Table. 3. *Hydrogen-bond distances* (Å) *and angles* (°)

Donor	Acceptor	Bond length	Symmetry operation
OW1	O1	2·761 (3)	x, y, z
OW1	H1	2·01 (3)	x, y, z
OW1···H1—O1	179· (3)		
OW1	O3	2·761 (2)	$x-1, y, z+1$
HW1	O3	1·95 (3)	$x-1, y, z+1$
OW1—HW1···O3	161· (3)		
N1	O2	2·867 (1)	$x-1, y, z$
HN1	O2	1·99 (2)	$x-1, y, z$
N1—HN1···O2	174· (2)		
N2	O2	2·657 (1)	$x-1, y+1, z$
HN2′	O2	1·77 (2)	$x-1, y+1, z$
N2—HN2′···O2	172· (2)		
N2	O3	2·903 (1)	$x, y+1, z$
HN2	O3	2·15 (2)	$x, y+1, z$
N2—HN2···O3	147· (2)		

Table 4. *Selected torsion angles* (°)

C10—N1—C8—C7	168·2 (1)	
C10—N1—C8—C9	−67.9 (2)	φ_{Tyr}
C8—N1—C10—C11	174·4 (1)	$\omega_{Tyr\text{-}Pro}$
C4—C7—C8—C9	61.0 (2)	
C4—C7—C8—N1	−175·6 (1)	
N1—C8—C9—O2	146·5 (1)	ψ_{Tyr}
N1—C8—C9—O3	−35.0 (2)	ψ_{Tyr}
N1—C10—C11—N2	162·2 (1)	ψ_{Pro}
N1—C10—C11—C12	−82·0 (2)	

Geoffre, Hospital & Precigoux, 1979). The torsion angles in the L-Pro-L-Tyr fragment of the tetrapeptide are very similar to those obtained in the dipeptide. These are $\varphi_{Tyr} = 71·4°$, $\omega_{Tyr\text{-}Pro} = 170·3°$ and $\psi_{Tyr} = -47·9°$. Proline is in the *cis* conformation ($\psi \simeq 180°$) in the dipeptide with $\psi_{Pro} = 162·2\ (1)°$ as it is in the tetrapeptide with $\psi_{Pro} = 169°$. The pyrrolidine ring is puckered with C13 −0·611 (3) Å out of the plane defined by C11, N2, C14 and C13. The plane of the carboxylate group in the tyrosine is 45·2 (2)° to the plane of the aromatic ring. The peptide bond C10—N1 is 1·329 (1) Å in length. This is shorter than other N—C bonds due to the partial double-bond character of CO═NH found in the peptide.

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Structure of the 1:1 Complex Formed from 4-Nitropyridine *N*-Oxide and 2-Aminobenzoic Acid

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Abstract. $C_7H_7NO_2.C_5H_4N_2O_3$, $M_r = 277·2$, monoclinic, Cc, $a = 9·522\ (3)$, $b = 10·637\ (4)$, $c = 12·611\ (3)$ Å, $\beta = 104·31\ (2)°$, $V = 1237·7\ (4)$ Å^3, $Z = 4$, $D_m = 1·49\ (1)$, $D_x = 1·488$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $F(000) = 576$, $\mu = 0·111$ mm^{-1}, $T = 295$ K, $R = 0·0401$, $wR = 0·0392$, 834 observed reflections. The complex is formed by alternate stacking of 4-nitropyridine *N*-oxide and 2-aminobenzoic acid molecules. The resulting stacks follow the [$\bar{1}$10] and [110] directions and exhibit overlap between aromatic rings with interplanar distances equal to 3·32 (3) and 3·46 (3) Å. Besides an intramolecular hydrogen bond with an N···O distance of 2·675 (7) Å between amino and carbonyl groups, intermolecular hydrogen bonds with an O···O distance of 2·629 (5) Å and an N···O distance of 2·999 (6) Å are observed between the carboxyl and *N*-oxide groups, and the amino and *N*-oxide groups, respectively, from molecules in neighboring stacks.

