Simplified Synthesis of the Precursor for the Azo Dye Chlorindazone DS

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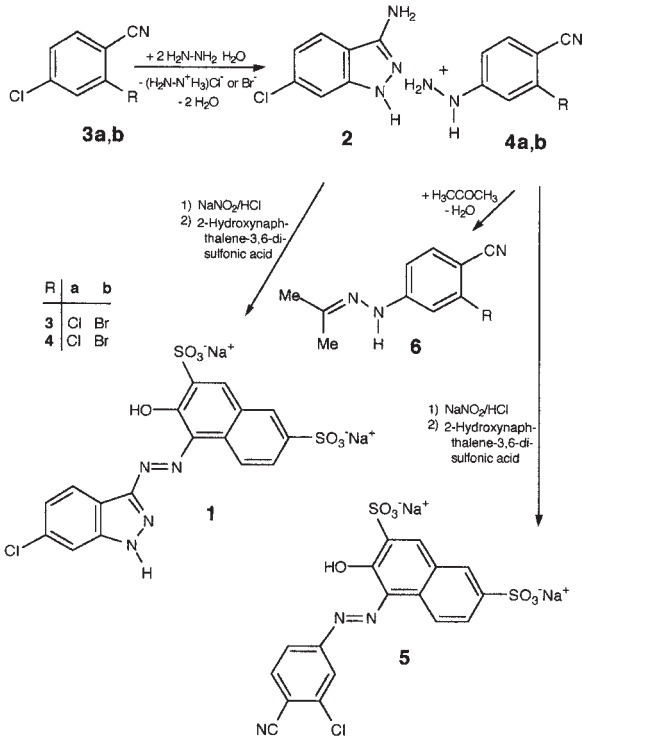
Abstract. Recently, Chlorindazone DS **1** has become an important analytical reagent for the detection of gunshot residues from newly introduced ammunition. A simplified synthesis of the precursor of the azo dye **1**, 3-amino-6-chloroindazole (**2**), from commercially available 2,4-dichlorobenzonitrile (**3a**) has been described. The physical and spectroscopical properties of the known compounds **1** and **2** have been completed. 2-Chloro-4-hydrazinobenzonitrile (**4a**), 2-bromo-4-hydrazinobenzonitrile (**4b**) and a new azo dye, 1-(3'-chloro-4'-cyanobenzene-1'-ylazo)-2-hydroxynaphthalene-3,6-disulfonic acid, disodium salt (**5**), have been investigated.

For the reconstruction of shooting events, gunshot residues are an indispensable aid in forensic investigations. For example, the analysis of gunshot residues provides evidence for the type of ammunition used. The area distribution of residues around the target is a measure for the shooting distance.

The gunshot residue is in many cases invisible for the naked eye. Its detection is performed by measuring certain typical components of the ammunition (leading elements) in residues by chemical or spectroscopic means. For common ammunition, these leading elements are typically heavy metals such as lead, barium, or antimony. Preferentially, sensitive wet-chemistry colour reactions with certain complex-forming agents have been used for visualizing the area distribution of these compounds on a target (*e.g.*, rhodizonic acid, disodium salt, $C_6Na_2O_6$, for lead and barium [1]). Physical methods are also used for the detection of residues (*e.g.*, X-ray fluorescence analysis, scanning electron microscopy, and ICP mass spectrometry [2]).

For more than ten years a new ammunition is available, the so-called 'toxin-reduced' or 'lead-free' ammunition. For this type of ammunition, the classical methods for analysis of gunshot residues are naturally not applicable. The bullets have lead cores that are surrounded by a copper/zinc alloy and do not leave behind traces of lead or of other heavy metals typical for conventional ammunition. However, such ammunition leaves behind copper and zinc as telltale metals, sometimes boron. For the detection of copper and zinc, the azo dye Chlorindazone DS **1** has been used in criminology as a suitable reagent [2]. The coloured reaction products are highly specific for these elements: Chlorindazone DS **1** generates a purple complex with zinc ions and a blue one with copper ions [3]. Chlorindazone DS **1** was first described in 1969 as a reagent for the formation of coloured metal ion complexes including of copper and zinc [3]. These complexes were measured by spectrophotometric methods [4]. Besides these applications, indicator strips containing Chlorindazone DS **1** subsequently have been used for measuring calcium and magnesium ions in water [5].

