1-Ethyl-1,4-dihydro-4-oxo-5-amino-6,7-methylenedioxy-3-quinoline-carboxylic acid (Aminooxolinic Acid)

By Mátyás Czugler and Gyula Argay

Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525-Budapest, P.O.B. 17, Hungary

Judit Frank and Zoltán Mészáros

Chinoin Pharmaceutical and Chemical Works Ltd, H-1045-Budapest, Tó-u. 5, Hungary

and Leo Kutschabsky and Günter Reck

Akademie der Wissenschaften der DDR, Zentralinstitut für physikalische Chemie, 1199-Berlin-Adlershof, Rudower Chaussee 5, Germany (DDR)

Abstract. $C_{13}H_{12}N_2O_5$, M.W. 276, monoclinic, space group $P2_1/c$; $a = 7.485$ (1), $b = 10.449$ (1), $c = 15.087$ (1) Å, $\beta = 99.69$ (1)° (from single-crystal diffractometry); $Z = 4$, $D_c = 1.55$ g cm^{-3}. The title compound is a derivative of oxolinic acid [Kaminsky & Meltzer, *J. Med. Chem.* (1968), **11**, 160–163] and shows excellent antibacterial activity [Frank, Mészáros & Kovács, (1974), Hung. Pat. Appl. CI-1485]. The 5 position of an amino group formed from an entering nitro group was revealed.

Introduction. Intensities of 2449 independent reflexions were collected in Berlin on a Hilger & Watts four-circle diffractometer with Mo $K\bar{\alpha}$ ($\lambda = 0.7107$ Å) radiation and a graphite monochromator. 1650 reflexions with $|F_o| - 3\sigma|F_o| > 0$ were taken as observed. The structure was solved independently by a graphical convolution molecule technique combined with three-dimensional R-value field analysis [*cf.* the CORDAL method (Kutschabsky & Reck, 1976; Kutschabsky, Reck, Kulpe & Höhne, 1975)], developed in Berlin, and by a direct method included in the program *SHELX* (G. M. Sheldrick). Both solutions resulted in the same model with an R of 0.23. Full-matrix least-squares adjustment of the atomic parameters converged to an R of 0.070 and an $R_w[= \sum w^{1/2}\Delta/\sum w^{1/2}|F_o|]$ of 0.080 for the observed reflexions ($R_{tot} = 0.103$). H(181), H(182) and H(16) were taken from a difference map while the rest were generated geometrically. Constrained refinement was applied for the latter group. The weighting scheme was $w = 24.44/(\sigma^2|F_o| + 0.000122F_o^2)$. Calculations for the three-dimensional R-value field analysis were performed on a BESM-6 computer in Berlin. The other

Table 1. *Fractional coordinates and anisotropic thermal parameters* ($\times 10^4$)

Estimated standard deviations are in parentheses. The anisotropic temperature factor has the form:

