154. Chemical Degradation of Lasalocid: (A) The *Mannich* Reaction (B) *Baeyer-Villiger* Oxidation of the Retro-Aldol Ketone

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Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

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Summary

Under *Mannich* reaction conditions (diethylamine and formaldehyde in toluene under reflux) lasalocid (**1**) undergoes a unique transformation in which the carboxyl group is replaced by a diethylaminomethyl group. The resulting *Mannich* base **2** was converted back to lasalocid, proving that none of the other chemical and stereochemical features of the molecule were disturbed. Like other phenolic *Mannich* bases, the one derived from lasalocid readily alkylated mercaptans.

The known thermal and base-induced retro-aldol degradations of lasalocid both produce a ketone fragment **9** containing the cyclic ether units. *Baeyer-Villiger* oxidation of this ketone afforded a carboxylic acid fragment which still contained these ether units. The normal regiochemistry involved in oxidizing this ketone ($R-CH_2-CO-CHR'R''$ type) was cleanly reversed by first converting it into the hydroxymethylidene derivative **10**.

Introduction. – The structures of sixty odd polyether antibiotics have been determined in recent years [1] by physical methods, particularly X-ray crystallography, and very few chemical degradation studies. Lasalocid (**1**) is, however, an exception, its chemistry having been explored extensively by *Westley et al.* in connection with its commercially important biological properties. This chemistry, which includes degradations, electrophilic substitutions, and some functional group transformations was recently reviewed by *Westley* [1]. In at least two other laboratories [2] [3], lasalocid has been the target of chemical synthesis campaigns.

We now report some novel features of this natural product.

Results and Discussion. – *Part A.* Lasalocid (**1**) undergoes a variety of electrophilic substitutions as expected of a phenolic substance with an open *para*-position. Examples of halogenation [4], nitration [5], and azocoupling [6] leading to monosubstituted products have been published. Under more severe conditions of bromination and nitration, dibromo and dinitro derivatives are obtained in which the second electrophile has displaced the carboxyl group [4] [5].

In this context it was of interest to explore the outcome of the *Mannich* reaction with lasalocid. When exposed to the conditions developed for benzomorphans [7],

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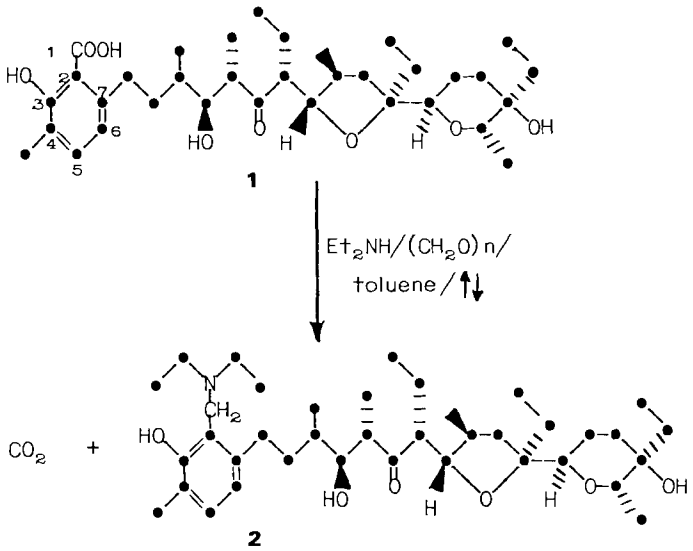
lasalocid (**1**) underwent decarboxylation with simultaneous introduction of a formaldehyde C-atom at C(2), C(6), *para* to the phenolic OH, remaining unsubstituted.

