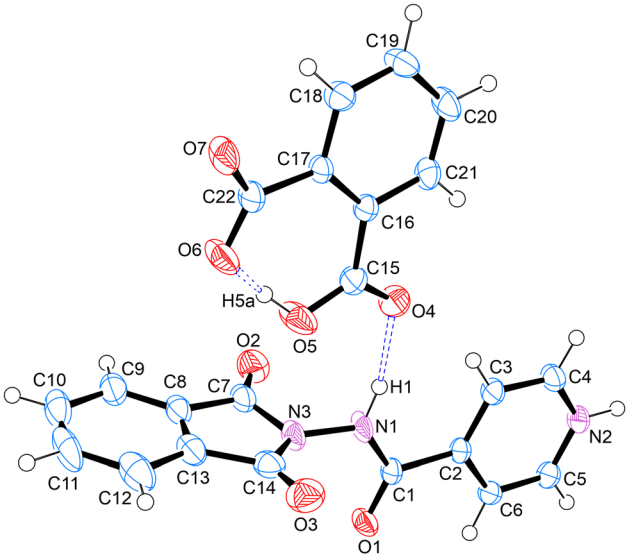
Mark G. Smith*

The crystal structure of the salt: 4-((1,3-dioxoisoindolin-2-yl)carbamoyl)pyridine-1-ium 2-carboxybenzoate, $C_{14}H_{10}N_3O_3{\cdot}C_8H_5O_4$



https://doi.org/10.1515/ncrs-2023-0417
Received September 20, 2023; accepted October 20, 2023; published online November 1, 2023

Abstract

$C_{14}H_{10}N_3O_3{\cdot}C_8H_5O_4$, triclinic, $P\bar{1}$ (no. 2), a = 8.1312(3) Å, b = 10.5732(4) Å, c = 12.0961(4) Å, α = 110.933(2)°, β = 101.603(2)°, γ = 91.295(2)°, V = 946.37(6) Å^3, Z = 2, $R_{gt}(F)$ = 0.0493, $wR_{ref}(F^2)$ = 0.1369, T = 173 K.

CCDC no.: 2295386

Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless needle
Size:	0.47 × 0.12 × 0.11 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.12 mm^{-1}
Diffractometer, scan mode:	Bruker D8 Venture Photon, ω
θ_{max}, completeness:	28.0°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	14,217, 4561, 0.045
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2937
$N(param)_{refined}$:	299
Programs:	Bruker [1], SHELX [2, 3], WinGX/ORTEP-3 [4, 5], PLATON [6]

1 Source of materials

All reagents were commercially available and used without further purification. An amount of 0.1123 g of isonicotinic acid hydrazide (0.819 mmol), 0.1364 g of phthalic acid (0.821 mmol), 0.1619 g of 2,2-dihydroxybenzophenone (0.818 mmol) and 3.0 mL of methanol were added into a screw-top dram vial (with rubber septum) and stirred at 300 rpm at 60 °C for 10 min. The vial was closed, and the solution was allowed to reflux at 60 °C for 24 h. The solution was then left slightly open to allow slow evaporation at room temperature. Colourless needles were observed after 3 days.

2 Experimental details

C-bound hydrogen atoms were located in the difference map then positioned geometrically and were allowed to ride on their respective parent atoms with thermal displacement parameters 1.2 times of the parent C atom. The coordinates and isotropic displacement parameters of all N-bound and O-bound H atoms were allowed to refine freely. Diagrams and publication material were generated using ORTEP-3 [4], WinGX [5] and PLATON [6].

3 Comment

For over 50 years, isoniazid has been used as a first-line pharmaceutical drug for the treatment of *Mycobacterium tuberculosis*. However, the mycobacterium has developed resistance to isoniazid due to certain genetic mutations (Shehzad *et al.* [7]). It is therefore beneficial to modify the NH_2 functional group of isoniazid, as this covalent modification

***Corresponding author: Mark G. Smith**, Chemistry Department, University of South Africa, Unisa Science Campus, 28 Pioneer Avenue, Florida, Roodepoort, Gauteng, South Africa, E-mail: smithm2@unisa.ac.za. https://orcid.org/0000-0003-2553-2540

