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Synthesis and structure of novel 6-(pyrazol-1-yl)-4-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-ol derivatives

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Abstract New 6-(pyrazol-1-yl)pyrazolo[3,4-b]pyridin-3-ol compounds were synthesized by cyclization reaction from 2,6-dichloro-4-methylnicotinonitrile. Their derivatives exist as the 3-hydroxy tautomer. The structure of the compound **1a** of one of the resulting compounds was studied in detail by X-ray diffraction.

Keywords Pyrazol · Pyrazolo[3,4-b]pyridine · 3-Hydroxy tautomer · X-ray diffraction

Introduction

Pyrazolo[3,4-b]pyridines belong to an important class of heterocyclic compounds which are attractive targets in organic synthesis due to their wide variety of biological and pharmacological properties. A number of pyrazolo[3,4-b]pyridines are well known for their properties as antitubercular [1], anxiolytic [2], antiviral [3], hypnotic [4], inhibitors of xanthine oxidases [5], and analgesic [6], and for treatment of Alzheimer's disease, gastrointestinal diseases, and anorexia nervosa [7]. In addition, they have been proved to be cholesterol formation-inhibiting compounds [8]. More importantly, these compounds are also promising for inhibition of glycogen synthase kinase-3 [9].

Since the mid-1990s, the chemistry and biology of pyrazolo[3,4-b]pyridines have attracted the attention of many researchers. In order to synthesize a series of pyrazolo[3,4-b]pyridine derivatives decorated with useful pharmacophores, some research workers have established an array of new and innovative strategies to prepare diverse pyrazolo[3,4-b]pyridine cores [10]. For example, Lipson and

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co-workers have reported the synthesis of pyrazolo[3,4-b]pyridin-6-ones by reaction of 3-methyl-5-aminopyrazole with an equimolar amount of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and ketones in methanol and in DMF [11]. Kolosov and co-workers [12] have reported the synthesis of pyrazolo[3,4-b]pyridines by treatment of α-cyanochalcones with phenylhydrazine. Here, we report the efficient methodology for the synthesis of several new 6-(pyrazol-1-yl)-4-methyl-1*H*- pyrazolo[3,4-b] pyridine-3-ol derivatives.

Materials and methods

General

All chemicals were of reagent grade and used as commercially purchased without further purification. All solvents were dried and distilled before use. For TLC analysis, pre-coated plates of silica gel 60 F_{254} were used. Melting points were determined using a WRS-1B apparatus and were uncorrected. The IR spectra were recorded in the range of 400–4,000 cm^{-1} with a Magna 550 FT-IR spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV600 spectrometer. UV–Vis spectra were recorded a U-4100 (Hitachi). High resolution mass (HRMS) spectra were obtained in ESI mode on a Finnigan MAT95XP HRMS system (Thermo Electron).

Synthesis and characterization

2,6-Dichloro-4-methylnicotinonitrile (**2**, 5.0 g, 26.7 mmol) in concentrated H_2SO_4 (25 mL) was stirred at 80 °C for 4 h, then cooled to 25 °C, and poured into ice water (100 mL). The suspension was filtered and the filter cake recrystallized from acetone to obtain the product **3** (4.05 g, 80.9 %) as a white solid. m.p.: 173.5–175 °C (lit 169–173 °C) [13]. ^{1}H NMR ($(CD_3)_2SO$): δ 8.10 (s,1H), 7.93 (s, 1H), 7.55 (s, 1H), 2.31 (s, 3H). IR (KBr): 3,444, 3,343, 3,169, 1,682, 1,577, 1,081, 917, 848 cm^{-1}.

*6-Hydrazino-4-methyl-1-H-pyrazolo[3,4-b]pyridine-3-ol (**4**)*

2,6-Dichloro-4-methylnicotinamid (5.000 g, 4.9 mmol) was added to 80 % hydrazine hydrate (5 mL) and stirred at 100 °C for 5 h, cooled to room temperature, and a yellow solid formed. The yellow solid product was isolated filtration, washed with 95 % ethanol, and dried to give **4** (3.443 g, 71.8 %). m.p. > 300 °C. ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 11.56 (s, 1H), 10.35 (s,1H), 7.97 (s,1H), 6.09 (s, 1H), 4.2 (brs, 2H). 2.37 (s, 3H). IR (KBr): 3,395, 3,325, 3,207, 1,619, 1,505, 1,306, 1,015, 747 cm^{-1}. The product was used without further purification.

