Structure proof was provided by converting IV to 3,20-diketo-4-pregnen-18-oic acid (V) by hydrolysis in 60% sulfuric acid. A base-soluble product thus obtained was identical in melting point, paper-chromatographic migration rate and infrared spectrum with a genuine sample obtained from conessine.[4]

[4] R. Pappo, THIS JOURNAL, **81**, 1011 (1959). We wish to thank Dr. Pappo for his kindness in providing us with the comparison sample.

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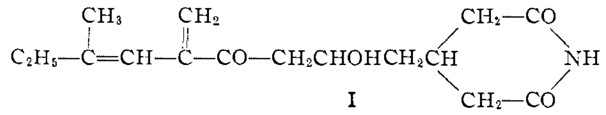
RECEIVED APRIL 29, 1960

STRUCTURE OF THE ANTIBIOTIC STREPTIMIDONE

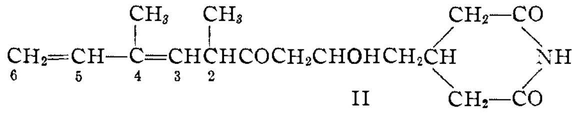
Sir:

Recently structure I was proposed for a new



I

Streptomyces antibiotic, streptimidone.[1] It appeared to us that certain of the recorded properties, in particular the base-catalyzed conversion of the existing chromophore to a 2,4-dienone system, could be better interpreted in terms of an alternative, II. We have now found that, by employing



II

nuclear magnetic resonance data, a clear decision in favor of the latter possibility can be made.

The n.m.r. spectrum[2] of O-acetylstreptimidone[3] displays the following major absorptions, due to hydrogens of the type indicated: (a) −106 (imide); (*b*) *ca.* −25 to +75 (olefinic, and acetoxyl methine); (c) *ca.* +100 to +175 (saturated methine and methylene); (d) +178 and +186 (4- and acetyl methyls), (e) +214 (2-methyl). The hydrogen peak ratio (1:5) of (a) to (b) supports formulation II, but not I. Furthermore, proposal I predicts essentially a simple three peak pattern in region (b), whereas that area features in fact an irregular quadruplet centered at about 0 (one hydrogen), and broadened doublets at about +45 and +62 (four hydrogens). This absorption character corresponds to a superimposition of an "AB" (2- and 3-hydrogens) upon an "ABX" (5- and 6-hydrogens) pattern,[4] and corresponds well to that exhibited by isoprene,[5] a close model for the unsaturated portion of II. Finally, the C-methyl group designated as (e) is split, as required, by the methine hydrogen at position 2; structure I, on the other hand, bears a methyl group in the ethyl unit, and would have given rise to a triplet in (e).

The ultraviolet spectrum ($\lambda_{\text{Max}}^{\text{MeOH}}$ 232 and 291 mμ, ϵ 23,100 and 790)[1] and infrared absorption *in solution* (*inter alia*, 5.8 μ, ketone –CO–; 5.9 μ, imide –CO–; 6.0 (w) and 6.1 (w), diene)[1] are consistent with the revised structure, II. This formula is also compatible with the recorded chemical behavior,[1,6] and has been confirmed by additional chemical findings obtained more recently in the laboratories of the Research Division of Parke, Davis and Company.[7]

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[1] R. P. Frohardt, H. W. Dion, Z. L. Jakubowski, A. Ryder, J. C. French and Q. R. Bartz, THIS JOURNAL, **81**, 5500 (1959).

[2] Obtained in $CDCl_3$ solution with a Varian Associates instrument operating at 40 mc. Chemical shifts given in cps. relative to benzene = 0.

[3] We wish to thank Dr. Q. R. Bartz (Parke, Davis and Company) for his coöperation, especially for his kindness in supplying a sample of the derivative used in this investigation.

[4] Pople, Schneider and Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York, N. Y., 1959, p. 132.

[5] Pople, Schneider and Bernstein, *ibid.*, p. 244.

[6] The positive *m*-phenylenediamine test for an α,β-unsaturated ketone is regarded as due to either prior isomerization of II to a conjugated ketone system, or to dehydration of the aldol moiety.

