Maytoline, Maytine, and Maytolidine, Novel Nicotinoyl Sesquiterpene Alkaloids from *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek[1]

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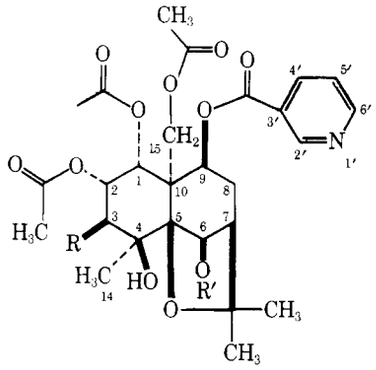
Three novel nicotinoyl sesquiterpene alkaloids, maytoline (**1**, $C_{29}H_{37}NO_{13}$), maytine (**2**, $C_{29}H_{37}NO_{12}$), and maytolidine (**4**, $C_{36}H_{41}NO_{14}$), have been isolated from the fruit of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek. The structure of **1** was determined by x-ray crystallography of its methiodide and is the prototype of a new class of alkaloids found in the Celastraceae. The structures of **2** and **4** were shown to be 3-deoxymaytoline and 3-acetyl-6-deacetyl-6-benzoylmaytoline, respectively, by a study of the physical properties, in particular mass and NMR spectroscopy.

Maytoline (**1**) and maytine (**2**), the major alkaloids from the fruit of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek, have been reported to be the prototypes of a new alkaloid family present in the Celastraceae.[2] We report herein our detailed studies on the isolation and physical and chemical properties of maytoline (**1**) and maytine (**2**) and of the related compound, maytolidine (**4**).



1, R = OH; R′ = Ac
2, R = H; R′ = Ac
3, R = OAc; R′ = Ac
4, R = OAc; R′ = Bz

The aqueous ethanol extract of the dried fruit of *M. serrata*[3] was chromatographed on SilicAR CC-7. The 5% methanol-chloroform eluate was separated by chromatography on alumina into a chloroform eluate and a methanol eluate. Rechromatography of the methanol eluate, followed by acid extraction and TLC of the bases, yielded the major component, maytoline (**1**), $C_{29}H_{37}NO_{13}$. Rechromatography of the chloroform eluate followed by TLC yielded the related alkaloid maytine (**2**), $C_{29}H_{37}NO_{12}$. The remainder of the chloroform eluate on acid extraction gave a mixture, which was separated by chromatography to yield maytolidine (**4**), $C_{36}H_{41}NO_{14}$. Although separable by TLC on alumina, **1** and **2** were inseparable by TLC on silica gel. The three alkaloids were weakly basic and gave faint positive reactions with Dragendorff's reagent. The molecular formulas were determined by comparison of the elemental analysis and high-resolution mass spectroscopic measurements.[4]

The mass spectral fragmentations of **1** and **2** were similar and both showed ions for the loss of CH_3 (presumably from the C-11 *gem*-dimethyl group), H_2O, and CH_3CO_2H, but little additional information could be derived from the high mass region.

The infrared spectra of **1** and **2** were very similar, and both contained bands assignable to hydroxyl (2.8 μ), ester carbonyl (5.75 μ, broad), and a pyridine ring (6.29 μ). The ultraviolet spectra [λ_{max} 221, 258 (infl), 265, and 271 nm (infl) (ϵ 9600, 2500, 2700, 2300) for **1**] were almost identical, and on addition of acid showed very similar changes [λ_{max} 220, 257 (infl), 263, 268 nm (infl) (ϵ 8300, 4300, 4800, 4200)], characteristic of a nicotinoyl chromophore [e.g. nicotinic acid, λ_{max} (MeOH) 212, 262.5 nm (ϵ 6600, 3600); λ_{max} (MeOH + H^+) 217, 263 nm (ϵ 4900, 4900)[5]]. Confirmation of this assignment came from the NMR spectra of **1** and **2**, which both contained signals at τ 2.62 (dd, $J_{5',6'}$ = 5, $J_{4',5'}$ = 8 Hz, 5′-H), 1.73 (dt, $J_{4',5'}$ = 8, $J_{4',6'}$ = $J_{2',4'}$ = 2 Hz, 4′-H), 1.21 (dd, $J_{5',6'}$ = 5, $J_{4',6'}$ = 2 Hz, 6′-H), and 0.77 (d, $J_{2',4'}$ = 2 Hz, 2′-H), which were shown by double resonance studies to be intercoupled. These signals could be assigned to the protons on a 3-carboxypyridine ring [e.g., ethyl nicotinate,[6] τ 2.65 (dd, J = 4.7, 7.9 Hz, 5-H), 1.73 (dt, J = 7.9, 1.9 Hz, 4-H), 1.27 (dd, J = 1.9, 4.7 Hz, 6-H), and 0.81 (d, J = 1.9 Hz, 2-H)]. Intense peaks present in the MS of both **1** and **2** at *m/e* 124.0397 (100%, $C_6H_6NO_2$ requires 124.0398) and 106 were assigned to the protonated nicotinic acid ion formed with double hydrogen migration[7] and to the nicotinoyl ion, respectively.