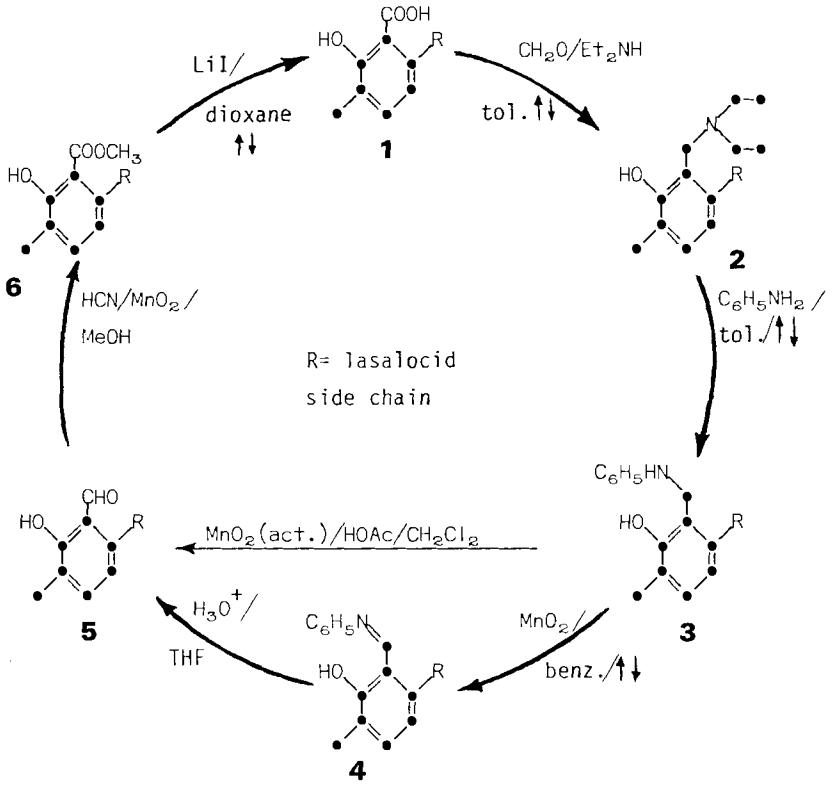


The reaction was carried out with diethylamine and paraformaldehyde in toluene under reflux. It does not work with the sodium salt of lasalocid (equally soluble in toluene), nor does salicyclic acid, a simple model for the aromatic component, give the corresponding *Mannich* base under these conditions.

The structure **2** assigned to this *Mannich* base was readily deduced from its spectral properties and is secured by its conversion back to lasalocid (**1**). The MS. contains a molecular ion peak at *m/z* 631. The appearance of the molecular ion is rare in the electron impact MS. of the polyether antibiotics and compound **2** is the only compound of those mentioned here to show one. The IR. spectrum retains the ketone carbonyl band at 1720 cm^{-1} but has lost the acid carbonyl band which would have appeared at 1660 cm^{-1}. The NMR. spectrum still shows two aromatic protons (6.54 and 6.95 ppm) with *ortho* coupling ($J = 8$ Hz). In addition, it contains the signals expected for a diethylaminomethyl group (see experimental part).

Several possibilities for converting the *Mannich* base **2** back to **1** were explored, including the obvious route through a *Polonovski* reaction. The successful approach is shown in the cyclic reaction scheme below. Because of the pronounced sensitivity of the side chain to destruction by acids, bases, and strong oxidizing agents, mild reagents and conditions were essential for each step. Both of the crucial steps to raise the oxidation level of the formaldehyde-derived C-atom involved manganese dioxide.

The propensity for the dialkylamino group of phenolic *Mannich* bases to undergo displacement by various nucleophiles, including amines, has been known for many years [8]. Thus boiling a toluene solution of **2** and aniline gave the anilino derivative **3**. The oxidation of this material to the anil **4** was accomplished with



ordinary manganese dioxide buffered with acetic acid, as suggested by oxidations in benzodiazepine area [9]. Activated manganese dioxide used with acetic acid in methylene chloride also worked and was perhaps preferable in that much of the product is hydrolyzed to the aldehyde **5** at the same time. A characteristic signal in the ^{1}H-NMR. spectrum of **4** at 8.99 ppm (CH=N) was used to monitor this oxidation. Its appearance accompanied the disappearance of the Ar-CH_2N singlet at 4.40 ppm in the spectrum of **3**.

Hydrolysis of the anil to lasalocid aldehyde (**5**) was readily effected with dilute hydrochloric acid in tetrahydrofuran at RT. The NMR. signals of the phenolic and aldehydic protons of **5** are at 12.27 and 10.32 ppm. The ketone and aldehyde carbonyl groups absorb at 1710 and 1635 cm^{-1} in the IR. spectrum.

