tion. It should be further pointed out that Baumgarten[2] suggested that the hydrolysis probably proceeds by way of the dipolar ion.

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RECEIVED APRIL 7, 1952

EVIDENCE OF NEW LINKAGES IN DEXTRANS

Sir:

We have been able to demonstrate that a significant fraction of the anhydroglucose units in a certain dextran apparently is not attacked by sodium metaperiodate at 25°. Previous investigations[1] of several dextrans showed that substantially all the units were attacked. Methylation studies[2] on dextrans so far investigated indicate that the principal glucosidic linkage is 1,6′, and that, in some cases, 1,4′-linkages are also present. Units at branch points carry linkages on both the 4- and 6-positions. Our results strongly suggest that this dextran contains units linked in the 3-positions, or both the 2- and 4-positions (branch points), or a combination of these possibilities.

This dextran, produced by *Leuconostoc mesenteroides* NRRL B-742, and purified by precipitation between 41 per cent. and 90 per cent. ethyl alcohol, consumed 1.43 moles of periodate and produced 0.64 mole of formic acid per anhydroglucose unit when oxidized at 25°[1] for 250 hours, at which time the consumption of oxidant and production of acid had ceased. Sixty-four per cent. of the glucopyranosyl units are therefore substituted only on the 6-position. Two moles of periodate are consumed by each unit so linked. The percentage of anhydroglucopyranose units consuming only one mole of periodate is then 15% [1.43 − (2 × 0.64)]. These are probably linked on the 4- and 6-positions. According to these calculations, the remaining 21 per cent. of the anhydroglucose units are not oxidized.

To confirm the presence of unoxidized units, a method developed by Smith[3] and his associates at the University of Minnesota has been applied. After removal of salts, the oxidized polymer was catalytically reduced and then hydrolyzed in 2 *N* sulfuric acid on the steam-bath. The only optically active products expected from a polyanhydroglucopyranose treated as above are D-glyceraldehyde, from 2- or 2- and 6-linked units, and D-glucose, from unoxidized units. The optical activity of the hydrolysate, if assumed to be due entirely to glucose, corresponded to 11.7% of unoxidized anhydroglucose units in the original dextran. Catalytic reduction of the neutralized hydrolysate yielded a solution having a small negative optical rotation in good agreement with that expected from the conversion of glucose to sorbitol. Sorbitol was isolated as the pyridine complex[4] and characterized as the hexaacetate, m.p. and mixed m.p., 98–99°; $[\alpha]^{25}D + 10.0°$ (*c*, 3.8; $CHCl_3$). The yield of the hexaacetate corresponded to 5.8% unoxidized anhydroglucopyranose in the original dextran.

The simplest explanation for the lack of oxidation by periodate is the presence of 1,3′-glucosidic linkages. Linkage in the 3-position, regardless of other linkages on the same anhydroglucopyranosyl unit, would prevent oxidation. Oxidation wuld be prevented also by the presence of units at branch points linked in both the 2- and 4-positions. However, the fact that the optical activity of the reduced hydrolysate indicated conversion of D-glucose to sorbitol, rather than of D-glyceraldehyde to glycerol, seems to rule out the presence of 1,2′-glucosidic linkages. Hence, if any 2-linked units are present, they probably occur only at branch points.

Dextran from *L. mesenteroides* NRRL B-742 has been found by Dr. Hellman at this Laboratory to consist of at least two discrete fractions.[5] Periodate analysis of the less soluble fraction, *i.e.*, that portion *precipitated* by 41% ethyl alcohol, does not indicate the presence of unoxidized anhydroglucose units. The fractions have been found by other workers here to differ also in specific rotation, viscosity, and infrared absorption.

Periodate oxidation data on dextrans produced by several other organisms have exhibited similar indications of unoxidized anhydroglucose units. In those cases where calculations indicate the presence of such units, unusual infrared absorption[6] is also found.

Methylation studies are in progress at this Laboratory to establish the positions involved in glycosidic linkage.

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RECEIVED AUGUST 4, 1952

(1) Allene Jeanes and C. A. Wilham, THIS JOURNAL, **72**, 2655 (1950).

(2) M. Stacey and C. R. Ricketts, *Fortschr. Chem. Org. Naturstoffe*, **8**, 28 (1951).

(3) F. Smith, personal communication.

(4) H. H. Strain, THIS JOURNAL, **56**, 1756 (1934).

(5) N. N. Hellman, in "Report of Working Conference on Dextran," National Research Council, Subcommittee on Shock, and Northern Regional Research Laboratory, Peoria, Illinois, Oct. 29, 1951, p. 36.

(6) S. C. Burket and E. H. Melvin, *Science*, **115**, 516 (1952).

