REGIOSELECTIVE THERMAL CYCLIZATION OF 3-SUBSTITUTED ARYLENAMINOIMINE HYDROCHLORIDES, A CONVENIENT METHOD FOR THE SYNTHESIS OF FUNCTIONALIZED POLYCYCLIC QUINOLINE DERIVATIVES

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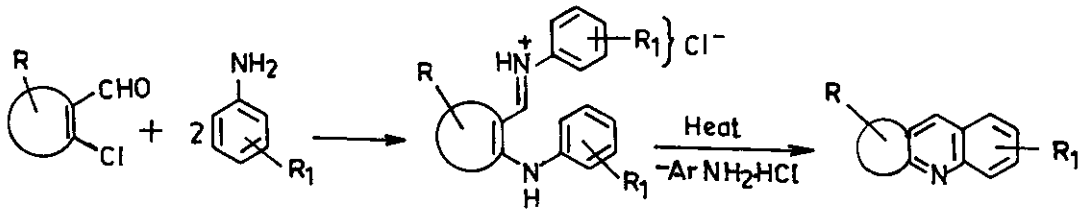
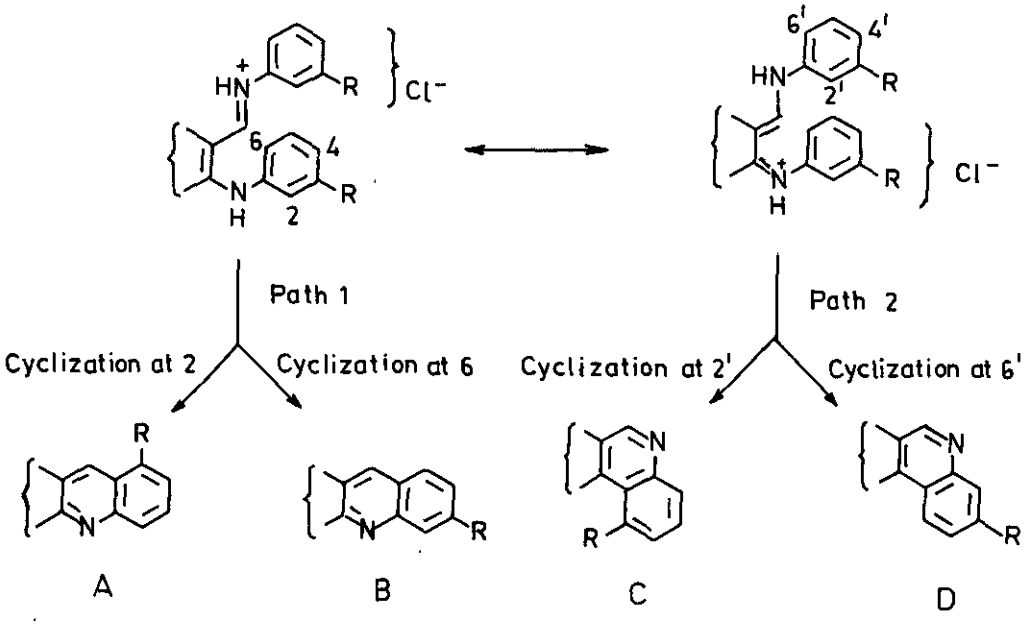
Abstract - 3-Substituted arylenaminoimine hydrochlorides on heating produced exclusively one regioisomer for electron donating groups at 3 position whereas two regioisomers for electron withdrawing/weakly electron donating groups present at the 3 positions.

Thermal cyclization of arylenaminoimine hydrochlorides (anil hydrochlorides) provides an important entry to polycyclic azaarenes (PAA).[1,2] In recent years PAA's have attracted organic chemist's attention because of interesting properties exhibited by these classes of compounds in the form of cavity shaped molecules,[3] bay region diol epoxides,[2,4,5] molecular tweezers[6] and heterohelicenes.[7] There are several methods for the synthesis of polycyclic azaarenes but for some time we found that thermal cyclization of anil hydrochlorides would be a convenient, short and high yielding method for the synthesis of these molecules,[1,8] along with the scope of introduction of various substitutions in PAA moiety which is most essential for comparison of structure activity relationship - as a result, this method in most cases are found to be superior one to the other methods.

