Maytanprine and Maytanbutine, New Antileukaemic Ansa Macrolides from *Maytenus buchananii*[1]

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Summary The structures of maytanprine (**2**) and maytanbutine (**3**), new antileukaemic ansa macrolides from *Maytenus buchananii* (Loes.) R. Wilczek, have been determined.

RECENTLY, we reported the isolation and structural elucidation of maytansine (**1**), a novel antileukaemic ansa macrolide tumour inhibitor from *Maytenus ovatus*.[2] We now describe two new and potent antileukaemic ansa macrolides isolated from *Maytenus buchananii* (Loes.) R. Wilczek, maytanprine (**2**) and maytanbutine (**3**). The new principles showed antileukaemic activity against P-388 lymphocytic leukaemia over a 50—100-fold dosage range at the μg kg^{-1} level.[3]

The alcoholic extract of stems collected in Kenya in 1970 was fractionated by the procedure summarized earlier,[2] to yield a highly enriched concentrate. Preparative t.l.c. on silica gel afforded maytansine (**1**) (0·00015%) and two bands of higher R_F. Purification by high pressure liquid chromatography yielded maytanprine (**2**) (0·00012%), $C_{35}H_{48}ClN_3O_{10}$, m.p. 169—170°, $[\alpha]_D^{30}$ − 125° (*c* 0·0559, $CHCl_3$), and maytanbutine (**3**) (0·00009%), $C_{36}H_{50}ClN_3O_{10}$, m.p. 170—171°, $[\alpha]_D^{30}$ − 122° (*c* 0·0492, $CHCl_3$). The i.r. and u.v. spectra of (**2**) and (**3**) were almost identical to those of (**1**).

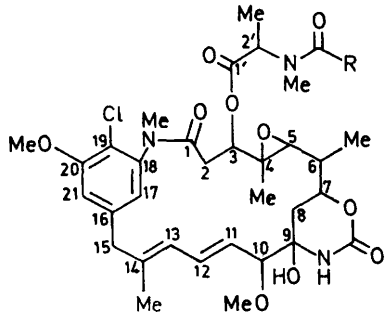
The principal peaks in the mass spectra of (**1**)—(**3**) are listed in the Table; the compositions of the fragment ions were determined by high resolution m.s. The m.s. characteristics indicated that (**2**) and (**3**) have ansa macrolide structures similar to (**1**) except for differences in the *R*-groups of the ester side chains.

The relationships among the three compounds were confirmed by comparisons of their n.m.r. spectra. Thus, the n.m.r. spectra of (**2**) and (**3**) differed from that of (**1**) solely in the signals corresponding to the terminal R–CO groups. The n.m.r. signals for the propionyl group of (**2**) [τ 8·82 (3H, t, *J* 7), 7·63 (1H, m), 7·59 (1H, m)] indicated the non-equivalence of the methylene protons, and this was confirmed by spin-decoupling studies.[4,5] The n.m.r. signals for the isobutyryl group of (**3**) [τ 8·88 (3H, d, *J* 7), 8·81 (3H, d, *J* 7), 7·20 (1H, m)] suggested the non-equivalence of the two methyl groups, and this also was supported by the results of spin decoupling and solvent shift studies. The signals for the C-2′ N–CH_3 of (**3**) [τ 7·13 (3/4H, s), 7·08 (2-1/4H, s)] indicated that the rate of rotation about the carbonyl to nitrogen bond was reduced by the steric interaction of the isopropyl group and the aromatic ring[4,5]

TABLE. *Mass spectral characteristics*[a]

	M⁺−(a)	*M*⁺−(a + b)	485−(Me)	485−(Cl)	[(b)−(OH)]⁺	[(b)−(COOH)]⁺	$C_3H_8N^+$	$C_2H_6N^+$
(**1**)	630	485	470	450	128	100	58	44
(**2**)	644	485	470	450	142	114	58	44
(**3**)	658	485	470	450	156	128	58	44

[a] (a) = H_2O + HNCO; (b) = R·CO·NMe·CHMe·COOH



(**1**) R = Me
(**2**) R = CH_2Me
(**3**) R = $CHMe_2$

Studies of other active principles of *M. buchananii* are in progress.

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[1] For previous paper in the series 'Tumor Inhibitors' see: S. M. Kupchan, W. A. Court, R. G. Dailey, jun., C. J. Gilmore, and R. F. Bryan, *J. Amer. Chem. Soc.*, in the press.
[2] S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1972, **95**, 1354.
[3] Anti-leukaemic activity was assayed under the auspices of the National Cancer Institute, by the procedures described in *Cancer Chemotherapy Reports*, 1962, **25**, 1.
[4] T. H. Siddall and W. E. Stewart, in 'Progress in N.M.R. Spectroscopy,' ed. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Pergamon Press, New York, 1969. Volume 5, p. 33.
[5] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon Press, New York, 1969, p. 368.