140°, $[\alpha]^{25}D$ −51.4, was identical with the antibiotic obtained from the *Streptomyces* fermentation.

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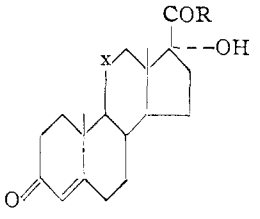
RECEIVED MAY 9, 1952

ALDEHYDES DERIVED FROM CORTISONE AND HYDROCORTISONE

Sir:

Cortisone (I) and hydrocortisone (X), Kendall's compounds E and F, have been converted to the corresponding 21-aldehydes, Δ^4-3,11,20-triketo-17α-hydroxypregnene-21-al (V) and Δ^4-3,20-diketo-11β,17α-dihydroxyprenene-21-al (XIII), which are biologically active.

On treatment of cortisone (I) with *p*-toluenesulfonyl chloride a mixture of the pyridinium *p*-toluenesulfonate and chloride (II, III) was obtained. The latter salt was treated with *p*-nitrosodimethylaniline to give the nitrone (IV), isolated in two forms, red plates and yellow needles, having identical decomposition points. The nitrone was hydro-



	X	R	M. p., °C.	$[\alpha]^{25}D$ (CH_3OH, $c=2$)
I	C=O	CH_2OH		
II	C=O	$CH_2Py^+OTs^-$	285–290 dec.	
III	C=O	$CH_2Py^+Cl^-$	290–291 dec.	+231°
IV	C=O	$CH{=}N(O)C_6H_4N(CH_3)_2$	189–190 dec.	
V	C=O	CHO	210–215 dec.	
VI	C=O	$CH(OH)_2$	*ca.* 225 dec.	+182°
VII	C=O	$CH(OCH_3)_2$	142	+176°
VIII	C=O	$CH(OC_2H_5)_2$	77	+165°
IX	C=O	$CH(OCOCH_3)_2$	169	+ 99°
X	CHOH	CH_2OH		
XI	CHOH	$CH_2Py^+Cl^-$	295–296 dec.	+232°
XII	CHOH	$CH{=}N(O)C_6H_4N(CH_3)_2$	186–188 dec.	
XIII	CHOH	CHO		
XIV	CHOH	$CH(OH)_2$	155–160 dec.	+155°

lyzed by dilute acid to cortisone-21-aldehyde (V), which crystallized from aqueous acetone as the colorless hydrate (VI). (*Anal.* (after drying at 25° (1 mm.) 4 hr.) Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.01; H, 7.75). The yellow free aldehyde was regenerated from the hydrate by several hours drying at 110° (1 mm.). (*Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.36; H, 7.31. Found: C, 70.09; H, 7.52).

By an analogous procedure, hydrocortisone (X) was converted *via* the pyridinium chloride (XI) and nitrone (XII) to hydrocortisone-21-aldehyde hydrate (XIV). (*Anal.* Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.94; H, 7.69).

The ultraviolet absorption spectra of cortisone aldehyde hydrate (max. 2380 Å., E_m 15,700) and hydrocortisone aldehyde hydrate (max. 2420 Å., E_m 16,000) in methanol resemble those of cortisone and hydrocortisone. Cortisone free aldehyde in anhydrous chloroform has an additional band at 4500 Å. (E_m 36) which is characteristic of α-dicarbonyl compounds. Chemically the hydrates behave as typical aldehydes. Positive Schiff and silver mirror tests are observed and three derivatives involving the aldehyde group have been prepared from cortisone aldehyde, the dimethyl and diethyl acetals (VII, VIII) and the diacetate (IX).

