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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—XXVII†

SYNTHESIS OF THIONO-, THIOLO- AND DITHIOLACTONES

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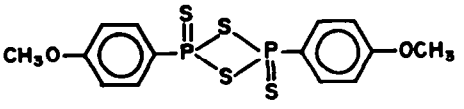
Abstract—Unsubstituted and alkyl- or cyanosubstituted lactones such as dihydro-2(3 H)-furanone, dihydro-5-methyl-2(3 H)-furanone, dihydro-5,5-dimethyl-4-propyl-2(3 H)-furanone and tetrahydro-2,2-dimethyl-5-oxo-3furancarbonitrile react with the dimer of *p*-methoxyphenylthionophosphine sulfide, 1, in anhydrous xylene or toluene to give the corresponding thionolactones, 3a–d, in good yields. Dihydro-2(3 H)-thiophenone and 1 produce dihydro-2(3 H)-thiophenthione. Aromatic lactones such as 2 H-1-benzopyran-2-one give the corresponding 2-thione. 1-Oxa-4-thiaspiro[4,5]decan-2-one, when treated with 1 at 120–125°, gave 1,4-dithiaspiro[4,5]decan-2-one and 1,4-dithiaspiro[4, 5]decan-2-thione. Tetrahydro-5,5-dimethyl-2-oxo-4-propyl-3-furancarboxylic acid ethyl ester reacted with 1 at 110° giving the corresponding 2-thione and 5,5-dimethyl-4-propyl-4,5-dihydrothieno[2,3-c]-1,2-dithiole-3-thione.

INTRODUCTION

Non-aromatic thionolactones and dihydro - 2(3 H) - thiophenthione derivatives have—to our knowledge—only been reported in a few cases.[1,2] As the dimer of *p*-methoxyphenylthionophosphine sulfide, 1, seems to be a convenient thiation reagent[3–7] it was found natural to use it in the synthesis of thiono- and dithiolactones.



1

This paper reports on the preparation of dihydro - 2(3 H) - furanthiones, 3a–d, dihydro - 2(3 H) - thiophenthione, 3e, 2 H - 1 - benzopyran - 2 - thiones, 4b, 5b, 1,4 - dithiaspiro[4,5]decan - 2 - ones, 7a–c, 1,4 - dithiaspiro[4,5]decan - 2 - thiones, 8a,c, tetrahydro - 5,5 - dimethyl - 2 - thione - 3 - furancarboxylic acid ethyl esters, 10a,b, and 5,5 - dimethyl - 4,5 - dihydrothieno[2,3-c] - 1,2 - dithiole - 3 - thiones, 11a,b.

RESULTS AND DISCUSSION

Simple lactones and thiololactones (2a–e) give the corresponding thiocarbonyl compounds (3a–e) in high yields when treated with 1 in anhydrous xylene or toluene.

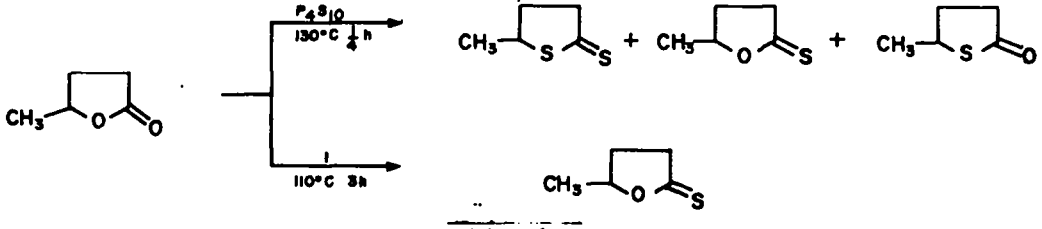
The reaction temperature is significantly lower and the reaction time is shorter (Table 1) than in the case of esters.[5] The increased ractivity might be due to less steric hindrance. ^{13}C NMR chemical shifts for the CO and corresponding thiocarbonyl absorptions of the lactones 3a–d and 10a,b are given in Tables 1 and 2. A least square linear regression analyses led to the following equation $\delta_{C=S} = \delta_{C=O} \cdot 1.42 - 27.5$ ppm for nonaromatic thionolactones. The correlation coefficient of the relation is found to be 0.996. A marked difference to the relation for thionoesters[5] is noted.

