Crystal Structure of Tryptanthrin (Indolo[2,1-*b*]quinazoline-6,12-dione)

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The structure of tryptanthrin, an antibiotic produced by the yeast *Candida lipolytica* has been determined by *X*-ray crystallographic analysis. The structure has been solved by direct methods and refined by block-diagonal least-squares to R 0·089 using 1207 independent reflections. The crystals are monoclinic, space group $P2_1/c$, with a = 7·46, b = 7·66, c = 20·78 Å; β = 109·0°, Z = 4. Tryptanthrin has thus been proved to be indolo[2,1-*b*]-quinazoline-6,12-dione: the structural features are consonant with the spectroscopic behaviour.

TRYPTANTHRIN is an antibiotic isolated[1] from the yeast *Candida lipolytica*. Crystallographic analysis was carried out in order to determine its structure as the preliminary chemical and spectroscopic (u.v., i.r., and n.m.r.) evidence was not sufficient for this purpose.

EXPERIMENTAL

Single yellow-green crystals were obtained as monoclinic prisms from a methanol solution by slow evaporation at room temperature.

Crystal Data.—$C_{15}H_8N_2O_2$, M = 248·2. Monoclinic, a = 7·46(6), b = 7·66(6), c = 20·78(16) Å, β = 109·0° (5); U = 1122·7 Å^3, D_o = 1·47 (by flotation), D_c = 1·47, Z = 4, $F(000)$ = 512. Space group: $P2_1/c$ (C_{2h}^5, No. 14) from systematic absences $h0l$, $l = 2n + 1$; $0k0$, $k = 2n + 1$. Ni filtered Cu-K_α radiation, λ = 1·5418 Å, μ(Cu-K_α) = 8·4 cm^{-1}.

The unit cell dimensions and the space group were determined from oscillation and Weissenberg photographs. The errors quoted for cell dimensions are the maximum. The molecular formula and molecular weight were calculated from microanalyses and confirmed by the highest molecular ion peak in the mass spectrum (m/e 248).[2] Intensity data were collected by the multiple-film equi-inclination Weissenberg technique with Nickel-filtered Cu-K_α radiation.

Layers from 0 to 5 around both the a and b axes were recorded with two different crystals. Altogether 1207 independent non-zero reflections were estimated visually and used in the final refinement. Lorentz, polarization, and spot-extension[3] corrections were applied, but not absorption or extinction. The two sets of data were scaled by the method of Hamilton *et al.*[4] and the resulting structure amplitudes were put on an approximate absolute scale by a Wilson plot.

Determination and Refinement of the Structure.—The overall temperature and scale factors obtained from the Wilson plot were used to generate the normalized structure factors $[E_{hkl}]$ from the observed structure amplitudes.

A direct methods technique developed by one of us,[5] which makes use of Sayre's equation, was applied to 300 reflections with the highest $[E_{hkl}]$ values. The set of phases obtained was used to calculate an E map where 19 positions with the highest peak values corresponding to a possible chemical model were chosen. All the atomic positions were assigned carbon form-factors and an overall isotropic temperature factor and then refined by the block-diagonal (4 × 4), least-squares method.

The chemical species were recognized both by inspection of the variation of thermal parameters during the refinement and by electron population analysis of the peaks found in the Fourier synthesis. Further least-squares refinement computed after assignment of the correct form-factors and individual isotropic thermal parameters to all the atomic positions, reduced R to 0·14. After anisotropic, block-diagonal (9 × 9), least-squares refinement a difference Fourier synthesis was calculated and showed residual electron density in all the positions expected for hydrogen atoms. These were included and further refinement of all the parameters, except the temperature factors of the hydrogen atoms, which were assigned a fixed overall value of 4 Å^2, lowered R to the final value of 0·089.

During the refinement the weighting scheme $w = a + |F_0| + b|F_0|^2$ was used: this was checked at intervals, and the values of a and b adjusted by means of a least-squares procedure in order to keep the average values of $w|\Delta F|^2$ approximately constant over equally populated regions of $|F_0|$.[6]

The final difference Fourier synthesis showed no significant positive or negative electron density residuals. Atomic scattering factors for oxygen, nitrogen, and carbon were from ref. 7, and for hydrogen from ref. 8.

All the calculations were carried out on a UNIVAC 1108 computer, Rome University, using the program library[9] of the Laboratorio di Strutturistica Chimica ' Giordano Giacomello.' The thermal vibration ellipsoids shown in Figure 3 were produced by the ORTEP program.[10] Observed and calculated structure factors as well as final anisotropic temperature factors for the non-hydrogen atoms are listed in Supplementary Publication No. SUP 21021 (5 pp.).

