Synthesis and X-ray powder diffraction data of 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*]azepine

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The stereoselective synthesis of 7-fluoro-2-exo-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[b]azepine was developed by intramolecular 1,3-dipolar cycloaddition of the nitrone derived from the corresponding 2-allyl-4-fluoro-*N*-(3-methylbut-2-enyl)aniline. The X-ray powder diffraction (XRPD) pattern for the new compound was analyzed and found to crystallize in a monoclinic system with space group $P2_1/m$ (No. 11) and refined unit-cell parameters $a = 11.655(5)$ Å, $b = 5.850(2)$ Å, $c = 18.314(4)$ Å, $\beta = 104.27(3)$ and $V = 1210.1$ (6) Å^3. © *2013 International Centre for Diffraction Data.* [doi:10.1017/S0885715612000966]

Key words: 1, 4-Epoxytetrahydrobenzoazepines, antiparasitic activity, X-ray powder diffraction data

I. INTRODUCTION

Previously, we have described a simple and efficient synthetic pathway to obtain a wide range of new substituted 1,4-epoxy-2,3,4,5-tetrahydro-1-benzazepines and their reduced 2,3,4,5-tetrahydrobenzo[*b*]azepin-4-ols starting from appropriate N-substituted *ortho*-allylanilines (Gómez-Ayala *et al.*, 2006; Acosta *et al.*, 2010). Compounds of this type showed promising activity *in vitro* against *Trypanosoma cruzi* and *Leishmania chagasi* parasites (Palma *et al.*, 2009; Gómez-Ayala *et al.*, 2006, 2010). As a continuation of our structural study of 2-substituted 1,4-epoxytetrahydro-1-benzazepines and as part of a program to identify structurally novel antiparasitic compounds with new modes of action to combat both *T. cruzi* and *L. chagasi*, here we report the synthesis and the X-ray powder diffraction (XRPD) data of the new compound 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*]azepine.

The synthesis of this compound involved treating the corresponding 2-allyl-4-fluoro-*N*-(3-methylbut-2-enyl)aniline with an excess of hydrogen peroxide solution in the presence of catalytic amounts of sodium tungstate, and subsequent internal 1,3-dipolar cycloaddition of the resulting nitrone across the terminal C = C bond of the pendant allylic fragment, according to the methodology reported by Murahashi *et al.* (1990).

II. EXPERIMENTAL

A. Synthesis

For the preparation of the title compound (Figure 1), sodium tungstate dihydrate (10 mol% $Na_2WO_4.2H_2O$), followed by 30% aqueous hydrogen peroxide solution (30 mmol), were added to a stirred and cooled (ice-bath) solution of the 2-allyl-4-fluoro-*N*-(3-methylbut-2-enyl)aniline (10 mmol), 1a, in methanol (30 ml). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for an additional 6 h. The mixture was filtered and then extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and toluene (30 ml) was added to the organic black residue. The resulting solution was heated at reflux for 7 h. After cooling the solution to ambient temperature, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel using heptane-ethyl acetate (compositions in the range from 50:1 to 2:1 v/v) as eluent. The new compound 2a (M.p. 72 °C) was obtained as a colorless solid with a 35% yield.

B. Powder data collection

A small amount of the new compound $C_{14}H_{16}FNO$ was gently ground in an agate mortar and sieved to a grain size of less than 38 μm. The specimen was mounted on a zero-background specimen holder (Buhrke *et al.*, 1998) for the respective measurement. The XRPD data were collected at 295 K with a D8 FOCUS BRUKER diffractometer operating in Bragg-Brentano geometry equipped with an X-ray tube (Cu$K\alpha$ radiation: $\lambda = 1.5406$ Å, 40 kV, and 40 mA) using a nickel filter and a one-dimensional LynxEye detector. A fixed antiscatter slit of 8 mm, receiving slit of 1 mm, soller slits of 2.5°, and a detector slit of 3 mm were used. The scan range was from 2 to 70 °2θ with a step size of 0.02 °2θ and a counting time of 0.4 s per step.

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

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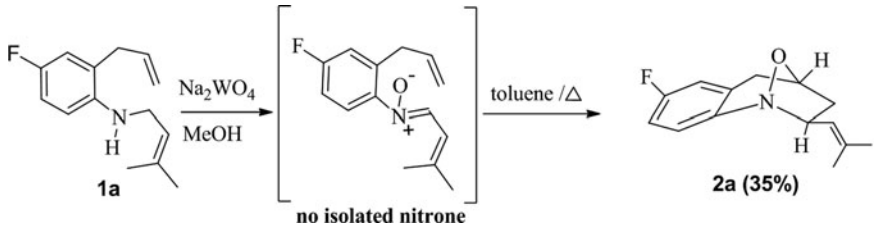

Figure 1. Synthesis of the 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*]azepine.

