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Synthesis Of 2,5-Disubstituted-1,3,4-Oxadiazoles Using Ethyl Oleate As Precursor

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Abstract: Ethyl oleate (1) reacts with hydrazine hydrate to form stearic acid hydrazide (2), the reaction proceeds with the simultaneous reduction of 9,10 C=C bond of ethyl oleate. The stearic acid hydrazide formed on intermolecular cyclisation with different aliphatic acids, aromatic acids (3), or ethyl oleate (1) in the presence of phosphorus oxychloride forms 2,5-disubstituted 1,3,4-oxadiazoles (4) in good yield. The structure proofs of the product were confirmed by spectral studies and elemental analysis.
Key words: Ethyl oleate, reduction, hydrazide, $POCl_3$,1,3,4-oxadiazoles.

Introduction

Human body requires fats to function properly; fatty acids serve as the components of more complex membrane lipids and as major components of stored fat in the body. Chemically, fatty acids and their esters are used in the synthesis of oxazoles, the utility of these adducts for structural investigations of natural and artificial fatty acids are now well established[1]. Oxazolines of highly unsaturated fatty acids were used to determine the double bond position by mass spectrometry[2]. Heterocyclic compounds particularly nitrogen heterocycles they have been successfully tested against several diseases and therefore received special attention in pharmaceutical chemistry due to their diverse medicinal potential. Among the heterocycles; five-member heterocycles such as 1,3,4-oxadiazoles continuously draws interest for development of newer drug moiety[3-5]. They have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. Substituted 1,3,4-oxadiazole derivatives have known to exhibit enormous biological activities such as CNS depressant[6], anti-inflammatory activity[7], as anticonvulsant, herbicidal and HIV properties[3]. They also show a remarkable analgesic, anti-convulsant, diuretic, hypnotic and sedative properties[8].

Symmetric and unsymmetric 1,3,4-oxadiazoles were synthesized *in situ* from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloropyridazin-3-ones as acylating agents in PPA[9]. 2,5-Disubstituted 1,3,4-oxadiazoles synthesized by cyclisation of 3-aroylpropionic acid hydrazides in the presence of phosphorous oxychloride showed anti-inflammatory and analgesic effects with reduced gastric irritation[10]. 2-Chloro-bis-1,3,4-oxadiazoles were synthesized by the reaction of 2-chloro-1.4-phenylene-dioxybis-acetyl hydrazine with aromatic carboxylic acids in the presence of phosphorous oxychloride[11]. Fatty acid hydrazides are used as cheap starting materials in the synthesis of important biologically active 1,3,4-oxadiazoles using cyanogen bromide and benzoyl chloride or benzoic acid as reagents respectively[12]. Oxadiazoles synthesized via 1,3-dipolar

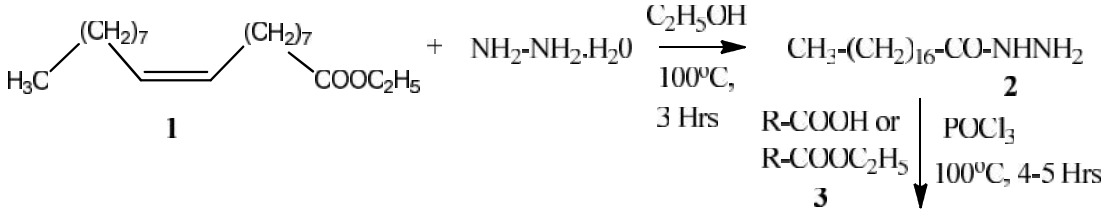
cycloaddition of nitrile oxides with imines showed promising antifungal and antibacterial activity[13]. Prompted by the varied applications of 1,3,4-oxadiazoles, the present study has been undertaken with a hope of getting more biologically potent molecules.

