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4-Functionally Substituted 3-Hetarylpyrazoles: VI.* 1,3-Diaryl-4-isocyanatopyrazoles

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Abstract—1,3-Diaryl-4-isocyanatopyrazoles were obtained by reaction of 1,3-diarylpyrazole-4-carboxylic acids with ethyl chloroformate and sodium azide or by reaction of 1,3-diarylpyrazole-4-carbonyl chloride with trimethylsilyl azide. The title compounds react with amines, hydrazine hydrate, alcohols, phenols, and monochloroacetic acid to afford 4-pyrazolyl-substituted ureas, semicarbazides, urethanes, and amides respectively.

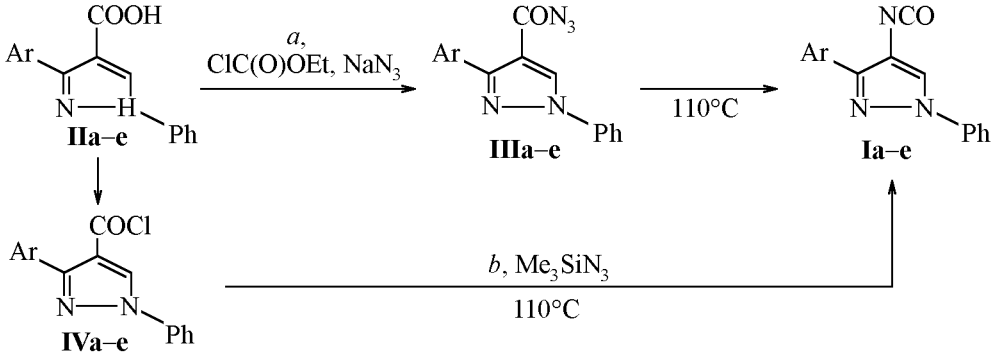
1,3-Diarylpyrazole-4-carboxylic acids that we have formerly synthesized [2] can be applied as convenient precursors to preparation of new derivatives with a highly electrophilic isocyanate group. Note that pyrazolyl isocyanates up till now remain a poorly studied heterocumulene type. The only such compounds described in the literature are 5-pyrazolyl isocyanates [3], and 4-pyrazolyl isocyanates are unknown. Yet taking into account the high pharmacological [4–7] and physiological [8, 9] activity of a number of 4-substituted pyrazoles the synthesis of 4-isocyanatopyrazoles as initial compounds for preparation of versatile derivatives presents an important task.

We tried two approaches to the synthesis of 1,3-diaryl-4-isocyanatopyrazoles **Ia–e** which were both improved preparative modifications of Curtius reaction. The "formate" method [10] (procedure *a*) provides a possibility to use directly acids **IIa–e** (Scheme 1). Under mild conditions of the reaction between the acids and ethyl chloroformate and sodium azide we were able to isolate and characterize by IR spectra 4-pyrazoyl azides **IIIa–e** that were solid compound stable to prolonged storage in a refrigerator but decomposing at melting. The target isocyanates were obtained by decomposing the azides by heating for 4 h in toluene or dioxane.

In the second, "organosilicon", procedure [11] (*b*) into the reaction with pyrazole-4-carbonyl chlorides **IVa–e** [2] was brought trimethylsilyl azide instead of sodium azide. The heating of the reagents for 4 h in boiling toluene furnished isocyanates **Ia–e** in 46–59% yield (Scheme 1).

Isocyanatopyrazoles **Ia–e** (Table 1) are crystalline solids stable to prolonged storage protected from

Scheme 1.



I–**IV, Ar = Ph (a)**, 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-EtC_6H_4 (**e**).

* For communication V see [1].

