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Molecular Recognition in Proton-Transfer Compounds of Brucine with Achiral Substituted Salicylic Acid Analogues

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Abstract
The 1:1 proton-transfer brucinium compounds from the reaction of the alkaloid brucine with 5-nitrosalicylic acid, 3,5-dinitrosalicylic acid, and 5-sulfosalicylic acid, namely anhydrous brucinium 5-nitrosalicylate (1), brucinium 3,5-dinitrosalicylate monohydrate (2), and brucinium 5-sulfosalicylate trihydrate (3) have been prepared and their crystal structures determined by X-ray crystallography. All structures further demonstrate the selectivity of brucine for meta-substituted benzoic acids and comprise three-dimensional hydrogen-bonded framework polymers. Two of the compounds (1 and 3) have the previously described undulating brucine sheet host-substructures which incorporate interstitially hydrogen-bonded salicylate anion guest species and additionally in 3 the water molecules of solvation. The structure of 2 differs in having a three-centre brucinium–salicylate anion bidentate N+–H···O(carboxyl) hydrogen-bonding association linking the species through interstitial associations involving also the water molecules of solvation. A review of the crystallographic structural literature on strychnine and brucine is also given.

The Strychnos alkaloids strychnine (strychninidin-10-one) and its 2,3-dimethoxy-substituted analogue brucine (Scheme 1) were first reported by Fischer[1] in 1899 as agents for the separation of enantiomeric mixtures of the optically active N-benzoyl-protected alanines. Optical resolution using these alkaloids and various other

resolving agents has over the intervening years been largely a trial-and-error process although a systematization of the methods has evolved.[2] Both strychnine and brucine exhibit almost identical physicochemical and physiological properties (e.g. pKa1 6.04 (N9); pKa2 11.7 (N19)),[3] but with respect to resolving potential brucine has proved to be the better one, with a brucine/strychnine incidence of 22 to 8 among compounds with chiral organic molecules, and 14 to 3 with achiral organic molecules, among the 47 known crystallographically characterized structures. Because of the relatively high base strength of the N19 atom, reaction with many acids will occur, resulting in proton transfer with the subsequent generation of a cationic strychninium or brucinium species. This is evident in the high proportion of proton-transfer compounds among the known structures. Such compounds are important in many biological transfer processes and these alkaloids in their protonated forms may also be involved in their mode of toxic action.

Although the two compounds differ only in the presence, in brucine, of the two methoxy groups, these appear to influence the formation of a relatively common undulating sheet host-substructure which is present in several proton-transfer and neutral organic brucine structures, including the solvates. In all of the reported examples, the two methoxy groups assume the same conformation, being anti-related and lying in the plane of the benzene ring. Accommodated within the host inter-sheet spaces are complementary guest molecules (anions, adduct, and solvent molecules), which associate with the brucine host-framework through hydrogen-bonding interactions. This structure type provided an early example of molecular recognition first described by Gould and Walkinshaw in 1984,[4] with the structure of the brucinium salt of the Fischer-type N-benzoyl-protected d-alanine. This feature is not present in the structure of the analogous strychnine salts of d- or l-alanine.[5] The brucine solvate structures brucine–ethanol–water (1/1/2,[6] found to be isomorphous with brucine–isopropanol–water 1/1/2[7]) also show the guest molecules accommodated within the interstitial cavities, acting in a space-filling capacity but hydrogen-bonded to the nitrogen acceptor sites of the brucine host. This substructure is also found in the structure of anhydrous brucine[7] where there is no interstitial guest spatial requirement, but not in the minimally associative brucine–acetone (1/1) solvate.[7] In the case of compounds with acidic organic molecules, proton-transfer to N19 of the brucine or strychnine molecule occurs and the resultant site acts as a donor site for hydrogen-bonding association with the guest molecule. In the structure of brucinium–3-nitrobenzoate–methanol (1/1/1), Oshikawa[8] also demonstrated a selectivity of brucine for the meta-substituted benzoic acids which included the meta-chloro- and meta-bromo-substituted analogues, whereas no interaction was given with the ortho- or para-isomers.

The rigid stereochemistry of the strychnine and brucine cage is considered to be an important contributing factor to the regularity particularly of the brucine substructures and a large number of crystal structures of the resultant cocrystals have been reported. The X-ray crystal structure determination of strychninium bromide dihydrate by Robertson and Beevers in 1951[9] confirmed the Robinson and Woodward molecular structure,[10,11] and subsequently the structures of several inorganic strychninium compounds and their analogues have now been determined. These include the sulfate, nitrate, chloride, iodide, perchlorate, hydrogensulfate, dihydrogenphosphate, and the hexasulfide, whereas the structure of brucinium sulfate has only recently been reported.[12] As well, the structures of the anhydrous parent compounds

strychnine[6,13] and brucine[7] have been determined as have those of other substituted strychnines.[14]

We have categorized the organic strychnine and brucine compounds as follows:

(a) Those with chiral acidic species, giving mostly 1:1 proton-transfer compounds.

(b) Those with chiral neutral species, giving molecular adducts.

(c) Those with achiral acidic species also giving proton-transfer compounds; this category contains occasional 2:1 compounds with strong diprotic acids.

(d) Those with achiral neutral species.

In all of these the absolute configuration determined by Peerdeman[15] is invoked, giving for the six chiral centres of neutral strychnine or brucine the Cahn–Ingold–Prelog designation[16] of the molecules as C7(R), C8(S), C12(S), C13(R), C14(R), C16(S). Of the four categories of compounds, totalling 47 organic strychnine and brucine compounds referenced in this work, category (a) contains a larger proportion of the examples (51%) because these compounds are more often the types giving good crystalline materials with strychnine and brucine in enantiomorph resolution. Examples include the strychninium and brucinium salts of the N-benzoyl-protected alanines,[4,5] the N-phthaloyl-protected alanines,[17] N-acetyl-protected l-tryptophane,[18] as well as those of the N-phthaloyl-β-hydroxy-d- and l-leucines (three compounds).[19] Other chiral acid types include hydroxy acids: d-glucuronic and d-galacturonic acids (both with brucine),[20] both d- and l-tartaric acid (with strychnine),[21] a disaccharide acid,[22] l-glyceric acid,[23] l-malic acid,[24] l-tartaric acid,[24] and citric acid[25] (latter five all with brucine), other miscellaneous acid types (all with brucine),[26–32] a phosphodithiol salt with methylstrychnine,[33] as well as S-(+)-bromochlorofluoroacetate with strychnine.[34] With these proton-transfer compounds, the protonated N19 of the strychnine or brucine molecule subsequently generates another chiral centre in the cation (S).[16] In category (b) (15%), the types of compound giving neutral adducts include those with chiral alcohols (both with brucine),[35,36] lactones (all with brucine),[8,37–39] and cyanohydrins (two with brucine).[40] Falling into categories (c) and (d) are the structures of several compounds of strychnine and brucine with achiral acidic and neutral organic molecules. The proton-transfer compounds again comprise the larger group, the category (d) examples (8.5%) being limited to the brucine solvates with acetone, ethanol, and isopropanol,[6,7] with isopropanol also being a common inclusion molecule in brucine salts.[41] We also reported the first example of a brucine or strychnine compound with a zwitterionic acid species in the hydrated strychnine adduct with the achiral 1,7-Cleve's acid (8-amino-2-naphthalenesulfonic acid).[42]