As well as the nicotinoyl proton signals, the NMR spectrum of **1** (see Table I) contained signals assignable to a D_2O-exchangeable proton (τ 6.32) and to protons on carbon atoms carrying a primary ester group, four secondary ester groups, and a secondary alcohol. From the coupling constants the partial structure ·CHOAc·CHOAc·CHOH· could be deduced and this was assigned to C-1, C-2, and C-3. The spectrum of **2** (Table I) was very similar, except that it lacked the signal for the proton on the carbon carrying the secondary hydroxyl, and the signal assigned to the adjacent proton appeared as a multiplet, superimposed upon the signal assigned to the C-9 proton. Attempts to resolve this system by changing the solvent were unsuccessful. The partial structure, ·CHOAc·CHOAc·CH_2·, was consequently proposed for maytine.

The spectra both contained seven singlets for methyl groups at τ 7.70–7.91 (3 Me) and at 8.35–8.50 (4 Me). Of the second group three signals were assigned to quaternary methyl groups and one to a C-1 acetyl methyl group, which must be shielded by the diamagnetic effects of the nicotinoate ring substituted at C-9.

These assignments were confirmed by protonation or hydrogenation of the heteroaromatic ring. When trifluoroacetic acid was added to the solution of **2** the methyl signals appeared at τ 7.61, 7.73, 7.76, *8.20*, 8.31, 8.36, 8.46, and the signals for the protons on the protonated pyridine ring appeared at τ 0.50, 0.72, 0.89, 1.72. Attempts to hydrogenate **2** in ethyl acetate over Pd/C failed, but with a PtO_2 catalyst hydrogenation yielded tetrahydromaytine (**5**). The ultraviolet spectrum, λ_{max} 290 nm (ϵ 13 600), was very similar to that of 3-ethoxycarbonyl-2-piperidine, λ_{max} 290 nm (ϵ 20 000),[8] and in agreement the NMR spectrum contained a signal for only one olefinic proton at τ 2.61 (d, J = 6.5 Hz). The positions of the methyl group signals τ 7.78, 7.90 (6 H), *8.18*, 8.46 (6 H), and 8.52 were

Table I. NMR Spectra of Nicotinoate Alkaloids and Derivatives from *Maytenus serrata*[a]

Compd	C-1	C-2	C-3	C-6	C-9	C-15[b]	CH_3C	CH_3CO	OH
1[c]	4.09 d (3.5)	4.40 t (3.5)	6.40 d (3.5)	3.84 s	4.51 bd (7.5)	5.04, 5.60 (13)	8.39 (3 H), 8.46 (6 H)	7.70, 7.82, 8.35[d] 7.85	6.32
2[c]	4.41 d (3.5)	4.53 m		3.87 s	4.53 m	5.07, 5.61 (13)	8.44 (3 H), 8.49 (6 H)	7.74, 7.90, 8.40[d] 7.91	6.90
3[c]	4.20 d (3.5)	4.60 t (3.5)	5.13 d (3.5)	3.92 s	4.54 bd (8)	5.10, 5.62 (13)	8.41 (3 H), 8.45 (3 H), 8.48 (3 H)	7.72, 7.87, 8.39[d] 7.74, 7.88	6.60
4[e]	4.16 d (3.5)	4.58 t (3.5)	5.10 d (3.5)	3.77 s	4.48 bd (7.5)	5.10, 5.57 (13)	8.41 (3 H), 8.39 (3 H), 8.45 (3 H)	7.66, 7.86, 8.36[d] 7.70	6.41

[a] Spectra measured as $CDCl_3$ solutions at 100 MHz. Coupling constants in parentheses in hertz. Multiplicity: d, doublet; t, triplet; bd, broadened doublet; m, multiplet; s, singlet. [b] AB quartet. [c] Spectrum also contained signals for four nicotinoate protons. [d] Acetyl peak at high field distinguished by its sharpness compared to CH_3C. [e] Spectrum also contained signals for benzoate and nicotinoate protons.