$$T = \exp\left[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)\right].$$

	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	6219 (5)	1770 (3)	−367 (2)	320 (18)	319 (17)	315 (16)	−3 (14)	−14 (14)	40 (14)
C(2)	6085 (6)	1402 (4)	−1229 (3)	448 (25)	385 (22)	320 (20)	46 (17)	−23 (18)	−31 (19)
C(3)	6682 (6)	250 (4)	−1483 (3)	469 (27)	363 (22)	279 (19)	−18 (17)	−10 (18)	−92 (19)
C(4)	7544 (6)	−631 (4)	−815 (3)	359 (23)	303 (20)	306 (19)	−52 (16)	16 (17)	−53 (17)
C(4a)	7720 (6)	−235 (4)	114 (3)	327 (23)	284 (19)	297 (19)	2 (16)	20 (16)	16 (17)
C(5)	8535 (6)	−1068 (4)	826 (3)	311 (22)	328 (21)	328 (20)	21 (17)	68 (17)	27 (18)
C(6)	8619 (6)	−592 (4)	1683 (3)	438 (26)	363 (22)	263 (19)	44 (17)	−44 (17)	67 (20)
C(7)	8002 (7)	587 (4)	1868 (3)	452 (27)	356 (23)	300 (20)	3 (17)	56 (18)	38 (20)
C(8)	7194 (6)	1426 (4)	1224 (3)	464 (27)	310 (21)	297 (20)	5 (16)	66 (18)	77 (20)
C(8a)	7067 (6)	995 (4)	330 (3)	361 (23)	318 (20)	271 (18)	13 (15)	5 (16)	−17 (18)
O(9)	9405 (5)	−1209 (3)	2466 (2)	703 (25)	455 (19)	305 (15)	53 (14)	−15 (16)	165 (17)
C(10)	8928 (10)	−429 (5)	3161 (3)	950 (45)	495 (29)	327 (24)	57 (21)	19 (26)	212 (29)
O(11)	8302 (5)	787 (3)	2780 (2)	776 (25)	429 (18)	257 (14)	6 (13)	68 (15)	108 (18)
C(12)	5558 (7)	3064 (4)	−189 (3)	481 (27)	325 (21)	388 (21)	28 (17)	29 (19)	99 (20)
C(13)	7100 (8)	4010 (5)	−28 (4)	695 (34)	366 (23)	582 (29)	−17 (21)	173 (25)	10 (24)
O(14)	5692 (5)	675 (4)	−3038 (3)	845 (28)	612 (22)	297 (16)	49 (16)	−52 (17)	−14 (20)
C(15)	6421 (7)	−53 (5)	−2461 (3)	583 (31)	482 (26)	305 (21)	−53 (20)	19 (20)	−120 (24)
O(16)	7053 (6)	−1179 (4)	−2670 (2)	1059 (33)	522 (22)	331 (17)	−114 (16)	34 (19)	38 (21)
O(17)	8067 (5)	−1728 (3)	−1038 (2)	763 (26)	374 (17)	380 (17)	−91 (14)	47 (16)	68 (17)
N(18)	9233 (6)	−2244 (4)	692 (3)	632 (29)	363 (21)	398 (22)	27 (18)	58 (20)	154 (20)

calculations were processed with the program *SHELX* on a CDC 3300 computer in Budapest. Scattering factors for bonded H atoms were taken from Stewart, Davidson & Simpson (1965) and for the remaining atoms from Cromer & Mann (1968) and Cromer & Liberman (1970). Final atomic coordinates and thermal parameters for non-hydrogen atoms are given in Table 1, the parameters for the H atoms with corresponding X–H bond distances in Table 2. The bond distances and angles for the non-hydrogen atoms, with estimated standard deviations derived from the full variance–covariance matrix, are shown in Fig. 1.*

Discussion. The nitration of 4,6,7-substituted quinolines can yield both 5- and 8-nitro derivatives depending on the nature of the 6,7 substituents (Heindel, Ohnmacht, Molnár & Kennewell, 1969).

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31887 (16 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.
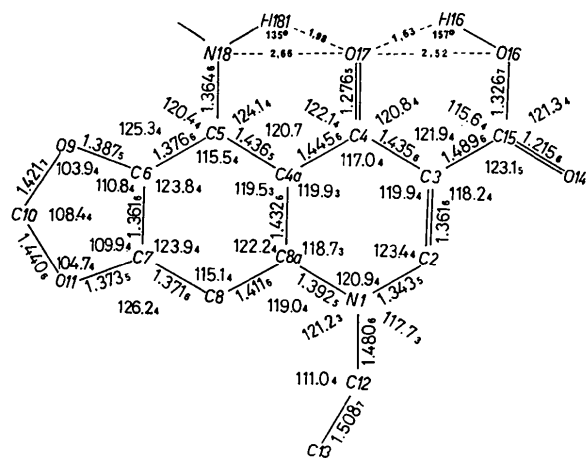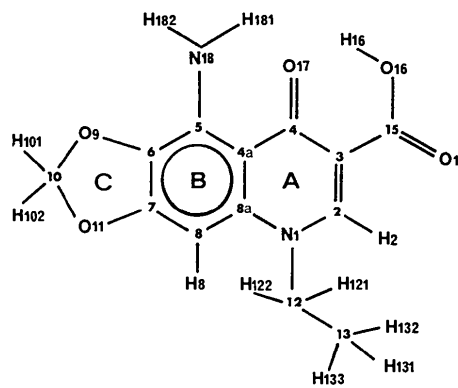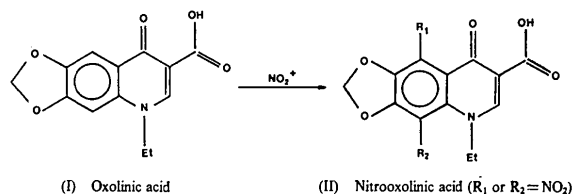

