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Synthesis of Isoxazole, Pyrazole, Thiadiazole Cyclohexanol Analogues of 1,5-Benzodiazepines through Phenoxy/Phenylamino Linkage

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The modification in the structures of these compounds offers high degree of diversity and provides a gateway for the production and development of new therapeutic agents with enhanced potency and lesser toxicity. The present study involves the design and synthesis of some newer derivatives of isoxazole, pyrazole and thiadiazole by incorporating the phenoxyl/phenylamino linkage. The chemical structures of the synthesized compounds was confirmed by ^{1}H NMR, ^{13}C NMR, IR, UV-Vis spectroscopy, mass spectrometry and elemental analysis

Keywords: Isoxazole, Pyrazole, Thiadiazole, Cyclohexane.

INTRODUCTION

Isoxazole and their derivatives plays an important role in the chemistry of heterocyclics and these heterocyclic compounds are exclusively important in pharmacophores and as starting materials in the field of organic chemistry [1]. Because of the versatile nature of these heterocyclic compounds as chemotherapeutics, a significant amount of research effort has been focused on these nuclei. Isoxazole and its derivatives possess many biochemical properties like antibacterial [2], anticonvulsant [3], anticancer [4], anthelmintics [5], anti-inflammatory [6], adenosine antagonist [7], fungicidal [8], herbicidal [9], hypoglycemic [10], muscle relaxant [11], nematocidal [12], insecticidal [13], antiviral [14], antimicrobial [15], antitubercular [16], *etc*. At present several isoxazole compounds which act as drugs are in the world market, while hundreds are in clinical trials.

Pyrazoles (1*H*-pyrazole) are five-membered heterocyclic aromatic ring compounds which consists of three carbons and two nitrogen atoms at 1, 2-positions [17]. *N*-Unsubstituted pyrazoles have three tautomers which seems identical and are interconvertible in solution, and difficult to differentiate them in their NMR spectrum. Also three other forms exist, which are semi-reduced: 1-pyrazolines, 2-pyrazolines and 3-pyrazolines and a complete reduced form exists known as pyrazolidine [18]. Pyrazoles and its derivatives have occupied highest place in medicinal and pharmaceutical chemistry, as they exist in many drugs with medicinal importance, like (Celebrex®), sildenafil (Viagra®), penthiopyrad, fomepizole, rimonabant, lonazolac, doramapimod, sulfaphenazole and these remarkable compounds have wide range of pharmacological activities, like anticancer [19], analgesic, anti-inflammatory and antioxidant [20-22], antibacterial and antifungal [23,24], antipyretic, antidepressant and anticonvulsant [25,26], antidiabetic [27], cannabinoid activities [28,29] and among others [30-36]. In addition to medicinal applications, pyrazoles also have agrochemical properties like herbicides, fungicides and insecticides [37] and also have other day to day applications like they exist in dyestuffs, sunscreen materials [38,39], analytical reagents and pluripotent ligands in coordination chemistry [40,41]. The polyaromatic pyrazole compounds also have important biochemical, photophysical, optical and electronic properties [42-44].

Many compounds associated with thiadiazoles possess a wide range of biochemical applications and shows many interactions with antifungal agents [45,46], antimicrobial molecules [47], anti-inflammatory components [48] and anticancer medicines [49]. These heterocycles acting as azo dyes have gained more concern from the scientific fraternity because of their excessive, clarity, shining and interaction for various fibers

[50,51]. The simple and easy way to induce these type of molecules into azo compound family takes place in a two-step way using an accurate and exact set of diazonium salts [52].

The aromatic amines show more diazotization reactions and the coupling of 1,3,4-thiadiazole-2-amines or its derivatives [53-55], as also thiadiazoles possess a thiazole chromophore in their structure because of an additional electronegative nitrogen atom, which decreases the basicity of an external amino group. Because of the versatile nature and the easy synthesis of 1,3,4-thiadiazole conjugates [56-58], the structural elucidations of a series of 2-phenylazo-1,3,4-thiadiazoles, in connection with aryl constituents becomes easy.