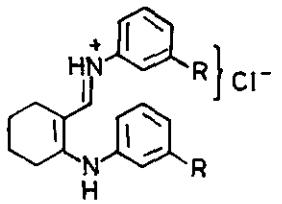
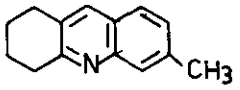
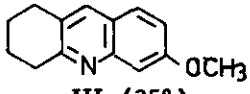
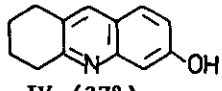
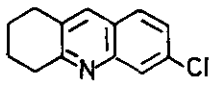
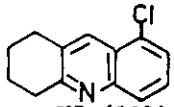
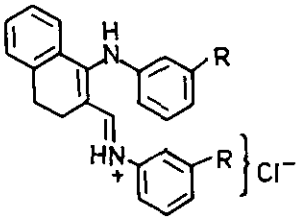
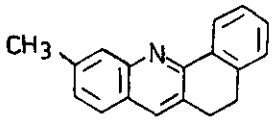
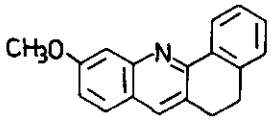
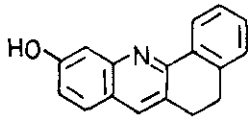
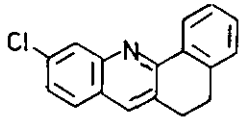
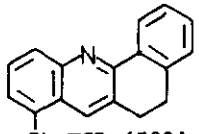
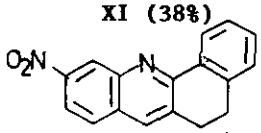
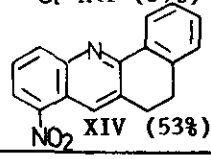
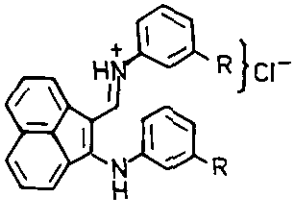
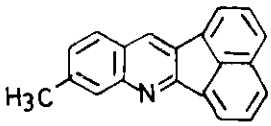
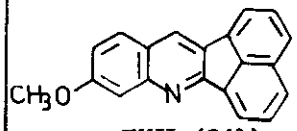
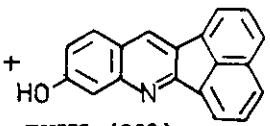
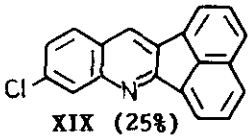
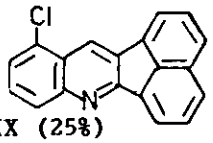


Extensive studies on the thermal cyclization of anil hydrochlorides derived from 4-substituted arylamines have been made in last few years and the results showed that the process leads to only single isomer which is expected also (neglecting the possibility of cyclization of the other resonating form of anil hydrochloride which in practice have never been found to occur).[1,8] However, surprisingly the studies on thermal cyclization of anil hydrochlorides derived from 3-substituted arylamines and different chloroaldehydes are rare.[9] Though we have reported[9] one such case, no generalization has been made earlier. Here, we report the results of our studies on thermal cyclization of 3-substituted arylenaminoimine hydrochlorides (Entries 1-12 in Table 1). Interestingly, theoretically, the anil *hydrochlorides* containing 3-substituted arylamine moiety can lead to formation of four possible products.



Formation of products C/D via path 2 have been ruled out in analogy with previous reports[10] where no such cyclizations have been observed. We found that the ratios of the products formed are influenced highly by the nature of the substitution (R). When R is an electron donating group (say, CH_3 as in entry Nos. 1,5 and 9 in Table 1) the cyclization showed high regioselectivity and took place at position