*6-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-1H-pyrazolo[3,4-b]pyridin-3-ol (**1a**)*

A mixture of the 6-hydrazino-4-methyl-1-*H*-pyrazolo[3,4-b]pyridine-3-ol (0.9 g, 5.0 mmol) and 2,4-pentanedione (1 mL, 9.7 mmol) were stirred in ethanol (10 mL)

at room temperature for 30 min. Then the reaction mixture was heated to 80 °C for 3 h. The yellow solution was evaporated in vacuum, the residue was isolated by filtration and recrystallized from ethanol to give **1a** as a white solid (1.0 g, 75.8 %). m.p.: 270.1–271.9 °C. IR(KBr) 3,638, 3,141, 3,089, 2,929, 1,602, 1,567, 1,553, 1,390, 1,289, 903, 827 cm^{-1}. ^1H NMR (600 MHz, $(CD_3)_2SO$): δ 11.89 (s, 1H), 10.94 (s,1H), 7.32 (s,1H), 6.11 (s,1H), 2.61 (s, 3H), 2.49 (s, 3H), 2.19 (s,3H). ^{13}C NMR (150 MHz, $(CD_3)_2SO$): δ 157.1, 153.0, 151.8, 149.0, 146.2, 141.2, 109.3, 107.9, 102.3, 17.8, 14.5, 13.5. HRMS (*m/z*): Calcd. for $C_{12}H_{13}N_5O$: 243.1120 Found: 243.1117.

*6-(5-Hydroxy-3-methyl-pyrazol-1-yl)-4-methyl-1H-pyrazolo[3,4-b]pyridin-3-ol (**1b**)*

A mixture of the 6-hydrazino-4-methyl-1-*H*-pyrazolo[3,4-b]pyridine-3-ol (0.9 g, 5.0 mmol) and ethyl acetoacetate (1.2 mL, 9.5 mmol) in ethanol (15 mL) with the addition of catalytic amounts conc. HCl was refluxed gently for 4 h. Cooling the reaction mixture gave a yellow solid **1b** (0.67 g, 54.5 %). m.p. > 300 °C. ^1H NMR (600 MHz, $(CD_3)_2SO$): 12.76 (s, 1H), 11.59 (s,1H), 11.08 (s,1H), 7.56 (s,1H), 6.54 (s,1H), 2.61 (s, 3H), 2.41 (s,3H). ^{13}C NMR (150 MHz, $(CD_3)_2SO$): δ 157.0, 156.3, 153.0, 149.6, 144.2, 141.0, 110.0, 106.3, 103.1, 18.1, 14.7. IR(KBr) 3,746, 3,228, 2,929, 1,619, 1,522, 1,407, 1,049, 1,015 cm^{-1} HRMS (*m/z*): Calcd. for $C_{11}H_{11}N_5O_2$: 245.0913 Found: 245.0917.

*5-Hydroxy-1-(3-hydroxy-4-methyl-1H-pyrazolo[3,4-b]pyridine-6-yl)-1H-pyrazole-3-carboxylic acid methyl ester (**1c**)*

Dimethyl acetylenedicarboxylate (DMADC) (6.00 mL, 48.9 mmol) in methanol (60 mL) was added dropwise to a solution of 6-hydrazino-4-methyl-1-*H*-pyrazolo[3,4-b]pyridine-3-ol (**4**) (5.00 g, 34.8 mmol) in methanol (50 mL) and the mixture was stirred vigorously for 5 h at 0 °C. The resulting suspension was filtered and the filter cake was washed thoroughly with cold methanol to obtain 2-[(3-hydroxy-4-methyl-1*H*-pyrazolo[3,4-b]pyridine-6-yl)-hydrazono]-succinic acid dimethyl ester (**5**) (8.12 g, 82.7 %) as a yellow solid. ^1H NMR ($CDCl_3$): δ 11.23 (s, 1H), 10.92 (s, 1H), 10.71 (s, 1H), 6.82 (s, 1H), 3.82 (s, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 2.50 (s, 3H). IR (KBr): 3,329, 3,169, 2,957, 1,723, 1,710, 1,605, 1,445, 1,400, 1,195, 834 cm^{-1}.

