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TANACETOLS A AND B, NON-VOLATILE SESQUITERPENE ALCOHOLS, FROM *TANACETUM VULGARE*

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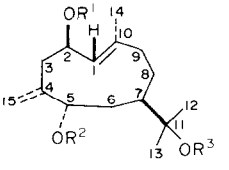
Key Word Index *Tanacetum vulgare*; Compositae; chemotaxonomy; sesquiterpenes; tanacetol A; tanacetol B; sesquiterpene lactones; flavonoids.

Abstract—Chemical investigation of a rare chemotype of *Tanacetum vulgare* afforded a series of non-volatile sesquiterpene alcohols which have been called tanacetols. The structures of tanacetols A and B, the two most abundant, have been established on the basis of spectroscopic data, chemical reactions and X-ray diffraction analysis of tanacetol A and tanacetol B acetate.

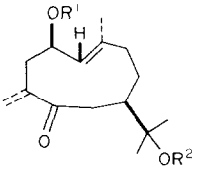
INTRODUCTION

The sesquiterpene lactones of *Tanacetum vulgare* have been the subject of several studies, and various germacranolides [1, 2], some eudesmanolides [3–5] and one modified germacranolide [6] were isolated from different chemotypes of this plant. All these compounds possess an α-methylene-γ-lactone moiety. The presence of sesquiterpenes having this feature has been claimed to be characteristic for the whole genus *Tanacetum* [7].

During our chemosystematic investigation on *T. vulgare* [1, 5, 6, 8, 9], we found that chloroform extracts of some samples of this plant lacked the characteristic IR absorption band of γ-lactones at *ca* 1770 cm^{-1} and, therefore, probably did not contain sesquiterpene lactones. Chemical investigation of this rare chemotype confirmed this, and led to the isolation of a series of non-volatile sesquiterpene alcohols all possessing an α-hydroxyisopropyl moiety. The structural elucidation of the two most abundant and least polar of them, which have been called tanacetols A and B, is presented here.

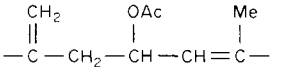


	R^1	R^2	R^3
1a	Ac	H	H
1b	Ac	Ac	H
1c	Ac	TAC	TAC
1d	Ac	Ac	TAC
1e	H	H	H
1f	Ac	Bz	H



	R^1	R^2
2a	Ac	H
2b	Ac	TAC
2c	H	H

TAC = CCl_3–CO–NH–CO–



A

RESULTS AND DISCUSSION

Tanacetol B (**1a**) was the main constituent of this chemotype (yield: 0.11 % of dried plant material). It was crystallized from diethyl ether to afford shining crystals of mp 163° and $[\alpha]_D^{25} - 65.4°$.

HRMS showed a MW of 296.1968, corresponding to the molecular formula $C_{17}H_{28}O_4$. Compound **1a** contained an acetate group (IR absorption bands at 1735 and 1240 cm^{-1}; a three proton singlet at δ 2.00 in the ^1H NMR spectrum; a singlet at δ 170.2 and a quartet at δ 21.2 in the ^{13}C NMR spectrum) and two hydroxyls, one of which was tertiary, since upon acetylation of **1a** under usual conditions, a monoacetyl derivative (**1b**) still containing a hydroxyl group (IR absorption band at 3510 cm^{-1}) was obtained. Both the acetylable hydroxyl group and the acetate were secondary, as the ^{13}C NMR spectrum of **1a** showed the presence of two doublets (δ 73.6 and 72.1) besides the singlet (72.6) of the tertiary hydroxyl group in the region of sp^3 hybridized carbons carrying oxygen atoms.

Oxidation of the secondary hydroxyl group of **1a** afforded the ketol **2a**, identical with tanacetol A a crystalline compound isolated from less polar fractions of the extract.

The ^{13}C NMR spectrum of **1a** revealed the presence of two double bonds and, therefore, this compound, which had an acetate group and a total of four degrees of unsaturation, had to be a monocyclic acetoxy sesquiterpene diol.