Experimental

The reagents and chemicals used were of analytical grade and were purchased from sigma-aldrich chemicals (India), and Merck Chemicals (India) Ltd. Melting points were determined using open capillary tube method and are uncorrected. Thin layer chromatography (TLC) was performed on a pre-coated Silica Gel sheets (HF 254, sd-fine) to monitor the reactions and purity of the compounds. n-Hexane:ethyl acetate (7:1) were used as eluent, visualization of the spots was done in iodine vapour and UV light. Chromatographic separations were carried carried out on silica gel (70-230 mesh, Merck) column using n-hexane:ethyl acetate (7:1)as eluent. IR spectra were recorded using KBr disk on a Shimadzu Perkin-Elmer 8201 FTIR. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500MHz spectrophotometer in $CDCl_3$ using TMS as internal reference. The Chemical shifts are expressed in δ ppm. The mass spectra (LCMS) were obtained on a Shimadzu LCMS-2010A spectrophotometer as APCI-POS1. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyser.

Synthesis of stearic acid hydrazide (2)[14]: A mixture of ethyl oleate (0.01 mol) and hydrazine hydrate (0.01 mol) in absolute alcohol (30ml) was refluxed on a water bath for 3 hrs. After the completion of the reaction, the solvent was removed to dryness; the residue was poured into ice cold water with stirring. The mass obtained was filtered, washed with water and recrystallised from ethanol. After purification the stearic acid hydrazide obtained in 82% yield, m.p. 114-116^{0}C (Scheme 1).

General procedure for the synthesis of 1,3,4-oxadiazoles (4): A mixture of hydrazide (0.01mol), suitable aliphatic or aromatic acids or ethyl oleate (0.01mol) and phosphorous oxychloride (0.03 mol) were refluxed on water bath for 4-5 hrs. Then the reaction mixture was cooled to room temperature and poured into ice cold water, and was neutralized with sodium bicarbonate solution. The resulting solid was filtered, dried and crystallized from 80% ethyl alcohol (Scheme 1).



4 a) R = CH_2-Cl; b) R = C_6H_5-CH_2;
c) R = C_6H_5; d) R = C_6H_5-CH=CH;
e) R = 2-(OH)C_6H_4; f) R = 2-(CH_3)C_6H_4;
g) R = 4-(NO_2)C_6H_4; h) R = 4-(NH_2)C_6H_4;
i) R = CH_3-$(CH_2)_{16}$.

Scheme 1

Results And Discussion

2-(Chloromethyl)-5-heptadecyl-1, 3, 4-oxadiazole **(4a):** Obtained from stearic acid hydrazide **2** and chloroacetic acid **3a** in 64% yield, m.p. 56-58°C. IR (KBr, γ cm^{-1}): 3087 (C-H str), 1619 (C=N str), 1251(N-N=C str), 1090 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.94 (3H,t,CH_3), 1.27 (26H,m, $(CH_2)_{13}$), 1.34 (2H,m,CH_2),1.62 (2H,m,CH_2 β to ring), 2.58 (2H,t,J = 7.5 Hz, CH_2 α to ring),4.63 (2H,CH_2, α to Cl atom). ^{13}C NMR ($CDCl_3$): δ 14.6 (1C, $\underline{C}H_3$), 23.0 (1C, $\underline{C}H_2$), 27.3 (2C, $\underline{C}H_2$), 29.8 (3C, $\underline{C}H_2$), 30.1 (1C, $\underline{C}H_2$), 30.9 (3C, $\underline{C}H_2$), 31.4 (4C, $\underline{C}H_2$), 32.4 (1C, $\underline{C}H_2$), 33.5 (1C, $\underline{C}H_2$), 36.6 (1C, $\underline{C}H_2$), 45.2 (1C, $\underline{C}H_2$), 159.2 (1C, $\underline{C}$-5), 164.6 (1C, $\underline{C}$-2). Anal.Cald.for $C_{20}H_{37}ClN_2O$: C, 67.29, H, 10.45, N, 7.85; Found: C, 67.30, H, 10.47, N, 7.86%.