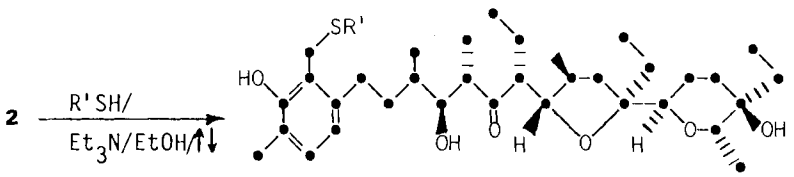
Permanganate and silver (I or II) oxides are frequently used to oxidize aromatic aldehydes to acids. However, neither these nor various other reagents for direct oxidation to the acid were found to be compatible with the lasalocid side chain. The knowledge that the side chain could withstand exposure to MnO_2 prompted us to try *Corey's* procedure for the oxidation of aldehydes to the corresponding methyl esters [10]. Activated MnO_2 was needed for this but nevertheless the known methyl ester **6** of lasalocid could be obtained, even though the yield was 30–50%. The ester **6** was characterized spectroscopically. Its optical rotation $-9.50°$, when compared with the value of $-7.20°$ reported [4] for an ester sample prepared from lasalocid,

indicates that epimerization at the asymmetric centers flanking the ketone function in the side chain may not be appreciable.

Hydrolysis of the methyl ester **6** did not occur in dilute acid and could not be seriously attempted in strong acid or with base. Nucleophilic demethylation using iodide [11] or mercaptide [12] ions seemed more reasonable and of these, demethylation with lithium iodide in dioxane at reflux was most satisfactory.

The reconstituted lasalocid was obtained in an overall yield of 3.2% based on starting lasalocid (**1**). It was characterized both as the free acid and sodium salt by comparison (IR. and ^{1}H-NMR. spectra, m.p., TLC., and optical rotations) with authentic samples. The rotations of the acid and salt are $-38.31°$ and $-81.85°$ which, when compared with $-41.2°$ and $-85.1°$ reported for authentic samples [4], confirm the suspicion that epimerization is minimal in proceeding through the cyclic reaction sequence.

Thioether derivatives. The *Mannich* bases of phenol are known to alkylate mercaptans [13] and, accordingly, thiophenol reacted smoothly with the *Mannich* base from lasalocid to give the phenyl thioether **7**. A second example was carried out with mercaptoacetic acid, in which case thioether derivative **8** was obtained.

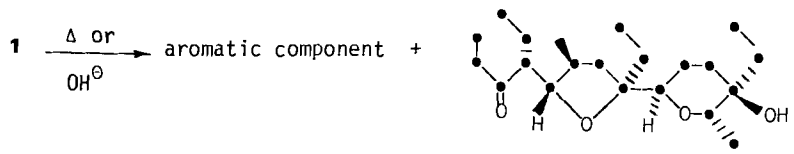


7 R' = phenyl

8 R' = CH_2COOH

In screening these derivatives for biological activity, it was found that **7** possesses interesting antihypertensive properties in DOCA-Na hypertensive rats [14]. The ionophoric properties of lasalocid, lost in the *Mannich* reaction, are restored in **8**. The antibiotic activity was not restored however.

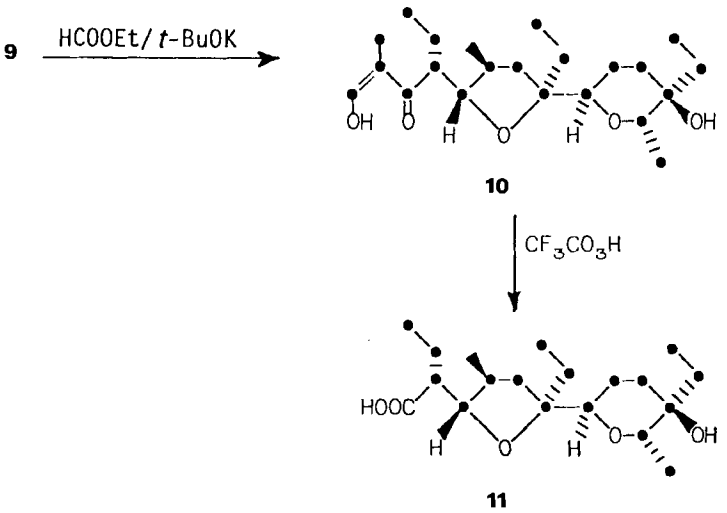
Part B. The most prominent chemical feature of lasalocid (**1**) is its tendency to undergo retro-aldol cleavage [4] [15].



9

Both thermal and base-induced conditions have been used for this reaction and the aromatic component depends on which conditions are used. Reversing this reaction in the aldol sense is a key step in the syntheses of lasalocid [2] [3], making **9** a valuable synthon. In connection with biosynthetic considerations **9** was further degraded by a *Baeyer-Villiger* oxidation on the methylene side of the ketone.

