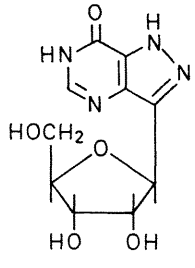
Synthesis of the Nucleoside Antibiotic Formycin B

By EDWARD M. ACTON,* KENNETH J. RYAN, DAVID W. HENRY, and LEON GOODMAN
(*Life Sciences Division, Stanford Research Institute, Menlo Park, California* 94025)

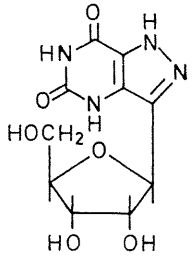
Summary Curtius rearrangement of the 4-azide of 5-(tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-3,4-dicarboxylic acid gave the *N*-carboxy-anhydride of the 4-amino-3-acid the methyl ester of which, on heating in formamide followed by catalytic hydrogenolysis, gave formycin B.

RECENT communications[1-3] have elaborated a promising synthetic approach to the *C*-nucleoside formycin B (**1**), but so far only the metabolite, oxoformycin B (**2**), has been synthesized. We now report the successful synthesis of formycin B.

A key intermediate in this general approach is the pyrazole *C*-nucleoside (**3a**), a 3-ribosyl tri-*O*-benzyl ether with the two pyrazole carboxy-groups selectivity functionalized as the 4-hydrazinocarbonyl-3-carboxamide. Previously,[3] the azide (**4a**), formed from (**3a**), gave, by a Curtius rearrangement, the dione (**6a**), the tri-*O*-benzyl derivative of

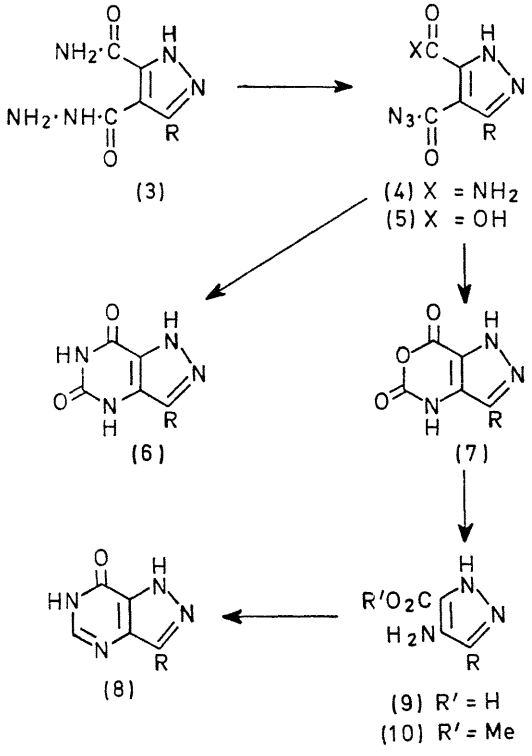


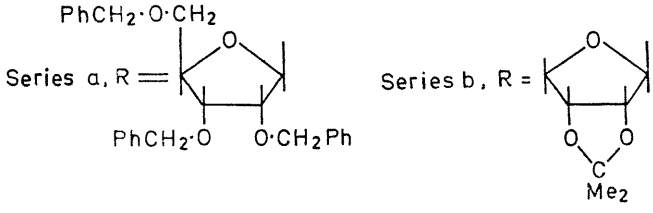
(1)



(2)

oxoformycin B. Similar treatment of analogous 4-azidocarbonyl-3-carboxamides[1,4] as models for (**4a**) also gave the corresponding diones, exclusively. Presumably in each case the intermediate pyrazole-4-isocyanate cyclized readily with the adjacent 3-carboxamide group. This reaction could not be adjusted, except in the simplest model series,[1] to give

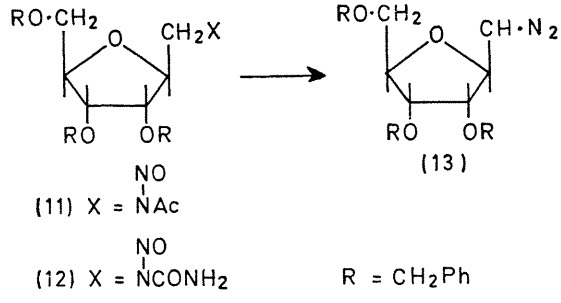




pyrazole-4-amines (or derivatives thereof) which were required for synthesis of pyrazolo[4,3-*d*]pyrimidine-7-ones [e.g., (**1**) and (**8**)], in the formamide-cyclization method of Robins.[5]