The category (c) examples, comprising 25.5% of the total are as follows: brucinium–4-hydroxybenzoate–isopropanol (1/1/1),[41] brucinium 4-nitrophenate,[43] brucinium hydrogen fumarate sesquihydrate and brucinium hydrogen maleate,[44] brucinium–2,2′-bis(3-phenyl-1-naphthol)phosphate–ethanol–water (1/1/1/2),[45] brucinium–2,2-dimethoxy-1-oxonaphthalene-4-carboxylate–2,2-dimethoxy-1-oxonaphthalene-4-carboxylic acid (1/1/1),[46] and brucinium 3-nitrobenzoate.[8] Because of the

demonstrated selectivity shown by brucine for meta-substituted benzoic acids, we subsequently synthesized and crystallographically characterized the 1:1 strychninium salts of the meta-substituted analogues 3,5-dinitrosalicylic acid (DNSA; an anhydrate) and 5-nitrosalicylic acid (5-NSA; an unusual bis(5-NSA acid) adduct),[47] the 1:1 brucinium salts of 3-nitrophthalic acid (a dihydrate),[48] toluene-4-sulfonic acid (a trihydrate),[49] and isophthalic acid (a trihydrate).[24] The 1:1 brucinium salts of 5-NSA, DNSA, and 5-sulfosalicylic acid (5-SSA), namely anhydrous brucinium 5-nitrosalicylate (1), brucinium 3,5-dinitrosalicylate monohydrate (2), and brucinium 5-sulfosalicylate trihydrate (3) have been prepared and their solid-state crystal structures are reported herein.

General Structural Features of 1–3

The structures of compounds 1–3 fit into the general category (c) group of strychnine/brucine compounds, all involving, as expected on the basis of the strengths of the acids involved, proton transfer to N19 of the brucine molecule cage. The atom numbering scheme for the brucinium cation is shown in Fig. 1 for compound 1 and is identical to that used for 2 and 3. Also, since the brucine cage is conformationally inflexible, this molecular entity is essentially invariable across the three structures. This inflexibility extends to the conformations of the two methoxy substituent groups which invariably lie in the plane of the indole ring system and are mutually anti-related. The atom numbering schemes for the 5-NSA anion in 1 (Fig. 1) and the DNSA and 5-SSA anionic species in 2 and 3 (Fig. 2) are consistent with previous structures completed by our group.[50–52]

All three crystals possess the three-dimensional hydrogen-bonded polymer structures which are common in all strychnine and brucine compounds. However, the undulating head-to-tail sheet substructure which exerts the molecular recognition characteristics for many guest molecular species is found in only two of the three structures (1 and 3). With 2, the brucinium cations form the much less common head-to-tail homomolecular hydrogen-bonded chains. The structural differences probably result from the fact that as far as hydrogen bonding is concerned, DNSA and particularly 5-NSA have a much lesser tendency to form hydrate structures than 5-SSA and consequently stable crystal structures. This has been observed in the structures of the proton-transfer compounds of both 5-NSA[50] and DNSA[51] when compared with those of 5-SSA[52] (which because of its flexibly interactive O(sulfonate) acceptors and its additional carboxylic acid substituent is usually hydrated), which give rise to a profusion of stable crystalline compounds. In the case of the hydrated compounds 2 and 3, the interstitial cavities between the brucinium host-substructures are occupied as expected by either the DNSA or 5-SSA anion guest molecule together with the water molecules. In all compounds, stable hydrogen-bonded polymer structures result from several inter-species hydrogen-bonding interactions both between the brucinium host-substructure and the guest molecules as well as inter-guest interactions (Table 1). In the absence of water in the structure of 1, little hydrogen bonding is present with the 5-NSA anion tending more to π-stack above the aromatic portion of the brucinium cation substructure. None of the compounds have any intermolecular interactions involving phenolic or nitro oxygen atom acceptors.

It is also of particular interest that in these brucine compounds the basic substructure is generated most commonly by a rotation–translation operation about a

crystallographic 21 axis in the unit cell either in the chiral orthorhombic P212121 or the monoclinic P21 space group, into which about 95% of the structures of both brucine and strychnine fall. This is consistent with the earlier observation[53] for 430 general examples of enantiomerically pure compounds that there was a 67 to 27 to 1% incidence of the space groups P212121, P21, and C2 respectively. With the 47 organic strychnine and brucine compounds contained in this reference set (not including compounds 1–3) there is the same very minor incidence of other chiral space groups: One example each of the C2, P21212, and P43212 space groups and three with space group P1 (which comprise a set of essentially isomorphous brucine compounds with α-hydroxy acids — l-glyceric,[23] l-malic,[24] and citric acids[25] — although the anhydrous compound with l-tartaric acid[24] is not). In the substructures generated by the 21 rotation–translation operation, which is present in the P212121 examples (compounds 1 and 3; best seen in the packing diagram for 3), the ribbons forming the sheets often comprise overlapping head-to-tail brucine species which lie either along the propagating axis or perpendicular to it with an approximate 12.5-Å cell repeat along this ribbon axis. In the majority of the examples, the ribbons have the anti-parallel mode of packing (such as found in the brucinium d-galacturonate structure[20] and in both 1, Figs 3a and 3b, and 3) whereas in a small number of compounds the ribbons have the parallel mode, for example the structures of brucinium d-glucuronate[20] and anhydrous brucine[7] (Fig. 3c).

We have recently described[54] the relationship between the dimer repeat period along the propagating direction in these structures and the angle α between the lines drawn through the centres of the indole rings in adjacent brucine molecules in the chain. In the anti-parallel mode examples 1 and 3 this angle α is approximately 119° (12.45 Å repeat) and 118° (12.57 Å repeat) respectively, and compares with 115° (12.43 Å repeat) in the brucinium N-benzoyl-d-alanine structure[4] and 115° (12.33 Å repeat) in brucine–isopropanol–water (1/1/2).[7] In the parallel mode anhydrous brucine structure (Fig. 3c), where no interstitial guest cavity exists, the brucine repeat period increases (to 12.70 Å) as does the angle α (to about 123°).

With the examples belonging to space group P1 the brucinium cation repeat is generated by a pseudo-21 symmetry operation, the degeneration to the lower symmetry being considered the result of both the conformational flexibility of the hydroxy acid and the invariable presence of numerous water molecules of solvation (typically 6–10 in the P1 bimolecular crystallographic asymmetric unit).[23–25] The examples having space group C2, which include 2, form double-layer substructures best seen in Fig. 5, which shows a projection of the brucinium host molecules viewed down the 2-fold rotation axis of the substructure (perpendicular to the propagating direction).

Individual Structures

[(Brucine)+(5-NSA)–] 1

The anhydrous structure of 1, as indicated previously is based on the common anti-parallel mode undulating brucine sheet host-substructure which is generated in the usual manner in 1 by a 21 rotation–translation operation along the b-axis and propagated along a (Fig. 4a). The structure is very similar to that found in anhydrous brucine,[20] with little inter-sheet space available to accommodate the guest

molecules. Instead, the 5-NSA anions occupy compressed positions above the aromatic portion of the brucinium cation, being linked to the protonated N19 group of the host structures through single hydrogen bonds with carboxyl oxygen atom acceptors (N19···O71N 2.657(5) Å; Fig. 4b).