A prominent peak (70 %) at *m/z* 59 in the mass spectrum of **1a** was attributed to the fragment $[Me_2COH]^+$, derived from an α-hydroxyisopropyl side chain [10]. This was confirmed by the presence of two high field methyl signals, significantly shifted downfield upon *in situ* trichloroacetyl carbamoylation of the tertiary hydroxyl group [11], in the ^1H NMR spectrum of **1a** and its derivatives.

Double-resonance experiments established the hydrogen succession depicted in partial formula **A**. As **2a**, the

Table 1. ^{1}H NMR spectral data for compounds **1a**–**1f** and **2a**–**2c** (200 MHz, $CDCl_3$ except **1b**, **1d** (C_6D_6) and **1e** (C_5D_5N). TMS as internal standard)

	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**2a**	**2b**	**2c**
H-1	5.06 *br d*	5.36 *br d*	5.10 *br d*	5.40 *br d*	5.67 *br d*	5.43 *br d*	5.06 *br d*	5.10 *br d*	5.10 *d q*
H-2	5.37 *d q*	5.60 *d q*	5.40 *m*	5.62 *m*	4.95 *d q*	5.60 *dq*	5.40 *t d*	5.46 *t d*	4.47 *br q*
H-3a	2.75 *q*	2.80 *q*	2.70 *q*	2.83 *q*	3.13 *q*	2.72 *q*	2.94 *dd*	3.12 *dd*	2.83 *dd*
H-3b	*	*	*	*	*	*	2.65 *dd*	2.50 *dd*	2.72 *dd*
H-5	4.00 *t*	5.55 *t*	5.40 *t*	5.50 *t*	4.48 *br s*	5.60 *t*			
H-6a	2.53 *ddd*	2.42 *ddd*	2.46 *m*	2.46 *m*	2.45 *d q*	2.14 *m*	3.12 *dd*	3.16 *dd*	3.06 *dd*
H-6b	*	2.06 *ddd*	*	*	*	*	2.34 *dd*	2.10 *dd*	2.45 *dd*
H-7	1.80 *m*	1.75 *m*	*	*	*	*	1.60 *m*	*	*
H-8a, b	*	*	*	*	*	*	*	*	*
H-9a, b	*	*	*	*	*	*	*	*	*
H-12	1.11 *s*†	0.94 *s*	1.38 *s*†	1.24 *s*	1.32 *s*†	1.14 *s*†	1.15 *s*†	1.36 *s*†	1.16 *s*†
H-13	1.21 *s*†		1.40 *s*†		1.39 *s*†	1.19 *s*†	1.24 *s*†	1.40 *s*†	1.25 *s*†
H-14	1.70 *br s*	1.78 *br s*	1.66 *br s*	1.80 *br s*	1.80 *br s*	1.88 *br s*	1.72 *br s*	1.68 *br s*	1.67 *br s*
H-15a	5.19 *br s*	5.18 *br s*	5.37 *br s*	5.32 *br s*	5.57 *br s*	5.34 *br s*	5.67 *br s*	5.84 *br s*	5.61 *br s*
H-15b	5.08 *br s*	4.95 *br s*	5.21 *br s*	5.10 *br s*	5.18 *br s*	5.28 *br s*	5.58 *br s*	5.40 *br s*	5.49 *br s*
OH		2.10 *br*			6.35 *br*	2.10 *br*	2.27 *br*		2.20 *br*
	3.80 *t br*				6.38 *br*				2.10 *br*
					6.88 *br*				
Ac	2.00 *s*	1.72 *s*	2.00 *s*	1.70 *s*		1.97 *s*	2.02 *s*	1.98 *s*	
		1.76 *s*		1.75 *s*				8.38 *s*	
NH			8.50 *s*	8.40 *s*					
			8.60 *s*						

Most coupling constants were virtually the same for compounds **1a**–**1f** and **2a**–**2c**; those for **1a** and **2a** are given as representative. For **1a**: $J_{1,2} = 11$ Hz; $J_{2,3a} = 10$ Hz; $J_{2,3b} = 5.0$ Hz; $J_{3a,3b} = 13$ Hz; $J_{5,6a} = J_{5,6b} = 4$ Hz. For **2a**: $J_{1,2} = 9$ Hz; $J_{2,3a} = 9$ Hz; $J_{2,3b} = 6$ Hz; $J_{3a,3b} = 12$ Hz; $J_{6a,6b} = 14$ Hz; $J_{6a,7} = 10$ Hz; $J_{6b,7} = 3$ Hz.