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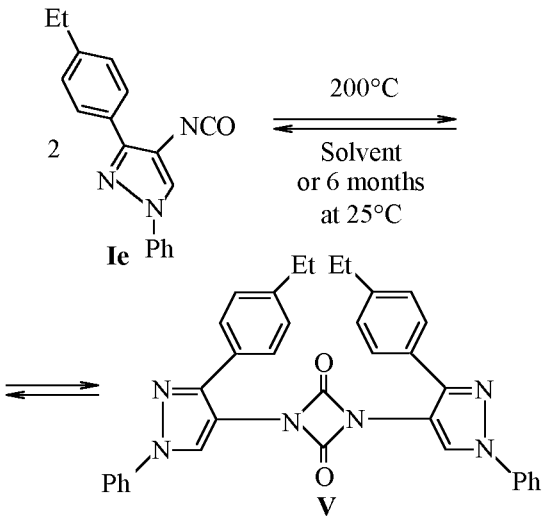
Scheme 2.



moisture. The best way to purify compounds **Ia, b, e** is by vacuum distillation, compounds **Ic, d** by recrystallization. The analysis of the IR spectra revealed that isocyanates **Ia–d** both in the solid state and in solution are monomeric. The lack in the IR spectrum of compound **Ie** taken in a KBr pellet of an absorption band in 2250–2300 cm^{-1} region and the presence of a band at 1730 cm^{-1} suggests that it probably has dimerized during distillation into urethinedione **V** with a melting point of 152°C. Yet in solution (independent of the solvent nature) compound **V** occurs exclusively as monomeric isocyanate **Ie**. Special spectral investigation showed that the dissociation of urethinedione **V** to isocyanate **Ie** can proceed also without solvent. Thus after 6 months of storage compound **V** completely converted into isocyanate **Ie** with a melting point 50–51°C (Scheme 2).

It should be noted that the chemical shift of the signal from the proton in the 5 position of the pyrazole ring in the ^1H NMR spectra of isocyanates **I** depends considerably on the solvent character. In particular, in polar solvents of DMSO type this proton gives rise to a signal at 8.90–8.75 ppm. At the same time in deuterobenzene the signal shifts upfield by 2 ppm to the region 6.72–6.85 ppm.

Table 1. Yields, constants, spectra, and elemental analyses of 1,3-diaryl-4-isocyanatopyrazoles **Ia–e**

Compd. no.	Yield, %		bp, °C (*p*, mm Hg)	mp, °C (solvent for crystallization)	IR spectrum (CH_2Cl_2), ν(N=C=O), cm^{-1}	^1H NMR spectrum (C_6D_6), δ, ppm
	a	*b*				
Ia	45	52	195–198 (0.04)	92	2270	8.06 d, 7.41 d (4H arom), 7.26–6.93 m (6H arom), 6.79 s (1H, CH=)
Ib	47	55	199–200 (0.04)	105	2280	8.07–7.89 m (4H arom), 7.57–7.21 m (5H arom), 6.73 s (1H, CH=)
Ic	52	59	–	105–106 (hexane–benzene, 10:1)	2275	7.79 d, 7.38 d (4H arom), 7.22–6.92 m (5H arom), 6.75 s (1H, CH=)
Id	46	53	–	121–122 (hexane–benzene, 5:1)	2280	7.74 d, 7.37 d (4H arom), 7.34–6.91 m (5H arom), 6.72 s (1H, CH=)
Ie	44	46	194–195 (0.04)	50–51	2270	8.03 d, 7.43 d (4H arom), 7.13–6.91 m (5H arom), 6.85 s (1H, CH=), 2.46 q (2H, CH_2), 1.03 t (3H, CH_3)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
Ia	73.82	4.08	15.81	$C_{16}H_{11}N_3O$	73.75	4.24	16.08
Ib	68.99	3.53	15.17	$C_{16}H_{10}FN_3O$	68.81	3.61	15.05
Ic	65.22	3.20	14.33	$C_{16}H_{10}ClN_3O$	64.98	3.41	14.21
Id	56.07	3.19	12.42	$C_{16}H_{10}BrN_3O$	56.49	2.96	12.35
Ie	74.95	4.97	14.29	$C_{18}H_{15}N_3O$	74.72	5.22	14.52

Table 2. Yields, constants, spectra and elemental analyses of *N*-(1,3-diaryl-4-pyrazolyl)ureas **IXa–g**

