20-dione acetate VII, m.p. 190–191°. *Anal.* Found: C, 69.87; H, 7.68. Acid hydrolysis of VII gave *dl*-11-dehydrocorticosterone 21-acetate, m.p. 154°; 166–168°; free *dl*-11-dehydrocorticosterone,[5] m.p. 173–179°. *Anal.* Found: C, 72.97; H, 8.11.

dl-Cortisone acetate,[5] m.p. 240–245° (*anal.* Found: C, 68.89; H, 7.47) was prepared from *dl*-VII by the same route; *dl*-20-cyanhydrin, dec. 220–225°; *dl*-unsaturated nitrile, m.p. 181–183°; *dl*-3-ethylenedioxy-Δ^5-pregnene-17α,21-diol-11,20-dione acetate, dec. 247–252°.

Acknowledgment.—The authors wish to express their indebtedness to Dr. J. van de Kamp, Mr. W. Paleveda, and Mr. R. Gasser, for the preparation of materials.

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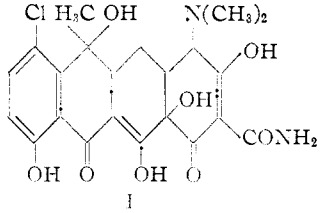
RECEIVED SEPTEMBER 20, 1952

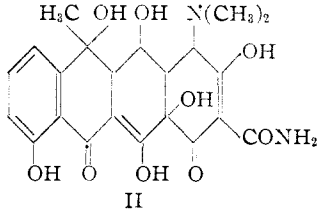
TERRAMYCIN. VIII. STRUCTURE OF AUREOMYCIN AND TERRAMYCIN

Sir:

Published physical data[1,2] on aureomycin and Terramycin and the results of our studies on the structure of Terramycin[3] require a relationship between these compounds which is expressed by structures I and II, respectively.



I



II

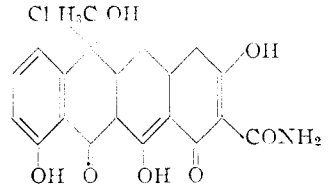
The structure I is in agreement with our analytical data which indicate that the molecular formula of aureomycin is $C_{22}H_{23}N_2O_8Cl$: *Anal.* Calcd. for $C_{22}H_{23}N_2O_8Cl$: C, 55.17; H, 4.84; N, 5.85; Cl, 7.40. Found: C, 55.10; H, 4.90; N, 5.72; Cl, 7.27. Calcd. for $C_{22}H_{23}N_2O_8Cl\cdot HCl$: C, 51.27; H, 4.69; N, 5.43; Cl, 13.76. Found: C, 51.24; H, 4.66; N, 5.40; Cl, 13.80.

(1) (a) R. Broschard, A. Dornbush, S. Gordon, B. Hutchings, A. Kohler, G. Krupka, S. Kushner, D. Lefemine and C. Pidacks, *Science*, **109**, 199 (1949); (b) B. M. Duggar, U. S. Patent 2,482,055 (1949); (c) P. P. Regna, I. A. Solomons, K. Murai, A. E. Timreck, K. J. Brunings and W. A. Lazier, THIS JOURNAL, **73**, 4211 (1951).

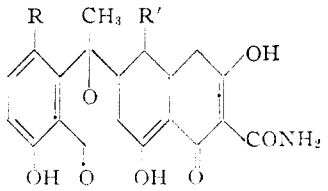
(2) (a) D. J. Hiscox, *J. Am. Pharm. Assoc.*, **40**, 237 (1951); (b) J. Dunitz and J. Robertson, THIS JOURNAL, **74**, 1108 (1952); (c) R. Pepinsky and T. Watanabe, *Science*, **115**, 541 (1952).

(3) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **74**, 3708 (1952).

The naphthacene skeleton in aureomycin is demonstrated, as in the case of Terramycin, by reduction to desdimethylaminodesoxyaureomycin (III) (*Anal.* Calcd. for $C_{20}H_{18}NO_7Cl$: C, 57.21; H, 4.31; N, 3.33. Found: C, 57.09; H, 4.64; N, 3.38) and the acid dehydration of this product to a red compound (*Anal.* Calcd. for $C_{20}H_{16}NO_6Cl$: C, 59.78; H, 4.00; N, 3.48; Cl, 8.83. Found: C, 60.13; H, 4.14; N, 3.57; Cl, 8.90) from which naphthacene has been obtained by zinc dust distillation.