*Signals could not be observed because of overlapping.

†Assignments are interchangeable.

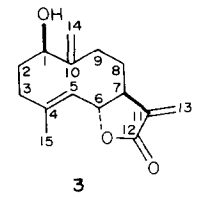
oxidation product of **1a**, was an α,β-unsaturated ketone (λ_{max}^{EtOH} 218 nm, $\log \varepsilon = 3.8$; IR absorption band at 1675 cm^{-1}, carbon signal resonance at δ 195.7 in the ^{13}C NMR spectrum), the secondary hydroxyl of **1a** had to be allylic. Comparison of the ^{1}H NMR spectra of **1a** and **2a** showed that the oxidation of this hydroxyl had caused a marked downfield shift of the exocyclic methylene protons ($\Delta\delta = 0.49$ and 0.50, respectively), while the allylic methyl and the olefinic methine had been practically unaffected. The carbon carrying the secondary hydroxyl group was, therefore, adjacent to the olefinic carbon bearing the exocyclic methylene. As the signal of the proton geminal to this hydroxyl was a triplet, it was also flanked by a methylene whose protons were clearly seen in the spectrum of **2a** as a doublet of quartets. The multiplicity of this pattern showed that this methylene was adjacent to a methine, which had to be the methine carrying the hydroxyisopropyl chain, as only this methine and two methylenes were still unassigned. The latter were placed between this methine and the trisubstituted olefinic carbon bearing the methyl group, obtaining the final structures **1a** for tanacetol B and **2a** for tanacetol A.*

*The bidimensional representation of tanacetols and their stereochemistry was done according to established rules [12–14]. Owing to the close relationship between configuration and conformation of these molecules, wedges and broken lines are used not only to indicate the α- or β- orientation of the allylic methyls and olefinic protons with regard to the plane of the molecule [12], but also for their biogenetically equivalent exocyclic methylenes.

Stereochemistry was deduced as follows. The proton on the carbon carrying the acetoxy group was placed axially on the basis of its eight peaks pattern, the Y part of an ABXY system, resulting from its interaction with one equatorial ($J_{2,3b} = 5.0$ Hz) and two axial ($J_{1,2} = 11$ Hz, $J_{2,3a} = 10$ Hz) protons. Irradiation of the allylic methyl (H-14) afforded a 10% intensity increase of the H-2 proton, showing that this methyl and H-2 were syn related. Since H-1 was anti to H-2 ($J_{1,2} = 11$ Hz), the configuration *trans* (*E*) for the endocyclic double bond could be deduced.

The hydrogen on the carbon bearing the hydroxyl group (H-5) appeared as a triplet at δ 4.00, whose narrow splitting ($J_{5,6a} = J_{5,6b} = 4$ Hz) showed a lack of *trans*-diaxial interactions with the protons at C-6, to which H-5 was equally coupled. The C-5 hydroxyl was placed syn to the exocyclic methylene on the basis of the high paramagnetic γ-shift of the exocyclic methylene upon *in situ* trichloroacetyl carbamoylation [11] of the hydroxyl group ($\Delta^{(5)}\delta_{H\text{-}15a,b} = +0.13$ and $+0.18$, respectively). The observed shifts were comparable with the ones noted for the C-14 protons of artemorin (**3**), a compound of established configuration [15] which was isolated from some chemotypes of *T. vulgare* [1, 6], upon *in situ* trichloroacetyl carbamoylation of their syn C-1 β-hydroxyl group ($\Delta^{(1)}\delta_{H\text{-}14a,b} = +0.15$ and $+0.17$, respectively). A similarity of conformation around the exocyclic double bond between the germacradiene rings of artemorin (**3**) and tanacetol B (**1a**) was assumed. The hydroxyisopropyl side chain was placed in a β (equatorial) position on biogenetic ground [16, 17].