There appears to be some weak π–π interaction between the host and guest ring systems (inter-ring centroid separation 3.889(6) Å; inter-plane dihedral angle 8.9(1)°). The π–π stacking phenomenon involving 5-NSA has been observed in the anhydrous strychninium–5-nitrosalicylate–5-NSA adduct (1/1/2)[47] but the interaction in that case was homomeric. The second carboxyl oxygen in 1 forms the expected intramolecular hydrogen bond with the phenolic oxygen (O···O 2.494(7) Å) while there is no secondary group participation in hydrogen bonding. This is typical of what is observed in the proton-transfer compounds of 5-NSA[50] where interactions of this type are usually minimal compared to those of the compounds of the analogous 3,5-dinitrosalicylic acid.[51] The carboxylate group of the 5-NSA anion is essentially coplanar with the benzene ring (torsion angle C2N–C1N–C7N–O71N 179.9(5)°) but the nitro group is rotated slightly out of the plane (C4N–C5N–N5N–O52N 166.8(7)°).

[(Brucine)+(DNSA)–·H2O] 2

The structure of 2 represents a rare hydrate (or solvate generally) among the DNSA proton-transfer compounds.[51] This water molecule (O1W) lies within the cavity between the brucinium double-ribbon structures generated by the 2-fold rotation operation and links the carbonyl oxygen atom (O25) of the brucine cation to the carboxyl oxygen atom (O71D) of the DNSA anion (O···O 2.849(12), 2.866(9) Å; Fig. 5).

The protonated N19 group provides an asymmetric cyclic three-centre R21(4) linkage to the two carboxylate oxygens of the DNSA anion (N19···O71D 2.864(10); N19···O72D 3.116(9) Å). In this respect, 2 differs markedly from that of the anhydrous strychninium compound with DNSA,[47] where the discrete strychnine cations are linked head-to-tail through linear homomolecular N+···O(carbonyl) associations with the DNSA anions peripherally linked. Conformationally, the DNSA anion shows significant rotation of the nitro groups out of the molecular plane (torsion angles C2D–C3D–N3D–O32D –158.2(8)°; C4D–C5D–N5D–O52D –168.6(7)°) but as expected the presence of the intramolecular salicylate hydrogen bond (O···O 2.425(9) Å), in which the proton is located on the phenolic oxygen atom, maintains coplanarity of this group with the benzene ring (torsion angle C2D–C1D–C7D–O71D 179.5(8)°).

[(Brucine)+(5-SSA)–·3H2O] 3

Because of the presence of three water molecules of solvation in 3, the hydrogen bonding is much more extensive than in 1 or 2. The characteristic anti-parallel mode undulating sheet host-structures are present (Fig. 6) with a repeat period of 12.57 Å along the a-axis of the P212121 cell. The 5-SSA anions and the three water molecules occupying the secondary interstitial cavity structure are hydrogen-bonded to the host-structure, through interactions to both the protonated N19 group and the O25 carbonyl group of the brucine cation (N19···O2W 2.896(7) Å; OW1···O25 2.849(6) Å). Other

associations within the cavity involve water···water, water···anion(sulfonate), and water···anion(carboxylic acid) associations.

The water···carboxylic acid hydrogen bond is strong (2.587(6) Å), typical of the interactions of this group found with proton-transfer compounds of 5-SSA.[52] The 5-SSA anions also arrange in an anti-parallel manner into pairs having a perpendicular aromatic ring plane separation of 3.69 Å but the minimum ring centroid separation (5.1 Å) is not suggestive of any π–π interaction. In most respects the structure of 3 is very similar to that of brucinium–toluene-4-sulfonate–trihydrate,[49] except that in that structure there is a direct N+–H···O(sulfonate) interaction.

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The ready formation of stable hydrogen-bonded proton-transfer compounds of brucine with the set of substituted salicylic acids reported here demonstrates further the molecular recognition shown by that compound for the meta-substituted benzoic acids. Furthermore, for brucine compounds (but not those of strychnine) the space group (most commonly P212121 or P21) and unit cell parameters (an approximately 12.5-Å unit cell repeat along a 21 screw axis, such as in 1 and 3) give a good indication of the presence of the common undulating 21 screw axis-generated sheet substructure, although the absence of the screw axis does not necessarily preclude this structuring. When considering the set of acids used in this study, strychnine also gives stable proton-transfer compounds but these lack the structuring found in 1 and 3, confirming the observation that brucine generally shows a much greater ability to form crystalline compounds, both proton transfer and non-transfer, with organic species. This is indicated by the 81% (brucine) to 19% (strychnine) ratio among their crystallographically characterized compounds.

Preparation

The title compounds 1–3 were synthesized by heating 1 mmol quantities of brucine tetrahydrate and respectively 5-nitrosalicylic acid, 3,5-dinitrosalicylic acid, and 5-sulfosalicylic acid in 50 mL of 50% ethanol/water under reflux for 10 min. After concentration to about 30 mL, partial room temperature evaporation of the hot-filtered solutions gave large yellow prisms of 1 (mp 270.1–273.6°C (dec), one week), yellow crystal blocks of 2 (mp 265.4–266.5°C, two weeks), and colourless prisms of 3 (mp 220.6–228.3°C (dec), about three weeks). All crystals were stable in air and in the X-ray beam during room-temperature intensity data collection.

Crystallography

Crystal Data

1 (C23H27N2O4)+(C7H4NO5)–, M 577.58, orthorhombic, space group P212121, a 12.446(4), b 18.548(3), c 11.753(2) Å, V 2713(1) Å 3, F(000) 1216, Z 4, Dc 1.414 g cm–3, μ(MoKα) 1.06 cm–1, temperature 298(2) K. 4387 reflections measured (2θmax 55°: –7 ≤ h ≤ 16; 0 ≤ k ≤ 24; –7 ≤ l ≤ 15), 3722 unique (Rint 0.035). Final R1* 0.048 (F); wR2 0.164 (F2) (1874 observed with I > 2σ(I)); S 0.881; Δρmax/min 0.232/–0.232; Δ/ρ 0.02. Crystal size 0.35 × 0.30 × 0.20 mm. CCDC no. 263758.

2 (C23H27N2O4)+(C7H3N2O7)–·H2O, M 640.60, monoclinic, space group C2, a 14.232(3), b 12.249(3), c 16.681(5) Å, V 2830.7(13) Å3, F(000) 1344, Z 4, Dc 1.503 g cm–3, μ(MoKα) 1.18 cm–1, temperature 298(2) K. 3847 reflections measured (2θmax 55°: –8 ≤ h ≤ 18; 0 ≤ k ≤ 15; –21 ≤ l ≤ 21), 3397 unique (Rint 0.057). Final R1 0.060 (F); wR2 0.190 (F2) (1704 observed with I > 2σ(I)); S 0.993; Δρmax/min 0.294/–0.267; Δ/ρ 0.007. Crystal size 0.30 × 0.25 × 0.15 mm. CCDC no. 263757.

3 (C23H27N2O4)+(C7H5O6S)–·3H2O, M 666.68, orthorhombic, space group P212121, a 12.5662(19), b 29.989(4), c 8.1122(10) Å, V 3057.0(7) Å 3, F(000) 1408, Z 4, Dc 1.449 g cm–3, μ(MoKα) 1.78 cm–1, temperature 298(2) K. 3705 reflections measured (2θmax 50°: –6 ≤ h ≤ 14; 0 ≤ k ≤ 35; –4 ≤ l ≤ 9), 3071 unique (Rint 0.014). Final R1 0.044 (F); wR2 0.146 (F2) (2162 observed with I > 2σ(I)); S 0.932; Δρmax/min 0.253/–0.365; Δ/ρ 0.03. Crystal size 0.40 × 0.30 × 0.15 mm. CCDC no. 263759.

