Tetrahedron Letters No.44, pp. 3873-3876, 1970. Pergamon Press. Printed in Great Britain.

STRUCTURE AND ABSOLUTE CONFIGURATION OF THE POLYENE MACROLIDE ANTIBIOTIC AMPHOTERICIN B

W. Mechlinski* and C. P. Schaffner

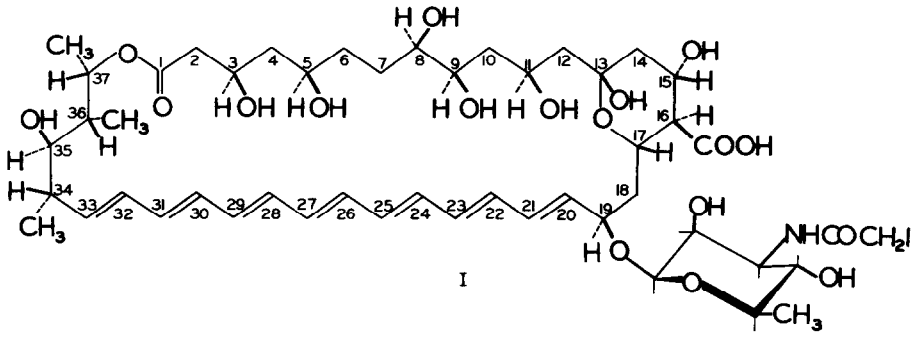
Institute of Microbiology
Rutgers University
The State University of New Jersey
New Brunswick, New Jersey 08903

P. Ganis** and G. Avitabile***

Polymer Research Institute
Polytechnic Institute of Brooklyn
Brooklyn, New York 11201

(Received in USA 12 August 1970; received in UK for publication 24 August 1970)

As a result of the x-ray single crystal analysis of N-iodoacetylamphotericin B the chemical and stereochemical absolute structure is presented (I). A similar structure and stereochemistry was extended to the parent compound itself, amphotericin B, a heptaene macrolide antifungal antibiotic possessing a free amino group in the sugar moiety.



I

The configuration of the asymmetric centers of the macrolide lactone ring based on the absolute stereochemistry of mycosamine[1,2] are given under the Cahn-Ingold-Prelog system[3] in Table 1.

* Visiting investigator from the Polish Academy of Sciences, Institute of Organic Chemistry, Warsaw, Poland.

** On sabbatical leave from Universita' di Napoli, Istituto Chimico, Via Mezzocannone 4 80134-Napoli, Italy.

*** Postdoctoral Fellow on leave from Universita' di Napoli, Istituto Chimico.

TABLE

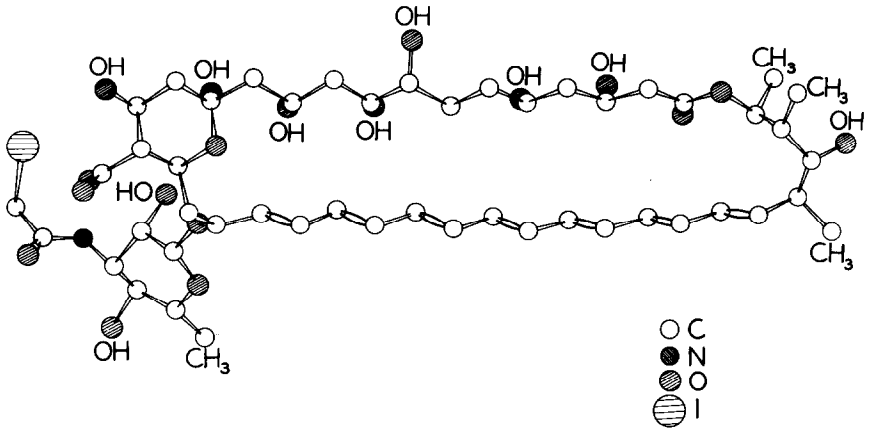
Carbon Atom	3	5	8	9	11	13	15	16	17	19	34	35	36	37
C.I.P.[1] System	R	R	R	R	S	R	S	R	S	R	S	R	R	S

The antifungal antibiotic amphotericin B[4] is produced by Streptomyces nodosus and was first isolated by Vandeputte et al[5] in 1956. Chemical studies by Dutcher[1,2,6], Borowski[7-11], Cope[12] and their co-workers, drew out the partial structure of amphotericin B[12].

Realizing the great difficulties involved in structural studies with the polyene macrolide antibiotics by strictly chemical means we made an attempt to employ the x-ray structure analysis of a single crystal for this purpose. The increasing importance of these antibiotics not only as antifungal agents but also as active substances in the treatment of prostatic hypertrophy[13] and hypercholesterolemia[14] is another reason for determining the total structure of these natural products. The N-iodoacetyl derivative of amphotericin B showing antifungal activity was crystallized from tetrahydrofuran solution. The intensities data were measured with MoKα radiation on a computer controlled automatic Picker diffractometer over a period of 8 days using one crystal. The decrease in standard intensities at the end of the measurements was about 30%. A total of 3702 independent reflections including 2658 non-zero ones were collected within $2\theta=40^{\circ}$.