These characteristics drift our interest towards these molecules and prompt to think about the structural modification of 1,5-benzodiazepine compound by incorporating on its 2-position imidazoles, benzimidazoles, oxadiazoles, nuclei through an aminophenyl or phenoxyl bridge to synthesize these novel heterocyclic analogues of 1,5-benzodiazepines.

EXPERIMENTAL

The melting points were determined by open glass capillaries and are uncorrected. The purification of the compounds was done by TLC plates. IR spectra by an Agilent tech, carry 660 FTIR spectrophotometer. ^{1}H NMR spectra by Advance II 400 SAIF (Bruker) in which $CDCl_3$ was used as solvent and TMS as reference. Microwave reactions were carried out on Microwave synthesizer (CEM Discover, Model No. 908010). All the samples were air dried before analysis.

Synthesis of 3-(4-(2,3,4,11a-tetrahydro-1*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-yloxyphenyl)isoxazole (A): Hydroxylamine hydrochloride (2.78 g, 0.04 mol) was reacted with sodium methoxide (3.24, 0.06 mol) in pure methanol (30 mL) with continuous stirring for 10 min. Then dimethylaminomethylene ketone derivatives (**II**) (1.56 g, 0.004 mol) was added and the reaction mixture was refluxed for about 5 h. The methanol was made to evaporate under reduced pressure, while the mixture was poured in an ice-cold water. The solid so obtained was separated, decanted and washed with diethyl ether and dried (**Scheme-I**). The solid residues were recrystallized using ethanol. Yield: 0.82 g, 70%; m.p.: 248-250 ºC.

Synthesis of 5-phenyl-3-(4-(2,3,4,11a-tetrahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin -11-yloxy)phenyl)isoxazole (B): Hydroxylamine hydrochloride (2.78 g, 0.04 mol) was mixed with sodium methoxide (3.24, 0.06 mol) in pure methanol (30 mL) and then stirred for 10 min. Compound **I** (1.56 g, 0.004 mol) was then added to the mixture and refluxed for 5 h. The methanol gets evaporated under reduced pressure and the residual mixture was added to ice-cold water. The solid precipitate so formed was filtered and diethyl ether was used for washing of the precipitate and finally dried. Recrystallization of the obtained residue was done using absolute ethanol (**BI**). Then 2-iodoxybenzoic acid (0.56 g, 0.0020 mol) was abruptly added to compound **BI** (1.27 g, 0.0029 mol) using double distilled water (6.5 mL, 0.0045 M). The mixture was then heated at 70-75 ºC for about 20 min with continuous stirring and then the mixture was kept at the same temperature for 3 h. The mixture shows continuous variation during the reaction, as initially a thick slurry coating forms on the walls of the flask which eventually disperse, the stirred suspension of solid was sedimented. The whole suspension was made to cool at about 5 ºC for 1.5 h with stirring. The precipitate was filtered and the residue was rinsed using water and acetone to give compound **B** (**Scheme-II**). Yield: 1.40 g, 80%; m.p.: 240-245 ºC.

Synthesis of 11-(4-(1*H*-pyrazol-3-yl)phenoxyl)-2,3,4,11a-tetrahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine (C): To a solution of dimethylaminomethylene ketone (**I**) (1.15 g, 0.0025 mol) in methanol, hydrazine hydrate was added (0.25 g, 0.0025 mol) and the solution was refluxed for 10 h and concentrated. The mixture was purified by column chromatography and eluted with chloroform: 2-propanol (10:1) to compound **C** (**Scheme-I**). Yield: (0.780 g, 72%; m.p.: 251-252 ºC.

Synthesis of 11-(4-(5-phenyl-1*H*-pyrazol-3-yl)phenoxy)-2,3,4,11a-tetrahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine (D): Chalcone (**II**) (0.84g, 0.002 mol) and hydrazine hydrate (2.50 g, 0.05 mol) were mixed and refluxed for 12 h using 25 mL of absolute ethanol and then cooled. The residual material (Di) was filtered off and the materials was recrystallized from DMF/water. Then 2-iodoxy benzoic acid (0.56g, 0.0020 mol) was added abruptly to a solution of Di (1.27 g, 0.0029 mol) using deionized water (6.5 mL, 0.0045 M). The synthetic procedure used for compound **B** was applied similarly to give compound **D** (**Scheme-III**). Yield: 0.65 g, 75%; m.p.: 220-222 ºC.