The procedure used is reported because it may be applicable in other instances and because the resulting acid **11** may also be a useful polyether fragment, readily available in view of the ready availability of lasalocid [16].



Direct *Baeyer-Villiger* oxidation of ketone **9** with trifluoroperacetic acid [17] gives a mixture of products which indicate that oxidative cleavage occurs mainly on the methine side [18], but after first converting the ketone to the hydroxymethylidene derivative **10**, the regioselectivity of this cleavage was diverted entirely to the methylidene side giving the acid **11** directly.

We are greatly indebted to Dr. *J. Westley* for the many ways in which he assisted this project.

Experimental Part

General. Melting points (m.p.) are uncorrected. ^{1}H-NMR. spectra were recorded on *Varian* T-60 and HA-100 instruments and are reported in ppm from internal TMS. IR. and mass spectra were recorded on *Perkin-Elmer* 137 and *CEC*-110B instruments respectively. Elemental analyses and optical rotation determinations were conducted under the supervision of Dr. *F. Scheidl* of our microchemical laboratory. Thin layer chromatography (TLC.) was done routinely with silica gel plates generally with chloroform/methanol 95:5.

2-(Diethylaminomethyl) decarboxylasalocid (**2**). A mixture of lasalocid ethanolate (5.0 g), paraformaldehyde (2.5 g), and diethylamine (2.5 g) in toluene (200 ml) was stirred and heated under reflux for 90 min. Water was collected in a trap during the reflux period. The resulting solution was diluted with ether and transferred to a separatory funnel. It was washed with water and then with *ca.* 0.05N HCl. The organic layer was dried, filtered, and the solvent was removed under reduced pressure leaving 5.9 g of pale yellow (sometimes colorless) resin. This crude *Mannich* base contains residual toluene but was used directly in the next step.

For characterization, toluene was removed by keeping a sample under high vacuum overnight, $[a]_D^{25} = -9.28°$ ($c = 1$, CH_3OH). – IR. (film): 3450, 1720, 1625, 1590. – ^{1}H-NMR. ($CDCl_3$): 0.66–4.2

[*m* with 2.20 (*s*, $ArCH_3$), 2.66 (*qa*, $J = 7$ Hz, NCH_2CH_3), and 3.81 (*s*, $ArCH_2N$)]; 6.54 (*d*, $J = 8$ Hz, 1 H); 6.95 (*d*, $J = 8$ Hz, 1 H). – MS.: 631 (M^+), 488, 325, 277, 211 (100), 155.

$C_{38}H_{65}NO_6$ (631.95) Calc. C 72.22 H 10.37 N 2.21% Found C 72.42 H 10.29 N 2.24%

2-Anilinomethyldecarboxylasalocid (**3**). A solution of crude *Mannich* base **2** (5.9 g) and aniline (15 ml) in toluene (200 ml) was heated under reflux for 24 h. After cooling, the solution was diluted with ether, washed twice with cold 3N HCl, and once washed with water, then dried and evaporated to give 5.3 g of pale yellow solid foam, which was used directly in the next step.

A sample from a different preparation was purified by preparative TLC. $[\alpha]_D^{25} = -11.43°$ ($c = 1$, CH_3OH). – IR. (KBr) 3450, 1715, 1600, 1585. – ^{1}H-NMR. ($CDCl_3$): 0.7–4.0 (*m* with *s* at 2.19, $ArCH_3$); 4.40 (*s*, $ArCH_2N$); 6.6–7.3 (*m*, arom. H with *d* at 6.68 ppm, $J = 8$ Hz, 1 H). – MS.: 309 (no M^+ peak observed), 211 (100), 155.

$C_{40}H_{61}NO_6$ (651.93) Calc. C 73.70 H 9.43 N 2.15% Found C 72.98 H 9.75 N 2.05%

Lasalocid aldehyde anil (**4**). Type # 32 MnO_2[1]) (65 g) was slurried in benzene (1 l.) and the mixture was stirred under reflux for 1 h while collecting water in a trap. Acetic acid (5 ml) was then added followed by a solution of the anilino compound 3 (5.3 g) in a small volume of benzene. After stirring under reflux for 4 h, the MnO_2 was filtered off on *Celite*, the filtrate evaporated and the residue treated with a fresh lot of MnO_2 (65 g) as above. After stirring under reflux for an additional 90 min, the reaction was complete (disappearance of 4.40 ppm signal of starting material in the ^{1}H-NMR.). Again the MnO_2 was removed on *Celite* and washed with benzene and ether. Evaporation of solvent from the filtrate and washing left 3.1 g of crude anil in which a very polar impurity was observed by TLC. This material was used directly in the next step.