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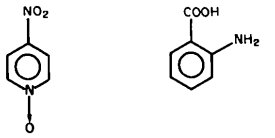
Introduction. 4-Nitropyridine *N*-oxide (NPNO) has been noted as potentially useful for non-linear optical applications (Nicoud & Twieg, 1987), owing to the high value of its molecular first-order hyperpolarizability (Zyss & Oudar, 1982). One of its derivatives, 3-methyl-4-nitropyridine *N*-oxide (POM), is one of the best electro-optic materials in the visible range (Sapriel, Hierle, Zyss & Boissier, 1989).

NPNO forms hydrogen-bond complexes with organic acids (Bueno, Blaz & Santos, 1984). The crystal structures of two such complexes, namely the 2:1 complex formed by NPNO and hydroquinone (Shiro & Kubota, 1972) and the 1:1 complex formed by NPNO and 3-aminophenol (AP) (Lechat, Almeida Santos & Bueno, 1981) have been reported.

This crystal structure determination is part of an ongoing study on designing non-centrosymmetric crystals based on NPNO.



NPNO ABA

Experimental. As in the case of the 1:1 complex formed by NPNO and AP, the formation of the complex between NPNO and 2-aminobenzoic acid (ABA) may be followed by the color change, from yellow to red, which develops by mixing finely ground powders of the starting materials. The phase diagram for the NPNO–ABA binary system shows that the only compound formed has 1:1 composition and a melting point of 410·1 K. The eutectic mixtures rich in NPNO (NPNO mole fraction = 0·72) and rich in ABA (NPNO mole fraction = 0·23), have melting points respectively equal to 399 and 396 K. The crystal used in this structure determination had a rhombic prism habit and was grown by slow evaporation from an equimolecular solution of the starting compounds in acetonitrile, melting point 410·1 K. Density measured pycnometrically. Single crystal 0·14 × 0·10 × 0·20 mm used for data collection. Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation; unit-cell parameters calculated by least-squares refinements on setting angles of 25 reflections with $8 < \theta < 14°$; ω–2θ scan mode, scan width $(0{\cdot}80 + 0{\cdot}35 \tan\theta)°$, scan speed 6·7° min^{-1}; 2374 reflections measured, $\theta_{max} = 25°$, $-11 \le h \le 10$, $0 \le k \le 12$, $0 \le l \le 14$. Three standard reflections ($\bar{4}0\bar{2}$, $\bar{3}1\bar{3}$, $\bar{2}2\bar{4}$), no decay or decomposition found; 1080 unique reflections, 834 of which considered observed [$I > 3\sigma(I)$, where $\sigma(I)$ is based on counting statistics], $R_{int} = 0{\cdot}0349$. Diffracted intensities corrected for Lorentz and polarization but not for absorption. Structure solved by direct methods (*MULTAN*80, Main, Hull, Fiske, Lessinger, Germain, Declercq & Woolfson, 1980). All non H-atoms readily located ($R = 0{\cdot}17$). Structure refined by full-matrix least squares minimizing $\sum w(|F_o| - |F_c|)^2$ where weighting $w^{-1} = \sigma(F_o)^2 + 0{\cdot}0001|F_o|^2$ for observed and $w = 0$ for unobserved reflections. Calculations carried out with anisotropic C, N, O and isotropic H (temperature factor = 6 Å^2) with *SHELX*76 (Sheldrick, 1976). H-ring atoms were introduced at calculated positions, H(O1), H(N11) and H(N12) located by difference Fourier synthesis and their positions were refined. Space group *Cc* determined by systematic absences and by structure solution and refinements. Refinement carried out in blocks with parameters of NPNO and ABA in alternate cycles. Refinements converged to $R = 0{\cdot}0401$ and $wR = 0{\cdot}0392$ and goodness-of-fit $S = 1{\cdot}69$ for 100 refined parameters. The max. and min. heights in the final difference Fourier synthesis were $+0{\cdot}192$ and $-0{\cdot}184$ e Å^{-3}, respectively, $(\Delta/\sigma)_{max} = 0{\cdot}01$ in last cycle, atomic scattering factors for neutral atoms (Cromer & Mann, 1968), with corrections for anomalous dispersion (Cromer & Liberman, 1970).

