Synthesis and X-ray diffraction data of 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno [2,1-*c*]quinoline

H.A. Camargo,[1] A. Sánchez,[1] J.A. Henao,[2,a)] Arnold R. Romero Bohórquez,[3] and Vladimir V. Kouznetsov[3]
[1]*Grupo de Investigación en Nuevos Materiales y Energías Alternativas (GINMEA), Facultad de Química Ambiental, Universidad Santo Tomás, Campus Universitario Floridablanca, Santander, Colombia*
[2]*Grupo de Investigación en Química Estructural (GIQUE), Escuela de Química, Facultad de Ciencias, Universidad Industrial de Santander, A.A. 678, Carrera 27, Calle 9 Ciudadela Universitaria. Bucaramanga, Colombia*
[3]*Laboratorio de Química Orgánica y Biomolecular (LQOBio), Escuela de Química, Facultad de Ciencias, Universidad Industrial de Santander, A.A. 678, Carrera 27, Calle 9 Ciudadela Universitaria. Bucaramanga, Colombia*

(Received 27 June 2013; accepted 20 August 2013)

The compound 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno[2,1-*c*]quinoline (**2**) (chemical formula $C_{23}H_{22}N_2$) was synthesized through the free-solvent oxidation reaction mediated by elemental sulfur from the corresponding 2-ethyl-6-(pyridin-4-yl)-5,6,6a,11b-tetrahidro-7*H*-indeno[2,1-*c*]quinoline (**1**), an adduct easily obtained, using the Lewis acid-promoted [4 + 2] cycloaddition reaction. Preliminary molecular characterization was performed by Fourier transform-infrared and gas chromatography-mass spectrometry. The X-ray powder diffraction (XRPD) pattern for the title compound was analyzed and found to be crystallized in monoclinic system, space group $P2_1/n$ (N° 14) with refined unit-cell parameters $a = 20.795$ (8) Å, $b = 7.484$ (2) Å, $c = 10.787$ (2) Å and $\beta = 93.96°$ (2). The volume of the unit cell is $V = 1674.8$ (6) Å^3. © *2013 International Centre for Diffraction Data.*
[doi:10.1017/S0885715613000730]

Key words: indeno[2, 1-*c*]quinolines, antitumoral activity, X-ray powder diffraction

I. INTRODUCTION

Quinoline derivatives are important natural and synthetic compounds with remarkable and diverse pharmacological properties (Kouznetsov *et al.*, 2005). Within the quinoline family, tetracyclic and pseudo-planar compounds with antitumoral activity as topoisomerases (topo) inhibitors are the more biological relevant examples (Gelderblom and Sparreboom, 2006).

Since the discovery of camptothecin, a natural topoisomerase (topo I) inhibitor (Priel *et al.*, 1991; Pommier, 2006), a constant search for new compounds with the ability to inhibit the topoisomerases I/II enzymes has been undertaken (Li *et al.*, 2006). The most relevant indenoquinoline compound because of its potent cytotoxicity against different leukemia lines (Ohyama *et al.*, 1999; Twelves *et al.*, 1999) is the 6-{[2 (dimethylamino)ethyl]amino}-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, known as TAS-103. The exhibited anticancer activity is because of its ability to function as a dual inhibitor of both topo I/II, and it has been investigated in clinical studies (Ewesuedo *et al.*, 2001; Ishida and Asao, 2002).

In our preliminary studies of TAS-103 analogs, we have reported a work where the diastereoselective synthesis of corresponding 6-pyridinyl-(tetrahydro)indeno[2,1-c]quinolines based on the Lewis acid-catalyzed imino Diels–Alder reaction (Kouznetsov *et al.*, 2009) was described and their biological activity was studied. It was found that these compounds were active against MCF-7, H-460, and SF-268 cancer cell lines making them potential anti-cancer agents (Kouznetsov *et al.*, 2006). However, the information about the crystallographic study by X-ray diffraction of this type of derivatives has been little explored.

