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STRUCTURAL CHARACTERIZATION OF 11-ETHYL-6,11-DIHYDRO-5H-DIBENZO[b,e]AZEPINE

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The title compound $C_{16}H_{17}N$, a potential pharmaceutical agent, crystallizes in the monoclinic $P2_1/n$ space group with unit cell parameters $a = 9.911(7)$ Å, $b = 5.542(3)$ Å, $c = 23.245(16)$ Å, $\beta = 96.25(2)°$. The dibenzazepine ring adopts a *twist-boat* conformation. The crystal packing is entirely dominated by cohesive weak N–H···Cg(π) and Cg(π)···Cg(π) interactions among the neighboring molecules producing an efficient packing with 66.4% of the occupied space.

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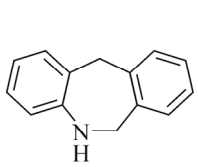
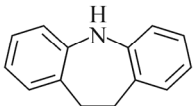
INTRODUCTION

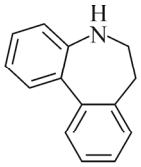
Heterocycles containing nitrogen in organic molecules have received considerable attention, mainly due to a broad range of biological properties in medicinal chemistry [1]. One of these heterocycles (benzoazepines) are drugs which exhibit the potent activity as selective agonists and antagonists to D-1 receptors [2] to treat Parkinson disease, esquezophrenia, renal disorder, hypertension, and cardiac arrest [3, 4]. These types of drugs are generally constructed from a seven-member ring fussed with benzene rings in different scaffolds (scheme 1). Due to their biological activity and diverse uses in agriculture [5], many synthetic routes for [b,e]dibenzazepines have been reported in the literature over the last 50 years.



1 [b, e]dibenzazepine



2 [b, f]dibenzazepine



3 [b, d]dibenzazepine

Scheme 1. Structural diagram of different scaffolds of dibenzazepines.

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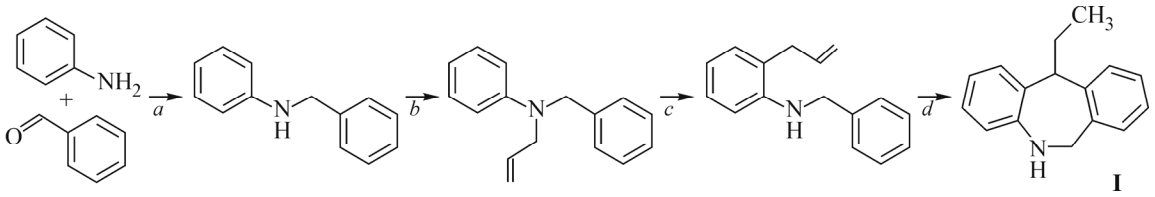
In recent works, Palma *et al.* [6, 7] have described an expedient synthetic route to construct a tetrahydro-1-benzazepine skeleton from readily available N-allyl-N-benzylanilines, through the aromatic amino-Claisen rearrangement and the intramolecular 1,3-dipolar cycloaddition as main transformations, and also applied the above synthetic route to the stereoselective synthesis and crystal structure analyses of different derivatives [8-10]. Compounds of this type show a promising action against *Trypanosoma cruzi* and *Leishmania chagasi* parasites [10].

The present work reports the crystal structure of 11-ethyl-6,11-dihydro-5H-dibenzo[b,e]azepine synthesized by the BF_3–Et_2O catalyzed aromatic amino-Claisen rearrangement and the intramolecular alkene Friedel–Crafts alkylation [6].

EXPERIMENTAL

Synthesis. 11-Ethyl-6,11-dihydro-5H-dibenzo[b,e]azepine (**I**) was synthesized by the BF_3–Et_2O catalyzed aromatic amino-Claisen rearrangement and the intramolecular alkene Friedel–Crafts alkylation (Scheme 2) explained elsewhere [6]. Reagents and conditions are: $NaBH_4$, MeOH (*a*), $BrCH_2CH{=}CH_2$, DMF, K_2CO_3, reflux (*b*), $BF_3{\cdot}OEt_2$, 140-155 °C (*c*), H_2SO_4, 80-90 °C (*d*). X-ray quality crystals suitable for the X-ray diffraction analysis were obtained from a chloroform solution after slow evaporation.



Scheme 2. Synthesis of 11-ethyl-6,11-dihydro-5H-dibenzo[b,e]azepine **I**.