Synthesis of 5-(4-(2,3,4,11a-tetrahydro-1*H*-dibenzo[*b*,*e*]-[1,4]diazepin-11-yloxy)phenyl)-1,3,4-thiadiazol-2-amine (E): Thiosemicarbazone (**III**) (0.740 g, 0.0016 mol) and ammonium ferric sulphate (3.2 g, 0.006 mol) was added in distilled water (10 mL) and the mixture was refluxed for about 10 h. Then the mixture was poured in ice cold water, containing 10% NaOH (pH = 5) and extracted three times with ethyl acetate. After the removal of organic solvent, the residue was purified by a silica gel column ($CHCl_3$/CH_3OH/AcOH 9:10:2) to obtain compound **E** (**Scheme-IV**). Yield: 0.346 g, 47%; m.p.: 275-278 ºC.

TABLE-1
PHYSICAL AN ANALYTICAL DATA OF COMPOUNDS (**A-E**)

Compd. No.	m.f.	m.w.	Yield (%)	m.p. (°C)	Elemental analysis (%): Calcd. (Found)			
					C	H	N	S
A	$C_{22}H_{19}N_3O_2$	357.41	70	248-250	73.93 (73.56)	5.36 (5.38)	11.76 (12.34)	–
B	$C_{28}H_{23}N_3O_2$	433.50	80	240-245	77.58 (77.19)	5.35 (5.37)	9.69 (9.73)	–
C	$C_{22}H_{20}N_4O$	356. 42	72	251-252	74.14 (74.51)	5.66 (5.68)	15.72 (14.93)	–
D	$C_{28}H_{24}N_4O$	432.52	75	220-222	77.75 (77.36)	5.59 (5.61)	12.95 (12.88)	–
E	$C_{21}H_{19}N_5OS$	389.47	47	275-278	64.76 (65.08)	4.92 (4.94)	17.98 (17.89)	8.23 (8.27)

TABLE-2
SPECTRAL DATA OF COMPOUNDS (**A-E**)

Compound	IR (KBr, ν_{max}, cm^{-1})	^1H NMR ($CDCl_3$/DMSO-d_6) δ ppm and MS (rel. abundance %)
A	2890 (C-H *str.* ArH), 1600 (C=C *str.* ArH), 1410 (C=N *str.*), 1230 (C-N *str.*), 1010 (C-O *str.*), 800 (C-O-N *str.*)	7.37-7.46 (m, 4H, ArH), 6.52 (d, 2H, phenoxyl group), 7.26 (d, 2H, phenoxyl group), 1.25-1.27 (m, 8H, cyclohexane ring), 6.42 (d, 1H, isoxazole ring), 8.02 (d, 1H, isoxazole ring), 1.95 (s, 1H, cyclohexane ring); *m/z*: 231.1 (100.0%), 151.0 (6.7%), 199.1 (3.8 %), 347.1 (1.9%), 357.1 (1.7%)
B	2950 (C-H *str.* ArH), 1560 (C=C *str.* ArH), 1525 (C=N *str.*), 1195 (C-N *str.*), 1055 (C-O *str.*), 810 (C-O-N *str.*)	7.26-7.47 (m, 4H, ArH), 2.10 (s, 1H, isoxazole ring), 6.81 (d, 2H, phenoxyl group), 7.49 (d, 2H, phenoxyl group), 1.12-1.89 (m, 8H, cyclohexane ring), 6.75 (s, 1H, soxazole), 7.51-8.10 (m, 5H, ArH), 1.89 (s, 1H, cyclohexane ring)
C	2953 (C-H *str.* ArH), 1570 (C=C *str.* ArH), 1505 (C=N *str.*), 1190 (C-N *str.*), 1035 (C-O *str.*), 3410 (NH *str.*)	7.38-7.75m, 4H, ArH), 6.87 (d, 2H, phenoxyl group), 7.49 (d, 2H, phenoxyl group), 1.24-1.27 (m, 8H, cyclohexane ring), 7.52 (d, 1H, pyrazole ring), 6.53 (d, 1H, pyrazole ring), 12.62 (s, 1H, NH, pyrazole ring), 1.92 (s, 1H, cyclohexane ring)
D	3010 (C-H *str.* ArH), 1585 (C=C *str.* ArH), 1470 (C=N *str.*), 1215 (C-N *str.*), 1045 (C-O *str.*), 3355 (NH *str.*)	7.26-7.39 (m, 4H, ArH), 6.42 (d, 2H, phenoxyl group), 8.02 (d, 2H, phenoxyl group), 1.25-1.27 (m, 8H, cyclohexane ring), 6.52 (s, IH, pyrazole ring), 12.02 (s, 1H, NH pyrazole ring), 7.39-7.99 (m, 5H, ArH), 1.95 (s, 1H, cyclohexane ring); *m/z*: 225.2 (100.0%), 272.2 (6.8%), 349.1 (5.9%), 360.2 (2.9%), 432.4 (0.8%)
E	3010 (C-H *str.* ArH), 1590 (C=C *str.* ArH), 1520 (C=N *str.*), 1160 (C-N *str.*), 1590 (NH, bending), 1035 (C-O *str.*), 1595 (N-N-*str.*), 745 (C-S *str.*)	7.43-7.45 (m, 4H, ArH), 6.81 (d, 2H, phenoxyl group), 7.62 (d, 2H, phenoxyl group), 1.20-1.90 (m, 8H, cyclohexane ring), 6.99 (s, 2H, NH, thiadiazole ring), 1.85 (s, 1H, cyclohexane ring)