2 → 3 (1, xylene/toluene)

	X	R^1	R^2	R^3
(a)	O	H	H	H
(b)	O	CN	CH_3	CH_3
(c)	O	C_3H_7	CH_3	CH_3
(d)	O	H	CH_3	H
(e)	S	H	H	H

The thionolactones are generally pale yellow oils or white crystals which are stable, whereas the orange-red oily dithiolactone 3e exhibits a most unpleasant odour and decomposes upon storage. The reaction conditions and yields are reported in Table 1. The physical, spectroscopic, and analytical data are recorded in the Experimental.

The quantitative formation of dihydro - 2(3 H) - furanthione, 3d, from 2d is of synthetic importance, because treatment of 2d with P_4S_{10} gives the products shown in Scheme 1.[8]



Scheme 1.

†Part XXVI see Ref. [7].

Table 1. Experimental conditions for the reactions and ^{13}C NMR of >C=O

Compound	Reaction temp. (°C)	Reaction time (h)	Solvent[a]	^{13}C NMR[b] C1	C2	Yields	
2a	120	5	X	177.2		98% 3a	
2b	120	6	X	171.4		90% 3b	
2c	125	8	X	173.7		66% 3c	
2d	110	3	T	177.2		97% 3d	
2e	110	3	T	209.1		100% 3e	
4a	110	2	T	160.5		99% 4b	
5a	140	11	X	166.8		87% 5b[c]	
6a	120	5	X	172.3		28% 7a	58% 8a
6b	120	7	X	175.0		33% 7b	0% 8b[d]
6c	125	3½	X	172.3/172.5		12% 7c	40% 8c
9a	110	8	T	170.9	168.5	31% 10a	19% 11a
9b	110	6	T	170.5	167.5	27% 10b	7% 11b

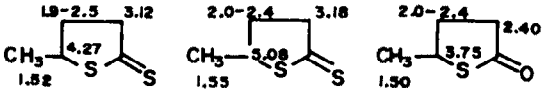
[a] X= xylene, T= toluene.

[b] Chemical shifts of >C=O. Solvent $CDCl_3$. Internal standard TMS.

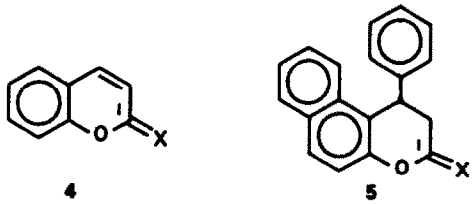
[c] 11% lactone recovered.

[d] Traces of 8b could be detected (TLC). For MS see experimental.

The products are easily distinguished by ^1H NMR using 2e, 3a and 3e as model compounds. ^{13}C NMR- and IR-spectra are also in accordance with the suggested structures.



Although it is known[9] that tetrahydro - 2 - pyranone (δ-valerolactone) easily polymerizes, its reaction with 1 in toluene for 2 hr was tried. The solution became yellow, but only the phosphorus product 12 (Experimental) could be isolated, indicating that a thiation reaction had taken place.

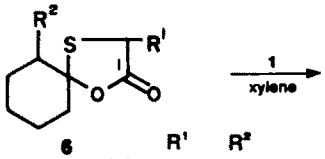


4 5

(a) X = O
(b) X = S

Two aromatic lactones have been converted to their thioanalogues, namely 2 H - 1 - benzopyran - 2 - one, 4a, and 3,4 - dihydro - 4 - phenyl - 2 H - naphtho[1,2-b]pyran - 2 - one, 5a.

Compound 4a was easily converted into 4b with an equimolar amount of 1, but total conversion of 5a was not possible though a great excess of 1 was used (2 moles of 1 per mole of 5a). When 1 - oxa - 4 - thiaspiro[4,5]decan - 2 - ones, 6a–c, are reacted with 1, 1,4 - dithiaspiro[4,5]decan - 2 - ones, 7a–c, and 1,4 - dithiaspiro[4,5]decan - 2 - thiones, 8a–c, can be isolated in low to moderate yields (Table 1).



