Synthesis of 2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazoles

Kurt Pilgram

Shell Development Company, Biological Sciences Research Center, P. O. Box 4248, Modesto, CA 95352

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Two novel 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole derivatives **7** and **8** have been prepared by hydrazinolysis with 2,4-dinitrophenylhydrazine of 1-(benzylideneamino)-2-(2-ethoxycarbonyl-2-nitromethylidene)-imidazolidine **4**. The precursor **4** was conveniently prepared from ethyl nitroacetate and 1-(benzylideneamino)-2-(methylthio)imidazoline **3**. Two examples are presented in which ethyl aceto(and trifluoroaceto)acetate 2-nitrophenyl-hyrazone, **9** and **10**, both of which also feature the β-hydrazinoacrylate arrangement, are refluxed in ethanol containing hydrochloric acid and thereby converted into pyrazolones **11** and **12**, pyrazoles **13** and **14**, and ketone 2-nitrophenylhydrazones **15** and **16**, respectively.

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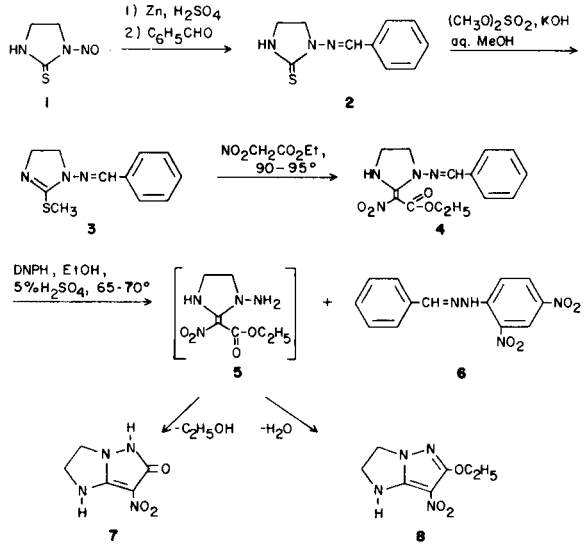
As part of a program of synthesis of 2-nitromethylene imidazolidine insecticides (1), a route was sought to prepare bicyclic heterocycles with *cis*-nitroeneamine structure. Use of 2,4-dinitrophenylhydrazone (DNPH) in the hydrazinolysis of benzaldehyde hydrazones for the preparation of herbicidally active *N*-amino compounds (2) and for synthetic purposes (3) has been reported. The preparation of two members of the novel 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole ring system featuring a *cis*-nitroeneamine arrangement as part of their structure is the subject of this paper.

Results and Discussion.

Nitrosation of 2-imidazolidine thione followed by reduction of the resulting *N*-nitroso derivative **1** (4) with zinc in 2*N*-sulfuric acid and treatment with benzaldehyde gave 1-(benzylideneamino)-2-imidazolidinethione, **2** in 54% yield. The methylation of **2** proceeded smoothly with dimethyl sulfate in alkaline 80% methanol to give 1-(benzylideneamino)-2-(methylthio)imidazoline **3** in 62% yield. Reaction of **3** with ethyl nitroacetate at 90-95° (1 hour) gave the desired starting material **4** in 65% yield. In contrast, prolonged treatment of **3** in refluxing nitromethane (8 hours) led to the recovery of starting material.

The aim was to subject **4** to a hydrazinolysis reaction initiated by 2,4-dinitrophenylhydrazine (DNPH) to warm (65-70°) ethanol containing about 5% of concentrated sulfuric acid, culminating in the formation of **5** with concomitant formation of benzaldehyde 2,4-dinitrophenylhydrazone **6**. The reaction mixture contained the expected co-reaction product **6** (91%), but none of the expected **5**. Obviously, **5** underwent further reaction under these reaction conditions. The formation of the bicyclic heterocycle **7** is suggested to be the result of an intramolecular hydrazinolysis of ester **5** (-C_2H_5OH). The formal elimination from **5** of water leads to **8**.

