TABLE I.—ANALYSIS OF COMPOUNDS

No.	M.P., °C.	Empirical Formulas	Analysis: Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I	...	$C_{26}H_{24}N_2O_{10}\cdot 2H_2O$	54.74	5.11	5.11	54.91	5.58	5.11 5.28
II	d. 186	$C_{19}H_{10}O_6N_2\cdot{}^1/_2H_2O$	60.48	4.61	...	60.78	4.88	...
III	d. 235	$C_{15}H_{16}N_2O_5\cdot H_2O$	55.89	4.96	...	55.87	4.78	...
IV	232	$C_{28}H_{30}N_2O_{12}\cdot H_2O$	55.62	5.29	...	55.66	5.37	...
V	...	$C_{16}H_{16}N_2O_6\cdot H_2O$	...	...	8.00	...	...	7.89

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Communications

New Alkaline-Stable Species for Selected Members of the Tetracycline Family

Sir:

We have recently observed a new modification of selected members of the tetracycline family which shows greatly enhanced stability under alkaline conditions. This derivative is a complex having the following general formula: (tetracycline - group - antibiotic) - $(aluminum)_a$-$(calcium)_b$-(gluconic acid)$_c$ where a, b, and c are the molar ratios of the respective constituents. Although the molar ratios a, b, and c can vary over a wide range in this derivative, greatly enhanced alkaline stability occurs only when the molar ratios of aluminum and calcium are three or greater. The molar ratio of gluconic acid does not appear to contribute significantly to the alkaline stability, but appears to play an important role in solubilizing the derivative.

In measuring the alkaline stability of derivatives in this series, extensive use has been made of half-life determinations, as reported by McCormick, *et al.* (1). Half-life values have been determined in 0.1 *N* sodium hydroxide at 90–100° by following the time change in (*a*) ultraviolet absorbance at 365 mμ and (*b*) the microbiological activity of the antibiotic.[1] Table I *demonstrates* the enhanced alkaline stability of selected members of the tetracycline family in this series of derivatives.

[1] Microbiological assays were performed under the direction of Dr. J. J. Corbett, Biological Assay Development Laboratory.

TABLE I.—RELATIVE ALKALINE STABILITY OF VARIOUS DERIVATIVES OF 6-DEMETHYLCHLORTETRACYCLINE (DMCTC),[a] CHLORTETRACYCLINE (CTC),[a] 6-DEMETHYLTETRACYCLINE (DMTC), TETRACYCLINE (TC),[a] AND 6-DEOXY-6-DEMETHYLTETRACYCLINE (DODMTC)

	Half-Life, min., in 0.1 *N* NaOH at 90–100°: Spectrophotometric Determination	Half-Life, min., in 0.1 *N* NaOH at 90–100°: Microbiological Determination
DMCTC·HCl	40	60
DMCTC-aluminum-gluconate (1:4:6.6)	95	..
DMCTC-aluminum-calcium-gluconate (1:4:1:12)	1,120	..
DMCTC-aluminum-calcium-gluconate (1:4:2:12)	3,000	..
DMCTC-aluminum-calcium-gluconate (1:4:3:12)	Very long[b]	..
DMCTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	Very long[b]
CTC·HCl	4	..
CTC-aluminum-calcium-gluconate (1:4:5:12)	12	..
CTC-aluminum-calcium-gluconate (1:4:7:12)	26	..
DMTC·HCl	32	..
DMTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..
TC·HCl	7	..
TC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..
DODMTC·HCl	200	..
DODMTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..

[a] The trademarks of the American Cyanamid Co. for 6-demethylchlortetracycline, chlortetracycline, and tetracycline are Declomycin, Aureomycin, and Achromycin, respectively.
[b] No change observed after 4 to 6 hours in 0.1 *N* sodium hydroxide at 90–100°.

The various members of the tetracycline family in the table above demonstrate the effects of methylation, chlorination, and deoxygenation of the tetracycline ring system on the ability of complex formation to slow the rate of alkaline degradation. Chlortetracycline is unusual in that repeated alkaline stability studies with complexes described with this antibiotic have failed to demonstrate greatly enhanced alkaline stability.

