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SYNTHESIS OF 2'-CHLORO-2',3'-DIDEOXY-2',3'-DIDEHYDRO NUCLEOSIDES

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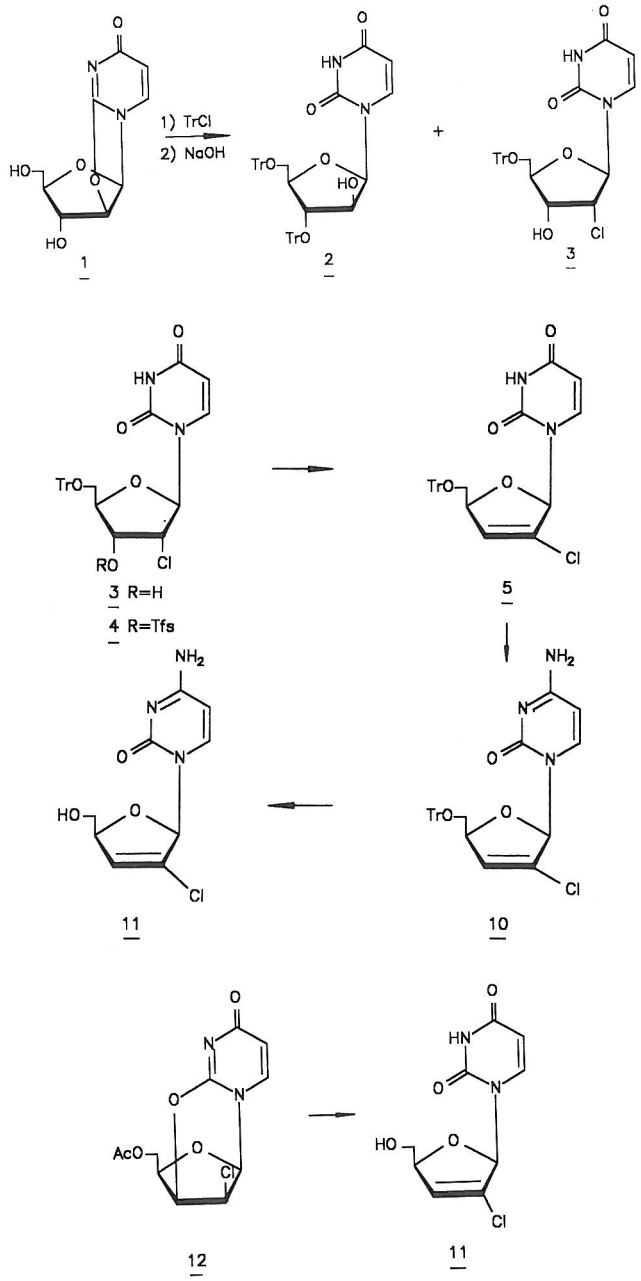
ABSTRACT

Treatment of O^2,2'-anhydrouridine with triphenylmethyl chloride in pyridine at 80°C gives mainly the 2'-chlorinated nucleoside 3. Reaction of 2'-chloro-3'-O-trifluoromethanesulfonyl-5'-O-trityl-2'-deoxyuridine (4) with NaOH led exclusively to the elimination product 5, opening the way to 2-chloro substituted glycero-pent-2-enofuranosyl nucleosides.

