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THE ABSOLUTE CONFIGURATION OF THE TETRACYCLINES

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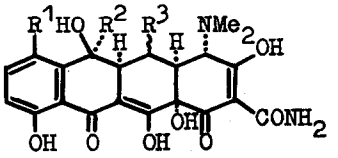
CHEMICAL[1] and X-ray[2] investigations had hitherto led to establishment of the relative configuration (I) for naturally occurring tetracyclines. Now we have found that formula (I) also expresses the absolute configuration of these antibiotics.



(I)

R^1= H, Cl or Br; R^2= H or Me; R^3= H or OH

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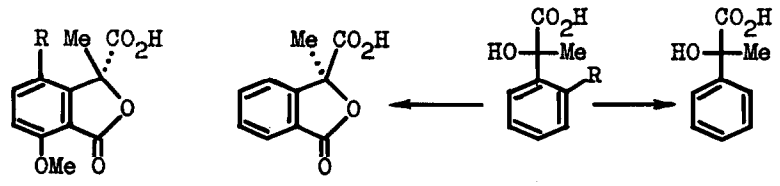
[1] C.W. Waller, B.L. Hutchings, R.W. Broschard, A.A. Goldman, W.J. Stein, C.F. Wolf and J.H. Williams, J. Amer. Chem. Soc. 74, 4981 (1952); L.H. Conover, Special Publication No. 5 p. 48. The Chemical Society, London (1956); J.R.D. McCormick, P.A. Miller, J.A. Growich, N.O. Sjolander and A.P. Doerschuk, J. Amer. Chem. Soc. 80, 5572 (1958); A. Green and J.H. Boothe, Ibid. 82, 3950 (1960); R.K. Blackwood, H.H. Rennhard and C.R. Stephens, Ibid. 82, 745, 5194 (1960); R.K. Blackwood, J.J. Beereboom, H.H. Rennhard, M. Schach von Wittenau and C.R. Stephens, Ibid. 83, 2773 (1961); H.H. Rennhard, R.K. Blackwood and C.R. Stephens, Ibid. 83, 2775 (1961).

[2] S. Hirokawa, Y. Okaya, F.M. Lovell and R. Pepinsky, Z. Krist. 112, 439 (1959).

We have proved the absolute configuration (I) by correlating the asymmetric centre 6 of the tetracyclines with that of atrolactinic acid as follows: methylation and $KMnO_4$ oxidation of aureomycin (I, R^1 = Cl, R^2 = Me, R^3 = H) yielded the previously described[3] (+)-4-chloro-7-methoxy-3-methylphthalide-3-carboxylic acid (IIa) [m.p. 187-189°, from 50% EtOH; $[\alpha]_D^{20}$ +29.5° (c 1 in EtOH)]. The product was then dehalogenated by hydrogenation in the presence of PdO in alkaline solution, forming (+)-7-methoxy-3-methylphthalide-3-carboxylic acid (IIb) [m.p. 193-195°, from water; $[\alpha]_D^{20}$ +69.5 (c 1 in EtOH); U.V.: 212, 235, 299 mμ (log ε 4.30, 3.77, 3.70); I.R.: 1745, 1786 cm^{-1}. Found: C, 59.62; H, 4.64; Eq. 222.0. Calc. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54; Eq. 222.2].



(IIa): R = Cl (III) (IVa): R = NHAc (V)

(IIb): R = H (IVb): R = N_2^+

On the other hand DL-o-acetylaminoatrolactinic acid (IVa) [m.p. 140-142°, from water; U.V.: 243 mμ (log ε 3.07); I.R.: 1667, 1719, 3350, 3450, 3560 cm^{-1}. Found: C, 54.69; H, 6.33; N, 5.83. Calc. for $C_{11}H_{13}NO_4 \cdot H_2O$: C, 54.76; H, 6.27; N, 5.81], prepared from 3-methyldioxindole[4] by alkaline hydrolysis and acetylation with Ac_2O, was resolved by crystallization of the cinchonidine salts from acetone. The less soluble salt [dec. 182-183°, $[\alpha]_D^{20}$ -25° (c 1 in EtOH). Found: C, 69.36; H, 6.71; N, 8.47. Calc. for $C_{30}H_{35}N_3O_5$: C, 69.69; H, 7.01; N, 8.11] on saponification with 1.5 N KOH,

[3] B.L. Hutchings, C.W. Waller, S. Gordon, R.W. Broschard, C.F. Wolf, A.A. Goldman and J.H. Williams, J. Amer. Chem. Soc. 74, 3710 (1952).

