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Efficient Hydrolysis of Dithioacetals by the *N*-Fluoro-2,4,6-trimethylpyridinium Triflate-Water System

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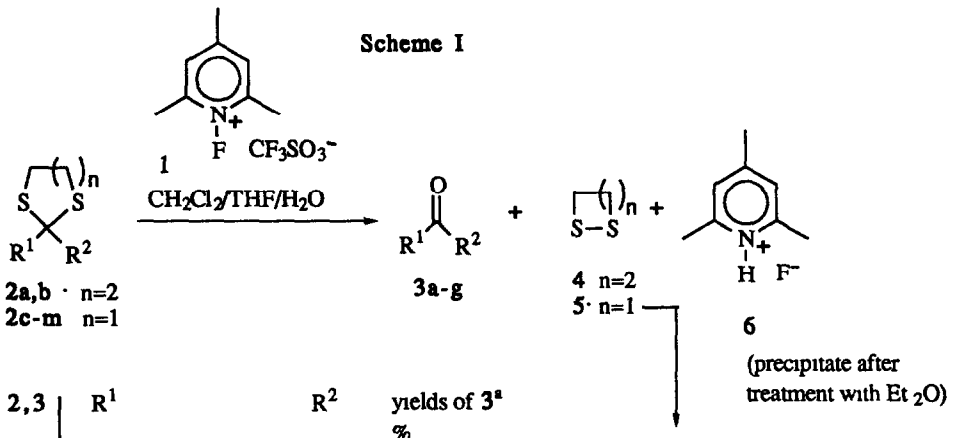
Abstract Dithioacetals including 1,3-dithianes and 1,3-dithiolanes are efficiently cleaved by the title reagent system to the parent carbonyl compounds The cleavage of diprotected symmetrical α-diketones and *p*-phenylene-diketones gives monoketones in good yields Amide, 1,3-dioxolane, disulfide, ester, ether, hydroxy, nitrile, nitro, and sulfide functions are relatively stable under the cleavage conditions but thiols are oxidized to disulfides

N-Fluoropyridinium salts, such as 1 (Scheme I), are useful reagents for fluorination of activated aromatic and aliphatic substrates [1] In particular, the treatment of aliphatic sulfides with 1 in anhydrous dichloromethane under an inert atmosphere produces α-fluoro sulfides [2] The fluorination of dithioacetals has not been reported

In our hands the treatment of 1,3-dithiane (**2a**) with 1 under the conditions described for sulfides[2] gave a number of products, none of them major, as shown by a GC analysis Surprisingly, the substrate **2a** was consumed in wet dichloromethane containing four equivalents of water to give a much simpler outcome Treatment of the mixture with ether gave a precipitate of 2,4,6-trimethylpyridinium fluoride (**6**), and the solution contained formaldehyde (3a) and 1,2-dithiacyclopentane (**4**) Obviously, **2a** was hydrolyzed in the reagent 1-mediated reaction

Dithioacetals including 1,3-dithianes and 1,3-dithiolanes are common protective groups for a carbonyl function [3] It was of interest, therefore, to determine whether or not dithioacetals derived from other carbonyl compounds can also be cleaved under similar conditions As can be seen from Scheme I the cleavage of dithioacetals **2** is highly efficient With a single exception (see footnote b in Scheme I) the best results were obtained with 1.2 equiv of **1** in a mixture of CH_2Cl_2/THF (1 1) containing 5 equiv of water under an inert atmosphere [4] The high yields correspond to isolated, analytically pure carbonyl compounds For the reaction of **2b**, after the pyridinium salt **6** had been precipitated with ether, a GC analysis of the solution showed aldehyde **3b** and 1,2-dithiacyclopentane (**4**) as the sole low molecular weight products In a similar way, only two peaks corresponding to a carbonyl compound (**3c-m**) and 1,2,5,6-tetrathiacyclooctane (**7**) were observed in the chromatograms of each of the remaining mixtures 1,2-Dithiacyclobutane (**5**) is the expected primary product but this compound is known to undergo a facile dimerization to **7**, the observed product [5]

