Synthesis, Structural and Conformational Study of 6-Hydroxy (or Acyloxy) Derivatives of the 1,3-Dimethyl-1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]decane System

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1,3-Dimethyl-1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]decan-6-ol, and his *p*-chlorobenzoxy and diphenylacetoxy derivatives have been synthesized and studied by ^{1}H and ^{13}C nmr spectroscopy. The crystal structure of the alcohol **2a** has been determined by X-ray diffraction. Each ring of the adamantane cage system is a nearly perfect chair. From the ^{1}H and ^{13}C nmr data, several stereoelectronic effects have been deduced.

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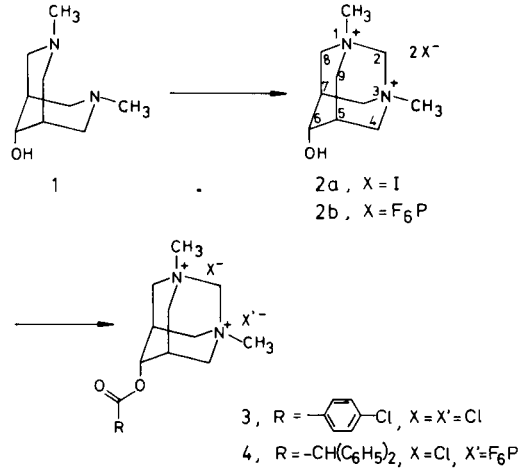
Introduction.

In previous papers [1,2] we reported the synthesis, ^{1}H, ^{13}C nmr study of 1-azatricyclo[3.3.1.1$^{3-7}$]decane-4-α-(β)-ol **5**, **6**, the corresponding p-chlorobenzoates **7**, **8**, (Scheme II) and the crystal structure of **7**.

By considering that the 1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]-decane (1,3-diazadamantane) derivatives are compounds of great importance as conformationally rigid analogues of pharmacological active molecules [3,4], we report here the synthesis and structural and conformational study of several derivatives of the 1,3-diazaadamantane system **2-4** (Scheme I), which are potentially interesting as anticholinergic compounds.

Results and Discussion.

3,7-Dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-ol **1** was prepared according to the reported procedure [5]. The synthesis of 1,3-dimethyl-1,3-diazonitricyclo[3.3.1.1$^{3-7}$]-decan-6-ol diiodide, **2a**, was achieved by treatment of **1** with diiodomethane by the method described for *N,N'*-dimethylbispidine [6]. The acyloxy derivatives **3** and **4** were obtained from the alcohol **2b**, due to the low solubility of **2a** in the common organic solvents.



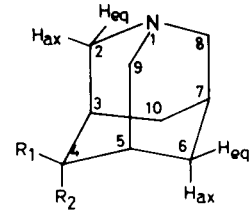
Scheme I

Description of the Structure of Compound **2a**.

The important crystallographic data and the structure determination conditions are given in Table 1. Table 2 lists the atomic parameters and Tables 3 and 4 show bond lengths, bond and torsion angles, respectively, Several significant torsion angles in which hydrogen atoms are involved are also given. Figure 1 displays the structural formula with the numbering used in the crystallographic study and Figure 2 shows a view of the molecular packing.

The adamantane cage system has mean bond lengths of 1.53 (2) Å (1.52 (2) Å for **7** [2]) and internal bond angles of 109 (1)° (109.4 (9)° for **7** [2]), in good agreement with those in similar molecules [15,16]. The mean value of the overall skeleton torsion angles is 60 (1)° (61 (1)° in **7**), so each ring is a nearly perfect chair.

In spite of the apparent symmetry of the molecule, and though, there is a plane through N1-C9-N2-C4, this is not



Compound	R_1	R_2
5	H	OH
6	OH	H
7	H	-OCO-C6H4-Cl
8	-OCO-C6H4-Cl	H

Scheme II

a mirror plane: the C atoms of the methyl groups lie also in this plane (C10 - 0.02 (2), C11 0.01 (2) Å) while the oxygen atom deviates slightly out of it (0.08 (1) Å). The different position of the I atoms with respect to the N1-C9-N2-C4 plane is responsible for the lack of symmetry: while I1 is 3.173 (1) Å apart, the distance of I2 to the plane is 3.409 (1) Å. These different values are due to the fact that I1 forms an hydrogen bond with O1 through H1. The geometry of this hydrogen bond is as follows:

O1...I1 (-X+1, Y+½, -Z+½+2) = 3.45 (1),
O1 - H1 = 1.03 (1), H1...I1 = 2.513 (1) Å,
O1 - H1...I1 = 151.3 (7)°.

