STRUCTURE, CHEMISTRY, AND ANTIMALARIAL PROPERTIES OF MEFLOQUINE-AZIRIDINE†

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Abstract - Mefloquine, a synthetic antimalarial, can be converted into a bicyclic aziridine which has photochromic properties in the solid state. The structure of this aziridine was corroborated by a single crystal X-ray analysis. Reaction of mefloquine-aziridine with acetic anhydride afforded derivatives of mefloquine, with retention of configuration. None of the tested compounds showed antimalarial activity.

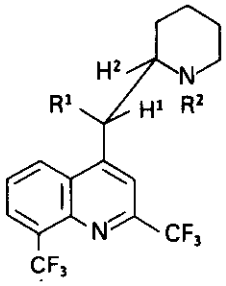
Derivatization of drugs affords compounds with altered physical properties and sometimes improved activity. This is exemplified in the case of antimalarials with N-acetylated pyrimethamines[2] and cycloguanil.[3] In further pursuing this line, it seemed interesting to explore whether dehydration of antimalarial 1,3-aminoalcohols[4] would afford aziridines, and to investigate whether this new species still shows antimalarial activity.

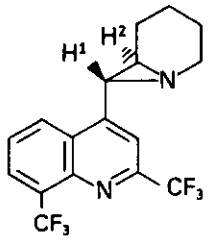
Mefloquine (WR 142,490), a new synthetic antimalarial,[5,6] and chemically the erythro isomer of (±)-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol-hydrochloride (1)·HCl,[7] seemed to be a logical candidate for such explorations.

When mefloquine base (1) was treated with triphenylphosphine, carbon tetrachloride and triethylamine in acetonitrile, following the procedure of Appel and Kleinstück for the preparation of monocyclic aziridines,[8] a new compound was obtained in high yield (for details see EXPERIMENTAL). A mass spectrum with a molecular ion of m/e = 360 and an unchanged UV, compared to (1), suggested the structure of the bicyclic aziridine (2), rather than the alternative structure of an olefinic

† Dedicated to Professor T. Kametani in honor of his stewardship as chairman of the Department of Chemistry at Tohoku University, Sendai, Japan.

compound, derived from dehydration without cyclization. Structure (2) was also consistent with the NMR, which showed no olefinic signals. A somewhat broadened singlet in the NMR at δ 3.19 could be assigned to the benzylic proton H^1 and the very small viciral coupling constant was in agreement with the structure of a trans-aziridine (2). For final confirmation of the structure it was decided to carry out an X-ray analysis, and the almost colorless prisms of (2) of mp 85.5-87°C, obtained by crystallization from petroleum ether, were used for this purpose.





(1) $R^1 = OH$, $R^2 = H$

(2)

(3) $R^1 = CH_3COO$, $R^2 = CH_3CO$

(4) $R^1 = OH$, $R^2 = CH_3CO$

Crystal Data: MW 360.3, habit: monoclinic prismatic, space group $P2_1/c$ (No. 14), cell dimensions (from LS refinement of $\pm\Theta$ data): a = 10.3385(8), b = 9.6629(8), c = 16.4989(17) Å, β = 95.693(8)°, V = 1640.1 $Å^3$; Dx = 1.459 g cm^{-3}; Dm = 1.45(1) g cm^{-3}; crystal size: sphere 0.2 mm diameter; maximum $\sin\Theta/\lambda$: 0.61 $Å^{-1}$; 2207 observed reflections (1010 unobserved 1 σ).

Determination of Structure: A fairly good sphere was obtained for data collection by stirring a crystal in hexane, and X-ray intensity data were collected using an Enraf-Nonius CAD-4 automatic diffractometer. The intensities of periodically measured standard reflections decreased by about 5% during data collection, probably indicating a small amount of radiation damage. The phase problem was solved fairly readily using MULTAN78[9] although the evidence for the fluorine atoms attached to C(10) was nebulous and C(12) was missing.

The model obtained was refined by the usual sequences of least squares and difference maps using the programs of XRAY72[10] (the program system used for all calculations unless otherwise indicated). There was no problem in finding the missing carbon atom but the fluorine atoms attached to C(10) gave rise to some difficulties. All ordered models produced physically unreasonable thermal parameters and it finally became apparent that a two-site model involving two sets of positions gauche with respect to either of N(1) or C(7) was most appropriate. Assuming equal site occupancy, it was possible to refine the model and find evidence for all hydrogen atoms. The final R-factor

was 5.7% using anisotropic thermal parameters for the heavier atoms and isotropic parameters for the hydrogen atoms. After the refinement had converged, both possible single site models were refined but R-factors were about 13% in either case.