The aldehyde hydrates have approximately the same activity as cortisone and hydrocortisone in rat liver glycogen deposition tests.[1] The nitrone and diacetate in the cortisone series are also active, while the acetals appear to be inert. It has, furthermore, been noted that cortisone and hydrocortisone aldehyde hydrates cause adrenal atrophy and thymus involution similar to that resulting upon administration of the parent hormones.[2] The approximate equivalence in biological activity of cortisone and hydrocortisone with the corresponding 21-dehydro compounds is in contrast to results with desoxycorticosterone and the related 21-aldehyde. This aldehyde is only one twenty-fifth as effective as desoxycorticosterone in the Everse–deFremery work test.[3]

(1) Several modifications of the procedure of Pabst, Sheppard and Kuizenga (*Endocrinology*, **41**, 51 (1947)) have been employed by Drs. C. C. Porter and R. H. Silber of the Merck Institute for Therapeutic Research, to whom we are indebted for the reported results.

(2) We are obliged to Dr. C. A. Winter, Merck Institute for Therapeutic Research, for these tests.

(3) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).

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A NEW STREPTOMYCES ANTIBIOTIC[1]

Sir:

A new antibiotic, exhibiting highly specific *in vitro* activity against *Mycobacteria*, has been isolated from a species of *Streptomyces*. The antibiotic may be recovered by successive *n*-butanol extractions of the culture broth after filtration from the mycelium at *p*H 2.0. The butanol extracts are combined and the acidic antibiotic extracted with sodium carbonate solution. The alkaline solution is adjusted to *p*H 4.5, and then repeatedly extracted with butyl acetate. Evaporation of the butyl acetate leaves a dark brown sirup which is dissolved in hot ethylene dichloride, treated with activated carbon, and filtered. On cooling, the antibiotic crystallizes in long white needles. Recrystallization can be effected from hot water, warm acetone, or methanol.

This new antibiotic is a monobasic acid, *pK* 5.1. Titration and molecular weight data are in agreement with the formula $C_9H_{15}O_3NS$, m.p. 139–140°, $[\alpha]^{23}D$ −54 (*c* 1, methanol). (*Anal.* Calcd. for $C_9H_{15}O_3NS$: C, 49.77; H, 6.91; N, 6.45; S, 14.75. Found: C, 49.96; H, 7.09; N, 6.51; S, 14.83).

Solutions of the pure material exhibit a blue fluorescence on exposure to ultraviolet light. There is no characteristic ultraviolet spectrum. The

(1) Since the completion of this work, we have learned that this antibiotic (actithiazic acid) has been independently isolated and synthesized by a group at Abbott Laboratories.

infrared spectrum indicates a carboxyl group and possible amide carbonyl.

The antibiotic gives negative Tollens, 2,4-dinitrophenylhydrazine, and ninhydrin tests. In glacial acetic acid or carbon tetrachloride, bromine is rapidly absorbed with evolution of hydrogen bromide. The color of permanganate is quickly discharged by the antibiotic in aqueous solution. On heating a strongly alkaline solution in the presence of lead acetate a slight darkening results and ammonia is evolved. A white precipitate results with mercuric chloride, but no reaction with mercuric oxide.

Aqueous solutions of the antibiotic are quite stable over a wide *p*H range at room temperature. The crystalline antibiotic can be stored for long periods of time with no loss in potency.

This antibiotic exhibits a very low order of toxicity, but preliminary animal protection studies indicate that the new antibiotic is not active *in vivo*.

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ACIDIC BEHAVIOR EXHIBITED BY METHYL BORATE TOWARD AMINES[1]

Sir:

The question of the ability of alkyl borates to form addition compounds with amines under ordinary conditions has not as yet been settled. Such compounds have not been reported, and it has been suggested[2] that they do not form.

We have found, however, that the lowest boric ester (and presumably the least hindered), methyl borate, forms white solid addition compounds when treated with a number of amines, including dimethylamine, diethylamine, di-*n*-propylamine, di-*n*-butylamine, di-*n*-amylamine, triethylamine, tributylamine, ethylenediamine, piperidine, methylamine, and *t*-butylamine. In the case of the last four amines, the compounds are stable enough to be purified by sublimation *in vacuo*, weighed, and analyzed. No evidence of interaction has been obtained in the case of the weaker bases pyridine and quinoline.

