Pyrrolylpolyenes. Part 6.[1] Synthesis of Wallemia A and Wallemia E

Fawzi R. Ahmed and Trevor P. Toube*
Department of Chemistry, Queen Mary College, Mile End Road, London E1 4NS

The pigments (4*E*,6*E*,8*E*,10*E*)-2,6-dimethyl-5-hydroxy-11-pyrrol-2-ylundeca-4,6,8,10-tetraen-3-one (wallemia A) and (4*E*,6*E*,8*E*,10*E*)-11-(3-chloropyrrol-2-yl)-2,6-dimethyl-5-hydroxyundeca-4,6,8,10-tetraen-3-one (wallemia E), identical with the compounds extracted from the fungus *Wallemia sebi*, have been synthesised. Analogous β-enamino ketones were by-products of the synthesis.

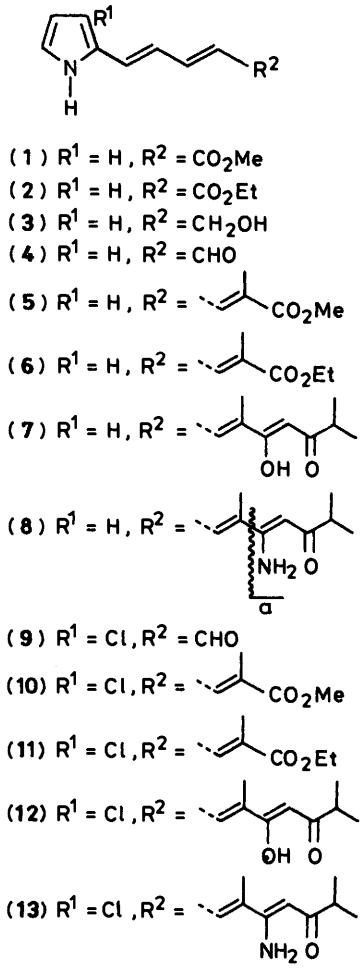
In Part 5 [1] we reported revised structures for the pyrrolylpolyene pigments isolated [2] from the fungus *Wallemia sebi* (Fr.) v. Arx. The syntheses of two of the principal pigments, wallemia A (**7**) and wallemia E (**12**), have now been carried out following routes established [3] in our earlier syntheses of pyrrolylpolyene β-diketones.

Reduction of pyrrolylpolyene esters such as (**1**) with lithium aluminium hydride yields the corresponding allylic alcohols, but these are highly unstable under the reaction conditions.[2,3] Reduction of (**1**) using di-isobutylaluminium hydride, however, permitted the isolation of the alcohol (**3**) in reasonable yield. Oxidation of this product with active manganese dioxide gave the dienal (**4**). This dienal had previously been reported [2] as a minor by-product from the preparation of its lower vinylogue by the Wittig condensation of 2-formylpyrrole and formylmethylenetriphenylphosphorane.[4] A modification of this latter method, involving two additions each of an excess of the phosphorane, gave (**4**) in yields of about 50%, contaminated with small amounts of its lower and higher vinylogues, from which it could be effectively purified by preparative t.l.c. This one-pot route to (**4**) gave a better overall yield than the aforementioned reduction–oxidation sequence.

A Wittig condensation between the dienal (**4**) and α-methoxycarbonylethylidenetriphenylphosphorane [5] proceeded smoothly to the trienoate ester (**5**). The ethyl ester (**6**) was prepared in an analogous manner. Condensation of the enolate anion derived from 3-methylbutan-2-one, using freshly prepared lithium amide with either of these esters, gave wallemia A (**7**). The reaction with the ethyl ester was the more efficient. The synthetic material was identical (m.p., i.r., u.v., n.m.r., mass spectra, h.p.l.c.) with the natural product.