Discussion of X-Ray Results: The final molecular dimensions are given in Table 1. Figure 1 is a PLUTO[11] picture showing the crystal conformation of the molecule and the numbering adopted in the discussion of the x-ray results. All bond lengths and angles, apart from those associated with the F(10) atoms are entirely reasonable. The actual numerical values of the dimensions involving the F(10) atoms are not improbable, given the large esd.s, but further discussion of their numerical values seems pointless. The torsion angles indicate that, in the terminology adopted by Bucourt[12] for cyclohexene, the ring fused to the aziridine ring has a monoplanar conformation. This ring and the quinoline moiety are relatively trans with respect to the aziridine. The anisotropic thermal parameters for the F(10) atoms are rather large and it is possible that a more sophisticated model of the disorder might be appropriate. However, the R-factor, if somewhat high, is entirely low enough to confirm the basic structure and, aside from the dimensions associated with the F(10) atoms, bond lengths and angles are of reasonable accuracy. The source of the disorder may lie in the fact that, unlike the F(9) atoms, there are no close intermolecular approaches to the F(10) atoms and, since either gauche position, with respect to C(7) or N(1), will produce close contacts with the other atom, both positions are adopted in a random fashion. Since the basic structural problem is essentially solved, it is not intended to investigate the disorder further.

Figure. X-Ray Structure of Mefloquine-Aziridine (2).

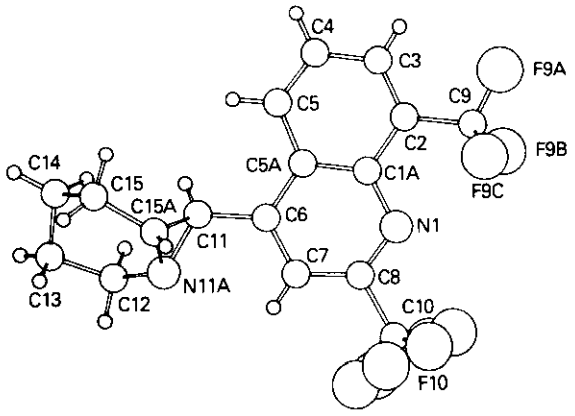


Table 1. Molecular Dimensions of Mefloquine-Aziridine (2), Bond Lengths (A), Esd.s in Parentheses.

N 01 - C 01A	1.359(3)	N 01 - C 08	1.316(3)	C 01A - C 02	1.431(3)
C 01A - C 05A	1.415(3)	C 02 - C 03	1.358(4)	C 02 - C 09	1.498(4)
C 03 - C 04	1.391(4)	C 04 - C 05	1.368(4)	C 05 - C 05A	1.410(3)
C 05A - C 06	1.427(3)	C 06 - C 07	1.370(3)	C 06 - C 11	1.486(3)
C 07 - C 08	1.391(3)	C 08 - C 10	1.516(4)	C 09 - F 09A	1.333(3)
C 09 - F 09B	1.330(4)	C 09 - F 09C	1.333(3)	C 10 - F 10A	1.314(15)
C 10 - F 10B	1.338(9)	C 10 - F 10C	1.232(10)	C 10 - F 10A1	1.227(11)
C 10 - F 10B1	1.274(16)	C 10 - F 10C1	1.325(13)	C 11 - N 11A	1.451(3)
C 11 - C 15A	1.450(4)	N 11A - C 12	1.488(4)	N 11A - C 15A	1.439(4)
C 12 - C 13	1.517(6)	C 13 - C 14	1.486(6)	C 14 - C 15	1.533(6)
C 15 - C 15A	1.530(6)				

Bond angles (degrees). Esd.s in parentheses.