Chlorindazone DS **1** can be readily prepared from 3-amino-6-chloroindazole (**2**) (see [6] for applications) and 2-hydroxynaphthalene-3,6-disulfonic acid, disodium salt (Fluka). However, the amine **2** is not easily obtained [7]. We present a substantially simplified preparation of **2** by using the commercially available 2,4-dichlorobenzonitrile (**3a**) (Merck) as starting material.



Scheme 1 Preparation of 3-amino-6-chloroindazole (**2**) and of the azo dyes Chlorindazone DS **1** and 1-(3'-chloro-4'-cyanobenzene-1'-yl-azo)-2-hydroxynaphthalene-3,6-disulfonic acid, disodium salt (**5**)

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Results and Discussion

Reaction of 2-bromo-4-chlorobenzonitrile **3b** with hydrazine hydrate [7] or treatment of the 4-chloro substituted diazotized 2-cyanoaniline with $SnCl_2$ in HCl [9] gives 3-amino-6-chloroindazole (**2**). The yield for the indazole derivative **2** is low, but the substance is the indispensable precursor of the complex-forming reagent **1**. The synthesis of the indazole **2** is the weak link in the preparation of Chlorindazone DS **1**.

We treated as starting material commercially available 2,4-dichlorobenzonitrile (**3a**) (Merck) with two equivalents of hydrazine hydrate in *N*-methylpyrrolidone to obtain in a final yield of 21% 3-amino-6-chloroindazole (**2**). Unfortunately, the hydrazine reacts preferentially with **3a** in the 4-position to form 2-chloro-4-hydrazinobenzonitrile (**4a**). As a result, the final reaction mixture contains besides the desired 3-amino-6-chloroindazole (**2**) an threefold excess of **4a** as determined by ^{1}H NMR spectroscopy. For the separation of these components one can take advantage of the different pK_a values of the amine **2** and the hydrazine **4a**: Acidified with hydrochloric acid, at pH 2 to 3 the less basic hydrazine **4a** precipitates exclusively although not quantitatively; the amine **2** stays in solution as ammonium salt. At pH 4 to 6, a mixture of equal amounts of the **2** and **4a** is obtained. From such a mixture, isolation and final purification of **2** can be achieved by repeated crystallization from ethanol. – Another method for removal minor amounts of the undesired **4a** is to form its hydrazone **6**: Short treatment of a mixture of **2** and **4a** with acetone at room temperature converts exclusively the substituted hydrazine **4a** as the stronger nucleophile into its hydrazone **6**, whereas the amine **2** remains unchanged. Because the hydrazone **6** (R_f = 0.58) is much less polar compared to **2** (R_f = 0.20) and to **4a** (R_f = 0.28), separation by column chromatography as the method of choice is straightforward (TLC in cyclohexane/AcOEt, 1:1).

The method described in the literature [7] for synthesizing 3-amino-6-chloroindazole (**2**) starts with the mixed halonitrile **3b**; but the synthesis of **3b** is cumbersome at best. The use of **3b** compared to **3a** has a certain advantage because it has a reactive bromo substituent in *ortho* position to the cyano group. It has been recorded that the synthesis of **2** from **3b** is almost quantitative and, surprisingly, no 2-bromo-4-hydrazinobenzonitrile (**4b**) was mentioned as a side product [7]. To confirm these results, we prepared in a multi-step synthesis [1]) 2-bromo-4-chlorobenzonitrile (**3b**) starting with 4-chloro-2-nitrotoluene (Merck) in six steps (overall yield about 15%). But, we were not able to obtain the sizeable yield of **2** reported [7] starting from **3b**. Only traces of **2** and also of the new compound **4b** were formed, most of the starting material **3b** remained unchanged. However, reaction of 2-bromo-4-chlorobenzonitrile (**3b**) with hydrazine hydrate at increased temperature and reaction time provided 41% of 3-amino-6-chloroindazole (**2**). Although, we achieved under these conditions a respectable yield, it is at the cost of difficult-to-obtain **3b** as starting material for the synthesis of **2.**

