Bis(trifluoromethyl)-containing 1-azatricycloheptanes
1. Synthesis and hydrohalogenation of 3-halo-7,7-bis(trifluoromethyl)-1-azatricyclo[2.2.1.$0^{2,6}$]heptanes

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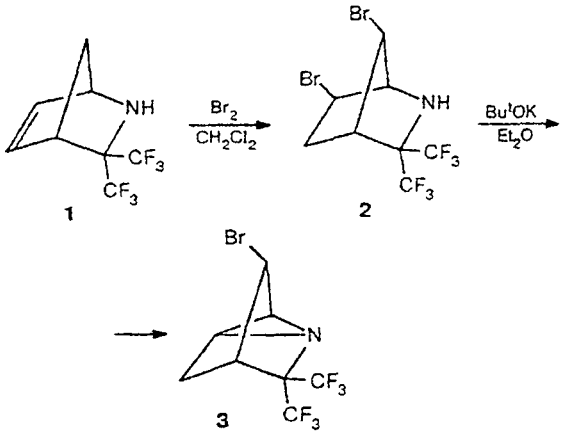
Methods for the synthesis of *anti*-3-halo-7,7-bis(trifluoromethyl)-1-azatricyclo[2.2.1.$0^{2,6}$]heptanes by conjugated halogenation of 3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]hept-5-ene have been developed. Hydrohalogenation of the synthesized 1-azatricyclic compounds gives exclusively 6,7-dihalo-3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptanes.

Key words: 2-azabicycloheptanes, conjugated halogenation; 1-azatricycloheptanes, hydrohalogenation; rearrangements; "nonclassical" cation.

In overcoming microorganism resistance with respect to existing microbicides, synthetic screening of series of compounds with new types of structures is of great importance. Substituted 2-azabicyclo[2.2.1]heptanes, including their trifluoromethyl derivatives, can be considered as such compounds. We have demonstrated that the series of bis(trifluoromethyl)-containing 2-azabicyclo[2.2.1]heptanes may be substantially extended by synthesizing them from bis(trifluoromethyl)-1-azatricyclo[2.2.1.$0^{2,6}$]heptanes. For instance (Scheme 1), one of these compounds, azatricyclane **3**, was synthesized (in 26% total yield) by successive bromination and dehydrobromination of the earlier obtained 3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]hept-5-ene (**1**).[1,2]

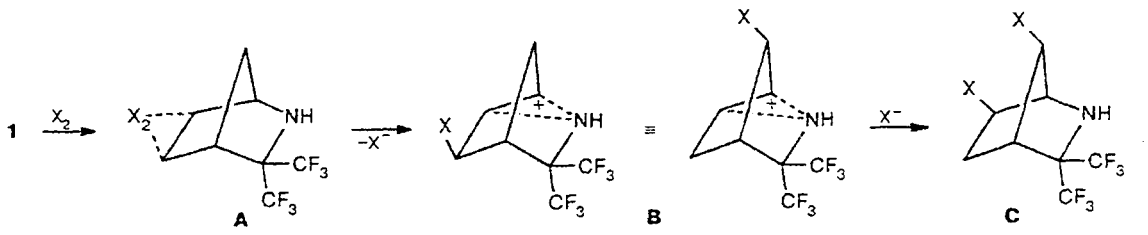
Scheme 1



The relative stability of 1-azanortricyclanes[3] is responsible for the chemists' interest in developing more efficient methods for the synthesis of bis(trifluoromethyl)-1-azatricyclanes from available[1] azabicyclene **1**. The major goal was to study the possibility of the synthesis of these compounds and their subsequent use as sources of various 2-azabicyclo[2.2.1]heptanes, which are rather poorly investigated materials. In planning this work, we were guided by the notion that halogenation of azabicyclene **1** is a multi-step process involving the Wagner—Meerwein rearrangement, which is typical of compounds of the bicyclo[2.2.1]heptene series[4] (Scheme 2).