C 01A - N 01 - C 08	115.8(2)	N 01 - C 01A - C 02	117.8(2)
N 01 - C 01A - C 05A	123.5(2)	C 02 - C 01A - C 05A	118.7(2)
C 01A - C 02 - C 03	119.9(2)	C 01A - C 02 - C 09	119.5(2)
C 03 - C 02 - C 09	120.6(2)	C 02 - C 03 - C 04	121.3(2)
C 03 - C 04 - C 05	120.4(3)	C 04 - C 05 - C 05A	120.5(2)
C 01A - C 05A - C 05	119.1(2)	C 01A - C 05A - C 06	117.7(2)
C 05 - C 05A - C 06	123.2(2)	C 05A - C 06 - C 07	118.0(2)
C 05A - C 06 - C 11	121.4(2)	C 07 - C 06 - C 11	120.6(2)
C 06 - C 07 - C 08	119.0(2)	N 01 - C 08 - C 07	126.0(2)
N 01 - C 08 - C 10	114.4(2)	C 07 - C 08 - C 10	119.6(2)
C 02 - C 09 - F 09A	111.9(3)	C 02 - C 09 - F 09B	113.3(2)
C 02 - C 09 - F 09C	112.8(2)	F 09A - C 09 - F 09B	105.9(2)
F 09A - C 09 - F 09C	105.5(2)	F 09B - C 09 - F 09C	106.9(3)
C 08 - C 10 - F 10A	111.8(6)	C 08 - C 10 - F 10B	110.0(5)
C 08 - C 10 - F 10C	115.5(4)	C 08 - C 10 - F 10A1	114.5(6)
C 08 - C 10 - F 10B1	114.1(6)	C 08 - C 10 - F 10C1	109.7(6)
F 10A - C 10 - F 10B	101.5(11)	F 10A - C 10 - F 10C	110.2(10)
F 10B - C 10 - F 10C	106.7(11)	F 10A1 - C 10 - F 10B1	110.0(10)
F 10A1 - C 10 - F 10C1	104.8(15)	F 10B1 - C 10 - F 10C1	102.7(12)
C 06 - C 11 - N 11A	117.4(2)	C 06 - C 11 - C 15A	122.6(2)
N 11A - C 11 - C 15A	59.5(2)	C 11 - N 11A - C 12	118.1(2)
C 11 - N 11A - C 15A	60.2(2)	C 12 - N 11A - C 15A	119.0(3)
N 11A - C 12 - C 13	114.3(3)	C 12 - C 13 - C 14	110.0(3)
C 13 - C 14 - C 15	109.4(4)	C 14 - C 15 - C 15A	111.8(3)
C 11 - C 15A - N 11A	60.3(2)	C 11 - C 15A - C 15	120.5(3)
N 11A - C 15A - C 15	121.9(3)		

Selected torsion angles (degrees) delineating molecular conformation.

N(11A)	C(15A)	C(15)	C(14)	-17.0	C(15A)	C(15)	C(14)	C(13)	+48.7
C(15)	C(14)	C(13)	C(12)	-66.7	C(14)	C(13)	C(12)	N(11A)	+51.1
C(13)	C(12)	N(11A)	C(15A)	-18.4	C(12)	N(11A)	C(15A)	C(15)	+1.9
N(11A)	C(11)	C(6)	C(7)	+2.3	C(15A)	C(11)	C(6)	C(5A)	-107.5
C(15)	C(15A)	C(11)	C(6)	+143.4	C(12)	N(11A)	C(11)	C(6)	-137.3
H(11)	C(11)	C(15A)	C(15)	-5.8	H(11)	C(11)	N(11A)	C(12)	+1.7

Photochromic Properties of Mefloquine-Aziridine (2): Compound (2) showed interesting photochromic properties. The almost colorless crystals of mefloqine-aziridine (2) turned deep purple when exposed to sunlight or irradiated with a long wavelength UV-lamp (366 nm). However, irradiation with short wavelength UV (254 nm) resulted in only a weak coloration. The purple color fades quickly upon exposure to the light of a normal light bulb and relatively slowly by storing the crystals in the dark. This process could be repeated several times without noticeable decomposition (TLC, UV, NMR).

Photochromic properties have been found in other bicyclic aziridines, e.g. in substituted 1,3-diazabicyclo[3.1.0]hex-3-enes[13] and 1,4-diazabicyclo[4.1.0]hept-4-enes.[14,15] The photochromic effect observed in these compounds was attributed to a 1.3 dipole (azomethine ylide) formed by cleavage of the CC-bond of the aziridine ring.[16] To our knowledge, photochromism was not reported for 1,4-diazabicyclo[4.1.0]heptanes[17] and 1-azabicyclo[4.1.0]heptanes[18,19,20] before, and

mefloquine-aziridine (2) seems to be the first example of a photochromic 1-azabicyclo[4.1.0]heptane.

Reaction of Mefloquine-Aziridine (2) with Acetic Anhydride: Treatment of (2) with acetic anhydride at room temperature afforded the N,O-diacetyl derivative (3) (mp 144-145°C), identical to (3) prepared from mefloquine (1) with acetic anhydride at 90°C (TLC, mp, mixed mp, IR, UV, MS, NMR). Hydrolysis of (3) with methanol/aqueous ammonia gave the known N-acetyl mefloquine (4) (mp 202.5°C, lit.[7] 202.5-203°C). In addition, (3) and (4) could be assigned to the erythro series by their NMR spectra, because the vicinal coupling constant of mefloquine (1) and its derivatives (3) and (4) was $J_{1,2}$ = 4 Hz, in good agreement with former data.[7]
Our investigations revealed that aziridine formation followed by ring opening obviously resulted in a retention of configuration by double inversion at the benzylic carbon atom. Therefore, these stereospecific reactions provide a new method for the preparation of erythro derivatives of mefloquine (1).

