# Reaction of Azole Condensed Quinoxaline *N*-Oxides with Acetic Anhydride



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The reaction of 7-chlorotetrazolo[1,5-*a*]quinoxaline 5-oxide **6a** with acetic anhydride gave 7-chloro-5-(7-chlorotetrazolo[1,5-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline **7a**, while the reaction of 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **6b** with acetic anhydride afforded 7-chloro-5-(7-chloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **7b** and 7-chloro-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**. The reaction of compound **6a** or **6b** with acetic anhydride/acetic acid provided 7-chloro-4,5-dihydro-4-oxo-tetrazolo[1,5-*a*]quinoxaline **8a** or compound **8b**, respectively.

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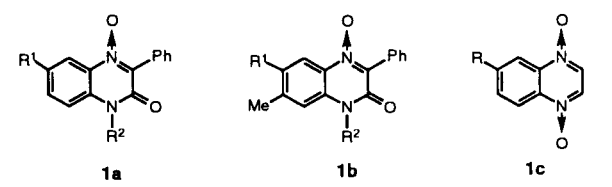
There have been many papers on the reaction of quinoxaline *N*-oxides with acetic anhydride [1-7]. For example, the reaction of the 3-phenylquinoxalin-2-one 4-oxides **1a** and **1b** with acetic anhydride gave the 7-acetoxy and 7-acetoxymethyl derivatives **2a** and **2b**, respectively [6,7], while the reaction of the quinoxaline 1,4-dioxides **1c** wtih acetic anhydride afforded the 1-acetoxyquinoxalin-2-ones **2c** [8] (Chart 1). Moreover, the reaction of quinoxaline 1-oxide **3** with acetic anhydride provided the quinoxalin-2-one **4** (13%) as a main product together with the quinoxaline 1,2'-dimer **5** (4%) as a by-product [9] (Chart 2). The formation of a quinoxaline dimer from a quinoxaline *N*-oxide has seldom been reported so far, and this might be only a paper dealing with the production of a quinoxaline 1,2'-dimer, while there has been a report on the formation of a quinoline 1,2'-dimer from a quinoline 1-oxide [10].

Chart 1



**1a** $R^1$ = H, Me; $R^2$ = Me, OH

**1b** $R^1$ = H, Me; $R^2$ = Me, OH

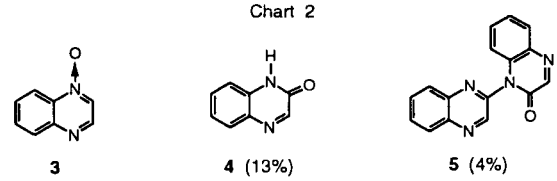
**1c** R = MeO, Me, H, EtO

**2a** $R^1$ = H, Me; $R^2$ = Me, OAc

**2b** $R^1$ = H, Me; $R^2$ = Me, OAc

**2c** R = MeO, Me, H, EtO

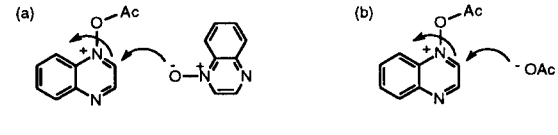
Chart 2



**3** **4** (13%) **5** (4%)

The initial step of the dimerization is explained as shown in Chart 3a [9], that is, the *N*-oxide anion attacks the $C_2$ atom of an acetylated intermediate. However, the nucleophilicity of acetoxy anion is stronger than that of the *N*-oxide anion (Chart 3b), and hence the dimer **5** is obtained as a by-product. In the present investigation, we found that

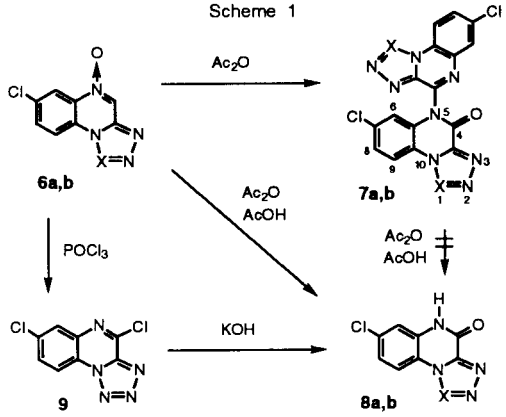
Chart 3



the reaction of the azole condensed quinoxaline *N*-oxides **6a,b** with acetic anhydride provided the dimers **7a,b** (83%, 36%), respectively, as main products (Scheme 1). The

