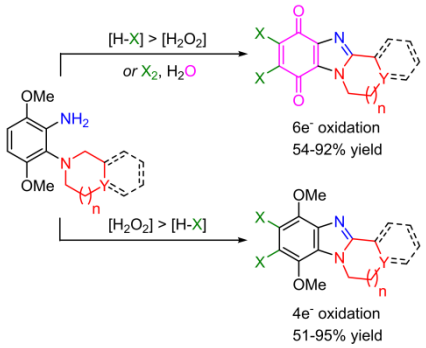
The One-Pot Synthesis of Dihalogenated Ring-Fused Benzimidazolequinones from 3,6-Dimethoxy-2-(cycloamino)anilines using Hydrogen Peroxide and Hydrohalic Acid

Martin Sweeney,[†] Lee-Ann J. Keane,[†] Michael Gurry,[†] Patrick McArdle[†] and Fawaz Aldabbagh*[,†,‡]

[†] School of Chemistry, National University of Ireland Galway, University Road, Galway, H91 TK33, Ireland

[‡] Department of Pharmacy, School of Life Sciences, Pharmacy & Chemistry, Kingston University, Penrhyn Road, Kingston upon Thames, KT1 2EE, United Kingdom

ABSTRACT: 3,6-Dimethoxy-2-(cycloamino)anilines undergo 4- or 6-electron oxidations to afford novel ring-fused halogenated benzimidazoles or benzimidazolequinones using H_2O_2/HCl or H_2O_2/HBr. Cl_2 and Br_2 are capable of the same oxidative transformation to the benzimidazolequinones. Labelling experiments indicate that water is necessary for oxidation of the *para*-dimethoxybenzenes to the corresponding quinones.



The cleanest method of generating elemental chlorine and bromine *in situ* is to mix hydrogen peroxide with excess hydrochloric and hydrobromic acid respectively, since the only by-product is water (Scheme 1).[1,2] The intermediate is hypohalous acid (HOX), which is commonly used to disinfect water. The molecular halogen (X_2) in water is in equilibrium with an acidic (HX) solution of HOX.[3,4]

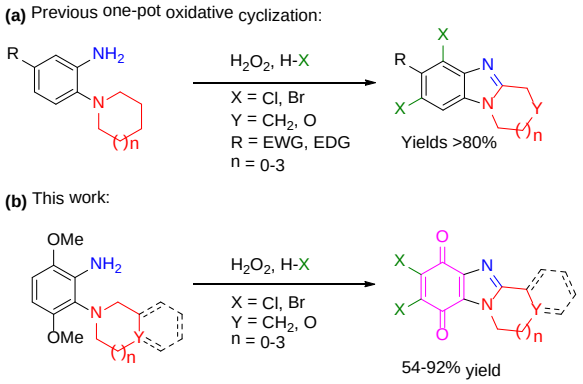
Scheme 1. Generation of X_2 from H_2O_2/HX

$$H_2O_2 + HX \longrightarrow HOX + H_2O \qquad (1)$$

$$HOX + HX \rightleftharpoons X_2 + H_2O \qquad (2)$$

The HOX solution has been used in the electrophilic halogenation of many aromatics.[2,5-8] On the other hand, H_2O_2 in trifluoroacetic acid (TFA) has traditionally been used to give ring-fused benzimidazoles from *o*-cyclic amine substituted anilines.[9] Recently, methanesulfonic acid (0.5-1 equiv) has replaced TFA in H_2O_2-mediated cyclizations to give alicyclic ring-fused benzimidazoles.[10] In comparison, the H_2O_2/HX system is relatively underutilized in the synthesis of heterocycles with H_2O_2/HBr used to catalyze the aziridination of alkenes with chloramine T.[11] One-pot H_2O_2/HX-mediated oxidative cyclization of *o*-cyclic amine substituted anilines with selective dichlorination and dibromination gave a series of five to eight-membered ring-fused benzimidazoles, generally in >80% yield (Scheme 2a).[8]

Scheme 2. H_2O_2/HX in the Preparation of Benzimidazoles and Benzimidazolequinones