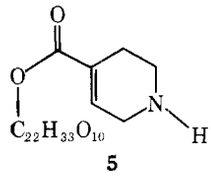
significantly changed compared to the spectrum of **2**, but the rest of the spectrum was quite similar. It was observed that the signal (in italics), which had changed downfield in protonated **2** and in **5**, was sharper than the other high field signals, which were thus assigned to quaternary methyl groups. (See Table I.)

On treatment with acetic anhydride in pyridine, **2** was unchanged and **1** formed the acetate (**3**). The NMR spectrum of **3** contained an additional methyl signal at τ 7.74 and the signal assigned to the C-3 proton now appeared at τ 5.13 (d, J = 3.5 Hz). Thus **3** contained the partial structure $-(CHOAc)_3-$. As the infrared spectra of **3** and **2** both contained a band at 2.8 μ, **1**, **2**, and **3** could be assumed to contain a tertiary hydroxyl group.

Hydrolysis of **1** and **2** led respectively to maytol (**6**, $C_{15}H_{26}O_8$) and 3-deoxymaytol (**7**, $C_{15}H_{26}O_7$). The formulas were determined by high-resolution mass spectral measurement of the strong $M^+ - 15$ peaks. The spectra also contained peaks for multiple losses of 18 mass units from both the molecular ion and the $M^+ - 15$ ion. The NMR spectra of **6** and **7** contained no signals below τ 5 (confirming an absence of olefinic protons), a multiplet at τ 5.0–6.5 (for protons on carbon carrying hydroxyl), and three quaternary methyl group signals at τ 8.2–8.5. The infrared spectra lacked carbonyl bands; thus the four acetyl groups and the nicotinoyl group had been hydrolyzed in each case. As **6** and **7** apparently contained no double bonds or carbonyl groups they must be tricyclic and a sesquiterpenoid origin was proposed.

In order to determine the structure of the nucleus and the location of the acyl substituents, the methiodide of maytoline was prepared and the relative stereochemical structure for **1** was determined by x-ray crystallographic analysis.[2,9] Unfortunately the results did not permit an assignment of absolute stereochemistry.

From the similarities of the NMR spectra of **1** and **2**, and of **6** and **7**, it was assumed that the structure of **2** was closely related to that of **1**. Although the differences in the NMR spectra suggested a change from C-3 CHOH to C-3 CH_2, the presence of a C-1 CH_2 group and a C-3 CHOAc group in **2** might be expected to result in a very similar spectrum. Examination of models of **1** and comparison with the x-ray crystallographic structure of the methiodide showed that only the C-1 acetyl group methyl should come under the diamagnetic influence of the pyridine ring. As the spectra of both **1** and **2** contained a high field acetyl group signal, sensitive to changes in the pyridine ring, maytine was proposed to contain a C-1 acetyl group and was therefore assigned structure **2**.



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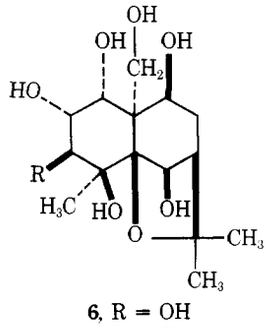

6, R = OH
7, R = H

The mass spectrum of the third alkaloid, maytolidine (**4**, $C_{36}H_{41}NO_{14}$), contained peaks corresponding to the loss of CH_3, H_2O, and CH_3CO_2H from the molecular ion. At lower masses peaks were present at *m/e* 124, 106, assignable to a nicotinoyl group, and also at *m/e* 105, assignable to a benzoyl ion. The molecular formula of **4** was derived from the elemental analysis and high-resolution mass spectral measurement and corresponded to benzoylmaytoline. The ultraviolet spectrum contained considerably increased absorption at 227 nm compared to **1** in addition to bands corresponding to a nicotinoyl group. The NMR spectrum was very similar to that of **3** but contained additional signals overlapping the nicotinoyl proton signals at τ 1.6–1.9 and 2.4–2.7, which were assigned to a benzoate group [e.g., methyl benzoate τ 1.99 (2 H), 2.66 (2 H), and 2.53 (1 H)[10]].

