STRUCTURAL INVESTIGATION OF THE ANTIBIOTIC RISTOMYCIN A
THE AMINO ACID CONSTITUENTS

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Hydrolysis of the O-methylated aglycone of ristomycin A by a mixture of KOH and $NaBH_4$ yielded a mixture of aromatic amino acids which, after N-acetylation and O-methylation, were separated by chromatography on silica gel. Compounds **III～VII** were isolated and identified by pmr and mass spectroscopy. Compounds **V～VII** were also oxidatively degraded to the corresponding benzoate esters. Compounds **III** and **IV** are derived from ristomycinic acid (**I**) and **V** from actinoidinic acid (**II**), both of which had been obtained in earlier acid hydrolyses of the antibiotic. Compounds **VI** and **VII** had not been detected previously nor glycine which was also found to be a product of base hydrolysis. It is postulated that the new products arise from bisdechlorovancomycinic acid (**X**). It is concluded that aglycoristomycin A comprises **I**, **II** and **X** which also constitute the aglycone of ristocetin A.

The glycopeptide ristomycin was isolated[1] in 1963 from the culture of *Proactinomyces fructiferi* var. *ristomycini* and has been shown to belong to the vancomycin group of antibiotics.[2] The antibiotic is highly effective against Gram-positive microorganisms[3]; moreover, it has recently found use in hematology—similar to ristocetin—for diagnosis of VON WILLEBRAND's disease.[4]

Ristomycin A contains a branched tetrasaccharide[5,6,7], O-β-D-arabinopyranosyl-(1→2)-O-α-D-mannopyranosyl-(1→2)-O-[α-L-rhamnopyranosyl-(1→6)]-D-glucopyranose, an additional molecule of mannose, and the amino sugar ristosamine, 3-amino-2,3,6-trideoxy-L-*ribo*-hexopyranose.[8,9,10] The glycosidic linkages to the peptide have not been investigated.

The peptide portion of the antibiotic has been shown to contain two unusual binuclear aromatic amino acids, ristomycinic acid[11] and actinoidinic acid,[12] which are released by acid hydrolysis of ristomycin A or its aglycone. The structure of ristomycinic acid (**I**) has been established by KATRUKHA *et al.*[13] and by HARRIS *et al.*[14] Some uncertainty remains as to the structure of actinoidinic acid; based on a mass spectroscopic study, KATRUKHA *et al.*[13] have proposed structure **II**, identical to that of a constituent of vancomycin,[15] but evidence that the two compounds have the same arrangement of substituents has not yet been obtained.

In this report we describe our studies of the base hydrolysis of ristomycin A. These studies serve to confirm the proposed structure of actinoidinic acid and reveal the presence of a hitherto unrecognized third component of the aglycone, a trinuclear compound (**X**) which is destroyed under both acidic and basic hydrolysis conditions.

