# Glycoside Cleavage Reactions on Erythromycin A. Preparation of Erythronolide A†

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Selective cleavage of the sugar, cladinose, by treatment of erythromycin A oxime (1) with 1% HCl in methanol provided 5-*O*-desosaminylerythronolide A oxime (2) which was purified as the corresponding 2′-acetyl acetoxime (4). Treatment of the 9-oxime 2 with nitrous acid yielded the corresponding ketone, 5-*O*-desosaminylerythronolide A (3). Vigorous acetylation of 4 followed by mild hydrolysis gave the 3-acetyl derivative 5. Oxidation of 4 with Jones reagent yielded the 3-ketone 7. Erythronolide A oxime (11) was obtained by treatment of 3′-de(dimethylamino)-3′,4′-dehydroerythromycin A oxime (10) with 3% HCl in methanol. Nitrous acid treatment of 11 then provided erythronolide A (13). The preparation of 3 and 13 was possible because the 9-ketone was protected as the oxime during sugar cleavage. Prior to this work compounds 3 and 13 had not been prepared due to acid-catalyzed transformations involving the unprotected 9-ketone.

It has not been possible previously to remove the sugars, cladinose and desosamine, from erythromycin A due to extensive acid-catalyzed transformations. These transformations involve formation of an internal enol ether by addition of the C-6 hydroxyl to the carbonyl at C-9 followed by dehydration. This is followed by the participation of the C-12 hydroxyl in an irreversible addition to the double bond giving a spiroketal.[3]

Selective removal of the sugars is possible, however, after reduction of the 9-ketone to dihydroerythromycin A. Thus, reaction of dihydroerythromycin A with hydrogen chloride–methanol removed cladinose and gave 5-*O*-desosaminyldihydroerythronolide A.[4] Further acid hydrolysis of 5-*O*-desosaminyldihydroerythronolide A removed desosamine to provide dihydroerythronolide A.[4] Erythronolide A had not been prepared previously and erythronolide B was available only by a fermentation procedure.[5] Erythromycin B, which lacks the hydroxyl group at C-12, on treatment with acid yields 5-*O*-desosaminylerythronolide B.[6] An intermediate in erythromycin biosynthesis, 3-*O*-mycarosylerythronolide B, is elaborated by a blocked mutant of *Streptomyces erythreus*.[7]

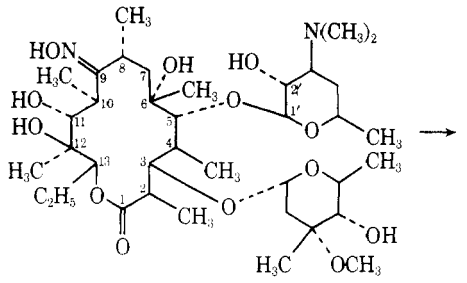
We wish to report the selective cleavage of cladinose to provide 5-*O*-desosaminylerythronolide A (3), as well as the cleavage of both sugars to yield the aglycone, erythronolide A (13). Protection of the ketone of erythromycin A as the oxime 1[8] permits the cleavage of the neutral sugar, cladinose, by treatment with 1% hydrogen chloride in methanol. This sequence provides the noncrystalline product 2. The nmr spectrum of 2 showed the $-N(CH_3)_2$ grouping of desosamine at $\delta$ 2.23 but the $-OCH_3$ absorption of cladinose was now absent. Further confirmation of the structure of 2 was obtained from the mass spectrum which revealed the molecular ion at $m/e$ 590. Treatment of 2 with nitrous acid under carefully controlled conditions yielded 3 after column chromatography. The uv spectrum of 3 shows the expected low-intensity absorption at 289 nm. The standard circular dichroism curve for erythromycin derivatives has a negative amplitude for both the ketone and lactone chromophores. The CD spectrum of 3 ($[\theta]_{291}$ −7700, $[\theta]_{212}$ −3700) when compared to that of erythromycin A[9] ($[\theta]_{290}$ −6600, $[\theta]_{220}$ −2400) indicates that the stereochemistry at the centers adjacent to the ketone and the lactone has not been altered in the reaction sequence. An increase in negative amplitude for both bands is also observed when the CD spectra of erythromycin B and 5-*O*-desosaminylerythronolide B are compared.[9] Acetylation of 2 gave the diacetate 4 with two acetyl peaks in the nmr spectrum and a molecular ion at $m/e$ 674 in the mass spectrum. The hydroxyl groups which would be most easily acetylated in 2 are certainly the desosamine and the oxime hydroxyls. The facile hydrolysis of 4 to 2 with hot aqueous methanol is also consistent with the structural assignment of 4. Hydrolysis of 2′-esters under neutral conditions is well known and is believed to involve intramolecular catalysis by the 3′-dimethylamino group.[10]