Data Collection, Structure Solution, and Refinement

X-ray diffraction data for compounds 1–3 were collected at room temperature on an Rigaku AFC 7R four-circle diffractometer using crystal-monochromatized MoKα X-radiation (λ 0.71073 Å) from a 12-kW rotating anode source. Datasets were processed using TeXsan,[55] no corrections were made for absorption and an extinction correction was made only with the data for 3. The maximum crystal decay observed (2.5%) occurred with 1 and this was allowed for using a linear correction. The structures were solved by direct methods using SIR92[56] and refined with anisotropic displacement parameters for all non-hydrogen atoms, using SHELXL 97[57] operating within the TeXsan system.[55] Hydrogen atoms attached to carbon atoms of the brucine and the benzene ring systems were included in the refinements at calculated positions as riding models while those potentially involved in hydrogen-bonding interactions (H19 of the brucinium cations, the carboxylic acid proton in 3, and water protons in 2 and 3) were located by difference-Fourier methods and included with their positional and isotropic displacement parameters fixed. The absolute configuration from the parent protonated brucine molecule[15] was invoked, giving the Cahn–Prelog–Ingold designations[16,58] for the seven chiral centres of the molecule (the lone pair S configuration is maintained at N19 upon protonation) as C7(S), C8(S), C12(S), C13(R), C14(R), C16(S), N19(S), confirmed in the case of 3 by the method of Flack[59] (Flack parameter 0.0(2) for 152 Friedel pairs). It has previously been noted[47,48] that protonation of N19 gives a hierarchal preference for this centre (compare N9) using the R,S convention, resulting in an apparent

configurational change at C7 (R to S; compare the neutral brucine (or strychnine) molecule).

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References

[1] E. Fischer, Ber. 1899, 32, 2451.

[2] S. H. Wilen, in Tables of Resolving Agents and Optical Resolutions (Ed. E. L. Eliel) 1972 (University of Notre Dame Press: Notre Dame, IN).

[3] The Merck Index, 13th edn (Ed. M. J. O'Neil) 2001, pp. 243, 1577 (Merck and Co.: Whitehouse Station, NJ).

[4] R. O. Gould, M. D. Walkinshaw, J. Am. Chem. Soc. 1984, 106, 7840.

[5] R. O. Gould, R. Kelly, M. D. Walkinshaw, J. Chem. Soc., Perkin Trans. 2 1985, 847.

[6] S. S. B. Glover, R. O. Gould, M. D. Walkinshaw, Acta Crystallogr. C 1985, 41, 990.

[7] A. Białońska, Z. Ciunik, Acta Crystallogr. C 2004, 60, o853.

[8] T. Oshikawa, S. Pochamroen, N. Takai, N. Ide, T. Takemoto, M. Yamashita, Heterocyclic Commun. 2002, 8, 271.

[9] J. H. Robertson, C. A. Beevers, Acta Crystallogr. 1951, 4, 270.

[10] (a) L. H. Briggs, H. T. Openshaw, R. Robinson, J. Am. Chem. Soc. 1946, 68, 903.

(b) R. B. Woodward, W. J. Brehm, A. L. Nelson, J. Am. Chem. Soc. 1947, 69, 2250.

[11] H. L. Holmes, in The Alkaloids, vol. II (Eds R. H. F. Manske, H. L. Holmes) 1952, p. 514 (Academic: New York, NY).

[12] (a) Strychninium sulfate: C. Bokhoven, J. C. Schoone, J. M. Bijvoet, Acta Crystallogr. 1951, 4, 275.

(b) Strychninium nitrate: A. Mostad, Acta Chem. Scand. Sect. B 1985, 39, 705.

(c) Strychninium chloride: R. Ghosh, P. Roychowdhury, D. Chattopadhyay, Y. Iitaka, Acta Crystallogr. C 1989, 45, 1794.

(d) Strychninium iodide: H. S. H. Yuan, R. C. Stevens, R. Bau, H. S. Mosher, T. F. Koetzle, Proc. Nat. Acad. Sci. USA 1994, 91, 12872.

(e) Strychninium perchlorate, hydrogensulfate, and dihydrogen-phosphate: A. Białońska, Z. Ciunik, Acta Crystallogr. C 2005, 61, o161.

(f) Strychninium hexasulfide P. Bottcher, H. Buchkremer-Hermans, Z. Naturforsch. B Chem. 1987, 42, 431.

(g) Brucinium sulfate heptahydrate: A. Białońska, Z. Ciunik, Acta Crystallogr. E 2005, 61, o4222.

[13] A. Mosher, Acta Chem. Scand. B 1985, 39, 705.

[14] (a) Strychnine sulfonic acid: D. S. Sake Gowda, L. Cartz, S. Natarajan, Acta Crystallogr. B 1973, 29, 2760.

(b) 20,21-Dihydrostrychnine: A. Mostad, Acta Chem. Scand. B 1986, 306, 64.

(c) Pseudostrychnine: A. Mostad, Acta Chem. Scand. A 1988, 42, 391.

(d) Neostrychnine: R. L. Beddoes, A. A. Gorman, A. L. Prescott, Acta Crystallogr. C 1994, 50, 447.

(e) Strychnidinium hydrogen succinate: J. K. Maurin, T. Lis, A. Zawadzka, Z. Czarnocki, Acta Crystallogr. E 2006, 62, o694.

[15] A. F. Peerdeman, Acta Crystallogr. 1956, 9, 824.

[16] E. L. Eliel, Stereochemistry of Carbon Compounds 1962, pp. 92–94 (McGraw-Hill: New York, NY). These configurational analyses may be conveniently completed using PLATON,[60] on crystallographic structural data such as the deposited CIF material for 1–3, as well as for other compounds referred to in this paper, available from the CCDC (www.ccdc.cam.ac.uk/products/csd/request/).

[17] A. Białońska, Z. Ciunik, CrystEngComm 2004, 6, 276.

[18] R. O. Gould, P. Taylor, M. D. Walkinshaw, Acta Crystallogr. A 1984, 40, C-65.

[19] S. Kuwata, J. Tanaka, N. Onda, T. Yamada, T. Miyazawa, M. Sugiura, Y. In, M. Doi, M. Inoue, T. Ishida, Bull. Chem. Soc. Japan 1993, 66, 1501.

[20] F. J. J. Dijksma, R. O. Gould, S. Parsons, P. Taylor, M. D. Walkinshaw, Chem. Commun. 1998, 745.

[21] R. O. Gould, P. Taylor, M. D. Walkinshaw, H. J. Bruins Slot, Acta Crystallogr. C 1987, 43, 2405.

[22] R. O. Gould, M. D. Walkinshaw, N. Wimmer, P. Kosma, Acta Crystallogr. A 2002, 58, C-126.

[23] A. Białońska, Z. Ciunik, T. Popek, T. Lis, Acta Crystallogr. C 2005, 61, o88.

[24] (a) Brucinium hydrogen-L-malate pentahydrate and brucinium hydrogen L-tartrate: G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. C 2006, 42, o353.

(b) Brucinium hydrogen isophthalate trihydrate: G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. E 2006, 42, o1533.

[25] G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. C 2005, 61, o621.

[26] G. Quinkert, H.-G. Schmalz, E. M. Dzierzynski, G. Dürner, J. W. Batz, Angew. Chem. Int. Ed. Engl. 1986, 25, 992.

