Thermal Rearrangement of 4-Alkyl-4*H*-1,2,4-triazoles to 1-Alkyl-1*H*-1,2,4-triazoles − A Study of the Mechanism by Cross-over Experiments

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The mechanism for the thermal rearrangement of 4-alkyl-1,2,4-triazoles to the corresponding 1-alkyl-1,2,4-triazoles, was studied by cross-over experiments with mixtures of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole and 3,5-bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole. This gave support to a proposed mechanism involving the formation of an ionic triazolium triazolate intermediate, and a subsequent nucleophilic attack of the triazolate anion at the 1- and 4-alkyl-group positions to form the observed products. Further support was obtained by thermolysis of a mixture of 1-ethyl-3,5-bis(4-methylphenyl)-4-propyl-1,2,4-triazolium tetrafluoroborate and potassium 3,5-diphenyl-1*H*-triazolate.

Introduction

We have studied the thermal rearrangement reactions of neat 4-alkyl-substituted 4*H*-1,2,4-triazoles to the corresponding 1-alkyl-1*H*-1,2,4-triazoles (see Figure 1), and discussed evidence for a consecutive nucleophilic displacement reaction, and the formation of an ion-pair. The possibility of a concerted [1,3]-migration has also been discussed, and cannot be totally excluded.[1] It is essential to establish whether the reactions are inter- or intramolecular, as evidence for an intermolecular reaction would exclude a concerted shift mechanism. One way to distinguish between inter- or intramolecular mechanisms would be through cross-over experiments. The rearrangements may proceed through a dialkyltriazolium-triazolate ion-pair intermediate or by reactions between neutral molecules in a chain reaction.

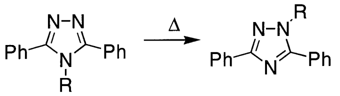
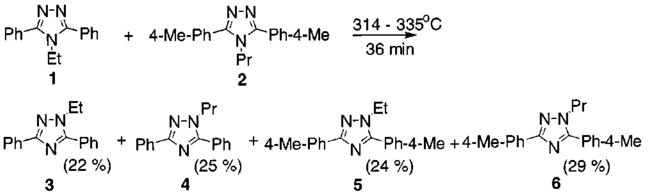


Figure 1. Thermolysis of 4*H*-1,2,4-triazoles

To elucidate the details of the mechanism we here describe a series of cross-over experiments.

Results and Discussion

Thermolysis of a 1:1 mixture of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole **(1)** and 3,5-bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole **(2)** at 314−335 °C for 36 min. under a nitrogen atmosphere in closed glass tubes yielded a series of products which were readily separated by thin layer chromatography. The tolyl-substituted triazole **2** was chosen to minimize the electronic effects that may influence the outcome of the reaction. The reaction mixture contained the four products 1-ethyl-3,5-diphenyl-1*H*-1,2,4-triazole **(3)** (22%), 3,5-diphenyl-1-propyl-1*H*-1,2,4-triazole **(4)** (25%), 1-ethyl-3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole **(5)** (24%), and 3,5-bis(4-methylphenyl)-1-propyl-1*H*-1,2,4-triazole **(6)** (29%) (Scheme 1). The products were identified by co-chromatography with standard materials prepared by independent syntheses. IR spectroscopy with GC-FTIR, and comparison with authentic samples gave further proof of identity. The yields were determined by GC analysis and mass spectrometric measurements.



Scheme 1. Cross-over experiment with **1** and **2**

In the latter case the intensities of the molecular ion peaks, **3** (249), **4** (263), **5** (277), and **6** (291) were measured and compared with a mixture of known composition of independently prepared standard materials. Good agreement was obtained in all cases. The products were obtained in approximately equal amounts, and any deviations in yield may be due to slight stereoelectronic substitution effects and errors in the analytical techniques. It can be concluded from these results, that the rearrangement of the triazoles is clearly bimolecular, and a concerted shift mechanism can be excluded.

