The Structure of the Macrolide Antibiotic Picromycin

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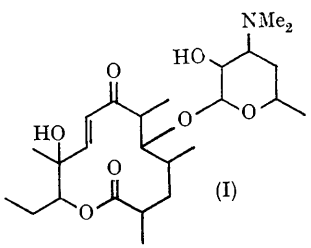
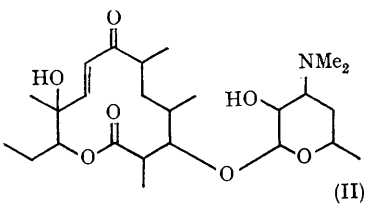
PICROMYCIN,[1-3] identical with albomycetin[4] and amaromycin,[5] has been assigned structure (I),[6,7] or (II).[7] If (II), picromycin would be stereoisomeric with methymycin (II),[7,8] although an attempt to relate them failed.[9]

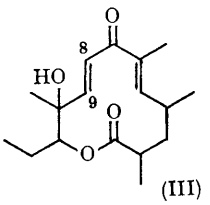
The published evidence,[1,6,7,10] however, is not in complete accordance with either formula (I) or (II). Mild treatment of picromycin with acid or base yielded the anhydro-aglycone, cromycin, which it was suggested[6,7b] was the dienone (III) arising by direct β-elimination of desosamine from structure (I) or by elimination involving a hydride shift from structure (II). Structure (III) for cromycin does not explain the production of 0·9 mole of carbon dioxide on refluxing with aqueous barium hydroxide.[10c] Furthermore, the i.r. spectrum (in KBr) of dihydrocromycin, which was prepared from dihydropicromycin and therefore had the 8,9-double bond reduced, showed in addition to maxima at 1723 (unconjugated lactone), 1666, and 1635 cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone), a further intense maximum at 1701 cm.$^{-1}$ the origin of which was not clear.[7a]

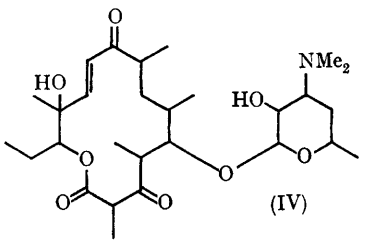
Our material, produced from *S. griseoflavus*,[3a] was identical with authentic picromycin. Mass spectroscopy showed a molecular ion at *m/e* 525 not at *m/e* 469 ($C_{25}H_{43}NO_7$) as required for structure (I) or (II). This corresponds to $C_{28}H_{47}NO_8$, in excellent agreement with published analyses.[1,7a] Kuhn–Roth analyses,[7a,10b] when applied to this new formula, indicate 7 C-methyl groups and suggest that the extra C_3H_4O moiety is present as an additional propionate biosynthetic unit,[11] –CO·CHMe–, overlooked in previous work. The decarboxylation mentioned above implies a β-ketolactone, and this was confirmed spectroscopically. The ^{1}H n.m.r. spectrum of picromycin (in $CDCl_3$) shows resonances centred at τ 6·10 (1H, 1 : 3 : 3 : 1 q, J 7·2 c./sec.) and 8·52 (3H, 1 : 1 d, J 7·2 c./sec.) corresponding[12] to the methine and methyl protons of the system –OCO·C*H*(CH_3)CO–, which collapse on appropriate double irradiation. The addition of alkali to picromycin (in EtOH) immediately produces a u.v. absorption maximum at 294 mμ (log ϵ 4·26) due to the enolate anion –OCO·CMe=C–O$^-$ (*cf.* ref. 13) whilst the conjugated ketonic maximum at 224 mμ (log ϵ 4·01) remains unchanged. Dihydropicromycin affords a similar alkaline maximum at 293 mμ (log ϵ 4·36).

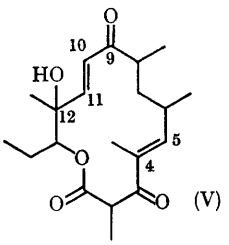
Reduction of cromycin with an excess of sodium borohydride afforded a product in which the only


(I)


(II)


(III)


(IV)


(V)

carbonyl function apparent from the i.r. or u.v. spectrum was a saturated lactone, but which could be re-oxidised with manganese dioxide to cromycin in good yield.[7b] This necessitates that both ketones of cromycin are conjugated, and taken in conjunction with other published evidence[1,6,7,10] leads to structure (V) for cromycin. In agreement with this structure, cromycin shows, in a variety of i.r. media,[6,7a,10c] only unconjugated lactone and conjugated ketone functions [*e.g.* ν_{max} (CCl_4) 1740, 1680, and 1635 cm.$^{-1}$], together with conjugated ketone u.v. absorption [λ_{max} (EtOH) 227 mμ (log ϵ 4·39)] almost twice as intense as that of picromycin.