To a solution of 2-[(3-hydroxy-4-methyl-1*H*-pyrazolo[3,4-b]pyridine-6-yl)-hydrazono]-succinic acid dimethyl ester (**5**) (5.00 g, 17.5 mmol) in methanol (100 mL) was added sodium methoxide (1 mL). The reaction was refluxed for 4 h, then cooled to 0 °C, and quenched with water. The suspension was filtered and the filter cake was washed thoroughly with cold methanol. The filter cake recrystallized from acetone to obtain the product (1.95 g, 43.3 %) as a light red solid m.p. > 300 °C. ^1H NMR (pyridine-d5): δ 7.71 (s, 1H), 6.38 (s, 1H), 3.88 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (150 MHz, pyridine-d5): δ 162.9, 157.0, 156.9, 153.1, 150.0, 148.6, 144.2, 106.3, 104.5, 90.1, 51.7, 18.3. IR (KBr): 3,603, 3,223, 2,967, 1,720, 1,612, 1,261, 1,048 cm^{-1}. HRMS (*m/z*): Calcd. for $C_{12}H_{11}N_5O_4$: 289.0811 Found: 289.0823.

Crystallography

The crystal was obtained from an ethanol solution by slow evaporation. Diffraction experiments for **1a** were carried out on with Mo Kα radiation ($\lambda = 0.71073$ Å) using a Bruker SMART APEX CCD diffractometer at 296 K. Raw frame data were integrated with the SAINT program. The structures were solved by direct methods which gave the positions of all non-hydrogen atoms and refined with full-matrix least-squares on F^2 using SHELXS-97 and SHELXL-97 [14]. The hydrogen atoms were set in the calculated positions and refined by riding model. The crystallographic and refinement data of **1a** are listed in Table 1.

Results and discussion

Synthesis

The synthesis of compounds **1a, 1b**, and **1c** reported in this article was started with 2,6-dichloro-4-methylnicotinonitrile (**2**). The compound **2** on reaction with

Table 1 Crystal data and refinement details for **1a**

Compound reference	**1a**
Empirical formula	$C_{12}H_{13}N_5O$
Formula weight	243.27
Crystal system	Monoclinic
Space group	P2(1)/*n*
Unit cell dimensions	$a = 7.648(7)$ Å, $\alpha = 90.00$
	$b = 7.992(7))$Å, $\beta = 92.482(11)$
	$c = 19.393(18)$ Å, $\gamma = 90.00$
Volume	1,184.3(19) Å^3
Z	4
Density (calculated)	1.364 g/cm^3
Absorption coefficient	0.0935 mm^{-1}
F(000)	512
Crystal size	0.20 × 0.18 × 0.17 mm^3
Theta range for data collection (°)	2.10–25.00°
Reflections collected	5,924
Completeness to θ max	0.997 %
Data/restraints/parameters	2,078/0/167
Goodness-of-fit on F^2	1.052
Final *R* indices [I > 2σ(I)][a,b]	$R_1 = 0.0447$, $wR_2 = 0.1151$
R indices (all data)	$R_1 = 0.0597$, $wR_2 = 0.1301$
Largest diff. peak and hole	0.268 and −0.200 e Å^{-3}

