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An efficient one-pot synthesis of spiro dihydrofuran oxindole and spiro 2-hydroxytetrahydrofuran oxindole derivatives via (3+2) oxidative cycloaddition mediated by CAN

G. Savitha, S. K. Niveditha, D. Muralidharan and P. T. Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

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Abstract—Spiro dihydrofuran oxindole derivatives were prepared via a (3+2) oxidative cycloaddition of 1,3-dicarbonyl compounds to 3-(phenyl-2-oxoethylidene)-1-methyloxindole and 3-benzylidene-1-methyloxindole derivatives mediated by ceric ammonium nitrate. In the case of the reaction of 3-(phenyl-2-oxoethylidene)-1-methyloxindole derivatives with acyclic 1,3-dicarbonyl compounds, spiro 2-hydroxytetrahydrofuran oxindole derivatives were obtained.

The construction of complex biologically active molecules by molecular modification has been of enormous interest in recent years. Spirocyclic systems containing one carbon atom common to two rings are structurally interesting.[1] The heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds and pharmaceuticals[2] and has generated interest in the development of new methods for constructing various diversely functionalized spirocyclic oxindoles.[3]

The oxidative addition of carbon-centered radicals to alkenes mediated by metal salts (Mn^{III}, Ce^{IV}, Co^{II}, and V^{V}) has received considerable attention over the last decade in organic synthesis.[4] The oxidative cycloaddition of 1,3-dicarbonyl compounds to exocyclic alkenes has served as the best method for the formation of spirofuran and poly functionalized furan derivatives, and is very important in terms of the synthesis of biologically active natural products such as aflatoxin, asteltoxin, monensin, and panacene which consist of furan rings.[5]

Recently Alcaide et al. have described a metal-mediated carbonyl-addition/cyclization approach for the construction of spironic dihydrofuran oxindole derivatives.[6]

Here, we describe an efficient one-pot method for the construction of spiro dihydrofuran oxindole derivatives via (3+2) oxidative cycloaddition of cyclic and acyclic 1,3-dicarbonyl compounds to 3-(phenyl-2-oxoethylidene)-1-methyloxindole and 3-benzylidene-1-methyloxindole derivatives mediated by ceric ammonium nitrate.

Initially, the reaction was explored by treating dimedone (**2a**) with 1 equiv of **1a** at 0 °C in the presence of 2.5 equiv of CAN and 3 equiv of $NaHCO_3$ in acetonitrile (Scheme 1, Table 1). The reaction proceeded smoothly within 15 min to afford **3a** as a single regio and stereoisomer in 75% yield after purification through column chromatography. No other isomer could be detected. In the ^{1}H NMR spectrum the proton of the dihydrofuran ring appeared as a singlet at δ 5.27 and in the ^{13}C NMR spectrum a signal due to the spiro carbon at δ 87.8 confirmed the formation of **3a**[7a].

The structure of **3a** and its stereochemistry was confirmed by X-ray diffraction studies (Fig. 1).[8] We explored the reaction between a variety of 3-(phenyl-2-oxoethylidene)-1-methyloxindole derivatives with cyclic 1,3-dicarbonyl compounds (**2a** and **2b**) and obtained the desired products in comparable yields. The results are summarized in Table 1.

Serendipitously, while treating **1a** with ethyl acetoacetate **4a** under similar conditions, the expected product was not obtained, but instead a product with a molecular

* Corresponding author. Tel.: +91 44 24911386; fax: +91 44 24911589; e-mail addresses: ptperumal@hotmail.com; ptperumal@gmail.com