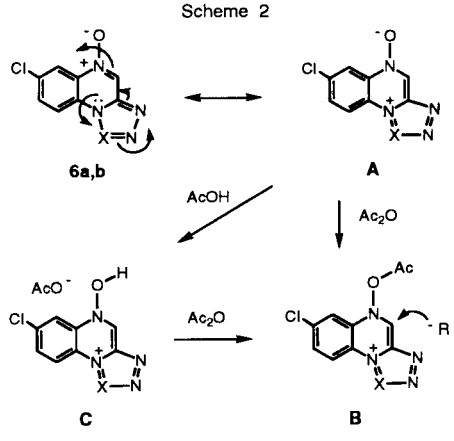
yield of the dimers **7a,b** (83%, 36%) was eminently higher than that of the dimer **5** (4%). This paper describes the reaction of quinoxaline *N*-oxides **6a,b**, **10** and **12a,b** with acetic anhydride or acetic anhydride/acetic acid together with an interpretation for a higher yield of the dimer **7a** (83%) or **7b** (36%) than that of the dimer **5** (4%).

Scheme 1




The reaction of 7-chlorotetrazolo[1,5-*a*]quinoxaline 5-oxide **6a** with acetic anhydride gave 7-chloro-5-(7-chlorotetrazolo[1,5-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline **7a** (83%), while the reaction of 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **6b** with acetic anhydride afforded 7-chloro-5-(7-chloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **7b** (36%) and 7-chloro-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **8b** (30%) (Scheme 1). On the other hand, refluxing of compound **6a** or **6b** in

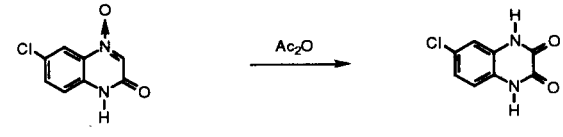
Scheme 2




acetic anhydride/acetic acid did not provide the dimer **7a** or **7b**, but furnished 7-chloro-4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline **8a** (46%) or compound **8b** (36%), respectively. Compound **8a** was also obtained by an alternate synthesis from 4,7-dichlorotetrazolo[1,5-*a*]-quinoxaline **9**, which was produced by the reaction of compound **6a** with phosphoryl chloride. Moreover, refluxing of the dimer **7a** or **7b** in acetic anhydride/acetic acid did not give compound **8a** or **8b**, but recovered the starting material, indicating that the dimers **7a,b** and compounds **8a,b** were produced in a different mechanism.

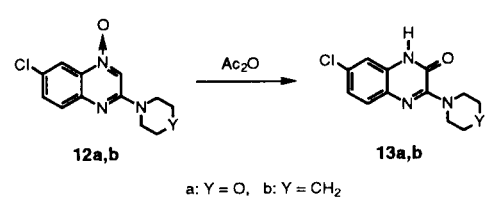
A high yield of the dimer **7a** (83%) or **7b** (36%) in comparison with a low yield of the dimer **5** (4%) might be explained by the assumption that a resonance isomer A (Scheme 2) participated in the initial dimerization step. Namely, an electron donating nature of $N_{10}$ atom would strengthen the nucleophilicity of the *N*-oxide