A sample from a different preparation was purified by preparative TLC. – IR. (KBr): 3460, 1715, 1610, 1585. – ^{1}H-NMR. ($CDCl_3$): 0.7–4.3 (*m* with *s* at 2.24, $ArCH_3$), 6.65 (*d*, $J = 8$ Hz, 1 H); 7.12 (*d*, $J = 8$ Hz, 1 H); 7.2–7.5 (*m*, arom.); 8.99 ppm (*s*, CH=N). – MS.: 295 (no M^+ peak observed), 238, 211 (100), 155. – The compound was analyzed as a monohydrate.

$C_{40}H_{59}NO_6 \cdot H_2O$ (667.92) Calc. C 71.93 H 9.20 N 2.10% Found C 72.02 H 9.32 N 2.00%

Lasalocid aldehyde (**5**). a) A solution of crude anil **4** (3.1 g) in THF (50 ml) and 3N HCl (10 ml) was stirred overnight at RT. It was then poured into water and the resulting mixture was extracted twice with CH_2Cl_2. The residue after drying and evaporation of the solvent consisted of 2.4 g of crude aldehyde **5** containing a polar impurity by TLC.

A sample from a different preparation was purified by preparative TLC. giving, after removal of solvent under high vacuum, a pale yellow solid foam. $[\alpha]_D^{25} = -17.38°$ ($c = 1$, MeOH). – IR. ($CHCl_3$): 3580, 3460, 1710, 1635. – ^{1}H-NMR. ($CDCl_3$): 0.7–4.1 (*m*, well-resolved with *s* at 2.20, $ArCH_3$); 6.65 (*d*, $J = 8$, 1 H), 7.23 (*d*, $J = 8$, 1 H); 10.32 (*s*, CHO); 12.27 (*s*, ArOH). – MS.: 211, 155, and 57 (100). – The compound was analyzed as a hemihydrate.

$C_{34}H_{54}O_7 \cdot \frac{1}{2}H_2O$ (583.80) Calc. C 69.94 H 9.49% Found C 69.89 H 9.33%

b) The crude anilino compound **3** (4.8 g from 5 g of lasalocid), activated MnO_2 (50 g), and glacial acetic acid (4 ml) in CH_2Cl_2 (500 ml) was stirred at RT. for 18 h. The mixture was filtered through a bed of *Florisil* and the solid thoroughly washed with ether. The filtrate was concentrated under reduced pressure and the residue, in CH_2Cl_2 solution, washed successively with 3N HCl, dilute $NaHCO_3$-solution, and water. After drying and evaporation of solvent, 2.8 g of crude lasalocid aldehyde was obtained. This material was used directly for the preparation of the ester **6**.

Lasalocid methyl ester (**6**). A mixture of crude aldehyde **5** (2.4 g), activated MnO_2 (24 g), NaCN (4.8 g), and acetic acid (2.4 g) in methanol (100 ml) was stirred at RT. for 64 h. The solid material was filtered off on *Celite* and washed several times with methanol. After a final washing with methanol/water 1:1 the combined filtrate and washings were transferred to a separatory funnel, diluted with CH_2Cl_2 and washed with water, dilute aq. $NaHCO_3$-solution and again with water. After drying and evaporation of solvent, the crude ester weighed 1.35 g. A polar impurity was removed by filtration through a short column of silica gel with hexane/ethyl acetate 4:1. After thoroughly washing the ester through with this solvent mixture, the solvent was evaporated using a vacuum pump to remove the last traces. This

[1]) Supplied by *General Metallic Oxides Co.*

left 0.85 g of fairly pure ester (TLC.) as a clear oil, $[a]_D^{25} = -9.50°$ ($c = 1$, MeOH) ($-7.20°$ reported for sample obtained by methylation of lasalocid). – IR. (film): 3430, 1715, 1660, 1625, 1585. – ^{1}H-NMR. ($CDCl_3$): 0.6–4.0 (*m* with *s* at 2.20, $ArCH_3$, and *s* at 3.90, OCH_3); 6.59 (*d*, $J = 8$ Hz, 1 H); 7.10 (*d*, $J = 8$ Hz, 1 H); 11.3 (*s*, ArOH).