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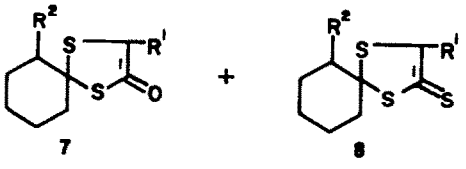
	R¹	R²
(a)	H	H
(b)	CH_3	H
(c)	H	CH_3



7 8

In contrast to the compounds already mentioned, it was not possible to isolate any thionolactone and it is suggested that the lactone is first converted to the thionolactone which rearranges to the thiololactone.[10] This subsequently is transformed into the dithiolactone. Accordingly, treatment of 7a with 1 yielded 8a as the only product.

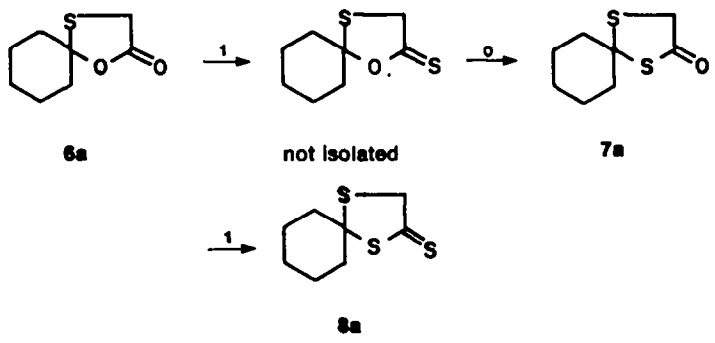
The compounds 7a–c and 8a,c are generally dark-red unstable oils. They partly decompose upon storage and heating and during separation on a silica gel column. Anhydrous conditions have to be observed as acetals are easily hydrolysed with wet silica gel.[11]

The structures of the compounds 7a–c are based on the fact, that strong IR-absorptions are found at 1680–1690 cm^{-1} and the ^{13}C NMR chemical shifts of the –C(S)O– carbon atoms are found at about 205 ppm in

Table 2. Physical, spectroscopic and analytical data

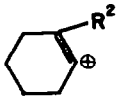
Compound	Bp(°C/Torr) (Mp)(°C)	^{13}C NMR[a] C1	C2	IR[b] (cm^{-1})	Analyses(%) calculated C	H	S	found C	H	S
3a	96-7/11	223.3			47.05	5.92	31.33	47.14	5.91	31.30
3b	(130)	214.3			54.19	5.85	20.62	54.15	5.89	20.65[d]
3c	(33)	220.7			62.79	9.30	18.61	62.48	9.22	18.61
3d	125-7/30	222.5			51.72	6.94	27.56	51.44	6.92	26.68
3e	105-7/10	246.8			40.64	5.12	54.24	41.56	5.12	52.47
4b	(99)[18]	197.8								
5b	(162)	212.7			78.61	4.86	11.02	78.61	4.88	10.82
7a	(45)	204.6		1680	51.06	6.43	34.01	51.04	6.38	33.64
7b	133-43/10(d)	206.3		1680						
7c	145/10(d)	204.6/204.8		1690						
8a	[e]	238.9								
8c	[e]	238.8/239.3								
10a	oil	214.2	168.5	1720	59.00	8.25	13.10	58.84	8.16	13.08
10b	(103)	213.7	167.6	1710	65.74	6.90	10.95	64.94	6.84	11.23
11a	oil	174.0	203.6		45.80	5.38	48.81	46.39	5.22	47.88
11b	(104)	173.8	203.1		54.20	4.55	41.26	53.90	4.51	41.13

[a] Chemical shifts of C=X.Solvent $CDCl_3$.Relative to TMS.
[b] Absorptions in the region 1600-1800 cm^{-1}.
[c] Decomposes upon heating.
[d] N calc. 9.02 found 9.07.
[e] Unsatisfactory due to instability.