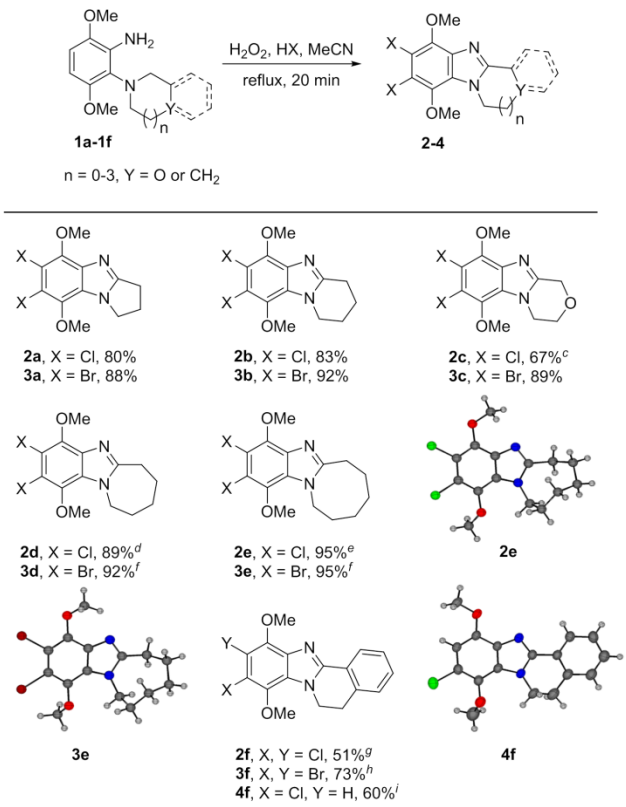
Skibo and co-workers popularized aziridinyl-substituted pyrrolo[1,2-*a*]benzimidazolequinones as bioreductive antitumor alternatives to the mitomycins,[12] and other groups reported benzimidazolequinones with useful cytotoxicity,[13-21] including specificity towards hypoxic tumor cells,[18] NAD(P)H:quinone oxidoreductase 1 (NQO1)[19] and Fanconi anemia cells.[20,21]

When *para*-dimethoxybenzenes are precursors, a two-step HBr-mediated demethylation to the hydroquinone followed by $FeCl_3$-mediated oxidation is used to give the benzimidazolequinone.[10,14,18,19] One step conversion of *para*-dimethoxybenzenes to the desired quinones has been effected with AgO,[22] $Ce(NH_4)_2(NO_3)_6$ (CAN),[13,23-25] CoF_3,[26] NBS with a catalytic amount of H_2SO_4,[20,27] and $PhI(OCOCF_3)_2$ (PIFA).[28] For one-step formation of quinones, H_2O_2/HX has advantages of high atom economy[29] and low cost. The simultaneous halogenation on the aromatic or the quinone can be useful for further nucleophilic aromatic substitution[14,15,30,31] and transition metal-catalyzed cross-couplings,[32,33] with the resultant functionalization significantly altering biological activity.[14,15,21,30,31,33] There are reports of low to moderate yields of oxidative demethylation with dihalogenation giving 5,6-dichloro- and 5,6-dibromobenzimidazolequinones using aqua regia (HNO_3/HCl (1:3))[15,16] and HBr/$NaBrO_3$, respectively.[16] However, the combination of 2-electron oxidation to the quinone with 4-electron oxidative cyclization in one-pot is unknown. Herein, we utilize H_2O_2/HX to carry out oxidative cyclization, aromatic

halogenation, and oxidative demethylation to give a new series of ring-fused dihalogenated benzimidazolequinones in mostly high yields (Scheme 2b). In all but one system, the protocol is tunable by adjusting the [H_2O_2] to [HX] ratio with high yields of the dihalogenated ring-fused dimethoxybenzimidazoles obtained when the [H_2O_2] is higher. Furthermore, the halogenation is selective to the activated aromatic or quinone moiety when an additional fused aromatic ring is in place.

