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Synthesis of some new carbohydrate-containing thiouriedonaphtho-quinones

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Abstract New alkyl, aryl, and glycosylthiouriedo derivatives of 2,3-diamino-1,4-naphthoquinone were synthesized via the reaction of isothiocyanates with 2,3-diamino-1,4-naphthoquinone. The new compounds were fully characterized through their physicochemical properties.

Keywords Thiourea · Quinones · Glycosylthioureido derivatives · 2,3-diaminonaphthoquinones

Introduction

Flora with naphthoquinone constituents are widely used in folk medicine in Asia and South America to treat malignant and parasitic diseases. Many naturally occurring compounds with a naphthoquinone nucleus are well known for their biological activities, such as alkanin [1], shikonin [1], lawsone [2], lapachol [3], plumbagone [2], juglone [2] or streptonigrin (**1**) [4], which is a potent antitumor agent. Many synthetic 1,4-napththoquinone-containing compounds exhibit significant pharmacological properties including antitumor, wound-healing,

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anti-inflammatory, antiparasitic, antibacterial, antifungal, antiviral, insecticidal, antipyretic, or cytotoxic [5, 6]. In fact, some clinically important anticancer drugs, such as daunorubicin or mitomycin C (**2**), contain the quinone moiety as a relevant part of their structures. These biological activities have justified the large number of studies found in the literature aimed at the synthesis and evaluation of either natural quinones or their analogs as potential pharmacological agents [7–9].

Among naphthoquinone derivatives, aminonaphthoquinones are considered as lead structures for the development of antifungal and antimalarial drugs. Simple 2-amino-3-chloro-1,4-naphthoquinone (**3**) shows good potency as an antimalarial agent, and its potency is greater than chloroquine (**4**) which has been used to treat malaria for many decades [2]. Also, 2,3-diamino-1,4-naphthoquinone (**5**) has promising antibacterial activity [2]. Several derivatives of aminonaphthoquinone have been reported in the literature including various amide [10], heterocycle [11–13], and alkyl derivatives (see Fig. 1).

As no uriedo or thiouriedo derivatives of naphthoquinone have so far appeared in the literature, we report in this paper selected derivatives of this class of compounds. The thiourea linkage is well known for its stability [14], ease of synthesis, and tendency to undergo various transformations including cycloaddition reactions. Thiourea was reported to be transformed into various heterocycles such as thiohydantoins [15], imidazolidines [16], isoxazoles [17], and imidazoles, or to be part of linkages [18]. Sugar derivatives of thioureas have been extensively studied and still constitute a field with a promising future due to the biological activities of some derivatives and their ability to be converted into different types of nucleosides [15].

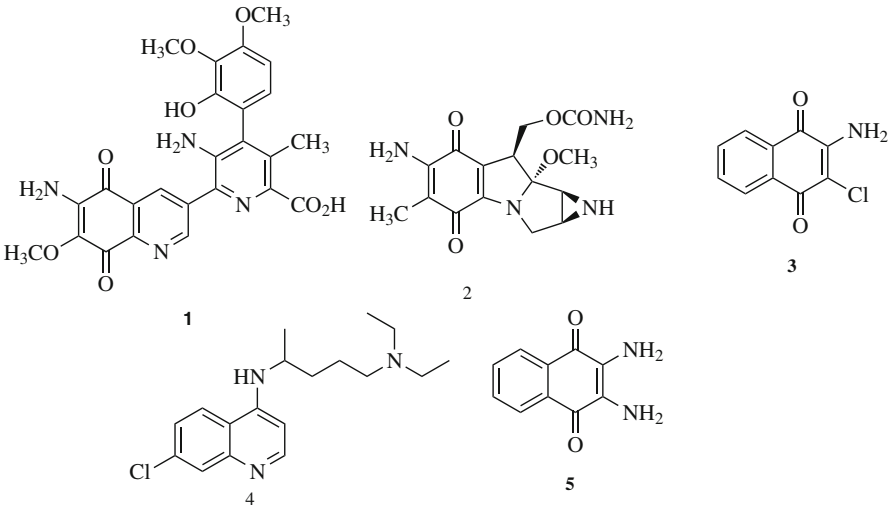


Fig. 1 Structures of streptonigrin (**1**), mitomycin C (**2**), 2-amino-3-chloronaphthoquinone (**3**), chloroquine (**4**), and 2,3-diaminonaphthoquinone (**5**)