***2-Benzyl-5-heptadecyl-1,3,4-oxadiazole* (4b):** Obtained from stearic acid hydrazide **2** and phenylacetic acid **3b** in 48% yield, m.p. 68-70˚C. IR (KBr, γ cm^{-1}): 3055 (C-H str), 1620 (C=N str), 1422 (C=C str), 1251(N-N=C str), 1082 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.96 (3H,t,CH_3),1.27 (26H,m, $(CH_2)_{13}$), 1.34 (2H,m,CH_3),1.69 (2H,m,CH_2 β to ring), 2.56 (2H,t,J = 7.5 Hz, CH_2 α to ring), 3.82 (2H, CH_2, α to ring), 7.05-7.15 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.1 (1C, $\underline{C}H_3$), 23.1 (1C, $\underline{C}H_2$), 27.3 (2C, $\underline{C}H_2$), 29.5 (1C, $\underline{C}H_2$), 30.1 (1C, $\underline{C}H_2$), 30.4 (3C, $\underline{C}H_2$), 30.9 (4C, $\underline{C}H_2$), 32.4 (1C, $\underline{C}H_2$), 33.7 (1C, $\underline{C}H_2$), 36.2 (1C, $\underline{C}H_2$), 125.4 (1C, C_6H_5-$\underline{C}$), 128.6 (2C, C_6H_5-$\underline{C}$), 127.2 (2C, C_6H_5-$\underline{C}$), 129.8 (2C, $\underline{C}H_2$), 137.2 (1C, C_6H_5-$\underline{C}$), 157.2 (1C, $\underline{C}$-5), 163.9 (1C, $\underline{C}$-2). MS (relative abundance) m/z: 399 (MH^+, 100), 371 (10), 308 (16), 160 (14). Anal.Cald.for $C_{26}H_{42}N_2O$: C, 78.34, H, 10.62, N, 7.03; Found: C, 78.36, H, 10.47, N, 7.15%.

***2-Heptadecyl-5-phenyl-1,3,4-oxadiazole* (4c):** Obtained from stearic acid hydrazide **2** and benzoic acid **3c** in 63% yield, m.p. 83-85˚C. IR (KBr, γ cm^{-1}): 3054 (C-H str), 1620 (C=N str), 1420 (C=C str), 1252(N-N=C str), 1084 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.91 (3H,t,CH_3), 1.26 (26H,m, $(CH_2)_{13}$),1.34(2H,m, CH_2), 1.66 (2H,m,CH_2 β to ring), 2.52 (2H,t,J = 7.5 Hz, CH_2 α to ring),7.20- 7.7.48 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.2 (1C, $\underline{C}H_3$), 22.5 (1C, $\underline{C}H_2$), 29.3 (2C, $\underline{C}H_2$), 29.6 (10C, $\underline{C}H_2$), 31.4 (2C, $\underline{C}H_2$), 32.6 (1C, $\underline{C}H_2$), 126.2 (1C, Ar-$\underline{C}$), 127.3 (2C, Ar-$\underline{C}$), 129.5 (2C, Ar-$\underline{C}$), 128.7 (1C, Ar-$\underline{C}$), 152.2 (1C, 5-$\underline{C}$), 164.2 (1C, 2-$\underline{C}$). Anal.Cald. for $C_{25}H_{40}N_2O$: C,78.07, H, 10.48, N, 7.28; Found: C, 78.02, H, 10.46, N, 7.26%.