Hydrolysis of **4** yielded maytol (**6**) and acetic and benzoic acids. A possible direct relationship between **1** and **4** was investigated by the benzoylation of **1** with benzoic acid anhydride in pyridine. 3-Benzoylmaytoline was obtained in very poor yield and its NMR spectrum contained acetyl methyl signals at τ 7.73, 7.85, 7.91 similar to the positions in the spectrum of **1** but different from the spectrum of **4** (Table I). In order to determine the position of the benzoate substituent the NMR spectra of **3** and **4** were compared (Table I). The only significant difference was in the position of the C-6 proton signal at τ 3.77 compared to τ 3.92 in **3**. This shift is of the magnitude and direction found in model compounds[11] and therefore structure **4** was proposed for maytolidine.

Small quantities of additional pyridine alkaloids were detected in the remaining chromatographic fractions and mother liquors but they could not be isolated. Further studies on the alkaloids of the fruit of *M. serrata* have yielded the ansamacrolide tumor inhibitor maytansine.[12]

Following the preliminary communication reporting the novel structure of maytoline, the structures of over 20 related alkaloids from the family Celastraceae have been elucidated.[13] All are polyesters of hydroxylated agarofurans and contain either a nicotinic or substituted nicotinic acid. Some of the alkaloids had been isolated previously but, although they had been recognized as nicotinate esters, the structure of the polyhydroxy agarofuran group had not been determined. These included evonine[14] from *Euonymus europeaus*, wilfordine[15] from *Tripterygium wilfordii*, and cathidine D[16] from *Catha edulis*, the last of these being based on 6-deoxymaytol. A number of related nonbasic polyesters have been also reported from the Celastraceae,[13] including euolalin, based on

7,[17] and alatolin, based on an isomer of **7**,[18] both from *E. alatus*.

Experimental Section

Uv spectra were measured on a Coleman Hitachi EPS-3T spectrometer. Ir spectra were measured on a Perkin-Elmer 257 spectrometer. NMR spectra were measured on $CDCl_3$ solutions with a Varian HA-100 spectrometer. Mass spectra were determined on Perkin-Elmer RMU-6E or AEI-MS9 spectrometers. Analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Isolation of Alkaloids from *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek. The dried ground fruit (5 kg) of *M. serrata* was extracted for 3 days with cold aqueous EtOH. The extract (780 g) was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (115 g) was chromatographed on a SilicAR CC-7 column (1.4 kg), which was eluted with $CHCl_3$ (6 l.). Elution with 5% MeOH/$CHCl_3$ (7 l.) then yielded an oil (44 g). The oil was chromatographed on neutral alumina (440 g), which was eluted with $CHCl_3$ to give fraction A (20 g) and with MeOH to yield fraction B (6 g).

Fraction A was chromatographed on silica gel (600 g). Elution with ether yielded fraction C (16 g), and then with EtOAc yielded fraction D (800 mg). Fraction D (292 mg) was separated by TLC on alumina (EtOAc) to yield the major component maytine (**2**, 57 mg): uv (MeOH) λ_{max} 221, 258 (infl), 265, and 271 nm (infl) (ϵ 10 700, 3200, 3300, 2700); uv (MeOH + H^+) λ_{max} 220 (infl), 255 (infl), 262, 268 nm (infl) (ϵ 7150, 4200, 5200, 4200); ir ($CHCl_3$) 2.83, 5.73 b, 6.29, 7.29, 11.5 μ; MS *m/e* 591.2316 (M^+, calcd for $C_{29}H_{37}NO_{12}$, 591.2315).

The other components from fraction D and fraction C were combined with corresponding fractions from other extractions to give an oil (20 g). The oil was dissolved in EtOAc (250 ml) and extracted with 2 N HCl (three 50-ml portions). The acidic solution was neutralized and extracted with EtOAc to give an oil (873 mg), which on examination by TLC on silica gel or alumina contained a number of basic components.

The non-acid-soluble EtOAc solution was evaporated and the residue dissolved in ether (500 ml). The ethereal solution was extracted with 2 N HCl (100 ml, two 50-ml portions). The combined acid solutions were washed with Et_2O, neutralized, and extracted with Et_2O. This Et_2O extract was dried and evaporated to give a solid (1.6 g), which by TLC on alumina (EtOAc) contain two major basic components.

