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The crystal structure of 13-(pyrazole-1-yl-4-carbonitrile)-matrine, $C_{19}H_{25}N_5O$

Table 1: Data collection and handling.

Crystal:	White needle
Size:	0.40 × 0.05 × 0.05 mm
Wavelength:	Cu K α radiation (1.54184 Å)
μ :	0.67 mm ⁻¹
Diffractometer, scan mode:	XtaLAB AFC12 (RINC), ω
$\theta_{\max}$, completeness:	74.4°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	19,482, 6659, 0.035
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 6104
$N(\text{param})_{\text{refined}}$:	451
Programs:	CrysAlis ^{PRO} [1], Olex2 [2], SHELX [3, 4]

Source of material

1H-pyrazole-4-carbonitrile (0.1380 g, 1.482 mmol), sophorcarpine (0.2000 g, 0.8117 mmol), cesium fluoride (0.1200 g, 0.37 mmol) were dissolved in 1,4-dioxane (8 mL). The resulting mixture reacted at 120 °C for 2.5 h. After stirring, the crude mixture was concentrated under reduced pressure and purified using flash chromatography on silica gel with acetonitrile and ethanol as eluent to give the desired product as white solid. A crystal suitable for diffraction was obtained by slow evaporation from its ethanol solution at room temperature.

Experimental details

Hydrogen atoms were placed in calculated positions and were refined in the riding model approximation, with $U_{\text{iso(H)}}$ set to $1.2U_{\text{eq}}$.

Comment

Matrine, a major alkaloid isolated from Traditional Chinese Medicine (TCM) *Sophora flavescens*, has attracted a growing interest due to its broad bioactivities, including pesticide activity, anti-tumor and anti-fibrotic [5–7]. So it is of great value to promote bioactivities through structure modification. Many matrine derivatives were synthesized in previous studies and showed better pesticidal activities than matrine [8, 9]. However, strict synthesis procedures and purification are needed to obtain the final product.

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Abstract

$C_{19}H_{25}N_5O$, monoclinic, $P2_1$ (no. 4), $a = 16.0600(2)$ Å, $b = 5.3992(1)$ Å, $c = 19.8514(2)$ Å, $\beta = 94.260(1)^\circ$, $V = 1716.58(4)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0350$, $wR_{\text{ref}}(F^2) = 0.0908$, $T = 100.00(10)$ K.