Antimalarial Activities: Aziridine (2) and the acetyl derivatives (3) and (4) were tested for antimalarial activity in mice infected with Plasmodium berghei.[21] After p.o. application of the drug, the survival time was measured and compared to the not medicated group of control mice. While mefloquine hydrochloride (1)·HCl, used as standard, had a curative effect at 13 mg/kg, none of the tested compounds (2-4) showed any antimalarial activity at this dose.[22] Data elaborated elsewhere showed that mefloquine ketone was inactive,[23] but N-methyl mefloquine[23] and the threo isomer of mefloquine[7] were found as active as mefloquine (1). This suggests that the structure-activity relationship in the mefloquine molecule follows similar rules to those established in the group of Cinchona alkaloids.[4] The presence of a β-aminoalcohol unit with a basic nitrogen and a free hydroxyl groups seems to be essential for antimalarial activity.

EXPERIMENTAL

Preparation of 7-[2,8-bis(trifluoromethyl)-4-quinolinyl-]-1-azabicyclo[4.1.0]heptane = Mefloquine-Aziridine (2): Mefloquine base (1) (7.6 g, 20 mmol), triphenylphosphine (5.5 g, 21 mmol), triethylamine (2g, 20 mmol), and carbon tetrachloride (3.1 g, 20 mmol) were stirred in 40 ml of acetonitrile at room temperature for 48 hours. The reaction mixture was evaporated under reduced pressure, and the crystalline residue was triturated with ether/petroleum ether (1:1; 3x100 ml). After evaporation of solvents the residue was dissolved in 50 ml of ether and kept in the refrigerator overnight. The yellow ethereal solution was separated from Ph_3PO, ammonium and phosphonium salts, filtered through Al_2O_3 (neutral, act. III, 25 x 60 mm), and eluted with an additional 250 ml of ether. Evaporation afforded 5.5 g (76%) of crude mefloqine aziridine (2) as a yellow oil, which crystallized from petroleum ether (30 ml) in the cold. Recrystallization from the same solvent (50 ml) yielded 4.1 g (57%) almost colorless prisms of (2), mp 85.5-87°C.

Atomic parameters for hydrogen atoms.
Positional parameters are multiplied by 1,000 and U-values by 100. The numbering of the atoms indicates the carbon atoms to which they are attached.

Atom	x/a	y/b	z/c	U
H 3	547(2)	-89(3)	190(1)	8(1)
H 4	601(2)	-257(3)	103(1)	7(1)
H 5	698(2)	-197(2)	-12(1)	6(1)
H 7	802(2)	220(3)	-118(1)	7(1)
H 11	740(2)	-116(2)	-133(1)	6(1)
H 12	828(3)	9(3)	-323(2)	12(1)
H 12'	735(3)	-88(3)	-271(2)	11(1)
H 13	1004(3)	-153(3)	-280(2)	11(1)
H 13'	867(3)	-223(3)	-342(2)	10(1)
H 14	931(2)	-377(3)	-239(1)	9(1)
H 14'	796(4)	-263(4)	-221(2)	13(1)
H 15	1053(5)	-227(5)	-168(3)	17(2)
H 15'	969(4)	-281(4)	-92(2)	14(2)
H 15"	999(3)	-38(4)	-96(2)	11(1)

Atomic parameters for the heavier atoms. Positional parameters are multiplied by 10,000 and thermal parameters by 1,000. The two sets of half occupancy fluorine atoms are designated as, for example, F 10A and F 10A1.