Compd. no.	Yield, %	mp, °C (solvent for crystallization)	IR spectrum (KBr), ν, cm^{-1}		^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm
			C=O	N–H	
IXa	55	253–255 (dioxane–ethanol, 1:10)	1710	3310	8.74 s (1H, CH=), 8.03 s (1H, NH), 7.88 d, 7.79 d (4H arom), 7.53–7.31 m (8H arom), 6.89 d (2H arom), 3.72 t (4H, CH_2O), 3.01 t (4H, CH_2N)
IXb	57	260–262 (dioxane–ethanol, 3:2)	1705	3300	9.71 s (1H, NH), 8.73 s (1H, CH=), 8.43 s (1H, NH), 8.12 d, 7.90 d, 7.80 d, 7.69 d (8H arom), 7.56–7.29 m (6H arom)
IXc	78	137–138 (benzene–hexane, 5:1)	1720	3290	8.52 s (1H, CH=), 7.22–7.05 m (14H arom), 6.30 s (1H, NH), 4.56 s (2H, CH_2), 3.07 s (3H, CH_3)
IXd	74	205–207 (dioxane–water, 3:1)	1720	3315	8.55 s (1H, CH=), 8.28 c (1H, NH), 7.87–6.81 m (14H arom), 3.61 m (4H, CH_2N), 3.16 m (4H, CH_2N)
IXe	77	229–231 (dioxane–ethanol, 1:6)	1715	3280	8.58 s (1H, CH=), 7.82–7.29 m (10H arom, NH), 6.38 s (1H, NH), 3.46 m (1H, CH), 1.79–1.66 m (8H, CH_2)
IXf	55	243–245 (ethanol–water, 5:1)	1710	3330	9.12 s (1H, NH), 8.93 s (1H, NH), 8.74 s (1H, CH=), 8.69 s (1H arom), 7.91–7.32 m (10H arom)
IXg	58	130–131 (benzene–hexane, 5:1)	1715	3315	8.57 s (1H, CH=), 7.83–7.34 m (10H arom, NH), 6.45 t (1H, NH), 3.55 t (4H, CH_2O), 3.09 q (2H, CH_2), 2.67 q (2H, CH_2), 2.32–2.28 m (2H, CH_2), 1.56 q (2H, CH_2), 1.23 s (3H, CH_3)

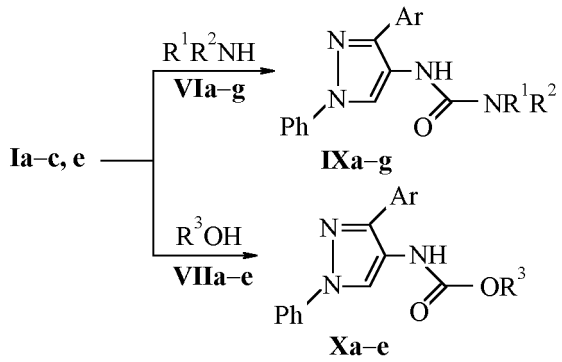
Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
IXa	70.77	5.77	16.10	$C_{26}H_{25}N_5O_2$	71.05	5.73	15.93
IXb	66.31	4.40	17.32	$C_{22}H_{17}N_5O_3$	66.15	4.29	17.53
IXc	71.54	5.41	13.62	$C_{24}H_{21}FN_4O$	71.99	5.28	13.99
IXd	70.87	5.70	15.67	$C_{26}H_{24}FN_5O$	70.73	5.48	15.86
IXe	66.71	5.59	14.07	$C_{22}H_{23}ClN_4O$	66.91	5.87	14.19
IXf	56.03	3.34	11.47	$C_{23}H_{15}Cl_2F_3N_4O$	56.25	3.08	11.40
IXg	69.46	7.50	16.31	$C_{25}H_{31}N_5O_2$	69.26	7.21	16.05

In order to prepare from the isocyanatopyrazoles **I** potential bioactive compounds we carried out their reaction with amines **VIa–g**, alcohols **VIIa–c**, phenols **VIId, e**, and acids **VIIIa, b**. The heating of isocyanates **Ia–c, e** in benzene with amines **VIa–g** affords in high yield *N*'-alkyl(aryl)-*N*-pyrazolylureas **IXa–g** (Table 2). The reaction of the isocyanates with alcohols **VIIa–c** and phenols **VIId, e** requires prolonged heating in benzene (4–5 h) in the presence of catalytic quantity of triethylamine. As a result form urethanes **Xa–e** (Scheme 3).

