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ANTITUMOR AGENTS, 79.[1] CYTOTOXIC ANTILEUKEMIC ALKALOIDS FROM *BRUCEA ANTIDYSENTERICA*

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ABSTRACT.—Two cytotoxic antileukemic alkaloids, the new 1,11-dimethoxycanthin-6-one (**3**) and the known 11-hydroxycanthin-6-one (**1**), as well as the known canthin-6-one (**2**) were isolated from the stem of *Brucea antidysenterica*. The structures of **1-3** were determined from their spectral data and X-ray analysis of the *o*-bromobenzoate of **1**.

We reported recently on the isolation and structural elucidation of four new antileukemic quassinoids, bruceantinoside A and B (1) and bruceanol A and B (2) from *Brucea antidysenterica* Mill. In the course of these isolations, we have also directed our attention to the cytotoxic antileukemic activity of the alkaloidal extracts from this plant.

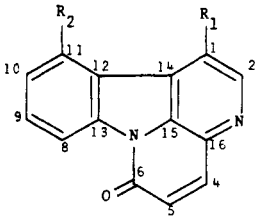
A number of canthin-6-one type alkaloids have been isolated from a variety of Simaroubaceous species. Included among these are 5-methoxycanthin-6-one, 5-hydroxy-4-methoxycanthin-6-one, and 4,5-dimethoxycanthin-6-one from *Picrasma quassioides* (3-6); 5-hydroxycanthin-6-one from *Simarouba amara* (7); canthin-6-one (**2**), 1-methoxycanthin-6-one (**4**), and 1-methoxy-11-hydroxycanthin-6-one from *Soulamea pancheri* (8); 8-methoxycanthin-6-one from *Simaba cuspidata* (9); 1-hydroxycanthin-6-one from *Ailanthus giraldii* (10); canthin-6-one (**2**) and 1-methoxycanthin-6-one (**4**) from *Ailanthus altissima* (11-13); canthin-6-one (**2**), 1-methoxycanthin-6-one (**4**), 5-methoxycanthin-6-one, and 8-hydroxycanthin-6-one from *Ailanthus excelsa* (14); 11-hydroxycanthin-6-one (**1**, amarorine) and 11-methoxycanthin-6-one (**5**) from *Amaroria soulameoides* (15); and canthin-6-one (**2**), 5-methoxycanthin-6-one, and 1-hydroxy-11-methoxycanthin-6-one from *B. antidysenterica* (16).

We here describe the isolation and characterization of a new cytotoxic canthin-6-one type alkaloid, 1,11-dimethoxycanthin-6-one (**3**), and two related, known compounds, 11-hydroxycanthin-6-one (**1**) and canthin-6-one (**2**) from *B. antidysenterica*. The significant cytotoxicity of **1** was reported previously (21).

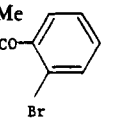
RESULTS AND DISCUSSION

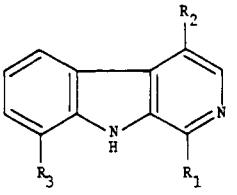
The new compound (**3**) showed a positive Dragendorff test and uv absorption typical of a canthinone alkaloid. Elemental analysis and high resolution mass spectral data indicated the molecular formula $C_{16}H_{12}N_2O_3$ which suggested that **3** was a dimethoxycanthinone. The presence of two methoxy groups was substantiated by two

[1]For part 78, see L.S. Thurston, H. Irie, S. Tani, F.S. Han, Z.C. Liu, Y.C. Cheng, and K.H. Lee, *J. Med. Chem.*, in press.



1 R_1=H, R_2=OH
2 R_1=R_2=H
3 R_1=R_2=OMe
4 R_1=OMe, R_2=H
5 R_1=H, R_2=OMe
8 R_1=H, R_2=OCOMe
9 R_1=H, R_2=





6 R_1=CO_2Me, R_2=R_3=H
7 R_1=CH_2CH_2OMe, R_2=R_3=OMe

three-proton singlets at δ 4.0 and 4.16 in the ^{1}H-nmr spectrum. An α,β-unsaturated carbonyl group was revealed by ir bands at 1675 (CO) and 1625 (C=C) cm^{-1}, ^{13}C-nmr signals at δ 160.2 (s, CO), 139.0 (d, C-4), and 131.8 (d, C-5), and ^{1}H-nmr peaks at δ 7.91 (1H, d, J=10 Hz, H-4) and 6.79 (1H, d, J=10 Hz, H-5).