The observations can be rationalized by a mechanism in which the *N*-1 atom in one triazole molecule participates in a nucleophilic displacement reaction and results in the formation of an ion-pair, and subsequent attack of the anion on the alkyl groups in the triazolium cation, Scheme 2. The proposed mechanism resembles one reported by Bentley et al. for the rearrangement of 4-(β-hydroxyethyl)-1,2,4-triazole[2] and finds further support in the work by other groups.[3]

The mechanism outlined in Scheme 2 accounts for the formation of the cross-over products **4** and **5**. The re-

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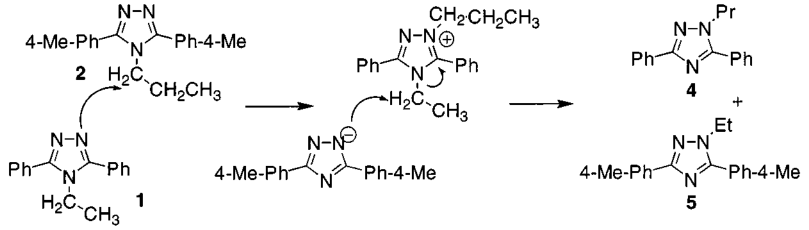
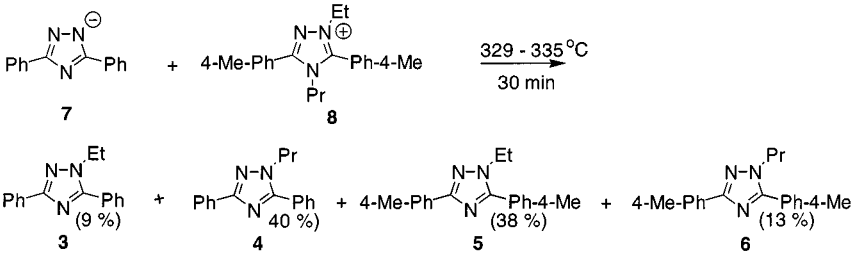


Scheme 2. Proposed mechanism for the formation of products **4** and **5**

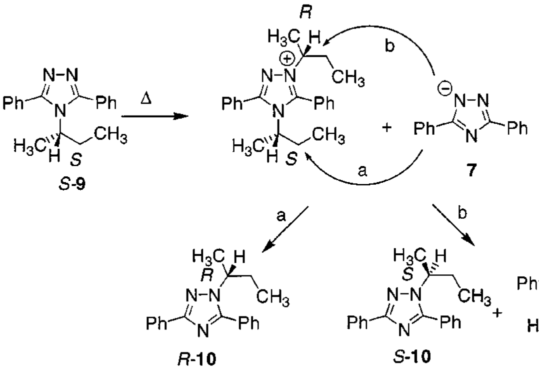


Scheme 3. Thermolysis of the "ion-pair" intermediate **7**/**8**

maining products, **3** and **6**, shown in Scheme 1 are the products expected for pure **1** and **2**. All products were formed in essentially equal amounts.

To take this one step further, we decided to mimic the ionic step in the proposed reaction mechanism, by thermolysis of a mixture containing the dialkyltriazolium ion and the triazole anion, and at the same time obtain cross-over information. This was achieved by thermolysis of a well blended 1:1 mixture of 1-ethyl-3,5-bis(4-methylphenyl)-4-propyl-1,2,4-triazolium tetrafluoroborate, **8**, and potassium 3,5-diphenyl-1*H*-triazolate, **7**, under nitrogen in a sealed glass tube at 329−335 °C for 30 minutes. The products formed were **3** (9%), **4** (40%), **5** (38%) and **6** (13%), Scheme 3. The product composition and yields were determined by GC-analysis using tetracosane, *n*-$C_{24}H_{50}$, as an internal standard.