Some derivatives of 4-isocyanatopyrazole can be prepared without isolation of the isocyanates in pure state since the isolation process is accompanied with significant decrease in the yield. In particular, ureas **IXh,i** and semicarbazides **IXj, k** were obtained in high yield by treating with aqueous ammonia and hydrazine hydrate crude isocyanates **Ia, c** prepared by decomposition of the corresponding 4-pyrazolyl azides in dioxane (Scheme 4).

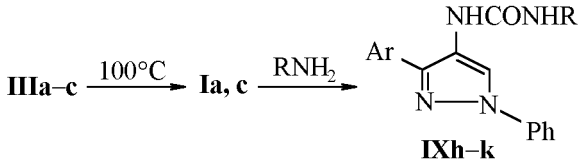
Isocyanate **Ia** with acids exhibits peculiar behavior. For instance, when treated with glacial acetic acid it

Scheme 3.



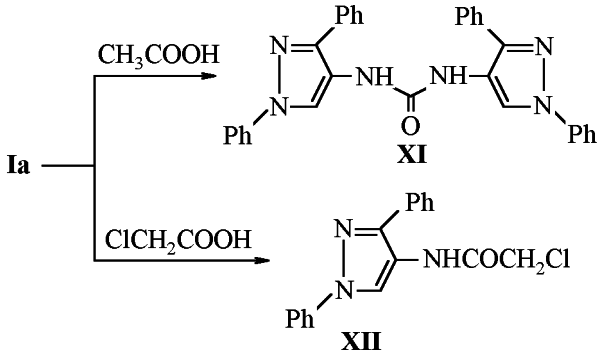
VI, R^1 = H, R^2 = cyclo-C_6H_{11} (**a**), 3-morpholinopropyl (**b**), 4-morpholinophenyl (**c**), 4-$NO_2C_6H_4$ (**d**), 2-Cl-5-$CF_3C_6H_3$ (**e**); R^1 = Me, R^2 = Bn (**f**); R^1R^2 = $(CH_2)_2NPh(CH_2)_2$ (**g**); **VII**, R^3 = 2-morpholinoethyl (`), (2-chlorophenyl)methyl (**b**), 2-furylmethyl (**c**), 4-$FC_6H_4$ (**d**), 3-$CH_3C_6H_4$ (**e**); **IX**, Ar = Ph, $R^1$ = H, $R^2$ = 4-morpholinophenyl (`), 4-$NO_2C_6H_4$ (**b**); Ar = 4-FC_6H_4, R^1 = Me, R^2 = Ph (**c**); R^1R^2 = $(CH_2)_2NPh(CH_2)_2$ (**d**); Ar = 4-ClC_6H_4, R^1 = H, R^2 = cyclo-C_6H_{11} (**e**), 2-Cl-5-$CF_3C_6H_3$ (**f**); Ar = 4-EtC_6H_4, R^1 = H, R^2 = 3-morpholinopropyl (**g**); **X**, Ar = Ph, R^3 = 2-morpholinoethyl (`), (2-chlorophenyl)-methyl (**b**); Ar = 4-ClC_6H_4, R^3 = 2-furylmethyl (**c**), 4-FC_6H_4 (**d**); Ar = 4-EtC_6H_4, R^3 = 3-$CH_3C_6H_4$ (**e**).

Scheme 4.



IX, Ar = Ph, R = H (**h**), NH_2 (**j**); Ar = 4-ClC_6H_4, R = H (**i**), NH_2 (**k**).

Scheme 5.



is hydrolyzed to afford *sym*-dipyrazolylurea **XI**. Yet the monochloroacetic acid with this compound affords amide **XII** (Scheme 5).

EXPERIMENTAL

IR spectra of compounds obtained were registered on spectrophotometer UR-20. ^{1}H NMR spectra were measured on spectrometer Varian Gemini (300 MHz).