Table 1

Anil Hydrochlorides	Entry	Compound	Product/products (Isolated yield)
 **I (a-d)** R = CH_3, OCH_3, Cl, NO_2	1	1a (R=CH_3)	 **II (76%)**
	2	1b (R=OCH_3)	 **III (35%)** +  **IV (37%)**
	3	1c (R=Cl)	 **V (50%)** +  **VI (10%)**
	4	1d (R=NO_2)	No Cyclized product
 **VII (a-d)** R=CH_3, OCH_3, Cl, NO_2	5	VIIa (R=CH_3)	 **VIII (95%)**
	6	VIIb (R=OCH_3)	 **IX (37%)** +  **X (61%)**
	7	VIIc (R=Cl)	 **XI (38%)** +  **XII (59%)**
	8	VIId (R=NO_2)	 **XIII (41%)** +  **XIV (53%)**
 **XV (a-d)** R=CH_3, OCH_3, Cl, NO_2	9	XVa (R=CH_3)	 **XVI (53%)**
	10	XVb (R=OCH_3)	 **XVII (24%)** +  **XVIII (30%)**
	11	XVc (R=Cl)	 **XIX (25%)** Tarry mass +  **XX (25%)**
	12	XVd (R=NO_2)	

6 of arylamine moiety leading to exclusively one regioisomer in each case. Identical mode of cyclization was observed in the cases where R = OCH_3 (as in entries 2,6 and 10) however in these cases along with the desired products, *i.e.* methoxy-azaarens a significant amount of the demethylated products were also formed. When R is weakly activating group like Cl (Entry Nos. 3,7 or 11) or strongly electron withdrawing group like NO_2 (Entry No.8) high regioselectivity was not observed in the cyclization and a mixture of products were obtained through cyclization at positions 2 and 6 of the arylamine moiety.

The anil hydrochlorides (I, VII and XV) were prepared in good yields involving the reaction of 3-substituted arylamine (2 equivalents) with one equivalent of 2-chloro-1-formylcyclohexene[11] or 1-chloro-2-formyl-3,4-dihydronaphthalene[12] or 1-chloro-2-formyl-acenaphthylene[10] respectively in ethanol containinng trace of HCl. Thermal cyclizations were performed by heating the anil derivatives at about 200-250°C for 2-3 minutes, to produce polycyclic azaarenes. In case of Id and XVd no cyclized products were obtained. In the former case, the product after usual work up was found to be m-nitroaniline while in the latter case heating of the anil derivative resulted in tarry mass. The results have been summarized in Table 1. The polycyclic azaarenes were characterized either by comparison with authentic sample or by usual spectroscopic methods.

EXPERIMENTAL

All melting points are uncorrected and were checked in one side open glass capillary using sulphuric acid bath or a Toshniwal melting point apparatus. ^{1}H-Nmr spectra were recorded with Varian (90 MHz), Brucker (250 MHz) and JEOL (100 MHz) machines using TMS as internal standard. Mass spectra were recorded on Perkin-Elmer 800 machine. Elemental analyses have been performed from CDRI, Lucknow (India).

Enaminoimine hydrochlorides I(a-d), VII(a-d) and XV(a-d) :

General Procedure

To an ice cooled solution of arylamine (6 mmol) in ethanol (15-20 ml) 2N hydrochloric acid (2-3 ml) is added. Now to this, 2.5 mmol of the chloroaldehyde (2-chloro-

1-formylcyclohexene,[11] or 1-chloro-2-formyl-3,4-dihydro-naphthalene[12] or 1-chloro-2-formylacenaphthylene[10]) are added in one batch. Stirring is continued for 10-15 min at 5-10°C and then for 2.5-3 h at room temperature. The reaction mixtue is then cooled in ice bath and filtered. The yellow to deep red residue is washed with little ice cold ethanol and dried in air. These are used directly for thermolysis without further purification.