The products **4** and **5**, derived from the direct reaction between **7** and **8** predominate. However, small amounts of products **3** and **6** were also formed, either owing to secondary reactions of the initial products formed or owing to attack of **8** at the ethyl site of **7**. From experience we decided the latter to be less likely.[4,5] However, results from the optically active 4-(*S*-2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole **(9)** which was reported in a previous paper,[5] may give new information. Partial thermolysis of the optically active triazole **9** at 330 °C for 10 min and purification by preparative TLC yielded 63% of recovered starting material, which by CD-analysis showed that no or very little racemization had taken place, (maximum 3−4% which may well be within the experimental error). Similarly, the corresponding triazole 1-(*S*-2-butyl)-3,5-diphenyl-1*H*-1,2,4-triazole **(10)** did not undergo any noticeable racemization when thermolyzed for 30 min. These results indicate that the racemization must take place during the rearrangement reaction. We have shown previously, that thermolysis of *S*-**9** produced *R*-**10** with approximately 70% *ee*, corresponding to 85% *R* and 15% of the *S*-enantiomer. This may take place by cleavage of the *N*-2-butyl bond and subsequent racemization of the "free" butyl group. However, as *S*-**9** was recovered unchanged, it must be the *N*-1 bonded butyl group that leaves, although from past experience this is predicted to be less likely as the *N*-4-position is the more reactive. These data are rationalized as outlined in Scheme 4.



Scheme 4. Partial thermolysis of *S*-**9**

This reaction scheme satisfies all the observed data. The quantities of products **3** and **6** in Scheme 3, are in a reasonable agreement with the degree of racemization indicated in Scheme 4. Thus, approximately 85% of the reaction follows route *a* and 15% route *b*. Alternative mechanisms, such as cleavage of the 2-butyl group from the dialkyltriazolium species shown in Scheme 4 and subsequent recombination may actually also account for the formation of a partially racemized product.

Conclusion

For the thermal rearrangement of 4-alkyl-1,2,4-triazoles to the corresponding 1-alkyl-1,2,4-triazoles, cross-over experiments with a mixture of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole and 3,5-bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole give support to a mechanism which involves the formation of an ionic triazolium triazolate intermediate, and subsequent nucleophilic attack of the triazolate component at the 1- and 4-alkyl groups forms the observed products.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400 FT NMR spectrometer, with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. IR and GC-IR spectra were obtained on a Nicolet 20-SXC FT-IR (GC Carlo Reba 5160, 25 m, CP-Sil-5 CB). Mass spectra were recorded on a AEI MS-902 spectrometer at 70 eV (IP) and 200 °C inlet temperature. CD spectra were recorded at room temperature on a Jobin Yvon Auto Dictograf Mark IV. GC measurements were performed on a Varian 3700 gas chromatograph equipped with a BP-1 capillary column (24 m).

4-Alkyl-4*H*-1,2,4-triazoles: The products were obtained by reacting bis(α-chlorobenzylidene)hydrazine [or bis(α-chloro-4-methylbenzylidene)hydrazine] with the respective alkyl amines.[6]

4-Ethyl-3,5-diphenyl-4*H*-1,2,4-triazole (1): This compound was obtained as previously described in the literature.[1]

3,5-Bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole (2): Bis(α-chloro-4-methylbenzylidene)hydrazine (9.7 g, 0.032 mol) was refluxed in propylamine (200 mL) for 99 h to yield, after crystallization from toluene, compound **2** (6.84 g, 69%), m.p. 202−203.5 °C of 99.7% purity (GC). − ^1H NMR (100 MHz): δ = 0.60 (t, J = 7.3 Hz, 3 H), 1.39 (hex, J = 7.3 Hz, 2 H), 2.43 (s, 6 H), 4.03 (t, J = 7.3 Hz, 2 H), 7.31 (d, J = 7.8 Hz, 4 H), 7.55 (d, J = 8.3 Hz, 4 H). − ^{13}C NMR (25 MHz): δ = 10.6, 21.4, 23.2, 46.3, 125.0, 128.7, 129.5, 140.0, 155.5. − IR (KBr): $\tilde{\nu}$ = 3068, 2976, 2958, 2944, 2921, 2876, 1479, 1474, 1465, 1449, 1417, 1383, 1347, 1339, 1021, 849, 822, 753 cm^{-1}. − MS: *m*/*z* (%) = 292 (23), 291 (100) $[M^+]$, 290 (12), 276 (19), 249 (26), 132 (21), 118 (35), 103 (26), 91 (18), 77 (17). − HR-MS ($C_{19}H_{21}N_3$): calcd. 291.1735; found 291.1737. − $C_{19}H_{21}N_3$ (291.39): C 78.32, H 7.26, N 14.42; found C 78.25, H 7.18, N 14.59.