Vigorous acetylation of 4 by heating in a pyridine solution with acetic anhydride overnight at 70° gave a triacetate which was selectively hydrolyzed with hot aqueous methanol to yield the monoacetate 5. The nmr spectrum of 5 revealed an acetyl singlet at $\delta$ 2.11 and the mass spectrum showed the molecular ion at $m/e$ 632. Treatment of 5 with nitrous acid regenerated the ketone to provide the monoacetate 6. The conformation of the lactone ring of erythromycin proposed by Perun[11] indicates that the C-3 hydroxyl is pseudo-equatorial, while the C-11 hydroxyl is pseudo-axial. It has also been shown that acetylation of the C-11 hydroxyl is accompanied by a shift of the ketone band in the ir spectrum from 1690 to 1705 $cm^{-1}$ due to decreased hydrogen bonding.[10] The ketone carbonyl band in the ir spectrum of 6 is not shifted and appears at 1690 $cm^{-1}$. This fact, coupled with the greater ease of equatorial over axial acetylation, enables us to propose the C-3 acetylated structure 6 for the monoacetate. The CD spectrum of 6 ($[\theta]_{293}$ −7935, $[\theta]_{215}$ −870) shows a substantial decrease in negative amplitude of the lactone band over that of 3. This decrease was also observed on comparison of the CD spectra of 6-deoxyerythronolide B with that of its 3-acetyl derivative.[12]

Oxidation of 4 with Jones reagent yielded the 3-ketone 7 which exhibited a new carbonyl band at 1720 $cm^{-1}$ in the ketone region of the ir spectrum and a molecular ion at $m/e$ 672 in the mass spectrum. Hydrolysis of 7 with sodium bicarbonate in aqueous methanol gave 8.

Our interest in the preparation of compounds 5–8 derived from the fact that other macrolide antibiotics are known with an ester or a ketone function at C-3. For example, magnamycin and spiramycin (16-membered ring

†The configurational notation used in this publication conforms to that used by Celmer.[1,2]



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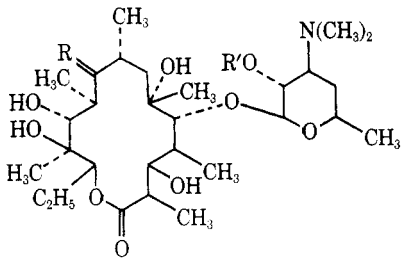
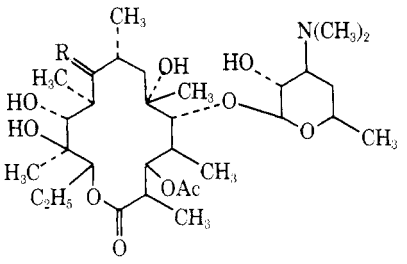
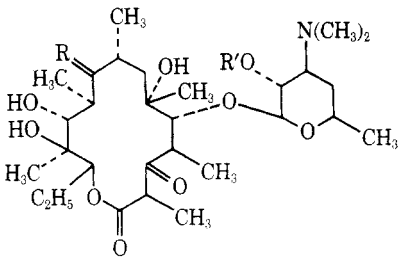


2, R = NOH; R′ = H
3, R = O; R′ = H
4, R = NOAc; R′ = Ac



5, R = NOH
6, R = O



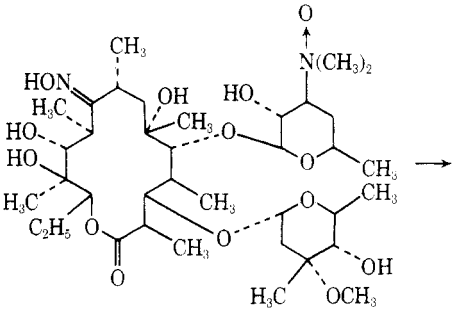
7, R = NOAc; R′ = Ac
8, R = NOH; R′ = H

macrolides) have an ester group at C-3, whereas narbomycin and pikromycin (14-membered ring macrolides) have a C-3 ketone group.