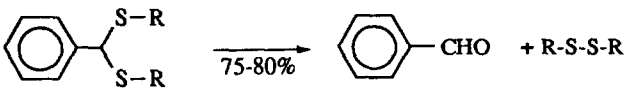
Scheme I



2,3	R^1	R^2	yields of 3[a] %
a	H	H	-
b	n-$C_{10}H_{21}$	H	80
c	Ph-CH=CH_2	H	81
d	2-NC-Ph	H	82
e	2-F_3C-Ph	H	91
f	4-Me-Ph	H	79
g	4-MeOCO-Ph	H	81
h	4-MeCOO-Ph	H	83
i	4-MeO-Ph	H	75
j	4-HO-Ph	H	68
k	4-MeS-Ph	H	72
l	4-MeCONH-Ph	H	68[b]
m	4-O_2N-Ph	Me	86

[a] Yields of isolated products.
[b] In contrast to facile hydrolysis of dithioacetals **2a-k** and **2m** with 1 2 equiv of the reagent **1** the cleavage of **2l** required at least 2 0 equiv of **1**.

The cleavage of two acyclic dithioacetals **8** derived from benzaldehyde (**9**) was also investigated (eq 1). The formation of disulfides **10** is in agreement with the pattern discussed above

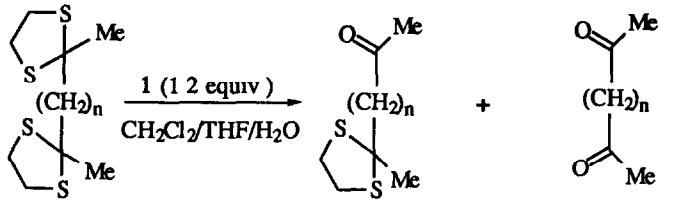


8a,b a R = *n*-Bu b R = Ph **9** **10a,b** (1)

A number of common functional groups included in Scheme I are compatible with reagent **1** Perhaps the most gratifying result is the stability of a methylthio function in compound **2k** because sulfides can be efficiently oxidized to sulfoxides by 1 in the presence of water [6] The identification of disulfides **4**, **7** or **10** in the mixtures strongly suggests that the disulfide function is also compatible with the reagent system **1**/H_2O Indeed, the treatment of dibutyl disulfide (**10a**) with **1**/H_2O under the conditions that cause complete hydrolysis of dithioacetals did not result in any appreciable changes of **10a**. The starting disulfide was recovered in an 80%

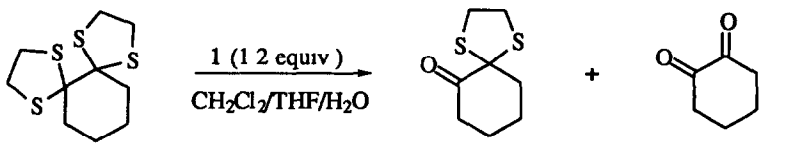
yield In a similar way it was shown that 2-phenyl-1,3-dioxolane, a cyclic acetal derived from **9** and ethylene glycol, is inert under these conditions. On the other hand, a thiol function undergoes efficient oxidation to a disulfide. A number of thiols, either alone or in competition experiments with dithioacetals, were allowed to react with the reagent system I/H_2O to give disulfides rapidly

Cleavage of one dithioacetal function in bis(dithiolanes) can be achieved with 1 2 equiv of **1** to give monoketones in reasonable yields (eqs 2-4) As can be seen from equation 2 the ratio of a monoketone to a diketone, **12/13**, for the reactions of **11** decreases with increasing separation between the two dithiolane functions in **11** [7] As expected, a bifunctional compound **14** derived from cyclohexane-1,2-dione (**16**) is cleaved to give monoketone **15** preferentially[8] (eq 3)



(2)

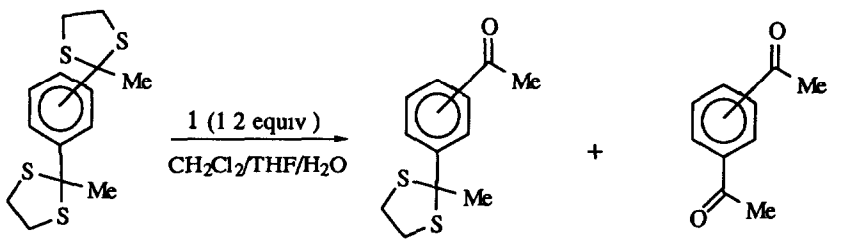
11a-c **a** n = 0, **b** n = 1, **c** n = 2 — **12a** (74%), **12b** (57%), **12c** (52%) + **13a** (5%), **13b** (15%), **13c** (21%)