However, according to the presented scheme of halogenation (**1** → **A** → **B** → **C**), we can assume that an alternative pathway involving stabilization of intermediate ion **B** is probable. This pathway consists of the conversion of **B** to an ammonium cation of the **D** type

Scheme 2



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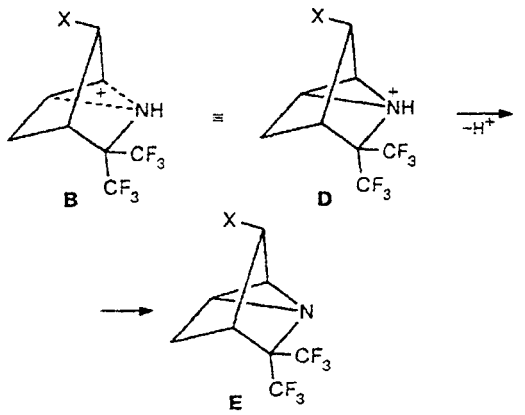
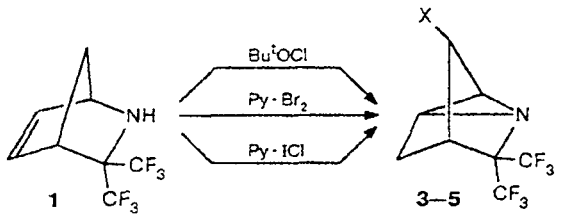
(Scheme 3) followed by deprotonation and the formation of azatricyclic compound **E**.

Scheme 3



We believed that this process (**1** → **A** → **B** → **D** → **E**, see Scheme 3) could be performed under conditions of the conjugated halogenation of azabicyclene **1**, in which an alkoxide anion of a tertiary amine acts as a proton acceptor. We succeeded in confirming this assumption experimentally. Thus, in one-pot reactions of azabicyclene **1** with *tert*-butyl hypochlorite and with either pyridine perbromide or pyridine iodochloride, the corresponding *anti*-3-halo-7,7-bis(trifluoromethyl)-1-azatricyclo[2.2.1.$0^{2,6}$]heptanes **4**, **3**, and **5** were isolated in high yields (75.5, 65.0, and 60.5%, respectively) (Scheme 4).

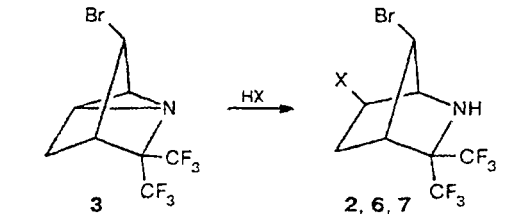
Scheme 4



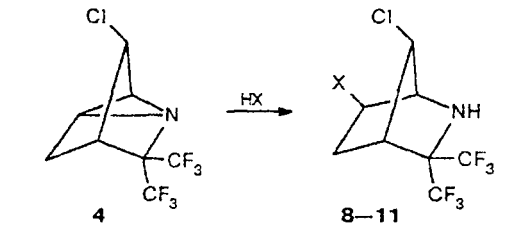
X = Br (**3**), Cl (**4**), I (**5**)

Brominated 1-azanortricyclane **3** is identical to the earlier synthesized product.[2] The structures of the chloro- and iodo-containing 1-azanortricyclanes **4** and **5** were assigned on the basis of their NMR spectra (Table 1). Under ordinary conditions, the synthesized 1-azanortricyclanes are stable liquids, which are soluble in conventional organic solvents. They are inert with respect to water, aqueous solutions of alkalies, and weak acids, but very sensitive to protonating reagents, for example, hydrogen halides. Hydrohalogenation of bromo- and chloro-containing 1-azanortricyclanes **3** and **4** is carried out using similar procedures to give the corresponding 6,7-dihalo-substituted 3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptanes in high yields (Scheme 5).