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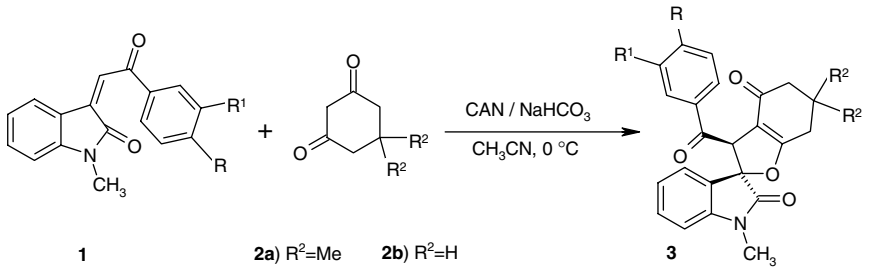
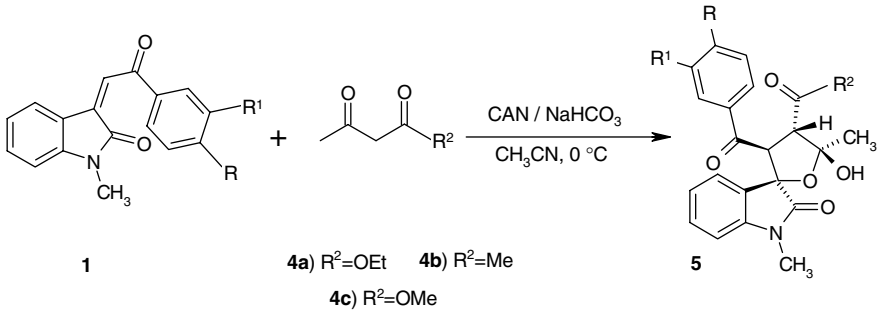


Scheme 1.

Table 1. Synthesis of spiro dihydrofuran oxindole derivatives from 3-(phenyl-2-oxoethylidene)-1-methyl oxindole derivatives

Entry	Oxindole **1**			1,3-Dicarbonyl **2**	Product[a] **3**				Yield (%)
		R	R^1			R	R^1	R^2	
1	**1a**	H	OMe	**2a**	**3a**	H	OMe	Me	75
2	**1b**	H	H	**2a**	**3b**	H	H	Me	76
3	**1c**	Cl	H	**2a**	**3c**	Cl	H	Me	68
4	**1d**	OMe	H	**2a**	**3d**	OMe	H	Me	74
5	**1d**	OMe	H	**2b**	**3e**	OMe	H	H	73

[a] All the reactions were complete within 15 min.



Scheme 2.

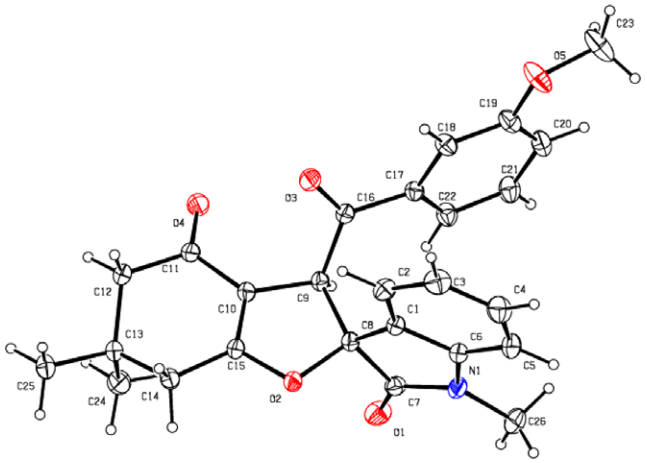


Figure 1. ORTEP diagram of **3a**.

weight greater by 18 than that of the expected product was isolated, which corresponds to the mass of a water molecule. In the IR spectrum, the appearance of a peak at 3368 cm^{-1} confirmed the presence of an OH group. The OH proton could not be detected in the ^1H NMR spectrum, but an additional proton in the aliphatic region was observed. Instead of a singlet, two doublets at δ 3.93 and 4.99 corresponding to one proton each with coupling constants of J 11.45 Hz were found which confirmed that these protons were located adjacent to one another with trans stereochemistry.[7b] Based on these results and further information from the ^{13}C NMR spectrum, the structure of the product was assigned as spiro 2-hydroxytetrahydrofuran oxindole derivative **5a**, a hemiacetal which is highly susceptible to further functionalization, and transformations and is a useful intermediate in the synthesis of several heterocyclic compounds (Scheme 2).[9] Recently, 2-hydroxytetrahydrofuran derivatives were found to have calpain inhibiting activity and are used as treatments for several diseases.[10] The structure of **5a** was confirmed through single crystal X-ray diffraction studies (Fig. 2).[11] A plausible mechanism for the formation of **5a** is given in Scheme 3.