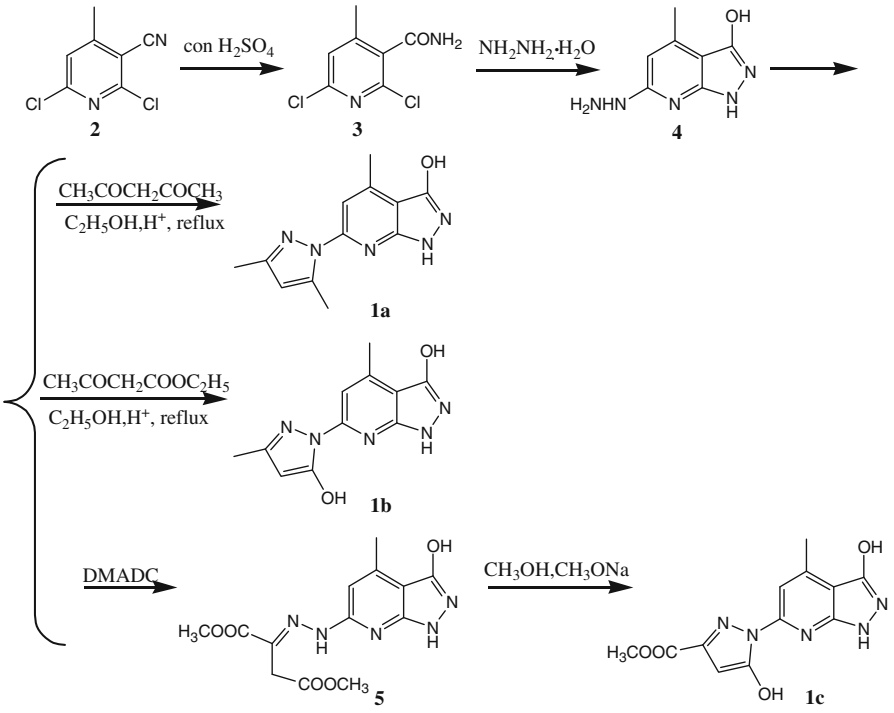
[a] $R_1 = \sum||Fo|-|Fc||/\sum|Fo|$

[b] $wR_2 = [\sum w(Fo2-Fc2)2/\sum w(Fo2)2]1/2$, $w = [2(Fo)2 + (0.1(\max(0, Fo2) + 2Fc2)/3)2]-1$

concentrated H_2SO_4 furnished 2,6-dichloro-4-methylnicotinamide (**3**) in 80.9 % yield. The cyclization of compound **3** and hydrazine hydrate produced compound **4**.

The formation of pyrazolo ring on pyridine moiety in compound **4** was achieved by the condensation reaction. 6-(3,5-dimethyl-pyrazol-1-yl)-4-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-ol (**1a**) could be obtained in 75.8 % yield, by reaction of substrate **4** with pentane-2,4-dione and ethanol as the solvent. 6-(5-hydroxy-3-methyl-pyrazol-1-yl)-4-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-ol (**1b**) was prepared from the heterocyclization of compound **4** with acetoacetic ester by intermediate hydrazones. When the hydrazone (**5**), prepared from the compound **4** and dimethyl acetylene-dicarboxylate (DMADC), was heated in methanol containing sodium methoxide the 5-hydroxy-1-(3-hydroxy-4-methyl-1*H*-pyrazolo [3,4-b]pyridine-6-yl)-1*H*-pyrazole-3-carboxylic acid methyl ester (**1c**) was obtained. The structures **1a–c** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS (Scheme 1). These data revealed the appearance of 3-hydroxy tautomer which have only rarely been reported, especially cases involving C=O → C=N tautomerism [15, 16].

Until now, 6-substituted pyrazole-1*H*-pyrazolo[3,4-b]pyridine derivatives have not been described, nor has a simple procedure been found to obtain substituted 1*H*-pyrazolo[3,4-b]pyridine at positions 6 of the pyridine ring. This makes the investigation of 6-hydrazino-4-methyl-1*H*-pyrazolo[3,4-b]pyridine-3-ol in reactions



Scheme 1 Synthesis of compounds **1a, 1b** and **1c**

with pentane-2,4-dione and their analogues to obtain the new 6-(pyrazol-1-yl)pyrazolo [3,4-b]pyridin-3-ol **1a**–**1c** compounds in (22–44 %) overall yield.