A second compound isolated from the reaction mixture differed from wallemia A in showing no highly deshielded enolic proton at about δ 16 in its ^{1}H n.m.r. spectrum. It did, however, show a broad signal significantly downfield at δ 10.25 and a second broad signal at δ 5.13. In other respects the n.m.r. spectrum resembled that of wallemia A in the number and multiplicity of its signals, although their chemical shifts differed somewhat from those of the natural pigments. Its electronic spectrum showed in an absorption maximum 23 nm to shorter wavelength and, unlike that of the β-diketone, was not shifted appreciably on the addition of base. The molecular ion in the mass spectrum, *m/z* 270, was shown by accurate mass measurement to correspond to $C_{17}H_{22}N_2O$, and the base peak at *m/z* 112 to $C_6H_{10}NO$. The structure (**8**) is therefore assigned to this product, the cleavage (a) [structure (**8**)] giving rise to the base peak. We have not previously observed the formation of a β-enamino ketone in similar condensations.

The preparation of wallemia E (**12**) was carried out in exactly analogous fashion. 3-Chloro-2-formylpyrrole [6] was converted into the dienal (**9**) by treatment with two portions (each in excess) of formylmethylenetriphenylphosphorane.[4] Condensation of (**9**) with α-ethoxycarbonylethylidenetriphenylphosphorane gave the ethyl trienoate (**11**), which was preferred to the methyl ester (**10**) for the final reaction with 3-methylbutan-2-one and lithium amide to produce wallemia E (**12**), identical (u.v., n.m.r., mass spectra, h.p.l.c.) with the natural pigment. A β-enamino ketone (**13**) was also isolated from the reaction mixture.



Experimental

Where appropriate, operations were carried out under nitrogen. Light petroleum refers to that fraction with b.p. 60—80 °C. M.p.s. were determined with a Reichert heated-stage microscope. Preparative t.l.c. was carried out on silica gel HF254 plates using ether as eluting solvent unless otherwise stated. Electronic spectra were determined with a Perkin-Elmer 552 spectrometer and i.r. spectra with a Perkin-Elmer 298 spectrometer. N.m.r. spectra were measured for dilute solutions in

deuteriochloroform using a Bruker WP-80DS or Bruker WH-400 instrument. Mass spectra were run on an A.E.I. MS902 spectrometer; exact mass measurements were made relative to heptacosafluorotributylamine.

Ethyl (2E,4E)-5-*Pyrrol*-2-*ylpenta*-2,4-*dienoate* (**2**).—3-Ethoxycarbonylprop-2-enylidenetriphenylphosphorane[6] (1 g, 2.7 mmol), 2-formylpyrrole (200 mg, 2.1 mmol), and benzene (20 cm^3) were heated under reflux for 4 h. The mixture was cooled, the solvent evaporated off under reduced pressure, and the resulting gum chromatographed to yield *ethyl* (2E, 4E)-5-*pyrrol*-2-*ylpenta*-2,4-*dienoate* (**2**) (224 mg, 60%) as yellow crystals, m.p. 136 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 365 nm; $\nu_{max.}$(KBr) 3 320, 1 690, 1 625, and 995 cm^{-1}; δ_H (80 MHz) 1.30 (3 H, t, *J* 7 Hz), 4.20 (2 H, q, *J* 7 Hz), 5.88 (1 H, d, *J* 15 Hz), 6.25 (1 H, m), 6.43 (2 H, m and dd, *J* 10 and 15 Hz), 6.75 (1 H, d, *J* 15 Hz), 6.88 (1 H, m), 7.40 (1 H, dd, *J* 10 and 15 Hz), and 8.70 (1 H, br); (Found: $M^{+\cdot}$, 191.095 (37%). $C_{11}H_{13}NO_2$ requires $M^{+\cdot}$, 191.095), *m*/*z* 118 (100%).

(2E,4E)-5-*Pyrrol*-2-*ylpenta*-2,4-*dien*-1-*ol* (**3**).—To a stirred solution of the ester (**2**) (20 mg, 0.11 mmol) in dry ether (10 cm^3) at −70 °C a solution was added of di-isobutylaluminium hydride in hexane (20%; 1 cm^3). The mixture was stirred at −70 °C for 30 min and methanol (10 cm^3) then added. The solvents were removed under reduced pressure and the resulting yellow oil was extracted with ether. Evaporation of the extracts under reduced pressure followed by chromatography of the residue yielded (2E,4E)-5-*pyrrol*-2-*ylpenta*-2,4-*dien*-1-*ol* (**3**) (8.3 mg, 53%) as pale yellow crystals, m.p.. 116—118 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 314 nm (ε 32 300); $\nu_{max.}$(KBr) 3 390, 3 260, and 980 cm^{-1}; δ_H (80 MHz) 1.40 (1 H, br), 4.23 (2 H, d, *J* 5 Hz), 6.15—6.45 (5 H, m), 6.78 (1 H, m), and 8.25 (1 H, br) (Found: $M^{+\cdot}$, 149.084 (63%). $C_9H_{11}NO$ requires $M^{+\cdot}$, 149.084), *m*/*z* 118 (100%).