Similar products were obtained with other acyclic 1,3-dicarbonyl compounds such as **4b** and **4c**. The results are summarized in Table 2.

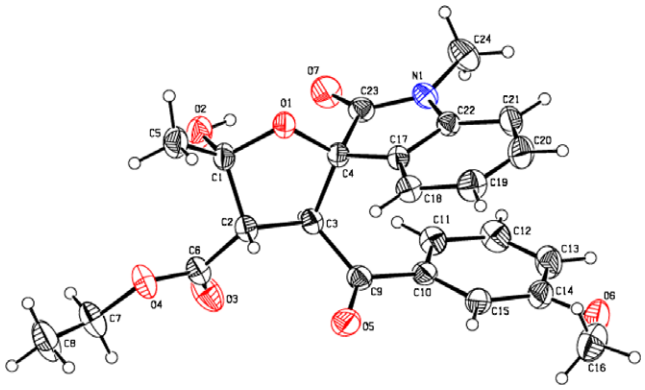
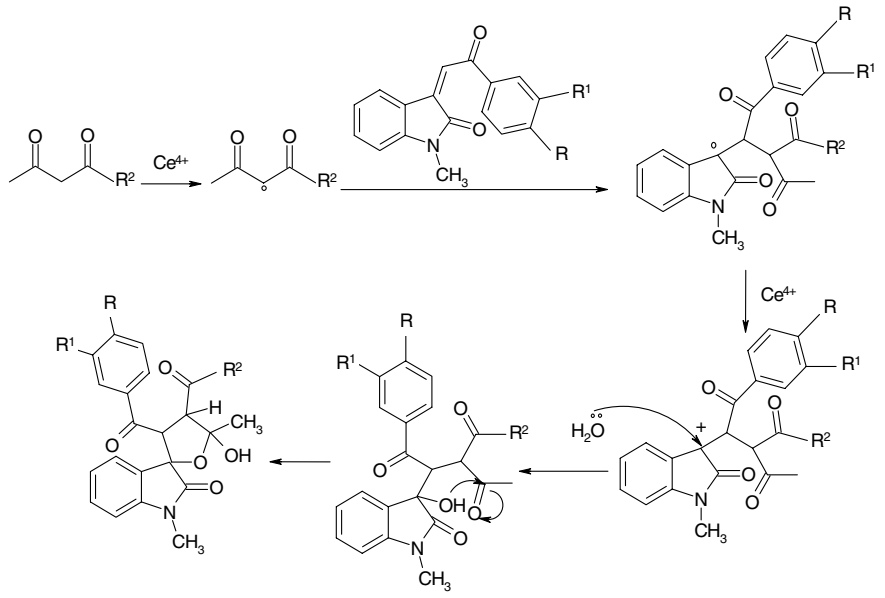


Figure 2. ORTEP diagram of **5a**.

In the case of the reaction of dimedone (**2a**) with 1 equiv of 3-(4-Cl-benzylidene)-1-methyloxindole (**6b**) in the presence of 2.5 equiv of CAN and $NaHCO_3$ (3 equiv) at 0 °C in acetonitrile, chromatographically separable diastereoisomers **7b** and **8b** were obtained in a 1:1 ratio (Scheme 4).