Structures of these molecules were established on the basis of their elemental analysis for nitrogen, IR, ^1H NMR and MS spectral data (Tables 1 and 2).

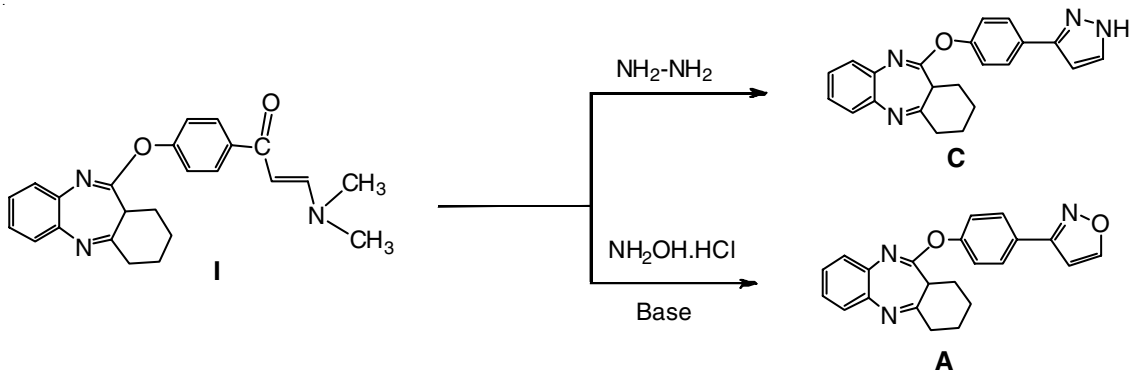
RESULTS AND DISCUSSION

Because of biological activities shown by 1,5-benzodiazepines, imidazoles, benzimidazoles, oxadiazoles, thiadiazoles, isoxazoles and pyrazoles derivatives makes an interest to work on the present system, which carried 1,5-benzodiazepine nucleus along with isoxazole, pyrazole, thiadiazole nuclei in the same molecule framework. The idea behind building such a system was to evaluate the better biological activities of these well-established molecules in a single molecular framework.