In this regard, our ongoing research program focused on the chemistry of the anti-tumoral bioactive (tetrahydro) indeno[2,1-*c*]quinoline derivatives and its X-ray crystallographic study. Here, we discuss a simple methodology for preparation of compound 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno [2,1-*c*]quinoline (**2**) through the free-solvent oxidation reaction mediated by elemental sulfur from the corresponding 2-ethyl-6-(pyridin-4-yl)-5,6,6a,11b-tetrahidro-7*H*-indeno[2,1-*c*] quinoline (**1**) (Kouznetsov *et al.*, 2006) and report the results of the molecular characterization (FT-IR, GC-MS) and X-ray powder diffraction (XRPD) data.

II. EXPERIMENTAL

A. Synthesis

As shown in Figure 1, the compound $C_{23}H_{22}N_2$ was synthesized according to the following experimental procedure: A homogenate mixture of 2-ethyl-6-(pyridin-4-yl)-5,6,6a,11b-tetrahydro-7*H*-indeno[2,1-*c*]quinoline (**1**) (0.5 mmol) and elemental sulfur (1.5 mmol) was melted at 210–215 °C for 10 min. After completion of the reaction indicated by the complete liberation of H_2S (*g*), the reaction mixture was directly purified by column chromatography using alumina and eluted with petroleum ether-ethyl acetate to obtain 2-ethyl-6-(pyridin-4-yl)-7H-indeno[2,1-*c*]quinoline (**2**) as white pale-yellow crystals with 82% yield. The purified compound was recrystallized by slow evaporation in methanol solution. The

a)Author to whom correspondence should be addressed. Electronic mail: jahenao@uis.edu.co

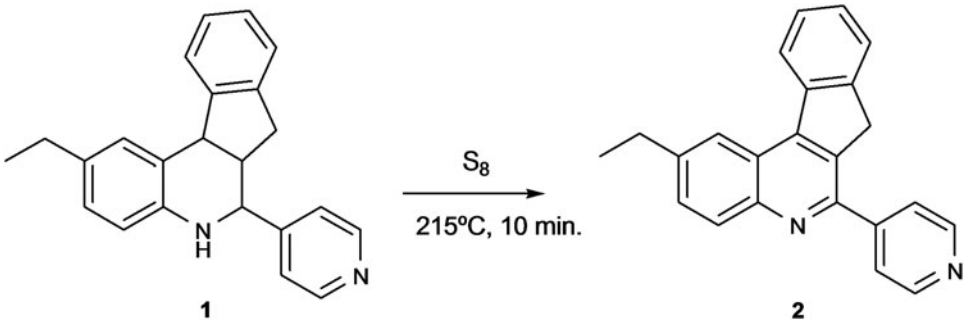

Figure 1. Synthesis of 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno[2,1-*c*]quinoline (**2**).

TABLE I. X-ray powder diffraction data of 2-ethyl-6-(pyridin-4-yl)-7H-indeno[2,1-c]quinoline (2).