Cross-over Experiments: A mixture of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole **(1)** (23.2 mg, 0.093 mmol) and 3,5-bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole **(2)** (26.6 mg, 0.091 mmol) was carefully mixed and placed in a sealed glass tube under nitrogen and heated in an oven (314−335 °C) for 30 min. The reaction mixture was purified by preparative TLC (Silica, $CHCl_3$). The fraction R_f = 0.19−0.66, yielded 40 mg of product which was analyzed by MS and GC-IR. Product components were next isolated and identified by comparison with authentic samples.

1-Ethyl-3,5-diphenyl-1*H*-1,2,4-triazole (3): 22% (by GC). − GC-IR: $\tilde{\nu}$ = 3072, 2986, 2950, 1519, 1476, 1444, 1349, 1295, 1197, 1177, 1130, 1065, 1024, 974, 767, 730 cm^{-1}.

3,5-Diphenyl-1-propyl-1*H*-1,2,4-triazole (4): 25% (by GC). − GC-IR: $\tilde{\nu}$ = 3073, 2979, 2947, 2889, 1558, 1515, 1474, 1444, 1402, 1378, 1348, 1296, 1179, 1130, 1064, 1023, 978, 917, 811, 784, 730 cm^{-1}.

1-Ethyl-3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole (5): 24% (by GC). − GC-IR: $\tilde{\nu}$ = 3072, 3029, 2989, 2935, 2888, 1619, 1475, 1421, 1345, 1296, 1183, 1129, 1019, 979, 825, 759, 702 cm^{-1}.

3,5-Bis(4-methylphenyl)-1-propyl-1*H*-1,2,4-triazole (6): 29% (by GC). − GC-IR: $\tilde{\nu}$ = 3070, 3029, 2977, 2935, 2835, 1616, 1474, 1420, 1342, 1297, 1182, 1128, 1017, 980, 825, 758 cm^{-1}.

Thermolysis of the "Ion-Pair Intermediate": The potassium salt of 3,5-diphenyl-1*H*-1,2,4-triazole (**7**) (21.2 mg, 0.0817 mmol) and compound **8** (32.4 mg, 0.0834 mmol) were carefully mixed, placed in a sealed glass tube under nitrogen and heated in an oven (329−335 °C) for 30 min. Composition and product yields were determined by GC measurements using tetracosane, n-$C_{24}H_{50}$, as the internal standard. The products were identified by comparison of their spectroscopic properties with those of authentic samples.
1-Ethyl-3,5-diphenyl-1*H*-1,2,4-triazole **(3)**: 3.5 mg, 9%.
3,5-Diphenyl-1-propyl-1*H*-1,2,4-triazole **(4)**: 17.6 mg, 40%.
1-Ethyl-3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole **(5)**: 17.2 mg, 38%.
3,5-Bis(4-methylphenyl)-1-propyl-1*H*-1,2,4-triazole **(6)**: 6.1 mg, 13%.
The MS of the crude product mixture gave the following results:

MS: *m*/*z* (%) = 292 (5), 291 (20) $[M^+$, **(6)**] 278 (22), 277 (100) $[M^+$, **(5)**] 264 (15), 263 (77) $[M^+$, **(4)**], 250 (8), 249 (43) $[M^+$, **(3)**].