(2E,4E)-5-*Pyrrol*-2-*ylpenta*-2,4-*dienal* (**4**).—(*a*) To a solution of the alcohol (**3**) (50 mg, 0.34 mmol) in dry ether (10 cm^3), active manganese dioxide (1 g; excess) was added and the mixture was stirred at room temperature for 2 h, then filtered. The filtrate was evaporated under reduced pressure and the residue was chromatographed to yield the aldehyde (**4**) (20 mg, 40%) as red crystals, m.p. 98—100 °C (from benzene–light petroleum) (lit.,[2] 95—98 °C); $\lambda_{max.}$(ethanol) 390 nm (lit.,[2] 392 nm); $\nu_{max.}$(KBr) 3 520, 1 650, 1 580, 980, and 960 cm^{-1}; δ_H (80 MHz) 6.18 (1 H, dd, *J* 8 and 15 Hz), 6.33 (1 H, m), 6.45 (1 H, dd, *J* 10 and 15 Hz), 6.50 (1 H, m), 6.93 (1 H, d, *J* 15 Hz), 6.95 (1 H, m), 7.25 (1 H, dd, *J* 10 and 15 Hz), 8.78 (1 H, br), and 9.59 (1 H, d, *J* 8 Hz); *m*/*z* 147.068 ($M^{+\cdot}$, 82%; C_9H_9NO) and 118 (100%).

(*b*) Formylmethylenetriphenylphosphorane (1.2 g, 4 mmol), 2-formylpyrrole (150 mg, 1.6 mmol), and dry xylene (15 cm^3) were heated under reflux for 3 h. The mixture was cooled and further formylmethylenetriphenylphosphorane (1.2 g, 4 mmol) added; the solution was then heated under reflux for another 3 h. The mixture was cooled and evaporated under reduced pressure (to 1 cm^3). Chromatography gave the aldehyde (**4**) (115 mg, 50%), identical with the foregoing sample.

Methyl (2E,4E,6E)-2-*Methyl*-7-*pyrrol*-2-*ylhepta*-2,4,6-*trienoate* (**5**).—The dienal (**4**) (30 mg, 0.2 mmol) and α-methoxycarbonylethylidenetriphenylphosphorane (200 mg, 0.6 mmol) were heated under reflux in dry benzene (10 cm^3) for 1 h. Evaporation under reduced pressure (to 1 cm^3) followed by chromatography gave *methyl* (2E,4E,6E)-2-*methyl*-7-*pyrrol*-2-*ylhepta*-2,4,6-*trienoate* (**5**) (22.6 mg, 51%) as yellow crystals, m.p. 130—132 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 392 nm (ε 41 000); $\nu_{max.}$(KBr) 3 330, 1 680, and 985 cm^{-1}; δ_H (80 MHz) 2.00 (3 H, d, *J* 1.5 Hz), 3.75 (3 H, s), 6.28 (1 H, m), 6.38 (1 H, m), 6.55 (4 H, m), 6.85 (1 H, m), 7.30 (1 H, dq, *J* 10 and 1.5 Hz), and 8.30 (1 H, br) [Found: $M^{+\cdot}$, 217.110 (100%). $C_{13}H_{15}NO_2$ requires $M^{+\cdot}$, 217.110].