$2\theta_{obs}$ (°)[a]	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
8.501	10.3930	100	2	0	0	8.518	10.3727	0.017
8.955	9.8671	15	−1	0	1	8.985	9.8346	0.030
9.485	9.3169	8	1	0	1	9.509	9.2935	0.024
12.536	7.0554	8	1	1	0	12.564	7.0400	0.028
14.720	6.0131	22	−3	0	1	14.729	6.0096	0.009
14.850	5.9608	5	−1	1	1	14.863	5.9557	0.013
15.161	5.8392	32	1	1	1	15.188	5.8290	0.027
15.687	5.6446	42	3	0	1	15.692	5.6428	0.005
16.430	5.3909	38	0	0	2	16.462	5.3806	0.032
			−2	1	1	16.462	5.3804	
17.033	5.2014	19	2	1	1	17.047	5.1972	0.014
			4	0	0	17.083	5.1864	
17.421	5.0864	1	−3	1	0	17.447	5.0790	0.026
18.008	4.9219	3	−2	0	2	18.025	4.9173	0.017
18.920	4.6867	1	−3	1	1	18.923	4.6859	0.003
19.683	4.5067	1	3	1	1	19.688	4.5056	0.005
20.319	4.3671	29	0	1	2	20.311	4.3688	−0.008
20.504	4.3281	52	−1	1	2	20.522	4.3242	0.018
20.977	4.2315	22	1	1	2	20.998	4.2274	0.021
21.595	4.1118	4	−2	1	2	21.607	4.1096	0.012
22.966	3.8694	12	−4	0	2	22.961	3.8702	−0.005
23.440	3.7922	4	−3	1	2	23.449	3.7908	0.009
			5	0	1	23.488	3.7845	
23.758	3.7421	4	0	2	0	23.758	3.7421	0.000
24.145	3.6830	10	1	2	0	24.148	3.6826	0.003
24.540	3.6246	2	−5	1	0	24.512	3.6288	−0.028
25.284	3.5196	36	2	2	0	25.281	3.5200	−0.003
25.642	3.4713	21	1	2	1	25.643	3.4712	0.001
26.437	3.3687	5	−2	2	1	26.434	3.3690	−0.003
26.839	3.3191	3	2	2	1	26.810	3.3226	−0.029
27.079	3.2903	10	−3	2	0	27.072	3.2911	−0.007
27.613	3.2278	11	−1	1	3	27.621	3.2269	0.008
28.076	3.1756	1	−3	2	1	28.068	3.1766	−0.008
29.049	3.0714	4	0	2	2	29.042	3.0721	−0.007
			2	1	3	29.408	3.0347	
29.427	3.0328	5	4	2	0	29.409	3.0346	−0.018
			−6	0	2	29.708	3.0048	
29.726	3.0030	4	−3	1	3	29.729	3.0028	0.003
31.221	2.8625	2	3	1	3	31.224	2.8623	0.003
			−4	1	3	31.648	2.8249	
31.672	2.8228	2	6	0	2	31.688	2.8214	0.016
32.068	2.7888	1	−6	1	2	32.073	2.7885	0.005
33.264	2.6913	2	0	0	4	33.276	2.6903	0.012
			−4	2	2	33.277	2.6902	
33.817	2.6485	3	−2	0	4	33.810	2.6491	−0.007
34.033	2.6322		−5	1	3	34.037	2.6319	0.004
			7	1	1	34.075	2.6290	
34.664	2.5857	2	−1	2	3	34.667	2.5855	0.003

Continued

https://doi.org/10.1017/S0885715613000730 Published online by Cambridge University Press

TABLE I. Continued

$2\theta_{obs}$ (°)[a]	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
35.020	2.5602	2	2	0	4	35.002	2.5615	−0.018
			−2	1	4	35.933	2.4972	
35.979	2.4941	1	1	1	4	35.987	2.4936	0.008
36.543	2.4569	10	−4	0	4	36.517	2.4586	−0.026
			0	3	1	36.959	2.4303	
36.995	2.4280	3	−3	1	4	36.979	2.4290	−0.016
			−7	0	3	37.992	2.3665	
38.058	2.3625	2	−4	2	3	38.026	2.3644	−0.032
38.495	2.3367	1	−4	1	4	38.510	2.3358	0.015
39.368	2.2869	1	−8	1	2	39.366	2.2870	−0.002
			−9	0	1	39.374	2.2865	
39.989	2.2528	2	6	2	2	39.989	2.2528	0.000
41.276	2.1855	1	−1	2	4	41.282	2.1852	0.006
			0	2	4	41.298	2.1844	
			1	0	5	42.492	2.1257	
42.530	2.1239	2	−6	2	3	42.524	2.1242	−0.006
43.096	2.0973	3	−4	3	2	43.106	2.0968	0.010
			−3	0	5	43.112	2.0966	
43.656	2.0717	3	−1	1	5	43.652	2.0719	−0.004
			6	0	4	44.018	2.0555	
			−2	1	5	44.033	2.0548	
			−4	2	4	44.033	2.0548	
44.063	2.0535	3	4	3	2	44.084	2.0526	0.021
44.888	2.0177	5	−3	1	5	44.860	2.0189	−0.028
			3	0	5	44.930	2.016	
			−7	2	3	45.304	2.0001	
45.321	1.9994	1	10	1	0	45.326	1.9992	0.005
45.818	1.9788	2	−5	2	4	45.809	1.9792	−0.009
46.172	1.9645	1	8	1	3	46.174	1.9644	0.002
			5	3	2	46.208	1.9630	
			9	2	0	46.219	1.9626	
			8	2	2	46.684	1.9441	
46.700	1.9435	1	3	3	3	46.713	1.9430	0.013
			10	1	1	46.727	1.9424	
			7	2	3	47.742	1.9035	
47.793	1.9016	1	−5	1	5	47.773	1.9023	−0.020