The resistance of certain of these derivatives to attack by alkali enables them to be prepared as stable solutions when the solution is sufficiently alkaline to avoid C·4 epimerization occurring in the pH range of 2–6 (2) and anhydro formation occurring under very acidic conditions.

Those derivatives showing enhanced alkaline stability experience little or no change in their susceptibilities toward acid degradation and toward C·4 epimerization in comparison to the uncomplexed antibiotic. The lack of significant change toward acid degradation is of particular interest because both alkaline degradation and acid degradation involve chemical alteration of the C·6 hydroxyl, together with other changes in ring C in the antibiotic. The fact that complexing can produce great changes in the alkaline reactivity of the C·6 hydroxyl and little change in the acid reactivity of the C·6 hydroxyl is an important clue to the mechanism of alkaline stability enhancement via complex formation. When 6-deoxy-6-demethyltetracycline is used as the antibiotic in this derivative, greatly enhanced stability toward acid (3) and alkali is observed.

Additional observations on this series of derivatives with the tetracycline family will be presented at a later date.

(1) McCormick, J. R. D., *et al.*, *J. Am. Chem. Soc.*, **79**, 2849(1957).
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Book Notices

Pharmacological Principles of Medical Practice. 5th ed. By JOHN C. KRANTZ, JR., and C. JELLEFF CARR. The Williams & Wilkins Co., 428 East Preston St., Baltimore 2, Md., 1961. xi + 1498 pp. 15 × 22.5 cm. Price $15.

The fifth edition of this excellent and widely used treatise and textbook has been extensively revised. The text material has been updated to include the very latest information available before printing. Although judicious pruning kept the book from being unwieldy, this edition contains 186 pages more than the fourth edition. Librarians will note that the first word in the title of the book has been changed from "Pharmacologic" to "Pharmacological." Students will be more concerned with the included nomenclature changes indicated for the psychotropic drug classifications; the beautiful color plate diagram of the normal menstrual cycle showing pituitary, ovarian, and endometrial activity; and many other additions in this edition. The index is exceptionally thorough and enhances the reference value of the book.

Microbial Cell Walls. By MILTON R. J. SALTON. John Wiley & Sons, Inc., 440 Park Ave., South, New York 16, N. Y., 1961. ix + 94 pp. 12.5 × 18.5 cm. Price $3.50.

Lectures on microbial cell walls, including the chemistry, enzymic degradation, and their biosynthesis are included in this booklet. A general index is appended.

Chemotherapy of Tuberculosis. By WILLIAM F. RUSSELL, JR. and GARDNER MIDDLEBROOK. Charles C Thomas, 301–327 East Lawrence Ave., Springfield, Ill., 1961. xiv + 130 pp. 15 × 23 cm. Price $6.50.

A concise monograph on tuberculosis with practical considerations on current chemotherapy. Part 1 covers measures for determining the appropriateness and the adequacy of chemotherapy; Part 2 considers parasite-drug-host relationships; and Part 3 considers combined drug treatment. An excellent review, with index.

Annual Review of Biochemistry. Vol. 30. Edited by J. MURRAY LUCK, FRANK W. ALLEN, and GORDON MACKINNEY. Annual Reviews, Inc., Palo Alto, Calif., 1961. vii + 758 pp. 15 × 22.5 cm. Price $7 in the U. S., $7.50 foreign.

Volume 30 in this excellent review series includes reports on: biological oxidation; chemistry of carbohydrates, lipids, and nucleotides; biochemistry of muscle, steroid hormones, polyamines, cultured mammalian cells, genetic factors, and the dividing cell; metabolism of lipids, nucleic acid (and biosynthesis), carbohydrates, and amino acids. Vitamins, proteins, and other subjects are covered in the total of 24 reports, with many references. Appended are author and subject indexes for volume 30 and a cumulative index of chapter titles for volumes 26–30.