Discussion. The structural basic unit consists of a pair of hydrogen-bonded NPNO and ABA molecules, depicted in Fig. 1. The corresponding atomic fractional coordinates and equivalent isotropic temperature factors (Hamilton, 1959) are given in Table 1.* Bond distances, bond angles and hydrogen parameters are given in Table 2.

The ABA molecule exhibits an intramolecular hydrogen bond between one amino H atom and the carbonyl group of the carboxyl group.

The complex formed by NPNO and ABA is better described by the alternate stacking of those molecules which gives rise to stacks parallel to 110 and $\bar{1}10$ directions. The interplanar distances between the

* List of structure factors, anisotropic thermal parameters, H-atom coordinates and C—H bond lengths have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54258 (10 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

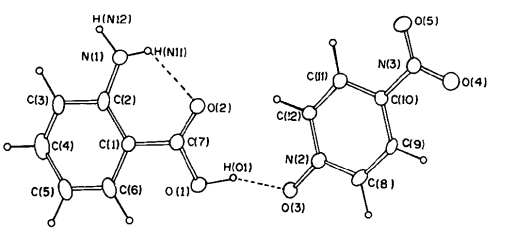


Fig. 1. Representation of a pair of hydrogen-bonded NPNO and ABA molecules, giving atomic numbering.

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors with e.s.d.'s in parentheses*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq} (Å^2)
O(1)	0·7650 (4)	0·2602 (3)	0·4853 (3)	4·3 (1)
O(2)	0·7221 (4)	0·2250 (3)	0·3065 (3)	4·4 (1)
O(3)	0·4963 (3)	0·2042 (3)	0·4861 (3)	4·3 (1)
O(4)	−0·0518 (4)	−0·0610 (4)	0·2189 (3)	5·4 (1)
O(5)	0·0564 (4)	−0·0267 (4)	0·0918 (3)	5·6 (1)
N(1)	0·9294 (5)	0·2863 (5)	0·2062 (4)	4·8 (2)
N(2)	0·3917 (4)	0·1503 (3)	0·4136 (3)	3·1 (1)
N(3)	0·0493 (4)	−0·0204 (3)	0·1861 (3)	3·6 (1)
C(1)	0·9502 (5)	0·3130 (4)	0·4006 (4)	3·0 (1)
C(2)	1·0030 (5)	0·3256 (4)	0·3063 (4)	3·6 (2)
C(3)	1·1388 (5)	0·3846 (5)	0·3177 (5)	4·7 (2)
C(4)	1·2165 (6)	0·4248 (5)	0·4169 (6)	5·4 (2)
C(5)	1·1679 (6)	0·4107 (5)	0·5113 (5)	5·1 (2)
C(6)	1·0336 (5)	0·3530 (5)	0·5016 (4)	4·2 (2)
C(7)	0·8038 (6)	0·2612 (4)	0·3911 (4)	3·2 (1)
C(8)	0·2771 (5)	0·1007 (4)	0·4466 (4)	3·4 (1)
C(9)	0·1645 (5)	0·0452 (4)	0·3732 (4)	3·0 (1)
C(10)	0·1684 (5)	0·0405 (4)	0·2649 (4)	2·9 (1)
C(11)	0·2829 (5)	0·0919 (4)	0·2315 (4)	3·4 (1)
C(12)	0·3940 (5)	0·1455 (4)	0·3072 (4)	3·4 (1)
H(O1)	0·659 (6)	0·240 (5)	0·465 (4)	6·00
H(N11)	0·840 (6)	0·243 (5)	0·187 (5)	6·00
H(N12)	0·976 (6)	0·293 (5)	0·147 (5)	6·00

Table 2. *Bond lengths* (Å), *bond angles* (°) *and hydrogen-bond parameters* (Å,°) *with e.s.d.'s in parentheses*

C(1)—C(2)	1·407 (8)	O(3)—N(2)	1·306 (5)
C(2)—C(3)	1·412 (7)	C(8)—N(2)	1·366 (4)
C(3)—C(4)	1·356 (8)	C(8)—C(9)	1·365 (4)
C(4)—C(5)	1·39 (2)	C(9)—C(10)	1·376 (7)
C(5)—C(6)	1·396 (8)	C(10)—C(11)	1·376 (8)
C(1)—C(6)	1·391 (6)	C(11)—C(12)	1·362 (6)
C(2)—N(1)	1·350 (6)	C(12)—N(2)	1·348 (6)
C(1)—C(7)	1·477 (8)	C(10)—N(3)	1·462 (5)
C(7)—O(2)	1·217 (5)	O(4)—N(3)	1·218 (6)
C(7)—O(1)	1·328 (7)	O(5)—N(3)	1·210 (6)