Lasalocid (reconstituted) (**1**). A mixture of methyl ester **6** (600 mg) and LiI (1.0 g) in dioxane (50 ml) was stirred and heated under reflux overnight using an oil bath at 120°. The cooled reaction mixture was diluted with water and extracted 3 times with CH_2Cl_2. After drying and evaporation, 800 mg of brown gum was obtained which contained lasalocid as the major component (TLC.). The product was purified by chromatography on 2 20×20 cm preparative TLC. plates (silica gel). The material from the fluorescent band was crystallized from $EtOH/H_2O$ containing a few drops of dilute aq. HCl-solution to give 160 mg of lasalocid as a light tan crystalline solid. The IR. spectrum (Nujol) of this material was identical with the spectrum of a reference sample. A 100 mg portion was recrystallized from $EtOH/H_2O$ giving 80 mg with m.p. 90–112° ([15]: 110–114°, reference sample 88–110°) and with the same ^{1}H-NMR. spectrum ($CDCl_3$) as the reference sample. The reconstituted sample had $[a]_D^{25} = -38.31°$ (2%, $CHCl_3$); reference sample value is $-41.2°$.

The solution used for the ^{1}H-NMR. spectrum was diluted with CH_2Cl_2, shaken with dilute aq. Na_2CO_3-solution and boiled with addition of hexane and occasional scratching. The lasalocid sodium salt crystallized giving 15 mg of colorless crystals m.p. 173–4° ([15]: 168–171°, mixed m.p. with reference sample 176°); $[a]_D^{25} = -81.85°$ ($c = 1$, MeOH); found for reference sample $-86.18°$. – IR. (Nujol) identical with that of a reference sample.

The reconstituted lasalocid was indistinguishable from starting lasalocid by TLC.

2-(Phenylthiomethyl)decarboxylasalocid (**7**). A solution of *Mannich* base **2** (9.7 g), thiophenol (4.5 ml), and triethylamine (4 ml) in ethanol (125 ml) was heated under reflux for 18 h. The solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2. After washing with water and dilute aq. Na_2CO_3-solution, the solution was dried and the solvent evaporated. The crude product was purified by chromatography on a silica gel (200 g) column. Hexane/ethyl acetate 8:1 eluted the thiophenol and hexane/ethyl acetate 6:1 eluted the product. Evaporation of solvent, finally with a vacuum pump, afforded 7.0 g (68%) of colorless solid foam. – IR. (Nujol): 3400, 1715, 1585. – ^{1}H-NMR. ($CDCl_3$): 0.7–4.1 (*m* with *s* at 2.19, $ArCH_3$); 4.21 (*s*, $ArCH_2S$); 6.64 (*d*, $J = 8$ Hz, 1 H); 6.93 (*d*, $J = 8$ Hz, 1 H); 7.2–7.5 (*m*, 5 H, arom. H). – MS.: 415 (no M^+ observed), 314, 211, 155, 135, 57 (100).

$C_{40}H_{60}O_6S$ (668.98) Calc. C 71.82 H 9.04 S 4.79% Found C 71.69 H 9.24 S 4.72%

2-(Carboxymethylthiomethyl)decarboxylasalocid (**8**). A solution of the *Mannich* base **2** (3 g), mercaptoacetic acid (3 ml), and triethylamine (3 ml) in ethanol 100 ml was heated under reflux for 36 h. The ethanol was then removed by evaporation under reduced pressure and the residue, in CH_2Cl_2, was washed with dilute aq. Na_2CO_3-solution, water, 0.5N HCl, and finally with water again. After drying and evaporation, the crude product was purified by chromatography on silica gel using $CHCl_3/CH_3OH$ 96:4. Since the product was found to absorb sodium ions from inorganic material, the eluate containing the product was washed with very dilute HCl-solution before evaporation. This gave 1.5 g (48%) of colorless solid foam. – IR. ($CHCl_3$): 3500, 1710, 1585. – ^{1}H-NMR. ($CDCl_3$): 0.7–4.2 (*m* with 3 *s*); 2.15 (*s*, $ArCH_3$); 3.18 (*s*, SCH_2COOH); 3.95 (*s*, $ArCH_2S$); 6.62 (*d*, $J = 8$ Hz, 1 H); 6.90 (*d*, $J = 8$ Hz, 1 H). – MS.: 211, 155, 57 (100).