Experimental

General

Thin-layer chromatography (TLC) was performed using Merck-GF254 silica gel plates with a 0.25-mm silica layer. TLC plates were developed in a variety of solvent systems as indicated. Solvent system ratios refer to volume per volume ratios. Detection of compounds was accomplished by their florescence under ultraviolet light (254 nm). Melting points were determined on a SMP2 Stuart apparatus. Infrared spectra (IR) were obtained as potassium bromide (KBr) disks on a Nicolet-MAGNA-IR-560 apparatus, and only characteristic peaks are indicated as wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DBX-300 spectrometer with DMSO-d_6 as solvent and TMS as standard. The peak multiplicities of the signals are abbreviated as follows: s, singlet; d, doublet; and m, multiplet. The coupling constants (J) were calculated and reported to the nearest 0.10 Hz. High-resolution mass spectral data (HRMS) were recorded on a FT-MS Bruker APEX IV mass spectrometer operated in the electron spray-ionization (ESI) mode.

Reactions of diamine 2 with isothiocyanates; typical procedure

An amount of 1 mmol of isothiocyanate [24] was added to a solution of 2,3-diamino-1,4-naphthoquinone (**5**, 206 mg, 1.1 mmol) in dichloromethane (10 ml). The mixture was stirred for 24 h at room temperature. The solvent was removed by evaporation under vacuum and the residue purified by column chromatography (hexane:ethyl acetate 2:1) to afford the thiourea products **6a–h.**

2-(*N′*-Phenylthiouriedo)-3-amino-1,4-naphthoquinone (**6a**)

Yield: 216 mg, 67 %; m.p. (206–208 °C). IR (KBr): $\overline{\nu}$ = 2,919, 1,572, 1,608, 1,741, 3,339 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 8.73 (s, 2H), 6.97–7.97 (m, 9H), 6.84 (s, 1H). ^{13}C NMR (DMSO-d_6): 182.1, 178.7, 153.3, 142.0, 140.2, 135.1, 133.1, 132.4, 130.7, 129.2, 126.1, 126.1, 122.3, 118.6, 114.8. HRESIMS *m/z*: calcd. for $C_{17}H_{13}N_3O_2SNa$ $[M + H]^+$ (346.06262), found (346.06207).

2-(*N′*-Methylthiouriedo)-3-amino-1,4-naphthoquinone (**6b**)

Yield: 208 mg, 80 %; m.p. (216–218 °C). IR (KBr): $\overline{\nu}$ = 3,395, 2,925, 1,608, 1,557 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.37 (s, 1H), 7.97 (t, J = 6.3 Hz, 2H), 7.83 (t, J = 7.2 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.60 (s, 1H), 6.92 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (DMSO-d_6): 182.2, 178.2, 146.8, 135.2, 133.1, 132.7, 130.8, 126.1, 126.0, 112.8, 31.9. HRESIMS *m/z*: calcd. for $C_{12}H_{12}N_3O_2S$ $[M + H]^+$ (262.06502), found (262.06447).

2-(*N′*-*p*-Chlorophenylthiouriedo)-3-amino-1,4-naphthoquinone (**6c**)

Yield: 318 mg, 82 %; m.p. (213–215 °C). IR (KBr): $\overline{\nu}$ = 3,339, 2,919, 1,644, 1,557 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 1H), 8.77 (s, 2H), 7.35–8.00 (m, 8H),

7.15 (s, 1H). ^{13}C NMR (DMSO-d_6): 182.3, 180.9, 178.0, 146.5, 139.2, 135.3, 133.1, 132.8, 130.8, 128.8, 128.5, 126.1. HRESIMS *m/z*: calcd. for $C_{17}H_{11}Cl_1N_3O_2S$ $[M–H]^+$ (356.02605), found (356.02660).