1,3-Diaryl-4-isocyanatopyrazoles Ia–e (Table 1). (a). To a dispersion of 0.01 mol of acid **IIa–e** in 30 ml of anhydrous acetone was added at stirring and cooling to 0°C 0.011 mol of triethylamine, and after 15 min 0.011 mol of ethyl chloroformate in 5 ml of acetone. The stirring was continued for 1 h more, and at the same temperature was added 0.011 mol of sodium azide in 15 ml of water. The reaction mixture was stirred for 4 h at 0°C and then poured into 100 ml of ice water. The product was filtered off and dried in a vacuum desiccator over P_2O_5. Thus were obtained pyrazole-4-carbonyl azides **IIIa–e**. Yields, melting points, and IR spectra of the crude compounds are as follows: 92%, 72–74°C, 2140 cm^{-1} (**IIIa**), 88%, 89–92°C, 2145 cm^{-1} (**IIIb**), 91%, 102–103°C, 2150 cm^{-1} (**IIIc**), 86%, 91–95°C, 2155 cm^{-1} (**IIId**), 76%, 73–76°C, 2145 cm^{-1} (IIIe). Azides **IIIa–e** in 50 ml of toluene were heated to boiling for 4 h till the liberation of nitrogen stopped. The solvent was removed at reduced pressure, the residue was purified by distillation or recrystallization.

(b) To a solution of 0.01 mol of pyrazole-4-carbonyl chloride was added at stirring within 0.5 h 0.012 mol of trimethylsilyl azide in 10 ml of toluene. The mixture was heated for 4–5 h till the liberation of nitrogen stopped. The solvent was removed at reduced pressure, the residue was purified by distillation or recrystallization.

***N*'-Alkyl(aryl)-*N*-(4-pyrazolyl)ureas IXa–g** (Table 2). To a solution of 4 mmol of isocyanate **Ia–c, e** in 30 ml of benzene was added 4 mmol of amine **VIa–g**, and the mixture was heated to boiling for 2 h. Then the solvent was evaporated, and the residue was purified by recrystallization.

***N*-(4-Pyrazolyl)ureas IXh, i, and 1-[*N*-(4-pyrazolyl)]semicarbazides IXj, k.** In 10 ml of dioxane was heated to boiling 2 mmol of pyrazolyl azide **Ia, c** for 3 h till the liberation of nitrogen stopped. The solution was cooled, and thereto was added 4 ml of 25% aqueous ammonia (hydrazine hydrate) in 10 ml of dioxane. The mixture was stirred for 1 h at room temperature and 1 h at boiling. Then the reaction

Table 3. Yields, constants, spectra, and elemental analyses of N-(1,3-diaryl-4-pyrazolyl)urethanes **Xa–e**

Compd. no.	Yield, %	mp, °C (solvent for crystallization)	IR spectrum (KBr), ν, cm^{-1}		^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm
			C=O	N–H	
Xa	82	120–122 (benzene–hexane, 4:1)	1740	3245	8.51 s (1H, CH=), 8.16 s (1H, NH), 7.93–7.83 m (4H arom), 7.56–7.31 m (6H arom), 4.25 m (2H, CH_2O), 3.59 m (2H, CH_2O), 2.61 m (2H, CH_2N), 2.47 m (4H, CH_2N)
Xb	60	125–127 (ethanol–water, 5:1)	1735	3260	8.34 s (1H, CH=), 7.81–7.35 m (15H arom, NH), 5.26 s (2H, CH_2O)
Xc	53	132–133 (benzene–hexane, 4:1)	1735	3250	9.13 s (1H, NH), 8.61 s (1H, CH=), 7.87–7.36 m (10H arom), 6.47 m (2H arom), 5.09 m (2H, CH_2O)
Xd	62	144–145 (benzene–hexane, 3:1)	1740	3245	8.66 s (1H, CH=), 8.39 s (1H, NH), 7.88–7.30 m (13H arom)
Xe	53	165–166 (ethanol–water, 6:1)	1735	3260	8.45 s (1H, CH=), 7.72–7.01 m (13H arom), 2.71 q (2H, CH_2), 2.37 s (3H, CH_3), 1.28 t (3H, CH_3)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
Xa	67.48	6.01	14.20	$C_{22}H_{24}N_4O_3$	67.33	6.16	14.28
Xb	68.58	4.57	10.03	$C_{23}H_{18}ClN_3O_2$	68.40	4.49	10.40
Xc	64.45	4.29	10.42	$C_{21}H_{16}ClN_3O_3$	64.04	4.09	10.67
Xd	67.14	4.04	10.67	$C_{22}H_{15}ClFN_3O$	67.44	3.86	10.72
Xe	75.75	5.54	10.28	$C_{25}H_{23}N_3O_2$	75.54	5.83	10.57

mixture was cooled and poured into ice water, the precipitate was filtered off, dried, and crystallized.

