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SYNTHESIS OF THE CARBOCYCLIC ANALOG OF ENTEROBACTIN

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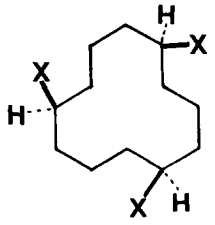
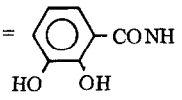
The accompanying note[1] describes a total synthesis of the microbial iron transporting agent enterobactin (1)[2] which has been developed in these laboratories. The question of how bacteria liberate ferric ion from the very stable enterobactin complex 2 ($K_{form} \cong 10^{30}$) remains unanswered. One reasonable possibility involves enzymic cleavage of the cyclic triester system of 2 either by ester hydrolysis or elimination of α-H and β-carboxylate to form a less stable complex. In connection with this point it seemed worthwhile to synthesize for biological study the carbocyclic analog 3 of enterobactin, a hitherto unknown substance.[3]

All cis-cyclodecan-1,5,9-triol[4] (4) (mp 171°) was converted to the tris tosylate 5[5] (4.5 equiv of p-toluenesulfonyl chloride in pyridine (10ml/g of 4) at 25° for 4 hr) (89% yield) which in turn gave the tris azide 6 upon treatment with 10 equiv of sodium azide in dimethylformamide (25ml/g of 5) at 80° for 18 hr. The tris azide 6 was used without purification in the next step,[6] catalytic reduction with hydrogen (1 atm) and 5% palladium-on-charcoal in methanol for 12 hr at 25° to form triamine 7. Acylation of crude 7 with 4.5 equiv of the acetonide of 2,3-dihydroxybenzoyl chloride[7] and 10 equiv of triethylamine in tetrahydrofuran for 12 hr at 25° afforded after chromatography on silica gel and recrystallization from benzene-hexane the triamide 8, mp 216-217°, R_f 0.25 using benzene-ethyl acetate 1:1 on silica gel plates, in ca. 50% yield overall from tosylate 5. Removal of the isopropylidene protecting groups from 8 was accomplished by heating in acetic acid - water (4:1) at 100° for 18 hr to form 3, mp 170-171° after recrystallization from amyl acetate in 90% yield; R_f 0.7 using ethyl acetate for development on silica gel plates.

As expected the carbocyclic analog of enterobactin 3 formed a very stable ferric complex (not affected by the addition of the sodium salt of ethylenediamine tetraacetic acid at pH 7) which showed light absorption at pH 7 in water (λ max 495 nm, ϵ 5500) closely comparable to that of ferric enterobactin (2) (λ max 495 nm, ϵ 5600).

Biological studies by Prof. J. B. Neilands with the ferric complex of 3 show it to be remarkably effective in bacterial iron transport (ca. 75% of 2); full details and their implications will be reported separately.[8,9]



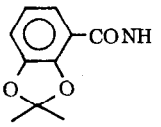
3, X = 

4, X = OH

5, X = OTs

6, X = N_3

7, X = NH_2

8, X = 

References

1. E. J. Corey and S. Bhattacharyya, Tetrahedron Lett., preceding paper.
2. For a general review see J. B. Neilands in "Inorganic Biochemistry," G. Eichorn, Ed., Elsevier, New York, 1973, p. 167.
3. After the completion of the synthesis described herein we learned of an unsuccessful previous attempt to prepare 3; see, D. J. Collins, C. Lewis and J. M. Swan, Aust. J. Chem., 28, 673 (1975). This attempt, in common with our own studies, involved the preparation of all cis-1,5,9-triamino cyclododecane. We are grateful to Prof. J. B. Neilands for drawing our attention to this publication.
4. (a) Stereochemical assignment: H. C. Brown and E. Negishi, J. Am. Chem. Soc., 91, 1226 (1969); (b) method of preparation: G. W. Rottermund and R. Köster, Ann. Chem., 686, 153 (1965).
5. Satisfactory spectral data were obtained for the various intermediates described herein.
6. The azide 6 was contaminated with ca. 20% of unsaturated mono and diazides formed as a result of elimination as a side reaction.
7. The synthesis of 2,3-dihydroxybenzoyl chloride acetonide was developed in these laboratories by S. Bhattacharyya. The acetonide of catechol was lithiated (1.1 equiv n-butyllithium, 1.0 equiv tetramethylethylenediamine in hexane at 0° for 6 hr) and carbonated using solid carbon dioxide to give the 2,3-acetonide of 2,3-dihydroxy benzoic acid, mp 155-156° after recrystallization from chloroform, (50% yield). Conversion to the 2,3-acetonide of 2,3-dihydroxybenzoyl chloride, mp 90-91°, was accomplished by treatment with 1.1 equiv of thionyl chloride, a catalytic amount of dimethylformamide and 1.2 equiv of triethylamine in methylene chloride at 0° for 4 hr, removal of volatile materials from the crude product in vacuo and recrystallization from hexane (90% yield).
8. We are indebted to Prof. Neilands for valuable advice and suggestions and a sample of enterobactin.
9. This work was assisted financially by a grant from the National Institutes of Health.