III



IV, R = Cl, R' = H
V, R = H, R' = OH

The ultraviolet absorption spectrum of aureomycin and its acidity constants (for the hydrochloride, pK_a's 3.4, 7.4, 9.2) are very similar to those of Terramycin (pK_a's 3.5, 7.6, 9.2). Thus, the polycarbonyl system of Terramycin is common to both compounds. The slightly longer wave length absorption of aureomycin is attributable to the effect of the aromatic chlorine atom, the position of which has been shown by the isolation of 5-chlorosalicylic acid[4] and 5-chloro-7-hydroxy phthalides[5] from aureomycin.

The desdimethylaminodesoxy compounds (*e.g.*, III) from both antibiotics have very similar absorption spectra, which exhibit marked shifts from the parent compounds. This shift is a consequence of the removal of the C_6 hydroxyl group since desdimethylaminoterramycin (*Anal.* Calcd. for $C_{20}H_{19}NO_9$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.42; H, 4.62; N, 3.34) and desdimethylaminoaureomycin (*Anal.* Calcd. for $C_{20}H_{18}NO_8Cl\cdot CH_3OH$: C, 53.91; H, 4.72; N, 2.99; Cl, 7.57; OCH_3, 6.62. Found: C, 54.08; H, 4.95; N, 3.12; Cl, 7.59; OCH_3, 6.24) possess absorption characteristics essentially identical with those of the respective antibiotics.

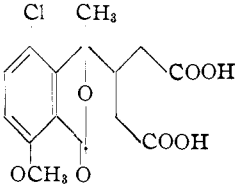
The presence of a C_{14}-hydroxyl in aureomycin is apparent from the alkali-induced rearrangement of desdimethylaminodesoxyaureomycin (III) to the substituted phthalide (IV) (*Anal.* Calcd. for $C_{20}H_{18}NO_7Cl$: C, 57.21; H, 4.31; N, 3.33. Found: C, 56.87; H, 4.50; N, 3.40). Similarly in the Terramycin series desdimethylaminodesoxyterramycin[3] yields an analogous compound (V) (*Anal.* Calcd. for $C_{20}H_{19}NO_8$: C, 59.85; H, 4.71; N, 3.49. Found: C, 59.82; H, 5.06; N, 3.55). Pyrolysis

(4) R. Kuhn and K. Dury, *Ber.*, **84**, 563 (1951).

(5) B. Hutchings, C. Waller, S. Gordon, R. Broschard, C. Wolf, A. Goldman and J. Williams, THIS JOURNAL, **74**, 3710 (1952).

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)

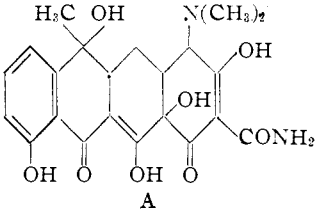


VIII

from aureomycin by methylation, followed by permanganate oxidation.[5]

(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.

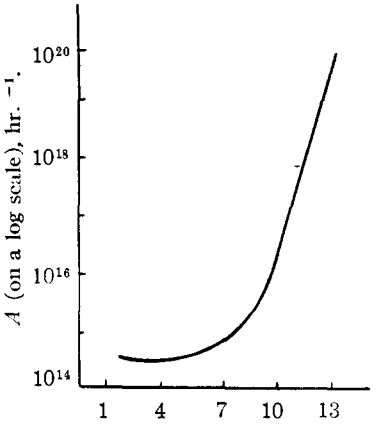

Fig. 1.—Frequency factor for hydrolysis of 1% tetramethylammonium tripolyphosphate in 10% tetramethylammonium bromide solution as a function of *p*H.

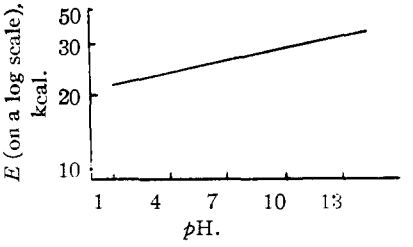

Fig. 2.—Activation energy for hydrolysis of 1% tetramethylammonium tripolyphosphate in 10% tetramethylammonium bromide solution as a function of *p*H.

(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).