N-(1,3-Diphenyl)-4-pyrazolylurea (IXh). Yield 68%, mp 152–153°C (ethanol–dioxane, 2:1). IR spectrum (KBr), cm^{-1}: 1695 (C=O), 3300–3350 (N–H). Found, %: C 69.34; H 4.86; N 20.27. $C_{16}H_{14}N_4O$. Calculated, %: C 69.05; H 5.07; N 20.13.

***N*-[1-Phenyl-3-(4-chlorophenyl)]-4-pyrazolylurea (IXi).** Yield 72%, mp 208–209°C (ethanol–dioxane, 1:1). IR spectrum (KBr), cm^{-1}: 1690 (C=O), 3280–3300 (N–H). Found, %: C 61.62; H 3.99; N 17.74. $C_{16}H_{13}ClN_4O$. Calculated, %: C 61.44; H 4.19; N 17.91.

1-(1,3-Diphenyl-4-pyrazolyl)semicarbazide (IXj). Yield 64%, mp 169–170°C (ethanol). IR spectrum (KBr), cm^{-1}: 1700 (C=O), 3300–3370 (N–H). Found, %: C 65.62; H 5.21; N 23.61. $C_{16}H_{15}N_5O$. Calculated, %: C 65.58; H 5.14; N 23.83.

1-[1-phenyl-3-(4-chlorophenyl)]-4-pyrazolylsemicarbazide (IXk). Yield 67%, mp 182–183°C (ethanol–dioxane, 10:1). IR spectrum (KBr), cm^{-1}: 1690 (C=O), 3290–3350 (N–H). Found, %: C 58.96; H 4.11; N 21.59. ¢$_{16}H_{14}ClN_5O$. Calculated, %: C 58.70; H 4.30; N 21.33.

***N*-(4-Pyrazolyl)-O-alkyl(aryl)urethanes Xa–e** (Table 3). To a solution of 4 mmol of isocyanate **Ia, c, e** in 30 ml of benzene was added 0.04 mol of alcohol **VIIa–c** or phenol **VIId, e**, and 5 drops of triethylamine. The mixture was heated to boiling for 4–5 h, then the solvent was evaporated, and the residue recrystallized.

***N,N'*-Bis[1,3-diphenyl-4-pyrazolyl]urea (XI) and (1,3-diphenyl-4-pyrazolyl)chloroacetamide (XII).** To a solution of isocyanate **Ia** in 15 ml of toluene was added 2 mmol of acetic or monochloroacetic acid, and the mixture was boiled for 3 h. The solvent was evaporated, and the residue recrystallized.

Compound XI. Yield 65%, mp 242– 243°C. IR spectrum (KBr), cm^{-1}: 1685 (C=O), 3215–3280 (N–H). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 8.68 s (2H, CH=), 8.46 s (2H, NH), 7.92 s, 7.81 d (8H arom), 7.58–7.31 m (12H arom). Found, %: 79.20; H 5.33; N 12.11. $C_{31}H_{24}N_4O$. Calculated, %: C 79.46; H 5.16; N 11.96.

Compound XI. Yield 58%, mp 113–114°C. IR spectrum (KBr), cm^{-1}: 1705 (C=O), 3280 (N–H). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 9.94 s (1H, NH), 8.74 s (1H, CH=), 7.87 d, 7.79 d (4H arom), 7.53–7.31 m (6H arom). Found, %: C 65.74; H 4.71; N 13.16. $C_{17}H_{14}ClN_3O$. Calculated, %: C 65.49; H 4.53; N 13.48.

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