Crystal data: N-iodoacetylamphotericin B monohydrate tri-tetrahydrofuran, $C_{49}H_{73}O_{18}N\,I\,H_2O\text{-}3C_4H_8O$; Mol.wt.; 1323.9; monoclinic, $a=21.28$, $b=8.78$, $c=18.69$ Å, $\beta=103^{\circ}58'$, $V=3387$ Å^3, $D_m=1.33$, $Z=2$, $D_c=1.30$, Space Group - $P2_1$.

After correction for the decrease in intensities, the structure was solved by the heavy atom method and has been refined to an R-factor of 0.14. The molecular structure of N-iodoacetylamphotericin B as viewed along b-axis is represented (II). We consider amphotericin B, the parent compound of N-iodoacetylamphotericin B, to be similar in structure to that shown (I). The only difference appears to be the N-iodoacetylation of the free amino group of the antibiotic. In the chemical structure the most interesting feature is the six-membered ketal ring formed from a ketone group at C-13 and the hydroxyl group at C-17.



II. The molecular structure of N-iodoacetylamphotericin B as viewed along b-axis.

The amino-sugar moiety as a pyranoside is β-glycosidically bound to the hydroxyl at C-19. It is interesting to speculate about the similarity of the amphotericin B moiety between carbon C-13 and C-19 in comparison with the corresponding moieties in the structures of nystatin[15, 16], pimaricin[17], lucensomycin[18], and tetrins A and B[19]. It seems to be possible that all of these other polyene antibiotics could form a six-membered ketal ring. Infrared spectral studies with nystatin and amphotericin B indicate that the free ketone group might not exist. Considering the biogenesis of amphotericin B the proposed total structure is in agreement with the normal polyketide pathway involving acetate and propionate condensation. The only exception involving the positioning of the hydroxyl group at C-8, might readily be explained by an epoxide intermediate mechanism.

ACKNOWLEDGEMENTS

We acknowledge in part the support of the National Institute of Allergy and Infectious Diseases under Public Health Service Grant No. AI-02095. Also we wish to call attention to the financial support in the Polymer Research Institute through a grant from the National Institute of Health (Grant No. GO-89974). We acknowledge the encouragement, support and helpful advice from Professor Benjamin Post in the pursuit of this project. We also thank Dr. William Brown of the Squibb Institute for Medical Research for pure amphotericin B (batch #91830-001).

REFERENCES

1. J. D. Dutcher, D. R. Walters, and O. Wintersteiner, J. Org. Chem., 28, 995 (1963).
2. M. von Saltza, J. D. Dutcher, J. Reid, and O. Wintersteiner, ibid., 28, 999 (1963).
3. R. S. Cahn, C. K. Ingold, and V. Prelog, Experentia, 12, 81 (1956).
4. W. Gold, H. A. Stout, J. F. Pagano, and R. Donovick, Antibiot. Ann., 1955-1956, 579 (1956).
5. J. Vandeputte, J. L. Wachtel, and E. T. Stiller, ibid., 1955-1956, 587 (1956).
6. J. D. Dutcher, M. B. Young, J. H. Sherman, W. Hibbits, and D. R. Walters, ibid., 1956-1957, 866 (1957).
7. E. Borowski, W. Mechlinski, L. Falkowski, T. Ziminski, and J. D. Dutcher, Tetrehedron Letters, 9, 473 (1965).
8. L. Falkowski, T. Ziminski, W. Mechlinski, and E. Borowski, Annales Societatis Chimicae Polonorum, 39, 225 (1965).
9. E. Borowski, W. Mechlinski, L. Falkowski, T. Ziminski, and J. D. Dutcher, ibid., 39, 400 (1965).
10. W. Mechlinski, T. Ziminski, L. Falkowski, and E. Borowski, ibid., 39, 497 (1965).
11. E. Borowski, W. Mechlinski, L. Falkowski, T. Ziminski, and J. D. Dutcher, ibid., 39, 1933 (1965).
12. A. C. Cope, V. Axen, E. P. Burrows, and J. Weinlich, J. Amer. Chem. Soc., 88, 4228 (1966).
13. H. W. Gordon, and C. P. Schaffner, Proceedings of the National Academy of Sciences, 60, 1201 (1968).
14. C. P. Schaffner and H. W. Gordon, Proceedings of the National Academy of Sciences, 61, 36 (1968).
15. M. Ikeda, M. Susuki, and C. Djerassi, Tetrehedron Letters, 38, 3745 (1967).
16. D. G. Mannering and R. W. Rickards, ibid., 60, 5319 (1969).
17. B. T. Golding, R. W. Rickards, W. E. Meyer, J. B. Patrick, and M. Barber, Tetrehedron Letters, 30, 3551 (1966).
18. G. Gaudiano, P. Bravo, and A. Quilico, ibid., 30, 3559 (1966).