Initially, 3,6-dimethoxy-2-(cycloamino)anilines **1a**-**1e** were treated with higher amounts of H_2O_2 (10 equiv) relative to HX (5 equiv) to give, in mostly high yields and without the need for chromatography, novel ring-fused dimethoxy-substituted benzimidazoles via a 4-electron oxidative cyclization and dihalogenation (Scheme 3). 2-(Pyrrolidin-1-yl)aniline **1a** and 2-(piperidin-1-yl)aniline **1b** were found to be consumed within 20 min in MeCN under reflux to give dichlorinated and dibrominated pyrrolo[1,2-*a*]benzimidazoles (**2a**, **3a**) and pyrido[1,2-*a*]benzimidazoles (**2b, 3b**) in yields of 80-92% (Scheme 3). For cyclizations of morpholine **1c**, azepane **1d** and azocane **1e** using H_2O_2/HCl, some oxidation to the benzimidazolequinone was detected at reflux. [1,4]Oxazino[4,3-*a*]benzimidazole **2c**, azepino[1,2-*a*]benzimidazole **2d**, and azocino[1,2-*a*]benzimidazole **2e** were selectively formed in good to high yields (67-95%) by lowering the reaction temperature (from reflux to 40 °C or rt) and increasing the reaction time (from 20 min to 2-24 h). Benzimidazolequinone formation was not detected in the HBr-mediated cyclizations of **1c**, **1d** and **1e** at reflux, with **3c** obtained in 89% yield, while a 6 h reaction time afforded complete dibromination to give **3d** and **3e** in excellent yield (92 and 95%, respectively). X-ray crystal structures for the eight-membered dichlorinated and dibrominated adducts **2e** and **3e** were obtained due to similarities of respective NMR spectra.

The utility of the H_2O_2/HX-mediated system was investigated using the more challenging 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3,6-dimethoxyaniline (THIQ substrate) **1f** with potential for halogenation on the additional aromatic ring (Scheme 3). Upon treatment of **1f** (0.07 M in MeCN) with H_2O_2 (10 equiv) and HBr (5 equiv) at reflux for 20 min, oxidative cyclization was observed at the benzylic position to afford **3f** in 73% yield. The isolation of dichlorinated analogue **2f** proved challenging under the same conditions due to the greater reactivity of the H_2O_2/HCl system. The H_2O_2/HCl system could be tuned to deliver mono- or dichlorination. At room temperature and a 4.5 h reaction time, only monochlorination was observed, affording **4f** in 60% yield, while reaction for 24 h afforded the dichlorinated product **2f** in 51% yield. The site of monochlorination was confirmed by X-ray crystallography on **4f**.



[a]Conditions: **1a**-**1f** (1.0 mmol), H_2O_2 (10 mmol), HX (5 mmol), MeCN (10 mL). [b]Isolated yields. [c]2 h, 40 °C. [d]24 h, rt. [e]5 h, 40 °C. [f]6 h. [g]MeCN (15 mL), 24 h, rt. [h]MeCN (15 mL). [i]MeCN (15 mL), 4.5 h, rt. X-ray crystal structures showing one of the two molecules in the asymmetric unit cell for **2e** and **3e** with thermal ellipsoids set at 40% probability (Figures S1 & S2), and for **4f** thermal ellipsoids set at 40% probability.

The room temperature reaction allowed reaction profiling by HPLC (Figure 1) with mass spectrometry detection of chlorinated aniline intermediate **1g**, suggesting that chlorination of **1f** occurs prior to oxidative cyclization. This observation may explain the selectivity, of other one-pot oxidative cyclizations to benzimidazoles with aromatic halogenations,[8] which can now be assumed to be a consequence of the NH_2 of the substrate strongly directing the initial electrophilic aromatic substitution.