The azo dye Chlorindazone DS **1** was obtained from 3-amino-6-chloroindazole (**2**) and 2-hydroxynaphthalene-3,6-disulfonic acid (Fluka) in an analytically pure form and excellent yield. Ultracentrifugation for the separation and subsequent isolation of **1** is essential. Physical and spectroscopical properties (NMR, IR) hitherto not reported have been determined. The dye **1** – prepared as described in the Experimental part – forms a compound with one molecule of ethanol in its molecular unit, as verified by thermogravimetric analysis (TGA), elemental analysis, and NMR spectra. Its thermical decomposition starts at 287 °C (T_{Onset}).

For the synthesis of the reagent Chlorindazone DS **1**, care should be taken not to use 3-amino-6-chloroindazole (**2**) contaminated with 2-chloro-4-hydrazinobenzonitrile (**4a**) for the following reason: Like the amine **2**, the substituted hydrazine **4a** forms with $NaNO_2$ and an excess of hydrochloric acid a substituted benzene diazoniumchloride (3-chloro-4-cyanobenzene diazoniumchloride), which finally reacts with the disodium salt of 2-hydroxynaphthalene-3,6-disulfonic acid to the azo dye **5** [14, 15]**.** We have characterized this dye **5**, which has not been reported before, by spectroscopic methods. The azo dye **5** forms – carefully dried *in vacuo* – a dihydrate, as confirmed both by TGA and elemental analysis. Thermic decomposition sets in at 326 °C (T_{onset}).

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Experimental

All solvents were distilled before use. – TLC: Silica gel 60 F_{254} glass plates (Merck). – Melting points: Buechi 510 apparatus. – TGA: STA 409 (Netzsch), heating rate 10 K/min. – UV/Vis: Photometer DMR 10 (Zeiss). – IR: Paragon 1000 FT IR-spectrometer (Perkin Elmer). – ^{1}H (270.17 MHz) and ^{13}C (67.94 MHz) NMR: JNM-EX 270 (JEOL), assignment of ^{13}C signals was done by ^{13}C,^{1}H-shift correlated 2D-NMR spectra or – for quarternary carbon atoms – by comparison of the experimental shifts with the calculated data [8]. – MS: MAT 8500 mass spectrometer (MAT). – Elemental Analysis: BITOEK Bayreuth, CHNO-Rapid instrument (Elementar).

3-Amino-6-chloroindazole (**2**) *and 2-Chloro-4-hydrazinobenzonitrile* (**4a**)

81.0 g (473 mmol) 2,4-dichlorobenzonitrile (**3a**) (Merck) and 50.6 ml (49.0 g, 1.0 mol) of hydrazine hydrate was treated in 125 ml of *N*-methylpyrrolidone (4.5 h, 130 °C). The reaction mixture was poured into 150 ml of 5M HCl and filtered (residue about 10 g); 5N KOH was added to the filtrate to adjust the pH to 2–3. From the mixture, 33.0 g of 2-chloro-4-hydrazinobenzonitrile (**4a**) separated as white solid and was removed by filtration. To the filtrate, some more 5M KOH was added (pH 4–6) and additional 34.0 g of the mixture of **2** and **4a** (1:1) separated. Repeated crystallization from ethanol

[1]) *via* 2-amino-4-chlorotoluene [11], 2-bromo-4-chlorotoluene and 2-bromo-4-chlorobenzoic acid [both 12], 2-bromo-4-chlorobenzoylchloride [13] and 2-bromo-4-chlorobenzamide[9] as intermediates