RESULTS AND DISCUSSION

The chemical structure, the atomic numbering, and the bonding scheme of tryptanthrin together with the molecular bond distances and angles resulting from the *X*-ray analysis are given in Figures 1 and 2. The e.s.d. values of the bond distances are of the order of 0·01 Å (the lowest and highest values are 0·008 and 0·011 Å respectively), while those of the valency angles range between 0·5 and 0·7°.

Tryptanthrin consists of a sequence of four fused rings

[†] For details see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index Issue. Items less than 10 pp. are supplied as full-size copies.

[1] F. Schindler and H. Zähner, *Arch. Mikrobiol.*, 1971, **79**, 187.

[2] Preliminary communication, M. Brufani, W. Fedeli, F. Mazza, A. Gerhard, and W. Keller-Schierlein, *Experientia*, 1971, **27**, 1249.

[3] D. C. Phillips, *Acta Cryst.*, 1954, **7**, 746.

[4] W. C. Hamilton, J. S. Rollett, and R. A. Sparks, *Acta Cryst.*, 1965, **18**, 129.

[5] W. Fedeli, Atti IV Convegno A.I.C., Cagliari, 1970, p. 13.

[6] D. W. J. Cruickshank, in ' Computing Methods in Crystallography,' ed. J. S. Rollett, Pergamon, Oxford, 1965, p. 114.

[7] D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **24**, 321.

[8] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

[9] A. Domenicano, R. Spagna, and A. Vaciago, *Atti Accad. Naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1969, **47**, 331.

[10] C. K. Johnson, ' ORTEP: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations,' Oak Ridge National Laboratory Report, ORNL 3794, 1965.

with the two benzene rings at the ends. The two carbonyl groups, showing stretching vibration bands at 1688 and 1725 cm^{-1} in the i.r. spectrum, belong respectively to the pyrimidine and five-membered rings of tryptanthrin: the respective bond lengths of 1·23 and 1·22 Å confirm that the carbonyl groups are in the keto-form. All eight protons found in the final difference Fourier synthesis are in accord with the observed n.m.r.

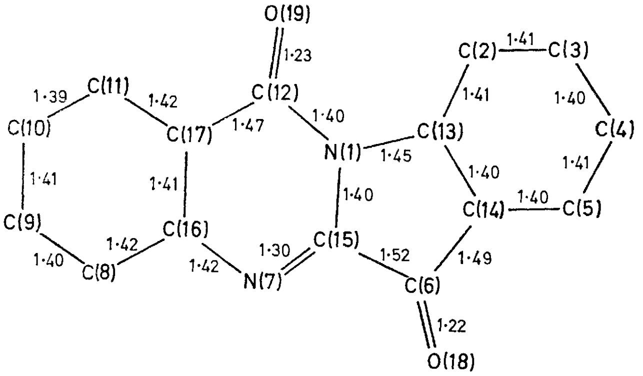

FIGURE 1 Intramolecular bond lengths (Å)

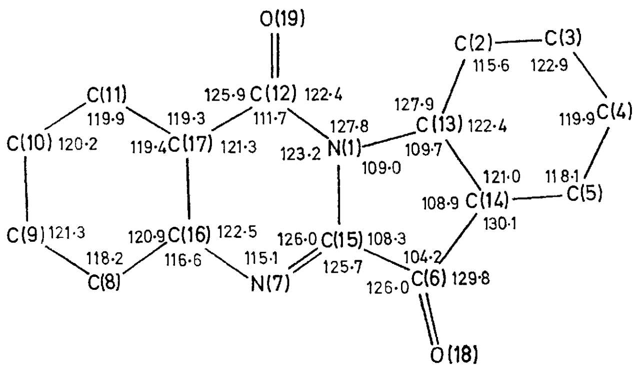

FIGURE 2 Intramolecular bond angles (°)