The ^{1}H nmr spectrum of **7** revealed the presence of a four-proton multiplet at δ 3.8 corresponding to the ring -CH_2-CH_2- group, and the presence of two NH groups at δ 9.6 (s). In the mass spectrum, the molecular ion is observed at m/e 170 (M^+) coupled with a facile loss of one hydroxyl group, corresponding to m/e 153 (M^+-OH). This, in conjunction with correct analytical data leads to formulation of the 2,3-dihydro-7-nitro-1*H*-imidazo[1,2-*b*]pyrazol-6-(5*H*)-one structure for **7**.



The ^{1}H nmr spectrum of **8** shows signals for a primary methyl group at δ 1.4 (t). The signal for the OCH_2 protons occurs at δ 4.25 (d). A four-proton singlet at δ 4.0 (ring -CH_2-CH_2-) and a one-proton singlet at δ 8.05 corresponding to an NH group complete the nmr spectrum of **8**. In the mass spectrum, the molecular ion is observed at m/e 198 (M^+). The initial fragmentation pattern is characterized by the loss of C_2H_5 (m/e 170 (M^+ -C_2H_5 + H)) and OC_2H_5 (m/e 153 (M^+ -OC_2H_5)). By analogy with the structure of **7**, the above structural units are most readily incorporated into the 2,3-dihydro-6-ethoxy-7-nitro-1*H*-imidazo[1,2-*b*]-pyrazole structure for **8**.

In order to test the generality of this cyclization procedure (**5** → **7** + **8**), ethyl acetoacetate 2-nitrophenylhydrazone **9** and ethyl trifluoracetoacetate 2-nitrophenylhydrazone **10**, both of which also feature the β-hydrazino-

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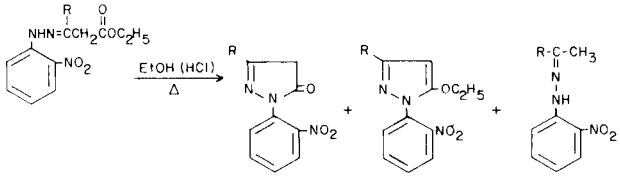
acrylate, HN-N-C=C-CO_2Et, arrangement as part of their structure, were allowed to react in refluxing ethanol containing a catalytic amount of hydrochloric acid or hydrogen chloride.

Reaction of **9** in refluxing ethanol (6 hours) containing a catalytic amount of concentrated hydrochloric acid gave, after work-up and silica gel chromatography, 15% of pyrazolone **11** and 29% of pyrazole **13**, as well as 49% of acetone 2-nitrophenylhydrazone **15**.



9 R=CH_3 **11** R=CH_3 **13** R=CH_3 **15** R=CH_3
10 R=CF_3 **12** R=CF_3 **14** R=CF_3 **16** R=CF_3

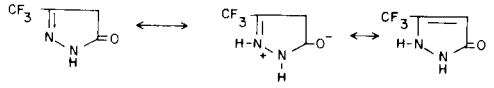
The reaction of the structurally related ethyl trifluoroacetoacetate 2-nitrophenylhydrazone **10** was much more sluggish. After refluxing in absolute ethanol containing a catalytic amount of anhydrous hydrogen chloride for five days, work-up followed by column chromatography gave 40% of pyrazolone **12** and 11% of pyrazole **14**, in addition to 20% of 1,1,1-trifluoroacetone 2-nitrophenylhydrazone **16**.

The evidence for the pyrazolone **11** and **12**, pyrazole **13** and **14**, and ketone 2-nitrophenylhydrazone **15** and **16**, structures was provided by a combination of correct analytical (C, H, N), spectral (infrared and nuclear magnetic resonance), and mass spectral data.

For example, the ^1H nmr spectrum (deuteriochloroform) of **11** showed a signal of δ 2.2 (s, 3H) for one methyl group, a two-proton singlet for a CH_2 group at 3.4 (s, 2H), and a four-proton multiplet in the aromatic region (7.7 ppm). The infrared spectrum (potassium bromide) showed characteristic carbonyl (1735 cm^{-1}) and nitro group (1540 and 1370 cm^{-1}) absorption, but no NH and was present.