2-(*N*′-Benzylthiouriedo)-3-amino-1,4-naphthoquinone (**6d**)

Yield: 202 mg, 60 %; m.p. (200–202 °C). IR (KBr): $\overline{\nu}$ = 3,288, 2,925, 1,608, 1,578 cm^{-1}. ^{1}H NMR (DMSO-d_6): 8.53 (s, 1H), 8.17 (s, 1H), 7.27–7.98 (m, 9H), 7.01 (s, 1H), 4.72 (d, J = 6.0 Hz, 2H). ^{13}C NMR (DMSO-d_6): 182.3, 178.3, 147.1, 139.8, 135.2, 134.5, 133.2, 132.7, 130.9, 128.5, 127.5, 127.0, 126.5, 126.1, 126.0, 48.0. HRESIMS *m/z*: calcd. for $C_{18}H_{15}N_3O_2S_1Na$ $[M + Na]^+$ (360.0783), found (360.0777).

2-(*N*′-2,3,4,6 Tetra-*O*-acetyl-β-D-glucopyranosylthiouriedo)-3-amino-1, 4-naphthoquinone (**6e**)

Yield: 410 mg, 71 %; m.p. (163–165 °C). $[\alpha]_D^{25}$ = + 84° (*c* 0.14, CH_2Cl_2). IR (KBr): $\overline{\nu}$ = 3,308, 2,925, 1,613, 1,536, 1,747 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.84 (s, 1H), 8.15 (s, 1H), 7.94 (d, J = 7.4 Hz,1H), 7.88 (d, J = 7.3 Hz,1H), 7.78 (t, J = 7.3 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 6.95 (s, 2H), 5.86 (t, J = 9.3, 1H), 5.24 (t, J = 9.2 Hz, 1H), 4.84 (d, J = 9.1 Hz, 2H), 4.15 (m, 1H), 3.93 (m, 2H), 1.86–2.01 (s, 12H). ^{13}C NMR (DMSO-d_6): δ 183.2, 182.2, 177.7, 170.5, 170.0, 169.8, 169.6, 135.2, 133.2, 132.7, 130.8, 126.2, 126.0, 82.9, 73.6, 72.6, 70.8, 68.0, 62.1, 21.1, 20.90, 20.8. HRESIMS *m/z*: calcd. for $C_{25}H_{27}N_3O_{11}SNa$ $[M + Na]^+$ (600.1264), found (600.1319).

2-(*N*′-2,3,4,6 Tetra-*O*-acetyl-β-D-galactopyranosylthiouriedo)-3-amino-1, 4-naphthoquinone (**6f**)

Yield: 311 mg, 54 %; m.p. (155–157 °C). $[\alpha]_D^{25}$ = + 440° (*c* 0.05, CH_2Cl_2). IR (KBr): $\overline{\nu}$ = 3,323, 2,919, 1,752, 1,623, 1,537 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.80 (s, 1H), 8.30 (s, 1H), 7.97 (d, J = 6.2 Hz, 1H), 7.93 (d, J = 7.4 Hz, 1H), 7.81 (t, J = 7.0 Hz, 1H), 7.74 (t, J = 7.1 Hz, 1H), 6.92 (s, 2H), 5.84 (m, 1H), 5.26–5.02 (m, 3H), 4.25 (m, 1H), 4.00 (m, 2H), 1.87,, 1.89, 2.11 (each s, each 3H, 4 CH_3). ^{13}C NMR (DMSO-d_6): δ 183.3, 182.2, 170.4, 170.1, 169.8, 135.2, 133.1, 132.7, 130.8, 126.2, 126.0, 92.1, 71.5, 68.7, 68.5, 68.0, 61.7, 21.3. HRESIMS *m/z*: calcd. for $[M-H]^-$ (576.1288), found (576.1294).