O(3)—N(2)—C(8)	119·0 (3)	C(3)—C(4)—C(5)	122·5 (5)
O(3)—N(2)—C(12)	121·1 (5)	C(4)—C(5)—C(6)	117·7 (5)
C(8)—N(2)—C(12)	119·9 (3)	C(1)—C(6)—C(5)	121·2 (5)
O(4)—N(3)—O(5)	123·8 (4)	O(1)—C(7)—O(2)	121·6 (5)
O(4)—N(3)—C(10)	118·2 (4)	O(1)—C(7)—C(1)	113·3 (4)
O(5)—N(3)—C(10)	118·1 (4)	O(2)—C(7)—C(1)	125·1 (6)
C(2)—C(1)—C(6)	120·2 (5)	N(2)—C(8)—C(9)	120·9 (3)
C(2)—C(1)—C(7)	119·6 (5)	C(8)—C(9)—C(10)	118·6 (4)
C(6)—C(1)—C(7)	120·2 (5)	N(3)—C(10)—C(9)	119·0 (4)
N(1)—C(2)—C(1)	123·3 (5)	N(3)—C(10)—C(11)	120·6 (4)
N(1)—C(2)—C(3)	118·9 (5)	C(9)—C(10)—C(11)	120·5 (4)
C(1)—C(2)—C(3)	117·8 (4)	C(10)—C(11)—C(12)	119·3 (4)
C(2)—C(3)—C(4)	120·7 (6)	N(2)—C(12)—C(11)	120·8 (5)

X—H···Y	X—H	H···Y	X···Y	X—H···Y
O(1)—H(O1)···O(3)	1·00 (5)	1·68 (6)	2·629 (5)	156 (5)
N(1)—H(N11)···O(2)	0·95 (6)	2·10 (6)	2·675 (7)	118 (4)
N(1)—H(N12)···O(3^i)	0·96 (6)	2·09 (6)	2·999 (6)	158 (4)

Symmetry code: (i) $\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$.

aromatic rings of NPNO and ABA are 3·32 (3) and 3·46 (3) Å. The principal features of the packing are represented in Fig. 2.

The stacks are interconnected by an intermediate strength hydrogen bond between the H atom of the carboxyl group of ABA and the *N*-oxide O atom of NPNO and by a weak hydrogen bond between the second amino H atom of ABA and the *N*-oxide O atom of NPNO. A representation of the hydrogen-bonding scheme is given in Fig. 3.

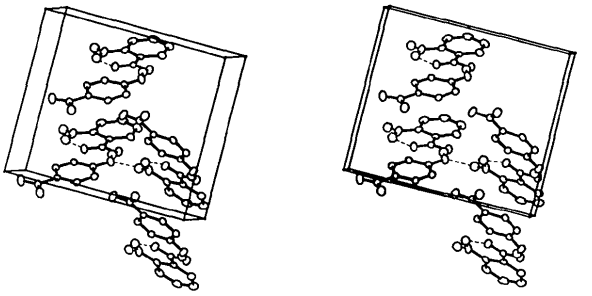


Fig. 2. Representation of the cell contents giving the intra- and intermolecular hydrogen-bonding scheme and showing also the alternate stacking of NPNO and ABA molecules (projection down **a**, **b** vertical and **c** horizontal).

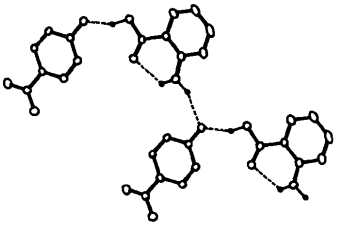


Fig. 3. Representation of the hydrogen-bonding scheme.

Contrary to what is observed in nitroanilines and their analogues (Panunto, Urbanczyk-Lipkowska, Johnson & Etter, 1987), the NPNO nitro group does not act as a hydrogen-bond acceptor in this structure.