The ^1H nmr spectrum (DMSO-d_6) of **12** showed a signal at δ 5.9 (s, 2H) for a CH_2 group and a four-proton multiplet in the aromatic region ($\approx$7.7 ppm). The mass spectrum (70 eV) showed a molecular ion at m/e 273 (M^+), and a sizeable peak at m/e 254, corresponding to a facile loss of one fluorine atom.

Both **11** and **12** exist exclusively in the carbonyl (C=O) forms as evidenced by the absence of signals for OH in the ^1H nmr and infrared spectra. However, the *N*-unsubstituted pyrazolone **17** showed strong absorption in the infrared at 2500-2400 cm^{-1}. It has been amply demonstrated that strong bands in that region are associated with salts and zwitterionic type compounds (5,6).



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Compelling evidence for the pyrazole structures of **13** and **14** was obtained from the ^1H nmr spectra. For example, the nmr spectrum of **13** showed the presence of a methyl group at δ 2.2 (s, 3H), an ethoxy group at 1.3 (t, 3H), and 4.15 (d, 2H), the signal of an olefinic proton, δ 5.7 (s, 1H), and all four aromatic protons as a multiplet at 7.7 ppm. The ^1H nmr spectrum of **14** was very similar to that of **13** with the signals for an ethoxy group at δ 1.3 (t, 3H) and 4.1 (d, 2H), that of the olefinic proton at 5.9 (s, 1H) and the four aromatic ring protons at 7.7 (m, 4H). The infrared spectra (potassium bromide) of **13** and **14** were characterized by an absence in both spectra of NH, OH, and C=O bands. Both spectra showed strong bands in the regions of 1545-1540 and 1360 cm^{-1} (NO_2), and 1625-1620 and 1595 cm^{-1} (C=). The presence of a CF_3 group in **14** was indicated (1130 cm^{-1}). The mass spectrum (70 eV) of **13** showed a molecular ion at m/e 247 (M^+) and prominent peaks at m/e 218 and m/e 186, corresponding to the facile loss of ethyl and ethoxy, respectively.

The structures of the ketone 2-nitrophenylhdyrazones, **15** and **16**, are based on the following spectroscopic evidence. The ^1H nmr (deuteriochloroform) spectrum of **15** showed the signals assigned to two non-equivalent methyl groups at δ 2.1 (s, 3H) and 2.2 (s, 3H), along with an NH signal at 10.7 (s, 1H), and the four-proton multiplet at 6.5-8.3 ppm. In the nmr (deuteriochloroform) spectrum of **16**, the signal at 2.1 (s, 3H) was assigned to the methyl group, that at 10.3 (s, 1H) to the NH group, and the multiplet at 6.7-8.3 to the four aromatic ring protons. The infrared spectra (potassium bromide) of both compounds exhibited the characteristic NH (3330 cm^{-1}) band, bands for the nitro group (1510 and 1330 cm^{-1}), and for CF_3 (1150 cm^{-1}) (**16** only), but no apparent carbonyl absorption.

In summary, the formation of pyrazolones **11** and **12** and ethoxypyrazoles **13** and **14** is similar to that of the imidazo[1,2-*b*]pyrazolone **7** and the 6-ethoxyimidazo-[1,2-*b*]pyrazole **8**, respectively. The formation of ketone 2-nitrophenylhydrazones **15** and **16** results from acidic hydrolysis of the ester group (ketonic cleavage) of **9** and **10**, respectively.

EXPERIMENTAL

1-(Benzylideneamino)-2-imidazolidinethione (**2**).

To a chilled (−5°) and stirred suspension of 105.0 g. (0.802 mole) of 1-nitroso-2-imidazolidinethione (**4**) **1** in 2400 ml. of 2*N* sulfuric acid, was added portionwise within 50 minutes, 120 g. of zinc dust. After 15 minutes, the reaction mixture was filtered. Benzaldehyde, 106.0 g. (1.0 mole), was added to the clear filtrate. After stirring for 1 hour, the white precipitate was collected and recrystallized from acetonitrile to give 88.0 g. (53.6%) of **2** as white solid, m.p. 203-204°; ir (potassium bromide): cm^{-1} 3160 (NH); ^1H nmr (DMSO-d_6): δ 3.8 (m, 4H, CH_2-CH_2), 7.4-7.7 (m, 7H, CH=), 9.0 (s, 1H, NH); ms: m/e 205 (M^+).

