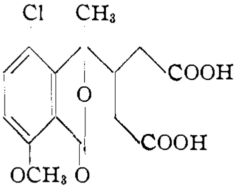
of IV yields 4-chloro-7-hydroxy-3-methylphthalide (VI), m.p. 101–103°, while pyrolysis of V yields 7-hydroxy-3-methylphthalide (VII).[6] Further evidence for the similarity of the two terminal ring systems in aureomycin and in Terramycin is provided by the virtual identity of the difference curves obtained by the subtraction of the ultraviolet absorption of VI from that of IV, and VII from V.

All eight oxygens in aureomycin have now been placed and, therefore, in addition to the substitution of a chlorine atom at C_{16}, aureomycin differs from Terramycin by the absence of a hydroxyl group at C_{12}.[7] These deductions are supported by the recently described isolation of the acid (VIII) from aureomycin by methylation, followed by permanganate oxidation.[5]



VIII

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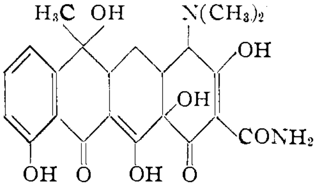
(6) F. Hochstein and R. Pasternack, THIS JOURNAL, **73** 5008 (1951).

(7) Common to both Terramycin and aureomycin is the structure A for which we propose the name tetracycline. Terramycin has, therefore, been assigned the generic name oxytetracycline.



A

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R. B. WOODWARD

RECEIVED AUGUST 8, 1952

HYDROLYSIS OF CONDENSED PHOSPHATES

Sir:

The ever-increasing importance of condensed phosphates and other polyelectrolytes to science and industry combined with the inadequacies and misconceptions of the published data on phosphate hydrolyses necessitated the initiation of a fundamental research program in this field. Some of the findings in the program are presented below. These results will be discussed more fully in a forthcoming paper.

Condensed phosphates hydrolyze in aqueous solutions to yield less condensed phosphates and ultimately pure orthophosphate. The rate of hydrolysis is dependent upon the temperature, *p*H, concentration of phosphate,[1–5] and ionic environment. The ionic environment may affect the rate by complexing with the phosphate and by forming an ionic atmosphere about the phosphate.[6,7]

Condensed phosphates are believed not to form complexes with tetramethylammonium ions. We have hydrolyzed tetramethylammonium tripoly- and pyrophosphates in solutions of ten per cent. tetramethylammonium bromide and in water.[7] Sodium tripoly- and sodium pyrophosphates have also been hydrolyzed in sodium bromide solutions of the same ionic strength as the tetramethylammonium bromide solutions. The *p*H of these solutions was continuously controlled to ±0.1 *p*H unit at *p*H 1, 4, 7, 10, or 13, whereas the temperatures were held at 30, 60, 90 or 125°. In every case the concentration of the solution was adjusted to give one per cent. of orthophosphate ion on complete hydrolysis.

The degradations from tripoly to pyro and from pyro to ortho were found to follow a first-order law. Although Watzel,[3] in agreement with other authors, finds a minimum rate for the hydrolysis of sodium tripolyphosphate at *p*H 10, our results show that the rate of hydrolysis of tetramethylammonium phosphate in 10% tetramethylammonium bromide solution continuously decreases with increase in *p*H from 1 to 13.

The temperature dependence of the first-order rate constant, k, in hr.^{-1} for the conversion from tripoly- to pyrophosphate can be given by the equation: $k = Ae^{-E/RT}$ where A is the frequency factor and E is the activation energy. The variation of these quantities with *p*H is given in Figs. 1 and 2.

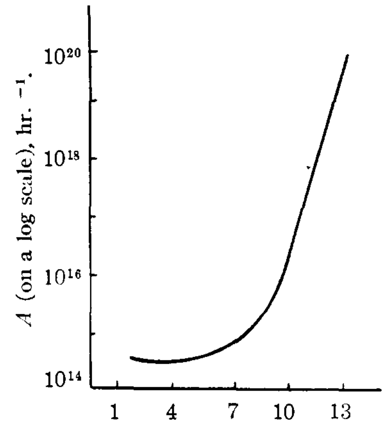

Fig. 1.—Frequency factor for hydrolysis of 1% tetramethylammonium tripolyphosphate in 10% tetramethylammonium bromide solution as a function of *p*H.