Scheme 3. Synthesis of Dihalogenated Benzimidazoles using H_2O_2/HX[a,b]

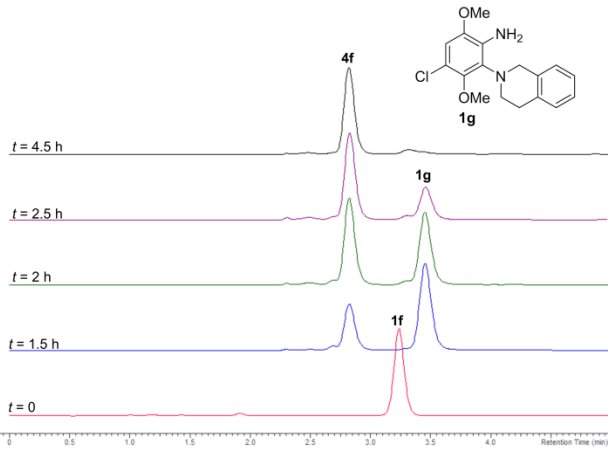
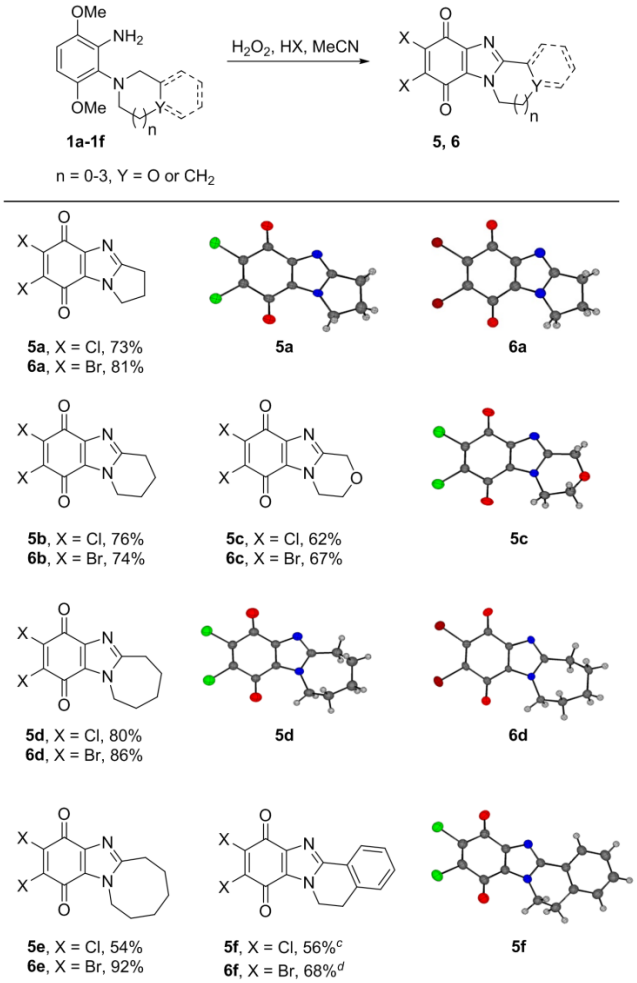


Figure 1. HPLC chromatograms as a function of time (*t*) for the reaction of 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3,6-dimethoxyaniline (**1f**) with H_2O_2 (10 equiv) and HCl (5 equiv) in MeCN (15 mL) at rt. ESI HRMS (Figure S3) was used to detect 4-chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)-3,6-dimethoxyaniline (**1g**).

To carry out the one-pot overall 6-electron oxidation, to afford dihalogenated quinones, conditions which favor X_2 formation were employed (Schemes 1 and 4). H_2O_2 (50 equiv) and HCl (180 equiv) converted anilines **1a-1d** into dichlorinated ring-fused benzimidazolequinones **5a-5d** in moderate to high yields (62-80%) after 4 h in MeCN at 80 °C, while **5e** was isolated in 54% yield. For the H_2O_2/HBr-mediated transformations, the high concentrations of HBr required for quinone formation made it desirable to perform brominations under solvent-free conditions (except for **6f**, which necessitated the use of MeCN due to the lower solubility of **1f** in HBr). Dibrominated analogues **6a-6e** were obtained in high yield (67-92%) using H_2O_2 (60 equiv) in neat HBr (30 mL) under reflux for 12 h. Ring-fused dihalogenated benzimidazolequinones (Scheme 4) were purified by flash column chromatography with the exception of dibrominated pyrrolo[1,2-*a*]benzimidazolequinones **6a**, which was isolated cleanly without purification. X-ray crystal structures of 7,8-dichloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole-6,9-dione (**5c**), dichlorinated and dibrominated pyrrolo[1,2-*a*]benzimidazolequinones **5a** and **6a**, and azepino[1,2-*a*]benzimidazolequinones **5d** and **6d** were obtained. Isolation of significant amounts of 9,10-dichloro-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline-8,11-dione (**5f**) was however not possible by treatment of THIQ **1f** with a high molar ratio of HCl relative to H_2O_2 at reflux. The reaction gave mainly inseparable products with ESI HRMS (*m/z* 388.9-392.9) indicative of tetrachlorination (Figure S4). This led us to employ the relatively mild conditions of H_2O_2 (10 equiv) and HCl (5 equiv) at rt, that allowed aromatic monochloride and dichloride **4f** and **2f** to be isolated in good yields after 4.5 and 24 h, respectively (Scheme 3, Figure 1), with extension to 72 h giving benzimidazolequinone **5f** in 56% isolated yield (Scheme 4, Figure S5 for the HPLC chromatographs). The structure of **5f** was confirmed by X-ray crystallography. In contrast the dibrominated analogue **6f** was isolated in 68% yield from a 7 h reflux in the presence of a large excess of HBr; overbromination adducts were not detected. This is in line with the greater reactivity of Cl_2 relative to Br_2 in electrophilic halogenation reactions.[34]