Anal. Calcd. for $C_{10}H_{11}N_3S$ (205.3): C, 58.5; H, 5.4; N, 20.5. Found: C, 58.6; H, 5.5; N, 20.3.

1-(Benzylideneamino)-2-(methylthio)-4,5-dihydroimidazole (**3**).

To a cold (5°) and stirred solution of 84.0 g. (0.41 mole) of **2** and 33 g. (0.575 mole) of sodium hydroxide in 200 ml. of water and 1000 ml. of methanol, was added dropwise 80 g. (0.635 mole) of dimethyl sulfate. After 4 hours, the reaction mixture was filtered, and the filtrate was concentrated on a rotary evaporator, diluted with water and filtered. The filter cake was washed with water and dried to give 55.5 g. (61.9%) of **3** as white solid, m.p. 78-79°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, CH_3), 3.5-4.2 (m, 4H, CH_2-CH_2), 7.2-7.8 (m, 6, CH=).

Anal. Calcd. for $C_{11}H_{13}N_3S$ (219.3): C, 60.2; H, 6.0; N, 19.2. Found: C, 60.2; H, 5.9; N, 19.1.

1-(Benzylideneamino)-2-(ethoxycarbonyl)nitromethylene)imidazolidine (**4**).

A suspension of 50.0 g. (0.228 mole) of **3** in 100 ml. of ethyl nitroacetate was heated on a steam bath to give a clear red-brown solution. After 1 hour, the reaction mixture was poured into 500 ml. of ethanol and filtered. The filter cake was washed with ethanol and dried to give 45.0 g. (64.8%) of **4** as white solid, m.p. 228-229° dec.; ir (potassium bromide): cm^{-1} 3380 (NH), 1710 (C=O), 1515 and 1340 (NO_2); ^{1}H nmr (DMSO-d_6): 1.3 (t, 3H, CH_3), 4.1 (d, 2H, CH_2O), 4.0 (m, 4H, ring CH_2-CH_2), 7.8 (m, 6H, CH=), 9.55 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{16}N_4O_4$ (304.3): C, 55.3; H, 5.3; N, 18.4. Found: C, 55.2; H, 5.3; N, 18.5.

2,3-Dihydro-7-nitro-1*H*-imidazo[1,2-*b*]pyrazol-6-(5*H*)one (**7**) and 2,3-Dihydro-6-ethoxy-7-nitro-1*H*imidazo[1,2-*b*]pyrazole (**8**).

A stirred suspension containing **4**, 25.7 g. (0.084 mole) and 2,4-dinitrophenylhydrazine, 16.8 g. (0.085 mole), in 500 ml. of ethanol to which 25 ml. of concentrated sulfuric acid had been added was heated at 65-70° for 12 hours. After removal of 250 ml. of ethanol by rotary evaporation, the reaction mixture was poured into 1000 ml. of water and filtered. The filter cake was separated and purified by silica gel column chromatography (7) followed by recrystallization of the fractions.

The first fraction consisted of benzaldehyde 2,4-dinitrophenylhydrazone **6**, 22.0 g. (91%) as orange solid, m.p. 239-240° [lit. (8) m.p. 232°]; ir (potassium bromide): cm^{-1} 3280 (NH), 1620 (C=), 1510 and 1330 (NO_2); ms: m/e 286 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_4O_4$ (286.3): C, 54.5; H, 3.5; N, 19.6. Found: C, 54.5; H, 3.6; N, 19.5.

The second fraction, 2.4 g. (14%) of **8**, was obtained as yellow solid; m.p. 142-144°; ir (potassium bromide): cm^{-1} 3300-3260 (NH), 1630 and 1620 (C=); ^{1}H nmr (DMSO-d_6): δ 1.4 (t, 3H, CH_3O, 4.25 (d, 2H, OCH_2), 4.0 (s, 4H, CH_2-CH_2), 8.05 (s, 1H, NH); ms: m/e 198 (M^+), 170 (M^+ -C_2H_3 + H), 153 (M^+ -OC_2H_5).