Scheme 3



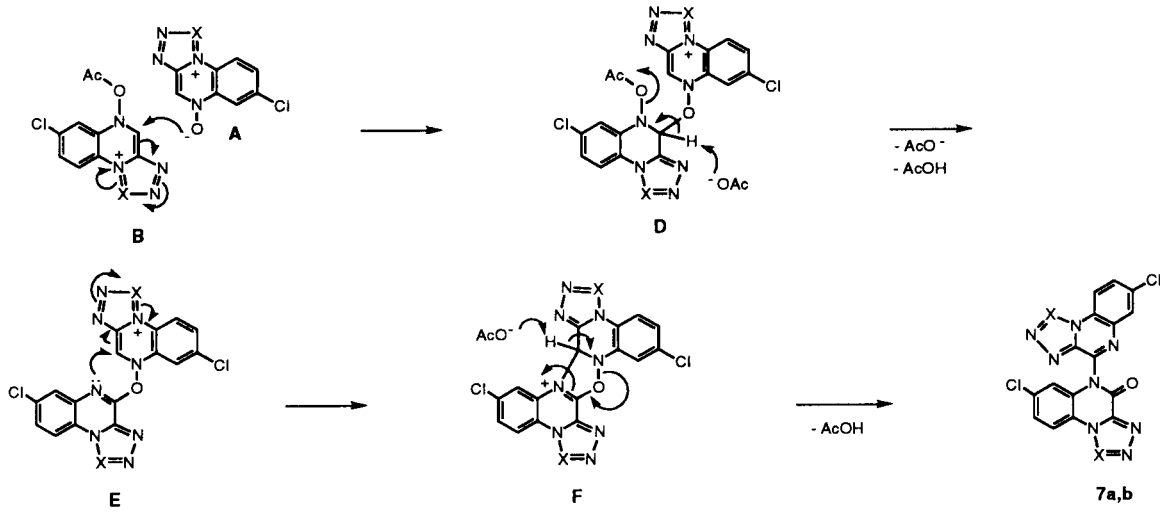

anion in compounds **6a,b**. This assumption was supported by the following results. The reaction of 6-chloro-1,2-dihydro-2-oxoquinoxaline 4-oxide **10** [11] with acetic anhydride afforded 6-chloro-1,2,3,4-tetrahydro-2,3-dioxoquinoxaline **11** [11] (53%), but not any dimer (Scheme 3). The electron withdrawing lactam carbonyl group of compound **10** would weaken the nucleophilicity of the *N*-oxide anion. In addition, the reaction of 6-chloro-2-(morpholin-4-yl)quinoxaline 4-oxide **12a** [12] or 6-chloro-2-(piperidin-1-yl)quinoxaline 4-oxide **12b** [12] with acetic anhydride provided 6-chloro-3,4-dihydro-2-(morpholin-4-yl)-3-oxo-quinoxaline **13a** (38%) or 6-chloro-3,4-dihydro-3-oxo-2-(piperidin-1-yl)-quinoxaline **13b** (58%), respectively (Scheme 4). The *N*-oxide moiety of compounds **12a,b** does not undergo any electron donation from the $C_2$-morpholinyl or $C_2$-piperidinyl moiety, respectively.

Scheme 4



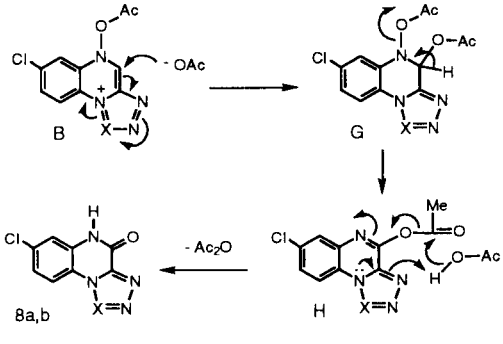

In acetic anhydride, an isomer **A** would be converted into an intermediate **B**, whose $C_4$ atom was immediately attacked by the strongly nucleophilic *N*-oxide anion of an isomer **A** (Schemes 2, 5), and hence the dimers **7a,b** were

Scheme 5



obtained in good yields (83%, 36%). However, in acetic acid/acetic anhydride, an isomer **A** would be predominantly protonated to change into an intermediate C, whose acetylation gave an intermediate **B** (Scheme 2). Accordingly, acetoxy anion preferentially attacks the $C_4$ atom of an intermediate **B** in acetic acid/acetic anhydride, leading to the predominant formation of compounds **8a,b** (Schemes 1, 6). Since refluxing of compound **6a** or **6b** in acetic acid did not afford compound **8a** or **8b**, but recovered the starting material, the species **B** is a key intermediate to the dimers **7a,b** and compounds **8a,b**. The reaction mechanism for the formation of the dimers **7a,b** *via* intermediates **D-F** [9] and compounds **8a,b** *via* intermediates **G**, **H** are shown in Schemes 5 and 6, respectively.

Scheme 6



The structural assignment of new compounds was based on the analytical and spectral data. The aromatic proton signals of the dimers **7a,b** were assigned by comparing the aromatic proton signals of compound **8a** observed in a higher magnetic field with those of compound **9** observed in a lower magnetic field.

## EXPERIMENTAL

All melting points were measured on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given on the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

7-Chloro-5-(7-chlorotetrazolo[1,5-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline **7a**.

