+5000, $[\theta]_{333}$ +52,500, $[\theta]_{324}$ +4970; ultraviolet, λ_{max}^{EtOH} 244–246 mμ (log ε 4.11), 300–304 (log ε 2.18); infrared, λ_{max}^{KBr} 2.82, 6.0, and 6.19 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.94; H, 9.73.

Registry No.—II, 13396-30-0; IIIb, 13341-86-1; IIIc, 13341-87-2; IIId, 13341-88-3; IV, 13319-96-5; V, 13341-89-4; VI, 13396-31-1; VII, 13428-11-0.

Acknowledgments.—We wish to express our gratitude to Dr. A. D. Cross for his help and advice in the interpretation of the nmr spectra.

The Structure of Resistomycin

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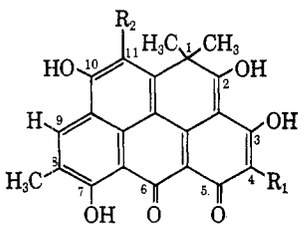
Resistomycin was isolated by Brockmann and Schmidt-Kastner[1] from *Streptomyces resistomycificus* in 1951. The partial structure of this gram-positive antibiotic was established by Brockmann and coworkers[2-5] as a methyl-2,3,7,10-tetrahydroxy-1,1-dimethyl-6H-benzo[*c*,*d*]pyrene-5(1H),6-dione. Only the position of the aromatic methyl group remains to be determined.

The nuclear magnetic resonance (nmr) spectrum of resistomycin (Figure 1, in concentrated deuteriosulfuric acid) is entirely consistent with the proposed structure (see structure **1**). The C-1 *gem*-dimethyl group exhibits two superposed 3-proton singlets at 131.5 cps. Superposition of these signals establishes that the methyl groups are equidistant from the plane of the ring and confirms the expectation of a highly aromatic ring system. The unassigned aromatic methyl group shows a 3-proton singlet at 204 cps. Three 1-proton singlets at 438, 466, and 475.5 cps are attributed to the aromatic protons. The absence of coupling between the latter protons locates the aromatic methyl group (204 cps) at position 8 or 9 (structure **1**). After 20 hr



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = Cl$
3, $R_1 = Br$; $R_2 = H$

in deuteriosulfuric acid, the protons exhibiting signals at 475.5 and 438 cps underwent complete deuterium exchange, while the 466-cps signal was essentially unchanged. Deuterium exchange of the 438-cps proton occurs at two to three times the rate observed for that of the 475.5-cps proton.

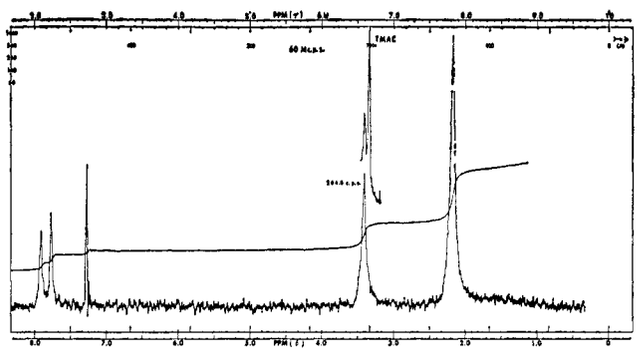


Figure 1.—Nmr spectrum of resistomycin (10% in concentrated deuteriosulfuric acid) after 5 min in solution with tetramethylammonium chloride as internal standard.

Since acid catalyzed deuterium exchange of aromatic protons was observed to follow electrophilic substitution,[6] the exchange-resistant 466-cps signal is assigned to a proton at the 9 position. This position is a *meta* position relative to both the C-7 and C-10 phenolic hydroxyl groups and would not be expected to undergo electrophilic substitution or, consequently, deuterium exchange. The aromatic methyl substituent of resistomycin must, therefore, be assigned to the 8 position.