[27] S. E. Boiadjiev, R. V. Person, G. Puzicha, C. Knobler, E. Maverick, K. N. Trueblood, D. A. Lightner, J. Am. Chem. Soc. 1992, 114, 10123.

[28] J. L. Wright, B. W. Caprathe, D. M. Downing, S. A. Glase, T. G. Heffner, J. C. Jaen, S. J. Johnson, S. R. Kesten, R. G. MacKenzie, L. T. Meltzer, T. A. Pugsley, S. J. Smith, L. D. Wise, D. J. Wustrow, J. Med. Chem. 1994, 37, 3523.

[29] K. Krajewski, Z. Ciunik, Pol. J. Chem. 1999, 73, 1687.

[30] M. Andersson, S. Sundell, S. Allenmark, Enantiomer 1999, 4, 411.

[31] S. Allenmark, U. Skogsberg, Enantiomer 2000, 5, 451.

[32] J. B. Laursen, C. G. Jørgensen, J. Nielsen, Bioorg. Med. Chem. 2003, 11, 723.

[33] C. E. Berkman, E. J. Fernandez, C. M. Thompson, S. F. Pavkovic, Acta Crystallogr. C 1993, 49, 554.

[34] J. Costente, N. Ehlinger, M. Perrin, A. Collet, Enantiomer 1996, 1, 377.

[35] F. Toda, K. Tanaka, H. Ueda, Tetrahedron Lett. 1981, 22, 4669.

[36] F. Toda, K. Tanaka, H. Ueda, T. Oshima, Isr. J. Chem. 1985, 25, 338.

[37] K. Tanaka, M. Kato, F. Toda, Heterocycles 2001, 54, 405.

[38] K. Chandramohan, K. Ravikumar, J. Chem. Crystallogr. 1999, 29, 121.

[39] M. Yamagishi, Y. Yamada, K. Ozaki, T. Da-te, K. Okamura, M. Suzuki, K. Matsumoto, J. Org. Chem. 1992, 57, 1568.

[40] A. A. Pinkerton, P.-A. Carrupt, F. Claret, P. Vogel, Acta Crystallogr. C 1993, 49, 1632.

[41] K. Sada, K. Yoshikawa, M. Miyata, Chem. Commun. 1998, 1763.

[42] G. Smith, U. D. Wermuth, P. C. Healy, D. J. Young, J. Chem. Crystallogr. 2006, in press.

[43] W.-S. Guo, F. Guo, M. Deng, C.-H. Ge, Q.-T. Liu, X.-Q. Hua, J.-L. Bai, Z.-Y. Tian, S.-C. Wang, Q.-T. Zheng, Huaxue Xuebao 2001, 59, 284.

[44] F. J. J. Dijksma, R. O. Gould, S. Parsons, M. D. Walkinshaw, Acta Crystallogr. C 1998, 54, 1948.

[45] J. Bao, W. D. Wulff, J. B. Dominy, M. J. Fumo, E. B. Grant, A. C. Rob, M. C. Whitcomb, S.-M. Yeung, R. L. Ostrander, A. L. Rheingold, J. Am. Chem. Soc. 1996, 118, 3392.

[46] E. Cheung, M. R. Netherton, J. R. Scheffer, J. Trotter, Tetrahedron Lett. 1999, 40, 8733.

[47] G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. C 2005, 61, o464.

[48] G. Smith, U. D. Wermuth, D. J. Young, P. C. Healy, Acta Crystallogr. E 2005, 61, o2008.

[49] G. Smith, U. D. Wermuth, P. C. Healy, D. J. Young, J. M. White, Acta Crystallogr. E 2005, 61, o2646.

[50] G. Smith, A. W. Hartono, U. D. Wermuth, P. C. Healy, J. M. White, A. D. Rae, Aust. J. Chem. 2005, 58, 47.

[51] (a) G. Smith, U. D. Wermuth, R. C. Bott, J. M. White, Aust. J. Chem. 2002, 55, 349.

(b) G. Smith, U. D. Wermuth, P. C. Healy, J. M. White, Aust. J. Chem. 2003, 56, 707.

(c) Smith G., Wermuth U. D., Healy P. C., White J. M., unpublished data.

[52] (a) G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. C 2004, 60, o575.

(b) G. Smith, U. D. Wermuth, J. M. White, Acta Crystallogr. C 2005, 61, o105.

(c) G. Smith, U. D. Wermuth, P. C. Healy, Acta Crystallogr. C 2005, 61, o555.

[53] J. Jacques, A. Collet, S. H. Wilen, Enantiomers, Racemates, and Resolutions 1981, p. 8 (Wiley: New York, NY).

[54] Brucine–water (1/4) and brucine–water (1/5.25): G. Smith, U. D. Wermuth, P. C. Healy, J. M. White, Acta Crystallogr. C 2006, 62, o203.

[55] TeXsan for Windows, ver. 1.06 1999 (MSC: The Woodlands, TX).

[56] A. Altomare, G. Cascarno, C. Giocovasso, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, J. Appl. Cryst. 1994, 27, 435.

[57] G. M. Sheldrick, SHELXL 97 1997 (University of Göttingen: Göttingen).

[58] (a) R. S. Cahn, C. K. Ingold, J. Chem. Soc. 1951, 515.

(b) R. S. Cahn, C. K. Ingold, C. V. Prelog, Experientia 1956, 12, 81.

[59] H. D. Flack, Acta Crystallogr. A 1983, 39, 876.

[60] (a) A. L. Spek, J. Appl. Crystallogr. 2003, 36, 7.

(b) A. L. Spek, L. Farrugia, PLATON for Windows 2005 (Utrecht University: Utrecht).

* R1 = (Σ |Fo| – |Fc|)/Σ|Fo|). wR2 = Σ[w(Fo2 – Fc2)2]/Σ[w(Fo2)2]1/2. S = Σ[w(Fo2 – Fc2)2]/(n – p)1/2.

Figures

Fig. 1. Atom numbering scheme for the individual brucinium cation and 5-NSA anion in 1. Atoms are s...

