

Benzo[*b*]thiophene Derivatives. XXII.
 Synthesis of the Isomeric 5-Methyl-6-methoxy- and
 5-Methoxy-6-methylbenzo[*b*]thiophene-2-carboxylic Acids (1)

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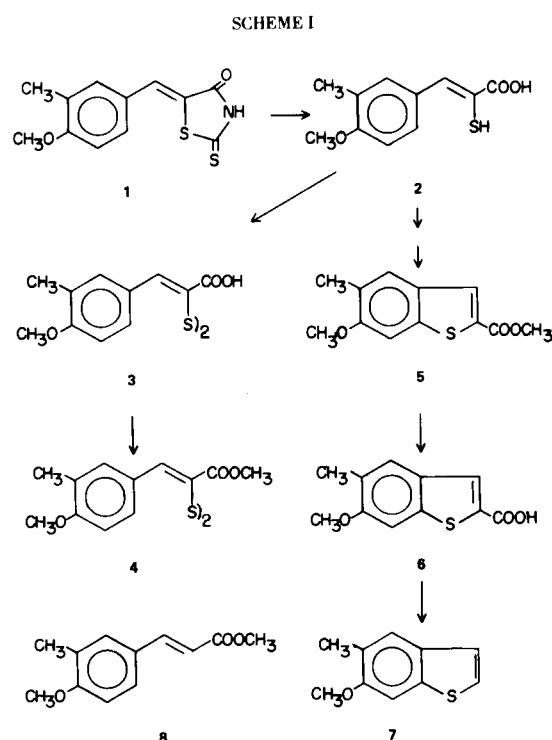
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Received April 21, 1975

The two isomeric benzo[*b*]thiophene-2-carboxylic acids having methyl and methoxy groups at positions 5 and 6 have been prepared and characterized. Both acids have been decarboxylated to the corresponding isomeric 5,6-disubstituted benzo[*b*]thiophenes, and esterified to their methyl esters. The intermediate rhodanines, α -mercaptocinnamic acids and corresponding disulfides are described. An unusual by-product in the oxidative cyclization of β -3-methyl-4-methoxyphenyl- α -mercaptoacrylic acid with iodine is shown to be *trans*-3-methyl-4-methoxycinnamic acid, which can also be formed directly from the mercaptoacrylic acid by reduction with hydrogen iodide.

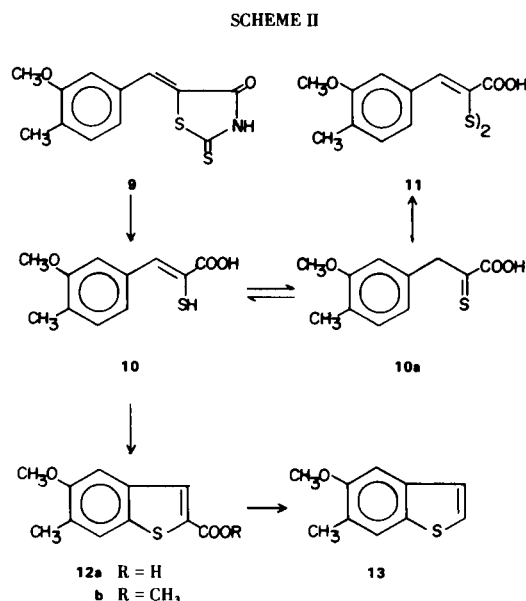
A number of benzo[*b*]thiophenes having various substituents on the benzene ring have been synthesized by the oxidative cyclization of substituted α -mercaptocinnamic acids (3). This synthesis is particularly effective when there are electron-releasing groups *para* to the site of ring-closure, and a number of alkoxy substituted benzothiophenes have been prepared by this procedure (4). However, when alkoxy groups were *meta* to sites of ring-closure, it has been our experience that tars and resinous by-products were formed, and the desired benzo[*b*]thiophene-2-carboxylic acids were obtained in low yield (4a). Chakrabarti and co-workers (4b) report improved yields even in these unfavored cyclizations, using chlorine in dry carbon tetrachloride. However, ring chlorination occurs to contaminate the product (5) and in our hands this method has not been satisfactory (4c,6).