This obstacle has now been surmounted by treating (**3a**), m.p. 120—122°, in acetic acid–carbon tetrachloride at 3° with dinitrogen tetroxide in the presence of sodium acetate, thereby generating the 4-azide (**5a**) with an adjacent carboxy-group at C-3, i.r., 3·7—3·8 br (OH) and 4·59 and 4·67 (N_3) μm. Curtius rearrangement of (**5a**) by heating in toluene solution at 100° then afforded the *N*-carboxylic anhydride (**7a**), i.r. 5·53 and 5·70 (C=O) μm, probably by cyclization of the intermediate isocyanate. These intermediates (**5a**) and (**7a**) were obtained as glasses, characterized by spectral comparison with (**5b**) and (**7b**). Ring opening of the anhydride occurred in tetrahydrofuran–water (5:1) under reflux, with loss of the i.r. bands at 5·53 and 5·70 μm, to give the 4-amino-3-acid (**9a**). *Treatment of* (**9a**) with 2,2-dimethoxypropane and hydrochloric acid afforded the ester (**10a**), purified by chromatography on silica gel in $CHCl_3$ [25% yield based on (**3a**)], 5·80 (C=O) and 3·0 and 6·17 (NH_2) μm, τ ($CDCl_3$; internal Me_4Si) 4·77 (d, 1′-H) and 6·12 (s, CO_2Me). Heating of (**10a**) in formamide at 218° (bath) for 1·75 h afforded 2′,3′,5′-tri-*O*-benzylformycin B (**8a**), purified chromatographically (silica gel; ethyl acetate–benzene, 1:1) and crystallized (40% yield) from MeOH–H_2O (2:1), m.p. 145—146°, τ 2·08 (s, 5-H) and 4·35 (d, 1′-H). Hydrogenolytic debenzylation with palladium chloride[6] in ethanol afforded formycin B (**1**), m.p. 245—249° (from ethanol) without depression on admixture with an authentic sample of the natural product, chromatographically identical, R_f 0·55 (silica gel; $CHCl_3$–MeOH, 1:1), λ_{max} (pH 1) 276 nm (ε 8318), (pH 13) 290 (9134).

This useful reaction sequence (**5**) → (**10**) was first explored in the model series (series **b**) previously described,[2] with 2,3-*O*-isopropylidene-β-DL-erythrofuranose as the sugar portion, where crystalline intermediates could be expected. The hydrazido-carboxamide (**3b**), treated as for (**3a**), afforded the azido-acid (**5b**) (66%), m.p. 137—139° (from $CHCl_3$–CCl_4), i.r. 3·7br (OH), 4·61 and 4·68 (N_3) μm. The *N*-carboxylic anhydride (**7b**) crystallized from the hot toluene of the Curtius reaction medium (90%), m.p. 200—210° (decomp.), i.r. 5·52 and 5·71 (C=O) μm. Hydrolysis of (**7b**) in hot water afforded an amino-acid as expected, but rather surprisingly a pH of 2·5 was attained in the solution and the 2′,3′-*O*-isopropylidene group was lost. The blocked amino-ester (**10b**) was therefore obtained by esterification of (**5b**) with diazomethane to an unstable azido-ester, which was heated with aqueous hydrogen carbonate solution to complete the Curtius rearrangement and accomplish the hydrolysis to (**10b**), m.p. 134—135°, τ 6·10 (s, CO_2Me). Heating (**10b**) in formamide gave the 7-one (**8b**), m.p.



245—253° (from water), λ_{max} (pH 1) 273 nm (ε 7000), (pH 13) 290 (7610).

If (**3b**) was treated more conventionally with aqueous nitrous acid in a two-phase system with ether to give the azide (**4b**), the Curtius rearrangement under various conditions then afforded only the 5,7-dione (**6b**), m.p. 305—307° (decomp.), λ_{max} (pH 1) 286 nm (ε 5480), (pH 13) 304 (4450).

The pyrazole *C*-nucleoside intermediates were synthesized from 1-diazo-sugars in 1,3-dipolar additions[2,3] with dimethyl acetylenedicarboxylate. The diazo-ether (**13**) was generated from the nitroso-acetamide (**11**) in preference to the

nitroso-urea[3] (**12**), since the latter was unavoidably contaminated with an isocyanate, presumably formed *via* nitrosation of the terminal nitrogen of the urea.

We thank Chemotherapy, the National Cancer Institute, the National Institutes of Health, the Public Health Service for support of this research.

(*Received, June 4th,* 1971; *Com.* 910.)

[1] M. Sprinzl, J. Farkaš, and F. Šorm, *Tetrahedron Letters*, 1969, 289.
[2] E. M. Acton, K. J. Ryan, and L. Goodman, *Chem. Comm.*, 1970, 313.
[3] M. Bobek, J. Farkaš, and F. Šorm, *Tetrahedron Letters*, 1970, 4611.
[4] See, for example, (**4b**) later; see also ref. 1.
[5] R. K. Robins, L. B. Holum, and F. W. Furcht, *J. Org. Chem.*, 1956, **21**, 833.
[6] C. P. J. Glaudemans and H. G. Fletcher, jun., *ibid.*, 1963, **28**, 3004.