In the ^1H NMR spectra of **7b** and **8b** the benzyl proton appeared as a singlet at δ 4.80 and 4.66, respectively. In the ^{13}C NMR spectra of **7b** and **8b** the signals for the spiro carbons appeared at δ 91.6 and 90.8, respectively.[7c] Isomer **8b** was obtained as a white crystalline solid and its stereochemistry was determined by X-ray studies (Fig. 3).[12]

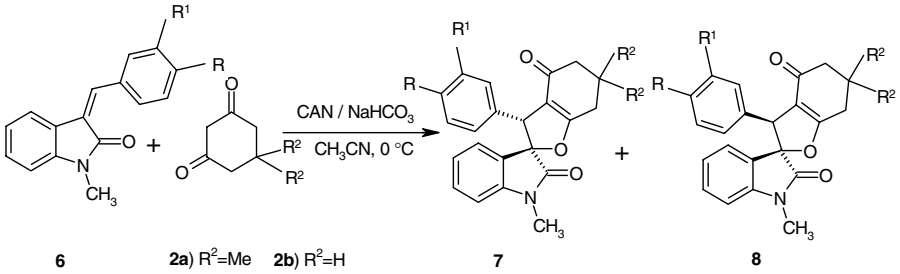


Scheme 3.

Table 2. Synthesis of spiro 2-hydroxytetrahydrofuran oxindoles from 3-(phenyl-2-oxoethylidene)-1-methyl oxindole derivatives

Entry	Oxindole **1**			1,3-Dicarbonyl **4**	Product[a] **5**				Yield (%)
		R	R^1			R	R^1	R^2	
1	**1a**	H	OMe	**4a**	**5a**	H	OMe	OEt	72
2	**1b**	H	H	**4c**	**5b**	H	H	OMe	68
3	**1c**	Cl	H	**4b**	**5c**	Cl	H	Me	65
4	**1d**	OMe	H	**4a**	**5d**	OMe	H	OEt	70
5	**1d**	OMe	H	**4b**	**5e**	OMe	H	Me	73
6	**1a**	H	OMe	**4b**	**5f**	H	OMe	Me	71

[a] All the reactions were complete within 15 min.



Scheme 4.

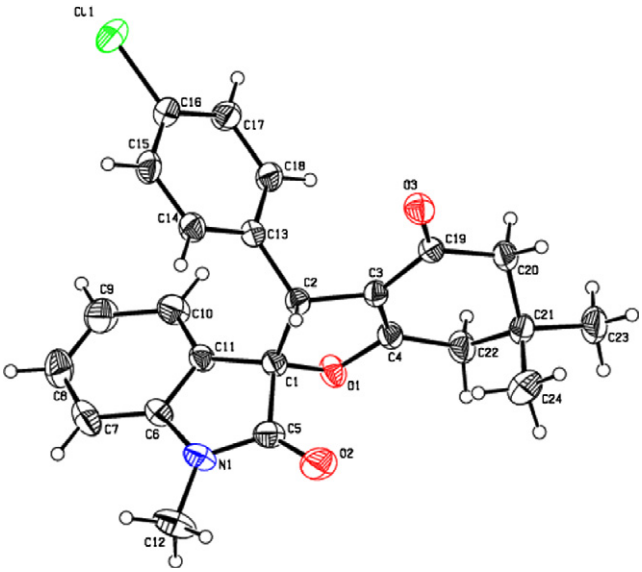


Figure 3. ORTEP diagram of diastereoisomer **8b**.

Various diastereoisomers were obtained in 1:1 ratios on reacting 3-benzylidene-1-methyloxindole derivatives with other 1,3-dicarbonyl compounds. The results are summarized in Table 3.

In conclusion, we have described an efficient one-pot method for the preparation of spiro dihydrofuran oxindole derivatives via (3+2) oxidative cycloaddition. Studies on the biological activity of these compounds and further transformation of the spiro 2-hydroxy-tetrahydrofuran oxindole derivatives are underway.