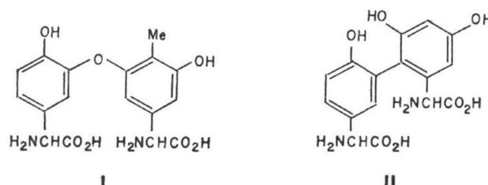

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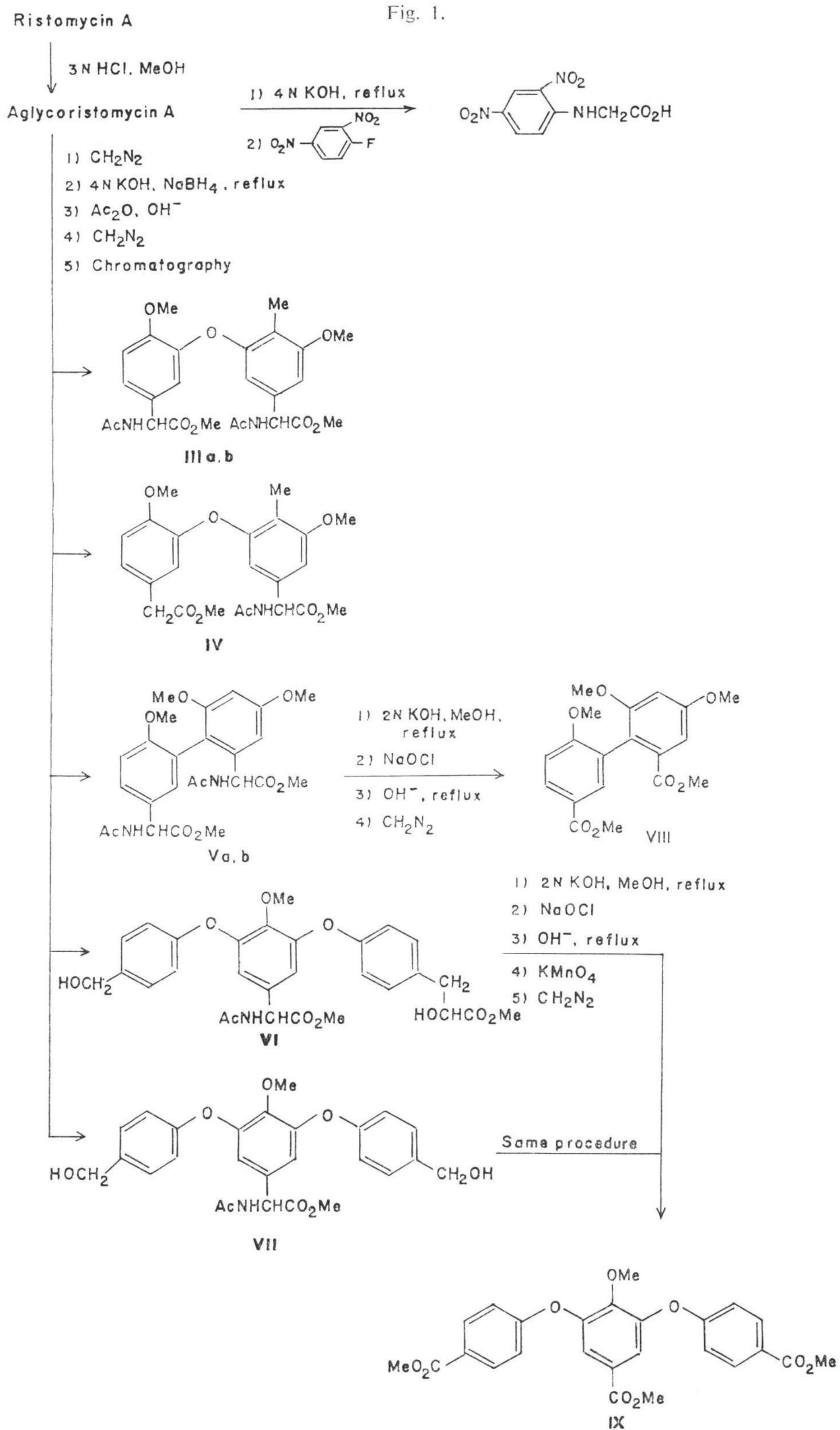
Fig. 1.



Aglycoristomycin, prepared by methanolysis of ristomycin A by the method of BOGNÁR *et al.*[8,11b], was methylated with a large excess of CH_2N_2; the O-methylated aglycone was hydrolyzed in refluxing aqueous KOH-$NaBH_4$*. Similar reaction conditions have been used by SMITH *et al.*[15] in a study of vancomycin and by HARRIS *et al.*[16] in a study of ristocetin A. The hydrolysis products were acetylated (Ac_2O, pH 9) and methylated (CH_2N_2 in MeOH). The resulting O-methylated, N-acetylated amino acid esters were partitioned on silica gel using a combination of open-column chromatography and high pressure liquid chromatography (HPLC) to give compounds **III**~**VII** (Fig. 1).

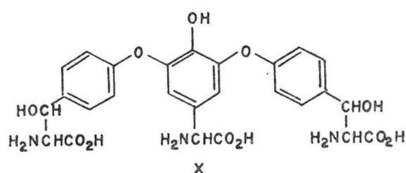
Compound **III** derived from ristomycinic acid (I) was isolated in two diastereoisomeric forms (**a** and **b**). The more mobile one (**IIIa**) is identical with correspondingly protected ristomycinic acid; **IIIb** arises by epimerization during base hydrolysis. A desamino derivative of ristomycinic acid was also isolated. Structure **IV** is provisionally assigned to the compound; the origin of **IV** is presently under investigation.

