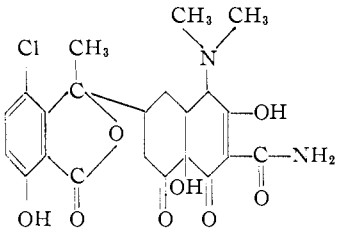
DEGRADATION OF AUREOMYCIN. VI. ISOAUREOMYCIN AND AUREOMYCIN

Sir:

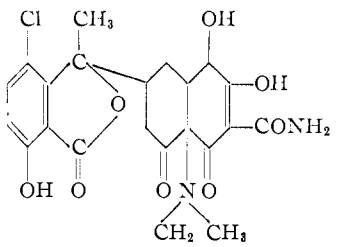
When aureomycin is dissolved in dilute alkali and allowed to stand for twenty-four hours at room temperature, isoaureomycin, I, m.p. 195–197°, and 248–250° as the hydrochloride,[1] $[\alpha]^{25}D$ −94° (dilute hydrochloric acid), *anal.* Calcd. for $C_{22}H_{23}NClO_8 \cdot HCl$: C, 51.26; H, 4.66; N, 5.44; Cl, 13.79. Found: C, 51.29; H, 4.91; N, 5.29; Cl, 13.88, is formed.

The infrared and ultraviolet absorption spectra of I establishes the presence of the phthalide nucleus. Alkaline hydrolysis[2] indicates the presence of the carboxamide grouping. The two acid functions of I have *pKa* values of 6.8 and 8.1, respectively. The latter value is due to the 7-hydroxyphthalide. When the ultraviolet absorption spectra of the phthalide nucleus are subtracted from the spectra of I, a chromophore similar to that in aureomycinic acid[3] is found to be present. The diketone bands in the 6–7 μ region of the infrared spectra again substantiates the conclusions from the *pKa* and ultraviolet data that a cyclic β-diketone structure exists in I. In addition, an absorption band at 5.80–5.85 μ is present. The absorption in this region is typical of a non-conjugated ketone of a cyclohexanone.[4]

When isoaureomycin subsequently reacts with 5 *N* sodium hydroxide in the presence of sodium hydrosulfite, α-aureomycinic acid is formed. This reaction involves a ketonic hydrolysis and causes the formation of a carboxyl group from the non-conjugated β-diketone of I. Since the central carbon atom of the hydrolyzed β-diketone is completely substituted, isoaureomycin has structures II or III.



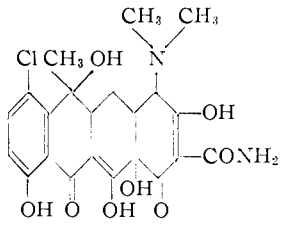
II



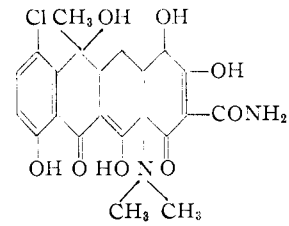
III

The infrared absorption spectrum of aureomycin[5,6] showed no absorption bands between 5 and 6 μ which not only eliminates the presence of a phthalide structure but also excludes the presence of a non-conjugated ketonic group. The formation of isoaureomycin involves the alkaline cleavage of a carbon to carbon bond of an enolizable β-diketone to form a carboxyl group which subsequently lactonizes to give a phthalide. The remaining ketonic group of the original β-diketone is now not capable of forming a conjugated system.

Since there are only two possible structures for isoaureomycin, aureomycin must have structure IV or V.



IV



V

(1) The compound reported by A. C. Dornbush, J. J. Oleson, A. L. Whitehill and B. L. Hutchings, *Proc. Soc. Exptl. Biol. Med.*, **76**, 676 (1951), when dried over boiling toluene lost water of hydration.

(2) S. Olesen, *Die Chemie*, **56**, 202 (1943).

(3) B. L. Hutchings, C. W. Waller, R. W. Broschard, C. F. Wolf, P. W. Fryth and J. H. Williams, THIS JOURNAL, **74**, 4980 (1952).

(4) Cyclopentanones absorb from 5.70–5.75 μ.

(5) B. M. Duggar, U. S. Patent 2,482,055 (1949).

(6) Analytical data obtained subsequent to the preliminary values reported by R. W. Broschard, *et al.*, *Science*, **109**, 2826 (1949), are: *Anal.* Calcd. for $C_{22}H_{23}N_2ClO_8 \cdot HCl$: C, 51.26; H, 4.66; N, 5.44; Cl, 13.79. Found: C, 51.12; H, 4.75; N, 5.39; Cl, 13.75.

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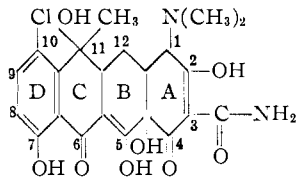
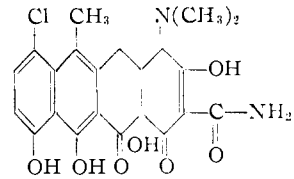
DEGRADATION OF AUREOMYCIN. VII.[1] AUREOMYCIN AND ANHYDROAUREOMYCIN

Sir:

The existence of a naphthacene nucleus in Aureomycin I has been postulated.[2]



Aureomycin I



Anhydroaureomycin II

Substituents and the nature of rings D and A have been rigorously established with the one exception the 1-dimethylamino and the 4a-hydroxyl groups may be reversed (the acidity of I would not allow the dimethylamino group to be on carbon 2 or 4).

Ring C of aureomycin is further established by dehydration and aromatization. In concentrated hydrochloric acid at 60° for thirty minutes I is converted in excellent yields to anhydroaureo-

(1) The data in this series of papers was presented at the Medicinal Section of the Gordon Research Conferences, New London, N. H., on August 20, 1952.