Atom	x/a	y/b	z/c	U11	U22	U33	U12	U13	U23
N 1	6785(1)	2521(1)	504(1)	71(1)	48(1)	48(1)	-4(1)	8(1)	-1(1)
C 1A	6610(2)	1146(2)	626(1)	55(1)	55(1)	40(1)	-1(1)	3(1)	1(1)
C 2	6042(2)	734(2)	1345(1)	59(1)	65(2)	43(1)	-3(1)	7(1)	1(1)
C 3	5811(2)	-625(3)	1480(1)	75(2)	74(2)	50(1)	-2(1)	15(1)	14(1)
C 4	6105(2)	-1637(3)	928(1)	83(2)	55(2)	65(1)	-3(1)	10(1)	15(1)
C 5	6686(2)	-1286(2)	247(1)	70(2)	47(1)	56(1)	1(1)	7(1)	4(1)
C 5A	6946(2)	111(2)	78(1)	53(1)	48(1)	44(1)	1(1)	4(1)	2(1)
C 6	7546(2)	544(2)	-621(1)	58(1)	51(1)	45(1)	0(1)	5(1)	0(1)
C 7	7719(2)	1934(2)	-733(1)	72(2)	53(1)	51(1)	-6(1)	13(1)	1(1)
C 8	7315(2)	2855(2)	-161(1)	79(2)	47(1)	51(1)	-7(1)	7(1)	1(1)
C 9	5709(2)	1812(3)	1943(1)	78(2)	87(2)	54(1)	-10(2)	20(1)	-9(1)
F 9A	5208(1)	1254(2)	2582(1)	128(1)	119(1)	64(1)	-15(1)	49(1)	-9(1)
F 9B	4834(1)	2723(1)	1629(1)	103(1)	89(1)	86(1)	17(1)	23(1)	-16(1)
F 9C	6741(1)	2533(2)	2253(1)	105(1)	126(2)	68(1)	-37(1)	16(1)	-38(1)
C 10	7471(4)	4397(3)	-287(1)	130(3)	54(2)	70(2)	-8(2)	23(2)	2(1)
F 10A	8033(17)	4668(12)	-950(7)	244(14)	61(4)	128(9)	-35(7)	106(11)	5(5)
F 10B	6306(8)	4987(8)	-460(12)	162(6)	67(4)	227(9)	34(4)	15(8)	44(6)
F 10C	8016(18)	5034(7)	296(4)	239(12)	65(4)	87(3)	-59(8)	-27(5)	-10(2)
F 10A1	7224(21)	4784(11)	-993(6)	271(15)	65(3)	88(6)	-3(9)	-13(8)	24(4)
F 10B1	6865(19)	5145(6)	186(10)	229(11)	51(3)	177(8)	3(6)	92(8)	-12(5)
F 10C1	8700(11)	4758(11)	-91(16)	147(7)	91(6)	382(22)	-65(5)	-43(9)	50(10)
C 11	7983(2)	-475(2)	-1211(1)	61(1)	55(1)	54(1)	-6(1)	15(1)	-3(1)
N 11A	8637(2)	59(2)	-1884(1)	92(2)	68(1)	56(1)	0(1)	28(1)	-1(1)
C 12	8286(3)	-537(4)	-2708(1)	102(2)	99(2)	57(2)	2(2)	18(2)	-8(2)
C 13	9069(4)	-1805(4)	-2895(2)	93(2)	111(3)	83(2)	1(2)	23(2)	-30(2)
C 14	9045(4)	-2835(4)	-2228(2)	129(3)	83(2)	106(3)	26(2)	23(2)	-22(2)
C 15	9778(4)	-2254(5)	-1448(2)	100(3)	131(3)	99(3)	51(3)	9(2)	-4(3)
C 15A	9343(3)	-780(4)	-1270(1)	60(2)	113(3)	68(2)	2(2)	5(1)	-16(2)

Anal. Calcd. for $C_{17}H_{14}F_6N_2$: C 56.67, H 3.92, N 7.77, F 31.64. Found: C 56.46, H 3.82, N 8.05, F 31.69. NMR (100 MHz, $CDCl_3$): δ 1.56 (closely spaced m, 4 H, $CH_2\underline{CH_2}\underline{CH_2}CH_2N$); 2.18 (broad s, 3H, $\underline{CH}\underline{CH_2}CH_2$); 3.19 (broad s, 1 H, Ar-$\underline{CH}$), 3.03 and 3.59 (2m, 1 H each, $CH_2\underline{CH_2}N$, irradiation at δ 1.56 changed these multiplets to two doublets with J_{gem} = 14 Hz); 7.70 (tr, J = 7.5 Hz, 1 H, Ar); 7.84 (s, 1H, Ar); 8.13 (d, J = 7.5 Hz, 1H, Ar); 8.37 (d, J = 7.5 Hz, 1 H, Ar). IR (cm^{-1}, $CHCl_3$): 2945m, 2870w, 1605m, 1585w, 1450w, 1412w, 1305s, 1272m, 1150s, 1105s, 989w, 943w, 835w. UV (nm, EtOH): 222 max (ε 44000), 292 max (ε 6800), 303 sh (ε 6300), 315 sh (ε 4400). MS (CI, NH_3): M^+ = 360.

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21. Five mice for each dose level; intraperitoneal inoculation with 4 x 10^6 parasitized erythrocytes per mouse; administration of drug orally, five times at each dose level (1 hour and 1,2,3,4 days after inoculation).

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