2-(*N*′-2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosylthiouriedo)-3-amino-1,4-naphthoquinone (**6g**)

Yield: 303 mg, 60 %; m.p. (132–134 °C). $[\alpha]_D^{25}$ = + 252° (*c* 0.11, CH_2Cl_2). IR (KBr): $\overline{\nu}$ = 3,323, 2,919, 1,752, 1,623, 1,537 cm^{-1}. ^{1}H NMR ($CDCl_3$-*d*): 8.18 (s, 1H), 8.06 (d, J = 6 Hz, 2H), 7.74 (t, J = 6.0 Hz, 1H), 7.65 (t, J = 6.0 Hz, 1H), 7.34 (s, 1H), 6.05 (s, 2H), 5.53 (d, J = 9.0 Hz, 1H), 5.27 (m, 2H), 4.04 (d, J = 12.0 Hz, 2H), 3.79 (d, J = 12.0 Hz, 1H), 1.92–2.15 (s, 9H). ^{13}C NMR ($CDCl_3$-

d): 182.0, 181.1, 179.1, 171.7, 170.1, 169.6, 134.9, 132.7, 132.3, 130.4, 126.6, 126.6, 84.0, 70.4, 68.4, 68.2, 66.0, 20.8, 20.7, 20.5. HRESIMS *m/z*: calcd. for $C_{22}H_{23}N_3O_9SNa$ $[M + Na]^+$ (528.1053), found (528.1047).

2-(*N*′-Hepta-*O*-acetyl-β-lactosylthiouriedo)-3-amino-1,4-naphthoquinone (**6h**)

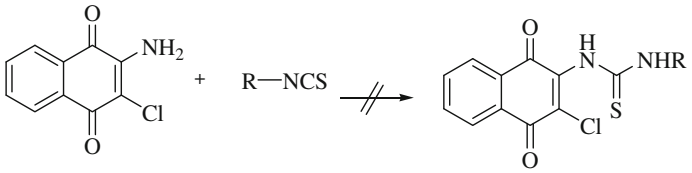
Yield: 545 mg, 63 %; m.p. (108–110 °C). $[\alpha]_D^{25} = -267°$ (*c* 0.06, CH_2Cl_2). IR (KBr): $\overline{v} = 3{,}334, 2{,}925, 1{,}747, 1{,}618, 1{,}536\ cm^{-1}$. ^1H NMR (DMSO-d_6): 8.80 (s, 1H), 8.15 (s, 1H), 7.94 (d, $J = 7.5$, 1H), 7.88 (d, $J = 7.5$ Hz, 1H), 7.80 (t, $J = 7.2$ Hz, 1H), 7.70 (t, $J = 7.3$ Hz, 1H), 6.90 (s, 2H), 5.76 (s, 1H), 5.18 (m, 1H), 5.09 (d, $J = 9.5$ Hz, 2H), 4.80 –4.71 (m, 3H), 4.02 (m, 2H), 3.97 (m, 3H), 3.75 (m, 2H), 1.86, 1.88, 1.93, 2.00, 2.06 (each s, 7 CH_3). ^{13}C NMR (DMSO-d_6): 183, 182.2, 170.8, 170.4, 170.4, 170.0, 169.9, 169.6, 135.2, 133.1, 132.8, 130.8, 126.2, 126.1, 100.0, 76.3, 73.8, 70.8, 70.1, 69.3, 67.6, 62.8, 61.4, 21.2, 21.1, 21.0, 20.9, 20.8. HRESIMS *m/z*: calcd. for $C_{37}H_{43}N_3O_{19}SNa$ $[M + Na]^+$ (888.2110), found (888.2002).

Results and discussion

Our strategy to prepare naphthoquinone-containing compounds starts with the reaction of 2-amino-3-chloro-1,4-naphthoquinone (**3**) [19] with two different isothiocyanates (Scheme 1). Under standard conditions [15], the target thiourea could not be isolated. Our attempt to prepare the desired compound was unsuccessful, even after using various solvents (DMSO, DMF, pyridine, acetonitrile) and temperatures (up to 80 °C), or the addition of a strong base, such as sodium hydride.