The ^{1}H-nmr spectrum contained three aromatic proton signals at δ 8.29 (1H, d, J=8 Hz), 7.54 (1H, t, J=8 Hz), and 6.86 (1H, d, J=8 Hz) in addition to a one-proton singlet at δ 8.41 suggesting that one of the methoxy groups should be placed at either C-8 or C-11 while the other must be located at either C-1 or C-2. That the aromatic proton signals for **3** were very similar to those of 11-methoxycanthine-6-one (**5**) [δ 8.11 (1H, d, J=8 Hz, H-8), 7.57 (1H, t, J=8 Hz, H-9), and 6.91 (1H, d, J=8 Hz, H-10)] (15), coupled with the fact that the aforementioned one-proton singlet at δ 8.41 coincided with that for 1-methoxycantin-6-one (**4**) [δ 8.46 (1H, s, H-2)] (11) (Table 1), led to the conclusion that **3** was 1,11-dimethoxycanthin-6-one. This assignment was further supported by an nOe experiment in which irradiation at δ 4.0 (OMe-11) caused a 13% enhancement of the proton signal at δ 6.86 (H-10) while irradiation at δ 4.16 (OMe-1) gave rise to a 12% enhancement of the H-2 signal at δ 8.41. A similar result

TABLE 1. ^{1}H-nmr Spectral Data[a] for Canthinones **1**, **2**, **3**, **4**, and **5**

Atom	Compounds				
	1[b]	**2**[c]	**3**[c]	**4**[c](11)	**5**[c](15)
H-1	8.05(1H,d,J=5)	7.82(1H,d,J=6)	—	—	7.93(1H,d,J=5)
H-2	8.76(1H,d,J=5)	8.75(1H,d,J=6)	8.41(1H,s)	8.46(1H,s)	8.71(1H,d,J=5)
H-4	8.09(1H,d,J=10)	7.94(1H,d,J=10)	7.91(1H,d,J=10)	6.82(1H,d,J=10)[d]	8.00(1H,d,J=5)[e]
H-5	6.96(1H,d,J=10)	6.91(1H,d,J=10)	6.79(1H,d,J=10)	7.93(1H,d,J=10)[d]	6.91(1H,d,J=10)
H-8	7.94(1H,d,J=8)	8.57(1H,d,J=8)	8.29(1H,d,J=8)	8.64(1H,d,J=8)	8.11(1H,d,J=10)[f]
H-9	7.54(1H,t,J=8)	7.46(1H,m)	7.54(1H,t,J=8)	7.59(1H,m)	7.57(1H,t,J=8)
H-10	7.0(1H,d,J=8)	7.64(1H,m)	6.86(1H,d,J=8)	7.42(1H,m)	6.91(1H,d,J=8)
H-11	—	8.01(1H,d,J=8)	—	8.15(1H,d,J=8)	—
OMe-1	—	—	4.16(3H,s)	4.25(3H,s)	—
OMe-11	—	—	4.0(3H,s)	—	[g]

[a]Chemical shifts are shown in δ-values (ppm) with coupling constants in Hz.
[b]Measured in DMSO-d_6.
[c]Measured in $CDCl_3$.
[d]The assignments for H-4 and H-5 should be interchanged.
[e]The coupling constant should be 10 Hz.
[f]The coupling constant should be 8 Hz.
[g]This value was not reported.

was obtained from the 2-D-nOe-nmr (NOESY) spectrum (Figure 1) which indicated that the signals at δ 4.0 and 4.16 corresponded to OMe-1 and OMe-11, respectively. Additional confirmation for these assignments was derived from the comparable ^{13}C-nmr signals for **3**, **6** (17), and **7** (17) (Table 2).