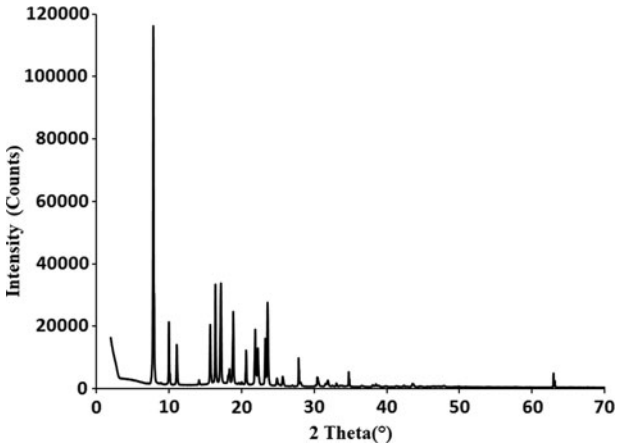

Figure 2. XRPD pattern of 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*]azepine.

III. RESULTS AND DISCUSSION

The XRPD pattern of 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*]azepine is shown in Figure 2 and the data for this compound are given in Table I. The XRPD pattern was successfully indexed using the DICVOL06 program (Boultif and Loüer, 2006) on a monoclinic cell with an absolute error of ±0.03°2θ in the calculations. The space group, $P2_1/m$ (No. 11) was estimated by the CHEKCELL program (Laugier and Bochu, 2002), which was compatible with the systematic absence and with the crystal density, 1.243 g cm^{-3}. The unit-cell parameters were refined with the NBS*AIDS83 program (Mighell *et al.,* 1981). The crystal data, X-ray density as well as figures of merit M_{20} (de Wolff, 1968) and F_{30} (Smith and Snyder, 1979) are compiled in Table II.

TABLE I. XRPD data of 7-fluoro-2-exo-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[b] azepine.

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
7.809	11.3124	100	1	0	0	7.821	11.2953	0.012
9.961	8.8727	18	0	0	2	9.959	8.8745	−0.002
11.047	8.0028	12	−1	0	2	11.049	8.0016	0.002
14.108	6.2726	2	1	0	2	14.118	6.2681	0.010
15.658	5.6549	18	2	0	0	15.678	5.6476	0.020
16.376	5.4086	28	−2	0	2	16.384	5.4061	0.008
17.095	5.1827	26	−1	1	0	17.056	5.1946	−0.039
18.157	4.8819	3	0	1	2	18.148	4.8842	−0.009
18.320	4.8388	5	1	1	1	18.316	4.8398	−0.004
18.836	4.7074	21	−2	0	3	18.845	4.7051	0.009
19.615	4.5222	1	−1	0	4	19.594	4.5271	−0.021
20.001	4.4358	1	0	0	4	19.994	4.4373	−0.007
20.621	4.3038	10	2	0	2	20.601	4.3080	−0.020
21.873	4.0602	16	2	1	0	21.857	4.0631	−0.016
22.226	3.9965	11	−2	0	4	22.202	4.0008	−0.024
23.256	3.8218	14	1	0	4	23.255	3.8219	−0.001
			−3	0	2	23.260	3.8211	
			2	1	1	23.290	3.8162	
23.579	3.7701	23	3	0	0	23.611	3.7651	0.032
24.868	3.5776	2	−1	1	4	24.849	3.5802	−0.019
25.659	3.4690	3	2	1	2	25.660	3.4689	0.001
			−2	1	4	26.978	3.3024	
26.993	3.3005	1	−3	0	4	26.998	3.2999	0.005
			1	1	4	27.862	3.1996	
27.867	3.1990	7	−3	1	2	27.866	3.1991	−0.001
			3	0	2	27.906	3.1945	
28.124	3.1703	2	1	0	5	28.123	3.1704	−0.001
			−3	1	0	28.163	3.1660	
30.201	2.9569	1	0	0	6	30.187	2.9582	−0.014
30.424	2.9357	3	−2	0	6	30.437	2.9345	0.013
30.511	2.9275	3	0	2	0	30.538	2.9250	0.027
			−4	0	3	31.539	2.8344	