(I) Oxolinic acid

(II) Nitrooxolinic acid (R_1 or $R_2 = NO_2$)

(III) Aminooxolinic acid

Fig. 1. A diagram of the title compound with bond distances and angles for the non-hydrogen atoms (e.s.d.'s are in small figures).

The analysis of the title compound confirmed the position of the amino group formed from the entering nitro group by reduction. This showed unambiguously that the nitration occurred in the 5 position, as had been assumed.

The most dominant feature of the structure is a strong intramolecular hydrogen-bond system maintained by O(17) towards H(16)–O(16) and H(181)–N(18) (Fig. 1). This may cause both the unusually long C(4)–O(17) distance of 1·276 Å, and a decreased aromaticity of ring *B*. The latter phenomenon might also be influenced by the amino group. Because of the strong intramolecular hydrogen bonds, intermolecular hydrogen bonds could not be formed.

The molecule lies in the plane described by the equation $0·9137X + 0·4027Y - 0·2080Z - 5·1369 = 0$ (constants are referred to crystallographic axes). All non-hydrogen atoms are ($\Delta_{max} = 0·02$ Å) lying on this plane,

Table 2. *Fractional coordinates* ($\times 10^4$) *and isotropic temperature factors* ($\times 10^3$) *of the hydrogen atoms with the corresponding* X–H *distance* (Å)

	x	y	z	U_{iso}	X–H
H(2)	5473 (6)	2053 (4)	−1748 (3)	76 (9)	1·080 (6)
H(8)	6664 (6)	2341 (4)	1387 (3)	76 (7)	1·080 (6)
H(101)	7888 (10)	−892 (5)	3463 (3)	76 (7)	1·080 (9)
H(102)	10114 (10)	−277 (5)	3667 (3)	76 (7)	1·080 (8)
H(121)	4586 (7)	3372 (4)	−761 (3)	82 (7)	1·080 (6)
H(122)	4914 (7)	3026 (4)	399 (3)	82 (7)	1·080 (7)
H(131)	6538 (8)	4927 (5)	110 (4)	82 (7)	1·080 (7)
H(132)	7671 (8)	4072 (5)	−638 (4)	82 (7)	1·080 (8)
H(133)	8148 (8)	3747 (5)	525 (4)	82 (7)	1·080 (7)
H(16)	7329 (69)	−1597 (54)	−2111 (41)	76 (9)	0·94 (6)
H(181)	9134 (71)	−2477 (56)	136 (41)	76 (9)	0·87 (6)
H(182)	9667 (71)	−2713 (57)	1170 (40)	76 (9)	0·89 (6)

except C(10) and C(13) which are out of plane by −0·204 and 1·415 Å respectively.

One of us (M.C.) is indebted to the D.A.W. der DDR and the Hungarian Academy of Sciences for providing the opportunity for studying the CORDAL method in Berlin.

References

CROMER, D. T. & LIBERMAN, D. (1970). J. Chem. Phys. 53, 1891–1898.

CROMER, D. T. & MANN, J. B. (1968). Acta Cryst. A24, 321–324.

FRANK, J., MÉSZÁROS, Z. & KOVÁCS, V. (1974). Hung. Pat. Appl. CI-1485.

HEINDEL, N. D., OHNMACT, C. I., MOLNÁR, J. & KENNEWELL, P. D. (1969). J. Chem. Soc. (C), pp. 1369–1371.