(7) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

STEREOSPECIFIC TOTAL SYNTHESIS OF CORTISONE

Sir:

We should like to report a stereospecific[1] total synthesis of 11-ketoprogesterone, dehydrocorticosterone and cortisone in both the natural and *dl* modifications. *dl*-4b-Methyl-7-ethylenedioxy-1, 2,-3, 4, 4aα, 4b, 5, 6, 7, 8, 10, 10aβ-dodecahydrophenanthrene-4β-ol-1-one[2] (I) with methyl iodide and potassium *t*-butoxide gave the 2-methyl derivative, m.p. 189–192°. *Anal.* Found: C, 70.58; H, 8.42. The latter was alkylated in turn with methallyl iodide to give 2β,4b-dimethyl-2-meth-

(1) "Stereospecific" is taken to mean that in each reaction producing a fixed asymmetric center, the ratio of isomer having the same configuration as the end product to all other isomers is greater than unity. In point of fact, each of such ratios in the present synthesis is 8:1 or greater.

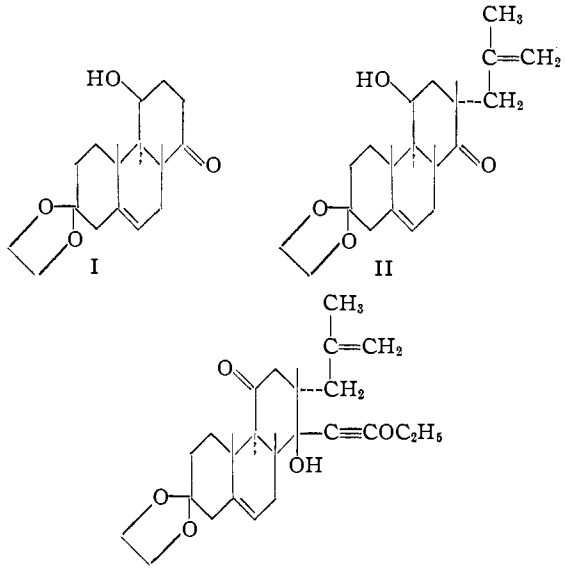
(2) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, in press.

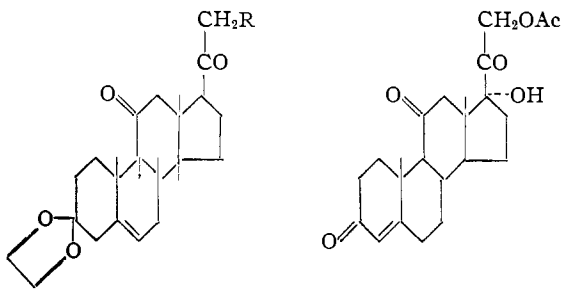
allyl - 7 - ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4β-ol-1-one (II), m.p. 166–168°. *Anal.* Found: C, 73.15; H, 8.96. Oxidation of II to the corresponding 1,4-diketone, m.p. 139° (*anal.* Found: C, 73.97; H, 8.42) with the chromium trioxide–pyridine complex[2] followed by condensation with ethoxyacetylene magnesium bromide[3] yielded 2β,4b-dimethyl-2-methallyl-1-ethoxyethinyl-7-ethylenedioxy-1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-1ζ-ol-4-one (III), m.p. 131–132°. *Anal.* Found: C, 72.88; H, 8.36. Treatment of III with dilute sulfuric acid afforded 2β,4b-dimethyl-2-methallyl-1-carbethoxymethylene - 7 - ethylenedioxy - 1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4-one, m.p. 94–96°. *Anal.* Found: C, 72.65; H, 8.25. Free acid, m.p. 203–205°. *Anal.* Found: C, 71.75; H, 7.78. Reduction of the keto acid with sodium borohydride to the 4α-hydroxy acid followed by reduction of the conjugated double bond with potassium–ammonia–isopropyl alcohol[4] gave 2β,4b-dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene - 4α - ol, m.p. 255–257°. *Anal.* Found: C, 71.36; H, 8.73. The 1β-(β-hydroxyethyl) derivative, m.p. 199–201°; 210–211° (*anal.* Found: C, 73.56; H, 9.55) was obtained by reduction with lithium aluminum hydride; 1β-(β-*p*-toluenesulfonate), m.p. 157–158°. *Anal.* Found: C, 68.10; H, 8.17. Successive oxidations of the monotosylate with the chromium trioxide–pyridine complex,[2] with osmium tetroxide, and with periodic acid gave 2β,4b-dimethyl-1β-(β-*p*-toluenesulfonyloxyethyl) - 2 - acetonyl - 7 - ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4-one (IV), m.p. 105–108°. *Anal.* Found: C, 66.15; H, 7.19. The initial reaction product of IV with sodium methoxide was *dl*-3-ethylenedioxy-Δ^5-17α-pregnene-11,20-dione, m.p. 212–214° (*anal.* Found: C, 74.26; H, 8.58) which on equilibration with alkali gave the 3-ethylenedioxy derivative of *dl*-ketoprogesterone (V), m.p. 181–182.5°. *Anal.* Found: C, 74.34; H, 8.36. (Acid hydrolysis of V gave *dl*-11-ketoprogesterone,[5] m.p. 175–176°; *anal.* Found: C, 76.72; H, 8.65). Resolution of V via the strychnine salt (dec. 212–214°; *anal.* Found: N, 3.21) of the *dl*-21-oxalyl acid (VI) dec. 174–177°; *anal.* Found: C, 67.36; H, 7.08) followed by hydrolysis of the oxalyl acid group gave 3-ethylenedioxy-Δ^5-pregnene-11,20-dione,[5,6] m.p. and mixed m.p. 175–176.5°, $[\alpha]^{25}D$ + 52 ±2° ($CHCl_3$). (*Anal.* Found: C, 74.37; H, 8.45). Acid hydrolysis of the ethylenedioxy derivative gave 11-ketoprogesterone,[5] m.p. and mixed m.p. 178°, $[\alpha]^{23}D$ + 231 ± 4° (acetone).