Anal. Calcd. for $C_7H_{10}N_4O_3$ (198.2): C, 42.4; H, 5.1; N, 28.3. Found: C, 42.2; H, 5.0; N, 28.3.

The third fraction, 7.9 g. (55%) of **7**, was obtained as tan solid; m.p. 248° dec. (from water); ir (potassium bromide): cm^{-1} 3000-3100 (NH), 1680, 1660 and 1640 (C=); ^{1}H nmr (DMSO-d_6): 3.8 (m, 4H, CH_2-CH_2), 9.6 (s, 2H, $(NH)_2$); ms: m/e 170 (M^+), 153 (M^+ -OH).

Anal. Calcd. for $C_5H_6N_4O_3$ (170.1): C, 35.3; H, 3.6; N, 32.9. Found: C, 34.9; H, 3.8; N, 32.8.

Ethyl Acetoacetate 2-Nitrophenylhydrazone (**9**).

A solution containing 10.3 g. (0.067 mole) of 2-nitrophenylhydrazine, 6.5 g. (0.067 mole) of 38% hydrochloric acid and 8.7 g. (0.067 mole) of ethyl trifluoroacetoacetate in 350 ml. of 60% ethanol was stirred at ambient temperature. After one hour, most of the ethanol was removed by rotary evaporation. The residue was extracted with ether. The dried ether extract was triturated with hexane to give 15.6 g. (87.2%) of **9** as orange-yellow solid, m.p. 50-51°; ir (potassium bromide): (cm^{-1}) 3350 (NH), 1740 (C=O), 1620 (C=); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, ester CH_3), 4.2 (d, 2H, OCH_2), 2.1 (s, 3, CH_3), 3.4 (s, 2, CH_2), 6.5-8.3 (m, 4H, aromatic H), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O_4$ (265.3): C, 54.3; H, 5.7; N, 15.8. Found: C, 54.4; H, 5.7; N, 15.8.

Acetone 2-Nitrophenylhydrazone (**15**), 2,3-Dihydro-5-methyl-2-(2-nitrophenyl)-3-pyrazolone (**11**) and 5-Ethoxy-3-methyl-1-(2-nitrophenyl)pyrazole (**13**).

A solution containing 4.0 g. (0.015 mole) of **9** and 2 ml. of concentrated hydrochloric acid in 30 ml. of ethanol was refluxed for 6 hours. The reaction mixture was concentrated under reduced pressure, neutralized with aqueous sodium bicarbonate and purified by silica gel column chromatography.

The first fraction, 1.4 g. (49%) of **15**, was a red solid, m.p. 65-67° (from hexane); ^{1}H nmr (deuteriochloroform): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 6.5-8.3 (m, 4H, aromatic H), 10.7 (s, 1H, NH); ir (potassium bromide): cm^{-1} 3330 (NH), 1630 (C=).

Anal. Calcd. for $C_9H_{11}N_3O_2$ (193.2): C, 56.0; H, 5.7; N, 21.8. Found: C, 56.3; H, 5.7; N, 21.8.

The second fraction, 1.1 g. (29.5%) of **13**, was a yellow solid; m.p. 70-71° (from hexane); (potassium bromide): cm^{-1} no apparent NH, OH, C=O; 1615, 1595 (C=), 1545 and 1360 (NO_2); ^{1}H nmr (DMSO-d_6): δ 1.3 (t, 3H, ether CH_3), 4.15 (d, 2H, OCH_2), 2.2 (s, 3H, CH_3), 5.7 (s, 1H, CH=), 7.7 (m, 4, aromatic H); ms: (70 eV) m/e 247 (M^+), 218, 219 (M^+ -C_2H_4 + H), 186 (M^+ -OC_2H_5).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$ (247.3): C, 58.3; H, 5.3; N, 17.0. Found: C, 58.6; H, 5.4; N, 17.2.