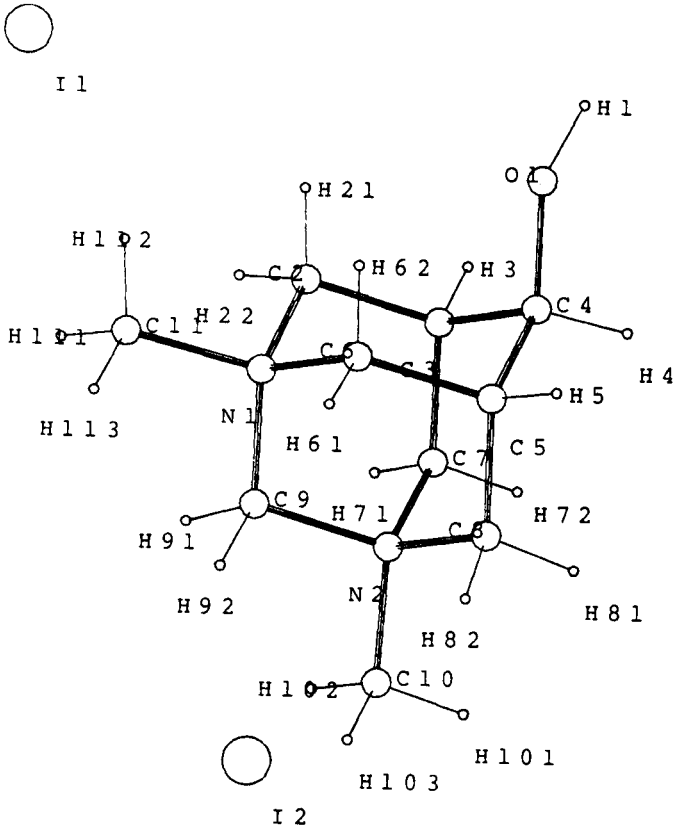


Figure 1. PLUTO [14] view of the molecule showing the atomic numbering.

Table 1

Crystal Data, Data Collection and Structure Refinement

Crystal Data	
Formula	$C_{10}H_{20}I_2N_2O$
Crystal size (mm)	0.25x0.31x0.23
Symmetry	Orthorombic, P212121
Unit cell determination	Least-squares fit from 61 reflexions (θ<45°)
Unit cell dimensions	13.298(2), 15.299(2), 8.093(1)A 90.0, 90.0, 90.0
Packing: V(A^3), Z	1646.6(3), 4
Dc ($g.cm^{-3}$), M, F(000)	1.7673, 438.090, 840
μ(cm^{-1})	302.267
Experimental data	
Technique	Four circle diffractometer: Philips PW 1100 Bisecting geometry Graphite oriented monochromator: Cu K_α ω/2θ scan
Scanning range for 0	2 < θ < 65°
Number or reflections:	
Measured	1630
Observed	1464 (I>3σ (I) ctiterion)
Range of hkl	0/16 0/8 0/9
Absorption	Correction applied [7]
Solution and refinement	
Solution	Patterson and Fourier synthesis
Refinement	I atoms anisotropic, remaining atoms isotropic and H atoms fixed
Variables	70
H atoms	Geometrical calculation; H of oxygen atom differencial Fourier synthesis
w-scheme	Empirical as to give no trends in $\langle w\Delta^2F\rangle$ vs. $\langle \|Fo\| \rangle$ and $\langle \sin\theta/\lambda \rangle$ [8]
Final shift/error	0.007
Final R and Rw	0.069, 0.080
Computer and programs	Wax 11/750, Multan 80 [9], Dirdif [10], X-Ray 76 [11], Parst [12]
Scattering factors	Int Tables for X-Ray Crystallog [13]
Anomalous dispersion	Int Tables for X-Ray Crystallog [13]

Spectral Analysis.