Compound **1**, $C_{14}H_8N_2O_3$, gave uv, ir, and ^1H-nmr (Table 1) spectral data which were very similar to those reported (15) for 11-hydroxycanthin-6-one. Upon acetylation with Ac_2O in pyridine, **1** yielded a monoacetate, $C_{16}H_{10}N_2O_3$. The complete molecular structure was established as 11-hydroxycanthin-6-one by a single-crystal X-ray analysis of the *o*-bromobenzoate (**9**). The crystal structure was solved by the heavy-atom approach. Full-matrix least-squares refinement of atomic parameters converged to $R=0.049$ over 2287 reflections. Final atomic positional parameters are in Table 3. A view of the solid-state conformation is provided in Figure 2.

Bond lengths and angles in **9** are in good accord with expected values. The unusually large differences between the C-1—C-14—C-15/C-11—C-12—C-13 and C-1—C-14—C-12/C-11—C-12—C-14 bond angles (115/124° and 139/129°, respectively) reported for the less precisely determined 11-hydroxycanthin-6-one **1** structure (15) are moderated somewhat in **9** where the corresponding pairs of values at 115.8/118.6° and 138.7/133.5°, although still significantly different, are more acceptable and indicate that the geometries involving C-12 and C-14 in the analysis of **1** are suspect. The endocyclic torsion angles, ω, in the fused ring system of **9** vary from −3.6° to 4.4° (mean $|\omega|=1.0°$) and, accordingly, the atoms comprising these rings are approximately coplanar. Oxygen substituents O-17 and O-18, however, are displaced quite significantly (Δ 0.132 and 0.183 Å, respectively) to the same side of the least-squares plane through C-1—C-16 (root-mean-square deviation=0.023 Å) to minimize nonbonded intra-

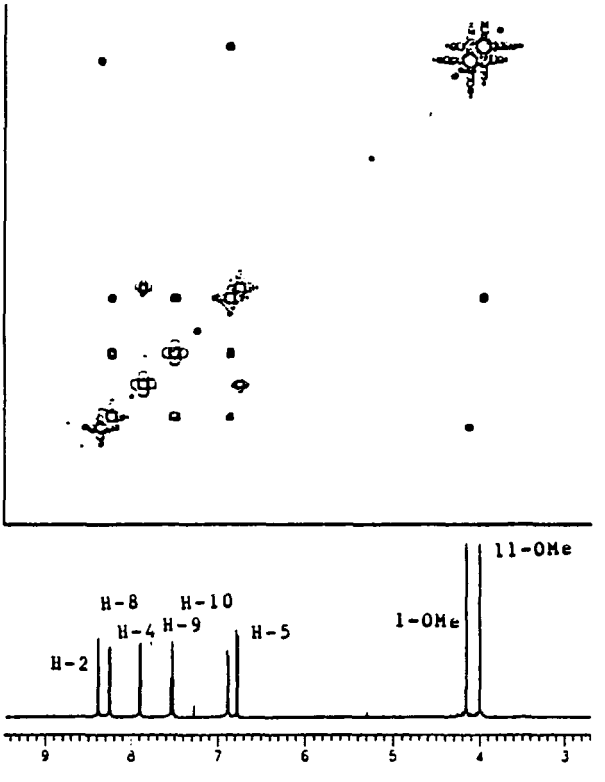


FIGURE 1. 2-D-nOe-nmr (NOESY) spectrum of **3**.

TABLE 2. ^{13}C-nmr Spectral Data[a] for **3**, **6**, and **7**

Atom	Compounds		
	3[b]	**6**[c](17)	**7**[b](17)
C-1	155.6(s)	118.91(d)	151.01(s)
C-2	131.3(d)[d]	137.95(d)	120.42(d)
C-4	139.0(d)		
C-5	131.8(d)[d]		
C-6	160.2(s)		
C-8	109.5(d)[d]	112.91(d)	146.0(s)
C-9	124.8(d)	120.11(d)	106.94(d)
C-10	107.5(d)[d]	129.09(d)	116.30(d)
C-11	151.0(s)	121.81(d)	120.04(d)
C-12	116.6(s)	129.78(s)	122.24(s)
C-13	132.6(s)	136.10(s)	135.79(s)
C-14	112.8(s)	120.11(s)	118.50(s)
C-15	130.2(s)	130.94(s)	130.25(s)
C-16	139.8(s)	141.50(s)	137.64(s)
OMe-1	57.4(q)		
OMe-11	56.0(q)		

[a]Chemical shifts are in δ-values (ppm).
[b]Measured in $CDCl_3$.
[c]Measured in DMSO-d_6.
[d]Interchangeable between C-2 and C-5, and between C-8 and C-10.

molecular repulsions between O-17 and H-8 and between O-20 and the C-8—C-13 ring.