Treatment of **2** under more vigorous acidic conditions did not enable us to cleave desosamine from the macrolide nucleus. The work of Celmer[13] demonstrated that the neutral sugar, resulting from removal of the dimethylamino group from the desosamine moiety of a lactone-opened oleandomycin derivative, could be cleaved under much milder acidic conditions than those needed to cleave a basic sugar. We therefore converted erythromycin oxime **1** to the *N*-oxide **9** by treatment with 3% hydrogen peroxide. Pyrolysis of **9** at 155° without solvent as described by Jones[14] for erythromycin A *N*-oxide gave the 3′-de(dimethylamino)-3′,4′-dehydro derivative **10**. Cleavage of **10** with 3% hydrogen chloride in methanol smoothly removed both sugars and yielded erythronolide A oxime **11** which exhibited a molecular ion at *m/e* 433 in the mass spectrum. Further characterization of **11** was accomplished by heating with acetic anhydride in pyridine to yield the triacetate **12**. The hydroxyls at C-3 and C-5 of erythronolide B are known to be acetylated under these conditions.[15] Compound **12** exhibited three acetyl methyls in the nmr spectrum and a molecular ion at *m/e* 559 in the mass spectrum. Nitrous acid treatment of **11** provided erythronolide A (**13**). The ketone group of **13** absorbs at 1688 $cm^{-1}$ in the ir spectrum and at 290 nm in the uv spectrum. Comparison of the CD spectrum of **13** ($[\theta]_{293}$ −10,600, $[\theta]_{215}$ −3400) with that reported for erythronolide B ($[\theta]_{290}$ −12,200, $[\theta]_{210}$ −4300)[9] demonstrates that the stereochemistry at epimerizable centers has not been altered. The mass spectrum of **13** did not give a molecular ion peak, but instead a peak at *m/e* 400 ($M^+ - 18$) was observed.

**Biological Activity.** *In Vitro* **Activity.** Compounds **3**, **6**, and **7** showed less than 1% the activity of erythromycin A when tested in an *in vitro* agar diffusion assay[16] against *Sarcina lutea* ATCC 9341 and *Bacillus megaterium* ATCC 8011; the remaining compounds were inactive at the maximum level tested, 100 μg/ml. In order to determine whether the structural modifications led to any change in antimicrobial spectrum of the compounds, agar diffusion tests were also carried out using *Escherichia coli* ATCC 27856, *Aerobacter aerogenes* ATCC 27858, *Saccharomyces cerevisiae* ATCC 4426, and *Paecilomyces varioti* ATCC 27857. None of the compounds were active against these organisms at 100 μg/ml.

*In Vivo* **Activity.** The *in vivo* antibacterial activities of compounds **3–7** and **11–13** were determined and compared with the activity of erythromycin A. Mice were infected with 100–1000 MLD's of representative gram-positive and gram-negative bacteria and treated by subcutaneous or



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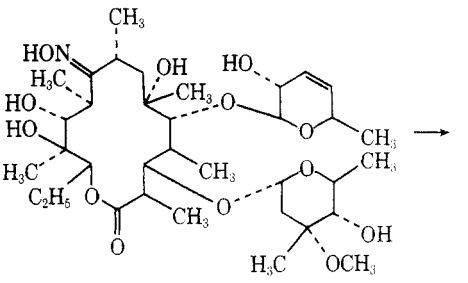

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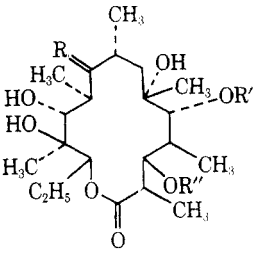