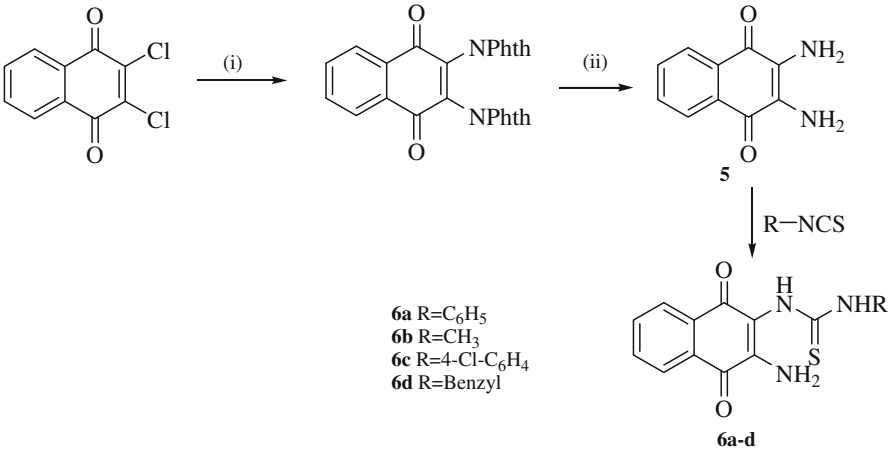
The low nucleophilicity of amine **3** could be attributed to the amide-like character of its nitrogen [20], due to the crowded presence of neighboring electron-withdrawing groups, in addition to electronic factors arising from the aromatic nature of the amine. As the nucleophilicity of the amine can be increased by introducing a neighboring amino group, thereby enlarging the electron density over the quinone ring, the naphthoquinone derivative **5** was prepared via reaction of 2,3-dichloro-1,4-naphthoquinone with potassium phthalamide followed by treatment with hydrazine as reported in the literature [21] (Scheme 2).

The available reactive diamine reacted smoothly with phenyl isothiocyanate in dichloromethane at room temperature affording the phenylthiourea **6a** in good yield.



3
R= Me, Ph

Scheme 1 Reaction of 2-amino-3-chloro-1,4-naphthoquinone with methyl and phenyl isothiocyanates



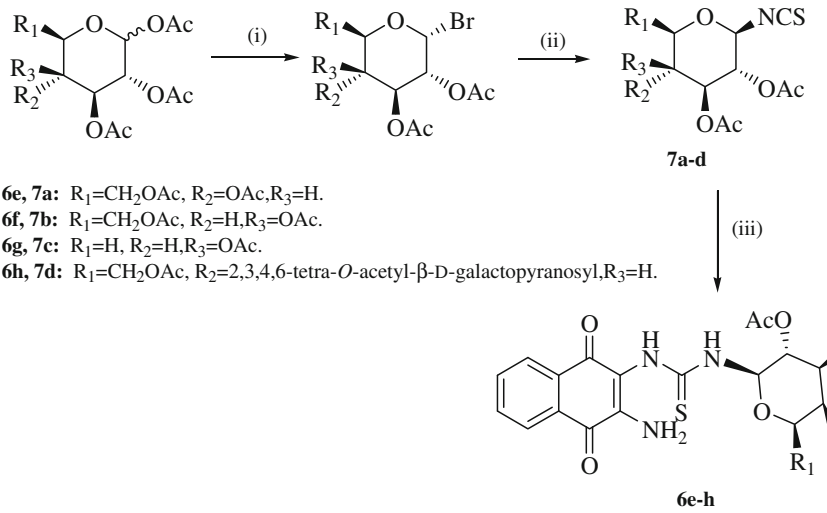
Scheme 2 Reagents and conditions: (*i*) potassium phthalamide, CH_3CN, reflux 5 h; (*ii*) $NH_2NH_2{\cdot}H_2O$

The result of this synthesis shows that only one amino group of the diamine reacts with the isothiocyanate, as no traces of bis-thiourea were observed, even when using excess isothiocyanate up to five equivalents.

All three applied isothiocyanate derivatives (methyl, *p*-chlorophenyl, and benzyl) produced monothiourea products only. The structures of the new compounds were confirmed by their ^{1}H NMR ^{13}C NMR, IR, and mass spectra. Signals at $\delta \approx 180$ ppm identified the C=S functional groups in the ^{13}C NMR spectra, and NH groups were characterized by IR-bands around 3,300 cm^{-1}. Exchangeable NH protons appear around 7–9 ppm downfield in the ^{1}H NMR spectra [22, 23].