Dihydrocromycin, ν_{max} (in CCl_4) 1735 (lactone), 1710 (ketone), 1685, and 1635 cm.$^{-1}$ (conjugated ketone), from its mode of preparation must have the 10,11-double bond of formula (V) reduced. The conjugated double bond formed by elimination of desosamine and responsible for the u.v. maximum (in EtOH) at 232 mμ (log ϵ 4·19) must occupy the 4,5-position as in cromycin (V), since ozonolysis and alkaline hydrolysis gave pentane-2,3-dione, characterised as 2-ethyl-3-methylquinoxaline[14] after reaction with *o*-phenylenediamine. Hemiacetal formation occurs readily between the C(12)-hydroxy and the C(9)-carbonyl groups of dihydrocromycin, subsequent dehydration then permitting the observed formation[7a] of laevulinic acid on ozonolysis followed by hydrolysis and periodate oxidation.

Provided that hydride shifts have not occurred during the formation of the 4,5-double bonds of both cromycin and dihydrocromycin, then picromycin must have the structure (IV).

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[1] H. Brockmann and W. Henkel, *Naturwiss.*, 1950, **37**, 138.
[2] R. B. Woodward, "Festschrift Arthur Stoll", Birkhauser, Basel, 1957, p. 524; *Angew. Chem.*, 1957, **69**, 50; M. Berry, *Quart. Rev.*, 1963, **17**, 343.
[3] (*a*) Z. Vaněk, L. Doležilová, and Z. Řeháček, *Čslká Microbiol.*, 1958, **3**, 255; (*b*) R. Hütter, W. Keller-Schierlein, and H. Zähner, *Arch. Mikrobiol.*, 1961, **39**, 158, and refs. therein; (*c*) S. E. DeVoe, H. B. Renfroe, and W. K. Hausmann, *Antimicrobial Agents and Chemotherapy*, 1963, 125.
[4] B. Takahashi, *J. Antibiotics, Tokyo, Ser. A*, 1954, **7**, 149.
[5] T. Hata, Y. Sano, H. Tatsuta, R. Sugawara, A. Matsumae, and K. Kanamori, *J. Antibiotics, Tokyo, Ser. A*, 1955, **8**, 9; H. Ogura, A. Otagoshi, Y. Sano, and T. Hata, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 682.
[6] H. Brockmann and R. Oster, *Chem. Ber.*, 1957, **90**, 605.
[7] R. Anliker and K. Gubler, *Helv. Chim. Acta*, (*a*) 1957, **40**, 119; (*b*) 1957, **40**, 1768.
[8] C. Djerassi and J. A. Zderic, *J. Amer. Chem. Soc.*, 1956, **78**, 6390.
[9] C. Djerassi, O. Halpern, D. I. Wilkinson, and E. J. Eisenbraun, *Tetrahedron*, 1958, **4**, 369.
[10] (*a*) H. Brockmann and W. Henkel, *Chem. Ber.*, 1951, **84**, 284; (*d*) H. Brockmann, H. Genth, and R. Strufe, *Chem. Ber.*, 1952, **85**, 426; (*c*) H. Brockmann and R. Strufe, *Chem. Ber.*, 1953, **86**, 876; (*d*) H. Brockmann, H. B. König, and R. Oster, *Chem. Ber.*, 1954, **87**, 856; (*e*) H. Brockmann and R. Oster, *Naturwiss.*, 1955, **42**, 1955.
[11] *Cf.* J. W. Corcoran and M. Chick, in "Biosynthesis of Antibiotics", ed. J. F. Snell, Academic Press, New York, 1966, p. 159, and refs therein.
[12] J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, 1964, **86**, 2105; *Canad. J. Chem.*, 1965, **43**, 1516.
[13] F. N. McMillan, *Analyt. Chem.*, 1956, **28**, 1532.
[14] I. M. Heilbron, E. R. H. Jones, P. Smith, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 54.