Compound **V** derived from actinoidinic acid, was also isolated in two diastereoisomeric forms (**a** and **b**). The mass spectra of **Va** and **b** confirmed the empirical formula which had been assigned to actinoidinic acid by KATRUKHA *et al.*[13] It should be noted that **III** and **V** have the same empirical formula but can be distinguished readily by analysis of the pmr spectra. The pmr spectra of **Va** and **b** show a 5: 2 ratio of OMe to $COCH_3$ groups, supporting the proposal that the phenylglycine moieties are joined via a biphenyl linkage. Oxidative degradation of a mixture of **Va** and **b** by a sequence involving base hydrolysis of ester and amide bonds, oxidation of the amino acids with NaOCl, hydrolysis with KOH, and esterification with CH_2N_2 gave diester **VIII**, which was identical with an authentic sample prepared by HARRIS *et al.*[16] using an unambiguous route involving an ULLAMANN coupling reaction. This sequence establishes the structure of actinoidinic acid derived from ristomycin A.

Finally, the chromatographic separation yielded **VI** and **VII**. Neither these nor any other triaryl compound has been detected in acid hydrolysates of ristomycin. The structures of **VI** and **VII** were indicated by pmr and mass spectra. Simplicity of the spectrum of **VII** dictated a symmetrical arrangement of substituents in the bis(aryloxy)benzene system. Oxidative degradation of **VII** (base hydrolysis, NaOCl oxidation, base hydrolysis, $KMnO_4$ oxidation, and CH_2N_2 esterification) gave trimethylester **IX**. The pmr spectrum of **IX** was of particular value in establishing the orientation of substituents. The aromatic protons on the central ring are identical, falling at δ 7.63. The flanking aromatic rings are also identical and produce a well-defined A_2X_2 pattern with the protons ortho to the CO_2Me group falling at δ 8.03 and the protons ortho to the oxy linkage at δ 7.12. The pmr spectrum of **VI** had many similarities to that of **VII** but contained signals at δ 3.12 and 4.48 of chemical shift, area and multiplicity consistent with an α-hydroxy phenylpropionate fragment. The alternative β-hydroxy formulation is considered unlikely because it could not be expected to have withstood the conditions of base hydrolysis. Oxidative degradation of **VI** also yielded triester **IX**. The structure of **IX** was established by comparison with an authentic sample which had been prepared by HARRIS *et al.*[16] by condensation of methyl *p*-hydroxybenzoate with methyl 3,5-dibromo-4-methoxybenzoate. Another

* Supplementation of basic hydrolyses with $NaBH_4$ is frequently used in studies of glycoproteins containing carbohydrate-serine or -threonine linkages. See: MARSHALL, R. D. & A. NEUBERG: Aspects of the structure and metabolism of glycoproteins. Adv. Carbohydr. Chem. & Biochem. (*ed.* by R. S. TIPSON & D. HORTON) 25: 407~478, 1970, and LINDBERG, B.; J. LÖNNGREN & S. SVENSSON: Specific degradation of polysaccharides. Adv. Carbohydr. Chem. & Biochem. (*Ed.* by R. S. TIPSON & D. HORTON) 31: 185~240, 1975.

product of base hydrolysis of aglycoristomycin is glycine, which was isolated as the N-(2,4-dinitrophenyl) derivative. Glycine is not present in acid hydrolysates, indicating that the amino acid *per se* is not a constituent of the antibiotic. We postulate that **VI**, **VII** and glycine arise from a tris (amino acid), bisdechlorovancomycinic acid (**X**). During base hydrolysis, retro-aldol cleavage of both β-hydroxytyrosine fragments in **X** followed by reduction of the resulting aryl aldehydes by $NaBH_4$ leads to **VII** and glycine. Compound **VI** apparently arises when one of the β-hydroxytyrosines of **X** undergoes dehydration, followed by deamination and reduction.



Ristomycinic acid (**I**), actinoidinic acid (**II**), and bisdechlorovancomycinic acid (**X**) appear to be the sole constituents of aglycoristomycin A. Amino acid analysis has indicated the molecular weight of the aglycone to be 1,200~1,300[17], which corresponds well to the calculated molecular weight (1,159) for heptapeptides comprised of the above three compounds. The small discrepancy may reflect entrapment of water or other solvent in the aglycone.