Compound **2**. $C_{14}H_8N_2O$, showed spectral data which were consistent with those reported for canthin-6-one (14,18).

It is of interest to note that both **1** and **3** showed equally significant ($ED_{50} \leq 4.0$ μg/ml) cytotoxicity in vitro against KB tissue cuture cells at $ED_{50} = 1.0$ μg/ml, whereas **2** was reported elsewhere (14) to be inactive in this same test system. Compound **3** also

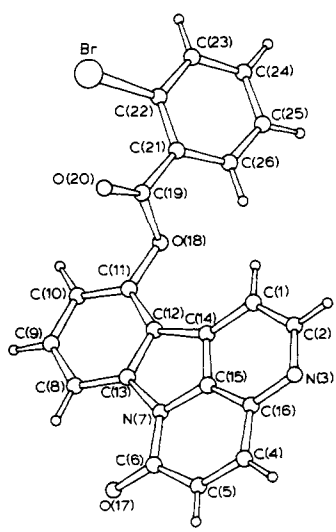


FIGURE 2. Structure and solid-state conformation of 11-*o*-bromobenzoylcanthin-6-one (**9**); small circles denote hydrogen atoms.

TABLE 3. Fractional Atomic Coordinates ($\times 10^4$; $\times 10^3$ for H[a]), with Standard Deviations in Parentheses

Atom	x	y	z	Atom	x	y	z
C(1)	1124(10)	1180(1)	3887(3)	C(15)	15(9)	456(1)	3081(2)
C(2)	−550(11)	967(1)	4590(3)	C(16)	−1632(9)	269(1)	3804(2)
N(3)	−1909(8)	527(1)	4572(2)	O(17)	−110(8)	−465(1)	1414(2)
C(4)	−2939(10)	−211(1)	3666(3)	O(18)	5451(7)	1722(1)	2312(2)
C(5)	−2450(11)	−442(1)	2879(3)	C(19)	4342(10)	2164(1)	2028(3)
C(6)	−649(10)	−250(1)	2111(3)	O(20)	2350(9)	2217(1)	1394(2)
N(7)	433(7)	220(1)	2262(2)	C(21)	5965(9)	2538(1)	2642(2)
C(8)	3121(10)	468(1)	808(2)	C(22)	6306(10)	3011(1)	2355(3)
C(9)	4748(10)	847(2)	414(3)	C(23)	7873(12)	3351(2)	2934(4)
C(10)	5480(11)	1269(1)	887(3)	C(24)	9063(12)	3216(2)	3808(4)
C(11)	4509(10)	1325(1)	1776(2)	C(25)	8744(13)	2758(2)	4117(3)
C(12)	2824(9)	960(1)	2190(2)	C(26)	7203(11)	2420(2)	3533(3)
C(13)	2189(9)	536(1)	1696(2)	Br	4784.2(15)	3227.4(2)	1166.8(4)
C(14)	1411(9)	911(1)	3083(2)				
H(1)	207	151	395	H(10)	670	153	59
H(2)	−77	116	516	H(23)	814	369	272
H(4)	−418	−37	415	H(24)	1020	346	423
H(5)	−339	−77	281	H(25)	962	267	476
H(8)	264	16	47	H(26)	696	208	376
H(9)	542	81	−23				

[a]Hydrogen atoms bear the same labels as the atoms to which they are bonded and were assigned the equivalent isotropic thermal parameters of these atoms.