Ia, Bright yellow solid, mp 167-168°C (decomp.), yield 77%, ir (KBr): ν_{max} 1606, 1632, 3160, 3260 cm^{-1}. **Ib,** Light yellow solid, mp 247-248°C (decomp.), yield 70%, ir (KBr): ν_{max} 1614, 1664, 3225, 3302 cm^{-1}. **Ic,** Bright yellow solid, mp 185-186°C (decomp.), yield 86%, ir (KBr): ν_{max} 1588, 1640, 3160, 3240 cm^{-1}. **Id,** Deep yellow solid, mp 196-197°C (decomp.), yield 96%, ir (KBr): ν_{max} 1348, 1530, 1634, 3100, 3335, 3410 cm^{-1}. **VIIa,** Light yellow solid, mp 265-266°C (decomp.) (ethanol), yield 50%, ir (KBr): ν_{max} 1604, 1638, 3000, 3400 cm^{-1}. **VIIb,** Light yellow solid, mp 246-247°C (decomp.) (ethanol), yield 30%, ir (KBr): ν_{max} 1604, 1642, 3182 cm^{-1}. **VIIc,** Deep orange solid, mp 148-149°C (decomp.), yield 74%, ir (KBr): ν_{max} 1578, 1634, 3070, 3150 cm^{-1}. **VIId,** Orange solid, mp 195-196°C (decomp.), yield 82%, ir (KBr): ν_{max} 1320, 1344, 1530, 1584, 1602, 1638, 3062 cm^{-1}. **XVa,** Deep red solid, mp 196-197°C (decomp.), yield 78%, ir (KBr): ν_{max} 1592, 1640, 3040, 3170 cm^{-1}. **XVb,** Deep red solid, mp 241-242°C (decomp.), yield 83%, ir (KBr) ν_{max} 1592, 1638, 3080, 3400 cm^{-1}. **XVc,** Deep red solid, mp 211-212°C (decomp.), yield 80%, ir (KBr): ν_{max} 1586, 1620, 1642, 3058, 3160, 3456 cm^{-1}. **XVd,** Red solid, mp 227-228°C (decomp.), yield 85%, ir (KBr): ν_{max} 1346, 1396, 1530, 1562, 1612, 1644, 3078, 3160, 3456 cm^{-1}.

Thermolysis of enaminoimine hydrochlorides :

General Procedure

The anil hydrochloride (**I** or **VII** or **XV**) (500-700 mg) is heated in a long necked tube at 200-275°C for 2-3 min in a salt bath. The anil derivative melts and a vigorous reaction sets in with the deposition of arylamine hydrochloride in the cooler part of the tube. After cooling to room temperature the fused mass is trerated with chloroform or benzene. [The residue left at this stage is reserved for **Ic, VIIc**

and **XVc**. From this residue after proper recrystallization, demethylated product (**IV, X** and **XVIII**) respectively are obtained.] Organic layer is then washed with water, dried (Na_2SO_4) and solvent removed to produce the crude product which is further purified by usual technique (i.e. column chromatography, prep. tlc and/or recrystallization from suitable solvent).

II. Colourless solid, mp 98-99°C (ether/0°C) (lit.,[13] mp 100°C), yield 76%.

III. Colourless solid, mp 58-59°C (ether/0°C) (lit.,[13] mp 60-61°C), yield 35%.

IV. Colourless solid, mp 272-273°C (decomp.) (ethanol), yield 37%, ^{1}H-nmr (DMSO-d_6) : δ 1.70-2.00 (m,4H), 2.85 (t,2H, J=6.5 Hz), 2.95 (t,2H, J=6.5 Hz), 7.05 (dd,1H, J=2.2 Hz and 8.7 Hz), 7.10 (d,1H, J=2.2 Hz), 7.65 (d,1H, J=8.7 Hz), 7.80 (s,1H), 9.95 (s,1H). Anal. Calcd for $C_{13}H_{13}NO$ C, 78.39; H, 6.53; N, 7.04 Found : C, 78.30; H, 6.46; N, 6.95.

V. Colourless solid, (purified by preparative tlc using silica gel/benzene + pet. ether (60-80°C, 1:1), mp 90-91°C (ether/0°C) (lit.,[13] bp 120-122/0.01 mm), Yield 50%, ^{1}H-nmr ($CDCl_3$): δ 1.81-2.04 (m,4H), 2.91-2.97 (t,2H, J=6.3 Hz), 3.06-3.13 (t,2H, J=6.3 Hz), 7.35 (dd,1H, J=2.0 Hz and 8.7 Hz), 7.59 (d,1H, J=8.7 Hz), 7.74 (s,1H), 7.97 (d,1H, J=2.0 Hz). Anal. Calcd for $C_{13}H_{12}NCl$: C, 71.72; H, 5.52; N, 6.44 Found : C, 71.55; H, 5.31; N, 6.24.

VI. Colourless solid, (separated by preparative tlc using silica gel/benzene + pet. ether (60-80°C, 1:1), mp 55-56°C (ether/0°C), yield $\sim$ 10%, ^{1}H-nmr ($CDCl_3$: δ 1.75-2.00 (m,4H), 2.85-3.20 (m,4H), 7.50 (d,2H, J=6.0 Hz), 7.90 (d,1H, J=6.0 Hz), 8.20 (s,1H).