Ethyl (2E,4E,6E)-2-*Methyl*-7-*pyrrol*-2-*ylhepta*-2,4,6-*trienoate* (**6**).—Using the procedure just described for the methyl ester, the dienal (**4**) (50 mg, 0.34 mmol) and α-ethoxycarbonylethylidenetriphenylphosphorane (300 mg, 0.83 mmol) were condensed to give the *ethyl ester* (**6**) (43 mg, 55%) as orange crystals, m.p. 118—120 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 393 nm (ε 41 000); $\nu_{max.}$(KBr) 3 300, 1 670, and 985 cm^{-1}; δ_H (400 MHz) 1.33 (3 H, t, *J* 7 Hz), 1.97 (3 H, d, *J* 1 Hz), 4.23 (2 H, q, *J* 7 Hz), 6.26 (1 H, m), 6.37 (1 H, m), 6.50 (1 H, dd, *J* 10.5 and 15 Hz), 6.51 (1 H, dd, *J* 10 and 15 Hz), 6.57 (1 H, *J* 15 Hz), 6.65 (1 H, dd, *J* 10 and 15 Hz), 6.84 (1 H, m), 7.28 (1 H, dq, *J* 10.5 and 1 Hz), and 8.35 (1 H, br); [Found: $M^{+\cdot}$, 231.126 (97%). $C_{14}H_{17}NO_2$ requires $M^{+\cdot}$, 231.126]; *m*/*z* 158 (100%).

(4E,6E,8E,10E)-2,6-*Dimethyl*-5-*hydroxy*-11-*pyrrol*-2-*yl*-*undeca*-4,6,8,10-*tetraene*-3-*one* (*Wallemia A*) (**7**).—Freshly prepared lithium amide (250 mg) suspended in dry tetrahydrofuran (300 cm^3) was heated under reflux and solutions of the ester (**6**) (50 mg, 0.22 mmol) and 3-methylbutan-2-one (0.5 g) in dry tetrahydrofuran (5 cm^3 each) were added alternately over 30 min. Heating was continued for 18 h and the mixture then cooled, treated with ice-cold water, and extracted with ether. The extracts were washed with water, hydrochloric acid (10%), and water, dried (Na_2SO_4), and evaporated under reduced pressure to yield a gum. Chromatography (20% acetone–light petroleum) gave (i) wallemia A (**7**) (13 mg, 22%) as orange crystals, m.p. 102—104 °C (from ether–light petroleum) (lit.,[2] m.p. 107 °C), identical with a sample of the natural pigment; $\lambda_{max.}$(ethanol) 428 nm (ε 51 500); $\nu_{max.}$(KBr) 3 500, 3 420, 3 300, 1 580, and 980 cm^{-1}; δ_H (400 MHz) 1.19 (6 H, d, *J* 7 Hz), 1.97 (3 H, d, *J* 1 Hz), 2.58 (1 H, septet, *J* 7 Hz), 5.82 (1 H, s), 6.27 (1 H, m), 6.39 (1 H, m), 6.60 (4 H, m), 6.76 (1 H, m), 7.22 (1 H, dq, *J* 11 and 1 Hz), 8.32 (1 H, br), and 15.88 (1 H, br); *m*/*z* 271.157 ($M^{+\cdot}$, 45%; $C_{17}H_{21}NO_2$), 106 (100%); and (ii) 5-*amino*-2,6-*dimethyl*-11-*pyrrol*-2-*ylundeca*-4,6,8,10-*tetraen*-3-*one* (**8**) (20.7 mg, 35%) as deep red crystals, m.p. 150 °C (decomp.) (from ether–light petroleum; $\lambda_{max.}$(ethanol) 405 nm; $\nu_{max.}$(KBr) 3 380, 1 575, 995, and 970 cm^{-1}; δ_H (80 MHz) 1.20 (6 H, d, *J* 7 Hz), 1.98 (3 H, d, *J* 1 Hz), 2.43 (1 H, septet, *J* 7 Hz), 5.13 (1 H, br), 5.52 (1 H, s), 6.25 (1 H, m), 6.50 (5 H, m), 6.93 (1 H, m), 7.05 (1 H, dq, *J* 10 and 1 Hz), 8.30 (1 H, br), and 10.25 (1 H, br) [Found: $M^{+\cdot}$, 270.175 (48%). $C_{17}H_{22}N_2O$ requires $M^{+\cdot}$, 270.173]; *m*/*z* 112.075 (100%) ($C_6H_{10}NO$ requires 112.076).