***2-Heptadecyl-5-styryl-1,3,4-oxadiazole* (4d):** Obtained from stearic acid hydrazide **2** and cinnamic acid **3d** in 62% yield, m.p. 60-62˚C. IR (KBr, γ cm^{-1}): 3050 (C-H str), 1622 (C=N str), 1422 (C=C str, 1256(N-N=C str), 1080 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.97 (3H,t,CH_3), 1.28 (26H,m,$(CH_2)_{13}$), 1.32 (2H,m,CH_2),1.67 (2H,m,CH_2 β to ring), 2.55 (2H,t,J = 7.5 Hz, CH_2 α to ring),6.50 (2H, d , CH=CH, α to ring), 7.15-7.29 (5H, m, Ar-H). ^{13}C NMR $CDCl_3$: δ 13.8 (1C, $\underline{C}H_3$), 23.2 (1C, $\underline{C}H_2$), 27.0 (2C, $\underline{C}H_2$), 29.5 (1C, $\underline{C}H_2$), 30.3 (1C, $\underline{C}H_2$), 30.7 (3C, $\underline{C}H_2$), 30.9 (4C, $\underline{C}H_2$), 32.5 (1C, $\underline{C}H_2$), 33.9 (1C, $\underline{C}H_2$), 124.3 (1C, $\underline{C}$H=C), 126.6 (2C, C_6H_5-$\underline{C}$), 127.4 (1C, C_6H_5-$\underline{C}$), 128.2 (2C, C_6H_5-$\underline{C}$), 130.2 (1C, $\underline{C}$H=C), 132.38 (2C, $\underline{C}H_2$), 135.2 (1C, C_6H_5-$\underline{C}$), 157.1 (1C, $\underline{C}$-5), 163.2 (1C, $\underline{C}$-2). MS (relative abundance) m/z: 411(MH^+, 100), 383 (12), 334 (08), 308 (22), 172 (18). Anal.Cald.for $C_{27}H_{42}N_2O$: C, 78.97, H, 10.31, N, 6.82; Found: C, 78.88, H, 10.27, N, 6.71%.

***5-Heptadecyl-2-(2-hydroxyphenyl)-1,3,4-oxadiazole* (4e):** Obtained from stearic acid hydrazide **2** and salicylic acid **3e** in 55% yield, m.p. 90-92˚C. IR (KBr, γ cm^{-1}): 3454 (phenolic –OH str), 3052 (C-H str),salicylic acid **3e** in 55% yield, m.p. 90-92˚C. IR (KBr, γ cm^{-1}): 3454 (phenolic –OH str),3052 (C-H str), 1619 (C=N str), 1424 (C=C str), 1252(N-N=C str), 1091 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.95 (3H,t,CH_3),1.27 (26H,m, $(CH_2)_{13}$), 1.30 (2H,m,CH_2),1.60 (2H,m,CH_2 β to ring), 2.56 (2H,t,J = 7.5 Hz, CH_2 α to ring), 5.00 (1H, s, OH,), 6.80 (2H, dd, Ar-H), 7.32 (2H, dd, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.3 (1C, $\underline{C}H_3$), 22.7 (1C, $\underline{C}H_2$), 29.4 (1C, $\underline{C}H_2$), 29.8 (10C, $\underline{C}H_2$), 31.3 (1C, $\underline{C}H_2$), 31.8 (1C, $\underline{C}H_2$), 32.7 (1C, $\underline{C}H_2$), 112.2(1C, Ar-$\underline{C}$), 116.6 (1C, Ar-$\underline{C}$), 121.8 (1C, Ar-$\underline{C}$), 128.8 (1C, Ar-$\underline{C}$), 130.3 ((1C, Ar-$\underline{C}$), 152.3 (1C, 5-$\underline{C}$), 155.4 (1C,Ar-$\underline{C}$), 164.3 (1C, 2-$\underline{C}$), Anal.Cald.for $C_{25}H_{40}N_2O_2$: C, 74.95, H, 10.06, N, 6.99; Found: C, 74.98, H, 10.46, N, 6.85%.