General procedure for **3a**: To a stirred mixture of 3-[(3-methoxyphenyl)-2-oxoethylidene]-1-methyloxindole **1a** (1.02 mmol, 0.3 g, 1 equiv), dimedone **2a** (1.02 mmol, 0.143 g, 1 equiv), and $NaHCO_3$ (3.07 mmol, 0.258 g, 3 equiv) in acetonitrile (10 mL), ceric ammonium nitrate (2.56 mmol, 1.4 g, 2.5 equiv) dissolved in acetonitrile (5 mL) was added dropwise at 0 °C under N_2. The reaction mixture was stirred until completion of the reaction as monitored by TLC. Water was added to the mixture and the product was extracted into ethyl acetate (2×20 mL) and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a crude product, which was purified by column chromatography on silica gel, with ethyl acetate–hexane (4:6) as eluent to afford the pure product 0.33 g (75%) as a white crystalline solid. Single crystals of **3a** were obtained by recrystallisation from ethyl acetate.

General procedure for **5a**: Following the general procedure as described above, **5a** was obtained from 3-[(3-methoxyphenyl)-2-oxoethylidene]-1-methyloxindole **1a** (1.02 mmol, 0.3 g, 1 equiv), ethyl acetoacetate **4a** (1.02 mmol, 0.133 g, 1 equiv), and $NaHCO_3$ (3.07 mmol, 0.258 g, 3 equiv) in the presence of ceric ammonium nitrate (2.56 mmol, 1.4 g, 2.5 equiv) in 72% yield as a white crystalline solid. Single crystals of **5a** were obtained by recrystallisation from ethyl acetate.

General procedure for **7b** *and* **8b**: Following the procedure as described above, **7b** and **8b** were obtained from 3-(4-Cl-benzylidene)-1-methyloxindole (**6b**) (1.11 mmol, 0.3 g, 1 equiv), dimedone **2a** (1.11 mmol, 0.154 g, 1 equiv), and $NaHCO_3$ (3.33 mmol, 0.277 g, 3 equiv) in the presence of ceric ammonium nitrate (2.78 mmol, 1.52 g, 2.5 equiv) as a crude mixture, which was purified and separated by column chromatography on silica gel, with ethyl acetate–hexane (3:7) as eluent to afford the two diastereoisomers in an overall yield of 0.294 g (65%). Diastereoisomer **8b**, which was obtained as a yellow crystalline solid, was recrystallized from ethyl acetate.

Acknowledgement

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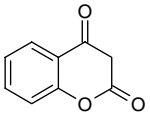
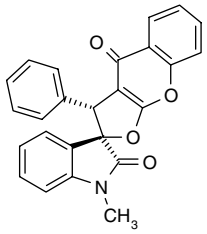
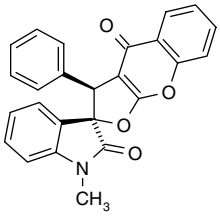
Table 3. Synthesis of spiro dihydrofuran oxindole derivatives from 3-benzylidene-1-methyl oxindole derivatives

Entry	Oxindole **6**			1,3-Dicarbonyl **2**	Product[a] **7**, **8**				Yield[b] (%)
		R	R^1			R	R^1	R^2	
1	**6a**	H	H	**2a**	**7a**, **8b**	H	H	Me	75
2	**6b**	Cl	H	**2a**	**7b**, **8b**	Cl	H	Me	65
3	**6c**	OMe	H	**2a**	**7c**, **8c**	OMe	H	Me	72
4	**6d**	OMe	OMe	**2a**	**7d**, **8d**	OMe	OMe	Me	70
5	**6c**	OMe	H	**2b**	**7e**, **8e**	OMe	H	H	69
6	**6a**	H	H		**7f**, **8f**				68

[a] All the reactions were complete within 15 min.
[b] Isolated overall yield.

