product of digestion, although a small amount of the heptapeptide was also present. This finding provides additional evidence for the view that the C-terminal alanine groups are not essential for the biological activity of insulin.

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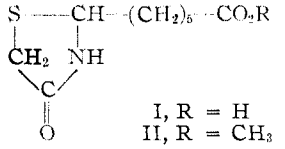
RECEIVED APRIL 30, 1952

THE STRUCTURE AND SYNTHESIS OF A NEW THIAZOLIDONE ANTIBIOTIC[1]

Sir:

We have established the structure (−)2-(5-carboxypentyl)-4-thiazolidone (I) for a new *Streptomyces* antibiotic[2] exhibiting *in vitro* antitubercular activity.



I, R = H
II, R = CH_3

Reaction of I in ether solution with excess diazomethane gave the microbiologically active methyl ester (II), crystallized from ether–hexane as colorless needles, m.p. 53–54°, $[\alpha]^{25}D$ −50.9°, (*c* 1, methanol). (*Anal.* Calcd. for $C_{10}H_{17}O_3NS$: C, 51.92; H, 7.41; N, 6.06; S, 13.86; CH_3O, 13.41. Found: C, 51.92; H, 7.43; N, 6.15; S, 13.62; CH_3O, 12.90.) Ultraviolet absorption studies of I (in methanol) and II (in 2,2,4-trimethylpentane) in the region 210–400 mμ revealed only end absorption. The infrared spectrum of I (Nujol mull) exhibits two characteristic carbonyl bands near 1640 and 1710 cm.$^{-1}$. Comparable bands at 1680 and 1720 cm.$^{-1}$ are apparent in the spectrum of II (chloroform solution). The lower frequency carbonyl band has been attributed to a carboxamide and the higher frequency carbonyl band to an aliphatic carboxyl grouping. Hydrogen bonded N–H absorption has been assigned to bands at 3140 cm.$^{-1}$ in I and 3170 cm.$^{-1}$ in II. A cleanly resolved band near 3450 cm.$^{-1}$ (free N–H) is apparent in the spectrum of II.

I rapidly loses optical activity in dilute alkali to give the racemate, obtained in two crystalline modifications: (1) from water as colorless needles, m.p. 122–123° and (2) from chloroform as colorless needles, m.p. 116–117°. The infrared spectra of (1), (2) and I in dioxane solution are indistinguishable. Mild alkaline hydrolysis of II gave racemic I.

Oxidation of I with alkaline permanganate or dilute nitric acid gave a crystalline dibasic acid, m.p. 104°, unequivocally identified as pimelic acid (III) by comparison with an authentic sample.

Mercuric chloride hydrolysis of I was accompanied by rapid loss of optical activity and liberation of an aldehyde identified as the semi-aldehyde of pimelic acid (IV), characterized as the oxime, m.p. 110–111°[3] and by oxidation to pimelic acid (III).

Desulfurization of I with Raney nickel in ethanol solution gave acetamide as well as a mixture of acidic products. However, when the desulfurization was carried out on the ester (II) in anhydrous dioxane under mild conditions, desthio-II was obtained in good yield. It crystallized from ether–petroleum ether as colorless needles, m.p. 31–32°. (*Anal.* Calcd. for $C_{10}H_{19}O_3N$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.55; H, 9.58; N, 6.87.) Alkaline hydrolysis of the desthio compound gave ω-aminoheptanoic acid, colorless plates from acetone–methanol–water, m.p. 193–194°.[4] (*Anal.* Calcd. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.11; H, 10.34; N, 9.57.) Desthio-II was shown to be methyl ω-acetamidoheptanoate (V) by comparison with an authentic sample prepared by hydrogenation of methyl ω-cyanocaproate in acetic anhydride.

$$CH_3CONH-CH_2-(CH_2)_5-CO_2CH_3$$
V

Oxidation of I in acetic acid solution with hydrogen peroxide gave the microbiologically inactive sulfone (VI), crystallized from water as colorless needles, m.p. 143°, $[\alpha]^{25}D$ +43 (*c* 1, methanol). (*Anal.* Calcd. for $C_9H_{15}O_5NS$: C, 43.37; H, 6.07; N, 5.62; S, 12.85. Found: C, 43.65; H, 6.18; N, 5.85; S, 13.10.) The infrared spectrum of VI (Nujol mull) exhibits a strong band in the region 1120 to 1160 cm.$^{-1}$, characteristic of sulfones.[5]

Dissolving VI in *N* sodium hydroxide at 27° resulted in extensive hydrolysis within a few minutes as evidenced by the rapid formation of titratable sulfite.

Mild hydrochloric acid hydrolysis of VI yielded products identified as sulfur dioxide, ammonium chloride and IV. Comparable acid hydrolysis of I also gave ammonium chloride together with a mixture of products identified as IV and a sulfur-containing dicarboxylic acid believed to be VII, which was purified as the dimethyl ester (VIII).

$$RO_2C-CH_2-S-CH=CH-(CH_2)_4-CO_2R$$
VII, R = H
VIII, R = CH_3

Compound VIII is a colorless, odoriferous oil, b.p. 162–168° (0.4 mm.), $n^{25}D$ 1.4850, d^{25}_4 1.128. The light absorption properties, $\lambda^{m\mu}_{max}$ 226, ε 4600 (in 2,2,4-trimethylpentane), are consistent with the above formulation.[6] (*Anal.* Calcd. for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.36; S, 13.02; CH_3O, 25.2; *M.R.*, 63.9. Found: C, 53.60; H, 7.49; S, 13.30; CH_3O, 22.3; *M.R.*, 62.6.)

The structure of I was confirmed by synthesis. Methyl ω-aldehydopimelate (IX)[7] was condensed with mercaptoacetamide in benzene in the presence of *p*-toluenesulfonic acid to give racemic II. Saponification of the synthetic ester yielded racemic I which was resolved by means of fractional crystallization of its brucine salts. Synthetic I, m.p. 139–

(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 the Abbott Laboratories.

(2) B. A. Sobin, THIS JOURNAL, **74**, 0000 (1952).

(3) M. Kershbaum, *Ber.*, **60**, 902 (1927).

(4) Lit. m.p. 186–187°. A. Manasse, *ibid.*, **35**, 1369 (1902); O. Wallach, *Ann.*, **312**, 205 (1900).

(5) (a) K. C. Schreiber, *Anal. Chem.*, **21**, 1168 (1949). (b) D. Barnard, J. M. Fabian and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

(6) K. Bowden, E. A. Braude and E. R. H. Jones, *ibid.*, 948 (1946).

(7) IX was prepared by a modified Rosemund reduction (5% palladium on carbon catalyst) of methyl pimelyl chloride in refluxing xylene solution. IX distilled at 70° (0.5 mm.), as a colorless liquid, $n^{25}D$ 1.4310.

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

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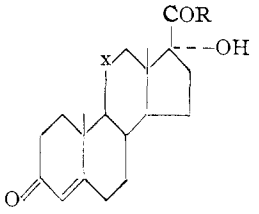
RECEIVED MAY 9, 1952

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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RECEIVED MAY 19, 1952

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

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