RESULTS AND DISCUSSION

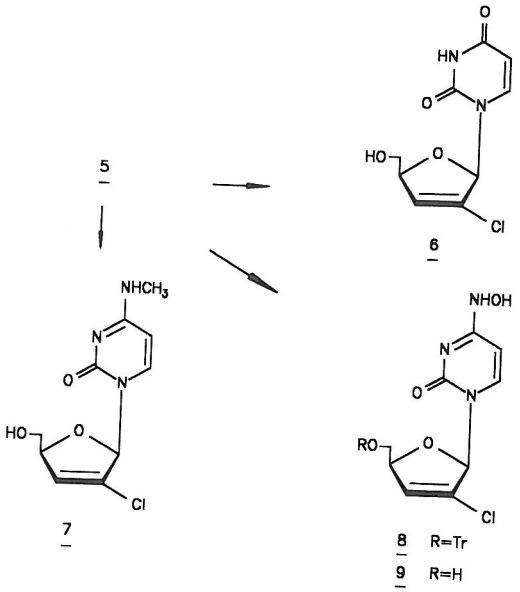
Reaction of either uridine or 1-(β-D-arabinofuranosyl)uracil with triphenylmethyl chloride leads to a mixture of the 2',5'- and 3',5'-bis-tritylated derivatives, which are difficult to separate[3,4]. We therefore treated O^2,2'-anhydrouridine[5] (1) with 4 equiv. of triphenylmethyl chloride at 80°C, followed by treatment with NaOH, to isolate the 3',5'-bis-tritylated nucleoside 2 in 41 % yield. The main product though appeared to be the 2'-chlorinated 2'-deoxyuridine analogue 3, isolated in 48 % yield. This can only be the result from nucleophilic attack of pyridine hydrochloride on the anhydro bond, affording the chlorinated analogue 3 with a ribo configuration. The structure of 3 was proven by detritylation, affording the known 2'-chloro-2'-deoxyuridine[11], which previously was prepared by treatment of O^2,2'-anhydrouridine with hydrogen chloride in dioxane. Physical data are in accordance with the literature. Reaction of 3 with trifluoromethanesulfonic anhydride followed by treatment of the resulting product with NaOH in a mixture of dioxane and methanol, afforded almost quantitatively product 5, resulting from β-elimination. To our knowledge this is the first example of a pyrimidine nucleoside with a ribo configuration, which gives exclusively β-elimination products in basic circumstances without formation of O^2,2'- or O^2,3'-anhydro bonds as side reaction. Reductive elimination on the other hand is well known[6], but this occurs in non-basic conditions and leads to unsubstituted 2',3'-dideoxy-2',3'-didehydro nucleoside derivatives. The product 5 was also obtained by treatment of O^2,3'-anhydro-1-(5-O-acetyl-2-chloro-2-deoxy-β-D-lyxofuranosyl)uracil (12) with base[7], avoiding possible attack of the heterocyclic base on the sugar moiety. The latter compound (12) though is very difficult to obtain and, thus, not a good starting material for the synthesis of 5.

Detritylation of 5 with 80 % acetic acid at 90°C, afforded 6 in 27 % yield. Attempts to prepare the cytosine analogues 7, 9 and 11, using phosphorus oxychloride and N-methylimidazole according to the procedure of Matsuda[8], met with limited success. Reaction of the thus formed intermediate with methylamine, yielded 31 % of the N^4-methyl-cytosine derivative 7, while treatment of the intermediate with hydroxylamine afforded 73 % of isolated 8, which was detritylated in 41 % yield to the N^4-hydroxycytosine derivative 9 (30 % yield from 5).



Reaction with ammonia on the other hand did not give a clean product. Alternatively[9], 5 was treated with trifluoromethanesulfonic anhydride at RT, followed by reaction with ammonia in methanol, affording 75 % of the cytidine analogue 10.

Detritylation with 80 % acetic acid finally gave 11 in 53 % yield. None of the products 6, 7, 9 or 11 showed any appreciable anti-HIV activity in a MT-4 cell system[10].



EXPERIMENTAL SECTION

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Beckman UV 5230 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal). Electron-impact mass spectra (70 eV, 100 µA trap current) were recorded on AEI-MS12 mass spectrometer by direct insertion at the indicated temperature : B = base and S = sugar, relative intensities are included between brackets. Elemental analyses were carried out by Dr. Rozdzinski at the Institut für Organische Chemie in Stuttgart. Precoated Merck silica gel F254 plates were used for TLC. Column chromatography was performed on Merck silica gel (0.063-0.200 mm). Anhydrous N,N-dimethylformamide was obtained by distillation with benzene followed by distillation in vacuo. Pyridine was dried by distillation after it had been refluxed on potassium hydroxide for 24 h. Dichloromethane and dichloroethane were dried with calcium chloride and distilled on phosphorus pentoxide. Tetrahydrofuran was refluxed for 10 h on lithium aluminium hydride and distilled.