(2E,4E)-5-(3-*Chloropyrrol*-2-*yl*)*penta*-2,4-*dienal* (**9**).—3-Chloro-2-formylpyrrole[6] (117 mg, 0.91 mmol), formylmethylenetriphenylphosphorane (0.7 g, 2.33 mmol), and dry xylene (15 cm^3) were heated under reflux for 5 h. The mixture was cooled, further formylmethylenetriphenylphosphorane (0.3 g, 1.16 mmol) was added, and the solution was heated under reflux for another 3 h. The mixture was cooled and evaporated under reduced pressure (to 1 cm^3). Chromatography yielded (2E,4E)-5-(3-*chloropyrrol*-2-*yl*)*penta*-2,4-*dienal* (**9**) (82 mg, 50%) as red crystals, m.p. 125—127 °C (from ether); $\lambda_{max.}$(ethanol) 383 nm (ε 29 600); $\nu_{max.}$(KBr) 3 320, 3 270, 1 655, and 980 cm^{-1}; δ_H (80 MHz) 6.18 (1 H, dd, *J* 8 and 15 Hz), 6.25 (1 H, t, *J* 3 Hz), 6.61 (1 H, dd, *J* 10 and 15 Hz), 6.90 (1 H, t, *J* 3 Hz), 7.00 (1 H, d, *J* 15 Hz), 7.29 (1 H, dd, *J* 10 and 15 Hz), 9.30 (1 H, br), and 9.58 (1 H, d, *J* 8 Hz) [Found: $M^{+\cdot}$, 181.030 (15%). $C_9H_8{}^{35}ClNO$ requires $M^{+\cdot}$, 181.019]; *m*/*z* 59 (100%).

Methyl (2E,4E,6E)-7-(3-*Chloropyrrol*-2-*yl*)-2-*methylhepta*-2,4,6-*trienoate* (**10**).—The dienal (**9**) (50 mg, 0.28 mmol) and α-methoxycarbonylethylidenetriphenylphosphorane (300 mg, 0.9

mmol) were heated under reflux in dry benzene (10 cm^3) for 3 h. Evaporation under reduced pressure (to 1 cm^3) followed by chromatography gave *methyl* (2E,4E,6E)-7-(3-*chloropyrrol*-2-*yl*)-2-*methylhepta*-2,4,6-*trienoate* (**10**) (33.3 mg, 48%) as orange crystals, m.p. 148–150 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 382 nm (ε 36 000); $\nu_{max.}$(KBr) 3 280, 1 675, and 980 cm^{-1}; δ_H (80 MHz) 1.98 (3 H, d, *J* 1.5 Hz), 3.78 (3 H, s), 6.20 (1 H, t, *J* 3 Hz), 6.58 (4 H, m), 6.75 (1 H, t, *J* 3 Hz), 7.30 (1 H, dq, *J* 10 and 1.5 Hz), and 8.35 (1 H, br) [Found: $M^{+\cdot}$, 251.072 (100%). $C_{13}H_{14}{}^{35}ClNO_2$ requires $M^{+\cdot}$, 251.071].

Ethyl (2E,4E,6E)-7-(3-*Chloropyrrol*-2-*yl*)-2-*methylhepta*-2,4,6-*trienoate* (**11**).—Using the procedure just described for the methyl ester (**10**), the dienal (**9**) (50 mg, 0.28 mmol) and α-ethoxycarbonylethylidenetriphenylphosphorane (300 mg, 0.83 mmol) were condensed to give the *ethyl ester* (**11**) (36.5 mg, 50%) as orange crystals, m.p. 155—157 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 382 nm (ε 37 000); $\nu_{max.}$(KBr) 3 280, 1 660, and 985 cm^{-1}; δ_H (400 MHz) 133 (3 H, t, *J* 7 Hz), 1.97 (3 H, d, *J* 1 Hz), 4.23 (2 H, q, *J* 7 Hz), 6.20 (1 H, t, *J* 3 Hz), 6.53 (1 H, dd, *J* 10.5 and 15 Hz), 6.55 (1 H, dd, *J* 10 and 15 Hz), 6.63 (1 H, d, *J* 10 Hz), 6.67 (1 H, dd, *J* 10 and 15 Hz), 6.76 (1 H, t, *J* 3 Hz), 7.28 (1 H, dq, *J* 10.5 and 1 Hz), and 8.35 (1 H, br) [Found: $M^{+\cdot}$, 265.088 (100%). $C_{14}H_{16}{}^{35}ClNO_2$ requires $M^{+\cdot}$, 265.087].