Scheme 4. Synthesis of Dihalogenated Benzimidazolequinones using H_2O_2/HX[a,b]

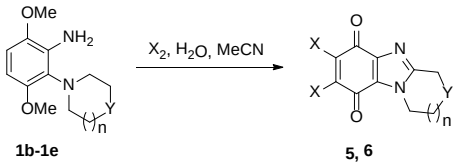


[a]Conditions: For the synthesis of dichlorides **5a-5e: 1a-1e** (1.0 mmol), H_2O_2 (50 mmol), HCl (180 mmol), MeCN (10 mL), 4 h, 80 °C. For the synthesis of dibromides **6a-6f**: **1a-1f** (1.0 mmol), H_2O_2 (60 mmol), HBr (30 mL), 12 h, reflux. [b]Isolated yields. [c]H_2O_2 (10 mmol), HCl (5 mmol), MeCN (15 mL), 72 h, rt. [d]HBr (135 mmol), MeCN (15 mL), 7h. X-ray crystal structures shown of **5a**, **5c**, **5d**, **5f**, **6a**, and **6d** have thermal ellipsoids set at 40% probability. Crystal structure of **6a** is one of the six molecules in the asymmetric unit cell (Figure S6).

Due to the suspected high concentration of Cl_2 or Br_2 in the one-pot 6-electron oxidative cyclizations with dihalogenation, we decided to investigate if the formation of ring-fused dihalogenated benzimidazolequinones could be effected by elemental X_2, with or without water. Chlorine gas was bubbled into a solution of anilines **1b-1e** in MeCN containing added H_2O (Table 1). Dichlorinated benzimidazolequinones **5b**, **5c** and **5d** were isolated, but in lower yields in comparison to H_2O_2/HCl method, although **5e** was given in a comparable yield of 58% in this 10 min reflux reaction. A comparative study, using **1c** and Cl_2 was carried out in an equivalent amount of water (10.75 mL) to the H_2O_2/HCl protocol, however the yield of **5c** was decreased further from 54% to 47%. Thus, water is required but not to the extent of the H_2O_2/HCl method. Moreover, yields deteriorated when the Cl_2 reaction was performed under anhydrous conditions with inseparable products given. Over-

chlorination of 1-methylnapthalene was observed by Johnson et al. when Cl_2 was used under aprotic conditions.[35] Higher yields (71-90%) were achieved for the analogous one-pot transformation giving dibrominated benzimidazolequinones **6b**, **6d** and **6e** using Br_2 and H_2O at 40 °C for 4 h, which is indicative of the greater control achieved with less reactive Br_2 (that is not susceptible to further bromination).