Scheme 5



X = Br (**2**), F (**6**), Cl (**7**)



X = F (**8**), Cl (**9**), Br (**10**), I (**11**)

Dibromide **2** is identical to that earlier described,[2] but the other 6,7-dihalides **6**—**11** were synthesized and characterized by us for the first time. In addition, 6,7-dichlo-

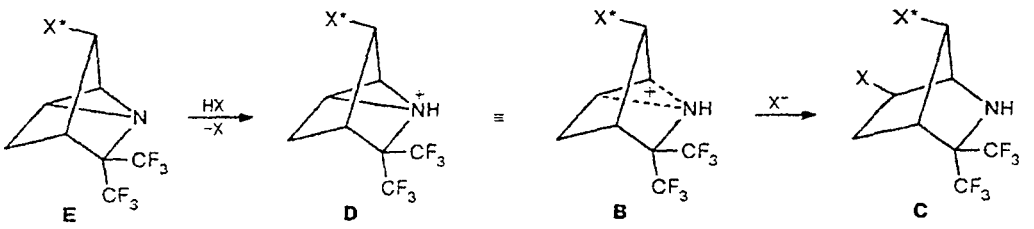
Table 1. ^{1}H and ^{19}F NMR spectra of 3-halo-7,7-bis(trifluoromethyl)-1-azatricyclo-[2.2.1.$0^{2,6}$]heptanes **3**—**5**

Compound	X	δ ^{1}H					δ ^{19}F (*J*/Hz)
		H(2) (s)	H(3) (s)	H(4) (s)	2 H(5)	H(6) (s)	(q)
4	Cl	2.85	4.70	2.75	2.45 (m)	2.85	63.0 (*J* = 13.0); 64.0
3	Br	2.95	4.75	2.85	2.50 (m)	2.95	62.3 (*J* = 13.0); 63.3
5	I	3.00	4.70	2.83	2.73 (s)	2.97	62.5 (*J* = 12.2); 63.5

Table 2. ^1H and ^{19}F NMR spectra of 6,7-dihalo-3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptanes (**2**, **6**—**11**)

Compound	X(C(7))	X(C(6))	δ ^1H (*J*/Hz)						δ ^{19}F (*J*/Hz)
			H(1) (s)	H—N (s)	H(4) (s)	2 H(5) (m)	H(6)	H(7) (s)	
6	Br	F	3.73	2.33	2.97	2.70	4.90 (m, J_{HF} = 50)	4.67	66.0 (q, *J* = 13); 72.0 (q); 165.0 (m, *J* = 50)
7	Br	Cl	3.83	2.30	3.00	2.80	4.07 (t, *J* = 7)	4.67	66.0 (q, *J* = 11.3); 72.0 (q)
2	Br	Br	3.73	2.43	3.05	2.47	4.17 (dd, *J* = 6, *J* = 5)	4.67	65.5 (q, *J* = 11.3); 72.5 (q)
8	Cl	F	3.90	2.43	3.13	2.83	5.06 (m, J_{HF} = 50)	4.67	66.0 (q, *J* = 13); 72.0 (q); 164.0 (m, *J* = 50)
9	Cl	Cl	3.83	2.30	3.00	2.80	4.07 (dd, *J* = 6, *J* = 5)	4.67	66.0 (q, *J* = 11.3); 72.0 (q)
10	Cl	Br	3.73	2.35	2.93	2.72	4.05 (t, *J* = 7)	4.65	66.0 (q, *J* = 11.3); 72.0 (q)
11	Cl	I	3.95	2.53	2.98	2.80	4.18 (t, *J* = 6)	4.86	66.0 (q, *J* = 11.5); 72.0 (q)

Scheme 6

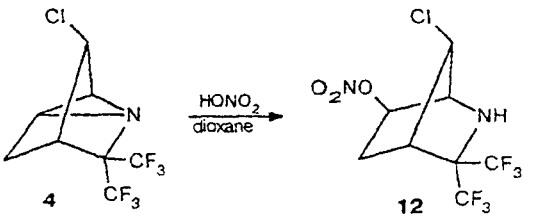


ride **9** was also obtained by direct chlorination of 2-azanorbornene **1** in *ca.* 40% yield. ^1H and ^{19}F NMR spectra of 6,7-dihalides are presented in Table 2. We should note that bromochloro-containing compounds **7** and **10** are regioisomers and their properties are different.

The ease with which the three-membered cycle opens is attributed to instability of the aziridine moiety with respect to protonating reactants.[5] Probably, the primary act is protonation of the 1-azanortricyclane **E** molecule at the N atom resulting in a **D** type ammonium cation, which then undergoes equilibrium transformation to a **B** type cation. The latter is stabilized by the addition of a halide ion as a nucleophilic component of the reaction system to form 6,7-dihalo-substituted 2-azanorbornanes **C**.