11, R = NOH; R′ = H; R″ = H
12, R = NOAc; R′ = Ac; R″ = Ac
13, R = O; R′ = H; R″ = H

oral administration of the respective substances.[17] As was to be expected, erythromycin A was appreciably active against the gram-positive organisms, *Streptococcus pyogenes* 4 and *Staphylococcus aureus* Smith, but was inactive when tested against the gram-negative rods, *Escherichia coli* 257 and *Proteus mirabilis* 190. Compound **5** was approximately one-tenth as active as erythromycin A when tested orally against *S. pyogenes* ($CD_{50}$'s: 192 and 19 mg/kg po, respectively) but was inactive at the highest dose tested (200 mg/kg po) against *S. aureus* as well as against *P. mirabilis* and *P. aeruginosa*. None of the remaining compounds showed activity against *S. pyrogenes*. No activity was detected when **6** and **7** were tested against *S. aureus*, *P. mirabilis* or *P. vulgaris*, and *P. aeruginosa* or when **3** and **11** were tested against *E. coli*.

The low antibacterial activity of our compounds in the erythromycin A series where one or both sugars have been removed indicates that sugars or sugar-like substituents at the C-3 and C-5 hydroxyls may be essential for activity. Corcoran[18] has discussed the importance of having sugars present in the macrolide antibiotics and has suggested that such compounds act by mimicking subunits of peptidyl-tRNA.

## Experimental Section

All melting points were taken in glass capillaries and are corrected. Ir spectra are in $CHCl_3$ solutions and nmr spectra were determined using a Varian A-60 or HA-100 spectrometer in $CDCl_3$ ($Me_4Si$). The low-resolution mass spectra were run on a CEC 21-110 instrument at 70 eV by direct insertion. CD spectra were obtained using a Jasco recording spectropolarimeter (ORD-CD-UV-5). All extracts were dried over anhydrous $MgSO_4$. Tlc's were done on Brinkmann silica gel plates by first immersing the plate in 15% formamide in acetone and using a solvent system of $CH_2Cl_2$-$C_6H_{14}$-EtOH (60:35:5). The rotations were determined in $CH_3OH$ solution unless otherwise specified.

**5-*O*-Desosaminylerythronolide A Oxime (2).** A solution of 2.0 g of erythromycin A oxime (**1**)[8] in 100 ml of MeOH containing 1% by weight of anhydrous HCl was left at room temperature for 20 hr. Saturated $NaHCO_3$ solution (100 ml) was added and most of the solvent was removed *in vacuo*. After extraction with three 50-ml portions of $CHCl_3$, the extract was washed with two 75-ml portions of 3 *N* HCl to separate the basic product. The combined HCl extract was made basic with 3 *N* NaOH, saturated with NaCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated *in vacuo* to a colorless residue (1.7 g) which could not be crystallized. Tlc showed a single spot slower moving than **1**. The nmr spectrum of crude **2** showed the $NMe_2$ grouping at $\delta$ 2.23 but the -OMe absorption of cladinose was not present. The mass spectrum showed a molecular ion at *m/e* 590.

**5-*O*-Desosaminylerythronolide A (3).** To a solution of 2.000 g (3.4 mmol) of **2** in 80 ml of MeOH was added a solution of 11.7 g (0.17 mol) of $NaNO_2$ in 60 ml of $H_2O$. While cooling this mixture in an ice bath, 170 ml (0.17 mol) of 1 *N* HCl was added dropwise over 1 hr with stirring. The solution was allowed to stand at 3° for 5.5 hr and then made basic with 5% $NaHCO_3$. The MeOH was removed *in vacuo* and the product was extracted with $CHCl_3$. After drying, the extract was concentrated to yield 1.911 g of crude product. Tlc showed mainly a spot moving faster than **2**.

A column was prepared by slurrying 100 g of silica gel with 50 g of $HCONH_2$ and 150 g of $(CH_3)_2CO$. The acetone was removed *in vacuo* and the column was packed using a solvent mixture of 60% $C_6H_{14}$-35% $CH_2Cl_2$-5% EtOH. Chromatography of the crude product using the same solvent mixture for elution gave several fractions containing less polar impurities. Fractions containing pure **3** were then obtained. These fractions were combined and crystallized from $Et_2O$-$C_6H_{14}$ to yield 0.880 g (45% yield) of **3**: mp 188–190°; $\lambda_{max}^{EtOH}$ 289 nm ($\epsilon$ 44); $[\alpha]^{25}D$ −24.5° (*c* 0.95). The ir showed an unresolved band at 1710 $cm^{-1}$. The mass spectrum gave a molecular ion at *m/e* 575. *Anal.* ($C_{29}H_{53}NO_{10}$) C, H, N.

