tablishes the structure of I as 3,4-dihydroxy-2,5-dioxocyclopentane-1-carboxamide (VIII).

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RECEIVED SEPTEMBER 15, 1952

DEGRADATION OF AUREOMYCIN. IV. DESDIMETHYLAMINOAUREOMYCINIC ACID

Sir:

The formation of β-(4-chloro-7-hydroxy-3-methylphthalide-3)-glutaric acid, I, and 3,4-dihydroxy-2,5-dioxocyclopentane-1-carboxamide, II, from desdimethylaminoaureomycinic acid, III, has been described.[1] In this "Communication" sufficient additional chemical data are presented for the structural formulation of III.

Desdimethylaminoaureomycinic acid, III, contains a phthalide nucleus as shown by the lactone band in the infrared spectra at 5.7 μ and by its ultraviolet absorption spectra before and after methylation. The presence of a free carboxyl group is apparent from the formation of the half ester of I on methylation and oxidation of III. A carboxamide grouping is shown by the formation of ammonia and carbon dioxide on hydrolysis of III with 1 *N* sodium hydroxide in ethylene glycol.[2] Furthermore, the ready elimination of carbon dioxide indicates this position to be activated.

The *pKa*'s of 6.4, 7.8 and 10.2 of III allows for the assignment of the carboxylic acid and the 7-hydroxyl of the phthalide to the *pKa*'s of 6.4 and 7.8, respectively, while the 10.2 value might be a polyhydroxylated benzene ring. The acidity of II (*pKa* 2.65) definitely excludes this structure in III.

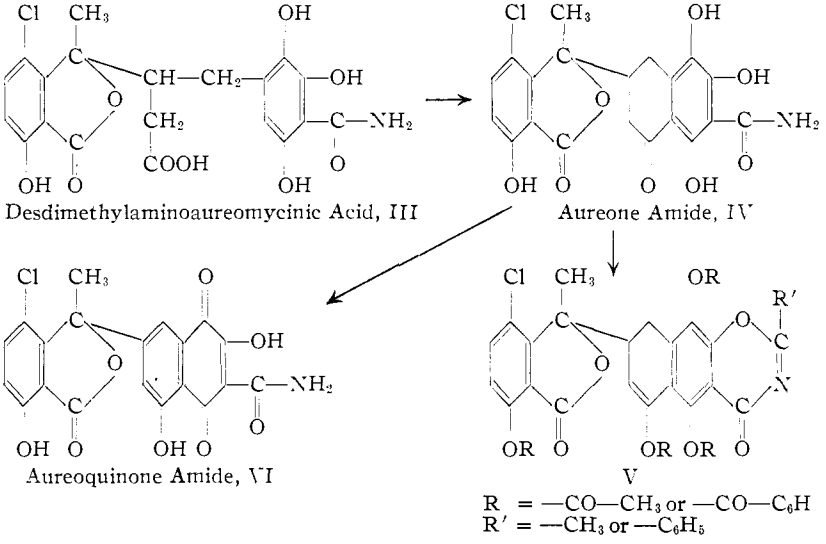
The subtraction of the ultraviolet absorption spectra of I from the spectra of III gives a remaining chromophore comparable to that of a 2,6-dihydroxybenzoic acid (dihydrocitrinin). Thus, the structure of I must contain a 2,6-dihydroxybenzamide further substituted with a hydroxyl group and with the γ-(β-[4-chloro-7-hydroxy-3-methylphthalide-3])-butyric acid radical.

When III is dehydrated with heat or sulfuric acid, aureone amide, IV, m.p. 295–305° (dec.), $[\alpha]^{25}D$ +24.6° (methyl cellosolve), *anal.* Calcd. for $C_{20}H_{16}NClO_8$: C, 55.35; H, 3.71; N, 3.25; Cl, 8.17; C—CH_3, 3.43. Found: C, 55.31; H, 4.11; N, 3.18; Cl, 7.97; C—CH_3, 3.41, is obtained. Acetylation or benzoylation of IV results in penta acylation with the loss of the elements of water. This acylation allows for the presence of three hydroxyl groups, an enolizable ketone and oxazine formation between one hydroxyl and the carboxamide group (Structure V). The presence of the ketonic group is also established by the formation of a 2,4-dinitrophenylhydrazone. Furthermore, the spectra of IV show this ketone to be conjugated with an existing chromophore.