This mechanism of the reaction is confirmed by its consistence with the schemes presented above for nonconjugated and conjugated halogenation of azabicyclene **1**, namely, **1** → **A** → **B** → **C** and **1** → **A** → **B** → **D** → **E**. The result of the interaction of 3-chloro-1-azanortricyclane **4** with nitric acid (Scheme 7) is also consistent with the proposed scheme for hydrohalogenation of 1-azanortricyclanes (**E** → **D** → **B** → **C**), in this case producing the corresponding 2-azabicycloheptyl-6 nitrate **12** in 64% yield.

Scheme 7



Therefore, the method for the synthesis of *anti*-3-halo-7,7-bis(trifluoromethyl)-1-azatricycloheptanes was developed and the selectivity of opening of the aziridine cycle offer new possibilities for the next syntheses of various substituted 3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptanes.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Varian EM-890 spectrometer in 30% solutions in CCl_4. Chemical shifts were given with respect to $SiMe_4$ and $CFCl_3$, respectively. IR spectra were recorded on a Perkin—Elmer PE-286 instrument. Mass spectra were obtained on a Varian MAT-CH-6 instrument (EI, 70 eV).

3,3-Bis(trifluoromethyl)-2-azabicyclo[2.2.1]hept-5-ene (1) was synthesized by the well known procedure,[1] b.p. 46 °C (10 Torr), n_D^{20} 1.3988. MS, *m/z* (I_{rel} (%)): 231 (0.8), 165 (0.8), 162 (3), 146 (7), 142 (1), 97 (5), 96 (100), 77 (10), 76 (2), 69 (100), 67 (13), 66 (100), 65 (80), 64 (10), 63 (16), 62 (10), 61 (6), 51 (67), 50 (23), 41 (3), 40 (63), 39 (76).

3-Chloro-7,7-bis(trifluoromethyl)-1-azatricyclo-[2.2.1.0^{2,6}]heptane (4). A solution of *tert*-butyl hypochlorite (3.0 g, 0.028 mol) in MeCN (10 mL) was added dropwise to a solution of azabicycloheptene **1** (4.6 g, 0.02 mol) in 10 mL of MeCN for 4 h at 60 °C with stirring. The reaction mixture was stirred for 0.5 h, and the subsequent fractional distillation *in vacuo* gave compound **4** (4.0 g, 75.5%), b.p. 65—66 °C (10 Torr), d_4^{20} 1.575, n_D^{20} 1.4150. Found (%): C, 37.20; H, 2.12; Cl, 13.74; N, 5.45. $C_8H_6ClF_6N$. Calculated (%): C, 36.16; H, 2.26; Cl, 13.37; N, 5.27.

3-Bromo-7,7-bis(trifluoromethyl)-1-azatricyclo-[2.2.1.0^{2,6}]heptane (3). A solution of $Py \cdot Br_2$ complex (2.4 g) was added dropwise to a solution of azabicycloheptene **1** (2.3 g, 0.01 mol) in 10 mL of CH_2Cl_2 with stirring for 0.5 h. The reaction mixture was stirred for 1 h and washed with water (4×25 mL). The organic layer was separated and dried over $CaCl_2$. Subsequent distillation of the mixture *in vacuo* gave compound **3** (2.0 g, 65%), b.p. 75 °C (10 Torr), d_4^{20} 1.804, n_D^{20} 1.4300. Found (%): C, 29.23; H, 1.79; Br, 24.49; N, 4.59. $C_8H_6BrF_6N$. Calculated (%): C, 30.97; H, 1.93; Br, 25.80; N, 4.52.