Iodination and acetoxylation[7] of the 21-oxalyl acid of 3-ethylenedioxy-Δ^5-pregnene-11,20-dione, m.p. 183–185°, $[\alpha]^{25}D$ + 61 ± 2° (THF) (*anal.* Found: C, 67.71; H, 7.17), obtained in the above resolution, yielded successively crystalline 3-ethylenedioxy - 21 - iodo - Δ^5 - pregnene - 11,20 - dione and 3-ethylenedioxy-Δ^5-pregnene-21-ol-11,20-dione acetate[5] (VII), m.p. and mixed m.p. 193.5–194°; $[\alpha]^{25}D$ + 52 ± 2° ($CHCl_3$). *Anal.* Found: C, 70.02; H, 7.65.

The 20-cyanhydrin of VII, dec. 220–224° (*anal.* Found: C, 68.17; H, 7.63) was dehydrated to the $\Delta^{5,17}$-20-cyanopregnadiene, m.p. 203°. Oxidation with potassium permanganate[8] gave 3-ethylenedioxy - Δ^5 - pregnene - 17α,21 - diol - 11,20 - dione acetate, dec. 262–267°. *Anal.* Found: C, 67.50; H, 7.49. Acid hydrolysis of the latter yielded cortisone acetate[5] VIII, m.p. and mixed m.p. 239–244°, $[\alpha]^{25}D$ + 210° ($CHCl_3$).

Alkaline iodination of the *dl*-21-oxalyl acid VI gave crystalline *dl*-3-ethylenedioxy-21-iodo-Δ^5-pregnene-11,20-dione which with potassium acetate yielded *dl*-3-ethylenedioxy-Δ^5-pregnene-21-ol-11,-





V R = H
VI R = $COCO_2H$
VII R = OAc

VIII

(3) *Cf.* D. A. Van Dorp and J. F. Arens, *Nature*, **160**, 189 (1947).

(4) *Cf.* A. J. Birch, *J. Chem. Soc.*, 430 (1944), and succeeding papers.

(5) Identity confirmed by infrared comparison.

(6) A sample prepared from 11-ketoprogesterone had $[\alpha]^{25}D$ + 52.5 ± 2°, m.p. 175–176°.

(7) *Cf.* C. R. Addinall, FIAT Final Report, 996, Jan. 29 (1947).

(8) Unpublished procedure of R. Tull, R. E. Jones and Huang-Minlon. See also von J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 859 (1951).

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°.

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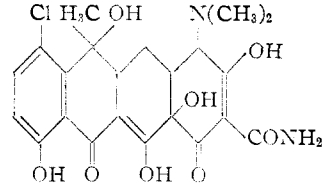
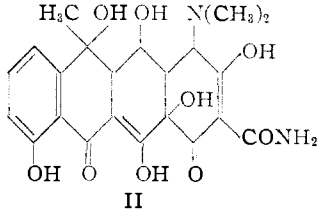
TERRAMYCIN. VIII. STRUCTURE OF AUREOMYCIN AND TERRAMYCIN

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

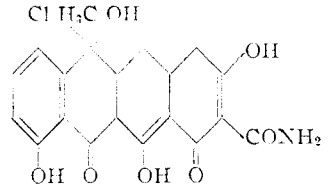
The structure I is in agreement with our analytical data which indicate that the molecular formula of aureomycin is $C_{22}H_{23}N_2O_8Cl$: *Anal.* Calcd. for $C_{22}H_{23}N_2O_8Cl$: C, 55.17; H, 4.84; N, 5.85; Cl, 7.40. Found: C, 55.10; H, 4.90; N, 5.72; Cl, 7.27. Calcd. for $C_{22}H_{23}N_2O_8Cl\cdot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

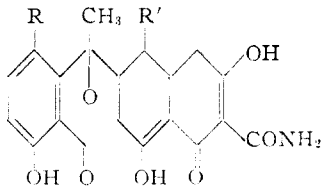
(2) (a) D. J. Hiscox, *J. Am. Pharm. Assoc.*, **40**, 237 (1951); (b) J. Dunitz and J. Robertson, THIS JOURNAL, **74**, 1108 (1952); (c) R. Pepinsky and T. Watanabe, *Science*, **115**, 541 (1952).

(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).