[4] B. Mills and K. Schofield, J. Chem. Soc. 5558 (1961).

diazotization and replacement of the diazo group by CN followed by hydrolysis with 1 N HCl gave (-)-3-methylphthalide-3-carboxylic acid [m.p. 105-106°, from benzene; $[\alpha]_D^{20}$ -60° (c 1 in EtOH); U.V. 273, 281 mμ (log ε 3.30, 3.32); I.R.: 1742, 1783, 3050 cm^{-1}. Found: C, 62.60; H, 4.42. Calc. for $C_{10}H_8O_4$: C, 62.50; H, 4.20]. This acid should possess the 3S-configuration (III) since the intermediate o-diazoatrolactinic acid (IVb) on reduction with H_3PO_2 forms L(+)-atrolactinic acid (V) [m.p. 114-116°, from benzene; $[\alpha]_D^{20}$ +36.5° (c 8 in EtOH)].

Spectropolarimetric comparison of the acid (III) with the aforementioned phthalidecarboxylic degradation products of aureomycin (II) revealed that the latter are of the opposite, i.e. 3R-configuration. Indeed, Fig. 1 shows the rotatory dispersion curve of the (+)-acid (IIb) to be almost antipodal to that of the (-)-acid (III). The curve for the (+)-acid (IIa) is less characteristic, evidently due to the deviation of the substituents at the asymmetric centre as the result of repulsion by the Cl atom (cf.[2]).

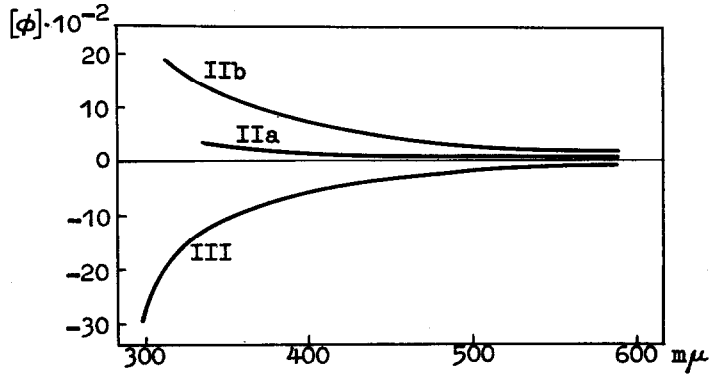


FIG. 1

Rotatory dispersion of 3-methylphthalide-3-carboxylic acids (IIa), (IIb) and (III) in dioxane at 20°.

The only asymmetric atom of the acids (II) stems from C_6 of aureomycin and doubtlessly retains the original configuration since this atom was not subjected to direct substitution during degradation of the antibiotic and does not epimerize in alkaline medium. Hence the correlation we have made of acids (II) with atrolactinic acid proves the absolute configuration for aureomycin, as well as for the sterically related tetracycline and 7-bromotetracycline (I; R^1 = Cl, H or Br, R^2 = Me, R^3 = H). The similarity of terramycin and 6-demethyltetracylines with the above tetracyclines in biogenesis and antibiotic action as well as in the direction and magnitude of the rotational shift (ca. -100°) on isomerization into 4-epitetracyclines[5] bears evidence of their stereochemical identity, so that these antibiotics with a high degree of assurance can be assigned the absolute configuration (I; R^1 = H, R^2 = Me, R^3 = OH) and (I; R^1 = H or Cl, R^2 = R^3 = H), respectively.

[5] J.R.D. McCormick, S.M. Fox, L.L. Smith, B.A. Bitler, J. Reichenthal, V.E. Origoni, W.H. Muller, R. Winterbottom and A.P. Doerschuk, J. Amer. Chem. Soc. 79, 2849 (1957); J.R.D. McCormick, N.O. Sjolander, U. Hirsch, E.R. Jensen and A.P. Doerschuk, Ibid. 79, 4561 (1957).