yielded 16.5 g (21%) of *3-amino-6-chloroindazole* (**2**) as colourless needles; *m.p.* 222–223 °C ([7] 221 °C); R_f = 0.20 (cyclohexane/AcOEt 1:1). – IR (KBr): ν/cm^{-1} = 3 210 (broad, NH), 1 690 (C=C). – MS (70 eV): *m/z*(%) = 169 (25) [M$^+$], 167 (100) [M$^+$], 138 (20), 132 (5) [M–Cl]. – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 5.45 (s, 2H, NH$_2$), 6.90 (dd, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1H, H-5), 7.26 (d, ^4J = 1.5 Hz, 1H, H-7), 7.69 (d, ^3J = 8.6 Hz, 1H, H-4), 11.50 (s, 1H, NH). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 109.3 (C-7), 113.4 (C-9), 118.4 (C-5), 122.4 (C-4), 131.8 (C-6), 142.2 (C-8), 149.8 (C-3).
For analysis, a sample of crude **4a** was recrystallized from ethanol to yield pure *2-chloro-4-hydrazinobenzonitrile* (**4a**) as a colourless solid; *m.p.* 166.2–167.9 °C, R_f = 0.28 (cyclohexane/AcOEt 1:1). – IR (KBr): ν/cm^{-1} = 3 317, 3 242 (all NH), 2 220 (CN), 1 600 (C=C), 1 488. – MS (70 eV); *m/z*(%): 169 (30) [M$^+$], 167 (100) [M$^+$], 138 (20), 132 (10) [M–Cl]. – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 4.42 (s, 2H, NH$_2$), 6.69 (dd, ^3J = 8.8 Hz, ^4J = 1.9 Hz, 1H, H-5), 6.90 (d, ^4J = 1.9 Hz, 1H, H-3), 7.49 (d, ^3J = 8.8 Hz, 1H, H-6), 8.11 (s, 1H, NH). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 96.1 (C-1), 110.2 (C-5), 110.5 (C-3), 118.5 (CN), 135.2 (C-6), 137.0 (C-2), 156.9 (C-4).
Exact Mass for $C_7H_6ClN_3$: Calcd.: 167.0250; Found: 167.0250.

2-Bromo-4-chlorobenzonitrile (**3b**)

A mixture of 6.72 g (28.6 mmol) 2-bromo-4-chlorobenzamide [9] and 4.38 ml (7.14 g, 60.0 mmol) thionylchloride was heated under reflux for 5.5 h. The product was poured into 50 g of ice/water and stirred for 1 h. The precipitate was removed by filtration, washed (water), and dried *in vacuo* to give 5.90 g (95%) *2-bromo-4-chlorobenzonitrile* (**3b**) as colourless powder. A sample for analysis was recrystallized from cyclohexane, *m.p.* 68.2–69.5 °C ([7] 60 °C), R_f = 0.60 (cyclohexane/AcOEt 9:1). – IR (KBr): ν/cm^{-1} = 3 075, 3 072 (all CH), 2 231 (CN), 1 581 (C=C). – MS (70 eV); *m/z*(%): 219 (19) [M$^+$], 217 (100) [M$^+$], 215 (86) [M$^+$], 138 (17) [M–Br], 136 (70) [M–Br], 100 (60). – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 7.71 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, H-5), 7.99 (d, ^3J = 8.4 Hz, 1H, H-6), 8.11 (d, ^4J = 1.9 Hz, 1H, H-3). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 113.9 (C-1), 117.2 (CN), 126.9 (C-2), 129.4 (C-5), 133.4 (C-3), 136.6 (C-6), 139.3 (C-4).

3-Amino-6-chloroindazole (**2**) and *2-Bromo-4-hydrazinobenzonitrile* (**4b**)

3.29 g (15.2 mmol) 2-bromo-4-chlorobenzonitrile (**3b**) was treated with 9.60 ml (9.70 g; 194 mmol) hydrazine hydrate in 9.6 ml of ethanol for 8 h at 80 °C. After pouring the mixture into 40 ml of 5M HCl and removing some solid substance by filtration, the filtrat was adjusted to pH 8–9 by 5N KOH. The resulting crystalline solid was removed by filtration and dried (a mixture of equal amounts of **2** and **4b**, ^{1}H NMR). Repeated recrystallization from ethanol gave 1.02 g (39%) of **2** (see above) and