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The asymmetric unit of the molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.61389 (12)	0.9919 (4)	0.35567 (9)	0.0391 (5)
N1	0.31671 (12)	0.4352 (4)	0.34687 (9)	0.0234 (4)
N2	0.51615 (12)	0.7128 (4)	0.31649 (9)	0.0246 (4)
N3	0.55200 (11)	0.9264 (3)	0.11484 (9)	0.0208 (4)
N4	0.55026 (12)	1.1484 (4)	0.08205 (9)	0.0245 (4)
N5	0.66689 (15)	0.6244 (5)	−0.08007 (10)	0.0356 (5)
C1	0.28799 (15)	0.3801 (5)	0.41368 (11)	0.0266 (5)
H1A	0.270856	0.208030	0.414943	0.032*
H1B	0.239600	0.481695	0.420793	0.032*
C2	0.35452 (16)	0.4269 (5)	0.47039 (11)	0.0287 (5)
H2A	0.401376	0.316388	0.465753	0.034*
H2B	0.332035	0.393528	0.513492	0.034*
C3	0.38406 (16)	0.6953 (5)	0.46834 (12)	0.0308 (5)
H3A	0.430722	0.718835	0.501631	0.037*
H3B	0.339245	0.804291	0.479830	0.037*
C4	0.41087 (15)	0.7630 (5)	0.39827 (11)	0.0267 (5)
H4	0.418567	0.942963	0.397370	0.032*
C5	0.34218 (16)	0.6977 (4)	0.34262 (11)	0.0231 (5)
H5	0.293288	0.800629	0.349550	0.028*
C6	0.37111 (14)	0.7575 (4)	0.27228 (11)	0.0224 (5)
H6	0.381337	0.936189	0.270310	0.027*
C7	0.30177 (14)	0.6943 (5)	0.21765 (11)	0.0254 (5)
H7A	0.254798	0.804905	0.221680	0.031*
H7B	0.322265	0.718606	0.173380	0.031*
C8	0.27309 (14)	0.4274 (5)	0.22442 (11)	0.0273 (5)
H8A	0.225660	0.395923	0.192408	0.033*
H8B	0.317782	0.315809	0.214201	0.033*
C9	0.24869 (14)	0.3798 (5)	0.29557 (11)	0.0264 (5)
H9A	0.200626	0.480975	0.303902	0.032*
H9B	0.232634	0.207489	0.299556	0.032*
C10	0.45480 (13)	0.6235 (4)	0.26312 (10)	0.0214 (4)
H10	0.445903	0.446846	0.271348	0.026*
C11	0.48917 (14)	0.6463 (4)	0.19419 (10)	0.0217 (4)
H11A	0.535635	0.532891	0.191442	0.026*
H11B	0.446196	0.600625	0.159492	0.026*
C12	0.51823 (14)	0.9082 (4)	0.18167 (10)	0.0219 (4)
H12	0.470491	1.020770	0.182956	0.026*
C13	0.58493 (14)	0.9838 (4)	0.23694 (11)	0.0229 (5)
H13A	0.638289	0.919942	0.224887	0.027*
H13B	0.588852	1.163081	0.237277	0.027*
C14	0.57123 (14)	0.8979 (5)	0.30799 (11)	0.0255 (5)
C15	0.49437 (15)	0.6444 (5)	0.38408 (11)	0.0281 (5)
H15A	0.537633	0.700455	0.417294	0.034*
H15B	0.490225	0.465712	0.387461	0.034*
C16	0.58419 (14)	1.1032 (5)	0.02445 (11)	0.0252 (5)
H16	0.591020	1.221134	−0.008828	0.030*
C17	0.60850 (14)	0.8539 (4)	0.02014 (11)	0.0239 (5)
C18	0.58693 (14)	0.7471 (4)	0.07974 (11)	0.0244 (5)
H18	0.595073	0.582984	0.092864	0.029*
C19	0.64161 (15)	0.7293 (5)	−0.03540 (12)	0.0273 (5)
O1A	0.69289 (10)	0.5096 (3)	0.20975 (8)	0.0280 (4)
N1A	0.94177 (12)	−0.0844 (4)	0.11555 (9)	0.0234 (4)
N2A	0.78851 (11)	0.2006 (4)	0.21440 (9)	0.0224 (4)
N3A	0.86964 (11)	0.3998 (4)	0.41541 (9)	0.0223 (4)
N4A	0.86554 (13)	0.6260 (4)	0.44492 (9)	0.0263 (4)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
N5A	0.95268 (13)	0.1140 (4)	0.63331 (10)	0.0328 (5)
C1A	0.92850 (15)	−0.1423 (5)	0.04309 (12)	0.0278 (5)
HP	0.938446	−0.317529	0.036489	0.033*
HQ	0.968730	−0.051015	0.018718	0.033*
C2A	0.84134 (16)	−0.0789 (5)	0.01399 (11)	0.0290 (5)
HU	0.800995	−0.181424	0.035023	0.035*
HV	0.836663	−0.112748	−0.034127	0.035*
C3A	0.82232 (15)	0.1936 (5)	0.02607 (11)	0.0279 (5)
HB	0.764585	0.227930	0.011161	0.034*
HC	0.857603	0.296117	−0.000082	0.034*
C4A	0.83760 (15)	0.2571 (4)	0.10097 (11)	0.0250 (5)
HI	0.833769	0.437432	0.105371	0.030*
C5A	0.92565 (14)	0.1789 (4)	0.12866 (11)	0.0223 (5)
HR	0.966176	0.277232	0.105556	0.027*
C6A	0.93890 (14)	0.2331 (5)	0.20508 (11)	0.0238 (5)
HD	0.932588	0.411970	0.211435	0.029*
C7A	1.02816 (14)	0.1625 (5)	0.23071 (12)	0.0264 (5)
HJ	1.067477	0.270893	0.210430	0.032*
HK	1.034998	0.184448	0.279304	0.032*
C8A	1.04677 (14)	−0.1054 (5)	0.21319 (12)	0.0284 (5)
HW	1.104972	−0.142122	0.225791	0.034*
HX	1.012704	−0.215452	0.238291	0.034*
C9A	1.02830 (15)	−0.1479 (5)	0.13786 (12)	0.0278 (5)
HS	1.065961	−0.047989	0.113183	0.033*
HT	1.038351	−0.320466	0.127531	0.033*
C10A	0.86944 (14)	0.1016 (4)	0.24192 (11)	0.0218 (4)
HA	0.870944	−0.074517	0.230181	0.026*
C11A	0.87720 (14)	0.1204 (4)	0.31866 (11)	0.0223 (4)
HN	0.839572	0.002709	0.337407	0.027*
HO	0.933726	0.078677	0.335445	0.027*
C12A	0.85639 (14)	0.3799 (4)	0.34144 (11)	0.0223 (5)
H	0.893394	0.497714	0.320869	0.027*
C13A	0.76625 (14)	0.4393 (4)	0.31696 (11)	0.0238 (5)
HE	0.728969	0.339940	0.342165	0.029*
HF	0.755077	0.612159	0.326069	0.029*
C14A	0.74803 (13)	0.3898 (4)	0.24193 (11)	0.0229 (4)
C15A	0.77126 (14)	0.1425 (5)	0.14267 (11)	0.0240 (5)
HL	0.716689	0.206129	0.127136	0.029*
HM	0.770641	−0.035699	0.136517	0.029*
C16A	0.88540 (15)	0.5855 (4)	0.51023 (12)	0.0266 (5)
HG	0.887428	0.707272	0.543434	0.032*
C17A	0.90290 (14)	0.3340 (4)	0.52224 (11)	0.0239 (5)
C18A	0.89178 (14)	0.2217 (4)	0.45980 (11)	0.0242 (5)
HH	0.898427	0.054348	0.450456	0.029*
C19A	0.92993 (14)	0.2143 (5)	0.58413 (12)	0.0261 (5)