demonstrated significant (T/C≥120%) antileukemic activity in vivo against P-388 lymphocytic leukemia (3-day dosing) at T/C=122% (25 mg/kg). Oxygenation at the C-1 and C-11 centers of the canthinone skeleton obviously contributes to significant cytotoxic antileukemic activity.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on an MRK air-bath type melting-point apparatus and were uncorrected. Ir and uv spectra were recorded on Hitachi 215 grating ir and 320-S uv spectrometers, respectively. ^{1}H-nmr and ^{13}C-nmr spectra were determined on JEOL JNM-GX400 (400 MHz for ^{1}H-nmr and 100 MHz for ^{13}C-nmr) and Hitachi R-22 (90 MHz) instruments using TMS as internal standard. Mass spectra were recorded on JEOL-JMS D100 (EI) and/or Hitachi M-80 (EI and FD) instruments. Silica gel (Merck, type 60, 70-230 mesh) was used for column chromatography, and precoated silica gel plates (Merck, 60 F-254, 0.25 and 2 mm) were used for analytical and preparative tlc, respectively. Detection of components was by use of a uv lamp. Hplc was performed on a Waters Associates Model ALC/GPC 244 liquid chromatograph using a μBondapak C18 column (3.9 mm×300 mm) for analytical, and M and S PAK C18-A (20 mm×250 mm) for preparative, purposes.

CHROMATOGRAPHY OF THE $CHCl_3$ FRACTIONS.—The crude $CHCl_3$ fraction (266 g), which constituted part of the $CHCl_3$ extract of the ground wood of *B. antidysenterica* (1,918 kg) reported previously (1,2), was subjected to column chromatography on silica gel (3 kg, 10 cm×90 cm) and eluted first with $CHCl_3$ and then with increasing amounts of MeOH in $CHCl_3$ to yield nineteen fractions. Concentration of fraction 11 by evaporation of the solvent afforded a brown gum (7.55 g).

ISOLATION OF 11-HYDROXYCANTHIN-6-ONE (**1**).—The foregoing brown gum (7.55 g) was subjected to hplc using a mixed solvent system of MeOH-H_2O (3:1, v/v). The first fraction eluted yielded a yellow powder (364 mg, 0.000019% yield) which was purified by recrystallization from MeOH to give **1**, mp 323-325°; uv λ max (EtOH) 326 (ε 8060) and 383 nm (ε 8330); ir (KBr) 3450 (OH), 1660 (α,β-unsaturated C=O), 1630 (C=C), 1600 (aromatic), 1468, 1440, 1382, 1352, 1310, 1285, 1245, 1140, 1122, 1058, 950, 855, 830, 785, 738 cm^{-1}; eims *m/z* 236 (M^+, 100), 209 (48), 180 (19). ^{1}H-nmr data are summarized in Table 1. Complete identification of **1** as 11-hydroxycanthin-6-one was based on the re-

sults of an X-ray analysis of 11-*o*-bromobenzoylcanthin-6-one (**9**, see below) as well as the close similarity of its spectral data to those reported elsewhere (15) for this alkaloid.

ISOLATION OF CANTHIN-6-ONE (**2**).—The second fraction eluted also afforded a yellow powder (317 mg, 0.000017% yield). Purification by recrystallization from MeOH/$CHCl_3$ gave **2**; mp 154-156° [lit. (14) mp 158-159°]; uv λ max (EtOH) 357 (ε 10660), 266 (ε 9926), 295 (ε 6990), 360 (ε 11400), and 378 nm (ε 10290); ir (KBr) 1670 (α,β-unsaturated C=O), 1638 (C=C), 1605 (aromatic), 1468, 1440, 1402, 1335, 1320, 1308, 1290, 1250, 1122, 1058, 1018, 965, 888, 845, 798, 762 cm^{-1}; eims *m/z* 220 (M^+, 100), 192 (47), 164 (11), 139 (9). The uv, ir, and ^{1}H-nmr (Table 1) and mass spectral data for **2** were consistent with those reported previously for canthin-6-one (18).