VIII. Colourless solid, mp 106-107°C (ethanol) [The compound (**VIII**) on aromatization with Pd-C in refluxing p-cymene afforded 9-methylbenz[c]acridine as yellow solid, mp 148-149°C identical with authentic sample (lit.,[14] mp 148°C)], yield 95%.

IX. Yellowish white solid, [purified by column chromatography, Al_2O_3 (neutral/pet. ether (60-80°C)], mp 90-91°C (ether/0°C), yield 37%, ^{1}H-nmr ($CDCl_3$) : δ 2.95-3.05 (m,2H), 3.05-3.15 (m,2H), 3.97 (s,3H), 7.13 (dd,1H, J=2.3 and 8.9 Hz), 7.25-7.50 (m,4H), 7.62 (d,1H, J=8.9 Hz), 7.85 (s,1H), 8.55 (d,1H, J=6.8 Hz). Anal. Calcd

for $C_{18}H_{15}NO$: C, 82.75; H, 5.75; N, 5.36. Found : C, 82.52; H, 5.49; N, 5.26.

X. Colourless solid, mp 263-264°C (THF-ethanol), yield 61%, ^{1}H-nmr (DMSO-d_6) : δ 2.85-3.05 (m,4H), 7.1 (dd,1H, J=2.1 and 8.8 Hz), 7.26 (d,1H, J=2.1 Hz), 7.30-7.42 (m,3H), 7.73 (d,1H, J=8.8 Hz), 8.02 (s,1H), 8.37-8.42 (m,1H), 10.04 (s,1H). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.59; H, 5.26; N, 5.67. Found : C, 82.51; H, 5.17; N, 5.60.

XI. Colourless solid, (separated from **XII** by prep. tlc using silica gel/benzene + pet.ether (60-80°C),2:1), mp 110-111°C, yield 38%, ^{1}H-nmr ($CDCl_3$) : δ 2.95-3.10 (brs,4H), 7.20-7.50 (m,4H), 7.65 (d,1H, J=8.7 Hz), 7.85 (s,1H), 8.15 (dd,1H, J=2.1 and 6.5 Hz), 8.50-8.65 (m,1H). Anal. Calcd for $C_{17}H_{12}NCl$: C, 76.84; H, 4.52; N, 5.27. Found : C, 76.73; H, 4.37; N, 5.12.

XII. Colourless solid, (separated from **XI** by prep. tlc using silica gel/benzene + pet. ether (60-80°C), 2:1), mp 115-116°C, yield 59%, ^{1}H-nmr ($CDCl_3$): δ 2.99-3.22 (m,4H), 7.26-7.45 (m,3H), 7.51-7.59 (m,2H), 8.02-8.08 (dd,1H, J=3.5 and 8.6 Hz), 8.32 (s,1H), 8.55-8.58 (m,1H). Anal. Calcd for $C_{17}H_{12}NCl$: C, 76.84; H, 4.52; N, 5.27. Found : C, 76.64; H, 4.31; N, 5.00.

XIII. Light yellow solid, (separated by column chromatography, silica gel/benzene + pet.ether (60-80°C), 3.5:6.5), mp 181-182°C, yield 41%, ir (KBr): ν_{max} 1350; 1525, cm^{-1}, ^{1}H-nmr ($CDCl_3$): δ 3.02-3.08 (m,2H), 3.16-3.23 (m,2H), 7.25-7.33 (m,1H), 7.42-7.48 (m,2H), 7.86 (d,1H, J=8.9 Hz), 8.01 (s,1H), 8.24 (dd,1H, J=2.2 and 8.9 Hz), 8.55-8.60 (m,1H), 9.02 (d,1H, J=2.2 Hz). Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.91; H, 4.35; N, 10.14. Found : C, 73.70; H, 4.12; N, 9.87.