In our previous study, a series of matrine derivatives were synthesized by introducing nitro-containing heterocyclic into the C-12 position of the matrine skeleton using a one-pot Michael addition [10–12]. In this study, 1*H*-pyrazole-4-carbonitrile was introduced into the C-12 position of the sophocarpine, and a bond (C12–N3, 1.473(3) Å) was formed, which transforms C-12 to a chiral carbon center. The

asymmetric unit contains two molecules, and they are connected to neighboring ones by C–H...N, and C–H...O hydrogen bonds. The length of the C-11–C-12 bond is longer (1.531(3) and 1.517(3) Å for each molecule in asymmetric unit) compared to the counterpart of sophocarpine (1.3229(18) Å) [13], indicating that the C-11–C-12 bond is saturated. All bond lengths and angles of this structure are in the expected ranges and in good agreement with a similar structure [14, 15]. These results indicate that 1*H*-pyrazole-4-carbonitrile was introduced into the matrine skeleton, and that introduction mainly affects nearby bonds.

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References

1. Agilent. CrysAlis^{Pro}; Agilent Technologies: Yarnton, Oxfordshire, England, 2013.
2. Dolomanov O. V., Bourhis L. J., Gildea R. J., Howard J. A. K., Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* 2009, 42, 339–341.
3. Sheldrick G. M. *SHELXTL* – integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, A71, 3–8.
4. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, C71, 3–8.
5. Yang N., Han F., Cui H., Huang J., Wang T., Zhou Y., Zhou J. Matrine suppresses proliferation and induces apoptosis in human cholangiocarcinoma cells through suppression of JAK2/STAT3 signaling. *Pharmacol. Rep.* 2015, 67, 388–393.
6. Liu Z., Zhang Y., Tang Z., Xu J., Ma M., Pan S., Qiu C., Guan G., Wang J. Matrine attenuates cardiac fibrosis by affecting ATF6 signaling pathway in diabetic cardiomyopathy. *Eur. J. Pharmacol.* 2017, 804, 21–30.
7. You L., Yang C., Du Y., Wang W., Sun M., Liu J., Ma B., Pang L., Zeng Y., Zhang Z., Dong X., Yin X., Ni J. A systematic review of the pharmacology, toxicology and pharmacokinetics of matrine. *Front. Pharmacol.* 2020, 11, 18, 01067.
8. Xu J., Sun Z., Hao M., Lv M., Xu H. Evaluation of biological activities, and exploration on mechanism of action of matrine-cholesterol derivatives. *Bioorg. Chem.* 2020, 94, 103439.
9. Huang J. L., Lv M., Xu H. Semisynthesis of some matrine ether derivatives as insecticidal agents. *RSC Adv.* 2017, 26, 15997–16004.
10. Cheng X., He H., Wang W. X., Dong F., Zhang H., Ye J., Tan C., Wu Y., Lv X., Jiang X., Qin X. Semi-synthesis and characterization of some new matrine derivatives as insecticidal agents. *Pest Manag. Sci.* 2020, 76, 2711–2719.
11. Cheng X., Ye J., He H., Liu Z., Xu C., Wu B., Xiong X., Shu X., Jiang X., Qin X. Synthesis, characterization and in vitro biological evaluation of two matrine derivatives. *Sci. Rep.* 2018, 8, 15686.
12. He H., Qin X., Dong F., Ye J., Xu C., Zhang H., Liu Z., Lv X., Wu Y., Jiang X., Cheng X. Synthesis, characterization of two matrine derivatives and their cytotoxic effect on Sf9 cell of *Spodoptera frugiperda*. *Sci. Rep.* 2020, 10, 17999.
13. Morinaga K., Ueno A., Fukushima S., Namikoshi M., Iitaka Y., Okuda S. Studies on lupin alkaloids. VIII. a new stereoisomer of sophocarpine. *Chem. Pharm. Bull.* 1978, 26, 2483–2488.
14. Jing-Min Y., Hui-Qing H., Xu-Hong J., Zhan-Mei L., Xing-An C., Zhao-Chang H. The crystal structure of a matrine derivative, 13-(4-Cl-pyrrole)-matrine, C₁₈H₂₆ClN₄O. *Z. Kristallogr. N. Cryst. Struct.* 2019, 234, 785–786.
15. Hui-Qing H., Fang-Yun D., Han-Hui Z., Jing-Min Y., Chun-Can T., Xu-Hong J., Zi-Zhao Z., Xiao-Jing L., Xing-An C. The crystal structure of a matrine derivative, 13-(methylamine-1-yl) carbodithioate matrine, C₁₇H₂₇N₃OS₂. *Z. Kristallogr. N. Cryst. Struct.* 2020, 235, 685–687.