We have now examined the cyclization of the isomeric β -aryl- α -mercaptoacrylic acids, having a methyl group *ortho* or *para* to the site of ring closure, and a methoxy group *meta* (2, Scheme I) or a methoxy group *ortho* or *para* to the site of ring closure, and a methyl group *meta* (10, Scheme II), using iodine in refluxing dioxane, as previously reported (7). As was expected, the yield of cyclized product 6 was relatively low (30%) when 2 was so treated, and resinous substances, as well as an unusual by-product (8), was isolated from the mixture. On the other hand, cyclization of 10 gave a quite satisfactory yield (63%) of the benzo[*b*]thiophene-2-carboxylic acid 12a, relatively free of other condensation products. The yield in the cyclization of 2 compares quite favorably to that obtained from β -4-methoxyphenyl- α -mercaptoacrylic acid (7.5%)



under similar conditions (4a), and the yield of 12a is also about equivalent to that reported in the cyclization of β -3-methoxyphenyl- α -mercaptoacrylic acid (4b).

The title compounds, not previously reported, were characterized by nmr spectra. Both the acids and their methyl esters exhibited characteristic singlets in the 60 megacycle spectrum for protons at the 3-position at $8.02 \pm$



0.05 δ , for a single proton adjacent to a methyl group at position 4 in the range of $7.73 \pm 0.10 \delta$, or at $7.41 \pm 0.14 \delta$ for a single proton adjacent to a methoxy group. The singlet protons at position 7 are in approximately the same range, at $7.43 \pm 0.18 \delta$ when flanked by a methoxy group at 6 (**5** or **6**) and at $7.75 \pm 0.08 \delta$ when flanked by a methyl group at 6 (**12a** or **12b**). These data are consistent with cyclization occurring only to positions *para* to methyl or methoxy groups, respectively, and the chemical shifts are in the range expected from previous data (4c). The structure of **6** was further confirmed by decarboxylation to form the known 5-methyl-6-methoxybenzo[*b*]thiophene, **7**, which had previously been prepared by cyclization of 3-methoxy-4-methylphenyl β,β -diethoxyethyl sulfide (**8**). The isomeric 5-methoxy-6-methylbenzo[*b*]thiophene **13** was also prepared from **12a**, and shown to have different physical properties.

The acid obtained when **2** was treated with excess iodine in dioxane was a tarry brown solid which could not be purified. It was therefore converted to a mixture of methyl esters which was amenable to column chromatography, yielding 37% of pure **5** and 12% of methyl *trans*-3-methyl-4-methoxycinnamate (**8**), identified by mass spectrum and previously reported characteristics (9). The presence of **8** as by-product in the iodine oxidative cyclization is surprising, as it must be formed by reduction of the mercaptoacrylic acid **2**. The most probable reducing agent is hydrogen iodide, formed during the reaction. Indeed, refluxing **2** in dioxane with concentrated hydriodic acid did produce *trans*-3-methyl-4-methoxycinnamic acid, isolated and identified as its methyl ester, in about 10% yield. Similar treatment of the isomeric **10** did not yield any of the corresponding cinnamic acid, suggesting that this reduc-

tion of α -mercaptocinnamic acids by hydrogen iodide is not a general reaction, but is limited to specific structural requirements.

The intermediate substituted α -mercaptocinnamic acids **2** and **10** are new compounds, which were synthesized by mild alkaline hydrolysis of the corresponding benzylidene-rhodanines **1** and **9**. The mercaptoacrylic acids were characterized by analytical and spectral data and by conversion to disulfides, and disulfide dimethyl esters as derivatives. The existence of these enethiols in tautomeric forms is well documented (10), but usually only traces of thione forms are observed. However, the nmr spectrum of **10** shows an abnormality in that the aromatic protons (a multiplet centered at 7.35 δ) integrate for about 3.3 protons, and the vinyl proton at 7.95 δ integrates for 1.3 protons. This may be accounted for by assuming some thione **10a**, which should show an extra proton on carbon, is present. The corresponding disulfide, **11**, exhibits a simpler nmr spectrum, with only two vinyl protons at 7.90 δ and 6 aromatic protons as two broad singlets at 7.28 δ (4H) and 7.60 δ (2H). On the other hand, the nmr spectrum of the isomeric **2** was quite straightforward, integrating for one vinyl proton at 7.88 δ and three aromatic protons.