Inspection of models showed that, owing to the con-



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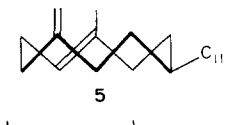

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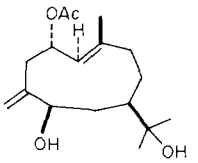

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formational flexibility of the cyclodecene ring, the reported data could fit either of the two pseudoenantiomeric stereostructures **1a** and **4**, according to the syn or anti orientation of the C-10 methyl and the C-4 methylene with the C-7 hydroxyisopropyl side chain. In the case of tanacetol B, the $\Delta^{1(10)}$, $\Delta^{4(15)}$ germacradiene ring can exist in two conformations, the double-chair and the boat-chair, which are pseudoenantiomeric (cf. their symbolic 'crown' representations **5** and **6** [18, 19]), and which, by placing the oxygenated functions at C-2 and C-5 in the topological relationship with the C-10 methyl and the C-4 methylene described above, give rise to the configurationally pseudoenantiomeric compounds represented by stereostructures **1a** and **4**. These structures were indistinguishable by our NMR data, owing to the lack of a substituent at C-6 or C-8, the endocyclic carbons next to C-7. The presence of such a group (e.g. a hydroxyl) could in fact allow the orientation of the C-7 side chain to be related to that of a ring substituent, and so, through the examination of the steric relationship of the latter with other substituents, to establish the correct stereochemistry of the compound.

Attempts to reach a decision between the stereostructures **1a** and **4** by application of the Horeau 'partial resolution' method [20] and the Brewster benzoate method [21] did not give consistent results. While the difference in molecular rotation between the benzoate of tanacetol B and the starting carbinol was $-143°$, suggesting the *R*-configuration (*β*-hydroxyl) for C-5 [21], acylation of tanacetol B with racemic α-phenylbutyric anhydride afforded (−)-α-phenylbutyric acid in an optical yield of 40%, thus requiring that the C-5 carbon have the *S*-configuration (α-hydroxyl) [20].

In order to decide between these two possibilities, X-ray analysis was so undertaken. Tanacetol B did not give suitable crystals, but its acetate was satisfactory and the results showed that stereostructure **1b** was correct for this compound, with the allylic methyl and the exocyclic methylene below the plane of the 10 membered ring. In the same way tanacetol A was shown to be represented by formula **2a** [Calleri, M., Chiari, G. and Viterbo, D., unpublished results].

The acetate group of tanacetols A and B was easily saponified, and after long standing some extracts were shown to contain **1e**, the saponification product of **1a**. Compound **1e**, originally called tanacetol F, is certainly an artefact as it was not present in freshly prepared extracts.

The occurrence of C-12 unoxidized analogs of sesquiterpene lactones clearly distinguishes the chemotype containing tanacetols from the other chemotypes of *T. vulgare* so far described. In this chemotype the biosynthesis of sesquiterpene lactones is blocked owing either to a primitive character or to the evolutionary loss of certain biosynthetic steps.

It is noteworthy that the chemotype containing tanacetols differed from the others we have so far investigated in its content of flavonoids. It lacked eupatilin, present in fairly large amounts in all the chemotypes we have studied [1, 5, 6, 8, 9] and instead contained large amounts of apigenin, which was not detected in the other chemotypes.

Table 2. ^{13}C NMR data for compounds **1a** and **2a** (25.18 MHz, $CDCl_3$, TMS as internal standard)

	1a	**2a**
C-1	125.5 *d*	124.7 *d*
C-2	72.1 *d*	71.2 *d*
C-3	39.3 *t**	36.5 *t*§
C-4	145.9 *s*	145.4 *s*
C-5	73.6 *d*	195.7 *s*
C-6	33.1 *t*†	42.0 *t*
C-7	41.7 *d*	46.0 *d*
C-8	28.7 *t*†	28.9 *t*
C-9	36.7 *t**	36.3 *t*§
C-10	138.1 *s*	139.9 *s*
C-11	72.6 *s*	72.9 *s*
C-12	24.5 *q*‡	25.6 *q*‖
C-13	29.8 *q*‡	28.4 *q*‖
C-14	19.1 *q*	20.9 *q*
C-15	115.1 *t*	122.5 *t*
OAc	21.2 *q*	21.2 *q*
	170.2 *s*	170.3 *s*

*,†,‡,§,‖ Assignments with the same sign are interchangeable.

