;1.5)	7.65t (7.2)	7.73tt (7.2;1.5)	-	-	6.96-7.08m		7.99bd (7.2)	9.89bs
4b.	Cl	19-OCH_3 3.85s	8.08d (8.4)	8.16d (8.4)	8.01d (8.3)	7.71d (8.3)	-	-	-	6.95-7.08m		7.98bd (7.4)	9.90bs
4c.	Br	19-OCH_3 3.39s	8.08d (8.6)	8.15d (8.6)	7.93d (8.8)	7.86d (8.8)	-	-	-	6.98-7.10m		7.99bd (7.4)	9.91bs
5a.	H	20-OCH_3 3.75s	8.09d (8.7)	8.12d (8.7)	8.00dd (7.6;1.7)	7.65t (7.6)	7.72tt (7.6;1.7)	7.29t (2.4)	-	6.60ddd (8.1;2.4;0.9)	7.25t (8.1)	7.13dd (8.1;2.4)	10.81bs
5b.	Cl	20-OCH_3 3.75s	8.08d (8.5)	8.15d (8.5)	8.00d (8.6)	7.72d (8.6)	-	7.28t (2.5)	-	6,82ddd (7.9;2.3;1.2)	7.26t (7.9)	7.17dd (7.9;2.5)	10.85bs
5c.	Br	20-OCH_3 3.74s	8.08d (8.4)	8.15d (8.4)	7.95d (8.5)	7.87d (8.5)	-	7.28t (1.9)	-	6.60ddd (8.1;1.9;1.1)	7.26t (8.1)	7.13bd (8.1)	10.80bs

s-singlet; d-doublet; dd-doublet of dublets; ddd-doublet of doublets of doublets; t-triplet; tt-triplet of triplets; m-multiplet; b-broad

Synthesis of 5-[4-(phenylsulfonyl)phenyl]-2-(3-methoxyphenylamino)-1,3,4-oxadiazole ***5a***

At a mixture of 1 mmol of thiosemicarbazide **5a** in 40 mL ethanol 0.320 g of mercury acetate are added. The mixture was refluxed for 3 h on water bath. The mercury sulfide formed in the reaction was filtered and the filtration result was evaporated under reduced pressure. The solid obtained is recrystallized from DMF:EtOH=1:1 (v/v). (m.p.=238-239°C; yield 63.5%).

Results and discussions

The compounds obtainment from the 1,3,4-oxadiazoles class by acylthiosemicarbazides with ethyl chloro- or bromoacetate and of anhydrous sodium acetate reaction was also observed by other authors [18-20].

The transformation of acylthiosemicarbazides in 1,3,4-oxadiazoles or thiazolidin-4-one is influenced by the substituent nature linked to the nitrogen atom in 4 position. If this substituent is of aryl type, it may be obtained predominantly 1,3,4-oxadiazoles. If the substituent is an alkyl type radical, less bulky, there may be obtained thiazolidin-4-ones [18-19]. There are cases in which, although the substituent is a radical of aryl type, the products obtained are thiazolidin-4-ones, or cases in which if the substituent is a bulky alkyl type radical, there may be obtained 1,3,4-oxadiazoles [20].

Reaction mechanism implies, in the first stage, the formation of the alkylate intermediary at the sulphur atom in the tiol tautomeric form of acylthiosemicarbazides. The intramolecular cyclization of this intermediary may take place with the elimination of one molecule of ethanol by NH group nucleophilic attack to the carbonic atom from the ester carbonyl group or by the elimination of one molecule of ethyl mercaptoacetate by the nucleophilic

Table 2

THE ^{13}C-NMR SPECTRA OF 5-[4-(4-X-PHENYLSULFONYL)PHENYL]-2-(2/3-METHOXYPHENYLAMINO)-1,3,4-OXADIAZOLES 4,5 a-c (DMSO-d_6; δ PPM, J)

No	X	R	C-2	C-5	C-6	C-7, C-11	C-8, C-10	C-9	C-12	C-13, C-17	C-14, C-16	C-15	C-18	C-19	C-20	C-21	C-22	C-23
4a.	H	19-OCH_3 55.76	161.03	156.79	126.99	128.48	127.49	142.45	140.53	126.51	129.90	134.03	128.28	148.99	111.39	123.62	120.62	119.20
4b.	Cl	19-OCH_3 55.75	161.03	156.76	126.98	128.55	126.54	141.97	139.34	129.47	130.03	128.46	139.18	148.98	111.37	123.61	120.61	119.50
4c.	Br	19-OCH_3 55.95	161.18	156.89	127.20	128.47	126.58	142.12	139.95	129.44	132.94	128.16	139.95	149.31	111.74	123.77	120.70	119.51
5a.	H	20-OCH_3 54.68	160.02	156.27	127.84	128.00	127.04	142.21	140.19	126.19	129.43	133.55	139.07	103.07	159.60	107.25	129.48	109.42
5b.	Cl	20-OCH_3 54.64	159.93	156.18	127.99	128.15	126.25	141.62	138.99	129.08	129.57	138.91	138.78	102.87	159.54	107.11	129.66	109.29
5c.	Br	20-OCH_3 55.22	160.53	156.75	128.35	128.62	126.78	142.18	139.93	130.05	133.10	128.55	139.56	103.57	160.12	107.78	129.59	109.93