^{1}H nmr.

The assignment and analysis of the proton signals of compounds **2-4** (Table 5) has been carried out by means of double resonance (DR) experiments and literature data of compounds **5-8** (Scheme II) [1,2] and several monoaza and diazabicyclic derivatives [5,17].

In the spectrum of compound **2a**, the saturation of the signal at 3.97 ppm simplifies the doublet at 3.78 that collapses to a singlet. On saturating the signal at 3.61 ppm the doublet at 4.0 ppm collapses to a singlet. These facts confirm the assignments for H 4 (10) ax, H 4 (10) eq, H 8 (9) ax and H 8 (9) eq.

^{13}C NMR.

The ^{13}C nmr chemical shifts of compounds **2-4** are summarized with the signal assignments in Table 6.

Substituent steric and electronic effects on ^{13}C chemical shifts and signal multiplicity obtained from DEPT spectra were taken into consideration. Previous ^{13}C nmr assignments of compounds **5-8** [1,2] and other monoaza and diazabicyclic systems [17] have been used as references.

From the ^{1}H and ^{13}C nmr data of compounds **2-4** the

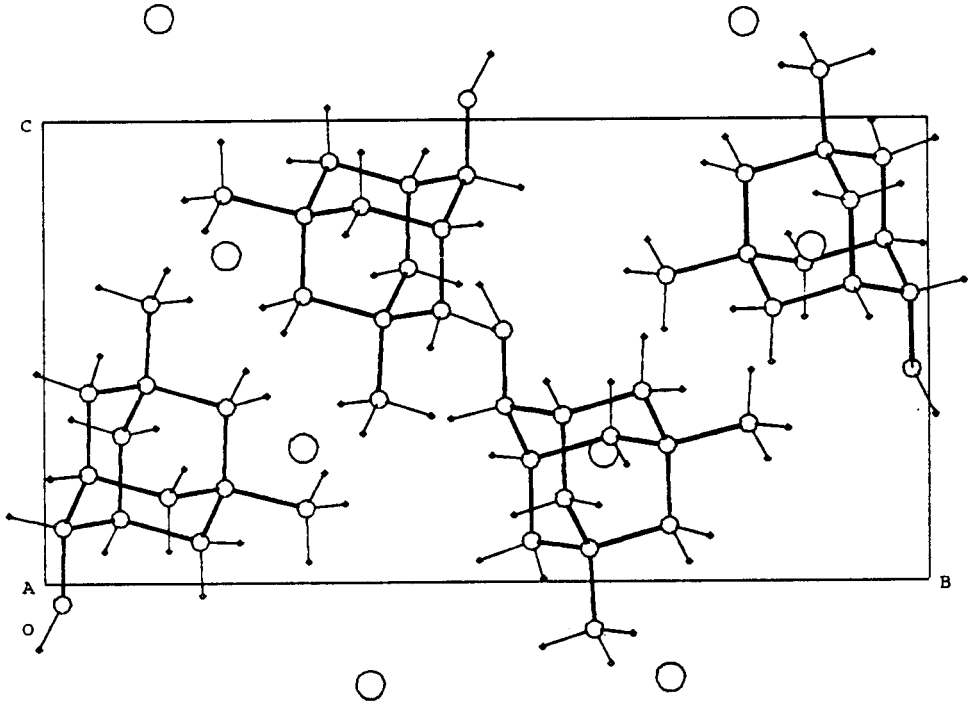


Figure 2. Molecular packing viewed down the axis.

Table 2
Coordinates and Thermal Parameters as
Ueq = (1/3) .Sum[Uij.ai*aj*.ai.aj.cos(ai,aj)].10**4