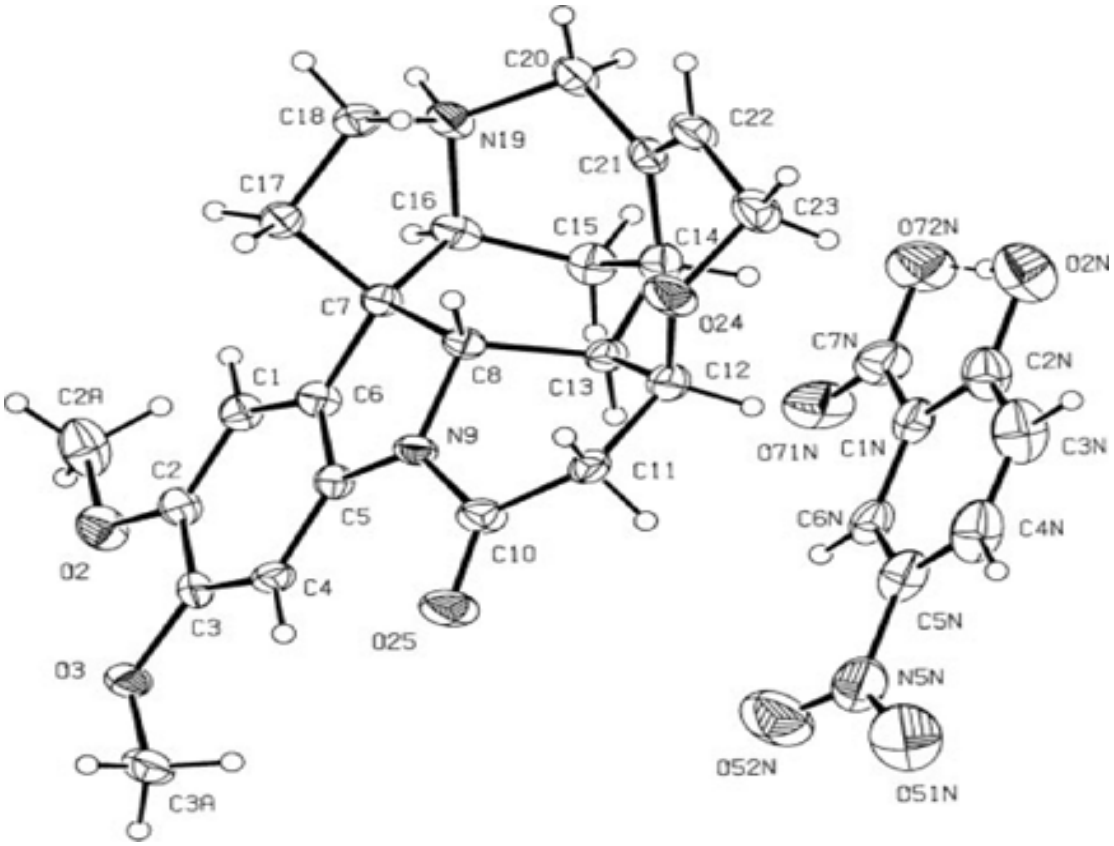


Fig. 2. The atom numbering schemes used for the separate (a) DNSA and (b) 5-SSA anion species in compounds...

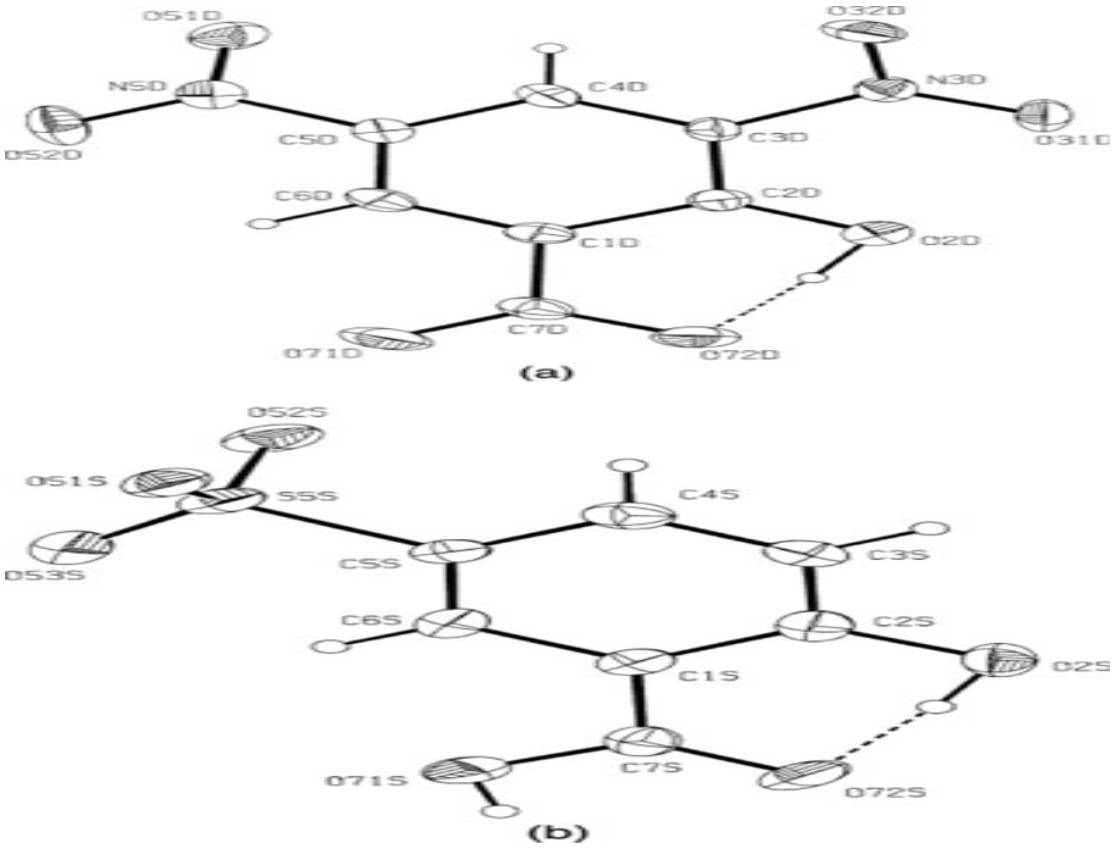


Fig. 3. Brucine ribbon host-substructures without guest molecules. Typical anti-parallel ribbon sub...

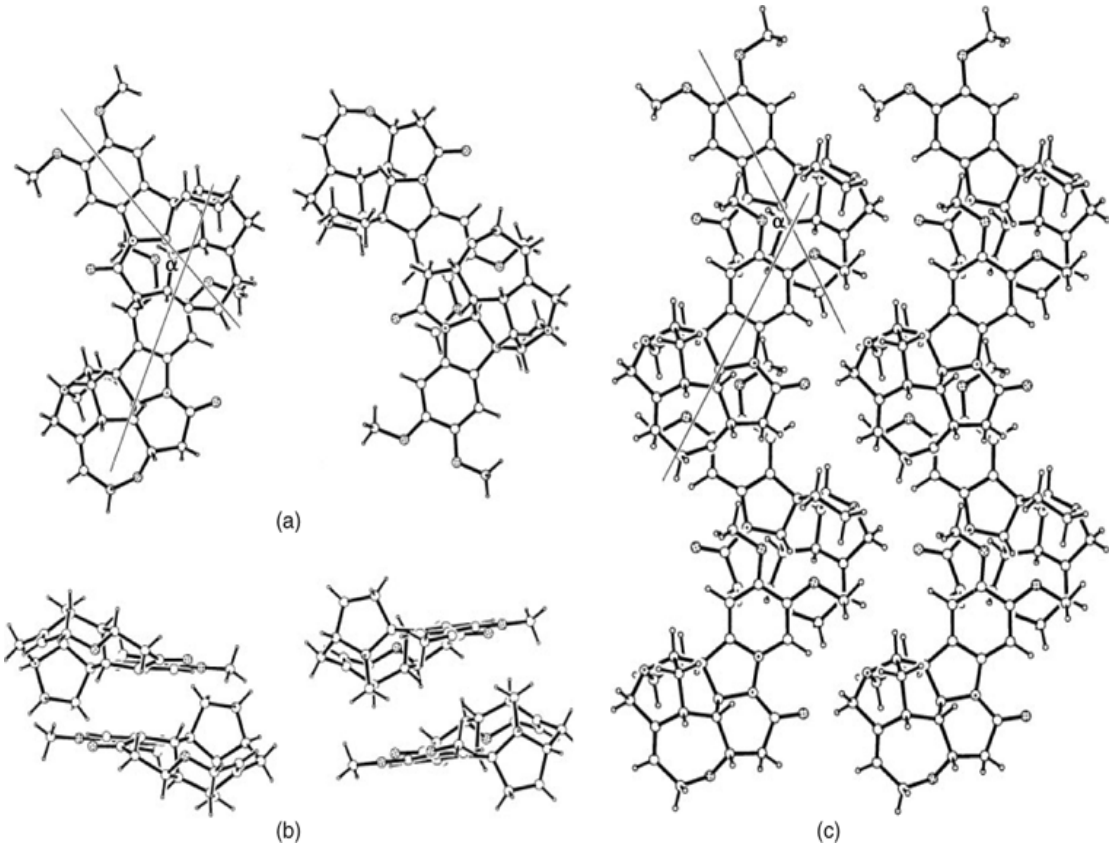


Fig. 4. (a) The anti-parallel chain mode in the structure of 1, less the guest 5-NSA anions,...