The aglycone of ristocetin A contains the same three complex amino acids[16]. In the present study, the structures of **IIIa** and **b**, **IV**, **Va** and **b**, **VI**, **VII**, **VIII** and **IX** were confirmed by comparison with the corresponding materials obtained from base hydrolysis of the protected aglycone of ristocetin A. It seems likely that the two antibiotics have the same peptide sequence, and it is, in fact, possible that the antibiotics themselves are identical. NIETO and PERKINS[18] have summarized many points of physicochemical similarity between the two compounds and have concluded that they are identical or nearly identical, which is supported by the similarity of the peptide constituents. Further investigations of the peptide and carbohydrate portions of the two compounds will be required to resolve this question.

Experimental

Melting points were determined on a Kofler hot stage apparatus or in open capillaries and are uncorrected. PMR spectra were recorded with JEOL MH-100 and FX-90Q spectrometers. Mass spectra were obtained with an LKB 9000 spectrometer. Open column chromatography was carried out on silica gel (60) HF-254 (Merck) using for development the following solvent systems: (A) $CHCl_3$ - MeOH (98: 2) and (B) CH_2Cl_2 - MeOH (95: 5). High pressure liquid chromatography was carried out on a Waters Associates system with UV detector using a 61-cm μ-Porasil column and the following solvent systems: (C) CH_2Cl_2 - MeOH (99: 1), (D) CH_2Cl_2 - MeOH (97: 3), and (E) CH_2Cl_2 - MeOH (96: 4). Analytical and preparative TLC were performed on precoated silica gel (Merck) 60F-254 and F-254 plates, respectively, using the following solvent mixtures. (F) $CHCl_3$ - MeOH (95: 5), (G) $CHCl_3$ - MeOH (9: 1), (H) $CHCl_3$ - MeOH (1: 1), (I) EtOAc - heptane (3: 7), (J) EtOAc - pentane (1: 3), and (K) EtOAc - pentane (1: 2).

O-Methylated Aglycoristomycin

Aglycoristomycin was prepared by methanolysis of ristomycin A with 3 N methanolic hydrochloric acid in a sealed ampoule at 105°C for 5 hours. Aglycoristomycin (1.30 g, 1 mmol) was dissolved in 40 ml of 70% acetone and treated with excess (5~8 mmol) of CH_2N_2 at room temperature for 24 hours. After filtration, the solution was concentrated to dryness at 30°C *in vacuo*. O-Methylated aglycone (1.20 g, 87%) was obtained as a light yellow, amorphous solid after washing the residue with water and drying. The UV spectrum of material dissolved in ethanol showed a maximum at 280 nm, unaltered by the addition of NaOH.

Base Hydrolysis of Methylated Aglycoristomycin

A mixture of O-methylated aglycoristomycin (660 mg, 0.50 mmol) and $NaBH_4$ (2.0 g) in 4 N KOH (30 ml) was refluxed for 23 hours under N_2. The light yellow solution was cooled, adjusted to pH 9 with 6 N HCl (17 ml) and treated with Ac_2O (6.0 ml) and 4 N KOH (15 ml) added dropwise alternately. After standing at ambient temperature for 2 hours, the solution was acidified to pH 1 with 6 N HCl (16 ml) and extracted 4 times (3×20 and 1×10 ml) with EtOAc - MeOH (9:1). The extracts were combined, dried ($MgSO_4$), and evaporated to dryness. The residue (599 mg) was dissolved in MeOH (10 ml) and treated with excess CH_2N_2 (1 hour, 20°C). The solvents were evaporated; the residue was dissolved in 1 ml of $CHCl_3$ - MeOH (95:5) and chromatographed on a 30 g silica gel column (10×3 cm) with 200 2-ml fractions being collected (flow rate: 2 ml/0.5 hr). The initial fractions were eluted with solvent mixture A. After the 58th fraction the eluant was changed to solvent mixture B. The fractions were pooled on the basis of analytical TLC using solvent F.

Fractions 36~45 (71.6 mg) contained compound **IV** which was further purified by preparative TLC (solvent G) and then by HPLC (solvent C): PMR ($CDCl_3$) δ 2.06 (s, 3H, $COCH_3$), 2.19 (s, 3H, C-CH_3), 3.58 (s, 2H, CH_2), 3.76, 3.78, 3.91 and 3.96 (4s, 12H, OCH_3's), 5.60 (d, 1H, J=8 Hz, α-CH), 6.60~7.46 (m, 6H, arom and NH); MS *m/e* 445 (M^+, 95), 413 (95), 402 (100), 386 (83).

Fractions 55~78 (62.5 mg) contained mainly **IIIa** and **Va** which were separated in pure form by HPLC using solvent D; **Va** was more mobile than **IIIa**.