**2′-Acetyl-5-*O*-desosaminylerythronolide A Acetoxime (4).** To 1.255 g of **2** in 50 ml of anhydrous EtOAc was added a solution of 12 ml of $Ac_2O$ and 0.03 ml of 70% $HClO_4$ in 50 ml of anhydrous EtOAc and left at room temperature for 1 hr. The reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* finally with an oil pump to yield a yellow solid. Tlc showed one spot faster moving than **2** along with a minor impurity. Two crystallizations from $CH_2Cl_2$-$Et_2O$ gave 0.780 g (55%) of **4**, mp 141–144°. The nmr spectrum showed acetyl peaks at $\delta$ 2.02 and 2.12 and the $NMe_2$ peak at $\delta$ 2.24; $[\alpha]^{25}D$ −81.6° (*c* 1.03, $CHCl_3$). The molecular ion appeared at *m/e* 674 in the mass spectrum. *Anal.* ($C_{33}H_{58}N_2O_{12}$) C, H, N.

**3-Acetyl-5-*O*-desosaminylerythronolide A Oxime (5).** A solution of 1.00 g (1.5 mmol) of **4** in 20 ml of $C_5H_5N$ and 4 ml of $Ac_2O$ (40 mmol) was heated at 70° for 17 hr under argon. The solvent was removed on the oil pump and the residue was dissolved in EtOAc. After washing the solution with 5% $NaHCO_3$, it was dried and concentrated *in vacuo*. The residue was treated with 10 ml of MeOH and 1 ml of $H_2O$ and heated at reflux for 2 hr. Tlc showed a spot moving slower than **4** along with minor impurities. Water was added to saturation and the product was allowed to crystallize to yield 0.41 g (44%) of pure **5**: mp 247–250°; nmr acetyl at $\delta$ 2.11; $[\alpha]^{25}D$ −13.4° (*c* 0.99). The mass spectrum showed the molecular ion at *m/e* 632. A second crop of 0.10 g, mp 247–249°, was obtained from the filtrate. Recrystallization from the same solvent provided the analytical sample, mp 248.5–250°. *Anal.* ($C_{31}H_{56}N_2O_{11}$) C, H, N.

**3-Acetyl-5-*O*-desosaminylerythronolide A (6).** To 0.385 g (0.61 mmol) of **5** in 20 ml of MeOH was added a solution of 2.1 g (30 mmol) of $NaNO_2$ in 15 ml of $H_2O$. While cooling in an ice bath and stirring, 30 ml (30 mmol) of 1 *N* HCl was added dropwise over 10 min. After standing 5.5 hr at 3°, 25 ml of saturated $NaHCO_3$ was added and the MeOH was removed *in vacuo*. The product was extracted with $CHCl_3$ and the extract was dried and concentrated *in vacuo* to a foam. Tlc showed mainly one spot moving slightly faster than **5**. Silica gel (15 g) was treated with 7.5 g of $HCONH_2$ in 25 ml of $(CH_3)_2CO$ and the $(CH_3)_2CO$ was removed *in vacuo*. Chromatography of the crude product on this treated silica gel gave several fractions of pure **6** on elution with a solvent mixture of $C_6H_{14}$-$CH_2Cl_2$-EtOH (60:35:5). After concentration *in vacuo*, each fraction was dissolved in $CH_2Cl_2$, washed twice with $NaHCO_3$ solution, and dried. The combined pure fractions were crystallized from $Et_2O$-$C_6H_{14}$ to provide 0.096 g (26% yield) of **6**: mp 183–187°; ir 1740 (lactone and acetate) and 1690 $cm^{-1}$ (ketone); nmr acetyl at $\delta$ 2.12; $[\alpha]^{25}D$ −24.70° (*c* 0.59). The mass spectrum showed the molecular ion at *m/e* 617. *Anal.* ($C_{31}H_{55}NO_{11}$) C, H, N.