***2-Heptadecyl-5-(2-methylphenyl)-1,3,4-oxadiazole* (4f):** Obtained from stearic acid hydrazide **2** and 2-methyl benzoic acid **3f** in 54% yield, m.p. 48-50˚C. IR (KBr, γ cm^{-1}): 3052 (C-H str), 1605 (C=N Str),(C=C str, 1243(N-N=C str), 1087 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.98 (3H,t,CH_3), 1.27 (26H,m,$(CH_2)_{13}$),1.38 (2H,m,CH_2),1.64 (2H,m,CH_2 β to ring), 2.35(3H,s,CH_3) 2.53 (2H,t,J = 7.5 Hz, CH_2 α to ring), 7.10-7.28 (4H, m, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.2 (1C, $\underline{C}H_3$), 17.8 (1C, $\underline{C}H_3$), 22.8 (1C, $\underline{C}H_2$), 29.8 (10C, $\underline{C}H_2$), 29.2 (1C, $\underline{C}H_2$), 31.1 (1C, $\underline{C}H_2$), 31.7 (1C, $\underline{C}H_2$), 32.8 (1C, $\underline{C}H_2$), 126.4 (1C, Ar-$\underline{C}$), 127.5 (1C, Ar-$\underline{C}$), 129.6 (1C, Ar-$\underline{C}$), 128.6.3 ((1C, Ar-$\underline{C}$), 136.7 (1C, Ar-$\underline{C}$), 137.3 (1C,Ar-$\underline{C}$), 152.0 (1C, 5-$\underline{C}$), 164.4 (1C, 2-$\underline{C}$). MS (relative abundance) m/z: 399(MH^+, 100), 370 (16), 308 (20), 160 (24). Anal.Cald.for $C_{26}H_{42}N_2O$:C, 78.34, H, 10.62, N, 7.03; Found: C, 78.98, H, 10.46, N, 7.10%.

***2-Heptadecyl-5-(4-nitrophenyl)-1,3,4-oxadiazole* (3g):** Obtained from stearic acid hydrazide **2** and 4-nitro benzoic acid **3g** in 69% yield, m.p. 97-99˚C. IR (KBr, γ cm^{-1}): 3051 (C-H str), 1642 (C=N str),1410 (C=C str), 1552,1342 (NO_2 str) 1284(N-N=C str), 1083 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.92 (3H,t,CH_3), 1.24(26H,m, $(CH_2)_{13}$),1.30 (2H,m,CH_2),1.68 (2H,m,CH_2 β to ring), 2.50(2H,t,J = 7.5 Hz, CH_2 α to ring), 7.75 (2H, dd, Ar-H), 8.25 (2H, dd, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.0 (1C, $\underline{C}H_3$), 22.7 (1C, $\underline{C}H_2$), 29.5 (1C, $\underline{C}H_2$), 29.9 (10C, $\underline{C}H_2$), 31.2 (1C, $\underline{C}H_2$), 31.9 (1C, $\underline{C}H_2$), 32.9 (1C, $\underline{C}H_2$), 121.5 (2C, Ar-$\underline{C}$), 128.6 (2C, Ar-$\underline{C}$), 132.3 (1C, Ar-$\underline{C}$), 148.6 (1C, Ar-$\underline{C}$), 152.4 (1C, 5-$\underline{C}$), 164.6 (1C, 2-$\underline{C}$). Anal.Cald.for $C_{25}H_{39}N_3O_3$:C, 69.90, H, 9.15, N, 9.78; Found: C, 70.00, H, 9.20, N, 9.80%.

***2-(4-Aminophenyl)-5-Heptadecyl-1,3,4-oxadiazole* (3h):** Obtained from stearic acid hydrazide **2** and 4-amino benzoic acid **3h** in 70% yield, m.p. 132-134˚C. IR (KBr, γcm^{-1}): 3049 (C-H str), 3320 (NH_2 614 (C=N Str), 1467 (C=C str, 1249(N-N=C str), 1098 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.94 (3H,t,CH_3), 1.27 (26H,m,$(CH_2)_{13}$),1.34 (2H,m,CH_2),1.67 (2H,m,CH_2 β to ring), 2.58 (2H,t,J = 7.5 Hz, CH_2 α to ring), 3.98 (2H, s, NH_2), 6.52 (2H, dd, Ar-H), 7.24 (2H, dd, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.2 (1C, $\underline{C}H_3$), 22.7 (1C, $\underline{C}H_2$), 29.4 (1C, $\underline{C}H_2$), 29.8 (10C, $\underline{C}H_2$), 31.6 (2C, $\underline{C}H_2$), 32.6 (1C, $\underline{C}H_2$), 116.4 (1C, Ar-$\underline{C}$), 116.9 (2C, Ar-$\underline{C}$), 128.4 (2C, Ar-$\underline{C}$), 148.7 (1C, Ar-$\underline{C}$), 152.5 (1C, 5-$\underline{C}$), 164.7 (1C, 2-$\underline{C}$). Anal.Cald.for $C_{25}H_{41}N_3O$: C, 75.14, H, 10.34, N, 10.52; Found: C, 75.08, H, 10.31, N, 10.45%.