(2) (VI) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. W. Broschard, and J. H. Williams, THIS JOURNAL, **74**, 4981 (1952).

mycin II, m.p. 220–235° (dec.), *pKa* 5.5 and 8.5, $[\alpha]^{25}D$ + 16° (in cellosolve), *anal.* Calcd. for $C_{22}H_{21}N_2ClO_7$: C, 57.32; H, 4.56; N, 6.08; Cl, 7.70. Found: C, 57.30; H, 4.62; N, 5.81; Cl, 8.02.

The infrared absorption spectrum of II shows no bands from 5 to 6 μ (amide carbonyl at 6.0 to 6.1 μ) thus eliminating the presence of a phthalide, other lactones, and any non-conjugated ketonic groups. The ultraviolet absorption spectra in 0.1 *N* sodium hydroxide exhibits maxima at 230 (*E* 25,500), 272 (*E* 37,200), 345 (*E* 6,440) and 445 mμ (*E* 11,000) and in 0.1 *N* hydrochloric acid at 227 (*E* 26,500), 277 (*E* 44,000) and 445 mμ (*E* 8,250).

The aromatization of ring C by the loss of the water is not only shown by spectral changes but also by the failure of the compound to form 5-chlorosalicylic acid on alkali fusion (all previously discussed C_{20} and C_{22} compounds do give 5-chlorosalicylic acid) yet ring D is found to be unaffected since on alkaline peroxide oxidation 5-chloro-6-acetylsalicylic acid is obtained.

Dimethylamine and ammonia (with loss of carbon dioxide) are eliminated from II as from other C_{22} compounds.

It is unlikely that rings B and A are affected since optical activity persists after the acid treatment.

When 48% hydriodic acid is used in lieu of hydrochloric acid for the elimination of water from I there is produced deschloroanhydroaureomycin (III), m.p. 225–226° (dec.), *pKa*'s 6.0 and 8.6 $[\alpha]^{25}D$ +24° (in cellosolve), *anal.* Calcd. for $C_{22}H_{22}N_2O_7$: C, 62.00; H, 5.15; N, 6.57. Found: C, 61.88; H, 5.36; N, 6.02. Anhydroaureomycin, II, also forms III on heating with hydriodic acid.

The absorption spectra and chemical properties of II and III are very similar.

Since the removal of the chlorine atom from II changed only its first *pKa* (5.5 to 6.0), this acid function is represented by the 1,8-dihydroxynaphthalene portion of the molecule.

Not only is ring C established as a six-membered ring but also the steric relationship of the hydroxyl group at carbon 11 and the hydrogen at carbon 11a is indicated to be *trans*.

Ring B of aureomycin cannot be seven membered. Each carbon of ring A in aureomycinic acid carries at least one substituent. The γ-butyric acid group must be *para* to the carboxamide and the closing of ring B to form a seven-membered ring would then involve one of the ketonic carbons. Such an involvement would destroy the acidity of the β-diketones of ring A.

The infrared spectra of iso-aureomycin shows a band at 5.80 to 5.85 μ which demands a six rather than a five membered ring for B.

The difficulty of eliminating dimethylamine or water from the A and B rings suggests that the dimethylamino group at 1 (or 4a) the hydroxyl group at carbon 4a (or 1) and the hydrogen at carbon 12a may be a *cis,cis*-configuration. The relationship of the configuration at carbons 11 and 11a to those at carbons 1, 4a and 12a cannot be stated at this time.

Further work is in progress to establish unequivocally the position of the dimethylamino group in aureomycin.

The independent and quite dissimilar methods of proof of structure for aureomycin and terramycin[3] tend to substantiate the structures of these two compounds.

(3) F. A. Hochstein, *et al.*, THIS JOURNAL, **74**, 3708 (1952).

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BOOK REVIEWS

The Enzymes. Chemistry and Mechanism of Action. Volume II, Part 1 and Part 2. By JAMES B. SUMNER, Laboratory of Enzyme Chemistry, Cornell University Ithaca, New York, and KARL MYRBACK, Institute for Organic Chemistry and Biochemistry, University of Stockholm, Sweden (Editors). Academic Press, Inc., 125 E. 23rd Street, New York 10, N. Y. Part 1—1951. Pages xi + 790. 16.5 × 23.5 cm. Price, $14.80. Part 2—1952. Pages xi + 791–1440. 16.5 × 23.5 cm. Price, $14.00.

Reviews of Volume I, Parts 1 and 2 of this encyclopedic presentation of the important aspects of the chemistry and mechanism of action of the enzymes appeared recently in THIS JOURNAL [**74**, 284 (1952)]. Volume II, Parts 1 and 2, composed of thirty-five chapters, has now appeared. This comprehensive survey of the present knowledge in this field is now complete in two volumes, four parts, seventy-eight chapters, 1743 pages. Each chapter is on a well defined specific topic and is written by one of the seventy-five authorities who contributed to the work.

Volume II continues the same high quality of organization and presentation as shown previously. Although the reviews naturally reflect to some extent the individuality of the respective writers, there is a remarkable degree of uniformity and a minimum of unessential repetition for a work shared by so many individuals. The editors have unquestionably fulfilled their aim expressed in the introduction to the first volume "to gather and sift available knowledge and present it in an orderly fashion," for the use of those interested in advancing the field of enzymology. Time was ripe for undertaking this tremendous task. The available information in this field has become too extensive for even an expert to obtain it from the original literature; the number interested in enzymes has expanded far beyond biochemistry into all the allied fields in chemistry and biology, and the subject, while still changing rapidly, has reached a stage sufficiently definitive to be summarized on a broad basis.

These volumes, as was pointed out by a previous reviewer, will be valuable not only for reference but as a source of in-