EXPERIMENTAL

Mps are uncorr. Si gel 60 (70–230 mesh) was used for CC. Si gel precoated plates were used for prep. TLC (thickness: 2 mm). ^1H and ^{13}C NMR spectra were run at 200 and 25.18 MHz, respectively. Trichloroacetyl isocyanate (TAI) was added to solns of **1a**, **1b** and **2a** as described in ref. [11].

Plant material. In spite of the large area investigated (north of Italy) and the number of samples (*ca* 150) analysed, the chemotype containing tanacetols has only been found in an alpine valley (Vermenagma) to the south of Piedmont. Tansy chemotypes generally grow together in the same area and in order to have homogeneous plant material, single plants were collected in two areas of *ca* $4 \times 3\ m^2$ and analysed one by one, according to a general procedure [22], for the presence of non-volatile sesquiterpenoids.

From Roccavione, Cuneo, 15 plants were collected: 10 contained tanacetols, while the others belonged to a chemotype containing the eudesmanolide santamarine [5]. From Limone Piemonte, Cuneo, (quota 1400) four plants containing tanacetols were mixed with three containing 6-hydroxysesquiterpen-7,8-olides [Appendino, G., unpublished results].

Plant material was identified by P. A. Silvio Stefenelli (Giardino Botanico Alpino Paradisia, Cogne, Aosta); voucher specimens and seeds of the chemotype containing tanacetols are held at the Herbarium of the Giardino Botanico Alpino Paradisia, Cogne, Aosta (Italy).

Isolation of tanacetols. Dried non-woody aerial parts (leaves

and flowers, 2.4 kg) were extracted with $CHCl_3$ (1 × 15 l.; 3 × 10 l.) at room temp. The tarry residue remaining after removal of the solvent at red. pres. was purified by standard procedures [23] affording a thick syrup (57 g), part of which (29 g) was chromatographed on a Si gel (400 g) column, eluted with $CHCl_3$ containing increasing amounts of MeOH. Fractions eluted with $CHCl_3$–MeOH (97:3) yielded 60 mg **2a** (0.005%); the ones eluted with $CHCl_3$–MeOH (95:5) afforded 2.570 g **1a** (0.11%). In addition to these compounds, fractions eluted with $CHCl_3$ gave 210 mg *trans*-chrysanthenyl acetate, and fractions eluted with $CHCl_3$–MeOH (9:1) afforded 800 mg apigenin.

Tanacetol B (**1a**). Shining needles from Et_2O, mp 163°; $[\alpha]_D^{25}$ −65.4° (MeOH; *c* 1.5); IR ν_{max}^{KBr} cm^{-1}: 3200, 1735, 1670, 1240, 1030; EIMS 70 eV, *m/z* (rel. int.): 296 $[M]^+$ (0.16), 236 $[M-60]^+$ (4.16), 160 $[236-Me_2CO-H_2O]^+$ (36), 145 $[160-Me]^+$ (70), 59 $[C_3H_7O]^+$ (70), 43 (100).

Acetylation of **1a**. Compound **1a** (100 mg) was acetylated at room temp. with Ac_2O–pyridine overnight. After the usual work-up, the crude product was purified by prep. TLC ($CHCl_3$–Me_2CO, 6:1) to give 102 mg **1b**, which was crystallized from C_6H_6 affording 84 mg of shining needles. Larger crystals were obtained by slow crystallization from C_6H_6–Et_2O. Mp 140°; $[\alpha]_D^{25}$ −205° ($CHCl_3$; *c* 0.4); IR ν_{max}^{KBr} cm^{-1}: 3510, 3080, 1725, 1260, 1245, 1020; EIMS 70 eV, *m/z* (rel. int.): 338 $[M]^+$ (0.6), 320 $[M-18]^+$ (1.8), 278 $[M-60]^+$ (10), 218 $[M-60-60]^+$ (51), 43 (100).

