Synthesis of 2′-Deoxytubercidin {4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine} from the Parent Antibiotic

By MORRIS J. ROBINS* and WOLFGANG H. MUHS

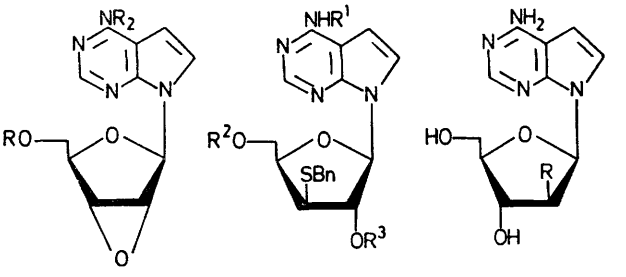
(*Department of Chemistry, The University of Alberta, Edmonton, Alberta, Canada* T6G 2G2)

Summary Desulphurisation of 4-amino-7-(2-*S*-benzyl-2-thio-2-deoxy-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**7**), obtained by intramolecular episulphonium ion rearrangement of the isomeric 3′-*S*-benzyl-thio-*xylo*-2′-*O*-methylsulphonyl derivative (**5**) [obtained in three steps from 2′,3′-anhydrotubercidin (**1**)] using sodium benzoate in *NN*-dimethylformamide, gave the elusive 2′-deoxytubercidin (**8**).

TUBERCIDIN (4-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]-pyrimidine) was discovered in 1957 and its synthesis was reported[1] in 1968. A comprehensive review[2] of chemical base modifications, biochemical and biological studies, and clinical applications is available.

Ribonucleotide reductase from bacterial sources was reported to effect deoxygenation of tubercidin on a micro scale,[3] and deoxynucleotides of tubercidin have been detected in enzymic digests of DNA from radioactive tracer feeding experiments.[3] However, although 2′-deoxytubercidin has been a synthetic target of significant biochemical and biological interest for over ten years, no chemical or enzymatic preparation on a scale allowing characterisation or investigation has appeared. Attempted nucleophilic displacement of arylsulphonates at C(2′) led to sulphur–oxygen cleavage or else resulted in decomposition to intractable materials. Halide attack on 2′,3′-*O*-acyloxonium species which gave 10—15% of C(2′)-substitution in the corresponding adenosine intermediates[4,5] produced exclusive C(3′)-substitution with tubercidin.[4,6,7] A synthesis of 2′-deoxytubercidin (**8**) from the parent antibiotic is now outlined employing intramolecular migration of *S*-benzyl from C(3′) to C(2′) *via* episulphonium ion rearrangement as the key step.

Benzoylation of 2′,3′-anhydrotubercidin[4,7] (**1**) (obtained in 96% overall yield from tubercidin) gave the *N*(4)*N*(4)-*O*(5′)-tribenzoyl derivative† (**2**), m.p. 201—202 °C, quantitatively. This soluble and stabilised [against N(1) → C(3′) intramolecular cyclisation] product was treated with sodium benzylthiolate in hot tetrahydrofuran to give (**3**),† m.p. 142—144 °C, in 68% yield plus 22% of its O(5′)-deblocked derivative† (**4**), m.p. 121—124 °C. No product of C(2′)-attack was detected. Mesylation in the usual manner gave a quantitative yield of the 2′-mesylate (**5**), ν 1170 cm^{-1} (OSO_2R), δ 3·15 (3H, s, OSO_2Me), *m/e* 562·16710 [calc. for $C_{32}H_{26}N_4O_4S$ (M^+ — $HOSO_2Me$): 562·16757]. Treatment of this amorphous glass with sodium benzoate in hot *NN*-dimethylformamide (DMF) and deblocking with methanolic sodium methoxide gave (**6**),† m.p. 98—101 °C, and its 2′-*S*-benzylthioarabino isomer (**7**),† m.p. 146—148 °C, in 90% combined yield from (**3**) and in a ratio of 2:3, respectively. The ratio and formation of (**7**) are compatible[8] with benzoate attack on a 2′,3′-*lyxo*-thiiranium intermediate.



(1) R = H
(2) R = Bz
(3) R^1=R^2=Bz, R^3=H
(4) R^1=Bz, R^2=R^3=H
(5) R^1=R^2=Bz, R^3=Ms
(6) R^1=R^2=R^3=H
(7) R = SBn
(8) R = H

Bn = CH_2Ph, Bz = COPh, Ms = SO_2Me

Desulphurisation‡ of (**7**) gave 2′-deoxytubercidin (**8**) (77%), m.p. 217—218 °C; $[\alpha]_D^{24}$ −43° (*c* 0·58, EtOH); λ (0·1 N HCl) (max) 272 (ε 12,800) and 227 (26,500) nm, (min) 245 (ε 3900) nm; λ (0·1 N NaOH) (max) 270 (ε 13,500) nm, (min) 240 (ε 3200) nm; δ [$(CD_3)_2SO$, rel. to Me_4Si] 2·14 (1H, octet, $J_{2'a,2'b}$ 13·5 Hz, H-2′b), 2·5 (m, Me_2SO and H-2′a), 3·53 (2H, 't', H-5′a and H-5′b), 3·82 (1H, m, H-4′), 4·34 (1H, m, $J_{3',2'a}$ 5·5, $J_{3',2'b}$ 3 Hz, H-3′), 5·10 (1H, t, $J_{OH,5'a,5'b}$ 5 Hz, OH-5′), 5·20 (1H, d, $J_{OH,3'}$ 4 Hz, OH-3′), 6·49 (1H, d of d, $J_{1',2'a}$ 8, $J_{1',2'b}$ 6 Hz, H-1′), 6·58 (1H, d, $J_{5,6}$ 4 Hz, H-5), 7·0 (2H, s br, NH_2-4), 7·35 (1H, d, $J_{6,5}$ 4 Hz, H-6), 8·07 (1H, s, H-2); *m/e* (70 eV, 180 °C, direct probe) (% R.I., peak) 250·1073 [6·5, M^+ (calc. 250·1066)], 220 (2·4, M^+ — OH_2C), 161 (23·8, BHCH=CH_2), 135 (15, B+2H), 134 (100, B+H) (B = pyrrolopyrimidine base).

Analogous desulphurisation‡ of (**6**) gave 3′-deoxytubercidin.[4,6,7] The overall yield of (**8**) in eight stages from the parent antibiotic is 27% in addition to an equivalent quantity of the 3′-deoxy isomer.

We acknowledge generous support from the National Cancer Institute of Canada, the National Research Council of Canada, and The University of Alberta.

(*Received, 26th January* 1976; *Com.* 077.)

† Elemental analyses and u.v., ^1H n.m.r., and high resolution mass spectra are compatible with these structures.

‡ Raney Nickel (W. R. Grace & Co. No. 28) in DMF at 100 °C.

[1] R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, 1968, **90**, 524; *ibid.*, 1969, **91**, 2102.
[2] R. J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970, ch. 8.
[3] See ref. 2, pp. 336, 338, 340, 345, and 346.
[4] M. J. Robins, R. Mengel, and R. A. Jones, *J. Amer. Chem. Soc.*, 1973, **95**, 4074.
[5] A. F. Russell, S. Greenberg, and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1973, **95**, 4025.
[6] M. J. Robins, J. R. McCarthy, Jr., R. A. Jones, and R. Mengel, *Canad. J. Chem.*, 1973, **51**, 1313.
[7] T. C. Jain, A. F. Russell, and J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 3179.
[8] C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, 1959, **81**, 3967.