[7] Re-examination of the ozonolysis of streptimidone has revealed that formaldehyde and pyruvaldehyde are the end products, not formaldehyde and methyl ethyl ketone as reported previously (ref. 1). The latter ketone originated as an impurity in the reagent ethyl acetate (distilled from 2,4-dinitrophenylhydrazine) which was used as a solvent in the isolation procedure (personal communication from H. W. Dion, Parke, Davis and Company).

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RECEIVED APRIL 8, 1960

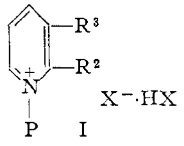
ANTIPARASITIC DRUGS. III. THIAMINE-REVERSIBLE COCCIDIOSTATS

Sir:

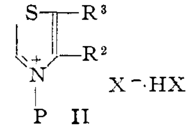
We have found that many 1-(2-alkyl-4-amino-5-pyrimidinylmethyl)-alkylpyridinium salts possess marked prophylactic activity in coccidiosis, a protozoan disease of importance in poultry production. Analogous 3-thiazolium compounds are also effective.

The new anticoccidial agents are related structurally to thiamine (II: R^1 and R^2, CH_3, R^3, CH_2CH_2OH) and function by a reversible thiamine inhibition mechanism. These quaternaries, administered in feed, are selectively effective against coccidia of the digestive tract and make possible adequate disease prevention without adverse effect upon the growth of chickens. Another relative of the new coccidiostats is the thiamine antagonist pyrithiamine (neopyrithiamine, I: R^1 and R^2, CH_3, R^3, CH_2CH_2OH).[1]

Compounds of types I and II are made by reaction of 2-alkyl-4-amino-5-pyrimidinylmethyl halide



I



II

P is 2-R′-4-amino-5-pyrimidinylmethyl

dihydrohalide with excess pyridine or thiazole base in acetonitrile or other solvents. The synthesis of the 2-methylpyrimidine intermediate has been described by Grewe.[2] Data on typical quaternaries are given in Table I.

---

[1] A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 54 (1941); A. N. Wilson and S. A. Harris, THIS JOURNAL, **71**, 2231 (1949).

[2] R. Grewe, *Naturwiss.*, **24**, 657 (1936); *Z. physiol. Chem.*, **242**, 89 (1936).

TABLE I

	R¹ Substituent[a]	Formula[b]	M.p., °C.[c]	Minimum effective feed level, %	Antithiamine index, C = chick, M = microbiological
I-a	CH_3	$C_{12}H_{15}N_4Br \cdot HBr$	233–234	0.006	270 C 320 M
I-b	C_2H_5	$C_{13}H_{17}N_4Br \cdot HBr$	266–270	.001– 0.002	140 C 345 M
I-c	*n*-C_3H_7	$C_{14}H_{19}N_4Cl \cdot HCl$	248–249	.003	500 C >1000 M
I-d	CF_3	$C_{12}H_{12}F_3N_4Br$	208	.002	200 C
II-a	*n*-C_3H_7	$C_{12}H_{17}N_4SBr \cdot HBr$	241–243	.0125	1400 C

[a] R^2, CH_3; R^3, H. [b] Acceptable analyses were obtained on all compounds. [c] With decomposition.

In the same table are presented the results of anticoccidial evaluation with *Eimeria tenella*, obtained by a previously described method.[3] Antithiamine indices for the chick[4] and *Lactobacillus fermentum*[5] also are listed.

Considerable anticoccidial activity was found with the compounds listed. Of these practical interest centers on the compound 1-(4-amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride (I-c) which has been assigned the generic name of amprolium.[6] In laboratory tests amprolium is effective at 0.0125% feed level against a mixed infection of *Eimeria tenella, necatrix* and *acervulina*.

The antithiamine indices of these and related compounds reveal a definite although rough correlation between antithiamine and anticoccidial action. In addition, reversal of anticoccidial action is demonstrated by the fact that chickens on a normal diet are protected against an *Eimeria tenella* infection by 0.0125% amprolium but addition to the diet of 0.003% thiamine causes a marked decrease in protection.

Pyrithiamine is ineffective against coccidiosis at the maximum tolerated feed level of 0.05%, despite a chick antithiamine index of 16. Apparently the absence of the hydroxyethyl side chain in the analogous active quaternary (I-a) is an advantage for inhibition of the target enzyme system, which is possibly protozoal thiamine phosphorylase located at the cell wall.