(3)

14 — **15** (65%) + **16** (15%)

The order of cleavage selectivity, as a function of a linker length between two dithiolane groups in the molecule, is reversed for the reactions of aromatic derivatives **17** (eq 4) Chemoselectivity is greater for the formation of the para-substituted ketone **18a** than the meta isomer **18b**



(4)

17a, b **a**. para, **b** meta — **18a** (76%), **18b** (52%) + **19a** (5%), **19b** (21%)

We have compared the chemoselectivity of cleavage of bis(dithiolanes) **11a** and **17a** by **1** in the presence of water to those of the selected reagent systems[3] commonly used for cleavage of a dithioacetal function (Table 1). As can be seen, the use of **1** is superior not only in producing monoketones **12a** and **18a** in higher yields but also with greater selectivities **12a/13a** and **18a/19a**. It is likely that the reagent system **1**/H_2O will also compare favorably with other reagents when used for the desired selective cleavage of **11**, **14**, **17**, and structurally related bis(dithioacetal) derivatives of other diketones [9]

Table 1 Percent Yields[a] of the Products in the Cleavage Reactions of Bis(dithiolanes) **11a** and **17a** by Selected Reagent Systems[b]

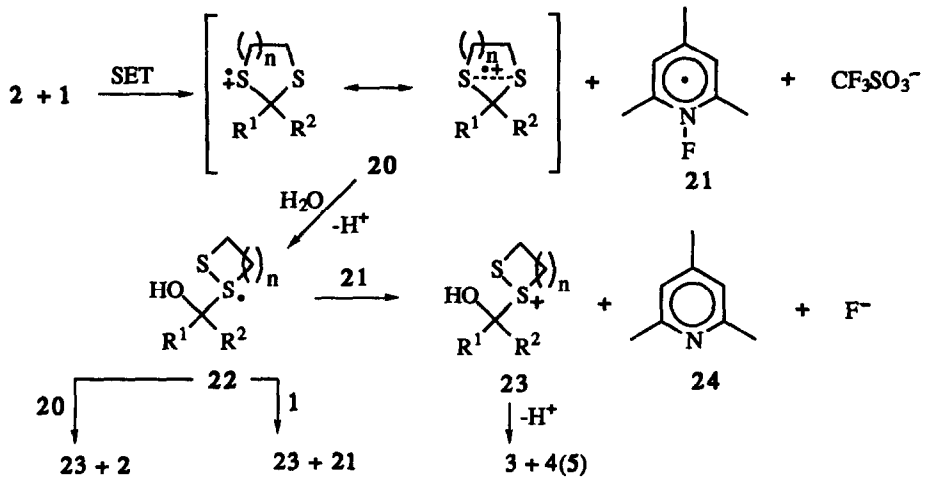
	Cleavage of **11a**		Cleavage of **17a**	
Reagent System	**12a**	**13a**	**18a**	**19a**
1/CH_2Cl_2/THF/H_2O	74	5	76	5
NBS/acetone/H_2O [c]	51	32	51	28
MeI/MeOH/H_2O [c]	62	30	42	37
I_2/DMSO [c]	40	31	35	32
$Et_3O^+BF_4^-$/$CuSO_4$/H_2O [c]	62	17	57	22

[a]Yields of isolated products [b]Conditions were optimized to arrive at the best yields of monoketones **12a** and **18a**. [c]Selected from reference 3