Atom	x	y	z	Ueq
I1	0.5007(1)	0.1323(0)	1.2222(2)	268(3)
I2	0.8024(1)	0.2930(1)	0.2916(2)	236(3)
N1	0.6252(9)	0.2957(8)	0.7939(18)	109(24)
N2	0.5542(9)	0.3840(8)	0.5698(17)	75(24)
C2	0.5406(12)	0.3240(11)	0.9107(22)	136(33)
C3	0.5001(13)	0.4141(9)	0.8599(18)	91(28)
C4	0.5889(10)	0.4790(9)	0.8801(18)	44(27)
C5	0.6761(11)	0.4504(9)	0.7637(19)	105(30)
C6	0.7139(11)	0.3598(10)	0.8133(21)	125(32)
C7	0.4696(11)	0.4124(10)	0.6793(19)	90(30)
C8	0.6411(11)	0.4495(10)	0.5870(19)	92(29)
C9	0.5905(11)	0.2936(11)	0.6197(21)	134(31)
C10	0.5193(13)	0.3788(12)	0.3961(23)	190(35)
C11	0.6616 (16)	0.2040(15)	0.8394(30)	327(45)
O1	0.6281(9)	0.4805(8)	1.0440(16)	182(25)

Table 2 (continued)
Coordinates and Thermal Parameters as
exp[-8.pi**2.U.(sin(theta)/lambda)**2

Atom	x	y	z	U
H21	0.562 (0)	0.322 (0)	1.028 (0)	12 (0)
H22	0.484 (0)	0.279 (0)	0.914 (0)	12 (0)
H3	0.441 (0)	0.432 (0)	0.932 (0)	9 (0)
H4	0.562 (0)	0.540(0)	0.852 (0)	4 (0)
H5	0.730 (0)	0.494 (0)	0.773 (0)	7 (0)
H61	0.775 (0)	0.342 (0)	0.752 (0)	14 (0)
H62	0.743 (0)	0.359 (0)	0.930 (0)	14 (0)
H71	0.408 (0)	0.374 (0)	0.664 (0)	8 (0)
H72	0.440 (0)	0.469 (0)	0.644 (0)	8 (0)
H81	0.618 (0)	0.509 (0)	0.545 (0)	8 (0)
H82	0.695 (0)	0.437 (0)	0.506 (0)	8 (0)
H91	0.537 (0)	0.248 (0)	0.596 (0)	15 (0)
H92	0.644 (0)	0.272 (0)	0.541 (0)	15 (0)
H101	O.493 (0)	0.438 (0)	0.359 (0)	19 (0)
H102	0.463 (0)	0.335 (0)	0.386 (0)	19 (0)
H103	0.575 (0)	0.360 (0)	0.322 (0)	19 (0)
H111	0.601 (0)	0.160 (0)	0.830 (0)	33 (0)
H112	0.684 (0)	0.201 (0)	0.956 (0)	33 (0)
H113	0.714 (0)	0.183(0)	0.763 (0)	33 (0)
H1	0.590 (0)	0.507 (0)	1.142 (0)	21 (0)

Table 3
Bond Distances (Å)

N1-C2	1.53(2)	C2-C3	1.54(2)
N1-C6	1.54(2)	C3-C4	1.55(2)
N1-C9	1.48(2)	C3-C7	1.52(2)
N1-C11	1.53(3)	C4-C5	1.56(2)
N2-C7	1.50(2)	C4-O1	1.43(2)
N2-C8	1.54(2)	C5-C6	1.53(2)
N2-C9	1.52(2)	C5-C8	1.50(2)
N2-C10	1.48(2)		

Table 4
Bond Angles (°)

C9-N1-C11	108(1)	C2-C3-C7	110(1)
C6-N1-C11	108(1)	C2-C3-C4	106(1)
C6-N1-C9	110(1)	C4-C3-C7	108(1)
C2-N1-C11	110(1)	C3-C4-O1	113(1)
C2-N1-C9	111(1)	C3-C4-C5	109(1)
C2-N1-C6	109(1)	C5-C4-O1	107(1)
C9-N2-C10	108(1)	C4-C5-C8	110(1)
C8-N2-C10	111(1)	C4-C5-C6	110(1)
C8-N2-C9	109(1)	C6-C5-C8	110(1)
C7-N2-C10	110(1)	N1-C6-C5	107(1)
C7-N2-C9	110(1)	N2-C7-C3	112(1)
C7-N2-C8	109(1)	N2-C8-C5	109(1)
N1-C2-C3	110(1)	N1-C9-N2	109(1)

Some Torsion Angles (°)