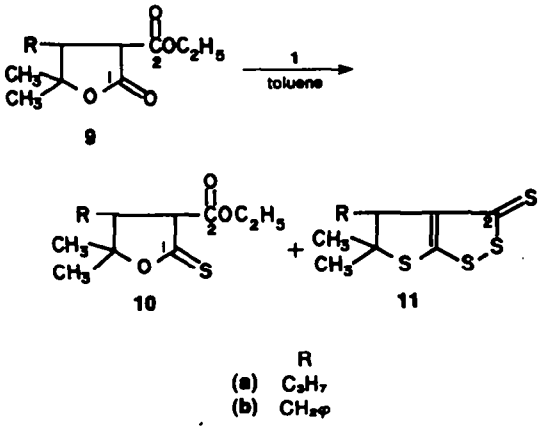
agreement with earlier findings.[5] From ^{13}C and ^{1}H NMR spectra of compounds **6c**, **7c** and **8c** mixtures of isomers are observed as two different chemical shifts of the >C=X (X=O, S) carbon atoms are found (Tables 1 and 2) and two different chemical shifts are found for some of the protons (Experimental).

The mass spectra of the compounds **7a–c** all show a fairly abundant ion at $M^+ - 60$ (M^+–COS) and in both **7a–c** and **8a,c** the most intense peak corresponds to the fragment.



m/e 81 $R^2 = H$
m/e 95 $R^2 = CH_3$

As a consequence of the lower reaction temperature for lactones as compared to esters, treatment of tetrahydro - 2 - oxo - 3 - furancarboxylic acid ethyl ester **9** with 1 yielded the corresponding 2-thione compound and no thiono ester. As a byproduct a 4,5 - dihydrothieno[2,3-c] - 1,2 - dithiole - 3 - thione, **11**, could be isolated.



R
(a) C_3H_7
(b) $CH_2\varphi$

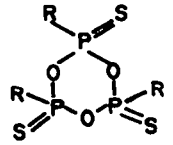
The reactions were followed by glc. Total conversion of **9** was not possible to obtain regardless of the amount of **1** used. The best yield of **10** was found after 6–8 hr and prolonged heating increased the yield of **11**, decreasing the yield of **10**. It is noteworthy that **11a,b** contains a S-atom in the original lactone ring, indicating that a rearrangement takes place analogous to what was observed for the compounds **7a–c** and **8a,c**. The formation of the 1,2 - dithiole - 3 - thione is in accordance with the results found for β-ketoamides and β-ketoesters.[12]

The compounds **10a,b** and **11a,b** are characterized by means of ^{1}H NMR and ^{13}C NMR spectroscopy, MS, IR and microanalyses. The IR spectra of **9a,b** show two strong CO absorptions in the region 1700–1800 cm^{-1} whereas **10a,b** show only one and **11a,b** no absorptions. In the ^{13}C NMR spectra it is noted that the ester CO group is unaffected whether it is attached to a lactone or a thionolactone. The mass fragmentation pattern of **10a,b** is similar to that of **9a,b**.[14] As a final remark it should be stated, that by means of the dimer of *p*-methoxyphenylthionophosphine sulfide it has been possible to synthesize, in high yields, simple γ-thionolactones from γ-lactones and in certain cases condensed δ-lactones to the corresponding δ-thionolactones. As thionolactones are an almost unknown class of compounds, further investigations in this field will be made.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer and the ^{13}C NMR spectra at 20 MHz on a Varian CFT-20 instrument. Chemical shifts are expressed in δ-values relative to TMS. IR spectra were recorded on a Beckmann IR 18 spectrometer. Mass spectra were recorded on a V. G. Micromass 7070F spectrometer operating at 70 eV using direct inlet. Elementary analyses were carried out by Novo Microanalytical Laboratory, NOVO Industri A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler. Silica gel 60 (Merck) was used for column chromatography. M.ps and b.ps are uncorrected.

Preparation of **1** (see *Ref.* 3). The starting compounds **2a**, **2d**, **2e** and **4a** were commercial. The following compounds were prepared according to known methods: **2b**,[14] **2c**,[14] **6a**,[15] **6b**,[15] **6c**[15] and **9a**.[14] Compound **5a** was kindly placed at our disposal by Dr. D. Berney, Wander Ltd., Berne, Schwitzerland.[16,17] In all the reactions described compound **12** could be isolated in different yields (see also *Ref.* [3]).



R = *p*-methoxyphenyl

Reaction conditions, CO absorptions (^{13}C NMR) and yields are given in Table 1, and physical data, thiocarbonyl absorptions (^{13}C NMR), IR absorptions and analytical data are given in Table 2.