[a]Cu$K\alpha_1$ with $\lambda = 1.5406$ Å.

melting point (uncorrected) was between 162 and 164 °C and the density was 1.268 g cm^{-3}, which was measured by the flotation method in an aqueous solution of potassium iodine.

Its structural characterization was carried out by Fourier transform-infrared spectroscopy (FT-IR) and mass spectrometry with electron impact (MS-EI). Analysis of FT-IR revealed the following characteristic absorption bands (υ, cm^{-1}) 2968 (C-H); 1591 (C = C); 1541 (C = C) and 1375 (C-H), while MS-EI analysis showed the characteristic molecular peak $m/z = 326$ ($M^{+\bullet}$).

B. Powder data collection

A small portion of the compound $C_{23}H_{22}N_2$ was gently ground in an agate mortar and sieved to a grain size of less than 38 μm. The specimen was mounted on a polymethyl methacrylate (PMMA) specimen holder. The XRPD pattern was recorded with a D8 Advance Bruker diffractometer operating in DaVinci geometry equipped with a Cu-target X-ray tube (40 kV and 30 mA) using a nickel filter and a 1-dimensional LynxEye detector. A receiving slit (RS) of 0.6 mm and primary and secondary soller slits (SS) of 2.5° were used. The scan range was 2–70° 2θ with a step size of 0.015 26° and a count time of 2 s per step. XRPD data were collected at room temperature (25 °C).

PowderX program (Dong, 1999) was used to remove the background (Sonneveld and Visser, 1975), smoothing (Saviztky and Golay, 1964), to eliminate the Cu$K\alpha_2$ component (Rachinger, 1948) and the second derivative method was used to determine the position and intensities of the diffraction peaks.

III. RESULTS AND DISCUSSION

The X-ray powder diffraction data for the compound (**2**) are given in the Table I. All reflections were indexed

TABLE II. Parameters obtained by X-ray powder diffraction for the compound 2-ethyl-6-(pyridin-4-yl)-7H-indeno[2,1-c]quinoline (**2**).

a (Å)	20.795 (8)
b (Å)	7.484 (2)
c (Å)	10.787 (2)
β (°)	93.96 (2)
V (Å^3)	1674.8 (6)
Z	4
M_{20}	17.9
F_{30}	40.0 (0.0136, 55)
D_m (g cm^{-3})	1.268

https://doi.org/10.1017/S0885715613000730 Published online by Cambridge University Press