Although 3-methyl-4-methoxybenzaldehyde, the starting material for **6**, was commercially available, the isomeric 3-methoxy-4-methylbenzaldehyde, needed to prepare **12**, had to be synthesized. It had previously been prepared in 62% yield from the commercially available carboxylic acid by reduction of the acid chloride with lithium aluminum tri-*t*-butoxyhydride (11). This method gave poor yields in our hands, so we used a McFadyen-Stevens approach (12), by pyrolysis of the corresponding phenylsulfonylhydrazide, and achieved a 58% yield of the aldehyde from a commercial sample of 3-methoxy-4-methylbenzoic acid. Thus although several more steps were involved, the yields at all steps were quite good.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137-B Infracord Spectrometer using potassium bromide disks. Nmr spectra were determined on a Varian Associates EM 360 spectrometer, and mass spectra on a Varian MAT CH-7 spectrometer. Elemental analysis were performed by Midwest Microlabs, Inc. of Indianapolis, Indiana.

3-Methyl-4-methoxybenzylidenerhodanine (**1**)

Condensation of 10 g. (0.067 mole) of 3-methyl-*p*-anisaldehyde (Aldrich) with 9 g. of rhodanine, by refluxing in 75 ml. of glacial acetic acid containing 20 g. of fused sodium acetate (**3**) for 30 minutes, followed by dilution in 500 ml. of ice water, gave a crude yellow precipitate. On recrystallization from toluene, 16.4 g. (92%) of **1**, melting at 224-225° was obtained; ir: 5.97 (CO), 6.33 (C=C), 6.72 (1,2,4-trisubstituted benzene) μm .

Anal. Calcd. for C₁₂H₁₁NO₂S₂: C, 54.32; H, 4.18; N, 5.28;

S, 24.17; M.W. 265.4. Found: C, 54.61; H, 4.28; N, 5.00; S, 24.19; M⁺ 265.

β (3-Methyl-4-methoxyphenyl)- α -mercaptoacrylic Acid (**2**).

Hydrolysis of 13.3 g. (0.05 mole) of **1** in 100 ml. of 10% aqueous sodium hydroxide solution by warming to 70° for 30 minutes, then pouring over ice and concentrated hydrochloric acid gave an orange precipitate, which on recrystallization from toluene yielded 10.4 g. (93%) of yellow crystals melting at 159-161°: ir: 3.97 (SH), 6.06 (CO), 6.70 (1,2,4-trisubstituted benzene) μ m; nmr (acetone-d₆): δ 2.25 (s, 3H), 3.94 (s, 3H), 5.46 (s, 1H), 7.10 (d, 1H, J = 8 Hz), 7.61 (d, 1H, J = 3 Hz), 7.70 (dd, 1H, J = 8 Hz, 3 Hz), 7.88 (s, 1H).

Anal. Calcd. for C₁₁H₁₂O₃S: C, 58.91; H, 5.39; S, 14.30; M.W. 224.3. Found: C, 58.83; H, 5.36; S, 14.07; M⁺ 224.

Bis(β -3-methyl-4-methoxyphenylacrylic acid)- α,α' -disulfide (**3**).

Oxidation of **2** with one equivalent of iodine in ethanol at room temperature yielded **3** in 66% yield as yellow crystals, melting at 211-212° dec.; ir: 6.01 (CO), 6.72 (1,2,4-trisubstituted benzene) μ m.

Anal. Calcd. for C₂₂H₂₂O₆S₂: C, 59.18; H, 4.97; S, 14.36. Found: C, 59.21; H, 5.05; S, 14.57.

Dimethyl α,α' -Dithiobis(β -3-methyl-4-methoxyphenylacrylate) (**4**).