General procedure for the preparation of the compounds **3a–e** *and* **4b**. The lactone (0.01 mole) and **1** (0.005 mole) in 10 ml of anhydrous xylene or toluene (Table 1) were heated until no more starting material could be detected (tlc or glc). After cooling the solvent was stripped off and the mixture was purified on silica gel, using ether/light petroleum as eluant (compound, % v/v): **3b**, 100. **3c**, 10. **3d**, 25. **3a**, 50. **4b**, 15. For compound **3a** CH_2Cl_2 was used as eluant. After evaporation the compounds were distilled/recrystallized (CCl_4 or isopropyl ether/light petroleum).

Compound **3a**. ^{1}H NMR ($CDCl_3$): 2.0–2.6 (2 H, m) CH_2–CH_2–CH_2, 3.08 (2 H, t) CH_2–C=S, 4.71 (2 H, t) O–CH_2–. MS: *m/e* 102 (M^+, 100%), 71 (25%), 42 (62%).

Compound **3b**. ^{1}H NMR ($CDCl_3$): 1.68 (6 H, d) $C(CH_3)_2$, 3.47 (3 H, m) CH + CH_2. MS: *m/e* 155 (M^+, 28%), 140 (23%), 124 (100%).

Compound **3c**. ^{1}H NMR ($CDCl_3$): 1.30 (3 H, s) C–CH_3, 1.51 (3 H, s) C–CH_3, 0.8 (7 H, m) n-Pr, 1.92–2.51 (1 H, m) CH, 2.72–3.48 (2 H, m) CH_2. MS: *m/e* 173 (M^+, 100%), 139 (12%), 111 (18%), 97 (21%), 69 (50%).

Compound **3d**. ^{1}H NMR ($CDCl_3$): 1.52 (3 H, d) CH_3, 1.7–2.7 (2 H, m) CH–CH_2, 3.18 (2 H, sext) S–C–CH_2, 5.08 (1 H, m) CH. MS: *m/e* 116 (M^+, 100%), 83 (14%), 72 (21%), 56 (22%).

Compound **3e**. ^{1}H NMR ($CDCl_3$): 2.5 (2 H, m) CH_2–CH_2–CH_2, 3.1 (2 H, t) S–C–CH_2, 3.62 (2 H, t) S–CH_2. MS: *m/e* 118 (M^+, 100%), 85 (13%), 71 (48%), 42 (55%).

Compound **4b**. ^{1}H NMR ($CDCl_3$): 7.1–7.7 (m). MS: *m/e* 162 (M^+, 72%), 118 (100%).

Preparation of **5b**. 1.37 g lactone (0.005 mole) and 2.5 g **1** (0.005 mole) were stirred in xylene at 140° for 8 hr. 2.5 g **1** (0.005 mole) was added and heating prolonged for 3 hr. Work-up as usual using 25% ether/light petroleum as eluant, yield 87% **5b** and 11% **5a**. Recrystallization from isopropyl ether.

Compound **5b**. ^{1}H NMR ($CDCl_3$): 3.27 (1 H, dd), 3.90 (1 H, dd), 4.80 (1 H, dd) CH^1–$C(H^2)(H^3)$, $J_{H^1H^2}$ 6.5, $J_{H^1H^3}$ 2, $J_{H^2H^3}$ 16.5, 7.0–8.0 (11 H, m) aromatic. MS: *m/e* 290 (M^+, 100%), 257 (75%), 231 (100%).

General procedure for the preparation of the compounds **7a–c**, **8a,c**, **10a,b** *and* **11a,b**. The lactone (0.01 mole) and **1** (0.01 mole) in 10 ml of xylene or toluene were heated for 3 hr. Then 0.005 mole of **1** was added and the reaction was continued. The reactions were followed by glc. Total conversion of the starting compounds was not possible though an excess of **1** was used, and the reactions were stopped when the maximum amount of **7** and **10** respectively had been reached. After having stripped off the solvent the mixture was purified on silica gel using 2–10%, v/v anhydrous ether/light petroleum. The eluants were dried ($MgSO_4$). Additional column chromatography (2–10%, v/v ether/light petroleum or 30–50%, v/v CH_2Cl_2/light petroleum) was in most cases necessary to purify the samples.