H22	-C2	-C3	-H3	52.69	1.92
H21	-C2	-C3	-H3	-58.09	1.96
H3	-C3	-C7	-H71	-54.25	1.76
H3	-C3	-C7	-H72	54.15	1.80
H3	-C3	-C4	-H4	-56.01	1.64
C7	-C3	-C4	-O1	-175.64	1.18
H4	-C4	-C5	-H5	58.43	1.66
01	-C4	-C5	-C8	-178.48	1.16
H5	-C5	-C8	-H81	-51.65	1.78
H5	-C5	-C8	-H82	57.28	1.81
H5	-C5	-C6	-H61	-53.33	1.86
H5	-C5	-C6	-H62	57.11	1.81

following conclusions can be obtained:

a) The $\Delta\delta$ C 8 (9) **2a** - C 4 (10) **2a** = 3.62 ppm is due to the syn-diaxial effect exerted by the OH group on the C 4 (10) carbons; the $\Delta\delta$ C 2 (9) **5** - C 2 (9) **6** = 5.58 ppm. The difference 5.58-3.62 = 1.96 ppm can be attributed to the diminished electron-density at H 4 (10) ax in **2** with respect to H 2 (9) ax in **6**. The $\Delta\delta$ C 8 (9) **3** C 4 (10) **3** = 3.33 ppm and $\Delta\delta$ 8 (9) **4** - C 4 (10) **4** = 2.89 ppm can be explained in the same way.

b) The $\Delta\delta$ H 4 (10) ax **2a** - H 8 (9) ax **2a** = 0.22 ppm is due to the deshielding anisotropic and steric syn-diaxial effects exerted by the OH groups. In compounds **5, 6** the value of this effect is estimated in 0.51 ppm, the difference 0.51-0.22 = 0.29 is explained in the same terms as in the last paragraph. The same reasonement can be applied to compounds **3** and **4**.

c) δ H 8 (9) eq **2, 3** or **4** > δ H 4 (10) eq **2, 3** or **4**, this is attributed as in the case of compounds **5-8** to the W arrangement of the equatorial protons with respect to the electron-withdrawing groups.

The displacements of the tricyclic protons of **3** at lower field with respect to the same protons of **4** (Table 5) can be attributed to the more electronic attracting effect exerted by the oxygen atom conjugated with the π - aryl system.

Table 5
^{1}H NMR Chemical Shifts (δ; ppm) and Multiplicities (J, Hz)
for Compounds **2-4**

Compound	**2a**	**2b**	**3**	**4**
H2	5.13 (s)	5.06 (s)	5.92 (s)	4.82 (s)
H4(10)eq	3.61 (d)	3.57 (d)	4.02 (d)	3.41 (d)
	^{2}J 12.42	^{2}J 12.03	^{2}J 12.23	^{2}J 10.6
H4(10)ax	4.00 (d)	4.01 (d)	4.32 (d)	3.88 (d)
H5(7)	2.60 (s)	2.57 (s)	3.03 (s)	2.49 (s)
H6	4.02 (s)	4.01 (s)	5.41 (brs)	5.47 (s)
H8(9)eq	3.97 (d)	3.92 (d)	4.18 (m)	3.57 (m)
	^{2}J 12.25	^{2}J 12.38		
H8(9)ax	3.78 (d)	3.74 (d)	4.18 (m)	3.57 (m)
CH_3	3.16 (s)	3.13 (s)	3.29 (s)	2.78 (s)
CH_3	3.19 (s)	3.16 (s)	3.40 (s)	2.97 (s)
OH	6.12 (brd)	6.11 (d)		
		J 3.2		
H2'(6')			8.23 (d)	
			^{3}J 8.53	
H3'(5')			7.61 (d)	
C_6H_5				7.63 (s)
Ph_2CH				5.58 (s)

[a] Spectra recorded in dimethyl sulfoxide-d_6 at 200 MHz, except for **2a**, registered at 360 MHz. [b] Abbreviations: br, broad; s, singlet; d, doublet; m, multiplet.