Potassium Salt of 3,5-diphenyl-1*H*-1,2,4-triazole (7): ^1H NMR (400 MHz, CD_3OD): δ = 7.29 (t, J = 7.3 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 4 H), 8.06 (d, J = 7.3 Hz, 4 H). − IR (KBr): $\tilde{\nu}$ = 3071, 3056, 1648, 1605, 1465, 1419, 1399, 1073, 991, 722, 709 cm^{-1}.

1-Ethyl-3,5-bis(4-methylphenyl)-4-propyl-1,2,4-triazolium Tetrafluoroborate (8): Compound **8** was prepared as described in the literature for similar compounds,[7] from triethyloxonium tetrafluoroborate and 3,5-bis(4-methylphenyl)-4-propyl-4*H*-1,2,4-triazole (**2**). − ^1H NMR (400 MHz): δ = 0.63 (t, J = 7.6 Hz, 3 H), 1.45 (q, J = 7.7 Hz, 2 H), 1.56 (t, J = 7.3 Hz, 3 H), 2.45 (s, 3 H), 2.51 (s, 3 H), 4.13 (t, J = 7.8 Hz, 2 H), 4.24 (q, J = 7.3 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 7.50 (d, J = 8.3 Hz, 2 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.86 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (25 MHz): δ = 10.7, 13.9, 21.6, 21.7, 22.2, 46.6, 48.3, 116.5, 120.7, 129.5, 129.9, 130.8, 142.2, 144.1, 151.5, 154.4. − IR (KBr): $\tilde{\nu}$ = 3037, 2968, 2936, 2877, 1619, 1508, 1084, 1061, 1038, 831 cm^{-1}. − MS: *m*/*z* (%) = 340 (16), 339 (75) $[M^+ - BF_3]$, 338 (34), 325 (20), 324 (81), 321 (24), 320 (100) $[M^+ - BF_4]$, 319 (29), 318 (16), 292 (15), 291 (66), 290 (12), 278 (11), 227 (39), 276 (16), 250 (9), 249 (17), 145 (26), 132 (15), 131 (8), 118 (68), 117 (18), 116 (14), 103 (21), 91 (24), 77 (15).

Partial Thermolysis of Neat 4-(*S*-2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole [(*S*)-(+)-9]: This reaction was carried out as described above but for 10 min only (see also ref.[5]). Preparative TLC (silica/$CHCl_3$) yielded two fractions:
Fraction 1 (R_f = 0−0.04) was dissolved in dichloromethane (15 mL) and extracted with NaOH (2 M). The solvent was then evaporated under reduced pressure and dried under vacuum, to yield (*S*)-(+)-**9** (11.7 mg, 63%), 99% pure by GC. CD analysis was carried out and the CD spectrum was compared with that of an authentic sample, indicating that up to 3−4% was racemized. This number is near the error level of the measurements. 3,5-Diphenyl-1,2,4-triazole **(7)** (2.4 mg, 14.5%) was isolated from the basic extract.
Fraction 2 (R_f = 0.18−0.24) yielded 1.6 mg (8.6%) of 1-(*R*-2-butyl)-3,5-diphenyl-1*H*-1,2,4-triazole, **(*R*-10)**, (95% pure by GC).

1-Alkyl-3,5-diphenyl-1*H*- and 1-Alkyl-3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazoles. These compounds were prepared by alkylation of 3,5-diphenyl-1,2,4-triazole and 3,5-bis(4-methylphenyl)-1,2,4-triazole, respectively, as described in the literature,[8] using a modification described by Atkinson and Polya.[9] The following products were prepared:
1-Ethyl-3,5-diphenyl-1*H*-1,2,4-triazole (3): This compound has been described in the literature.[10]