Methylation of IV yields a methyl ether in the 7 position of the phthalide. This methylated compound (and IV) forms a stable crystalline diborate complex indicating the presence of two pairs of adjacent hydroxyl groups (or *peri* positions of a naphthalene type) in the non-phthalide portion of the molecule.

On air oxidation in 5*N* sodium hydroxide aureone amide is aromatized to aureoquinone amide, VI, m.p. 142–148°, *anal.* Calcd. for $C_{20}H_{12}NClO_8$: C, 55.81; H, 2.79; N, 3.26; Cl, 8.25. Found: C, 55.31; H, 3.15; N, 3.02; Cl, 8.15. The ultraviolet absorption spectra and *pKa* values of VI identify the compound as a 2-hydroxy-1,4-naphthoquinone.

Aureone amide on hydrolysis[2] yields aureone, VII, m.p. 296–300 (dec.), $[\alpha]^{25}D$ +19° (in ethanol), *anal.* Calcd. for $C_{19}H_{15}ClO_7$: C, 58.39; H 3.84; Cl, 9.09. Found: C, 58.16; H, 4.08; Cl, 9.04. Spectra studies and the formation of a mono 2,4-dinitrophenylhydrazone of aureone establish the presence of a ketonic group. Reduction of this ketone gives a product which has the same ultraviolet absorption spectra as a composite sample of I and 1,2,4-trihydroxybenzene.



The data allow the exact assignment of structure to III, IV and VI. The arrangement of the hydroxyl groups in the terminal benzene ring are in the 1,2,4-positions as shown by the spectra of reduced aureone and by the formation of a 2-hydroxy-1,4-naphthoquinone. The identification of II and the spectral characteristics of III and VI places the carboxamide at the 3 position. The cyclization of III to IV and the formation of a diborate complex of the ether of IV requires the arrangement in the dihydronaphthalene system of IV to be a 1,2,4,5-tetrahydroxy-7,8-dihydronaphthalene-3-carboxamide.

(1) C. W. Waller, B. L. Hutchings, C. F. Wolf, R. W. Broschard, A. A. Goldman, and J. H. Williams, THIS JOURNAL, **74**, 4978 (1952).
(2) S. Olesen, *Die Chemie*, **56**, 202 (1943).

The data further require that the benzamide nucleus of III have the three hydroxyl groups at the 2, 3 and 6 positions with the γ-(β-[4-chloro-7-hydroxy-3-methylphthalide-3])-butyric acid radical at position 4. Position 5 is free for ring closure in the formation of IV.

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RECEIVED SEPTEMBER 15, 1952

DEGRADATION OF AUREOMYCIN. V. AUREOMYCINIC ACID

Sir:

When aureomycin is treated with 5 *N* sodium hydroxide containing a reducing agent, α- or β-aureomycinic acid, I, is formed. With sodium hydrosulfite and a reaction time of 2.5 hours at room temperature α-aureomycinic acid, m.p. 225–230° for the hydrochloride, $[\alpha]^{25}D$ +54° (dilute hydrochloric acid), *anal.* Calcd. for $C_{22}H_{25}N_2ClO_9 \cdot HCl$: C, 49.53; H, 4.88; N, 5.25; Cl, 13.32; C-CH_3, 2.82. Found: C, 49.38; H, 5.20; N, 5.34; Cl, 13.58; C-CH_3, 2.54, is obtained. If the reaction time is increased to four days, β-aureomycinic acid, m.p. 174–185° (dec.) for the hydrochloride, $[\alpha]^{25}D$ −10.2° (dilute hydrochloric acid), *anal.* Calcd. as for the α-isomer. Found: C, 49.60; H, 5.62; N, 5.23; Cl, 13.35, is isolated. The β-isomer also results if zinc dust is used in lieu of hydrosulfite and the reaction mixture is heated for two hours on the steam-bath.