3-Iodo-7,7-bis(trifluoromethyl)-1-azatricyclo[2.2.1.0^{2,6}]-heptane (5). A solution of azabicycloheptene **1** (4.6 g, 0.02 mol) in MeCN (10 mL) was added to a suspension of $Py \cdot ICl$ complex (5 g, 0.021 mol) in MeCN (25 mL) with stirring. The reaction mixture was stirred for 2 h and diluted with 50 mL of water. The mixture separated into layers, the lower layer was separated and dissolved in 10 mL of CH_2Cl_2; the resulting solution was washed with 25 mL of a 20% $Na_2S_2O_3$ solution in water and dried over $CaCl_2$. Subsequent distillation of the mixture *in vacuo* gave compound **5** (4.3 g, 60.5%), b.p. 45—47 °C (0.5 Torr), d_4^{20} 2.005, n_D^{20} 1.4656. Found (%): C, 27.58; H, 1.37; I, 35.39; N, 3.94. $C_8H_6F_6IN$. Calculated (%): C, 26.89; H, 1.68; I, 35.55; N, 3.92.

7-Bromo-6-fluoro-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (6). Hydrogen fluoride (2.5 g, 0.125 mol) was added to a solution of tricycloheptane **5** (4.0 g, 0.013 mol) in $CHCl_3$ (75 mL) and THF (5 mL). The reaction mixture was stirred for 5 h at 40 °C, kept at 20—25 °C for 16 h, and neutralized with $NaHCO_3$. The precipitate that formed was filtered off, and subsequent fractional distillation of the filtrate *in vacuo* gave a fraction with b.p. 46—48 °C (1 Torr), which crystallized when stored. Recrystallization from hexane afforded azabicycloheptane **6** (2.9 g, 68.1%, m.p. 50 °C). Found (%): C, 29.37; H, 2.42; Br, 25.06; N, 4.18. $C_8H_7BrF_7N$. Calculated (%): C, 29.09; H, 2.12; Br, 24.24; N, 4.24.

7-Bromo-6-chloro-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (7). Hydrogen chloride (0.4 g, 11 mmol) was bubbled into a solution of compound **3** (1.0 g, 32 mmol) in 10 mL of Et_2O with stirring. The resulting solution was stirred for 1 h and neutralized with $NaHCO_3$. The precipitate that formed was filtered off and the filtrate was evaporated. Recrystallization of the residue from hexane gave compound **7** (0.7 g, 67.6%), m.p. 43 °C. Found (%): C, 28.16; H, 1.29; Br, 24.08; Cl, 10.68; N, 4.04. $C_8H_7BrClF_6N$. Calculated (%): C, 27.71; H, 2.02; Br, 23.09; Cl, 10.25; N, 4.04. IR (CCl_4), ν/cm^{-1}: 3390 (N—H). MS, *m/z* (I_{rel} (%)): 349 (2.7), 347 (11.2), 345 (9.2), 312 (0.7), 310 (0.7), 280 (1.5), 278 (6.1), 276 (5.3), 268 (0.8), 266 (0.8), 242 (1.4), 240 (1.4), 231 (3), 230 (10), 226 (3.8), 218 (12.3), 205 (10.7), 204 (100), 198 (4.6), 196 (13), 184 (20.7), 166 (1.7), 164 (3.4), 162 (3.8), 161 (2.7), 148 (2.1), 136 (5.4), 135 (11.5), 116 (3.4), 115 (2.3), 101 (2.3), 69 (2.3), 66 (10), 65 (14.6), 41 (1.9), 39 (3.4), 36 (1.7).

6,7-Dibromo-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (2). Dibromide **2** (0.8 g, 64.3%) was obtained similarly to compound **7** from tricycloheptane **3** (1.0 g, 32 mmol) and HBr (0.75 g, 92 mmol). The dibromide obtained was identical to compound **2** synthesized by bromination of compound **1** using the well known procedure;[2] b.p. 55—62 °C (0.2 Torr), m.p. 60 °C.

7-Chloro-6-fluoro-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (8). Compound **8** (2.9 g, 67.4%) was obtained similarly to compound **6** from tricycloheptane **4** (4.0 g, 15.1 mmol). B.p. 72—75 °C (5 Torr), m.p. 47 °C. Found (%): C, 33.48; H, 3.34; Cl, 12.32; N, 4.86. $C_8H_7ClF_7N$. Calculated (%): C, 33.63; H, 2.45; Cl, 12.43; N, 4.90. IR (CCl_4), ν/cm^{-1}: 3390 (N—H).