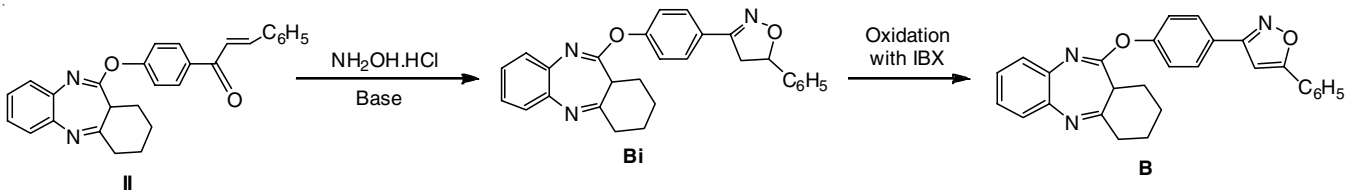
It was envisaged that the precursors which fulfilled this synthetic requirement were 1,5-benzodiazepine derivatives appended with amidines, imidate esters, thiosemicarbazones, dimethylaminomethylene ketone and chalcones from which isoxazoles (**A**) and (**B**), pyrazoles (**C**) and (**D**), thiadiazoles (**E**) were obtained easily in a one-pot reaction. Dimethylamino methylene ketone (**I**) was allowed to react with nucleophiles like hydrazine hydrate and hydroxyl amine hydrochloride to afford the corresponding isoxazole and pyrazole derivatives (**A**) and (**D**), respectively (**Scheme-I**).

Chalcones are known to react with nucleophiles, in the same way as do the dimethylaminomethylene ketone, therefore chalcone (**II**) was treated with bidentate nucleophiles such as hydroxylamine hydrochloride and hydrazine hydrate to produce the corresponding isoxazole (**B**) (**Scheme-II**) and pyrazole (**D**) derivatives (**Scheme-III**), respectively. The thiosemicarbazone derivatives **(III)** on treatment with ammonium ferric sulfate underwent cyclocondensation reaction to give 2-amino thiadiazole derivative (**E**) **(Scheme-IV)**.

IR studies: Structures of all the compounds (**A-E**) were established on the basis of elemental analysis, IR, ^1H NMR and MS data. The physical data of all the synthesized compounds were found to be consistent to the structures assigned to these molecules. The formation of compound isoxazole from dimethylamine methylene ketone (**I**) was ascertained by the appearance of two strong absorption bands at 1410 cm^{-1} (C=N *str.*) and 800 cm^{-1} (C-O-N *str.*) of isoxazole ring, along with the appearance of bands at 2890 cm^{-1} (C-H *str.*), 1600 cm^{-1} (arom. C=C *str.*), 1230 cm^{-1} (C-N *str.*) and 1010 cm^{-1} (C-O *str.*), which provided a good evidence to the formation of isoxazole (**A**). The formation of compound isoxazole (**B**) from chalcone (**II**) was indicated by the appearance of strong absorption bands at 810 cm^{-1} (C-O-N *str.*) of isoxazole ring. Along with this, the bands at 2950 cm^{-1} (C-H *str.*), 1560 cm^{-1} (arom. C=C

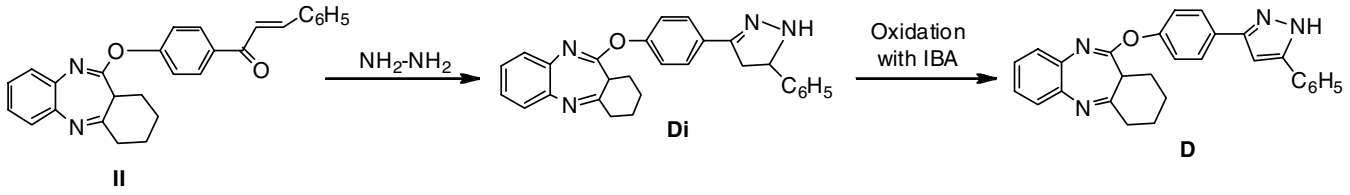


Scheme-I



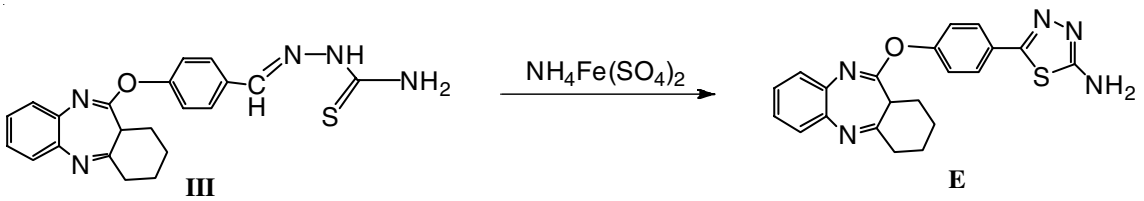
II Bi B

Scheme-II



II Di D

Scheme-III



III E

Scheme-IV

str.), 1150 cm^{-1} (C-N *str.*) 1525 cm^{-1} (C=N *str*.) and 1055 cm^{-1} (C-O *str.*), clearly suggested the formation of compound isoxazole (**B**).