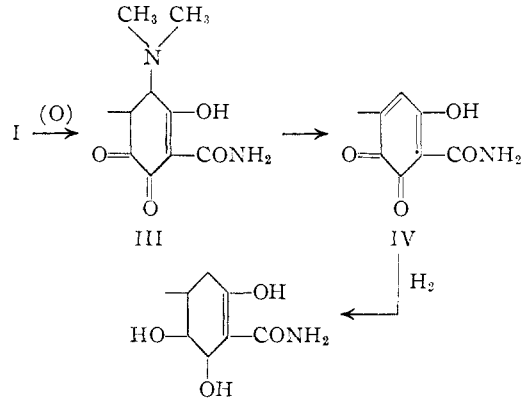
A free carboxyl group in I is indicated by the facile formation of a monoester, *anal.* Calcd. for $C_{21}H_{24}N_2ClO_7COOCH_3 \cdot HCl$: OCH_3, 5.66. Found: OCH_3, 5.11, with methanolic hydrogen chloride. The preparation of the monomethyl ester monomethyl ether, II, of I with diazomethane or methsulfate and sodium carbonate and the subsequent oxidation of II to the half ester of β-(4-chloro-7-methoxy-3-methylphthalide-3)-glutaric acid confirms the presence of a carboxyl group in I.

The lactone band at 5.7 μ in the infrared spectra of I establishes the presence of the phthalide nucleus. Similarly, the ultraviolet absorption spectra of I and II clearly show the presence of a phthalide moiety.

The titration curve of I, in addition to showing the acid functions due to the carboxyl and 7-hydroxyphthalide, demonstrates the presence of an acid function of *pKa* 7.2.

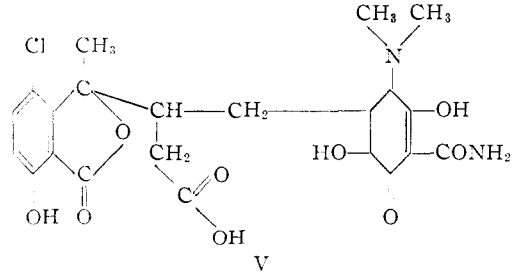
Subtraction of the ultraviolet absorption spectra of β-(4-chloro-7-methoxy-3-methylphthalide-3)-glutaric acid from those of I, gives spectra with absorption maxima at 282 mμ (*E* 15,500) in 0.1 *N* sodium hydroxide and at 267 mμ (*E* 15,400) in 0.1 *N* hydrochloric acid. The spectra of this added chromophore compares favorably with those of dimedone which has maxima at 282 mμ (*E* 23,700) in 0.1 *N* sodium hydroxide and at 260 mμ (*E* 14,000) in 0.1 *N* hydrochloric acid, except the extinction coefficient of dimedone in alkali is greater. The molecular extinction coefficient in alkaline solution is decreased when a carboxamide group is located on the central carbon of a β-diketone system.[1] The presence of this added chromophore and the acidic function at *pKa* 7.2 suggests that an isolated cyclic β-diketone is present in I. The infrared bands in the 6 to 7 μ region substantiate this conclusion.

When aureomycinic acid, I, is further treated with 5 *N* sodium hydroxide (in the absence of reducing agents), dimethylamine and desdimethylaureomycinic acid is formed. This elimination of dimethylamine with the introduction of a double bond readily explains the formation of the aromatic group, 2,3,6-trihydroxybenzamide, of desdimethylaminoaureomycinic acid.[2] The placing of dimethylamine in the 5 position of the cyclohexanedione ring makes possible the β-elimination of this group when a trace of oxygen forms the α-diketone, III, from I.



The final step in the reaction shows the *o*-quinone, IV, acting as a hydrogen acceptor for the oxidation of another molecule of I. If more than a trace of oxygen is present, further changes are initiated.

The formulation of the structure of aureomycinic acid as V is consistent with the chemical and physical data.



Aureomycinic Acid

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RECEIVED SEPTEMBER 5, 1952

(1) For comparison of 1,3-cyclopentanedione with that of 3,4-dihydroxy-2,5-dioxocyclopentane-1-carboxamide see C. W. Waller, B. L. Hutchings, C. F. Wolf, R. W. Broschard, A. A. Goldman and J. H. Williams, THIS JOURNAL, **74**, 4978 (1952).

(2) C. W. Waller, B. L. Hutchings, A. A. Goldman, C. F. Wolf, R. W. Broschard and J. H. Williams, *ibid.*, **74**, 4979 (1952).