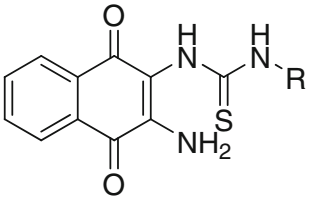
Our major goal in this work was to incorporate carbohydrate moieties into naphthoquinones via an urido linkage, and, as examples, four different sugar isothiocyanate derivatives (**7a–d**) were synthesized (Scheme 3) [24]: β-D-glucopyranosyl (**7a**), α-L-arabinopyranosyl (**7b**), β-D-galactopyranosyl (**7c**), and β-lactosyl isothiocyanates (**7d**) were reacted with the diamine **5**, under standard conditions as given in Scheme 2 to produce the new compounds **6e–h** (Scheme 3). The products were isolated in good to excellent yields as shown in Table 1.

All new sugar-containing naphthoquinones were characterized via their spectroscopic properties. The IR spectra of sugar thioureas **6e–h** show bands around 1,750 and 2,920 cm^{-1} corresponding to C=O of acetates and to stretching C–H bonds of the sugar moieties, respectively. The ^{1}H NMR spectra show signals in agreement with the proposed structures for the thioureas. Three exchangeable NH signals appear in the range of 6.05–8.73 ppm. Sugar proton signals resonate in the range of 3.79–5.84 ppm. The β-linkage of the sugar moiety (α in the case of **6g** was deduced via the coupling constant of the anomeric protons which were in all cases around 9 Hz [24]), clearly indicating a 1,2-*trans* configuration. The $^4C_1$ conformation of the pyranoid ring was established from the vicinal coupling constants between the protons in the sugar pyranoid ring ($J = 7$–10 Hz). The ^{13}C NMR spectra show peaks around 183 ppm arising from the C=S group. The carbonyls of the quinone



Scheme 3 (*i*) 33 % HBr in AcOH (glacial), (*ii*) KSCN, melt 190 °C, 5 min, (*iii*) 2,3-diaminonaphthoquinone, DCM, r.t.

Table 1 Preparation of thiouriedodiaminonaphthoquinone **6a-h**



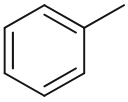
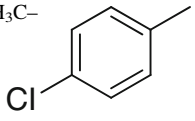
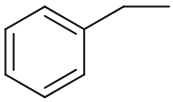
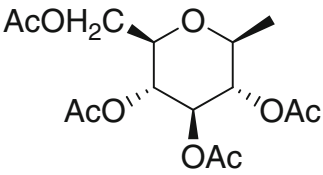
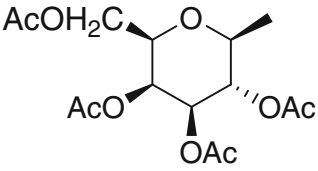
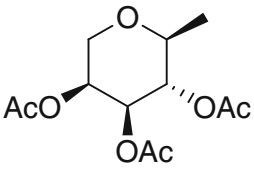
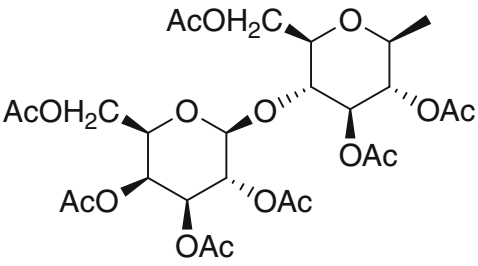
	R	Time (h)	% Yield	m.p.
6a		24	67	206–208
6b	H_3C–	24	80	216–218
6c		24	82	213–215

Table 1 continued

	R	Time (h)	% Yield	m.p.
6d		24	60	200–202
6e		24	71	163–165
6f		24	54	155–157
6g		24	60	132–134
6h		24	63	108–110

moiety resonate in the range of 177.7–182.2 ppm, which is in full agreement with the reported signals in the literature [25].

The biological evaluation of the new aminonaphthoquinone thioureido derivatives are in progress in our laboratory.

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