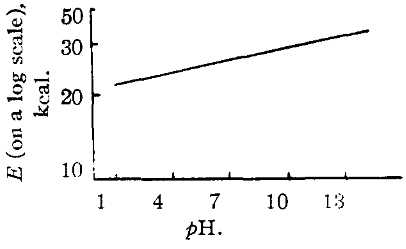

Fig. 2.—Activation energy for hydrolysis of 1% tetramethylammonium tripolyphosphate in 10% tetramethylammonium bromide solution as a function of *p*H.

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(1) J. Muus, *Z. physik. Chem.*, **159A**, 268 (1932).

(2) S. J. Kiehl and E. Claussen, THIS JOURNAL, **57**, 2284 (1935).

(3) R. Watzel, *Die Chemie*, **55**, 356 (1942).

(4) R. N. Bell, *Ind. Eng. Chem.*, **39**, 136 (1947).

(5) L. M. Postnikov, *Ser. Fiz-Mat. Estest. Nauk*, **3**, 63 (1950).

(6) J. Green, *Ind. Eng. Chem.*, **42**, 1542 (1950).

(7) J. R. Van Wazer, THIS JOURNAL, **72**, 639 (1950).

An ionic atmosphere of tetramethylammonium bromide decreases the rate of hydrolysis in both acidic and basic solutions. Thus, at 90° the tripoly-to-pyro rate constant in $hr.^{-1}$ decreases from 0.46 to 0.37 at *p*H 4 and from 0.0172 to 0.0158 at *p*H 10 on adding ten per cent. of tetramethylammonium bromide to the tetramethylammonium tripolyphosphate solution. This is added proof that the hydrolyses of pyro- and tripolyphosphates are not catalyzed by hydroxyl ions.

As would be expected from complex formation, it was found that substitution of tetramethylammonium ion by sodium ion increases the rate of hydrolysis, and this increase is intensified by the presence of excess sodium. For example, at 90° and *p*H 7 the tripoly-to-pyro constants in $hr.^{-1}$ are, for sodium ion, 0.192 and 0.152, and, for tetramethylammonium ion, 0.108 and 0.147, with the first number in each group corresponding to the presence of 0.6 *N* bromide of the respective cation and the second to a pure solution without swamping electrolyte.

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RECEIVED JULY 31, 1952

DEGRADATION OF AUREOMYCIN. III. 3,4-DIHYDROXY-2,5-DIOXOCYCLOPENTANE-1-CARBOXAMIDE

Sir:

The isolation and identification of dimethylamine and β-(4-chloro-7-hydroxy-3-methylphthalide-3)-glutaric acid as degradation products of aureomycin have been outlined.[1] Reported herein is the isolation and characterization of a $C_6H_7NO_5$ compound, I.

These degradation products thus account for the carbon, chlorine and nitrogen of the original molecule.

When aureomycin is treated with 5 *N* sodium hydroxide, desdimethylaminoaureomycinic acid, m.p. 210–212°, *anal.* Calcd. for $C_{20}H_{18}NClO_9$: C, 53.26; H, 4.04; N, 3.15; Cl, 7.86. Found: C, 52.83; H, 4.32; N, 2.99; Cl, 7.59, and dimethylamine are formed. The former compound is an optically active ($[\alpha]^{25}D$ + 100° (in methanol)), tribasic, monocarboxylic acid with *pKa*'s of 6.4, 7.8 and 10.2.