The solid was chromatographed on neutral alumina to give two fractions on elution with EtOAc. The first fraction (497 mg) was recrystallized twice from EtOAc/Et_2O to yield maytolidine (**4**, 152 mg): mp 128–132°C; uv (MeOH) λ_{max} 227, 259 (infl), 265, 271 (infl), 282 nm (infl) (ϵ 19 400, 4600, 5000, 4800, 3000); uv (MeOH + H^+) λ_{max} 227, 257 (infl), 263, 269, 283 nm (infl) (ϵ 17 500, 6200, 7350, 6900, 3000); ir ($CHCl_3$) 2.8, 5.71, 5.83, 6.29, 7.30, and 9.09 μ.

Anal. Calcd for $C_{36}H_{41}NO_{14}$: C, 60.75; H, 5.80; N, 1.97; M^+, 711.2526. Found: C, 60.29; H, 6.06; N, 1.88; M^+, 711.2597.

The second fraction (1.02 g) was rechromatographed on alumina to yield more **4** (500 mg). The remaining fractions showed the presence of other pyridine alkaloids but these could not be isolated in sufficient yield for identification, using a number of different solvent systems.

Fraction B (MeOH eluate from alumina) was chromatographed on silica gel and elution with EtOAc yielded a fraction (1.4 g) with the same R_f on silica gel as **2**. This fraction was dissolved in EtOAc (50 g) and extracted with 2 N HCl (three 25-ml portions). The acid was neutralized and extracted with EtOAc to give a mixture (650 mg). The mixture was separated by TLC on alumina (10% MeOH/EtOAc) to give the major component, maytoline (**1**, 123 mg): $[\alpha]^{25}D$ 0.3° (*c* 0.75, $CHCl_3$); uv (MeOH) λ_{max} 221, 258 (infl), 265, 271 nm (infl) (ϵ 9600, 2500, 2700, 2300); uv (MeOH + H^+) λ_{max} 220, 257 (infl), 263, 268 nm (infl) (ϵ 8300, 4300, 4800, 4200); ir ($CHCl_3$) 2.85, 5.75 b, 6.29 μ; MS *m/e* 607.2251 (calcd for $C_{29}H_{37}NO_{13}$, 607.2264), 592.2045 (calcd for $C_{28}H_{34}NO_{13}$, 592.2029), 547.2062 (calcd for $C_{27}H_{33}NO_{11}$, 547.2053).

Tetrahydromaytine (5). A solution of maytine (20 mg) in EtOAc (3 ml) was hydrogenated over PtO_2. The product was filtered through alumina to yield a mixture which was separated by TLC on silica gel to yield, as a gum, tetrahydromaytine (**5**, 4.9 mg): uv (MeOH) λ_{max} 290 nm (ϵ 13 600); ir ($CHCl_3$) 2.89, 5.75, 5.99, 6.17 μ; MS *m/e* 595.2628 (M^+, calcd for $C_{29}H_{41}NO_{12}$, 595.2628) and 537.

Acetylmaytoline (3). A solution of maytoline (30 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was left overnight. After workup the product was separated by TLC to give, as a gum, acetylmaytoline (**3**, 13 mg): uv (MeOH) λ_{max} 221.5, 258 (infl), 264, 271 nm (infl) (ϵ 8700, 2800, 2900, 2300); uv (MeOH + H^+) λ_{max} 207, 256 (infl), 262, 268 nm (infl) (ϵ 6900, 3600, 4600, 3800); ir ($CHCl_3$) 2.8, 5.71, 6.29, 7.29, 9.09 μ; MS *m/e* 649.2345 (M^+, calcd for $C_{31}H_{39}NO_{14}$, 649.2370).

3-Benzoylmaytoline. A solution of maytoline (25 mg) and benzoic anhydride (60 mg) in pyridine (1 ml) was left for 3 days at room temperature. Workup gave a product, which was separated by TLC on alumina to give 3-benzoylmaytoline (2.2 mg) with the same R_f as maytolidine on TLC on either silica gel (EtOAc) or alumina (EtOAc): MS *m/e* 711 (M^+) 686, 124, 105.

Maytol A. From Maytolidine. A solution of maytolidine (**4**, 38 mg) in 2 N NaOH (1 ml) and MeOH (0.5 ml) was kept at room temperature for 1.5 h. The solution was acidified and extracted with ether (two 10-ml portions), which was dried and evaporated to give a solid (4.2 mg) smelling of acetic acid. The solid was sublimed at 80 °C (10 mm) to yield benzoic acid, mp 120–121.5 °C.