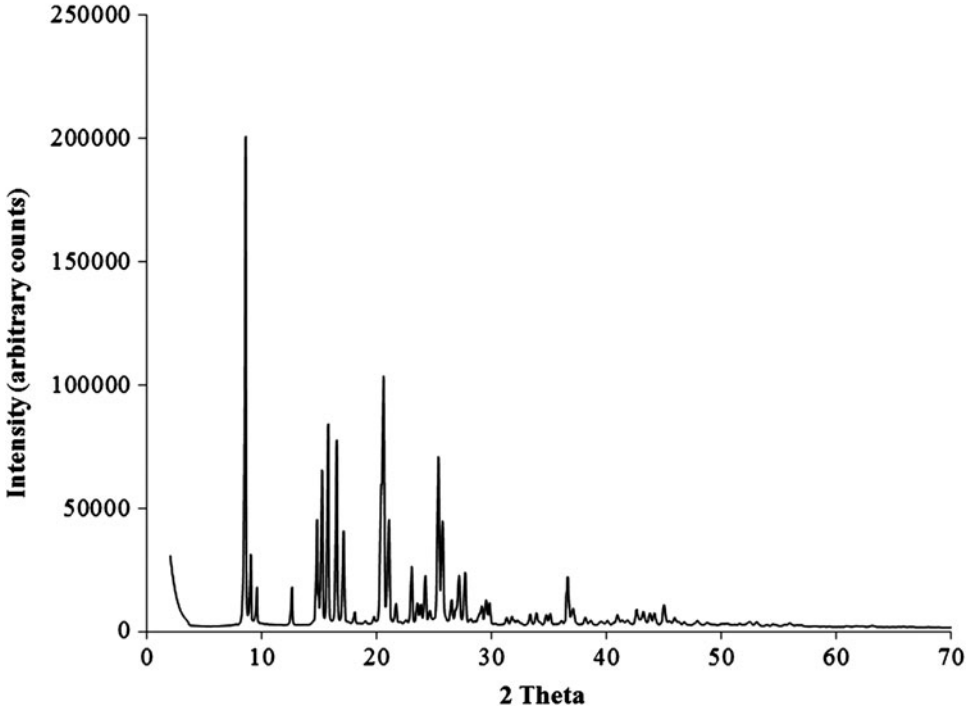

Figure 2. Powder X-ray diffraction pattern of 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno[2,1-*c*]quinoline (**2**).

successfully using the DICVOL06 program (Boultif and Louër, 2004) on a monoclinic system unit cell and the peak positions, each with an absolute error of 0.03° (2θ), were used in the calculations. The CHEKCELL program (Laugier and Bochu, 2002) was used to estimate the space group, $P2_1/n$ (No. 14), which was compatible with the systematic absences and with the crystal density. The unit-cell parameters of the compound (**2**) were refined with the program NBS*AIDS83 software (Miguell *et al.*, 1981). Its crystal data, X-ray density, and figures of merit M_{20} (de Wolff, 1968) and F_{20} (Smith and Snyder, 1979) are compiled in Table II. The X-ray powder pattern of the compound 2-ethyl-6-(pyridin-4-yl)-7*H*-indeno[2,1-*c*]quinoline (**2**) is shown in Figure 2.

ACKNOWLEDGEMENTS

H. A. Camargo thanks Universidad Santo Tomás (Bucaramanga-Colombia) for their support with the project which was approved in the VII internal call of research projects. A. R. R. Bohórquez is grateful for the financial support by the Universidad Industrial de Santander (VIE-UIS, project 5714) and COLCIENCIAS for support in the PhD studies (2005–2010).

Boultif, A. and Loüer, D. (**2004**). "Indexing of powder diffraction patterns of low symmetry lattices by successive dichotomy method," J. Appl. Crystallogr. **37**, 724–731.

de Wolff, P. M. (**1968**). "A simplified criterion for the reliability of a powder pattern," J. Appl. Crystallogr. **1**, 108–113.

Dong, C. (**1999**). "PowderX: Windows-95-based program for powder X-ray diffraction data processing," J. Appl. Crystallogr. **32**, 838–838.

Ewesuedo, R. B., Iyer, L., Das, S., Koenig, A., Mani, S., Vogelzang, N. J., Schilsky, R. L., Brenckman, W., and Ratain, M. J. (**2001**). "Phase I clinical and pharmacogenetic study of weekly TAS-103 in patients with advanced cancer," J. Clin. Oncol. **19**, 2084–2090.