A solution of compound **6a** (5 g) in acetic anhydride (200 ml) was refluxed in an oil bath for 4 hours. The solvent was evaporated *in vacuo* to give yellow crystals **7a**, which were triturated with ethanol/water and then collected by suction filtration (3.98 g, 83%). Recrystallization from acetic acid/water afforded yellow needles, mp above 330°; ir: ν $cm^{-1}$ 1700; ms: m/z 424 ($M^+$), 426 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.87 (d, J = 9.0 Hz, 1H, $C_{9'}$-H), 8.62 (d, J = 2.0 Hz, 1H, $C_{6'}$-H), 8.51 (d, J = 9.0 Hz, 1H, $C_9$-H), 8.30 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H, $C_{8'}$-H), 7.75 (d, J = 2.0 Hz, 1H, $C_6$-H), 7.68 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H, $C_8$-H).

*Anal.* Calcd. for $C_{16}H_6Cl_2N_{10}O$: C, 45.20; H, 1.42; Cl, 16.68; N, 32.94. Found: C, 45.40; H, 1.72; Cl, 16.45; N, 32.73.

7-Chloro-5-(7-chloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4-yl)-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **7b** and 7-Chloro-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**.

A solution of compound **6b** (2 g) in acetic anhydride (50 ml) was refluxed in an oil bath for 4 hours to precipitate brown needles **7b**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to give an analytically pure sample (690 mg, 36%). Evaporation of the filtrate *in vacuo* afforded yellow crystals **8b**, which were collected by suction filtration (600 mg, 30%).

Compound **7b** had mp above 330°; ir: ν $cm^{-1}$ 1700; ms: m/z 422 ($M^+$), 424 ($M^+$ + 2); pmr (deuteriotrifluoroacetic acid): 10.24 (s, 1H, $C_{1'}$-H), 10.10 (s, 1H, $C_1$-H), 8.24 (d, J = 9.0 Hz, 1H, $C_{9'}$-H), 8.08 (d, J = 2.0 Hz, 1H, $C_{6'}$-H), 8.04 (d, J = 9.0 Hz, 1H, $C_9$-H), 7.82 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H, $C_{8'}$-H), 7.34 (dd, J = 9.0

Hz, J = 1.5 Hz, 1H, $C_8$-H), 6.88 (d, J = 1.5 Hz, 1H, $C_6$-H).

*Anal.* Calcd. for $C_{18}H_8Cl_2N_8O$: C, 51.08; H, 1.90; Cl, 16.75; N, 26.48. Found: C, 51.30; H, 2.05; Cl, 16.64; N, 26.71.

Compound **8b** was recrystallized from acetic acid/ethanol/water to provide yellow needles, mp 272-273°; ir: ν $cm^{-1}$ 1700; ms: m/z 220 ($M^+$), 222 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 12.08 (br, 1H, $N_5$-H), 9.85 (s, 1H, $C_1$-H), 8.18 (d, J = 8.5 Hz, 1H, $C_9$-H), 7.38 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, $C_8$-H), 7.35 (d, J = 2.0 Hz, 1H, $C_6$-H).

*Anal.* Calcd. for $C_9H_5ClN_4O$: C, 49.00; H, 2.28; Cl, 16.07; N, 25.40. Found: C, 48.83; H, 2.41; Cl, 15.91; N, 25.53.

7-Chloro-4,5-dihydro-4-oxotetrazolo[1,5-*a*]quinoxaline **8a**.

From Compound **6a**.

A solution of compound **6a** (2 g) in acetic anhydride (80 ml)/acetic acid (80 ml) was refluxed in an oil bath for 4 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **8a**, which were triturated with ethanol/water and then collected by suction filtration (0.91 g, 46%). Recrystallization from ethanol furnished yellow needles, mp 283-284°; ir: ν $cm^{-1}$ 1700, 1680; ms: m/z 221 ($M^+$), 223 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 12.76 (s, 1H, $N_5$-H), 8.25 (d, J = 9.0 Hz, 1H, $C_9$-H), 7.46 (d, J = 9.0 Hz, 1H, $C_8$-H), 7.45 (s, 1H, $C_6$-H).

*Anal.* Calcd. for $C_8H_4ClN_5O$: C, 43.36; H, 1.82; Cl, 16.00; N, 31.61. Found: C, 43.57; H, 2.00; Cl, 16.19; N, 31.50.

From Dichloro Compound **9**.

A solution of compound **9** (5 g, 20.7 mmoles) and potassium hydroxide (1.28 g, 22.8 mmoles) in dioxane (200 ml)/water (50 ml) was refluxed in an oil bath for 1 hour. Evaporation of the solvent *in vacuo* gave yellow crystals **8a**, which were triturated with acetic acid/water and then collected by suction filtration (4.56 g, 99%).