On refluxing a 1 g. sample of **3** in 10 ml. of absolute methanol containing one drop of concentrated hydrochloric acid, 0.62 g. (58%) of **4** which melted at 96-97° crystallized; ir: 5.87 (CO), 6.31 (C=C), 6.70 (1,2,4-trisubstituted benzene) μ m; nmr (deuteriochloroform): δ 2.23 (s, 6H), 3.78 (s, 6H), 3.91 (s, 6H), 6.91 (d, 2H, J = 9 Hz), 7.77 (s, 2H), 7.82 (d, 2H, J = 9 Hz), 7.97 (s, 2H).

Anal. Calcd. for C₂₄H₂₆O₆S₂: C, 60.74; H, 5.52; S, 13.51. M.W. 474.6. Found: C, 60.72; H, 5.64; S, 13.37; M⁺ 474.

2-Carbomethoxy-5-methyl-6-methoxybenzo[*b*]thiophene (**5**).

A solution of 1 g. of **2** and 1.5 g. of iodine in 25 ml. of dry dioxane was refluxed for 15 hours, concentrated to one-half volume and poured into 100 ml. of water to which 5 ml. of saturated sodium bisulfite had been added. The crude brown precipitate (1.0 g.), which had a broad melting range, was not readily purified by recrystallization or column chromatography. A mass spectrum showed two major peaks, at m/e 222 and 192.

Refluxing the crude mixture in 20 ml. of methanol containing dry hydrogen chloride gas for 3 hours, followed by cooling, gave 0.40 g. of tan crystals, which were eluted from a column of Silica Gel grade 62, using a mixture of cyclohexane and ethyl acetate (25:1) to give 0.30 g. (30%) of pure **5**, melting at 151-152° after one recrystallization from methanol; ir: 5.89 (CO) μ m; nmr (deuteriochloroform): δ 2.30 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 7.25 (s, 1H), 7.63 (s, 1H), 7.97 (s, 1H).

Anal. Calcd. for C₁₂H₁₂O₃S: C, 61.00; H, 5.12; S, 13.57; M.W. 236.3. Found: C, 60.98; H, 5.38; S, 13.73; M⁺ 236.

The methanolic mother liquors (above) were diluted with water and extracted with benzene. The benzene extracts after washing with dilute sodium carbonate solution and water, were dried (magnesium sulfate) and the benzene evaporated. The residue on column chromatography as above, gave an additional 0.09 g. of **5** (total recovered, 37%), followed by elution of 0.13 g. (12%) of methyl 3-methyl-4-methoxycinnamate (**8**) which melted at 70-71° after recrystallization from cyclohexane, as previously reported (9). It had the following spectral characteristics: ir: 5.87 (CO), 6.25 (C=C), 6.69 (1,2,4-trisubstituted benzene) μ m; nmr (deuteriochloroform): δ 2.27 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.37 (d, 1H, J = 16 Hz), 6.88 (d, 1H, J = 9 Hz), 7.33-7.52 (m, 2H), 7.73 (d, 1H, J = 16 Hz); M⁺ = 206 (Calcd. for **8**, 206).

5-Methyl-6-methoxybenzo[*b*]thiophene-2-carboxylic Acid (**6**).

A methanol solution of 450 mg. (1.9 mmoles) of **5** was refluxed with 3 ml. of 20% sodium hydroxide solution for 15 minutes, cooled and acidified to give 390 mg. (92%) of **6**, melting at 300° on recrystallization from ethanol; ir: 3.50 (COOH), 6.01 (CO) μ m; nmr (DMSO-d₆): δ 2.33 (s, 3H), 4.06 (s, 3H), 7.61 (s, 1H), 7.82 (s, 1H), 8.04 (s, 1H).

Anal. Calcd. for C₁₁H₁₀O₃S: C, 59.44; H, 4.54; S, 14.43; M.W. 222.3. Found: C, 59.23; H, 4.41; S, 14.21; M⁺ 222.

5-Methyl-6-methoxybenzo[*b*]thiophene (**7**).