1-(3,5-di-O-trityl-ß-D-arabinofuranosyl)uracil (2) and 5'-O-trityl-2'-chloro-2'-deoxyuridine (3).

An amount of 4.52 g (20 mmol) of O^{2},2'-anhydrouridine[5] was reacted at 80°C with 22.4 g (80 mmol) triphenylmethyl chloride in 400 mL of anhydrous pyridine for 65 h. TLC analysis ($CHCl_3$-MeOH 95:5) revealed two major products, and the reaction mixture was concentrated and poured into 400 mL of a saturated $NaHCO_3$ solution. The mixture was extracted twice with 400 mL of $CHCl_3$ and the organic layers were washed with 400 mL of an aqueous $NaHCO_3$ solution. The organic layer was concentrated to about 200 mL, to which 200 mL MeOH and 25 mL of a 5 N NaOH solution was added. Only the product with the lower R_f value, was gradually converted to a more lipophilic product, indicating anhydro ring opening. After 45 min at room temperature, the solution was neutralized and the solvents were removed in vacuo. The residue was extracted twice with $CHCl_3$ and the organic layer was washed twice with water. Evaporation afforded a brown foam, which was purified on silica gel (200 g). Elution with $CHCl_3$-hexane (1:1), followed by $CHCl_3$, afforded 5.95 g (8.16 mmol, 41 %) of 2 and 4.83 g (9.56 mmol, 48 %) of 3 as a foam.

2 : UV (MeOH) λ_{max} 230 and 260 nm; ^{1}H NMR ($CDCl_3$) δ3.14 (m, H-5', H-5"), 3.78 (d, J=3 Hz, H-2'), 3.85-4.05 (m, H-3', H-4', 2'-OH), 5.29 (d, J=8Hz, H-5), 6.17 (d, J = 2.5 Hz, H-1'), 6.6-7.6 (m, arom-H), 9.7 (br, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 63.6 (C-5'), 74.6 (C-3'), 80.1 (C-2'), 84.0 (C-4'), 86.9 and 87.5 (2 Ph_3C), 88.2 (C-1') ppm + aromatic signals.

3 : UV (MeOH) λ_{max} 232 and 260 nm; ^{1}H NMR ($CDCl_3$) δ 3.55 (m, H-5', H-5"), 4.17 (m, H-4'), 4.49 (m, H-2', H-3'), 5.33 (d, J=8.1 Hz, H-5), 6.15 (d, J=3.5 Hz, H-1'), 7.05-7.60 (m, arom-H), 7.82 (d, J=8.1 Hz, H-6), 10.05 (br, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 62.0 (C-2'), 63.0 (C-5'), 69.8 (C-3'), 82.9 (C-4'), 87.8 (Ph_3C), 89.3 (C-1') ppm and aromatic signals.

Structure 3 was further identified by detritylation to 2'-chloro-2'-deoxyuridine with mp 205-206°C (lit[11] mp 207-212°C).

2'-Chloro-3'-O-trifluoromethanesulfonyl-5'-O-trityl-2'-deoxyuridine (4).
A solution of 8.8 g (17.4 mmol) of 3 in 300 mL dry dichloromethane and 4.2 mL (52 mmol) of anhydrous pyridine was cooled on an ice bath and 45 mL (27 mmol) of a 10 % stock solution of trifluoromethanesulfonic anhydride in dichloromethane was added over a period of 20 min. After 30 min stirring at 0°C, the mixture was poured into 30 mL of a 5 % aqueous $NaHCO_3$ solution. After separation of both layers, the water phase was extracted once with $CHCl_3$. The organic phase was dried and evaporated to yield a black tar. A small aliquot was purified on silica gel [$CHCl_3$-hexane (1:1), $CHCl_3$], yielding the title compound 4.