Table 6
Carbon-13 Chemical Shifts (δ, ppm) for Compounds **2-4**

Compound	**2a**	**2b**	**3**	**4**
C2	76.08	77.15	78.85	80.34
C4(10)	56.89	57.14	59.44	55.93
C5(7)	32.00	32.15	31.44	29.94
C6	61.39	61.82	62.76	58.82
CH_3	51.00	51.56	53.56	49.33
CH_3	51.42	51.77	53.22	51.75
$CH(Ph)_2$				59.24
C1'			128.31	138.86
C2'(6')			132.94	128.68
C3'(5')			130.46	128.82
C4'			141.25	127.45

[a] Spectra recorded in Dimethyl sulfoxide-d_6 at 50 MHz

Similar effects have been previously observed by us [18,19].

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin Elmer 883 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC-200 P spectrometer at 200 MHz and 50 MHz, respectively. In the case of compound **2a** ^1H nmr spectra were acquired using a Bruker WH 360 MHz. The elemental analysis were made in a Perkin-Elmer Elemental Analyzer model 240 B.

Synthesis.

1,3-Dimethyl-1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]decan-6-ol diiodide (**2a**).

To a refluxing solution of **1** (5 g, 29.37 mmoles) in dry ethanol (100 ml) was added dropwise (1.5 hours) a solution of diiodomethane (7.87 g, 29.37 mmoles) in the same solvent (50 ml). After that the solution was refluxed for 2 hours and stirred at room temperature for 48 hours. The solid which separated out was filtered off and the mother liquors were concentrated up to dryness. The resulting oily residue was chromatographed on a silica gel column using acetone as eluent obtaining an additional amount (0.4 g) of **2a**. The combined fractions were recrystallized from 2-propanol-water, mp 267-268°, yield 32%; ir (potassium bromide): ν (cm^{-1}) = 3298, 1472.

Anal. Calcd. for $C_{10}H_{20}N_2OI_2$: C, 26.69; H, 4.48; N, 6.22. Found: C, 26.90; H, 4.60; N, 6.40.

1,3-Dimethyl-1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]decan-6-ol Dihexafluorophosphate (**2b**).

A solution of **2a** (1 g, 2.22 mmoles) in a minimal amount of water was mixed with another aqueous solution (2 ml) of ammonium hexafluorophosphate (1.45 g, 8.9 mmoles). The resulting precipitate was filtered and recrystallized from 2-propanol-water, yield 73%, mp 270°; ir (potassium bromide): ν (cm^{-1}) = 3575, 3230-3430, 1482, 1470, 837.

1,3-Dimethyl-6-*p*-chlorobenzoyloxi-1,3-diazoniatricyclo[3.3.1-.1$^{3-7}$]decane Salt (**3**).

4-Chlorobenzoyl chloride (2.9 g, 16.5 mmoles) was added dropwise to a stirred solution of **2b** (0.5 g, 1.028 mmoles) and 4-dimethylaminopyridine (0.1 g, 0.82 mmoles) in dry pyridine (35 ml) at 0°. After that the mixture was maintained at 0° for 3 hours and then heated at 60° during 24 hours. By dilution with acetone the precipitate thus obtained was filtered, washed with dichloromethane and crystallized from 2-propanol to yield 0.15 g (30%) of product, mp 285°; ir (potassium bromide): ν (cm^{-1}) = 1727.

Anal. Calcd. for $C_{17}H_{23}N_2O\ Cl_3 \cdot 2H_2O$: C, 47.51; H, 6.33; N, 6.52. Found: C, 47.89; H, 6.28; N, 6.55.

1,3-Dimethyl-6-diphenylacetoxy-1,3-diazoniatricyclo[3.3.1.1$^{3-7}$]-decane Salt (**4**).

Diphenylacetic chloride (3.8 g, 16.5 mmoles) was added to a stirred solution of **2b** (0.5 g, 1.03 mmoles) and 4-dimethylaminopyridine (0.1 g, 0.82 mmoles) in dry pyridine (20 ml). The mixture was maintained at 0° for 1 hour and then heated at 60° during 24 hours, after which the solvent was removed *in vacuo* and the oily residue was treated with 2-propanol. The solid thus obtained was filtered and recrystallized from 2-propanol-water to yield 0.27 g (47%) of product, mp 230°; ir (potassium bromide): ν (cm^{-1}) = 1731, 837.

Anal. Calcd. for $C_{24}H_{30}N_2O_2F_6PCl$: C, 51.57; H, 5.41; N, 5.01. Found: C, 51.92; H, 5.45; N, 5.28.

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