TABLE 1

Final positional parameters (× 10^4) with standard deviations in parentheses

	x	*y*	*z*
N(1)	−2605(8)	5315(7)	54(3)
C(2)	−3340(10)	8287(10)	482(4)
C(3)	−3133(11)	9234(10)	1084(4)
C(4)	−2281(11)	8530(11)	1736(4)
C(5)	−1539(10)	6819(10)	1809(4)
C(6)	−1125(11)	4038(9)	1138(4)
N(7)	−1407(9)	2394(8)	64(3)
C(8)	−1791(11)	970(10)	−1008(4)
C(9)	−2444(12)	1002(10)	−1722(4)
C(10)	−3315(12)	2496(11)	−2088(4)
C(11)	−3611(11)	3692(10)	−1734(4)
C(12)	−3380(10)	5501(9)	651(4)
C(13)	−2622(9)	6572(8)	574(3)
C(14)	−1755(10)	5848(10)	1219(3)
C(15)	−1713(10)	3780(9)	371(4)
C(16)	−2103(10)	2467(9)	−655(3)
C(17)	−3019(10)	3954(9)	−1012(3)
O(18)	−0301(9)	2979(7)	1568(3)
O(19)	−4269(8)	6805(7)	−918(3)
H(2)	−4250(105)	8801(101)	−55(39)
H(3)	−3714(127)	10489(124)	1038(46)
H(4)	−2021(121)	9169(120)	2099(44)
H(5)	−717(120)	6484(117)	2295(44)
H(8)	−873(96)	98(95)	−703(35)
H(9)	−2284(132)	2(1)	−1901(47)
H(10)	−3913(135)	2661(134)	−2538(50)
H(11)	−4200(120)	4830(119)	−1989(44)

TABLE 2

Least-squares planes (in terms of monoclinic co-ordinates) with distances (Å) of the atoms from the plane

(*a*) Plane through the benzene ring C(2)—C(5), C(13), C(14)

$$0{\cdot}9397x + 0{\cdot}3419y - 0{\cdot}3149z + 0{\cdot}4900 = 0$$

Deviations

C(2)	−0·004	C(5)	−0·013
C(3)	−0·003	C(13)	0·002
C(4)	0·011	C(14)	0·006

(*b*) Plane through the benzene ring C(8)—C(11), C(16), C(17)

$$0{\cdot}9314x + 0{\cdot}3634y - 0{\cdot}2829z + 0{\cdot}3919 = 0$$

Deviations

C(8)	−0·010	C(11)	−0·005
C(9)	0·015	C(16)	−0·003
C(10)	−0·008	C(17)	0·010

(*c*) Plane through the pyrimidine ring N(1), N(7), C(12), C(15)—C(17)

$$0{\cdot}9271x + 0{\cdot}3749y - 0{\cdot}3043z + 0{\cdot}3264 = 0$$

Deviations

N(1)	−0·017	C(16)	0·005
N(7)	−0·001	C(17)	−0·014
C(12)	0·020	O(19)	0·090
C(15)	0·007		

(*d*) Plane through the five-membered ring N(1), C(6), C(13)—C(15)

$$0{\cdot}9347x + 0{\cdot}3556y - 0{\cdot}3038z + 0{\cdot}4011 = 0$$

Deviations

N(1)	0·002	C(14)	−0·001
C(6)	0·002	C(15)	−0·002
C(13)	−0·001	O(18)	−0·013

(*e*) Plane through the whole molecule (the two oxygen atoms were excluded)

$$0{\cdot}9347x + 0{\cdot}3554y - 0{\cdot}2996z + 0{\cdot}3773 = 0$$

Deviations

N(1)	0·026	C(11)	−0·017
C(2)	−0·004	C(12)	0·077
C(3)	−0·031	C(13)	0·019
C(4)	−0·028	C(14)	0·013
C(5)	−0·034	C(15)	0·019
C(6)	0·017	C(16)	0·010
N(7)	−0·008	C(17)	0·021
C(8)	−0·020	O(18)	−0·002
C(9)	−0·018	O(19)	0·175
C(10)	−0·042		

(*f*)	Dihedral angle between plane (*a*) and plane (*d*)	1·0°
	Dihedral angle between plane (*c*) and plane (*d*)	1·2°
	Dihedral angle between plane (*b*) and plane (*c*)	1·5°

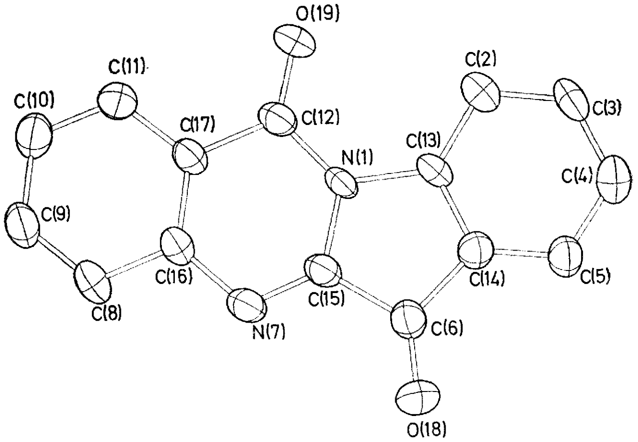

FIGURE 3 Thermal ellipsoids of the non-hydrogen atom of tryptanthrin drawn at the 50% probability level

spectrum ($CDCl_3$) where resonance signals appeared only in the region for aromatic protons.[2] The main feature of tryptanthrin is the nearly planar arrangement of all the atoms. Table 2 reports the least-squares planes of the individual rings and that of the whole molecule. While each of the four individual rings appears to be planar within experimental error, the atomic deviations from the plane of the whole molecule suggest that there may be small but significant departures from planarity, especially for O(19) and probably for C(12).