Compound **IIIa**: mp 61~65°C (Kofler); PMR ($CDCl_3$) δ 2.04 (s, 6H, $COCH_3$'s), 2.15 (s, 3H, C-CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 6H, OCH_3's), 5.47 (m, 2H, α-CH's), 6.18~6.95 (m, 7H, arom and NH's); MS *m/e* 502 (M^+, 33), 470 (33), 459 (66), 443 (33), 401 (100). Compound **Va**: mp 80~83°C (Kofler); PMR ($CDCl_3$) δ 2.09 and 2.13 (2s, 6H, $COCH_3$'s), 3.62, 3.69, 3.77, 3.81, and 3.87 (5s, 15H, OCH_3's), 5.41 (d, 2H, J=8 Hz, α-CH's), 6.45~7.73 (m, 7H, arom and NH's); MS *m/e* 502 (M^+, 29), 470 (47), 459 (59), 443 (59), 401 (100).

Fractions 93~113 (50.5 mg) contained mainly **IIIb** which was purified by HPLC using solvents D and E: mp 73~75°C (Kofler); PMR ($CDCl_3$) δ 1.99 (s, 6H, $COCH_3$'s), 2.11 (s, 3H, C-CH_3), 3.72 and 3.75 (2s, 6H, OCH_3's), 3.87 (s, 6H, OCH_3's), 5.42 (d, 2H, J=8 Hz, α-CH's), 6.37~6.97 (m, 7H, arom and NH's): MS *m/e* 502 (M^+, 29), 470 (59), 459 (88), 443 (41), 401 (100).

Fractions 140~147 contained **Vb** (10.5 mg) which was essentially homogeneous by TLC: mp 74~78°C (Kofler); PMR ($CDCl_3$) δ 1.90, 1.92, 2.00 and 2.03 (4s, 6H, $COCH_3$'s),* 3.56, 3.60, 3.69, 3.72, 3.78 and 3.85 (7s, 15H, OCH_3's), 5.40 (m, 2H, α-CH's), 6.52~7.32 (m, 7H, arom and NH's); MS *m/e* 502 (M^+, 50), 470 (82), 459 (100), 443 (55), 401 (82).

Fractions 157~159 (43.9 mg) contained compound **VI**: mp 67~69°C (Kofler); PMR ($CDCl_3$) δ 2.00 (s, 3H, $COCH_3$), 3.12 (m, 2H, $\underline{CH_2}$CHOH), 3.73, 3.78 and 3.80 (3s, 9H, OCH_3's), 4.48 (t, 1H, J=5 Hz, $CH_2C\underline{H}OH$), 4.62 (s, 2H, $\underline{CH_2}$OH), 5.48 (d, 1H, J=8 Hz, $C\underline{H}$NHAc), 6.66~7.44 (m, 11H, arom and NH); MS *m/e* 553 (M^+, 50), 535 (12), 521 (43), 510 (69), 503 (56), 494 (56), 493 (63), 452 (100).

Fractions 166~200 (80.2 mg) contained compound **VII**: mp 59~60°C (Kofler); PMR ($CDCl_3$) δ 1.95 (s, 3H, $COCH_3$), 3.68 and 3.76 (2s, 6H, OCH_3's), 4.60 (s, 4H, $\underline{CH_2}$OH), 5.42 (d, 1H, J=6 Hz, $C\underline{H}$NHAc), 6.82 (s, 2H, arom), 6.97 (d, 4H, J=10 Hz, arom), 7.33 (d, 4H, J=10 Hz, arom). The amide NH appeared as a broad peak superimposed on the aromatic region. MS *m/e* 481 (M^+, 54) 463 (45), 449 (100), 438 (100), 421 (100).