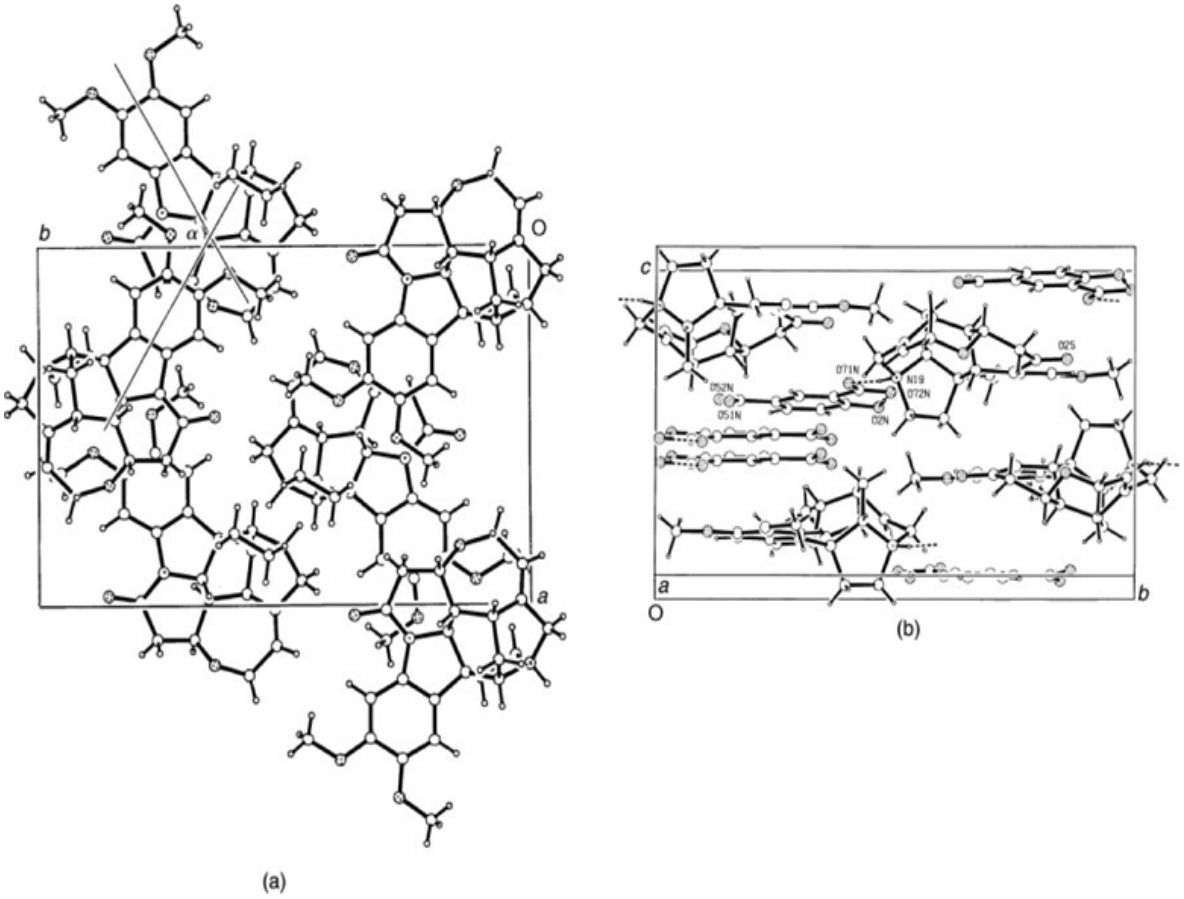


Fig. 5. The packing of 2 in the unit cell viewed down the b-axis showing the substructures g...