Finally, we would like to comment on a possible mechanism of cleavage of dithioacetals with the **1**/H_2O reagent system The much higher selectivity ratio **18a/19a** for cleavage of the para isomer **17a** in comparison to the ratio **18b/19b** for the reaction of the meta isomer **17b** strongly suggests the importance of electronic effects and is consistent with a cationic nature of intermediate products The monoketone **18a** would be more resistant to an electrophilic reaction at the dithiolane substituent to give diketone **19a** than the isomer **18b** to give **19b**, resulting in a better selectivity for the formation of **18a** than **18b**, as observed. In a similar fashion, the efficient synthesis of **12a** and **15** may be explained by the inductive effect of the carbonyl group in these compounds In agreement with the suggested importance of the electron-withdrawing effect the yields of monoketones decrease in the order **12a>12b>12c** with a concomitant increase in yields of the respective diketones **13** as the separation between the carbonyl group and the dithiolane function in the molecules of **12** increases In addition, the cleavage of dithioacetals to the parent carbonyl compounds was efficient only when conducted under an inert atmosphere of argon or nitrogen A number of unidentified additional products was observed for the reactions conducted in the presence of oxygen, a free radical scavenger, and/or nitrobenzene, a putative electron scavenger [10]

All these results are consistent with the suggested mechanism of cleavage (Scheme II), the first step of which involves single electron transfer[10] (SET) from a dithioacetal to the pyridinium cation of **1** It is known that sulfides are easily oxidized to radical cations under proper conditions,[11-13] and evidence has been

Scheme II



accumulating recently that *N*-fluoropyridinium cations can act as electron acceptors.[1,14] A driving force for the SET process would be the formation of a sulfur-centered radical cation **20** stabilized by interaction with the adjacent sulfur atom Such a stabilization has been consistently suggested in several independent studies [15-17] The suggested reaction of **20** with water to form a radical **22** also has precedence in the literature.[16] A second electron transfer process from **22** to the aromatic radical **21** would result in the formation of 2,4,6-trimethylpyridine (**24**) and fluoride ion, the observed products, and cation **23**, a postulated direct precursor to ketone **3** and cyclic disulfides **4** or **5** Alternatively, cation **23** would be produced in the oxidation reactions of radical **22** by radical cation **20** and/or pyridinium cation **1**. Again, closely related oxidation processes have been described previously [16,18]

In summary, it appears that the reagent **1**-assisted hydrolysis of dithioacetals does not involve transfer of an electrophilic fluorine atom This is in sharp contrast to the proposed mechanisms for fluorination of organic substrates with **1** and similar *N*-fluoropyridinium cations [1]

EXPERIMENTAL SECTION

All reagents were obtained from Aldrich GC analyses were conducted on an H-P 5890 Series II Gas Chromatograph equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column (25m x 0 32mm), and a 5970 Mass Selective Detector M ps (Pyrex capillary) are not corrected Unless indicated otherwise ^{1}H NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz) in $CDCl_3$ solutions with Me_4Si as an internal standard and ^{13}C NMR spectra were recorded on a Jeol GX-270 spectrometer (68 MHz) in $CDCl_3$ solutions with the solvent (77 0 ppm) as a secondary reference Compounds reported in the literature were identified by comparison of the spectral data obtained (MS and ^{1}H NMR) with those reported or by independent synthesis Syntheses of **2b**,[19] **2c**,[20] **2f**,[21] **2g**,[22] **2i**,[21] **2j**,[21] **2m**,[23] **11a**,[24] **11b**,[25] **11c**,[25] **12a**,[26] **12b**,[27] **12c**,[28] **14**,[8] and **15**[8] have been published

Preparation of N-Fluoro-2,4,6-trimethylpyridinium Trifluoromethanesulfonate[1] (1) A mixture of finely grounded lithium trifluoromethanesulfonate (15 6 g, 0.1 mol), anhydrous 2,4,6-trimethylpyridine (12.1 g, 0.1 mol), and anhydrous acetonitrile (400 mL) was stirred at 23°C under an atmosphere of argon or nitrogen for 15 min and then cooled to -40°C Molecular fluorine diluted with argon (10% F_2, available from Air Products and Chemicals, Inc , Allentown, PA 18195, USA) was slowly bubbled through the suspension at -40°C and with continuous stirring **Caution: molecular fluorine is a toxic gas and a strong oxidant!**[29] After about 4 5 L of the gas had been passed (0 2 mol of F_2), the mixture was flushed with argon or nitrogen to remove excess fluorine, and then filtered at 23°C through silica gel (10 g) to remove lithium fluoride The solution was concentrated to 30 mL on a rotary evaporator, diluted with ether (70 mL), and then cooled to -20°C. The resultant white precipitate was crystallized from dichloromethane/ether (1·2) to yield 17.2 g (60%) of 1. Product 1 is stable for several months at 23°C when stored under an argon atmosphere in the presence of phosphorus pentoxide