Gelderblom, H. and Sparreboom, A. (**2006**). "Topoisomerase inhibitors." *Drugs Affecting of Tumours*, edited by H. M. Pinedo and C. H. Smorenburg (Birkhuser Vergal, Switzerland), pp. 83–100.

Ishida, K. and Asao, T. (**2002**). "Self-association and unique DNA binding properties of the anti-cancer agent TAS-103, a dual inhibitor of topoisomerases I and II," Biochim. Biophys. Acta **1587**, 155–163.

Kouznetsov, V. V., Ochoa Puentes, C., Romero Bohorquez, A. R., Zacchino, S., Sortino, M., Gupta, M., Vásquez, Y., and Bahsas, A. (**2006**). "A straightforward synthetic approach to antitumoral pyridinyl substituted 7*H*-Indeno[2,1-*c*]quinoline derivatives via three-component imino Diels-Alder reaction," Lett.Org. Chem. **3**, 300–304.

Kouznetsov, V. V., Romero Bohórquez, A. R., and Astudillo, L. (**2009**). "A convenient procedure for the synthesis of new α-Pyridinyl-substituted *7H*-Indeno[2,1-*c*]quinoline derivatives based on a three-component imino Diels–Alder reaction," Synthesis **24**, 4219–4225.

Laugier, J. and Bochu, B. (**2002**). *CHEKCELL*. "LMGP-Suite–Suite of Programs for the interpretation of X-ray. Experiments," ENSP/ Laboratoire des Matériaux et du Génie Physique, BP 46. 38042, Saint Martin d'Hères, France. http://www.inpg.fr/LMGP and http://www.ccp14.ac.uk/tutorial/lmgp/.

Li, Q. -Y., Zu, Y. -G., Shi, R. -Z., and Yao, L. -P. (**2006**). "Review camptothecin: current perspectives," Curr. Med. Chem. **13**, 2021–2039.

Miguell, A. D., Hubberd, C. R., and Stalick, J. K. (**1981**). *NBS* AIDS80: A FORTRAN Program for Crystallographic Data Evaluation*. Tech. Note 1141. USA: National Bureau of Standards.

Ohyama, T., Li, Y., Utsugi, T., Irie, S., Yamada, Y., and Sato, T. (**1999**). "A dual topoisomerase inhibitor, TAS-103, induces apoptosis in human cancer cells," Jpn J. Cancer Res. **90**, 691–698.

Pommier, Y. (**2006**). "Topoisomerase I inhibitors: camptothecins and beyond," Nat. Rev. Cancer. **6**, 789–802.

Priel, E., Showalter, S. D., Roberts, M., Oroszlan, S., and Blair, D. G. (**1991**). "The topoisomerase I inhibitor, camptothecin, inhibits equine infectious anemia virus replication in chronically infected CF2Th cells," J. Virol. **65**, 4137–4141.

Rachinger, W. A. (**1948**). "A correction for the α_1 α_2 doublet in the measurement of widths of X-ray diffraction lines," J. Sci. Instrum. **25**, 254.

Saviztky, A. and Golay, M. J. (**1964**). "Smoothing and differentiation of data by simplified least squares procedures," Anal. Chem. **36**, 1627–1639.

Smith, G. S. and Snyder, R. L. (**1979**). "F_N: a criterion for rating powder diffraction patterns and evaluating the reliability of powder-pattern indexing," J. Appl. Crystallogr. **12**, 60–65.

Sonneveld, E. J. and Visser, J. W. (**1975**). "Automatic collection of powder diffraction data from photographs," J. Appl. Crystallogr. **8**, 1–7.

Twelves, C. J., Gardner, C., Flavin, A., Sludden, J., Dennis, I., de Bono, J., Beale, P., Vasey, P., Hutchison, C., Macham, M. A., Rodríguez, A., Judson, I., and Bleehen, N. M. (**1999**). "Phase I and pharmacokinetic study of DACA (XR5000): a novel inhibitor of topoisomerase I and II," Br. J. Cancer **80**, 1786–1791.

https://doi.org/10.1017/S0885715613000730 Published online by Cambridge University Press