The aqueous solution was evaporated to yield a solid, which was extracted with MeOH. The methanolic solution was evaporated and the residue extracted with $CHCl_3$ to yield a gum (5.6 mg). The gum was filtered through silica gel to yield maytol (**6**, 3.6 mg): mp 229–237 °C; no uv absorption; ir (KBr) 2.9 μ b; NMR (acetone-d_6) τ 8.48 (s, 3 H), 8.32 (s, 3 H), 8.27 (s, 3 H), 5.0–6.8 m; MS *m/e* 319.1401 (M^+ − 15, calcd for $C_{14}H_{23}O_8$, 319.1392), 316 (M^+ − 18), and repeated 18 mu losses from both ions.

B. From Maytoline. A solution of maytoline (24 mg) in MeOH (1 ml) and 2 N NaOH was kept at room temperature for 1.5 h. The solution was then acidified and washed with Et_2O (two 5-ml portions). The acid solution was evaporated and the residual solid repeatedly extracted with hot $CHCl_3$, which was evaporated to give a gum (8 mg). The gum was separated by TLC on silica gel (10% MeOH/EtOAc) to give maytol (2.6 mg), identical with material from maytolidine by NMR and MS.

Deoxymaytol (7). A solution of maytine (49 mg) in MeOH (1 ml) and 2 N NaOH (1 ml) was kept at room temperature for 1.5 h. The solution was acidified and washed with Et_2O (two 5-ml portions). The aqueous solution was evaporated and the residue was extracted with hot $CHCl_3$ to yield an oil (25 mg). The oil was separated by TLC on silica gel (25% MeOH/$CHCl_3$) to give the major component, deoxymaytol (**7**, 11.6 mg): NMR (acetone-d_6) τ 8.50 (s, 3 H), 8.32 (s, 3 H), 8.25 (s, 3 H), 5.3–6.5 m; MS *m/e* 303.1438 (M^+ − 15, calcd for $C_{14}H_{23}O_7$, 303.1445), 300 (M^+ − 18), and repeated losses of 18 Mu from both fragments.

Maytoline Methiodide. A solution of maytoline (30 mg) in benzene (0.4 ml) and methyl iodide (0.1 ml) was left in the dark at room temperature for 3 days. An oil separated and the mother liquor was decanted. The oil on precipitation from MeOH with Et_2O gave a solid, which was crystallized twice from MeOH/Et_2O to give crystals of maytoline methiodide (the crystals were unstable in air and rapidly lost solvent of crystallization to give a powder): mp 190–193 °C dec; uv (MeOH) λ_{max} 219, 260 (infl), 266, 272 nm (ϵ 20 000, 4000, 4950, 4100); ir ($CHCl_3$) 5.72 μ.

Registry No.—**1**, 31146-55-1; **2**, 31146-56-2; **3**, 60512-70-1; **4**, 60512-69-8; **5**, 31146-57-3; **6**, 31230-10-1; **7**, 31146-58-4; 3-benzoylmaytoline, 60512-71-2; maytoline methiodide 31146-59-5.

References and Notes

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Synthesis of DL-Methyl Meromycolate

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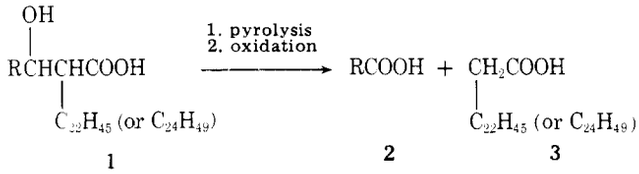
A flexible total synthesis is reported of a biscyclopropane methyl meromycolate, a product derived from the tuberculosis bacterium. The approach was to synthesize two major sections separately, namely, the bistrimethylenedithiol derivative of 10-oxo-*cis*-13,14-methylenedotriacontanal and the ethylene glycol acetal of 22-bromo-*cis*-19,20-methylenedocosanal, and then to combine them just before the final stages.