A sample of **6** was decarboxylated with copper in quinoline, as previously noted (13) to give 90% of **7**, recrystallized from methanol to melt at 61-62° (8); nmr (deuteriochloroform): δ 2.30 (s, 3H), 3.82 (s, 3H), 7.23 (s, 1H), 7.26 (d, 2H, J = 3 Hz), 7.57 (s, 1H); M⁺ 178 (Calcd. for **7**, 178).

Reduction of **2** with Hydrogen Iodide.

β (4-Methoxy-3-methylphenyl)- α -mercaptoacrylic acid (1 g.) was heated to reflux in 25 ml. of dioxane containing 1 ml. of concentrated hydroiodic acid for 7 hours. The cooled brown mixture was diluted with ether and water. The ether extract was washed with sodium thiosulfate solution, then water, dried over anhydrous magnesium sulfate, and the ether evaporated. The nmr spectra of the crude residue showed the presence of 4-methoxy-3-methylcinnamic acid and starting material. This mixture was esterified with methanol and acid catalyst, and 0.1 g. of **8** was isolated by column chromatography, as described above. It was identified by melting point (70-71°), mixture melting point and nmr spectrum with the previously isolated sample.

3-Methoxy-4-methylbenzaldehyde.

A solution of 4.73 g. (26 mmoles) of methyl 3-methoxy-4-methylbenzoate (from esterification of 3-methoxy-4-methylbenzoic acid [Aldrich]) and 3 ml. of 85% hydrazine hydrate in 6 ml. of ethanol was refluxed for 3 hours. On cooling, 3.98 g. (84%) of 3-methoxy-4-methylbenzoylhydrazide, melting at 138-139°, were collected; ir: 3.07 (NH), 6.13 (CO), 6.35, 8.00 (amide) μ m.

Anal. Calcd. for C₉H₁₂N₂O₂: C, 59.99; H, 6.71; N, 15.54; M.W. 180.2. Found: C, 60.73; H, 6.74; N, 15.63; M⁺ 180.

The above hydrazide was converted to *N*-3-methoxy-4-methylbenzoyl-*N'*-benzenesulfonylhydrazine in 93% yield by reaction with benzenesulfonylchloride in pyridine. On recrystallization from ethanol, the pale yellow crystals melted at 224-225° dec.; ir: 3.04 (-CONH-), 3.23 (-SO₂NH-), 6.06 (CO), 6.36 (amide), 7.12 (SO₂ amide), 8.04 (amide), 8.57 (SO₂ amide) μ m.

Anal. Calcd. for C₁₅H₁₆N₂O₄S: C, 56.24; H, 5.03; N, 8.74; S, 10.01; M.W. 320.4. Found: C, 56.04; H, 5.15; N, 8.81; S, 10.09; M⁺ 320.

Finely ground anhydrous sodium carbonate (5.5 g.) was stirred into 50 ml. of ethylene glycol containing 3.3 g. (10 mmoles) of the above sulfonylhydrazide at 160° for about 75 seconds. As soon as foaming ceased, the solution was poured into water, cooled, and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated to give 1.25 g. (81%) of 3-methoxy-4-methylbenzaldehyde, which recrystallized from dilute methanol to melt at 40-41° (11); M⁺ 150; nmr (acetone-d₆): δ 2.27 (s, 3H), 3.96 (s, 3H), 7.45 (s, 3H), 10.03 (s, 1H).

3-Methoxy-4-methylbenzylidenerhodanine (**9**).

Condensation of 1.25 g. (8.3 mmoles) of the above aldehyde with 1.1 g. of rhodanine, as previously described, gave 1.63 g. (74%) of yellow crystals from benzene melting at 222-223°; ir: 5.96 (CO), 6.31 (C=C), 6.70 (1,2,4-trisubstituted benzene) μ m;

nmr (DMSO- d_6): δ 2.22 (s, 3H), 3.90 (s, 3H), 7.13 (d, 1H, $J = 6$ Hz), 7.22 (s, 1H), 7.40 (d, 1H, $J = 6$ Hz), 7.70 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28; S, 24.17; M.W., 265.4. Found: C, 54.17; H, 4.19; N, 5.17; S, 23.98; M^+ 265.