7-Chloro-4,5-dihydro-4-oxo-1,2,4-triazolo[4,3-*a*]quinoxaline **8b**.

A solution of compound **6b** (2 g) in acetic anhydride (100 ml)/acetic acid (100 ml) was refluxed in an oil bath for 4 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **8b**, which were triturated with ethanol/water and then collected by suction filtration (0.71 g, 36%).

4,7-Dichlorotetrazolo[1,5-*a*]quinoxaline **9**.

A solution of compound **6a** (10 g) in phosphoryl chloride (100 ml) was refluxed in an oil bath for 1 hour. The solution was evaporated *in vacuo* to give crystals **9**, which were washed with ice-water and then collected by suction filtration (10.1 g, 93%). Recrystallization from dioxane/ethanol/water provided yellow needles, mp 179-180°; ir: ν $cm^{-1}$ 1570, 1535, 1480, 1425; ms: m/z 238 ($M^+$), 240 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.63 (d, J = 9.0 Hz, 1H, $C_9$-H), 8.42 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.07 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H, $C_8$-H).

*Anal.* Calcd. for $C_8H_3Cl_2N_5$: C, 40.03; H, 1.26; Cl, 29.34; N, 29.18. Found: C, 40.32; H, 1.32; Cl, 29.64; N, 29.06.

6-Chloro-1,2,3,4-tetrahydro-2,3-dioxoquinoxaline **11**.

A solution of compound **10** (3 g) in acetic anhydride (120 ml) was refluxed in an oil bath for 4 hours to precipitate yellow crystals **11**, which were collected by suction filtration (1.40 g). Evaporation of the filtrate *in vacuo* gave yellow crystals **11**, which were collected by suction filtration (0.20 g), total yield, 1.60 g (53%). Recrytstallization from *N,N*-dimethylformamide/-water gave yellow needles. The ir spectrum of this sample was identical with that of an authentic sample [11].

6-Chloro-3,4-dihydro-2-(morpholin-4-yl)-3-oxoquinoxaline **13a**.

A solution of compound **12a** (3 g) in acetic anhydride (150 ml) was refluxed in an oil bath for 4 hours. The solution was allowed to stand overnight to precipitate colorless needles **13a**, which were collected by suction filtration (1.13 g, 38%). Recrystallization from ethanol gave colorless needles, mp 241-242°; ir: ν $cm^{-1}$ 1655; ms: m/z 265 ($M^+$), 267 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 12.17 (br, 1H, NH), 7.31 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H, $C_8$-H), 7.12 (dd, J = 2.5 Hz, J = 0.8 Hz, 1H, $C_5$-H), 7.10 (dd, J = 8.0 Hz, J = 2.5 Hz, 1H, $C_7$-H), 3.86 (dd, J = 5.0 Hz, J = 4.0 Hz, 4H, $C_{3'}$-H and $C_{5'}$-H), 3.67 (dd, J = 5.0 Hz, J = 4.0 z, 4H, $C_{2'}$-H and $C_{6'}$-H).

*Anal.* Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.23; H, 4.55; Cl, 13.34; N, 15.81. Found: C, 54.26; H, 4.55; Cl, 13.09; N, 15.91.

6-Chloro-3,4-dihydro-3-oxo-2-(piperidin-1-yl)quinoxaline **13b**.

A solution of compound **12b** (3 g) in acetic anhydride (150 ml) in an oil bath for 4 hours. The solution was allowed to stand overnight to precipitate yellow needles **13b**, which were collected by suction filtration (0.88 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals **13b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (0.87 g), total yield, 1.75 g (58%). Recrystallization from ethanol provided yellow needles, mp 210-211°; ir: ν $cm^{-1}$ 1655; ms: m/z 263 ($M^+$), 265 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 12.09 (br, 1H, NH), 7.30 (dd, J = 8.0 Hz, J = 0.5 Hz, 1H, $C_8$-H), 7.10 (dd, J = 2.5 Hz, J = 0.5 Hz, 1H, $C_5$-H), 7.09 (dd, J = 8.0 Hz, J = 2.5 Hz, 1H, $C_7$-H), 3.85 (d, J = 5.5 Hz, 4H, $C_{2'}$-H and $C_{6'}$-H), 1.58 (d, J = 5.5 Hz, 6H, $C_{3'}$-H, $C_{4'}$-H and $C_{5'}$-H).

*Anal.* Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; Cl, 13.42; N, 15.93. Found: C, 59.14; H, 5.34; Cl, 13.54; N, 16.05.

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