The third fraction, 0.5 g. (15.2%) of **11**, was a tan solid; m.p. 114-115° (from hexane); ir (potassium bromide): cm^{-1} no NH, 1735 (C=O), 1540 and 1370 (NO_2); ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H, CH_3), 3.4 (s, 2H, CH_2), 7.7 (m, 4H, aromatic H).

Anal. Calcd. for $C_{10}H_9N_3O_3$ (219.2): C, 54.8; H, 4.1; N, 19.2. Found: C, 54.7; H, 4.1; N, 19.2.

Ethyl Trifluoroacetoacetate 2-Nitrophenylhydrazone (**10**).

A solution containing 12.5 g. (0.066 mole) of 2-nitrophenylhydrazine hydrochloride and 13.8 g. (0.075 mole) of ethyl trifluoroacetoacetate in 250 ml. of 40% aqueous ethanol was stirred for 6 hours at ambient temperature. Most of the solvent was removed by rotary evaporation. Recrystallization of the residue from hexane gave **10**, 17.0 (81%), as yellow solid, m.p. 36-37°; ir (potassium bromide): cm^{-1} 3310 (NH), 1735 (C=O), 1505 and 1330 (NO_2); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, CH_3), 4.3 (d, 2H, CH_2O), 3.5 (s, 2, CH_2), 6.7-8.4 (m, 4H, aromatic H), 11.3 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{12}F_3N_3O_4$ (319.3): C, 45.1; H, 3.8; N, 13.2. Found: C, 45.1; H, 3.8; N, 13.1.

1,1,1-Trifluoroacetone 2-Nitrophenylhydrazone (**16**), 5-Ethoxy-1-(2-nitrophenyl)-3-(trifluoromethyl)pyrazole (**14**) and 2-(2-Nitrophenyl)-5-(trifluoromethyl)-3-pyrazolone (**12**).

A solution containing 9.57 g. (0.030 mole) of **10** and 7.0 g. (0.2 mole) of anhydrous hydrogen chloride in 100 ml. of absolute ethanol was refluxed for 5 days. The reaction mixture was concentrated on a rotary evaporator. Purification of the residue by silica gel column chromatography (7) followed by recrystallization from ether-hexane gave the following products.

Compound **16**.

Compound **16**, 1.5 g. (20%) was obtained as a yellow solid, m.p. 77-79°; ir (potassium bromide): cm^{-1} no apparent C=O, 1620 and 1590 (C=), 1150 (CF_3, C-O-), 1510 and 1330 (NO_2); ^{1}H nmr (deuteriochloroform): δ 2.1 (s, 3H, CH_3), 6.7-8.3 (m, 4H, aromatic H), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_9H_8F_3N_3O_2$ (247.2): C, 43.7; H, 3.3; N, 17.0. Found: C, 43.8; H, 3.2; N, 16.8.

Compound **14**.

Compound **14**, 1.0 g. (11%) was obtained as a white solid, m.p. 46-48°; ir (potassium bromide): cm^{-1} 1620 and 1595 (C=), 1540 and 1360 (NO_2), 1130 (CF_3); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, CH_3), 4.1 (d, 2H, CH_2), 5.9 (s, 1H, CH=), 7.7 (m, 4H, aromatic H).

Anal. Calcd. for $C_{12}H_{10}F_3N_3O_3$ (301.2): C, 47.9; H, 3.3; N, 14.0. Found: C, 48.1; H, 3.3; N, 14.2.

Compound **12**.

Compound **12**, 3.3 g. (40%), was obtained as a tan solid, m.p. 185-186°; ir (potassium bromide): cm^{-1} 1615 and 1595 (C=), 1510 and 1350 (NO_2); ^1H nmr (DMSO-d_6): δ 5.9 (s, 2H, CH_2), ≈7.7 (m, 4H, aromatic H), no evidence for OH; ms: m/e 273 (M^+), 254 (M^+-F).

Anal. Calcd. for $C_{10}H_6F_3N_3O_3$ (273.2): C, 44.0; H, 2.2; N, 15.4. Found: C, 44.3; H, 2.2; N, 15.6.

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