NMR spectroscopic studies. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 model spectrometer in the DMSO-d_6 solution. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.91 (3H, t, *J* = 7.4 Hz, H13), 2.17 (2H, m, H12), 3.69 (1H, t, *J* = 7.3 Hz, H11), 4.00 (1H, d, *J* = 14.8 Hz, H6b), 4.95 (1H, d, *J* = 14.8 Hz, H6a), 6.50 (1H, d, *J* = 8.0 Hz, H4), 6.67 (1H, td, *J* = 8.0, 1,0 Hz, H2), 6.96 (1H, td, *J* = 8.0, 1.0 Hz, H3), 7.12 (1H, dd, *J* = 8.0, 1.0 Hz, H1), 7.19-7.30 (4H, m, H7–H10). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 13.0 (C13), 31.6 (C12), 51.1 (C6), 54.8 (C11) 117.9 (C4), 118.2 (C2), 127.2 (C3), 127.6-129.5 (C7–C10), 130.2 (C11a), 130.8 (C1), 136.5 (C6a), 142.1 (C10a), 146.2 (C4a).

X-ray data collection and structure determination. A colorless rectangular crystal (0.5×0.3×0.2 mm) was used for data collection. Diffraction data were collected at 298(2) K by the ω-scan technique on a Rigaku AFC7S Mercury diffractometer [11] with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). The data were corrected for Lorentz polarization and absorption effects. The structure was solved by direct methods using the SHELXS program [12] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [13]. All H atoms were placed at the calculated positions and treated using the riding model, with C–H distances of 0.97-0.98 Å, and N–H distances of 0.86 Å. The U_{iso} (H) parameters were fixed at $1.2U_{eq}$ (C, N) and $1.5U_{eq}$ (methyl groups). All geometrical calculations were made using the Platon program [14]. Table 1 summarizes the crystal data, intensity data collection, and refinement details for **I**. CIF file containing complete information on the studied structure was deposited with CCDC, deposition number 995653, and is freely available upon request from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

Title compound **I** $C_{16}H_{17}N$ crystallizes in the monoclinic space group $P2_1/n$. The crystal packing efficiency reaches 66.4%. Fig. 1 shows the molecular structure and the atom labeling scheme of 11-ethyl-6,11-dihydro-5H-dibenzo[b,e]azepine. Selected geometrical parameters are presented in Table 2. All bond distances and angles are normal [15] and are in agreement

TABLE 1. Crystal Data, Data Collection, and Structure Refinement

Chemical formula	$C_{16}H_{17}N$
Formula weight	223.31
Crystal system	Monoclinic
Space group	$P2_1/n$
a, b, c, Å; β, deg.	9.911(7), 5.542(3), 23.245(16); 96.25(2)
V, Å^3	1269.2(14)
Z	4
D_x, g/cm^3	1.169
F(000)	480
μ, mm^{-1}	0.068
Crystal size, mm	0.50×0.30×0.20
CCDC	995653
Radiation (MoK_α)	λ = 0.71073 Å
θ range, deg.	1.8-27.8
hkl range	–11, 11; –4, 6; –26, 26
Reflections unique / rint / with $I > 2\sigma(I)$	2321 / 0.039 / 1468
Refinement method	Full-matrix least-squares on F^2
Number of parameters	155
$R(F^2)$ / $wR(F^2)$ [$I > 2\sigma(I)$]	0.081 / 0.259
Goodness of fit on F^2	1.03
Max / min Δρ, e/Å^3	0.42 / –0.24

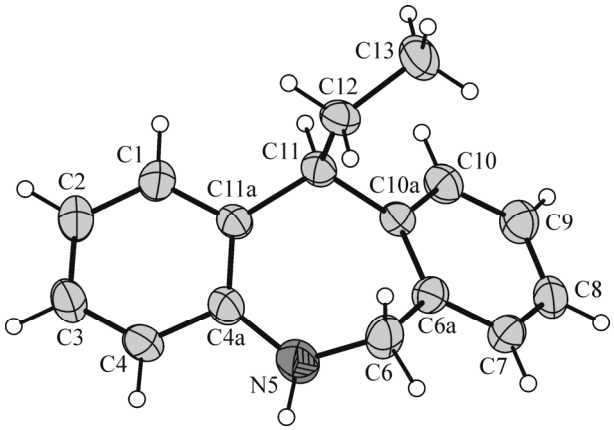


Fig. 1. Molecular structure of **I** showing the atomic numbering scheme. Displacement ellipsoids are drawn at a 25% probability level. H atoms are shown as spheres of arbitrary radii.