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Structure of the Antimalarial (±)-Mefloquine Hydrochloride

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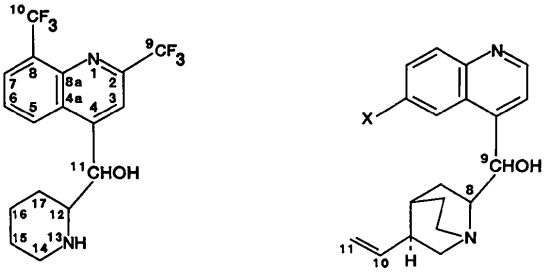
Abstract. (11*R**,12*S**)-(±)-α-2-Piperidinyl-2,8-bis-(trifluoromethyl)-4-quinolinemethanol monohydrochloride, $C_{17}H_{17}F_6N_2O^+.Cl^-.0{\cdot}5CH_3OH$, M_r = 430·8, tetragonal, $P4_2/n$ (origin at center of symmetry), $a = b = 24{\cdot}595$ (4), $c = 6{\cdot}398$ (2) Å, V = 3870·0 Å^3, $Z = 8$, $D_x = 1{\cdot}48$ g cm^{-3}, Cu $K\alpha$, λ = 1·54178 Å, $\mu = 24{\cdot}28$ cm^{-1}, $F(000) = 1768$, room temperature, final $R = 7{\cdot}5\%$ for 2067 reflections with $|F_o| > 3\sigma(F)$. Mefloquine hydrochloride crystallized as a secondary amine salt with channels of disordered methanol solvent. The trifluoromethyl group on the C adjacent to the quinoline N atom exhibited rotational disorder. Each chloride ion accepts three hydrogen bonds, one each from the hydroxyl group and the two H atoms of the amine group of mefloquine from three separate molecules. The angle between the average plane of the quinoline ring and the average plane of the piperidine ring is 110·5°.

Introduction. (±)-Mefloquine hydrochloride was developed by the Walter Reed Army Institute of Research and Roche Laboratories (Nutley, NJ) as an alternative treatment for multi-drug-resistant malaria. (±)-Mefloquine hydrochloride was approved for treating malaria in 1989 by the Food and Drug Administration and is marketed under the trade name Lariam. Not only is malaria a disease of worldwide epidemic proportions with estimated yearly cases in the 100 millions and an estimated yearly death rate in the millions, chloroquine-resistant malaria, first confirmed in South America and Southeast Asia in the 1960's, now resides in malaria endemic areas around the globe (Wyler, 1983; Payne, 1987).

Mefloquine is a quinoline-containing amino alcohol antimalarial whose structure is derived from the cinchona alkaloids (Fig. 1). Mefloquine has a different substitution pattern on the quinoline ring than the cinchona alkaloids and a piperidine ring substituting for the bulkier bicyclo quinuclidine ring of the cinchona alkaloids. All four of the cinchona alkaloids pictured in Fig. 1 have demonstrated clinical antimalarial activity against human-infecting parasites (Earle *et al.*, 1948; Taggart *et al.*, 1948).

Both mefloquine enantiomers have been individually tested for antimalarial activity against *Plasmodium berghei* in mice and demonstrated comparable antimalarial activity to mefloquine racemate (Sweeney, 1981). As is common with natural products, the cinchona alkaloids occur only in the enantiomeric form listed in Fig. 1. Although quinine and cinchonidine (the 8*S*,9*R* alkaloids) are diastereomers of quinidine and cinchonine (the 8*R*,9*S* alkaloids), due to other asymmetric centers in



Mefloquine: 11*R*,12*S* (11*S*,12*R*)

Quinine: *X* = OMe, 8*S*,9*R*
Quinidine: *X* = OMe, 8*R*,9*S*
Cinchonine: *X* = H, 8*R*,9*S*
Cinchonidine: *X* = H, 8*S*,9*R*

Fig. 1. Chemical structures of mefloquine and the active cinchona alkaloids drawn as the free base. The numbering scheme used for mefloquine is illustrated. The structures were drawn using *SLIDEWRITEPlus* from Advanced Graphics Software, Inc. (Sunnyvale, CA).

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