Table 1. Synthesis of Dihalogenated Benzimidazolequinones using Elemental Chlorine and Bromine[a,b]



1b-1e **5, 6**

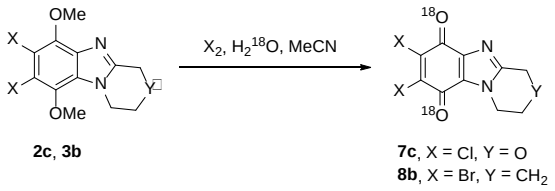
aniline	X	Y	n	yield (%)
1b	Cl	CH_2	1	**5b**, 41
1c	Cl	O	1	**5c**, 54
1c	Cl	O	1	**5c**, 47[c]
1d	Cl	CH_2	2	**5d**, 71
1e	Cl	CH_2	3	**5e**, 58
1b	Br	CH_2	1	**6b**, 71
1d	Br	CH_2	2	**6d**, 90
1e	Br	CH_2	3	**6e**, 90

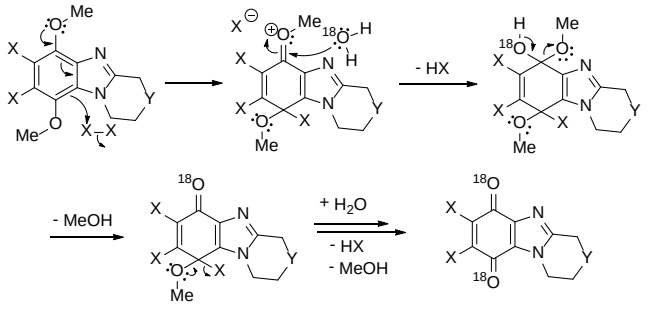
[a]Conditions: For synthesis of dichlorides: **1** (1.0 mmol), Cl_2 (50.0 mmol), H_2O (1.8 mL), MeCN (10 mL), reflux, 10 min. For synthesis of dibromides: **1** (1.0 mmol), Br_2 (50 mmol), H_2O (1.8 mL), MeCN (10 mL), 40 °C, 4 h. [b]Isolated yields. [c]H_2O (10.75 mL).

Finally we investigated the role of water in the quinone formation step. 7,8-Dihalo-6,9-dimethoxybenzimidazoles **2c** and **3b** were respectively treated with Cl_2 and Br_2 (both 50 equiv), and $H_2{}^{18}O$ (100 equiv) in MeCN (Scheme 5). The formation of the doubly ^{18}O-labelled dihalogenated benzimidazolquinones **7c** and **8b** was confirmed by EI-MS (Figure S7 & S8). It follows that for both the Cl_2 and Br_2-mediated reactions, MeO-aryl bond cleavage occurred, and quinone formation did not proceed through the hydroquinone. A control experiment treating 7,8-dichloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole-6,9-dione **5c** with $H_2{}^{18}O$ for 4 h indicated no exchange.

In conclusion, H_2O_2/HX has led to an unprecedented one-pot 6-electron oxidative transformation to yield a new series of ring-fused dihalogenated benzimidazolequinones. The elemental halogens (X_2) generated *in situ* from H_2O_2/HX are shown to be the active species in the oxidative synthesis. When a higher molar ratio of H_2O_2 relative to HX is employed, the X_2 concentration is lower, and the 4-electron oxidative cyclization is not accompanied by oxidation to the quinone, allowing the selective formation of a new series of ring-fused dihalogenated benzimidazoles.

Scheme 5. Detecting the role of water in Quinone formation with proposed mechanism[a]





[a]Reaction conditions: For dichloride **7c**: **2c** (0.07 mmol), Cl_2 (3.40 mmol), $H_2{}^{18}O$ (0.14 mL), dried MeCN (0.73 mL), reflux, 10 min. For dibromide **8b**: **3b** (0.04 mmol), Br_2 (2.05 mmol), $H_2{}^{18}O$ (0.08 mL), dried MeCN (1 mL), 40 °C, 4 h.

ASSOCIATED CONTENT

Supporting Information (SI)

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXXXXXXXXX.
SI contains detailed experimental, synthetic procedures, characterization data, NMR spectra and crystallographic data for all new compounds (PDF).

Accession Codes

CCDC 1863022-1863030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting, The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: f.aldabbagh@kingston.ac.uk

ORCID

Fawaz Aldabbagh: 0000-0001-8356-5258

Notes

The authors declare no competing financial interest.

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