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7. (a) Spectral data for compound **3a** (Table 1): mp = 182 °C. IR: ν_{max} = 1730, 1654, 1609 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.09–7.13 (m, 1H), 7.06–7.07 (m, 2H), 6.99–7.03 (m, 2H), 6.84–6.89 (m, 2H), 6.54 (d, 1H, J = 7.45 Hz), 5.27 (s, 1H), 3.66 (s, 3H), 3,13 (s, 3H), 2.44–2.54 (m, 2H), 2.31–2.40 (m, 2H), 1.28 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.3, 193.5, 177.0, 173.6, 159.5, 143.4, 138.0, 131.2, 129.2, 126.8, 123.5, 123.4, 120.4, 120.2, 112.6, 111.8, 108.5, 87.8, 55.4, 54.1, 37.9, 34.8, 31.0, 29.0, 28.3, 26.6. MS (EI) $m/z = 431^+$. Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25%. Found: C, 72.35; H, 5.85; N, 3.23%.
(b) Spectral data for compound **5a** (Table 2): mp = 128 °C. IR: ν_{max} (KBr) = 3368, 1734, 1707, 1612 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.18 (m, 2H), 7.12 (t, 1H, J = 7.6 Hz), 7.04 (d, 1H, J = 8.4 Hz), 6.92 (t, 1H, J = 7.65 Hz), 6.79 (d, 1H, J = 7.65 Hz), 6.64 (s, 1H), 6.52 (d, 1H, J = 7.65 Hz), 4.99 (d, 1H, J = 11.45 Hz), 4.10 (q, 2H, J = 6.85 Hz), 3.93 (d, 1H, J = 11.45 Hz), 3.65 (s, 3H), 2.73 (s, 3H), 1.70 (s, 3H), 1.17 (t, 3H, J = 6.85 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 175.2, 168.6, 159.5, 142.9, 138.1, 130.6, 129.9, 126.7, 125.8, 123.2, 120.1, 119.9, 111.8, 108.7, 105.6, 82.5, 61.1, 56.9, 55.6, 55.5, 27.1, 26.4, 14.5. MS (EI) $m/z = 439^+$. Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19%. Found: C, 65.57; H, 5.75; N, 3.20%.
(c) Spectral data for **7b** (Table 3): mp = 180 °C. IR: ν_{max} (KBr) = 1733, 1641 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, 1H, J = 7.65 Hz), 7.40 (t, 1H, J = 7.65 Hz), 7.16 (t, 1H, J = 7.65 Hz), 7.12 (d, 2H, J = 8.45 Hz), 6.80 (d, 2H, J = 8.4 Hz), 6.76 (d, 1H, J = 7.6 Hz), 4.80 (s, 1H), 2.83 (s, 3H), 2.66 (d, 1H, J = 17.5 Hz), 2.46 (d,2H, J = 16.05 Hz), 2.36 (d, 1H, J = 16.8 Hz), 1.29 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.8, 178.2, 171.3, 143.9, 133.5, 133.1, 131.4, 129.7, 128.2, 127.9, 124.1, 123.7, 112.9, 108.7, 91.6, 55.7, 51.6, 38.2, 34.6, 28.8, 28.7, 26.0. MS (EI) m/z = 407 (M^+), 409 (M^++2). Anal. Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43%. Found: C, 70.65; H, 5.45; N, 3.40%.
Spectral data for **8b** (Table 3): mp = 139 °C. IR: ν_{max} (KBr) = 1730, 1645 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.21 (m, 1H), 7.11 (d, 2H, J = 8.4 Hz), 6.79 (d, 2H, J = 8.45 Hz), 6.75 (d, 1H, J = 7.65 Hz), 6.70 (t, 1H, J = 7.65 Hz), 6.37 (d, 1H, J = 7.6 Hz), 4.66 (s, 1H), 3.21 (s, 3H), 2.57 (s, 2H), 2.39 (d, 2H, J = 4.6 Hz), 1.29 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.7, 177.6, 174.5, 143.9, 135.4, 133.3, 130.8, 129.7, 128.6, 126.6, 123.7, 122.8, 113.9, 108.5, 90.8, 51.7, 51.4, 38.0, 34.4, 29.1, 28.8, 26.6. MS (EI) m/z = 407 (M^+), 409 (M^++2). Anal. Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43%. Found: C, 70.68; H, 5.42; N, 3.40%.
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