2-Bromo-4-hydrazinobenzonitrile (**4b**), 1.35 g (42%), *m.p.* 156.0–157.1 °C, R_f = 0.50 (cyclohexane/AcOEt 1:1). – IR (KBr): ν/cm^{-1} = 3 347, 3 320, 3 286 (all NH), 2 213 (CN), 1 598 (C=C). – MS (70 eV): *m/z*(%) = 213 (95) [M$^+$], 211 (100) [M$^+$], 198 (36), 196 (40), 132 (20) [M–Br], 116 (30). – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 4.38 (s, 2H, NH$_2$), 6.73 (dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz, 1H, H-5), 7.06 (d, ^4J = 2.0 Hz, 1H, H-3), 7.47 (d, ^3J = 8.8 Hz, 1H, H-6), 8.05 (s, 1H, NH). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 98.7 (C-1), 110.5 (C-5), 113.8 (C-3), 119.6 (CN), 126.1 (C-2), 135.4 (C-6), 156.8 (C-4).
Exact Mass for $C_7H_6BrN_3$: Calcd.: 210.9745; Found: 210.9745.

1-(3-Chloro-4-cyanophenyl)-2-(2-propenyl)hydrazone (**6**)

2-Chloro-4-hydrazinobenzonitrile (**4a**) (170 mg, 1.02 mmol) was dissolved at room temperature in 20 ml of acetone. After about 5 min, the solvent was evaporated at room temperature *in vacuo* to yield 200 mg (95%) of **6** as a white solid, *m.p.* 163.5–164.2 °C (ethanol), R_f = 0.58 (cyclohexane/AcOEt 1:1). – IR (KBr): ν/cm^{-1} = 3 304 (NH), 2 217 (CN), 1 605 (C=C), 1 522, 1 483. – MS (70 eV); *m/z*(%): 209 (20) [M$^+$], 207 (100) [M$^+$], 152 (20), 56 (75). – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 1.91 (s, 3H, CH$_3$), 1.98 (s, 3H, CH$_3$'), 7.04 (dd, ^3J = 8.8 Hz, ^4J = 1.9 Hz, 1H, H-6), 7.21 (d, ^4J = 1.9 Hz, 1H, H-2), 7.62 (d, ^3J = 8.8 Hz, 1H, H-5), 9.62 (s, 1H, NH). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 18.1 (CH$_3$), 25.5 (CH$_3$'), 98.9 (C-4), 111.4 (C-6), 112.2 (C-2), 118.1 (CN), 135.6 (C-5), 137.0 (C-3), 150.5, 151.1 (C-1, C=N).
Exact Mass for $C_{10}H_{10}ClN_3$: Calcd.: 207.0563; Found: 207.0563.

1-(6'-Chloroindazole-3'-yl-azo)-2-hydroxynaphthalene-3,6-disulfonic acid, disodium salt · EtOH (Chlorindazone DS, **1**)