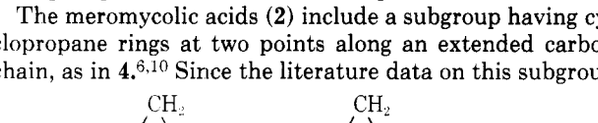
Degradation of the cell wall of tuberculosis organisms has given a number of products, among which is a family of lipids collectively called "mycolic acids".[1] These are all high molecular weight carboxylic acids **1** with a long straight chain at the carboxylic α position and a hydroxy group at the β position. Pyrolysis of mycolic acid (**1**) produces an aldehyde plus



1 2 3

either tetracosanoic or hexacosanoic acid (**3**). Oxidation of the aldehyde ("meromycolaldehyde"), generally with silver oxide, yields the corresponding meromycolic acid (**2**).[2-9] We wish to contribute to this area by developing flexible total syntheses leading to meromycolates of assured structure. Not only would these be available for reference and comparison but they would also be used for the synthesis of mycolic acids as well as larger liposaccharide cell wall components.

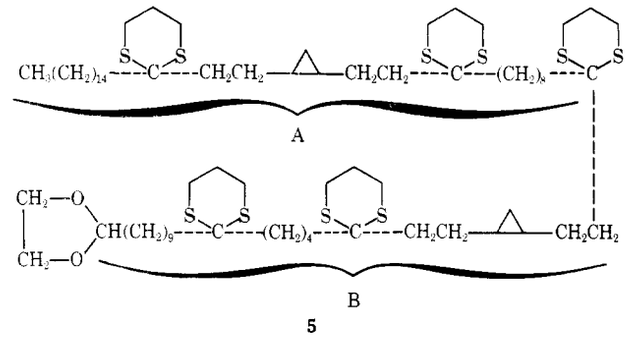
The meromycolic acids (**2**) include a subgroup having cyclopropane rings at two points along an extended carbon chain, as in **4**.[6,10] Since the literature data on this subgroup



4

provide a defensible basis for the structural assignment, we took this kind of meromycolic acid as our first synthesis target. Different sets of x, y, z values in **4** have been reported for the most abundant component in the samples investigated.[11] We chose the set $x = 17$, $y = 14$, $z = 17$,[12] because the corresponding meromycolic acid is representative, and because it has in fact been obtained as a degradation product. The present paper reports our work, which has for the first time furnished a large molecular weight synthetic meromycolate of unequivocal structure.

To assemble the pieces that would give meromycolic acids **4** we first tried the mixed Kolbe anodic coupling process,[13] which proved not to be satisfactory. Alkylation of metalated 1,3-dithianes[14] gave much better results, and we relied on the dithiane method throughout the synthesis. Formulation **5** shows the fragments contributing carbon atoms to the meromycolic ester selected as the synthesis target (**4**: $x = 17$, $y = 14$, $z = 17$). Moieties A and B were constructed separately—the dotted lines indicate the several bonding points—and then were combined to give the complete carbon skeleton. The cyclopropane rings in the two parts were both introduced in the form of the same 3,4-methylenehexane unit, specifically as compound **16**, whose synthesis is described below.



5

Synthesis of the Cyclopropane Portion (16). Norcarene (**7**), from 1,4-cyclohexadiene (**6**), can be converted by ozonolysis to *cis*-1,2-cyclopropanediacetic acid (**8**).[15] It was expected that anhydride formation from diacid **8** would give cyclic anhydride **9**, which would acylate methanol without complication to give half-ester **11** as the sole product. The half-ester was, in fact, obtained but only as a 2:1:1 mixture with the corresponding diester and diacid. This result is consistent with the formulation of the acid anhydride as a linear polymer **10** instead of the cyclic monomer **9**. The separated half-ester **11** was converted to the ester–acid chloride and then reduced with borohydride to ester alcohol **12**. Reaction with dihydropyran furnished intermediate **13**, which with lithium aluminum hydride gave alcohol **14**. Further conversions provided the properly functionalized tetrahydopyranyl–alkyl bromide synthon **16**. An alternate pathway called for direct sodium borohydride reduction of the ozonide from norcarene (**7**) to diol **15**, which could also be obtained from diacid **8**. The diol treated with dihydropyran under controlled conditions gave the desired monotetrahydropyranyl derivative **14** in modest single-pass conversions (35%) though in high yield when corrected for the recovered, reusable materials.[16] The shorter path via diol **15** was preferred.

Fragment **16** provides all the asymmetric centers of the finished meromycolic acid. In the present work we used racemic **16** and so obtained an optically inactive final product. In work to be continued we plan to insert the resolved forms