UV (MeOH) λ_{max} 230 and 258 nm; ^{1}H NMR ($CDCl_3$) δ 3.55 (m, H-5', H-5"), 4.40 (m, H-4'), 4.59 (t, H-2'), 5.17 (m, H-3'), 5.51 (d, J=8 Hz, H-5), 6.61 (d, J=7.2 Hz, H-1'), 7.18-7.60 (m, arom-H), 7.55 (d, J=8 Hz, H-6), 9.55 (br, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 56.5 (C-2'), 61.8 (C-5'), 81.7 (C-4'), 83.8 (C-3'), 88.5 (Ph_3C), 89.1 (C-1'), 103.5 (C-5), 139.0 (C-6), 149.9 (C-2), 162.3 (C-4) ppm and trityl signals.

1-(2-chloro-2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)uracil (5)
The remaining foam of the previous preparation was dissolved in 400 mL of dioxane-MeOH (1:1) and 25 mL of a 5 N NaOH solution was added, turning the solution brightly red. The solution was stirred at room temperature, for 18 h, the mixture was neutralized (colouring yellow-brown) and concentrated. The mixture was extracted twice with 300 mL of diethyl-ether, which was washed with a $NaHCO_3$ solution and with brine. Evaporation of the organic phase left 6.9 g (14.2 mmol, 85 % from 3) of 5 as a brown glass.

UV (MeOH) λ_{max} 258 nm; ^{1}H NMR ($CDCl_3$) δ 3.47 (d, J=3 Hz, H-5', H-5"), 4.90 (m, H-4'), 5.09 (d, J=8 Hz, H-5), 6.08 (t, J=1.5 Hz, H-1'), 6.89 (dd, J=1.5 and 3.5 Hz, H-3'), 7.10-7.45 (m, arom-H), 7.73 (d, J=8 Hz, H-6), 9.50 (br, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 64.2 (C-5'), 84.0 (C-4'), 87.7 (Ph_3C), 88.5 (C-1'), 102.9 (C-5), 128.9 (C-2'), 140.0 (C-3'), 142.8 (C-6), 150.7 (C-2), 162.9 (C-4) ppm.

1-(2-chloro-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (6).
An amount of 1.65 g (3.4 mmol) of 5 was dissolved in 100 mL of an aqueous 80 % acetic acid solution and heated for 40 min at 90°C. The solvent was removed in vacuo, and the residue was coevaporated twice with toluene. Chromatographic purification [$CHCl_3$-MeOH (96:4)] yielded 230 mg (0.94 mmol, 27 %) of the title product 6, of which 108 mg crystallized from MeOH-Et_2O.

mp 154°C (lit[7] 155-157°C); UV (MeOH) λ_{max} 258 (ε = 9050); MS (m/z) 244 ($M^{+\cdot}$, 3), 133 ($(M-B)^{+\cdot}$, 62), 112 ($(B+H)^{+\cdot}$, 60), 103 ($(M-B-CH_2O)^{+\cdot}$, 100) (analyzed at 125°C); ^{1}H NMR (DMSO-d_6) δ 3.67 (d, J=2.6 Hz, H-5', H-5"), 4.89 (m, H-4'), 5.13 (br, 5'-OH), 5.70 (d, J=8.1 Hz, H-5), 6.59 (t, J=1.5 Hz, H-1'), 6.76 (dd, J=1.5 and 3.5 Hz, H-3'), 7.87 (d, J=8.1 Hz, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 62.4 (C-5'), 86.7 (C-4'), 89.0 (C-1'), 103.2 (C-5), 125.4 (C-2'), 131.4 (C-3'), 141.1 (C-6), 151.6 (C-2), 164.1 (C-4) ppm.

Anal. Calcd. for $C_9H_9N_2O_4Cl$. 0.15 H_2O : C, 43.71; H, 3.79; N, 11.33.
Found: C, 43.62; H, 3.97; N, 11.47.

Cytosine analogues of 6.
An amount of 4.95 g (10.2 mmol) of 5 was coevaporated twice with anhydrous pyridine and dissolved in 150 mL pyridine. The solution was cooled on an ice bath, and 12 mL (150 mmol) of 1-methylimidazole and 3.8 mL (41 mmol) of phosphorus oxychloride were added. After stirring for 1 h at RT, the mixture was divided in 3 approximately even portions.