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Table I. Continued

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_0)_{obs}$	h	k	l	$2\theta_{calc}$ (°)	d_{calc} (Å)	$\Delta 2\theta$ (°)
31.583	2.8306	1	1	2	0	31.571	2.8316	−0.012
31.894	2.8037	2	3	1	2	31.893	2.8037	−0.001
32.580	2.7462	1	−1	2	2	32.568	2.7472	−0.012
33.065	2.7070	1	−1	1	6	33.080	2.7058	0.015
			−4	0	4	33.115	2.7031	
			1	0	6	33.115	2.7031	
33.600	2.6651	1	−3	0	6	33.573	2.6672	−0.027
33.910	2.6414	1	0	1	6	33.931	2.6398	0.021
34.773	2.5778	4	3	1	3	34.770	2.5781	−0.003
			3	0	4	34.815	2.5749	
36.561	2.4558	1	−1	2	4	36.545	2.4568	−0.016
			−4	1	4	36.592	2.4538	
			1	1	6	36.592	2.4538	
38.066	2.3621	1	−2	2	4	38.080	2.3612	0.014
38.516	2.3355	1	−3	2	1	38.504	2.3362	−0.012
			4	0	3	38.532	2.3346	
			−5	0	1	38.897	2.3135	
			4	1	2	38.914	2.3125	
38.942	2.3109	1	−3	2	0	38.961	2.3099	0.019
			−5	0	3	38.984	2.3085	
39.864	2.2596	<1	5	0	0	39.874	2.2591	0.010
			0	2	5	39.905	2.2574	
41.315	2.1835	<1	1	1	7	41.322	2.1832	0.007
			−4	1	6	41.331	2.1827	
42.388	2.1307	<1	−1	1	8	42.416	2.1294	0.028
43.565	2.0758	1	0	1	8	43.595	2.0744	0.030
			−2	2	6	43.658	2.0716	
43.696	2.0699	1	5	0	2	43.679	2.0706	−0.017
44.727	2.0245	<1	−3	1	8	44.722	2.0248	−0.005
			−2	0	9	44.751	2.0235	
46.352	1.9573	1	−3	0	9	46.376	1.9563	0.024
			5	0	3	46.386	1.9559	
47.516	1.912	1	−2	1	9	47.507	1.9123	−0.009
			2	0	8	47.544	1.9109	
			−6	0	4	47.555	1.9105	
47.916	1.8970	1	3	0	7	47.899	1.8976	−0.017
49.533	1.8388	<1	−6	1	3	49.528	1.8389	−0.005
			5	0	4	49.546	1.8383	
			−2	0	10	49.877	1.8269	
49.891	1.8264	1	−6	1	1	49.894	1.8263	0.003
			6	0	1	49.919	1.8255	
54.031	1.6958	<1	1	2	8	54.016	1.6963	−0.015
57.801	1.5939	<1	3	0	9	57.833	1.5931	0.032
			−1	1	11	57.839	1.5929	
57.888	1.5917	<1	3	2	7	57.878	1.5919	−0.010
			−7	0	6	57.918	1.5909	
			−7	1	4	57.930	1.5906	
63.028	1.4737	3	7	1	2	63.023	1.4738	−0.005
			−5	3	4	63.035	1.4735	

TABLE II. Crystal-structure data for 7-fluoro-2-*exo*-(2-methylpropen-1-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzo[*b*] azepine.

a (Å)	11.655 (5)
b (Å)	5.850 (2)
c (Å)	18.314 (4)
β (°)	104.27 (3)
V (Å^3)	1210.1 (6)
Z	4
M_{20}	14.8
F_{30}	26.9 (0.0128, 87)
D_m	1.243 g/cm^3

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Acosta, L. M., Palma, A., and Bahsas, A. (**2010**). "Rational use of substituted *N*-allyl and *N*,*N*-diallylanilines in the stereoselective synthesis of novel 2-alkenyltetrahydro-1-benzazepines," Tetrahedron **66**, 8392–8401.

Boultif, A. and Loüer, D. (**2006**). "Indexing of powder diffraction patterns of low symmetry lattices by successive dichotomy method," J. Appl. Crystallogr. **37**, 724–731.

Buhrke, V., Jenkins, R., and Smith, D. (**1998**). *Preparation of Specimens for X-ray Fluorescence and X-ray Diffraction Analysis* (Wiley, New York), pp. 141–142.

de Wolff, P. M. (**1968**). "A simplified criterion for the reliability of a powder pattern indexing," 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**, 833–838.

Gómez-Ayala, S., Castrillón, J. A., Palma, A., Leal, S. M., Escobar, P., and Bahsas, A. (**2010**). "Synthesis, structural elucidation and *in vitro* antiparasitic activity against *Trypanosoma cruzi* and *Leishmania chagasi* parasites of novel tetrahydro-1-benzazepine derivatives," Bioorg. Med. Chem. **18**, 4721–4739.

Gómez-Ayala, S. L., Stashenko, E., Palma, A., Bahsas, A., and Amaro-Luis, J. M. (**2006**). "Sequential amino-claisen rearrangement/intramolecular 1,3-dipolar cycloaddition/reductive cleavage approach to the stereoselective synthesis of *cis*-4-hydroxy-2-aryl-2,3,4,5-tetrahydro-1(1*H*)-benzazepines," Synlett **14**, 2275–2277.

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/

Mighell, A. D., Hubbard, C R., and Stalick, J. K. (**1981**). NBS* AIDS83: A FORTRAN Program for Crystallographic Data Evaluation, National Bureau of Standards (USA), Technical Note 1141.

Murahashi, S. I., Mitsui, H., Shiota, T., Tsuda, T., and Watanabe, S. (**1990**). "Tungstate-catalyzed oxidation of secondary amines to nitrones. α-Substitution of secondary amines via nitrones," J. Org. Chem. **55**, 1736–1744.

Palma, A., Yépes, A. F., Leal, S. M., Coronado, C. A., and Escobar, P. (**2009**). "Synthesis and *in vitro* activity of new tetrahydronaphtho[1,2-b]azepine derivatives against *Trypanosoma cruzi* and *Leishmania chagasi* parasites," Bioorg. Med. Chem. Lett. **19**, 2360–2363.

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**, 254–255.

Savitzky, 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.

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