(4E,6E,8E,10E)-11-(3-*Chloropyrrol*-2-*yl*)-2,6-*dimethyl*-5-*hydroxyundeca*-4,6,8,10-*tetraen*-3-*one* (*Wallemia E*) (**12**).—Freshly prepared lithium amide (500 mg) suspended in dry tetrahydrofuran (30 cm^3) was heated under reflux and solutions of the ester (**11**) (50 mg, 0.2 mmol) and 3-methylbutan-2-one (500 mg) in dry tetrahydrofuran (5 cm^3 each) were added alternately over 30 min. Heating was continued for 18 h and the mixture then cooled, treated with ice-cold water, and extracted with ether. The extracts were washed with water, hydrochloric acid (10%), and water, dried ($MgSO_4$), and evaporated under reduced pressure to yield a gum. Chromatography (20% acetone–light petroleum) gave (i) wallemia E (**12**) (12 mg, 20%), identical with a sample of the natural pigment, as orange crystals, m.p. 122—124 °C (from ether–light petroleum); $\lambda_{max.}$(ethanol) 425 nm (ε 50 000); $\nu_{max.}$(KBr) 3 350, 1 580, and 985 cm^{-1}; δ_H (400 MHz) 1.19 (6 H, d, *J* 7 Hz), 1.97 (3 H, d, *J* 1 Hz), 2.58 (1 H, septet, *J* 7 Hz), 5.82 (1 H, s), 6.21 (1 H, t, *J* 3 Hz), 6.60 (4 H, m), 6.76 (1 H, t, *J* 3 Hz), 7.22 (1 H, dq, *J* 11 and 1 Hz), 8.33 (1 H, br), and 15.88 (1 H, br) [Found: $M^{+\cdot}$, 305.119 (41%). $C_{17}H_{20}{}^{35}ClNO_2$ requires $M^{+\cdot}$, 305.118]; *m/z* 140 (100%); and (ii) 5-*amino*-11-(3-*chloropyrrol*-2-*yl*)-2,6-*dimethylundeca*-4,6,8,10-*tetraen*-3-*one* (**13**) (18 mg, 30%) as red crystals, m.p. 170 °C (decomp.) (from ether–light petroleum); $\lambda_{max.}$(ethanol) 405 nm; $\nu_{max.}$(KBr) 3 420, 3 240, 1 580, and 980 cm^{-1}; δ_H (400 MHz) 1.20 (6 H, d, *J* 7 Hz), 1.97 (3 H, d, *J* 1 Hz), 2.42 (1 H, septet, *J* 7 Hz), 5.22 (1 H, br), 5.52 (1 H, s), 6.16 (1 H, t, *J* 3 Hz), 6.57 (4 H, m), 6.72 (1 H, t, *J* 3 Hz), 7.02 (1 H, dq, *J* 10 and 1 Hz), 9.03 (1 H, br), and 10.25 (1 H, br) [Found: $M^{+\cdot}$, 304.135 (29%). $C_{17}H_{21}{}^{35}ClN_2O$ requires $M^{+\cdot}$, 304.134]; *m/z* 112 (100%).

References

1 Part 5, F. R. Ahmed, M. J. Buckingham, G. E. Hawkes, and T. P. Toube, *J. Chem. Research*, 1984, (*S*), 178; (*M*), 1709.
2 Y. Badar, W. J. S. Lockley, T. P. Toube, B. C. L. Weedon, and L. R. G. Valadon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1416.
3 Y. Badar, A. K. Chopra, H. W. Dias, M. B. Hursthouse, A. R. Khokhar, M. Ito, T. P. Toube, and B. C. L. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1372.
4 S. Trippet and D. M. Walker, *J. Chem. Soc.*, 1961, 1226.
5 E. Bucht and F. André, *Chem. Ber.*, 1959, **92**, 3111.
6 F. Bellamy, P. Martz, and J. Streith, *Heterocycles*, 1973, **3**, 395; F. Bellamy and J. Streith, *J. Chem. Research* (*S*), 1979, 18; (*M*) 0101.

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