A. 1-(2-chloro-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-N^4-methylcytosine (7)
About 50 mL of the reaction mixture was poured into 30 mL of a 40 % aqueous methylamine solution. After stirring for 3 h at room temperature, the mixture was evaporated and partitioned between EtOAC and a $NaHCO_3$ solution. Flash chromatographic purification of the organic phase removed the brown impurities, and the product containing fraction was treated with 80 % acetic acid for 45 min at 90°C. Purification on silica gel ($CHCl_3$-MeOH 98:2 to 92:8) afforded 280 mg (1.08 mmol, 31%) of the title product 7 from MeOH-$CHCl_3$.

mp 184-185°C; UV (MeOH) λ_{max} 267 nm (ε = 12.700); MS (m/z) 257 ($M^{+\cdot}$, 10), 133 ($(M-B)^{+\cdot}$, 4), 125 ($(B+H)^{+\cdot}$, 100) (analyzed at 160°C); ^{1}H NMR (DMSO-d_6) δ2.78 (d, J=4.5 Hz, CH_3), 3.59 (d, J=3.1 Hz, H-5', H-5"), 4.15 (br, 5'-OH), 4.82 (m, H-4'), 5.78 (d, J=7.5 Hz, H-5), 6.52 (t, J=1.5 Hz, H-1'), 6.85 (dd, J=1.5 and 3.5 Hz, H-3'), 7.66 (d, J=Hz, H-6), 7.85 (br, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 27.2 (CH_3), 62.5 (C-5'), 85.8 (C-4'), 89.2 (C-1'), 96.4 (C-5), 126.3 (C-2'), 130.3 (C-3'), 140.0 (C-6), 156.2 (C-2), 164.2 (C-6) ppm.

Anal. Calcd. for $C_{10}H_{12}N_3O_3Cl$. 0.2 H_2O : C, 45.97; H, 4.78; N, 16.08.
Found: C, 45.91; H, 4.53; N, 15.85.

B. 1-(2-chloro-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-N^4-hydroxycytosine (9)
One third of the reaction mixture was poured into 50 mL of a pyridine solution containing 5 g of hydroxylamine hydrochloride and 6 mL of triethylamine. The mixture was stirred overnight and evaporated, and the residue was partitioned between EtOAC and a $NaHCO_3$ solution. Flash purification yielded 1.25 g (2.5 mmol, 73%) of 1-(2-chloro-2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)-N^4-hydroxycytosine (8) as a foam.

UV (MeOH) λ_{max} 271 (broad) nm; ^{1}H NMR ($CDCl_3$) δ3.42 (d, J=3.3 Hz, H-5', H-5"), 4.86 (m, H-4'), 5.09 (d, J=8.3 Hz, H-5), 6.08 (t, J=1.5 Hz, H-1'), 6.80 (dd, H-3'), 6.90 (d, J=8.3 Hz, H-6), 7.1-7.6 (m, arom-H) ppm.

The foam 8 was treated with 60 mL of 80 % acetic acid at 90°C for 30 min. After evaporation and coevaporation with toluene to remove the acetic acid, the residue was purified on silica gel [$CHCl_3$-MeOH (95:5)] and the product containing fractions were crystallized from MeOH-$CHCl_3$, affording 265 mg (1.02 mmol, 41%) of 9 as white needles.

mp 178-180°C; UV (MeOH) λ_{max} 236 (ε = 12.100), 272 (broad, ε = 5.400) nm; MS (m/z) 259 ($M^{+\cdot}$, 4), 133 ($(M-B)^{+\cdot}$, 3), 127 ($(B+H)^{+\cdot}$, 100) (analyzed at 125°C); ^{1}H NMR (DMSO-d_6) δ3.60 (d, J=3 Hz, H-5', H-5"), 4.80 (m, H-4'), 5.05 (br, 5'-OH), 5.59 (d, J=8.3 Hz, H-5), 6.52 (t, J=1.3 Hz, H-1'), 6.66 (dd, H-3'), 7.05 (d, J=8.3 Hz, H-6), 9.65 (br) and 10.05 (br)(NH and NOH) ppm; ^{13}C NMR (DMSO-d_6) δ 62.5 (C-5'), 85.7 (C-4'), 88.3 (C-1'), 99.5 (C-5), 125.8 (C-2'), 129.8 (C-6), 130.6 (C-3'), 143.6 (C-2), 150.1 (C-4) ppm.