with the average values found in 22 entries with the dibenzo[b,e]azepine fragment in the Cambridge Structural Database (CSD, version 5.37, May 2016) [15]. The C6–N5–C4a bond angle 126.7(4)° is greater than the N5–C6–C6a bond angle of 116.9(3)°. This difference is also observed in all 22 fragments with average values of 119.2° and 116.3°, respectively. The N5–C6 bond distance is shorter than the N5–C4a bond distance by 0.028(5) Å (Table 2 and Fig. 1). This shortening is attributed to resonance effects between the benzene ring and the free electron pair of N5, giving a double bond character to the N5–C6 bond distance. This effect has also been observed in the related structures reported in the Cambridge Structural Database [15]. The dihedral angle between the benzene rings is 42.8(2)°. The azepinic ring presents a pseudo-mirror plane passing through C4a and bisecting the C6a–C10a bond, ΔCS = 22.78, thus adopting a twist-*boat* conformation [16, 17].

TABLE 2. Selected Geometrical Parameters (Å, deg.) for **I**

N5–C6	1.379(6)	C6–N5–C4a	126.7(4)	N5–C6–C6a	116.9(3)
N5–C4a	1.407(5)	N5–C4a–C11a	124.6(4)	N5–C4a–C4	115.9(4)
C6–C6a	1.472(5)	C4a–N5–C6–C6a	–63.1(6)	C6–N5–C4a–C4	–166.8(4)
C6a–C10a	1.385(4)	N5–C6–C6a–C10a	58.6(5)	N5–C6–C6a–C7	–120.9(4)
C9–C10	1.389(5)				
C11–C11a	1.525(4)				

TABLE 3. Parameters (Å, deg.) for Short Intermolecular Contacts

D–H···A	D–H	H···A	D···A	D–H···A
N5–H5a···Cg$^{(i)}$	0.860	2.910	3.730(5)	160

Symmetry codes: $^{(i)}$ 1/2–*x*, –1/2+*y*, 2–*z*.
(D – donor; A – acceptor; H – hydrogen). Cg1 represents the centroid of the C6a–C7–C8–C9–C10–C10a ring.

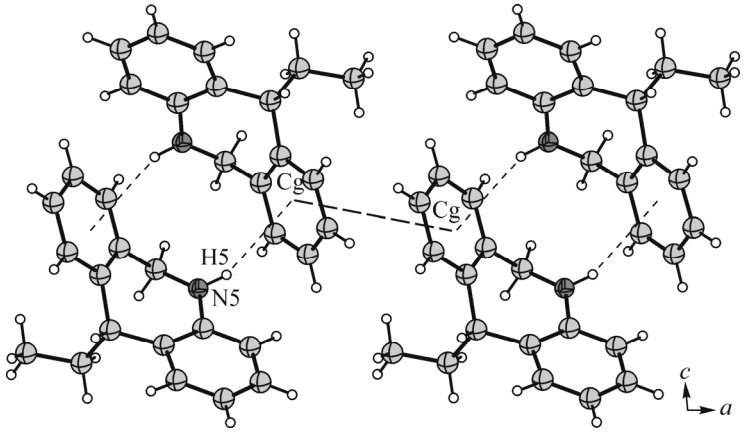


Fig. 2. Partial view of the crystal packing in the *ca* plane, showing the intermolecular weak N–H···*Cg*(π) and *Cg*(π)···*Cg*(π) contacts.

The crystal packing of title compound **I** is governed by non-conventional hydrogen bonds interacting with the π aromatic system of the benzene rings of the N–H···*Cg* type (Table 3), furthermore, the molecules are weakly linked in pairs by a single aromatic π–π stacking interaction to form dimeric units. Fig. 2 shows these interactions, and details of the hydrogen-bonding geometry are given in Table 3. In other to achieve an efficient packing of 66.4% of the occupied space [14], a pair of vessel-like molecules packed alternatively as concave and convex structures along the [010] direction.

CONCLUSIONS

The title compound has been prepared by the BF_3–Et_2O catalyzed aromatic amino-Claisen rearrangement and the intramolecular alkene Friedel–Crafts alkylation. The crystal packing is completely dominated by cohesive weak N–H···*Cg*(π) and *Cg*(π)···*Cg*(π) interactions among the neighboring molecules producing an efficient packing with 66.4% of the occupied space.

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