Synthesis of dithioacetals. All non-commercial dithioacetals were obtained from the corresponding carbonyl compounds in a BF_3-catalyzed reaction by using a general procedure [25] Solid products were crystallized from hexanes

2-(2-Cyanophenyl)-1,3-dithiolane (2d). M p 107-108°C, ^{1}H NMR δ 3 30-3 55 (m, 4 H), 5 95 (s, 1 H), 7 30 (t, J = 6 5 Hz, 1 H), 7 60-7 70 (m, 2 H), 7 90 (d, J = 8 1 Hz, 1 H); ^{13}C NMR δ 39 9, 52 8, 116.6, 117.0, 128 1, 128 6, 132 7, 144.8, MS m/z 146, 148, 178(100), 207(M^+). *Anal.* Calcd for $C_{10}H_9NS_2$: C, 57.94, H, 4 38 Found C, 57 79, H, 4 42

2-[2-(Trifluoromethyl)phenyl]-1,3-dithiolane (2e). An oil, ^{1}H NMR δ 3 30-3 65 (m, 4 H), 6.00 (s, 1 H), 7.35 (t, J = 6 5 Hz, 1 H), 7 50-7 70 (m, 2 H), 8.05 (d, J = 8 1 Hz, 1 H), ^{13}C NMR δ 40.4, 50.8, 122 2, 125 3, 126 1, 128.0, 131.1, 132.2, 140 4, MS m/z 153(100), 189, 250(M^+) *Anal.* Calcd for $C_{10}H_9F_3S_2$: C, 47 98, H, 3 62 Found C, 48 16, H, 3 70

2-[4-(Acetoxy)phenyl]-1,3-dithiolane (2h). M p. 99-100°C, ^{1}H NMR δ 3 44 (m, 4 H), 3 91 (s, 3 H), 5.65 (s, 1 H), 7.59 (d, J = 6 5 Hz, 2 H), 7 98, (d, J = 6.5 Hz, 2 H), ^{13}C NMR δ 20.8, 39 8, 54 8, 118 7, 128.4, 135 2, 148.6, 168 8, MS m/z 137, 169, 170(100), 198, 240(M^+) *Anal* Calcd for $C_{11}H_{12}O_2S_2$· C, 54 97; H, 5.03. Found. C, 54 88; H, 5 10

2-[4-(Methylthio)phenyl]-1,3-dithiolane (2k) M p 74-75°C, ^{1}H NMR δ 2.48 (s, 3 H), 3 42 (m, 4 H), 5 61 (s, 1 H), 7 18 (d, J = 6 5 Hz, 2 H), 7 44 (d, J = 6 5 Hz, 2 H), ^{13}C NMR δ 15 6, 39 7, 55 4, 125.8, 128 3, 136 6, 137 8, MS m/z 153(100), 167, 228(M^+). *Anal* Calcd for $C_{10}H_{12}S_3$. C, 52 59; H, 5 30 Found: C, 52 64, H, 5 35

2-[4-(Acetamido)phenyl]-1,3-dithiolane (2l) M.p 140-141°C; ^{1}H NMR (DMSO-d_6) δ 2 04 (s, 3 H), 3.41 (m, 4 H), 5 69 (s, 1 H), 7 42 (d, J = 6 5 Hz, 2 H), 7 51 (d, J = 6 5 Hz, 2 H), 10.00 (s, 1 H), ^{13}C NMR (DMSO-d_6) δ 23.6, 39 4, 54 2, 118.8, 128 2, 134.1, 138 2, 168 2, MS m/z 136(100), 137, 168, 211, 239(M^+). *Anal.* Calcd for $C_{11}H_{13}NOS_2$ C, 55 20, H, 5 47 Found C, 55 02, H, 5 41

1,4-Bis(2-methyl-1,3-dithiolan-2-yl)benzene (17a). M p 124-125°C, ^{1}H NMR δ 2 16 (s, 6 H), 3 25-3 55 (m, 8 H), 7 68 (s, 4 H), ^{13}C NMR δ 33 6, 39 8, 67 8, 126 2, 144 4, MS m/z 179, 225, 299(100), 314(M^+) *Anal.* Calcd for $C_{14}H_{20}S_4$ C, 53 46, H, 5 77 Found C, 53 55, H, 5 59