**2′-Acetyl-5-*O*-desosaminyl-3-oxoerythronolide A Acetoxime (7).** To a stirred solution of 10.00 g (6 mmol) of **4** in 200 ml of $(CH_3)_2CO$ (distilled from $KMnO_4$) cooled in an ice bath was added dropwise 7.5 ml of Jones reagent. After stirring in the ice bath for 30 min, 50 ml of MeOH was added followed by 50 ml of saturated $NaHCO_3$. The mixture was filtered through Celite, the solid was washed with $(CH_3)_2CO$, and the filtrate was concentrated *in vacuo* to remove the $(CH_3)_2CO$. The product was extracted with EtOAc; the extract was dried and concentrated to a solid. Tlc revealed two spots faster moving than **4**. Trituration with $Et_2O$ and cooling provided 5.00 g (50% yield) of **7**: mp 201–203°; ir 1750 (lactone and acetate) and 1720 $cm^{-1}$ (ketone); $[\alpha]^{25}D$ +1.0° (*c* 0.98, $CHCl_3$). The mass spectrum showed the molecular ion at *m/e* 672. The analytical sample, mp 203–206°, was obtained by recrystallization from $CH_2Cl_2$-$Et_2O$. *Anal.* ($C_{33}H_{56}N_2O_{12}$) C, H, N.

**5-*O*-Desosaminyl-3-oxoerythronolide A Oxime (8).** To 0.888 g (1.3 mmol) of **7** in 70 ml of MeOH was added 0.900 g (11 mmol) of $NaHCO_3$ dissolved in 50 ml of $H_2O$. After 3.5 hr at room temperature, the MeOH was removed *in vacuo* and the product extracted with EtOAc. The extract was washed with $H_2O$, dried, and concentrated to a foam. Two crystallizations from MeOH-$H_2O$ gave 0.188 g (24% yield) of pure **8**: mp 117–123°; $[\alpha]^{25}D$ −4.8° (*c* 0.97). The mass spectrum showed the molecular ion at *m/e* 588. *Anal.* ($C_{29}H_{52}N_2O_{10}$) C, H, N.

**Erythromycin A Oxime *N*-Oxide (9).** To 53.6 g (0.07 mol) of erythromycin A oxime (**1**) in 2150 ml of MeOH was added 1300 ml (1.1 mol) of 3% $H_2O_2$ and the solution was left at room temperature for 19 hr. Most of the MeOH was removed *in vacuo* and the crystalline product which separated was filtered and air-dried. Tlc showed a single spot slower moving than **1**. Recrystallization from MeOH-$H_2O$ provided 44.3 g (81% yield) of pure **9**: mp 181–183°; nmr $\delta$ 3.14 (-$NMe_2O$); $[\alpha]^{25}D$ −71.7° (*c* 0.56). *Anal.* ($C_{37}H_{68}N_2O_{14}\cdot H_2O$) C, H, N.

**3′-De(dimethylamino)-3′,4′-dehydroerythromycin A Oxime (10).** The solid *N*-oxide **9** (5.00 g, 6.5 mmol) was pyrolyzed for 3 hr at 155° (0.1 mm) in a slowly spinning flask. Tlc revealed a major spot faster moving than **9** along with two minor impurities. The product was dissolved in MeOH, decolorized with charcoal,

and crystallized from MeOH-$H_2O$ to yield 2.58 g (56% yield) of **10**: mp 155–158°; nmr $\delta$ 5.64 (s, -CH=CH-). The mass spectrum showed the molecular ion at *m/e* 703. *Anal.* ($C_{35}H_{61}NO_{13}$) C, H, N.

**Erythronolide A Oxime (11).** A solution of 22.55 g (0.032 mol) of **10** in 1.5 l. of 3% HCl in MeOH was left at room temperature for 21 hr. The MeOH was removed *in vacuo*, EtOAc was added to the residue, and the solution was washed with dilute $NaHCO_3$. After drying, the solution was stirred briefly with charcoal, filtered, and concentrated to dryness. Tlc revealed a major spot much slower moving than **10**, several minor impurities, and two fast moving spots. Two crystallizations from $(CH_3)_2CO$-$C_6H_{14}$ gave 9.64 g (69% yield) of pure **11**: mp 236–239°; ir 1710 $cm^{-1}$ (lactone). The mass spectrum showed the molecular ion at *m/e* 433. *Anal.* ($C_{21}H_{39}NO_8$) C, H, N.