6,7-Dichloro-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (9). Dichloride **9** (0.9 g, 60.9%) was obtained similarly to compound **7** from tricycloheptane **4** (1.3 g, 4.9 mmol) and HCl (0.5 g, 13.7 mmol). M.p. 40 °C. Found (%): C, 31.91; H, 2.38; Cl, 23.50; N, 4.73. $C_8H_7Cl_2F_6N$. Calculated (%): C, 31.90; H, 2.33; Cl, 23.59; N, 4.70. IR (CCl_4), ν/cm^{-1}: 3390 (N—H).

The identical compound was obtained by bubbling Cl_2 (1.5 g, 22 mmol) into a solution of compound **1** (4.6 g, 20 mmol) in CH_2Cl_2 (20 mL) for 1 h. The reaction mixture was then distilled and the fraction boiling at 70—75 °C (1 Torr) was collected. This fraction crystallized during storage. Recrystallization from hexane at 0 °C gave 2.6 g (43.3%) of compound **9**, m.p. 40 °C.

6-Bromo-7-chloro-3,3-bis(trifluoromethyl)-2-azabicyclo-[2.2.1]heptane (10). Compound **10** (1.8 g, 53%) was obtained similarly to compound **7** from tricycloheptane **4** (2.6 g, 9.8 mmol) and HBr (1.5 g, 18.4 mmol). M.p. 56 °C. Found (%): C, 27.72; H, 2.33; Br, 23.76; Cl, 11.41; N, 4.03. $C_8H_7BrClF_6N$. Calculated (%): C, 27.71; H, 2.02; Br, 23.09; Cl, 10.25; N, 4.08. IR (CCl_4), ν/cm^{-1}: 3398 (N—H). MS, *m/z* (I_{rel} (%)): 349 (24.6), 347 (95.4), 345 (79.9), 312 (1.5), 310 (1.5), 303 (0.7), 301 (1.1), 280 (10.7), 278 (44.6), 276 (33.8), 268 (16.9), 266 (53.8), 241 (7.7), 238 (16.9), 231 (7.7), 230 (32.3), 219 (3.1), 218 (35.4), 211 (1.5), 210 (2.6), 205 (12.4), 204 (100), 196 (15.3), 184 (26.1), 172 (2.5), 170 (4.9), 166 (3.2), 164 (3.7), 162 (7.7), 161 (11.5), 149 (3.8), 148 (12.3), 136 (7.7), 103 (3.8), 101 (12.3), 75 (6.1), 66 (6.1), 65 (18.8).

6-Iodo-7-chloro-3,3-bis(trifluoromethyl)-2-azabicyc-lo[2.2.1]heptane (11). Compound **11** (4.8 g, 75.3%) was obtained similarly to compound **7** from tricycloheptane **4** (4.3 g, 0.016 mol) and HI (4.0 g). M.p. 51 °C. Found (%): C, 24.44; H, 1.28; I, 32.43; N, 3.13. $C_8H_7ClF_6IN$. Calculated (%): C, 24.40; H, 1.78; I, 32.26; N, 3.56. IR (CCl_4), ν/cm^{-1}: 3393 (N—H).

7-Chloro-3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptyl-6 nitrate (12). Nitric acid (4.5 mL, d = 1.36 g cm^{-3}) was added dropwise to a solution of tricycloheptane **4** (5.2 g, 0.02 mol) in dioxane (20 mL) for 1 h with stirring, and the resulting mixture was stirred for an additional 3 h. The mixture was then poured into 100 mL of water and extracted with CH_2Cl_2 (2×15 mL); the extract was washed with a 10% $NaHCO_3$ solution (50 mL) and dried over $CaCl_2$. The solvent was evaporated and the residue was crystallized from hexane to give compound **12** (4.1 g, 64%), m.p. 65 °C. Found (%): C, 28.68; H, 1.87; Cl, 10.89; N, 8.84. $C_8H_7ClF_6N_2O_3$. Calculated (%): C, 29.22; H, 2.13; Cl, 10.81; N, 8.52. IR (CCl_4), ν/cm^{-1}: 3395 (N—H); 1646, 1281 (NO_2).

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