XIV. Faint yellow solid, (separated by column chromatography, silica gel/benzene + pet.ether (60-80°C), 3.5:6.5), mp 161-162°C (ethanol), yield 53%, ir (KBr): ν_{max} 1350, 1525 cm^{-1}. ^{1}H-nmr ($CDCl_3$) : δ 3.01-3.08 (m,2H), 3.17-3.24 (m,2H), 7.27-7.32 (m,1H), 7.41-7.45 (m,2H), 7.70 (t,1H, J=8.06 Hz), 8.29 (d,1H, J=8.2 Hz), 8.41 (d,1H, J=8.2 Hz), 8.53-8.58 (m,1H), 8.76 (s,1H). Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.91; H, 4.35; N, 10.14. Found : C, 73.72; H, 4.12; N, 9.84.

XVI. Colourless solid, mp 161-162°C (ethanol), yield 57%, ^{1}H-nmr (DMSO-d_6) :

δ 2.59 (s,3H), 7.35 (dd,1H, J=1.4 and 8.2 Hz), 7.65-7.85 (m,3H), 7.90 (d,1H, J=8.2 Hz), 7.95-8.05 (m,3H), 8.42 (d,1H, J=7.5 Hz), 8.44 (s,1H). Ms : m/z 267(M^+),266, 133, 120, 119, 106, 93. Anal. Calcd for $C_{20}H_{13}N$: C, 89.88; H, 4.86; N, 5.24. Found : C, 89.62; H, 4.59; N, 4.98.

XVII. Light yellow solid, (column chromatography, Al_2O_3/ benzene), mp 173-174°C (ethanol), yield 24%, ^{1}H-nmr ($CDCl_3$) : 4.02 (s,3H), 7.23 (dd,1H, J=2.5 and 9.0 Hz), 7.67-8.06 (m,7H), 8.51 (s,1H), 8.61 (brd,1H, J=7.2 Hz). Anal. Calcd for $C_{20}H_{13}NO$: C, 84.80; H, 4.59; N, 4.95. Found : C, 84.52; H, 4.24; N, 4.59.

XVIII. Light yellow solid, mp 317°C (THF-ethanol), yield 30%, ^{1}H-nmr (DMSO-d_6) : δ 7.20 (dd,1H, J=2.0 and 8.0 Hz), 7.40 (s,1H), 7.55-7.85 (m,3H), 8.05 (d,1H, J=8.0 Hz), 8.10-8.25 (t,2H, J=8.0 Hz), 8.35 (d,1H, J=8.0 Hz), 8.80 (s,1H), 10.25 (s,1H). Anal. Calcd for $C_{19}H_{11}NO$: C, 84.76; H, 4.09; N, 5.20. Found : C, 84.65; H, 3.95; N, 5.10.

XIX. Colourless solid, (separated by prep. tlc using silica gel/benzene + pet.ether (60-80°C), 7:6), mp 215-216°C (benzene-ethanol), yield 25%, ^{1}H-nmr ($CDCl_3$): δ 7.49-7.52 (dd,1H, J=2.0 and 8.7 Hz), 7.70-7.87 (m,3H), 7.98 (d,1H, J=8.3 Hz), 8.05 (d,2H, J=7.5 Hz), 8.23 (d,1H, J=1.3 Hz), 8.44 (d,1H, J=7.0 Hz), 8.50 (s,1H). Ms : m/z 289(M+2), 287(M^+), 251, 144, 112. Anal. Calcd for $C_{19}H_{10}NCl$: C, 79.30; H, 3.48; N, 4.87. Found : C, 79.20; H, 3.29; N, 4.61.

XX. Colourless solid, (separated by prep. tlc using silica gel/benzene + pet.ether (60-80°C), 7:6), mp 256-257°C (ethanol), yield 25%, ^{1}H-nmr ($CDCl_3$) : δ 7.62-7.64 (m,2H), 7.75 (t,1H, J=7.7 Hz), 7.81 (t,1H, J=7.7 Hz), 7.98 (d,1H, J=8.0 Hz), 8.04 (d,1H, J=8.0 Hz), 8.11-8.17 (m,2H), 8.44 (d,1H, J=6.8 Hz), 8.94 (s,1H). Ms : m/z 289(M+2), 287(M^+), 251, 226, 224, 144, 126, 112. Anal. Calcd for $C_{19}H_{10}NCl$: C, 79.30; H, 3.48; N, 4.87. Found : C, 79.18; H, 3.28; N, 4.60.

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