C. 1-(2-chloro-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine (11)
The last third of the reaction mixture was poured into 50 mL of concentrated ammonia and stirred for 3 h at RT. After evaporation the residue was dissolved in EtOAC and washed with a $NaHCO_3$ solution and with brine. Flash chromatographic purification ($CHCl_3$-MeOH 97:3) removed most of the brown impurities and the product containing fraction was treated with 80% acetic acid at 90°C for 45 min. Chromatographic purification yielded 210 mg (0.86 mmol, 25 %) of a yellow oil, which could not be crystallized. UV (MeOH) λ_{max} 270 nm.

Therefore, an amount of 1.31 g (2.70 mmol) of 5 was coevaporated twice with anhydrous pyridine and dissolved in 50 mL dichloroethane-pyridine (9:1). A 10 % stock solution of trifluoromethanesulfonic anhydride (9 mL, 5.4 mmol) was added dropwise, and the mixture was stirred for 3 h at RT, and poured into 100 mL of methanol saturated with ammonia, colouring brightly red. Evaporation after 2 h left a black oil, which was partitioned between EtOAc and an aqueous $NAHCO_3$ solution. The organic phase was dried, evaporated and purified on silica gel [$CHCl_3$-MeOH (96:4)], yielding 0.98 g (2.02 mmol, 75 %) of 1-(2-chloro-2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)cytosine (10).

UV (MeOH) λ_{max} 232 and 270 nm, λ_{min} 244 nm; ^{1}H NMR ($CDCl_3$) δ3.40 (d, J=3 Hz, H-5', H-5"), 4.87 (m, H-4'), 5.32 (d, J=7.5 Hz, H-5), 6.05 (t, J=1.5 Hz, H-1'), 7.05 (dd, J=1.5 and 3.8 Hz, H-3'), 7.18-7.60 (m, arom-H), 7.58 (d, J=7.5 Hz, H-6) ppm.

The foam 10 (640 mg, 1.31 mmol) was dissolved in 50 mL of a 80 % acetic acid solution and heated at 90°C for 45 min. The mixture was evaporated, coevaporated with ethanol and partitioned between water and Et_2O. The water phase was evaporated, adsorbed on silica gel and purified [$CHCl_3$-MeOH (85:15)] affording 170 mg (0.69 mmol, 53 %) of 11 which crystallized from MeOH-EtOAC.

mp 203-205°C; UV (MeOH) λ_{max} 241 (ε = 12400) and 268 (ε = 12400) nm, λ_{min} 259 nm; MS (m/z) 243 ($M^{+\cdot}$, 7), 132 ($(M-B-H)^{+\cdot}$, 17), 111 ($(B+H)^+$, 100) (analyzed at 140°C); ^{1}H NMR (DMSO-d_6) δ 3.60 (d, J=3.3 Hz, H-5', H-5"), 4.83 (m, H-4'), 5.04 (br, 5'-OH), 5.77 (d, J=7 Hz, H-5), 6.52 (t, J = 1.5 Hz, H-1'), 6.84 (dd, J=1.5 and 3.5 Hz, H-3'), 7.31 (br, NH_2), 7.73 (d, J=7 Hz, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 62.5 (C-5'), 86.0 (C-4'), 89.2 (C-1'), 95.8 (C-5), 126.2 (C-2'), 130.5 (C-3'), 141.7 (C-6), 156.3 (C-2), 166.1 (C-4) ppm.

Anal. Calcd. for $C_9H_{10}N_3O_3Cl$: C, 44.37; H, 4.14; N, 17.25.
Found: C, 44.32, H, 4.09; N, 17.20.

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