β -(3-Methoxy-4-methylphenyl)- α -mercaptoacrylic Acid (**10**).

Hydrolysis of 1.32 g. of **9**, as previously described for **1**, gave 0.80 g. (71%) of **10**, melting at 160-161° on recrystallization from benzene; ir: 3.38 (COOH), 5.95 (CO), 6.69 (1,2,4-trisubstituted benzene) μ m; nmr (acetone- d_6): δ 2.27 (s, 3H), 3.98 (s, 3H), 7.35 (s, 3.3H), 7.95 (s, 1.3H).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; S, 14.30; M.W., 224.3. Found: C, 58.73; H, 5.29; S, 14.14; M^+ 224.

Bis(β -3-Methoxy-4-methylphenylacrylic acid)- α,α' -disulfide (**11**).

Oxidation of **10** with 1.0 equivalents of iodine in ethanol at room temperature gave a nearly quantitative yield of **11**, melting at 216° dec., after one recrystallization from ethanol: ir: 3.47 (COOH), 6.03 (CO), 6.73 (trisubstituted benzene); nmr (DMSO- d_6): δ 2.20 (s, 6H), 3.83 (s, 6H), 7.28 (s, 4H), 7.60 (s, 2H), 7.90 (s, 2H).

Anal. Calcd. for $C_{22}H_{22}O_6S_2$: C, 59.18; H, 4.97; S, 14.36; M.W., 446.5. Found: C, 58.85; H, 4.94; S, 14.30; M^+ 446 (weak).

5-Methoxy-6-methylbenzo[*b*]thiophene-2-carboxylic Acid (**12a**).

A solution of 2.3 g. (10 mmoles) of **10** and 3 g. of iodine in 50 ml. of dry dioxane was refluxed for 17 hours, poured into 400 ml. of cold water and sodium thiosulfate solution added slowly with stirring until the iodine color disappeared. The tan precipitate was collected, washed with water, and recrystallized from ethanol (Norite) to yield 1.44 g. (63%) of **12a**, melting at 277-278°. Although this material gave all characteristics of a pure sample, it could not be decolorized by further recrystallizations or chromatography. However, on hydrolyzing the methyl ester (see below), a colorless product, having the same characteristics, was obtained as an analytical sample; ir: 3.50 (COOH), 6.00 (CO) μ m; nmr (DMSO- d_6): δ 2.30 (s, 3H), 3.90 (s, 3H), 7.55 (s, 1H), 7.83 (s, 1H), 8.07 (s, 1H).

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43; M.W., 222.3. Found: C, 59.25; H, 4.55; S, 14.48; M^+ 222.

2-Carbomethoxy-5-methoxy-6-methylbenzo[*b*]thiophene (**12b**).

A solution of 1.0 g. (4.8 mmoles) of **12a** in 50 ml. of methanol containing 1 drop of sulfuric acid was refluxed for 4 hours, diluted with water and extracted with ethyl acetate. After drying (magne-

sium sulfate), the solvent was evaporated and the residue subjected to column chromatography on Silica gel (grade 62) using a 25:1 cyclohexane-ethyl acetate mixture, to yield 0.9 g. (87%) of **12b**, melting at 133-134° after one recrystallization from methanol; ir: 5.92 (CO) μ m; nmr (deuteriochloroform): δ 2.38 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 7.27 (s, 1H), 7.67 (s, 1H), 8.05 (s, 1H).

Anal. Calcd. for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57; M.W. 236.3. Found: C, 60.93; H, 5.39; S, 13.34; M^+ 236.

5-Methoxy-6-methylbenzo[*b*]thiophene (**13**).

Decarboxylation of 0.54 g. (2.4 mmoles) of **12a** with copper in quinoline (**13**) gave 0.43 g. (100%) of **13**, melting at 65-66° after one recrystallization from methanol: nmr (carbon tetrachloride): δ 2.32 (s, 3H), 3.90 (s, 3H), 7.14-7.37 (m, 3H), 7.58 (s, 1H).

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99; M.W. 178.3. Found: C, 67.10; H, 5.35; S, 17.86; M^+ 178.

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