The near planarity of this system, which is not entirely conjugated, allows a certain amount of electronic delocalization and this confers to tryptanthrin partial aromatic character. Evidence for the stability of this compound is given from the peak heights of the molecular ion (*m/e* 248) and the doubly charged molecular ion (*m/e* 124) in the mass spectrum; furthermore the broad peak in the 280—420 nm region of the u.v. spectrum suggests a certain amount of aromatic character.[2]

Crystal Packing.—Intermolecular contacts shorter than 3·5 Å are reported in Table 3. The molecular packing projected down the *b* axis is shown in Figure 4. The mean plane of the molecule makes an angle of 21·3° with the *b* axis, so that the mean planes of the molecules related by the glide plane parallel to *c* make an angle of 42·6°.

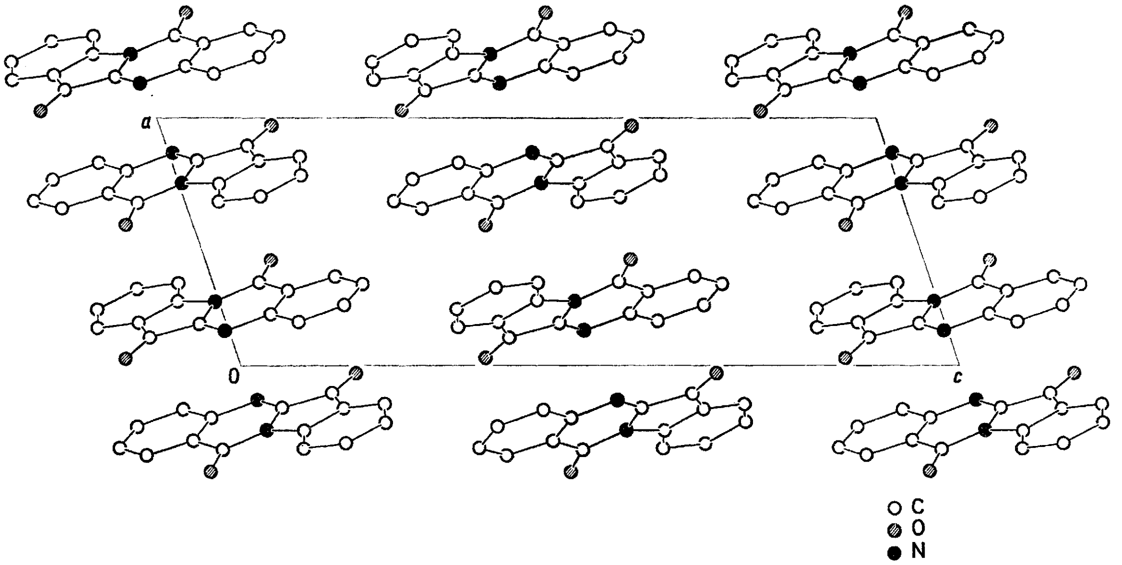

FIGURE 4 Crystal structure of tryptanthrin projected down the *b* axis

Chemical Remarks.—The *X*-ray analysis proves that tryptanthrin is indolo[2,1-*b*]quinazoline-6,12-dione, a compound that has already been synthesized twice,[11,12] although its occurrence in living cells and its biological activity were previously not known.

TABLE 3

Intermolecular contacts <3·50 Å

C(5)–C(9^{I})	3·46	O(18)–C(4^{III})	3·45
C(13)–C(12^{II})	3·43	O(18)–C(5^{III})	3·32
C(14)–O(19^{II})	3·48	O(19)–C(6^{II})	3·38

I $-x, 1 - y, -z$ II $-1 - x, 1 - y, -z$

III $-x, y - \frac{1}{2}, \frac{1}{2} - z$

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[11] P. Friedländer and W. Roschdestwensky, *Ber.*, 1915, **48**, 1841.

[12] C. W. Bird, *Tetrahedron*, 1963, **19**, 901.