On air (or oxygen) oxidation in *N* sodium hydroxide desdimethylaminoaureomycinic acid cleaves to yield β-(4-chloro-7-hydroxy-3-methylphthalide-3)-glutaric acid and a $C_6H_7NO_5$ monobasic acid, I, (*pKa* 2.65) m.p. 198–200° (dec.), *anal.* Calcd. for $C_6H_7NO_5$: C, 41.63; H, 4.05; N, 8.09. Found: C, 41.78; H, 4.19; N, 8.26. The bulk of the C_6 acid is isolated as a *dl* compound but the residual crops have a specific rotation of −65°. The product forms ketonic derivatives, crystalline basic salts, a triacetate (isolated as a pyridine or sodium salt), but no carboxylic acid derivatives. The compound exhibits an ultraviolet absorption spectra characteristic of a cyclic β-diketone with maxima at 252 mμ (*E* 22,500) in 0.1 *N* sodium hydroxide and at 247 mμ (*E* 17,200) in 0.1 *N* hydrochloric acid.

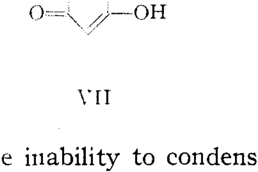
On refluxing I with hydriodic acid and red phosphorus a mole of ammonia and carbon dioxide is evolved, and a $C_5H_6O_2$ monobasic acid, II (*pKa* 4.5), m.p. 151–152° is isolated, *anal.* Calcd. for $C_5H_6O_2$: C, 61.22; H, 6.12. Found: C, 61.33; H, 6.56. This latter product was identified as 1,3-cyclopentanedione by oxidation to succinic acid and by a positive iodoform reaction. The compound has a characteristic ultraviolet absorption spectrum with maxima at 257 mμ (*E* 29,400) in 0.1 *N* sodium hydroxide and 242 mμ (*E* 20,700) in 0.1 *N* hydrochloric acid.

When I is heated in 48% hydrobromic acid, a mole of ammonia and carbon dioxide is evolved and a $C_5H_4O_3$ monobasic acid, III (*pKa* 3.0), m.p. 172.5–173° (dec.) is formed, *anal.* Calcd. for $C_5H_4O_3$: C, 53.6; H, 3.57. Found: C, 53.56, H, 3.90. The ultraviolet absorption spectra are characterized by maxima at 310 mμ (*E* 13,450) in 0.1 *N* sodium hydroxide and at 267 mμ (*E* 10,850) in 0.1 *N* hydrochloric acid. The compound was identified as 1,2,4-cyclopentanetrione by a positive iodoform reaction and by formation of an *o*-phenylenediamine derivative. Reduction of III with zinc and hydrochloric acid gives 4-hydroxy-1,3-cyclopentanedione, IV. This product and III can be converted to 1,3-cyclopentanedione by treatment with hydriodic acid and phosphorus. The synthesis[2] of II and III unequivocally proved their assigned structures.

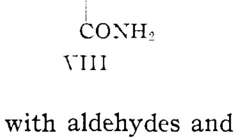
When the pyridine salt of the triacetate of I is refluxed with acetic anhydride, a descarboxamido triacetate, $C_5H_3\overset{\|}{O}(OCOCH_3)_3$, V, is formed. The acetyl groups are removed by dilute acid hydrolysis to yield a monobasic acid, $C_5H_6O_4$, VI, m.p. 153–154°, *anal.* Calcd. for $C_5H_6O_4$: C, 46.2; H, 4.62. Found: C, 46.77; H, 4.84, positive iodoform reaction. This acid is also obtained from barium hydroxide hydrolysates of I. On refluxing V or VI with hydrobromic acid or hydriodic acid and phosphorus III and II are formed, respectively.

The ultraviolet and infrared spectra and the chemical characteristics of the $C_5H_6O_4$ compound (VI) are consistent with its formulation as 4,5-dihydroxy-1,3-cyclopentanedione.

Structures VII or VIII are therefore possible for the $C_6H_7NO_5$ compound.



VII



VIII

The inability to condense I with aldehydes and the marked stability of I to alkaline hydrolysis[3] es-

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[1] B. L. Hutchings, C. W. Waller, S. Gordon, R. W. Broschard, C. F. Wolf, A. A. Goldman, and J. H. Williams, THIS JOURNAL, **74**, 3710 (1952).

[2] J. H. Boothe, R. G. Wilkinson, S. Kushner and J. H. Williams, to be published.

[3] The stability of I is analogous to the stability of C-acetyl dimedone to alkaline cleavage, A. J. Birch, *J. Chem. Soc.* 3026 (1951).