The successful formation of compound pyrazole (**C**) from dimethylamino methylene ketone (**I**) was indicated by the appearance of peak in pyrazole (**C**) at 3410 cm^{-1} (NH *str*.) for pyrazole ring NH, 1570 cm^{-1} (C=C *str*.), 2953 cm^{-1} (C-H *str*.), 1035 cm^{-1} (C-O *str*.), 1140 cm^{-1} (C-N *str*.) for pyrazole and disappearance of band for C=C *str*. of α,β-unsaturated ketones at 1580 cm^{-1} of compound (**I**). It clearly indicated the formation of pyrazole ring in pyrazole (C) from its precursor (**I**). Appearance of the peak at 3355 cm^{-1} (NH *str*.), clearly ascertained the formation of pyrazole ring in pyrazole (**D**). Along with this, the appearance of bands at 3010 cm^{-1} (C-H *str*.), 1585 cm^{-1} (arom. C=C *str*.), 1215 cm^{-1} (C-N *str*.), 1470 cm^{-1} (C=N *str*.) and 1045 cm^{-1} (C-O *str*.) provided a good evidence for the formation of compound pyrazole (**D**) from chalcone (**II**). The formation of thiadiazole ring in compound thiadiazole (**E**) was shown by the appearance of peaks 1590 cm^{-1} (NH_2 bending *str*.), 1595 cm^{-1} (-N-N- *str*.) and C-S *str*. at 745 cm^{-1} of thiadiazole ring and other peak approximately in same region of as that benzimidazole (**III**).

^{1}H NMR spectra: The formation of isoxazole (**A**) from dimethylamine methylene ketone (**I**) was supported by the appearance of a downfield singlet at δ 6.75 ppm for proton of isoxazole ring. On comparison of the spectra of Dimethylamine methylene ketone (**I**) and isoxazole (**A**), the conversion of isoxazole (**A**) from its precursor dimethylamine methylene ketone (**I**) was clearly evident. The formation of the former from later was further supported by the disappearance of two downfield doublets at δ 8.10 and δ 7.40 ppm for HC=CH group of α,β-unsaturated ketone in dimethylamine methylene ketone (**I**). In this way, the formation of isoxazole ring in the compound isoxazole (**A**) from dimethylamine methylene ketone (**I**) was established from ^{1}H NMR spectrum. Similarly, the formation of compound isoxazole (**B**) from chalcone (**II**) compound was confirmed on the basis of their ^{1}H NMR. The formation of pyrazole (**C**) from dimethylamine methylene ketone (**I**) was supported by the appearance of broad downfield singlet at δ 12.62 ppm for one proton of NH of pyrazole ring, two doublets at δ 7.52 and δ 6.53 ppm for the proton of pyrazole ring and disappearance of two downfield doublets at δ 8.06 and δ 7.59 ppm for HC=CH group of α,β-unsaturated ketone, a sharp singlet at δ 3.04 ppm for $N(CH_3)_2$ group in ^{1}H NMR spectrum is also appeared of pyrazole (C). Similarly, the formation of compounds pyrazole (D) from compound chalcone (**II**) was confirmed on the basis of their ^{1}H NMR.

The formation of thiadiazole ring in compound thiadiazole (**E**) was evident from the singlet which appeared at δ 6.99 for NH_2 group attached to thiadiazole ring and disappearance of upfield singlet δ 2.20 ppm for =NH group and singlet at δ 8.34 ppm for =CH group of the thiosemicarbazone (**E**).

Conclusion

Various derivatives of isoxazole, pyrazole and thiadiazole were synthesized using cyclohexanol analogues of 1,5-benzodiazepines through phenoxyl/phenylamino linkage. The synthesized compounds were analyzed by elemental analysis and ^{1}H NMR, IR, mass spectrometric techniques. The ability to change the structures of these compounds affords a wide range of possibilities for the synthesis and development of novel therapeutic medicines with improved potency and lower toxicity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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