Halogenation of resistomycin verifies the presence of only two aromatic protons susceptible to electrophilic substitution. Only a dichloro derivative (**2**) was obtained, whose aromatic proton (a 1-proton singlet at 476 cps, 10% in deuteriosulfuric acid) did not undergo perceptible deuterium exchange and whose C-1 methyl groups were deshielded by 20 cps (a 6-proton singlet at 152 cps). A paramagnetic shift of this magnitude can only be explained by chlorination at the 11 position, which results in a close spatial relationship of the C-1 methyl protons with the chlorine atom. The second chlorine substituent must be assigned to the 4 position by logical elimination of the 8 and 9 positions. Bromination yielded only a monobromo derivative (**3**) which exhibited an exchangeable 1-proton singlet at 475.5 cps and a second unexchangeable 1-proton singlet at 468.5 cps. The bromine substituent had no effect on the chemical shift of the C-1 methyl groups (132 cps) and was therefore assigned to the 4 position. Molecular models demonstrate that bromine would encounter considerably more steric hindrance from the C-1 methyl groups than would chlorine during substitution at the 11 position. These data corroborate the assignment of the 466-cps signal in the nmr spectrum of resistomycin to a proton at the 9 position and enable the 438- and 475.5-cps signals to be assigned to protons at positions 4 and 11, respectively.

Brockmann,[5] on the basis of unspecified reflection on the biogenesis of resistomycin, has tentatively assigned the aromatic methyl group to the 9 position. Deuterium exchange of the aromatic protons, nmr spectra, and the failure to derive a perchlororesistomycin dictate assignment of the aromatic methyl group of resistomycin to the 8 position (**1**).

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(3) H. Brockmann and G. Schmidt-Kastner, *ibid.*, **87**, 1460 (1954).
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Experimental Section[7]

Resistomycin (1).—Resistomycin was isolated from cultures of an unidentified actinomycete (Abbott M10782) and crystallized from acetone as yellow needles (mp >300°; sublimes near 210° at 50 μ of Hg): ultraviolet absorption, λ_{max} 268 mμ (ϵ 24,000), 290 (23,000), 320 (14,400), 337 (13,900), 366 (11,000), 457 (15,400).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29; O, 25.50; mol wt 376.4. Found: C, 69.72; H, 4.37; O, 25.86.

4,11-Dichlororesistomycin (2).—Resistomycin (2.5 g, 6.8 mmoles) was suspended in 2 l. of glacial acetic acid and chlorine (1.5 g, 21 mmoles) dissolved in 50 ml of glacial acetic acid was added over a period of 15 min at room temperature. The mixture was stirred vigorously for 1 hr, then cooled and filtered. Yellow micro needles were washed with distilled water and triturated with hot acetone (yield 2.3 g, 76% of theory). Thin layer chromatography on silica gel G developed with chloroform–ethanol (9:1, v/v) showed a single spot with R_f 0.35: ultraviolet absorption, λ_{max} 220 mμ (ϵ 65,000), 273 sh, 293 (56,000), 310 sh, 370 (19,000), 523 (29,000).

Anal. Calcd for $C_{22}H_{14}Cl_2O_6$: C, 59.35; H, 3.17; Cl, 15.92; O, 21.56; mol wt, 445.2, Found: C, 59.59; H, 3.58; Cl, 15.48; O, 21.56.

4-Bromoresistomycin (3).—Finely divided resistomycin (1 g, 2.7 mmoles) was suspended in 1 l. of glacial acetic acid and bromine (1.3 g, 8.1 mmoles) dissolved in 150 ml of glacial acetic acid was added with vigorous stirring under a nitrogen atmosphere and in the dark over a period of 30 min. The temperature of the reaction mixture was raised to 80° over a period of 3 hr, residual bromine was then removed with a nitrogen sweep, and the solution slowly cooled to 20°. Bright yellow micro needles were harvested, washed with distilled water, and triturated with hot acetone (yield 0.95 g, 78% of theory). Thin layer chromatography on silica gel G developed with chloroform–ethanol (9:1, v/v) showed a single component with R_f 0.69 (resistomycin, 0.76): ultraviolet absorption, λ_{max} 218 mμ (ϵ 48,200), 270 (26,500), 291 (24,800), 326 (13,800), 338 sh (12,500), 370 (10,300), 429 (14,200).