Compound **7a**. ^{1}H NMR ($CDCl_3$): 1.10–2.35 (10 H, m) $(CH_2)_5$, 3.78 (2 H, s) O=C–CH_2. MS: *m/e* 188 (M^+, 27%), 145 (18%), 128 (50%), 81 (100%).

Compound **7b**. ^{1}H NMR ($CDCl_3$): 1.2–2.4 (10 H, m) $(CH_2)_5$, 1.48 (3 H, d) CH_3, 4.10 (1 H, q) O=C–CH. MS: *m/e* 202 (M^+, 25%), 142 (85%), 81 (100%).

Compound **7c**. ^{1}H NMR ($CDCl_3$): 1.18 (3 H, d) CH_3 (only one doublet observed), 1.2–2.5 (9 H, m) $(CH_2)_4CH$–CH_3, 3.78/3.82 (2 H, s) S=C–CH_2 (two isomers present). MS: *m/e* 202 (M^+, 30%), 142 (71%), 95 (100%).

Compound **8a**. ^{1}H NMR ($CDCl_3$): 1.2–2.4 (10 H, m) $(CH_2)_5$, 4.22 (2 H, s) S=C–CH_2. MS: *m/e* 204 (M^+, 51%), 171 (35%), 81 (100%).

Compound **8b**. Traces could be detected. MS: *m/e* 218 (M^+, 30%), 81 (100%).

Compound **8c**. ^{1}H NMR ($CDCl_3$): 1.20/1.22 (3 H, d) CH_3 (two isomers present), 1.20–2.70 (9 H, m) $(CH_2)_4CH$–CH_3, 4.23/4.27 (2 H, s) S=C–CH_2 (two isomers present). MS: *m/e* 218 (M^+, 100%), 185 (48%), 95 (95%).

Compounds **10a**. ^{1}H NMR ($CDCl_3$): 0.92 (3 H, t) CH_3–CH_2, 1.1–1.8 (7 H, m) CH_2–CH_2 + O–CH_2–CH_3, 1.35 (3 H, s) C–CH_3, 1.60 (3 H, s) C–CH_3, 2.75 (1 H, m) CH_2–CH–CH, 3.65 (1 H, d) CH–COO–, J_{HH} 12, 4.26 (2 H, q) O–CH_2. MS: *m/e* 244 (M^+, 38%), 184 (10%), 141 (100%), 97 (58%).

Compound **10b**. ^{1}H NMR ($CDCl_3$): 1.10 (3 H, t) CH_3–CH_2, 1.40 (3 H, s) C–CH_3, 1.49 (3 H, s) C–CH_3, 2.5–3.3 (3 H, m) CH–CH_2–φ, 3.80 (1 H, d) CH–COO–, 3.86 (2 H, q) O–CH_2–CH_3, 7.27 (5 H, s) φ. MS: *m/e* 292 (M^+, 14%), 204 (15%), 145 (35%), 118 (65%), 91 (100%).

Compound **11a**. ^{1}H NMR ($CDCl_3$): 0.91 (3 H, t) CH_3–CH_3, 1.1–2.0 (4 H, m) CH_2–CH_2, 1.55 (3 H, s) C–CH_3, 1.60 (3 H, s) C–CH_3, 2.90 (1 H, t) CH. MS: *m/e* 262 (M^+, 33%), 229 (42%), 205 (24%), 172 (37%), 97 (100%).

Compound **11b**. ^{1}H NMR ($CDCl_3$): 1.45 (3 H, s) C–CH_3, 1.60 (3 H, s) C–CH_3, 3.16 (1 H, t) CH, 3.20 (2 H, d) CH_2, 7.27 (5 H, s) φ. MS: *m/e* 310 (M^+, 60%), 219 (100%).

Formation of **9a** *and* **7a**. 0.280 g **7a** (0.0015 mole) and 0.3 g **1** (0.00075 mole) were heated in toluene for 3 hr. Then a new portion of 0.3 g **1** was added. After 6 hr 0.2 g **1** was added. After 9 hr the mixture was allowed to cool and the general procedure was followed. The only product isolated was **8a**, yield 0.21 g ~65%.

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