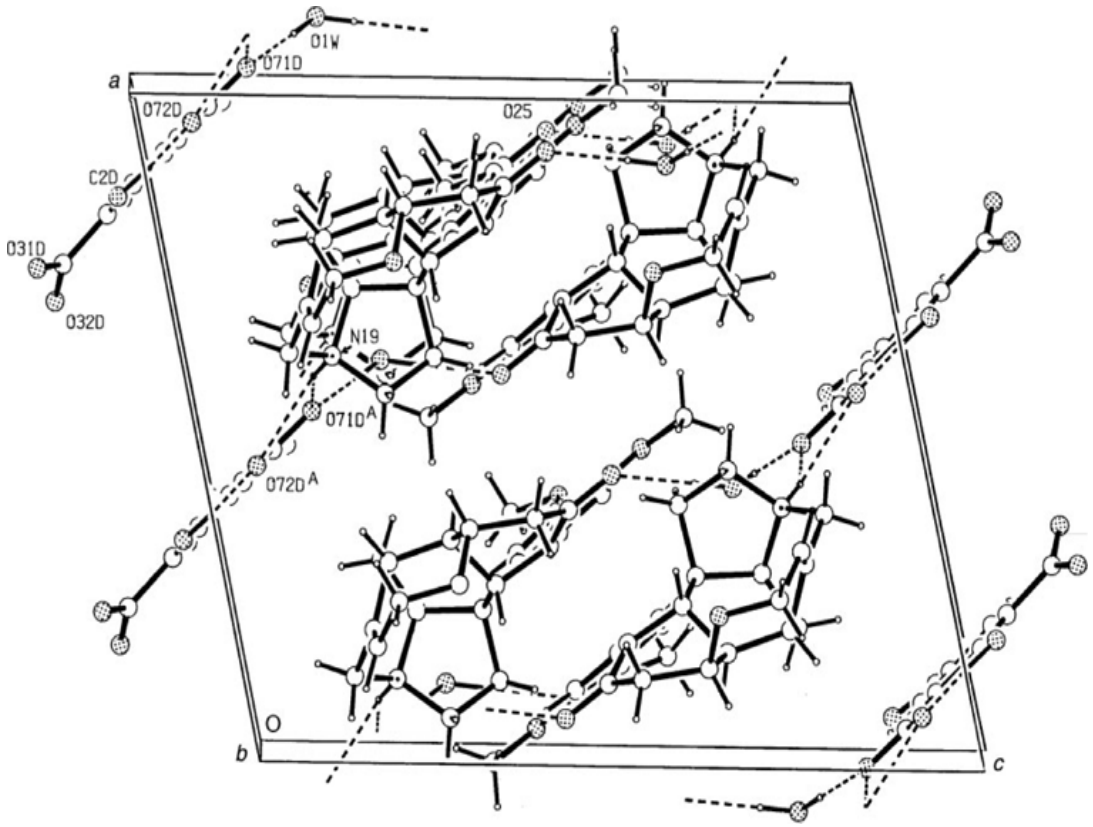
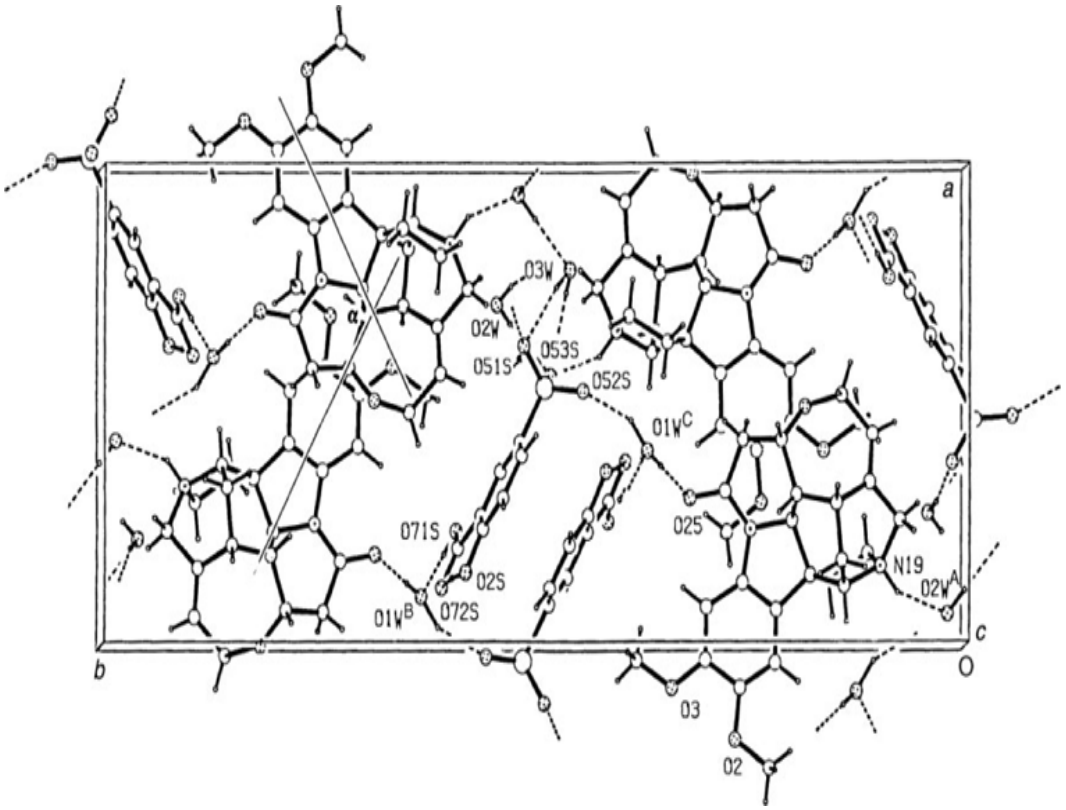
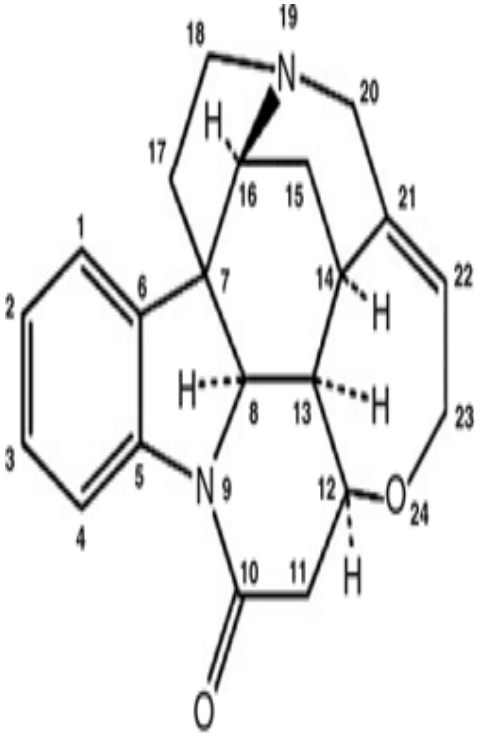


Fig. 6. Hydrogen bonding in 3 in the unit cell viewed down the c-axis, showing the anti-para...

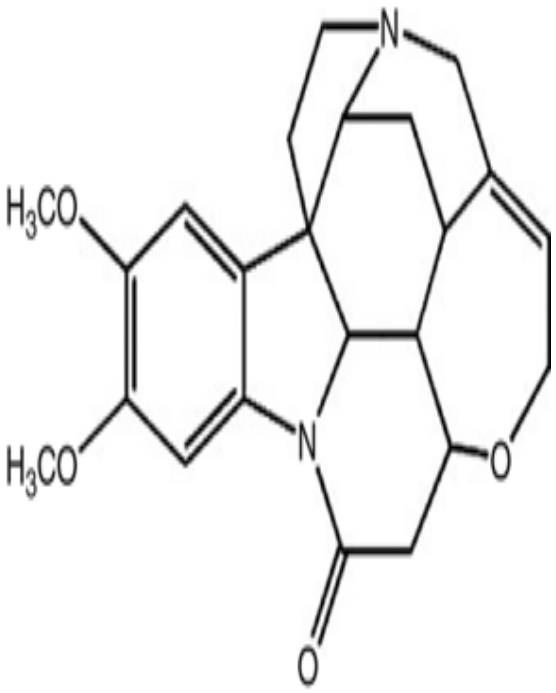


Schemes

Scheme 1.



Strychnine



Brucine

Tables

Table 1. Hydrogen-bonding associations [Å, °]

Table 1. Hydrogen-bonding associations [Å, °]

	D–H···A	D–H	H···A	D···A	D–H···A
Compound **1**	O2N–H2N···O72N	0.96	1.53	2.494(7)	177
	N19–H19···O71N^{A}	0.96	1.71	2.657(5)	173
Compound **2**	O2D–H2D···O72D	1.00	1.44	2.425(9)	170
	N19–H19···O71D^{B}	0.95	1.98	2.864(10)	153
	N19–H19···O72D^{B}	0.95	2.33	3.116(9)	140
	O1W–H1A···O71D	0.91	1.94	2.849(12)	179
	O1W–H1B···O25^{C}	0.91	1.96	2.866(9)	179
Compound **3**	O2S–H2S···O72S	0.96	1.63	2.570(6)	163
	N19–H19···O2W^{D}	0.93	2.07	2.896(7)	147
	O71S–H71S···O1W^{E}	0.82	1.79	2.587(6)	166
	O1W–H1A···O52S^{F}	0.99	1.89	2.792(5)	150
	O1W–H1B···O25^{F}	0.90	1.95	2.849(6)	179
	O2W–H2A···O3W^{G}	0.93	1.94	2.872(8)	173
	O2W–H2B···O53S	0.91	1.88	2.788(7)	178
	O3W–H3A···O51S^{G}	0.83	1.92	2.735(8)	166
	O3W–H3B···O51S	0.83	2.33	3.161(8)	172

$^{A}\frac{1}{2}-x, -y, \frac{1}{2}+z$. $^{B}-\frac{1}{2}+x, -\frac{1}{2}+y, z$. $^{C}2-x, y, 1-z$. $^{D}-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$. $^{E}-x, \frac{1}{2}+y, 1\frac{1}{2}-z$. $^{F}-\frac{1}{2}+x, \frac{1}{2}-y, 2-z$. $^{G}1\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$.