Saponification of **1a**. A soln of **1a** (180 mg) in MeOH (5 ml) was stirred for 2 hr with 5 ml aq. K_2CO_3 (11%) at room temp. The reaction mixture was diluted with H_2O (15 ml), neutralized with 2% HCl and extracted with $CHCl_3$, affording 162 mg crude **1e**. Purification by prep. TLC ($CHCl_3$–Me_2CO, 3:1) yielded 130 mg pure **1e** as a white powder. Mp 175°; $[\alpha]_D^{25}$ −87° (MeOH; *c* 0.92); IR ν_{max}^{KBr} cm^{-1}: 3400, 3080, 1665, 1650, 1020; EIMS 70 eV, *m/z* (rel. int.): 254 $[M]^+$ (1), 239 $[M-15]^+$ (2), 236 $[M-18]^+$ (10), 97 (100).

Horeau esterification of tanacetol B. 60 mg **1a** (0.20 mM) and 212 mg racemic α-phenylbutyric anhydride were stirred in 2.5 ml pyridine for 24 hr at room temp. H_2O (3 ml) was then added, stirring was continued for 6 hr, and then the soln was further diluted with H_2O (9 ml) and extracted with Et_2O. Work-up as in ref. [24], which was preferred to the original procedure [20] because of the instability of tanacetol B in the presence of KOH, gave 136 mg α-phenylbutyric acid as a colorless oil, whose purity was checked by TLC and ^1H NMR. The recovered acid had $[\alpha]_D^{25}$ −5.7°, corresponding to an optical yield of 40%. The neutral fractions contained 72 mg pure tanacetol B 2-phenylbutyrate (colorless oil).

Benzoylation of **1a**. 60 mg (0.20 mM) **1a** was dissolved in 1 ml pyridine and 0.2 ml benzoyl chloride was added. After 24 hr the reaction mixture was diluted with H_2O (15 ml) and extracted with $CHCl_3$. The $CHCl_3$ phase was washed successively with dilute HCl, H_2O, 5% $NaHCO_3$ and H_2O. The dried organic phase gave a residue that was purified by prep. TLC ($CHCl_3$–MeOH, 6:1) affording 66 mg **1f** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1730, 1715, 1603, 1585, 1275, 1250. $[\alpha]_D^{25}$ −83.6° (MeOH; *c* 1.5).

Oxidation of **1a** *to* **2a**. To a stirred suspension of pyridinium chlorochromate (PCC) (580 mg, 2.70 mM) and powdered NaOAc (33 mg, 0.4 mM) in 5 ml dry CH_2Cl_2, 400 mg (1.35 mM) **1a** dissolved in 6 ml dry CH_2Cl_2 was added in one step. After 1 hr, 15 ml dry CH_2Cl_2 was added and the supernatant was decanted from the black gum. The organic soln was passed through a short pad of Florisil, washed successively with dilute HCl, H_2O and then dried ($MgSO_4$). Removal of the solvent left 347 mg of a colorless oil, which was purified by prep. TLC ($CHCl_3$–Me_2CO, 6:1) to give 295 mg **2a**. Mp 98°, either alone or in mixture with natural **2a**; $[\alpha]_D^{25}$ −92° ($CHCl_3$; *c* 1.15). The ^1H NMR, UV, IR and mass spectra were also identical with those of natural **2a**.

Tanacetol A (**2a**). Needles from C_6H_6–EtOAc; mp 98°; $[\alpha]_D^{25}$ −99° ($CHCl_3$; *c* 1.0); IR ν_{max}^{KBr} cm^{-1}: 3510, 3100, 1720, 1675, 1250, 1025, 950; UV λ_{max}^{EtOH} nm (log ε): 218 (3.8); EIMS 70 eV, *m/z* (rel. int.): 294 $[M]^+$ (4.73), 279 $[M-15]^+$ (2.3), 276 $[M-28]^+$ (4.7), 234 $[M-60]^+$ (89), 97 (100).

Saponification of **2a**. Compound **2a** (100 mg) was saponified as described for **1a**, giving 70 mg **2c** as a TLC pure white powder; mp 114°; $[\alpha]_D^{25}$ −121° (MeOH; *c* 0.8); IR ν_{max}^{KBr} cm^{-1}: 3400, 3080, 1650, 1635, 1035; UV λ_{max}^{EtOH} nm (log ε): 220 (4.0); EIMS 70 eV, *m/z* (rel. int.): 252 $[M]^+$ (1.6), 237 $[M-15]^+$ (4.1), 234 $[M-18]^+$ (58), 97 (100).

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