**3,5-Diacetylerythronolide A Acetoxime (12).** To 0.300 g (0.69 mmol) of **11** dissolved in 6 ml of anhydrous $C_5H_5N$ was added 1.2 ml (12 mmol) of $Ac_2O$ and the solution was heated at 70° for 16 hr. Solvent was removed using an oil pump, and the residue was dissolved in EtOAc and washed with dilute $NaHCO_3$. After drying, the solution was concentrated *in vacuo* to a solid residue. Crystallization from $CH_2Cl_2$-$Et_2O$ provided 0.302 g (77% yield) of pure **12**: mp 234–235°; nmr $\delta$ 2.08, 2.11, and 2.20 (acetyl methyls); $[\alpha]^{25}D$ −51.2° (*c* 0.97, $CHCl_3$). The mass spectrum showed the molecular ion at *m/e* 559. *Anal.* ($C_{27}H_{45}NO_{11}$) C, H, N.

**Erythronolide A (13).** To a solution of 0.303 g (0.7 mmol) of **11** in 15 ml of MeOH was added 2.4 g (35 mmol) of $NaNO_2$ in 10 ml of $H_2O$. After cooling in an ice bath, 35 ml (35 mmol) of 1 *N* HCl was added dropwise with stirring over 15 min. The solution was left at 3° for 5.5 hr and made basic with saturated $NaHCO_3$, and most of the MeOH was removed *in vacuo*. The product was extracted with $CHCl_3$; the extract was dried and concentrated to a foam. Three crystallizations from $(CH_3)_2CO$-$C_6H_{14}$ gave 0.115 g (40% yield) of pure **13**: mp 172–173°; ir 1712 (lactone) and 1688 $cm^{-1}$ (ketone); $\lambda_{max}^{EtOH}$ 290 nm ($\epsilon$ 37). The mass spectrum did not give a molecular ion peak but instead gave a peak for $M^+ - 18$ at *m/e* 400. *Anal.* ($C_{21}H_{38}O_8$) C, H.

**Acknowledgment.** We wish to thank the following members of our physical chemistry department: Dr. W. Benz, Dr. V. Toome, Mr. S. Traiman, and Dr. T. Williams for the mass, ultraviolet, infrared, and nmr spectra, respectively. Thanks are also due Dr. F. Scheidl for the microanalyses. It is a pleasure to acknowledge the encouragement of Dr. A. Brossi throughout the course of this work.

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# "Hantzsch-Type" Dihydropyridine Hypotensive Agents. 3[1]

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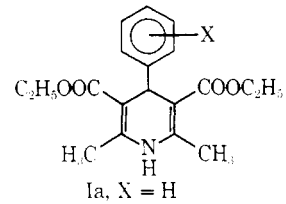
A variety of Hantzsch-type dihydropyridines and related compounds have been prepared in the course of a structure–activity study of these potent hypotensive agents. The biological activity of one of these compounds (Ib) is described. This compound may be exerting its cardiovascular effects through a direct action on vascular smooth muscle. In comparative tests with hydralazine, a clinically used vasodilator, the effects of hydralazine tended to decrease over the treatment period, whereas Ib did not show this same tendency.

The discovery in the 1930's that a dihydropyridine (NADH, a dihydronicotinamide derivative) was a "hydrogen-transferring coenzyme" and consequently of utmost importance in biological systems[2,3] has generated numerous studies of the *biochemical* properties of dihydropyridines. However, there have been relatively few studies of the *pharmacological* activities of such compounds. At the time this work was initiated, the only such reports described weak analgesic and curare-like properties.[4] Consequently, we undertook to evaluate some of these compounds, in particular the "Hantzsch-type" dihydropyridines,[5,6] in a number of standard test systems. Subsequent to our work, antitumor[7] and coronary dilating activities have been reported[8] for certain dihydropyridines.

Early in our studies compound Ia was found to be very potent in producing marked hypotension of long duration (more than 17 min) when administered intravenously to the anesthetized animal. However, it had essentially no activity when administered orally, even at high doses. This paper summarizes the study of structural parameters which was undertaken to determine which features were necessary for activity and which features were necessary for *oral* activity.

Most of the dihydropyridines (Table I) were prepared




Ia, X = H
b, X = 2-$CF_3$