Anal. Calcd for $C_{22}H_{15}BrO_6$: C, 58.04; H, 3.32; Br, 17.55; O, 21.09; mol wt, 455.3. Found: C, 58.17; H, 3.18; Br, 18.15; O, 21.04.

Registry No.—1, 13341-63-4; 2, 13318-35-9; 3, 13421-94-8.

Acknowledgment.—Appreciation is expressed to various members of Abbott Laboratories who contributed to this work. The interest and advice of Dr. M. Levenberg is especially acknowledged as is the excellent technical assistance of Mr. R. E. Carney.

(7) Microanalyses were performed by O. Kolsto, Scientific Services Laboratories, Abbott Laboratories, and ultraviolet absorption spectra were taken in methanol solution. Nmr spectra were taken with a Varian A-60 spectrometer at 36° in concentrated deuteriosulfuric acid using tetramethylammonium chloride as internal standard (200 cps relative to tetramethylsilane).

Orientational Effects in the Addition of Acetylthiolsulfenyl Chloride to Olefins

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Our recent work on the mechanism of sulfenyl chloride additions to unsaturates[2-4] indicated that the structures of both the olefin and the sulfenyl chloride influence the ratio of electronically *vs.* sterically controlled ring opening of the episulfonium ion intermediate. It was, therefore, of interest to study the electron-withdrawing effect of an acetyl group on the relative charge distribution in the episulfonium ion.

Earlier workers found[5] that the addition mechanism of acetylthiosulfenyl chloride departs from the usual ring opening of the episulfonium ion intermediate. The chloride ion attacks the carbonyl rather than the ring carbon of the intermediate, forming acetyl chloride and propylene episulfide which undergoes further reaction with acetylsulfenyl chloride.

The reaction of acetylthiosulfenyl chloride (CH_3-C(=O)SSCl) with styrene, ethylene, and cyclohexene has been found by previous workers[5,6] to follow the normal addition mechanisms. No attempt was made to study adduct orientation factors, although this reagent appears to be a convenient probe to test the steric *vs.* electronic factors influencing the reaction. To determine these factors, acetylthiosulfenyl chloride was added to several selected olefins. Propylene, isobutylene, and 3,3-dimethylbutene were chosen to study the influence of alkyl substituents with increasing substituent bulkiness. Styrene, butadiene, and piperylene were selected as electronically more biased substrates. Acenaphthylene was used to determine the stereochemical course of the addition.

Acetylthiosulfenyl chloride was added under anhydrous conditions to a solution of the unsaturate in methylene chloride generally at −15 to −20°. The methylene chloride solution contained a small amount of calcium carbonate to prevent possible postisomerization of the adducts.[2] In the case of dienes, a fivefold excess of the unsaturate was used in order to ensure monoaddition. The reaction is exothermic and takes place very rapidly during the addition of the sulfenyl chloride. Conversions of >95% were obtained in each case. With the exception of the adducts of styrene and acenaphthylene, analytical samples were obtained by fractional distillation *in vacuo* as pale yellow liquids (Table I).

The relative amounts of isomeric adducts could be deduced from nmr analysis of the crude product mixtures. In general, protons α to chlorine are considerably deshielded relative to those α to sulfur.[3,7] A similar difference was observed in the chemical shift of methyl group protons β to chlorine and sulfur, respectively. The relative intensities of the two types of methyl signals were of considerable assistance in computing isomer ratios. A detailed compilation of the nmr parameters for each adduct is given in Table II.

Propylene.—The addition of acetylthiosulfenyl chloride to propylene afforded 40% of the Markovnikov adduct I and 60% of the anti-Markovnikov adduct II[8] (eq 1). The product mixture was analyzed quantitatively by the intensities of the characteristic nmr signals of the methyl groups β to either chlorine or sulfur. The methyl group β to chlorine in I is a doublet

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(8) In the present paper, Markovnikov orientation indicates adducts with the chlorine on a secondary or tertiary carbon atom while anti-Markovnikov adducts have the chlorine on the terminal carbon.