X-ray crystal structure

The molecular structure of compound **1a** determined in the crystalline phase with atomic numbering scheme is illustrated in Fig. 1. The molecular structure **1a** can be described as being built from planar pyrazolo[3,4-b]pyridin fragments linking one pyrazole ring. Compound **1a** exhibits three possible tautomeric form as shown in Scheme 2. Crystals of **1a** shows a possible tautomerism of this compound. The C1–O1 bond length of 1.332(3) Å is close to that of a nearly pure C–O single bond (average length of C–O sp^3–O single bond is 1.34 Å), in accordance with recently reported pyrazole-OH bond length (1.331(2) Å) [17]. The X-ray crystal structural research proves conclusively that the tautomer present in the crystal is the tautomeric form A.

The fused core pyrazolo[3,4-b]pyridin fragment lies approximately in one planar with a maximum mean plane deviation of −0.031 Å for atom N1. The dihedral angles between the substituted pyrazolyl ring plane and pyridine plane is 38.3°, as seen for similar cases [18]. Substituted, the nitrogen of the pyrazolyl rings is oriented away from the pyridine nitrogen, in order to reduce the nitrogen lone pairs of the electronic repulsion.

All bond distances in the pyrazole and pyrazolopyridine rings exhibit partial double bond character, which means that a delocalized π-electronic system is in the entire ring. The significant bond distances and angles of the compounds **1a** are: C1–N1 1.317(3)Å, N1–N2 1.387(2)Å, N2–C2 1.352(3)Å, C2–N3 1.347(3)Å, N4–N5 1.375(2)Å, N5–C12 1.329(3)Å, C1–N1–N2 105.87(17)°, C2–N2–N1 110.53(17)°, C7–N3–C2 113.16(18)°, C9–N4–N5 111.60(17)°, and C12–N5–N4 105.15(17)°. These bond length and angles are all comparable with the similar literature data

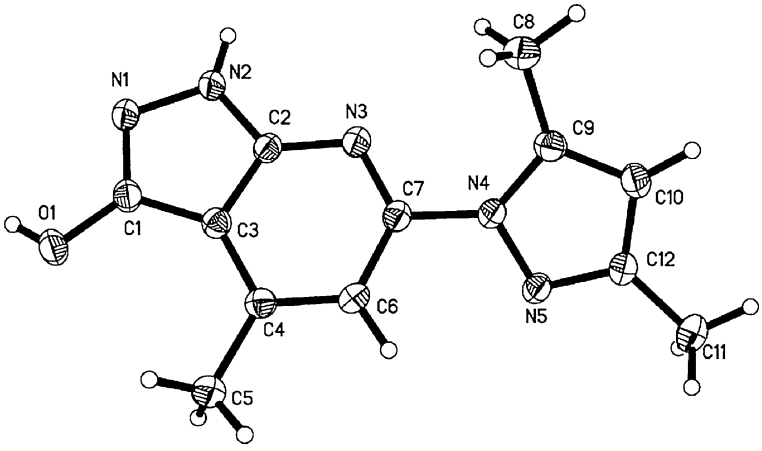
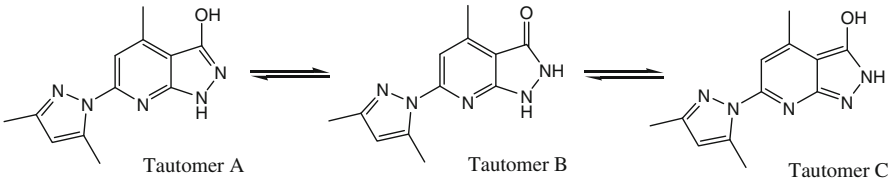


Fig. 1 The molecular structure of the compound **1a** with atom-numbering scheme; displacement ellipsoids are drawn at the 30 % probability level



Scheme 2 Tautomeric forms of compounds **1a**

reported for 2,6-bis(3,5-dimethyl-*N*-pyrazolyl) pyridine [18] and parent pyrazolo[3,4-b]pyridine reported in the CSD [16].

UV–Vis absorption spectral

The UV–Vis optical absorption of compounds **1a–c** were measured in tetrahydrofuran solution with the concentration of 2.5×10^{-5} M, respectively, as shown in Fig. 2.