KAMINSKY, D. & MELTZER, R. I. (1968). J. Med. Chem. 11, 160–163.

KUTSCHABSKY, L. & RECK, G. (1976). The Application of the Convolution Molecule Method and Residual Analysis to the Determination of Organic Structures with Partially Known Molecules, Summer School on Crystallographic Computing, Prague, 1975. Edited by F. R. AHMED. Copenhagen: Munksgaard. To be published.

KUTSCHABSKY, L., RECK, G., KULPE, S. & HÖHNE, E. (1975). Krist. Tech. 10, 731–739.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). J. Chem. Phys. 42, 3175–3187.

5,6:12,20-Diepoxy-19,20-methylimino-14,20-cyclo-ent-kaur-16-ene-2,11-diol: An Oxidation Product of Anopteryl Alcohol

By C. KOWALA AND B. J. POPPLETON

Division of Applied Organic Chemistry, CSIRO, P.O. Box 4331, Melbourne, Victoria, Australia 3001 and Division of Chemical Physics,* CSIRO, P.O. Box 160, Clayton, Victoria, Australia 3168

Abstract. $C_{21}H_{27}NO_4$, orthorhombic, $P2_12_12_1$; $a = 9.892$ (1), $b = 12.093$ (1), $c = 14.545$ (1) Å; $Z = 4$, $D_x = 1.364$, $D_m = 1.35$ g cm^{-3}; $F(000) = 808$; $U = 1739.9$ Å^3; μ(Cu $K\alpha$) = 8.68 cm^{-3}, $\lambda = 1.5418$ Å. The atom fractional coordinates and individual isotropic temperature factors were refined by full-matrix least-squares methods to an R of 0·10 for 1328 structure magnitudes ($F \geq 3\sigma_F$). The structure analysis has shown that the oxidation of anopteryl alcohol by potassium ferricyanide introduces an epoxide group across C(5) and C(6), and ring closure, through an ether link, between C(12) and C(20).

I R = CH₃Ċ=Ċ–CO.
II R = H.
III

Introduction. On the basis of preliminary screening tests, the *Anopterus* alkaloids are potential anti-tumour agents. Anopterine itself (I) is the major alkaloid from the bark and leaves of the Queensland species *Anopterus macleayanus* F. Muell (family Escalloniaceae) and has also been isolated from the Tasmanian species *Anopterus glandulosus* Labill. Its structure, an *ent* kaurene derivative with a bond linking C(20) to C(14) (see I), was inferred from spectral data and an X-ray structural study of a crystalline azomethine iodide derived from O,O,O,O-tetraacetylanopteryl alcohol (Denne, Johns, Lamberton, Mathieson & Suares, 1972).
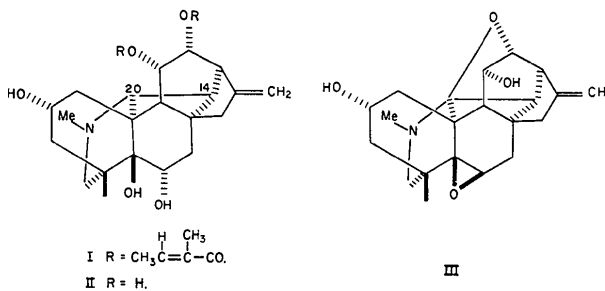
The title compound (III) was produced as part of a chemical study of the *Anopterus* alkaloids, by oxidation of anopteryl alcohol (II) with potassium ferricyanide in ethanol (Lamberton, 1975). The present crystal structure analysis was undertaken to elucidate the unexpected changes in the ring skeleton on oxidation, which were indicated by proton and ^{13}C magnetic resonance studies, but not understood at the time.

The crystal used had dimensions 0·25 × 0·62 × 0·25 mm and was mounted about the *b* axis on a Picker diffractometer. A set of 1634 unique reflexions were measured to a sin θ/λ limit of 0·58 Å^{-1} with Ni-filtered Cu $K\alpha$ radiation in the θ–2θ scanning mode: of these, 306 had intensities less than $3\sigma_F$ and were coded as

---

* Address for correspondence.