$C_{36}H_{58}O_8S$ (650.92) Calc. C 66.43 H 8.98 S 4.93% Found C 66.24 H 9.15 S 4.73%

(4R, 5S, 6S, 8S, 9R, 12R, 13S)-4, 8, 12-Triethyl-12-hydroxy-2-hydroxymethylidene-6-methyl-5, 8-oxido-9, 13-oxidotetradecan-3-one (**10**). Lasalocid sodium salt (5 g) was vacuum-pyrolyzed (0.05 Torr) with distillation of pyrolysis products in a bulb tube. The distillate was taken up in dry benzene (50 ml) and treated with ethyl formate (5 ml) and potassium *t*-butoxide (5 g), adding the latter gradually in portions. After 0.5 h, the reaction was complete (TLC.). The solution was extracted with water (200 ml) and the aq. layer was washed with ether. Both organic layers were discarded. The aq. layer was acidified with dilute aq. HCl-solution and then brought to pH 10 with aq. Na_2CO_3-solution. It was again washed with ether and the ether layer discarded. After reacidification with aq. HCl-solution, the aq. layer was extracted twice with CH_2Cl_2 (2× 100 ml) giving a solution of pure hydroxymethylideneketone (*ca.* 80%) used directly in the *Baeyer-Villiger* step. The phenolic component of the pyrolysis products is removed during the extraction sequence.

A solution from a different preparation was evaporated and the product distilled (0.05 Torr) in a bulb tube. – IR. ($CHCl_3$): 3580, 1733, 1700, 1630 (the relative intensities of the last 3 bands vary with the enol content of the sample). – ^{1}H-NMR. ($CDCl_3$): 0.8–4 (*m* with *s* at 1.96, vinyl CH_3); 8.27 (*s*, 1 H, vinyl). – MS.: 239 (no M^+ peak observed), 211, 155, 57 (100).

$C_{22}H_{38}O_5$ (382.54) Calc. C 69.08 H 10.01% Found C 69.82 H 10.02%

*(2*R*, 3*S*, 4*S*, 6*S*, 7*R*, 10*R*, 11*S*)-2, 6, 10-Triethyl-10-hydroxy-4-methyl-3, 6-oxido-7, 11-oxidododecanoic acid* (**11**). A stock solution of trifluoroperacetic acid was prepared by dropwise addition of trifluoroacetic anhydride (51 ml) to an ice-cold, stirred suspension of 90% H_2O_2-solution (8.2 ml) in CH_2Cl_2 (50 ml). Within 15 min a single phase formed. The solution was stored in a freezer.

A solution of hydroxymethylideneketone **10** (prepared from 5 g of lasalocid sodium salt) in CH_2Cl_2 (200 ml) was dried (Na_2SO_4) and then stirred with solid Na_2HPO_4 (20 g). The solution of trifluoroperacetic acid (10 ml) was added in 1 ml portions. The starting material disappeared (TLC.) during the addition. After stirring for a few min, water (50 ml) was added and stirring was continued for 64 h. The mixture was then diluted with more water and dilute aq. HCl-solution. The organic layer was combined with a CH_2Cl_2 extract of the aq. layer and extracted twice with dilute aq. Na_2CO_3-solution. The combined basic extracts were washed with ether and then acidified and extracted twice with CH_2Cl_2. After drying and evaporation of solvent (vacuum pump), the CH_2Cl_2 extract gave 2.15 g (79% yield on on lasalocid sodium salt) of nearly colorless resin which showed a single spot on TLC. A sample was vacuum distilled in a bulb tube (180°/0.05 Torr) giving a very pale yellow resin. – IR. (CCl_4): 3300–3100, 2750–2400, 1708. – ^{1}H-NMR. ($CDCl_3$): 0.7–2.6 (*m*, 29 H); 3.6 (*m*, 3 H); 6.47 (br. *s*, 2 H, washed out by D_2O). – MS.: 199 (100), 57. – Mol-wt. by titration = 329 (within exp. error); mol-wt. by osmometry in $CHCl_3$ = 344 ± 7 (Calc. mol-wt. 342).

$C_{19}H_{34}O_5$ (342.48) Calc. C 66.64 H 10.00% Found C 66.60 H 9.95%

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