As can be seen, the three compounds displayed two major absorption spectra band: one at λ_{max} 247–251 nm and second absorption band with λ_{max} 296–313 nm, corresponding to $\pi \rightarrow \pi^*$ transition depending on the consequence of the extended aromaticity of the pyrazolopyridine rings. The three compounds showed values of the molar absorptivity coefficient (ε) that exceeded 10,000; the long wavelength bands at 300 nm also displayed values of $\varepsilon > 10{,}000$.

UV–Vis absorption spectra of the compound **1a** in tetrahydrofuran, methanol, ethanol, acetonitrile, and dimethylsulfoxide with the concentration of 2.5×10^{-5} M are given in Fig. 3. The UV–Vis absorption spectra of compound **1a** in protic solvents are not very different. In protic solvents like methanol and ethanol, the

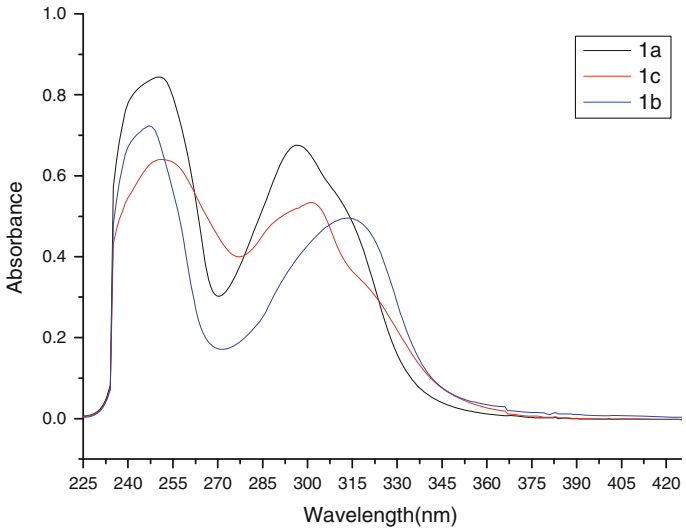


Fig. 2 UV–Vis spectra of **1a–c** in THF solution

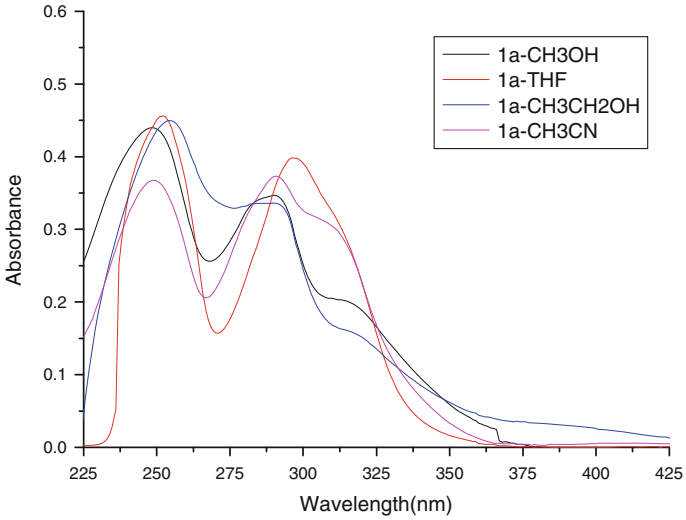


Fig. 3 UV–Vis spectra of **1a** in different solvents

absorption spectra of **1a** have a slight decrease in absorbance in second absorption band. This is caused by the interactions between the solutions and solute molecules.

Conclusions

In this study, we have described an efficient method for the synthesis of three 6-(pyrazol-1-yl)-pyrazolo[3,4-b]pyridin-3-ol novel derivatives that are important building blocks in the fields of pharmacy. Their structures were experimentally characterized by means of NMR, IR, and HRMS, and typical compound **1a** was also determined by X-ray diffraction. The UV–Vis absorption spectra of compounds of **1a–c** in THF were observed to be similar.

Crystallographic data for compound **1a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 888113. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: + 44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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