3,5-Diphenyl-1-propyl-1*H*-1,2,4-triazole (4): Yield 102 mg (87%), as an oil (94% pure by GC). − ^{1}H NMR (100 MHz): δ = 0.92 (t, *J* = 7.3 Hz, 3 H), 1.97 (sextet, *J* = 7.3 Hz, 2 H), 4.19 (t, *J* = 7.3 Hz, 2 H), 7.31−7.60 (m, 6 H), 7.60−7.75 (m, 2 H), 8.10−8.24 (m, 2 H). − ^{13}C NMR (25 MHz): δ = 11.0, 23.5, 50.8, 126.3, 126.9, 128.5, 128.9, 129.0, 130.0, 131.1, 155.6, 161.3. − IR (neat): ṽ = 3067, 2966, 2935, 2876, 1477, 1464, 1443, 1409, 1385, 1355, 1291, 1249, 1132, 1071, 1017, 789, 772, 732 cm^{-1}. − MS: *m/z* (%) = 264 (11), 263 (58) [M$^+$], 234 (32), 221 (28), 131 (32), 118 (18), 105 (100), 104 (76), 103 (17), 89 (33), 77 (60). − HR-MS ($C_{17}H_{17}N_3$): calcd. 263.1423; found 263.1418. − $C_{17}H_{17}N_3$ (263.34): C 77.54, H 6.51, N 15.96; found C 77. 36, H 6.67, N 15.77.

1-Ethyl-3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole (5): Yield 70 mg (63%), m.p. 95−96 °C (> 99% purity by GC). − ^{1}H NMR (100 MHz): δ = 1.53 (t, *J* = 7.3 Hz, 3 H), 2.39 (s, 3 H), 2.44 (s, 3 H), 4.27 (q, *J* = 7.3 Hz, 2 H), 7.28 (t, *J* = 7.5 Hz, 4 H), 7.57 (d, *J* = 7.8 Hz, 2 H), 8.04 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (25 MHz): δ = 15.2, 21.4, 44.2, 126.2, 128.6, 129.2, 129.5, 138.9, 140.1, 155.2, 161.4. − IR (KBr): ṽ = 2973, 2960, 2918, 1470, 1428, 1383, 1350, 1349, 1186, 1176, 1132, 1106, 1091, 1033, 1024, 1016, 830, 802, 754, 727 cm^{-1}. − MS: *m/z* (%) = 278 (19), 277 (100) [M$^+$], 249 (9), 145 (51), 118 (30), 84 (10). − HR-MS ($C_{18}H_{19}N_3$): calcd. 277.1579; found 277.1576. − $C_{18}H_{19}N_3$ (277.37): C 77.95, H 6.90, N 15.15; found C 77.69, H 7.08, N 15.28.

3,5-Bis(4-methylphenyl)-1-propyl-1*H*-1,2,4-triazole (6): Yield 90 mg (79%), m.p. 101−102.5 °C (recryst. from toluene, > 99% purity by GC). − ^{1}H NMR (100 MHz): δ = 0.91 (t, *J* = 7.3 Hz, 3 H),1.93 (sextet, *J* = 7.3 Hz, 2 H), 2.38 (s, 3 H), 2.43 (s, 3 H), 4.16 (t, *J* = 7.3 Hz, 3 H), 7.28 (t, 4 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 8.04 (d, *J* = 8.2 Hz, 2 H). − ^{13}C NMR (25 MHz): δ = 11.0, 21.4, 23.5, 50.7, 125.5, 126.2, 128.4, 128.7, 129.2, 129.5, 138.8, 140.0, 155.5, 161.1. − IR (KBr): ṽ = 2962, 2947, 2934, 2917, 2877, 1472, 1468, 1425, 1352, 1182, 1129, 1018, 840, 826,759 cm^{-1}. − MS: *m/z* (%) = 292 (24), 291 (100) [M$^+$], 263 (12), 262 (58), 249 (48), 145 (48), 132 (13), 119 (21), 118 (76), 117 (28), 116 (17), 103 (28), 91 (21), 77 (21). − HR-MS ($C_{19}H_{21}N_3$): calcd. 291.1736; found 291.1731. − $C_{19}H_{21}N_3$ (291.39): C 78.32, H 7.26, N 14.42; found C 78.47, H 7.41, N 14.67.

Acknowledgments

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