ISOLATION OF 1,11-DIMETHOXYCANTHIN-6-ONE (**3**).—Continued elution of the column after removal of **1** and **2** yielded a third fraction which furnished another yellow powder (206 mg, 0.000011% yield). Recrystallization from MeOH/$CHCl_3$ gave yellow crystals of pure **3**; mp 217-220° (decomp.); uv λ max (EtOH) 253 (ε 8790), 271 (ε 8600), 280 (ε 8470), and 355 nm (ε 16400); ir (KBr) 1675 (α,β-unsaturated C=O), 1625 (C=C), 1595 (aromatic), 1510, 1435, 1422, 1360, 1315, 1282, 1258, 1222, 1182, 1128, 1072, 1015, 992, 835, 785, 745 cm^{-1}; eims *m/z* 280 (M^+, 100), 265 (35). 237 (48), 207 (82), 180 (27), 140 (26); eims *m/z* 280.0766 (calcd. for $C_{16}H_{12}N_2O_3$: 280.0774), 265.0611 (calcd. for $C_{15}H_9N_2O_3$): 265.0611), 237.0633 (calcd. for $C_{14}H_9N_2O_2$: 237.0663); Found: C, 68.44; H, 4.44; N, 9.88%. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00%.

11-ACETYLCANTHIN-6-ONE (**8**).—Acetylation of **1** with Ac_2O in pyridine by the normal procedure yielded **8**; mp 209-210°; ^{1}H nmr: δ 2.52 (OAc); ms *m/z* 278.0695 (calcd. for $C_{16}H_{10}N_2O_3$: 278.0690) and 236 [base peak, M-42 ($COCH_2$)].

11-*O*-BROMOBENZOYLCANTHIN-6-ONE (**9**).—Treatment of **1** with *o*-bromobenzoyl chloride in dry pyridine in the usual manner furnished **9** as pale yellow needles ($CHCl_3$/EtOH); mp 254°.

X-RAY CRYSTAL STRUCTURE ANALYSIS OF 11-*O*-BROMOBENZOYLCANTHIN-6-ONE (**9**)[2].—Recrystallization of **9** from DMSO/DMF gave crystals suitable for an X-ray analysis. *Crystal data.*—$C_{21}H_{11}BrN_2O_3$, mol wt=419.24, Monoclinic, a=4.015(1) Å, b=27.962(3) Å, c=14.516(2) Å, β=94.13(1), V=1625 Å^3, Z=4, $D_{calc.}$=1.713 g cm^{-3}, μ (Cu-*K*α radiation, λ=1.5418 Å)=36.8 cm^{-1}. Space group $P2_1/c(C_{2h})$ uniquely from systematic absences: *0k0* when $k \neq 2n$, *h0l* when $l \neq 2n$. Sample dimensions: 0.18×0.18×0.70 mm.

Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs. Intensity data ($hk\pm l$) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-*K*α radiation, incident-beam graphite monochromator; ω-$2\theta_{scans}$, θmax=67°). From a total of 2894 independent reflections after averaging equivalent forms, those 2287 with $I>3.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Empirical absorption corrections, based on the φ-dependence of intensities of several reflections with χ.ca. 90°, were also applied to these data. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 high order ($58°<\theta<67°$) reflections widely separated in reciprocal space.

The crystal structure was solved by the heavy-atom approach. Coordinates for the bromine atom were derived from a Patterson map, and those for the other nonhydrogen atoms were obtained from a bromine-phased F_o Fourier synthesis. Full-matrix least-squares adjustment of positional and anisotropic thermal parameters reduced R to 0.064 at which point it was verified that all calculated hydrogen atom positions coincided with significant positive regions in a difference Fourier synthesis. Continuation of the least-squares iterations, with hydrogen atoms included at their calculated positions, converged to R=0.049 (R_w=0.070). Final atomic positional parameters are in Table 3. For the structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from reference 19. In the least-squares iterations, $\Sigma w\Delta^2[w=1/\sigma^2(|F_o|), \Delta=||F_o|-|F_c||]$ was minimized. A list of observed and calculated structure amplitudes is available from the authors.

BIOLOGICAL ACTIVITY.—In vitro and in vivo antitumor assays were carried out according to standard National Cancer Institute procedures described in the literature (20). The in vitro and in vivo activities of **1** and **3** have been described above; the control, 5-fluorouracil, had T/C=135% (200 mg/kg, 1-day dosing).

[2]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

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