Chlorindazone DS **1** was synthesized from 6.60 g (39.5 mmol) of 3-amino-6-chloroindazole (**2**) in 120 ml of 1N HCl, 3.30 g (46.5 mmol) of sodium nitrite as 20% (w/w) aqueous solution, and 21.44 g (40 mmol) of 65% (w/w) aqueous 2-hydroxynaphthalene-3,6-disulfonic acid (Fluka) in 120 ml 1N NaOH at 5 °C [2]. At pH 7, **1** was collected as a red solid from the supernatant by centrifugation (30 min, 10 000 rpm) and carefully washed: (1) with a small amount of water, (2) several times under vigorous stirring with hot ethanol, and (3) finally with diethyl ether. After drying, 19.71 g (86%) **1** was obtained as a dark red powder; TGA (a sample was dried for 16 h at 130 °C/0.001 Torr; dried **1** is slightly hygroscopic): T_{onset} = 287 °C; loss of weight until 180 °C is 9.59% (EtOH: 8.03%). – UV/Vis (H_2O): λ_{max} (lg ε) = 466 nm (4.05) with shoulders at 420 nm and 540 nm ([4a] 465 nm (3.99) and [4e] 466 nm (4.08)). – IR (KBr): ν/cm^{-1} = 3448 (broad, NH, OH), 1 618, 1 459, 1 190, 1 194, 1 056, 1 038. – ^{1}H NMR (d$_6$-DMSO): δ/ppm = 7.45 (dd, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1H, H-5'), 7.77 (d, ^4J = 1.5 Hz, 1H, H-7'), 7.95 (dd, ^1J = 8.6 Hz, ^4J = 1.5 Hz, 1H, H-7), 8.12 (d, ^4J = 1.5 Hz, 1H, H-5), 8.39 (s, 1H, H-4), 8.43 (d, ^3J = 8.6 Hz, 1H, H-4'), 8.56 (d, ^3J = 8.6 Hz, 1H, H-8), additionally the signals for EtOH at 1.05 (q) and 3.46 (t). – ^{13}C NMR (d$_6$-DMSO): δ/ppm = 111.4 (C-7'), 112.5 (C-1), 121.8 (C-4'), 124.5 (C-8), 124.8 (C-5'), 126.1 (C-10), 126.3 (C-5), 128.0 (C-7), 130.9 (C-9'), 132.2 (C-6'), 133.2 (C-9), 135.4 (C-4), 138.3 (C-3), 142.6 (C-6), 145.9 (C-8'), 151.8 (C-3'), 156.9 (C-2), additionally the signals for EtOH at 18.6 and 56.1.
$C_{17}H_9ClN_4Na_2O_7S_2$ · EtOH (572.9)
Calcd.: C 39.83 H 2.64 N 9.78
Found: C 39.00 H 2.80 N 9.85.

1-(3'-Chloro-4'-cyanobenzene-1'-yl-azo)-2-hydroxynaphthalene-3,6-disulfonic acid, disodium salt dihydrate (**5**)

Prepared from 1.67 g (10.0 mmol) of 4-hydrazino-2-chlorobenzonitrile (**4a**) in 30 ml of 1N HCl, 2.40 g (35 mmol) of sodium nitrite as 20% (w/w)aqueous solution and 5.36 g (10 mmol) of 65% (w/w) aqueous 2-hydroxynaphthalene-3,6-disulfonic acid (Fluka) in 30 ml 1N NaOH at 5 °C. At pH 7, the orange-red precipitate was collected by centrifugation and washed with a small amount of water, ethanol, and diethylether, then dried, yielding 1.08 g (21%) orange-red powder of **5** as dihydrate, TGA (a sample was dried for 16 h at 130 °C/0.001 Torr): T_{onset} = 326 °C, loss of weight until 180 °C is 5.83% ($2H_2O$: 6.6%). – UV/Vis (H_2O): λ_{max} (lg ε) = 320 (4.08), 480 (4.34) with shoulders at 403 nm and 504 nm. – IR (KBr): ν/cm^{-1} = 3 445 (broad, OH), 2 228 (CN), 1 599, 1 553, 1 500, 1 478, 1 199, 1 039, 995. – ^{1}H NMR: δ/ppm = 7.81 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1H, H-7), 7.87 (d, dd, ^3J = 8.8 Hz, ^4J = 1.8 Hz 1H, H-6'), 7.90 (d, ^4J = 1.2 Hz, 1H, H-5), 8.01 (d, ^3J = 8.8 Hz, 1H, H-5'), 8.06 (d, ^4J = 1.8 Hz, 1H, H-2'), 8.24 (s, 1H, H-4), 8.37 (d, ^3J = 8.4 Hz, 1H, H-8). – ^{13}C NMR: δ/ppm = 107.8 (C-1), 115.7 (C-4'), 116.7 (C-6'), 116.8 (CN), 118.2 (C-2'), 122.8 (C-8), 126.9 (C-10), 127.6 (C-5), 128.3 (C-7), 132.0 (C-3'), 133.4 (C-9), 136.4 (C-5'), 137.5 (C-3), 141.3 (C-4), 142.1 (C-6), 148.4 (C-2), 152.8 (C-1').
$C_{17}H_8ClN_3Na_2O_7S_2 \cdot 2H_2O$ (547.8)
Calcd.: C 37.27 H 2.21 N 7.67
Found: C 37.20 H 2.46 N 7.47.

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