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(3) A. C. Cuckler, L. R. Chapin, C. M. Malanga, E. F. Rogers, H. J. Becker, R. L. Clark, W. J. Leanza, A. A. Pessolano, T. Y. Shen and L. H. Sarett, *Proc. Soc. Exptl. Biol. Med.*, **98**, 167 (1958).

(4) The chick antithiamine index is the number of milligrams of compound calculated to counterbalance the vitamin activity of one milligram of thiamine mononitrate in the chick.

(5) H. P. Sarett and V. H. Cheldelin, *J. Biol. Chem.*, **155**, 153 (1944). *Lactobacillus fermentum* (36 ATCC 9833) was grown in standard thiamine assay medium. Increasing amounts of thiamine, up to 0.2 γ, were added to tubes containing 25 γ of the test compound. Growth was measured turbidimetrically after 16 hours of incubation at 36°. The ratio test compound (25 γ) divided by the quantity of thiamine required for 50% transmittance is given in Table I as the antithiamine index (M). We are obliged to Mr. Hyman Wallick for the microbiological data.

(6) AMPROL is the trademark of Merck & Co., Inc., for this compound.

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RECEIVED MAY 16, 1960

BOOK REVIEWS

Landolt-Börnstein. Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik. Sechste Auflage. Band II. **Eigenschaften der Materie in Ihren Aggregatzuständen.** Teil 6. **Elektrische Eigenschaften I.** Edited by K. H. HELLWEGE and A. M. HELLWEGE. Springer-Verlag, Heidelberger Platz 3, Berlin-Wilmersdorf, Germany. 1959. xvi + 1018 pp. 20 × 27.5 cm. Price, DM. 448.—.

This volume is a compilation of values of the electrical properties of matter. [The editors have announced that electrochemical and magnetic properties will be treated in Parts 7 (1960) and 9 (in preparation), respectively.] The 1018 pages give evidence of the same high level of scholarship and thoroughness that have gone into the preparation of earlier parts of this compendium. The five sections, each prepared by one or more experts, cover the following subject areas: (1) Electrical conductivity of metals and solid ionic conductors, by W. Meissner, F. Schmeissner, R. Doll, M. Näbauer, R. Jaggi and F. Hulliger, 250 pp.; (2) semiconductors, by W. Jost, H. G. Wagner, K. Weiss, H. Welker, G. Heiland, and E. Mollwo, 162 pp.; (3) the elastic, piezoelectric and dielectric constants of piezoelectric crystals, by R. Bechmann, 33 pp.; (4) dielectric properties, by H. Stuart, Th. Gast, W. Maier, A. W. Fink, E. Truscheit, and E, Gast, 459 pp.; and (5) thermoelectric and emission effects, by W. Kluge, J. Nyström and R. Kollath, 109 pp. The extensive tables and graphs of each main section are preceded by a short introduction containing definitions and explanatory material. A complete list of references follows the tabular material.

The section on electrical conductivities of metals and solid ionic conductors covers specific resistance and its temperature coefficient for pure metals and binary alloy systems, resistance ratio relative to 0°C. or other specified temperature, effect of pressure and tension on resistance, Wiedeman–Franz–Lorenz number, superconductivity, galvanomagnetic and thermomagnetic transverse effects, ionic conductivity in crystals, and transport number in solids. The second section deals with properties of semiconductors such as energy gaps, electron and hole mobilities, conductivity or resistance *vs.* temperature, and Hall coefficient *vs.* temperature, and with the effects of doping, imperfections or dislocations on the foregoing properties. In section three, values are presented for the elastic, piezoelectric and dielectric constants of piezoelectric crystals and their temperature coefficients. The forth section, on dielectric properties, is by far the largest. It covers the dielectric properties of crystals and crystalline substances, glasses, plastics, liquid crystals, the elements, and organic and inorganic compounds and their aqueous and non-aqueous solutions. The properties treated include the dielectric constant and its dependence on temperature and pressure; and the molar polarization. The last section, on thermoelectric and emission effects, is subdivided into thermionic emission, thermal e.m.f., Peltier and Thompson effects, and photoemission and secondary electron emission of solids.