These addition reactions are strongly catalyzed by the lower aliphatic alcohols, the degree of catalysis increasing with the acidity of the alcohol.

The addition compounds thus far characterized are listed in the accompanying table.

Compound	M.p., °C.	Analyses, % Calcd.	Found
$(CH_3O)_3B{:}NH_2CH_2CH_2NH_2$	81–82	B, 6.71	6.72
$(CH_3O)_3B{:}H{-}N$⟨⟩	75	B, 5.82	5.77
$(CH_3O)_3B{:}NH_2CH_3$	67	N, 10.37	10.44
$(CH_3O)_3B{:}NH_2C(CH_3)_3$	67–70	B, 6.01	6.22

Solid compounds do not seem to separate when the amines and ethyl borate are mixed under the same conditions. However, there is considerable heat evolved during mixing, indicating some chemical interaction between components. When amines are added to the higher esters, *n*-butyl- and *n*-amyl borates, there is no appreciable heat effect. It seems likely, therefore, that the stabilities of such amine-borate complexes are governed largely by steric factors.

We are at present unable to propose a reasonable mechanism explaining the catalysis of these addition reactions by alcohols. Studies on the heats of formation of these complexes are being carried out.

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RECEIVED APRIL 15, 1952

(1) Based on research carried out under Signal Corps Contract DA 36-039 Sc-5492 between the Squier Signal Laboratory and the Polytechnic Institute of Brooklyn.

(2) N. V. Sidgwick, "Chemical Elements and Their Compounds," Oxford University Press, London, 1950, p. 403.

SOME ANTIMETABOLITES OF SEROTONIN AND THEIR POSSIBLE APPLICATION TO THE TREATMENT OF HYPERTENSION

Sir:

The recent elucidation of the structure of serotonin, the vasoconstrictor of serum,[1-3] has provided an opportunity for the testing of a basic postulate in the chemotherapy of non-infectious diseases. This postulate is that if such diseases arise from excess of specific hormones or other metabolities, they may be susceptible to treatment by antimetabolities, which would thus nullify these extra amounts.[4] Experimental models to test this idea have been described for thyroxine, and for other metabolities.[5,6] The use of some of the antihistamines in medicine is an unconscious application of the same principle.[6] If serotonin, which is the naturally occurring vasoconstrictor in mammals were to be increased in an animal, either by excessive synthesis or decreased destruction, it would not be difficult to envision it as the cause of certain clinical hypertensions. We have therefore attempted to produce antimetabolities of serotonin, in the hope that they may be useful pharmacological agents.

Several new 5-aminoindoles with alkyl groups in positions 2 and 3 have been made by reduction of the corresponding 5-nitroindoles prepared by the Fischer synthesis.[7,8] The structural resemblance to serotonin, 3-aminoethyl-5-hydroxyindole, is clear. These were tested on ring-shaped segments of sheep carotid artery for ability to prevent the constriction which serotonin causes. A roughly quantitative test was developed to allow comparison of various analogs, and to permit study of the competitive nature of the antagonism.

The most active antimetabolite examined was 2-methyl-3-ethyl-5-aminoindole, m.p. 148–149° (calcd. C, 75.84; H, 8.10; N, 16.08; found, C, 75.77; H, 7.83; N, 16.33). A maximal contraction

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(2) K. E. Hamlin and F. E. Fischer, THIS JOURNAL, **73**, 5007 (1951).
(3) M. E. Speeter, R. V. Heinzelman and D. I. Weisblat, *ibid.*, **73**, 5515 (1951).
(4) D. W. Woolley, *Science*, **100**, 579 (1944).
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(7) H. Bauer and E. Strauss, *Ber.*, **65**, 308 (1932).
(8) K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 1505 (1950).