***2-(Heptadec-8-enyl)-5-heptadecyl-1,3,4-oxadiazole* (4i):** Obtained from stearic acid hydrazide **2** and ethyl oleate **1** in 56% yield, m.p. 112-114˚C. IR (KBr, γcm^{-1}): 3049 (C-H str), 1614 (C=N str), 1467 (C=C str), 1249 (N-N=C str), 1098 (C-O-C str). ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 6H, CH_3), 1.30 (m, 42H, *m*, $(CH_2)_{18}$), 1.32 (s, 6H, CH_2), 1.36 (m, 4H, CH_2 β to ring), 2.06-2.19 (m, 4H, =C-CH_2), 2.82 (t, 4H, *J=8.0 Hz*, CH_2 α to ring), 5.30 (m, 2H, -CH=CH-). ^{13}C NMR $CDCl_3$: δ 14.1 (2C, $\underline{C}H_3$), 23.2 (2C, $\underline{C}H_2$), 23.7 (4C, $\underline{C}H_2$), 27.6 (4C, $\underline{C}H_2$), 29.2 (2C, $\underline{C}H_2$), 30.0 (2C, $\underline{C}H_2$), 30.6 (4C, $\underline{C}H_2$), 31.5 (6C, $\underline{C}H_2$), 32.6 (2C, $\underline{C}H_2$), 33.3 (2C, $\underline{C}H_2$), 131.8 (2C, =$\underline{C}$H), 157.7 (2C, $\underline{C}$-5), 163.5 (2C, $\underline{C}$-2). MS (relative abundance) m/z: 545 (MH^+, 100), 517 (14), 432 (28), 406 (22), 308 (12), 306 (30). Anal.Cald.for $C_{36}H_{68}N_2O$: C, 79.35, H, 12.58, N, 5.14; Found: C, 79.24, H, 12.28, N, 5.09%.

The structures proof of the products was provided by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis. For instance in IR Spectra, the stretching absorption bands due to C=N appeared in the region 1610-1620 cm^{-1}, due to N-N=C in the region 1240-1260 cm^{-1} and due to C-O-C in the region 1090-1100 cm^{-1}. In ^{1}H NMR spectra, the signals expected due to –CH=CH- (9, 10 positions) protons of the starting material ethyl oleate in the region δ 5.00-6.00 ppm were found absent. Though there is a report that during the hydrazide formation of ethyl oleate with hydrazine hydrate that the –CH=CH- bond is unaffected[12]. On contrary to this, the synthesized compounds showed the spectrum corresponding –CH_2-CH_2- (9, 10 positions) protons. This suggests that, during hydrazide formation with hydrazine, the 9,10 double bond of ethyl oleate underwent reduction. This was further supported by MS studies, the mass spectrum of the compounds showed the mass peak (M+1) corresponding to molecular weight of the reduced form of ethyl oleate as side chain in the products. The formation of the products with reduced double bond of ethyl oleate moiety was supported the literature[14]. In addition to this, all the compounds gave the signals due to aromatic protons and substituent protons at the expected region.

In ^{13}C NMR spectra, the signals due to C_2-carbon appear in the region δ 161.0-164.0 ppm., the signals due to C_5-carbon appear in the region δ 151.0-154.0 ppm. All showed the signals due to aromatic carbons and substituent carbons in the expected region. All the cycloadducts gave significantly stable molecular ion peaks with a relative abundance ranging from 08-30% and base peak at (M+1). Further, all showed satisfactorily elemental analysis with a deviation of ± 0.02% from the theoretically calculated values. These observations strongly favor the formation of the products 4a-i.

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