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.5449 (2)	0.16425 (18)	0.46116 (15)	0.0262 (4)
C2	0.5811 (2)	0.24257 (18)	0.59650 (15)	0.0242 (4)
C3	0.5145 (2)	0.36283 (19)	0.65133 (16)	0.0287 (4)
H3	0.437264	0.399733	0.603863	0.034*
C4	0.5618 (3)	0.4278 (2)	0.77525 (16)	0.0322 (5)
H4	0.514936	0.509225	0.813737	0.039*
C5	0.7394 (3)	0.26249 (19)	0.79175 (16)	0.0306 (5)
H5	0.818914	0.229485	0.841257	0.037*
C6	0.6934 (2)	0.19145 (18)	0.66885 (15)	0.0278 (4)
H6	0.738003	0.10787	0.633413	0.033*
C7	0.5057 (3)	0.2320 (2)	0.21158 (17)	0.0360 (5)
C8	0.4229 (3)	0.1658 (2)	0.08092 (17)	0.0389 (5)
C9	0.4670 (3)	0.1833 (2)	−0.01673 (19)	0.0482 (6)
H9	0.558923	0.2469	−0.005792	0.058*
C10	0.3744 (4)	0.1060 (3)	−0.1309 (2)	0.0541 (7)
H10	0.402815	0.115695	−0.20008	0.065*
C11	0.2406 (4)	0.0145 (3)	−0.1459 (2)	0.0607 (8)
H11	0.177295	−0.0371	−0.225503	0.073*
C12	0.1953 (3)	−0.0042 (3)	−0.0451 (2)	0.0536 (7)
H12	0.104157	−0.067956	−0.054859	0.064*
C13	0.2909 (3)	0.0752 (2)	0.06797 (17)	0.0410 (6)
C14	0.2794 (3)	0.0800 (2)	0.19166 (19)	0.0374 (5)
N1	0.4383 (2)	0.21912 (18)	0.39431 (13)	0.0362 (4)
N2	0.6728 (2)	0.37790 (16)	0.84223 (14)	0.0301 (4)
N3	0.4174 (2)	0.16765 (17)	0.26974 (13)	0.0348 (4)
O1	0.61114 (18)	0.06184 (13)	0.41769 (11)	0.0355 (4)
O2	0.6216 (2)	0.31991 (16)	0.26162 (14)	0.0491 (4)
O3	0.1775 (2)	0.02278 (16)	0.22208 (15)	0.0500 (4)
H2	0.706 (3)	0.425 (2)	0.926 (2)	0.06*
C15	0.1524 (3)	0.4397 (2)	0.34621 (17)	0.0317 (5)
C16	0.0454 (2)	0.55637 (18)	0.35745 (15)	0.0256 (4)
C17	−0.0721 (2)	0.57976 (18)	0.26479 (15)	0.0259 (4)
C18	−0.1433 (3)	0.70270 (19)	0.29432 (17)	0.0331 (5)
H18A	−0.2186	0.720511	0.23181	0.04*
C19	−0.1093 (3)	0.7999 (2)	0.41054 (18)	0.0376 (5)
H19A	−0.1594	0.883056	0.427275	0.045*
C20	−0.0016 (3)	0.7741 (2)	0.50174 (17)	0.0369 (5)
H20A	0.0197	0.838038	0.582865	0.044*
C21	0.0750 (3)	0.6555 (2)	0.47516 (16)	0.0313 (5)
H21A	0.15074	0.640106	0.53886	0.038*
C22	−0.1345 (3)	0.4846 (2)	0.13344 (16)	0.0321 (5)
O4	0.25504 (19)	0.44073 (15)	0.43538 (12)	0.0408 (4)
O5	0.1388 (2)	0.34188 (16)	0.24257 (14)	0.0564 (5)
O6	−0.0670 (2)	0.37799 (15)	0.08790 (13)	0.0526 (5)
O7	−0.2573 (2)	0.51703 (15)	0.07231 (12)	0.0453 (4)
H5A	0.056 (4)	0.354 (3)	0.174 (2)	0.068*
H1	0.383 (3)	0.295 (2)	0.421 (2)	0.049 (7)*

has often shown to be effective against multi-drug resistant tuberculosis strains (Setshedi *et al.* [8]). In this study, isoniazid was covalently modified with phthalic acid, and a salt was formed from an interaction with a second phthalic acid molecule, resulting in the product presented here.

As shown in the figure, the asymmetric unit contains a salt formed via one molecule of 4-((1,3-dioxoisoindolin-2-yl)carbamoyl)pyridine-1-ium and one molecule of 2-carboxybenzoate. The two molecules are held together by a hydrogen bond between H2 on the pyridinium ring and O7 of the carboxylate moiety on the phthalic acid molecule. Furthermore, a hydrogen bond exists between the H1 donor on the carbohydrazide moiety of the modified isoniazid and the O4 acceptor atom of the carboxylic acid moiety of phthalic acid. The carboxylic acid and carboxylate moieties on phthalic acid form an expected intramolecular S(6) hydrogen bond [9], between the H5a donor and the O6 acceptor. All bond lengths and angles are as expected [10, 11].

Author contributions: The author has accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: This work was supported by the University of South Africa.

Conflict of interest statement: The author declares no conflict of interest regarding this article.

References

1. Bruker. *APEX2 (Version 2012.10-0), SAINT (Version 27B), SADABS (Version 2012/1)*; Bruker AXS Inc: Madison, Wisconsin, USA, 2012.
2. Sheldrick G. M. *SHELXTL* – integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, *A71*, 3–8.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Farrugia L. J. WINGX and ORTEP for Windows: an update. *J. Appl. Crystallogr.* 2012, *45*, 849–854.
5. Farrugia L. J. WINGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* 1999, *32*, 837–838.
6. Spek A. L. Structure validation in chemical crystallography. *Acta Crystallogr.* 2009, *D65*, 148–155.
7. Shehzad A., Rehman G., Ul-Islam M., Khattak W. A., Lee Y. S. Challenges in the development of drugs for the treatment of tuberculosis. *Braz. J. Infect. Dis.* 2013, *17*, 74–81.
8. Setshedi I. B., Lemmerer A., Smith M. G. Co-crystallization of *N*′-benzylidenepyridine-4-carbohydrazide and benzoic acid via autoxidation of benzaldehyde. *Acta Crystallogr.* 2023, *E79*, 682–685.
9. Bernstein J., Davis R. E., Shimoni L., Chang N. L. Patterns in hydrogen bonding: functionality and graph set analysis in crystals. *Angew. Chem., Int. Ed.* 1995, *34*, 1555–1573.
10. Lemmerer A., Bernstein J., Kahlenberg V. One-pot covalent and supramolecular synthesis of pharmaceutical co-crystals using the API isoniazid: a potential supramolecular reagent. *CrystEngComm* 2010, *12*, 2856–2864.
11. Turdybekov K. M., Nurkenov O. A., Fazylov S. D., Makhmutova A. S., Turdybekov D. M., Seilkhanov T. M., Arinova A. E. Synthesis, crystal structure, and conformation of *N*-isonicotinoylphthalimide. *J. Struct. Chem.* 2021, *62*, 1279–1284.