Oxidative Degradation of V

A mixture of **Va** and **b** (18 mg) was hydrolyzed in 50% methanolic 2 N KOH (2 ml) for 3.5 hours. The methanol was evaporated *in vacuo*, the residue was dissolved in H_2O (3 ml), and the pH adjusted to 10~11 with concentrated HCl. A 5% solution (0.5 ml) of NaOCl (Clorox) was added in portions at room temperature. After 3 hours, the pH of the solution had not changed significantly. The

* The presence of two pairs of acetyl signals is ascribed to hindered rotation around the biphenyl linkage creating a third center of asymmetry in the molecule. Thus, fully racemized actinoidinic acid exists in four forms. In the study of ristocetin[16], **Vb** was resolved by HPLC into two narrowly separated fractions, the less mobile of which still contained more than one form as evidenced by multiple acetyl and methoxyl peaks.

reaction was monitored periodically by the starch-iodine test and by TLC in solvent J (nitrile Rf: 0.25). The excess NaOCl was destroyed with Na_2SO_3, 4 N KOH (1 ml) was added, and the mixture was refluxed for 14 hours. After cooling, the mixture was acidified to pH 1 with conc.HCl and extracted (2×10 ml) with CH_2Cl_2 - EtOAc (1:1) and (1×10 ml) with Et_2O - EtOAc (1:1). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue (5.0 mg, 37%), dissolved in MeOH (1.5 ml), was treated with ethereal CH_2N_2 for 14 hours. The product was purified by analytical TLC in solvent system K to give crystalline diester **VIII**: (1.5 mg): mp 144~145°C (Kofler); Rf 0.31 (solvent K); PMR ($CDCl_3$) δ 3.56, 3.70, 3.77, 3.86, 3.87 (5s, 15H, OCH_3's), 6.70~7.25 (m, 3H, arom), 7.68~8.05 (m, 2H, arom); MS *m/e* 360 (M^{+}, 100), 329 (72). Synthetic **VIII**: mp 143~144.5 °C (Kofler); Rf 0.31 (solvent K).

Oxidative Degradation of **VI** and **VII**

Compound **VII** (69.9 mg) was hydrolyzed with refluxing 50% methanolic 2 N KOH (2 ml) for 3 hours. After the evaporation of methanol *in vacuo*, the product was treated with 5% NaOCl (0.45 ml) and then hydrolyzed with refluxing 4 N KOH as described above. The hydrolysate was adjusted to pH 7.5~8 with conc.HCl and oxidized further with 5% $KMnO_4$ (10 ml) at room temperature for 3 hours. Excess $KMnO_4$ was destroyed with Na_2SO_3. The mixture was filtered, acidified with 2 N H_2SO_4 to pH 2, and extracted with Et_2O (3×10 ml). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give 31.5 mg (51%) of the triacid of **IX**, mp 143~144°C. Treatment with excess CH_2N_2 in Et_2O - EtOAc (1:1) gave **IX** in quantitative yield: mp 64~65°C; Rf: 0.71 (solvent I); PMR (d_6-acetone) δ 3.79 and 3.85 (2s, 6H, OCH_3's), 3.87 (s, 6H, OCH_3's), 7.12 (d, 4H, J=8.8 Hz, arom), 7.63 (s, 2H, arom), 8.03 (d, 4H, J=8.8 Hz, arom); MS *m/e* 466 (M^{+}, 100), 435 (38). Synthetic **IX**: mp 67°C; Rf 0.71 (solvent I).

Oxidative degradation of **VI** in like manner gave a low yield of **IX**. The compound was compared with the synthetic sample by TLC, Rf: 0.70 (solvent I).

Base Hydrolysis of Aglycoristomycin and Isolation of DNP-Glycine

Aglycoristomycin (260 mg, 0.2 mmol) was hydrolyzed in refluxing 4 N KOH (15 ml) for 20 hours under N_2. After cooling, the hydrolyzate was adjusted to pH 10 with conc.HCl (5 ml) and treated with 2,4-dinitrofluorobenzene (300 mg in 6 ml of EtOH) for 2 hours at room temperature. The precipitate was removed by filtration. The solution was extracted with Et_2O (2×15 ml), acidified to pH 1 and extracted again with Et_2O (2×15 ml). The latter extracts were combined, washed with water, dried ($MgSO_4$), and concentrated to give crude DNP-glycine (55.1 mg, 57%) which was purified by preparative TLC (solvent H). Recrystallization from 50% MeOH gave 15.6 mg of DNP-glycine: mp 198~201°C (dec); Rf 0.11 (solvent H); PMR (d_6-acetone) 4.54 (br s, 2H, CH_2), 7.39 (d, 1H, J=9 Hz, arom), 8.59 (d×d, 1H, J=9×3 Hz, arom), 9.28 (d, 1H, J=3 Hz, arom); MS *m/e* 241 (M^{+}, 25), 196 (100), 150 (12). Lit.:[19] mp 203°C (dec). Authentic DNP-glycine: Rf 0.15 (solvent H).

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