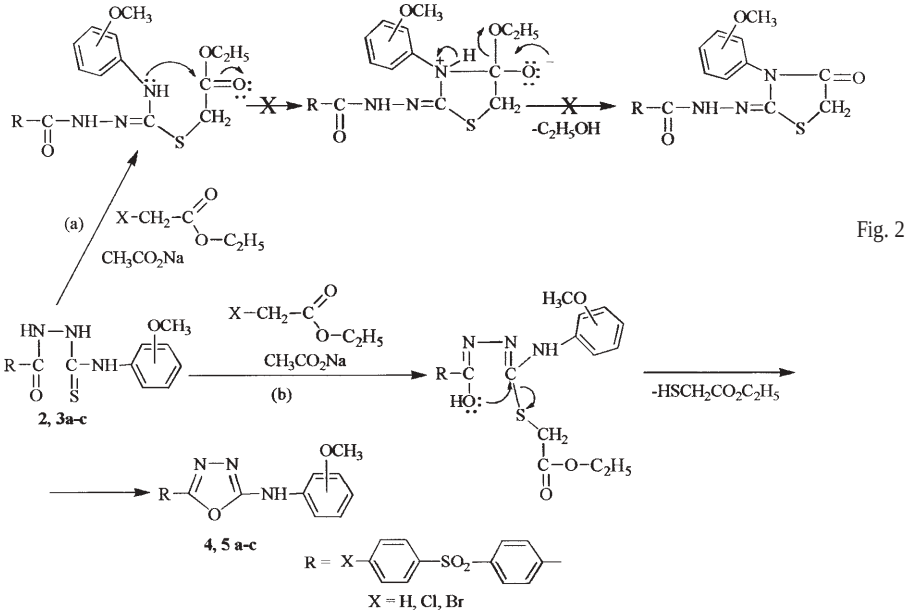

Fig. 2

attack of OH group at the carbonic atom linked to the sulfuric alkylate atom [21] (fig. 2).

In this case, the cyclization with the elimination of ethanol is not possible because of low NH aryl group nucleophilicity and consequently, the reaction of the acylthiosemicarbazides **2,3a-c** with ethyl chloro- or bromoacetate in anhydrous sodium acetate presence follows the (b) way, the final products being 1,3,4-oxadiazoles **4,5a-c.**

The IR Spectra

In the IR spectra of the compounds **4,5a-c** the absorption band due to the valence vibration of C=O group from the thiosemicarbazides **2** and **3** (1675-1702 cm^{-1}), is not found. Besides, the another absorption band absence due to the vibration of C=O group from the thiazolidin-4-ones nucleus, leads to the conclusion that the reaction products do not contain the carbonyl group.

The synthesized compounds present one single absorption band at 3305-3438 cm^{-1} characteristic for NH group valence vibration in contradiction with the thiosemicarbazides **2,3a-c** who present two or three bands in the range 3157-3443 cm^{-1}.

In the region 1624-1627 cm^{-1} appears a band of high intensity, due to the group C=N valence vibration which is characteristic of the 1,3,4-oxadiazole 2-aminosubstituted [22].

The NMR Spectra

In the ^{1}H-NMR spectra of compounds **4,5a-c** are present two subspectra characteristic of the diarylsulfone fragment [14,16] and of the 1,3,4 oxadiazole ring.

In the ^{1}H-NMR spectra of this new compounds the signal attributed to the two protons of the methylene group from the thiazolidin-4-one is not present and this proves that these compounds have not been obtained.

The signal under the broad singlet attributed to NH group proton from the 1,3,4-amino-oxadiazoles (table 1) appears at a chemical displacement δ comprised between 9,89-10,85 ppm [18,19].

The ^{13}C-NMR spectra of the compounds **4,5a-c** are not presenting any characteristic signal to the carbon atoms C=O (-CONH-N= or C=O from the thiazolidinone nucleus) in the thiazolidin-4-one molecule. Besides, it is not present the S-CH_2 carbonic atom group corresponding signal of the thiazolidin-4-ones from ~33 ppm [19].

It can be noticed the apparition of the signal attributed to the quaternary carbonic atom C-2 at 159,93-161,18 ppm from the 1,3,4-oxadiazole nucleus, the carbonic atom signal attributed to the thionic group (~181 ppm) not being present anymore. Instead of amidic carbonyl group corresponding signal from the thiosemicarbazides that appears at ~164 ppm, one may observe a new signal at ~157 ppm that belongs to the carbonic atom C-5 from the 1,3,4-oxadiazole ring [23,24] (table 2).

The mass spectra of the compounds **4b, 4c** and **5a** confirm the presence of these 2-amino substituted 1,3,4-oxadiazoles.

Conclusions

The purpose of this paper was to obtain new compounds from the 1,3-thiazolidin-4-ones class through the acylthiosemicarbazides reaction with ethyl chloro- or bromoacetate and anhydrous sodium acetate. The spectral data and the elemental analysis invalidate the presence of these compounds, pleading for a structure 2-R-amino-1,3,4-oxadiazole type confirmed also through the alternative synthesis between thiosemicarbazide **3a** with mercury (II) acetate.

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