1,3-Bis(2-methyl-1,3-dithiolan-2-yl)benzene (17b). M p. 94-95°C, ^{1}H NMR δ 2.12 (s, 6 H), 3.20-3.60 (m, 8 H), 7.25 (t, J = 6.5 Hz, 1 H), 7.55-7.70 (d, J = 6 5 Hz, 2 H), 8.17 (s, 1 H); ^{13}C NMR δ 33 7, 39.9, 68.6, 125.3, 125.7, 127 7, 145 4, MS m/z 225, 299(100), 314(M$^+$). *Anal.* Calcd for $C_{14}H_{20}S_4$. C, 53.46; H, 5.77 Found C, 53.33; H, 5 83

Cleavage of dithioacetals. A solution of **1** (0.35g, 1.2 mmol) in CH_2Cl_2/THF (1·1, 15 mL) was stirred at -10°C under an argon or nitrogen atmosphere and treated dropwise with a solution of dithioacetal (1 0 mmol of **2a-k, 2m, 8a,b, 11a-c, 14, 17a,b,** 0 55 mmol of **2l**; 0 55 mmol of **11a** for cleavage of two dithiolane functions) in CH_2Cl_2 (3 mL) Water (0 1 mL) was then added at -10°C, and the mixture was stirred at 23° until TLC or GC analysis showed the absence of the dithioacetal (24-32 h) The mixture was concentrated on a rotary evaporator at 23°C to 5 mL, treated with ether (25 mL), and the resultant precipitate of salt **6** was filtered off The ether was washed with water (5 mL), a saturated solution of NaCl (5 mL), dried (Na_2SO_4), and then concentrated Chromatographic separation was conducted on a chromatotron (silica gel, hexanes/ether, 2·1) Solid products **18a, b** were crystallized from hexanes/cyclohexane (1·1)

2-(4-Acetylphenyl)-2-methyl-1,3-dithiolane (18a). M p 63-64°C; ^{1}H NMR δ 1.63 (s, 3 H), 2.58 (s, 3 H), 3 60-4.20 (m, 4 H), 7 60 (d, J = 8 0 Hz, 2 H), 7 94 (d, J = 8 0 Hz, 2 H); ^{13}C NMR δ 24.7, 33.2, 40.2, 68 4, 126.9, 128 4, 142 6, 142 8, 151.8; MS m/z 151, 223(100), 238(M$^+$) *Anal* Calcd for $C_{12}H_{14}OS_2$. C, 60 46, H, 5 92 Found C, 60 31, H, 5 86

2-(3-Acetylphenyl)-2-methyl-1,3-dithiolane (18b). M p 112-113°C; ^{1}H NMR δ 2.08 (s, 3 H), 2.66 (s, 3 H), 3 15-3 45 (m, 4 H), 7.45 (t, J = 6 5 Hz, 1 H), 7.87-7 96 (2d, J = 6.5 Hz each, 2 H), 8.06 (s, 1 H), ^{13}C NMR δ 24 1, 33 6, 40 6, 64 2, 126 2, 128 2, 142 4, 145.2, 152.1, MS m/z 151, 162, 223(100), 238(M$^+$) *Anal* Calcd for $C_{12}H_{14}OS_2$. C, 60 46, H, 5 92 Found. C, 60 34; H, 6.01.

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4 Lower yields of the carbonyl products **3** were obtained for the reactions conducted in CH_2Cl_2 alone, THF alone, ether, hexanes, or acetonitrile Dithioacetals **2** could not be cleaved in DMF (compare footnote b in Scheme 1)

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7 The treatment of bis(dithiolane) **11a** with 2 2 equiv. of **1** in the presence of 10 equiv of water under otherwise identical conditions gave diketone **13a** in an 81% yield

8. This two-step preparation of **15** is more efficient than the reported direct synthesis of **15** from **16** and ethane-1,2-dithiol· Jaeger, R H., Smith, H *J. Chem. Soc* **1955**, 160-165
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