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Synthesis of some deuterated dialkylaminoethyls as possible standards for the mass spectrometric monitoring of chemical warfare agents

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Deuterium-labelled derivatives of 2-(dialkylamino)ethanols, 2–(dialkylamino)ethyl chlorides and 2-(dialkylamino)ethanethiols have been prepared in which completely deuterated *N*-alkyls (Me, Et, n-Pr, iso-Pr) have been introduced as substituents. Such labelled derivatives are of great interest in mass spectrometry as standards for monitoring chemical warfare agents and their precursors.

Keywords: 2-(dialkylamino)ethanol; 2-(dialkylamino)ethyl chloride; 2-(dialkylamino)ethanethiol; deuterium labelled; precursors of chemical warfare agents

Introduction

The detection of chemical warfare agents (CWAs) is an important task in today's world especially in connection with the ever-present threat of terrorism and ongoing military operations. Modern approaches to analytical monitoring involve primarily the direct detection of hazardous compounds. In addition to the methods for unambiguous control of precursors and by-products of synthesis or degradation, other tools are important in blocking the illegal movement of the base material for CWA production and verifying monitored disposal. Another essential task is to prove the use of the CWA in suspected location or the exposure of humans to them (e.g. identification of products of their transformation).[1] The majority of these activities and tasks are defined and listed in The Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (OPCW).[2]

A class of chemicals of concern in monitoring CWAs are 2-(dialkylamino)ethyl chlorides (Me, Et, n-Pr, iso-Pr), related alcohols and thiols as well as the corresponding protonated salts, which are listed as Schedule 2B precursors in the Convention. This Schedule comprises precursors in one of the chemical reactions at the final stage of CWA formation or compounds with CWA capacity.[2] As a well-known example 2-(diisopropylamino)ethyl chloride can be mentioned. This substance is one of the compounds directly usable for the synthesis of VX compound (O-Ethyl S-[2-(diisopropylamino)ethyl]methylphosphonothioate).

Labelled compounds (mostly deuterated) are crucially important in the field of CWAs control, for several reasons. Firstly, the benefits of direct integration into the analytical procedure are appreciated and quite typically the use of labelled compounds in the methods based on mass spectrometry – labelled compounds serve as perfect internal standards[3] (i.e. confirmation of recovery of sample preparation,[4] correction of suppression/enhancement during the ionization process,[5] quantification using the isotopic dilution method[6] and so on). Secondly, labelled compounds facilitate the study on the CWA transformation processes and allow their products to be traced in the environment. Similarly, they allow the identification of metabolites arising in humans exposed to CWA or their precursors (either on potential terrorists or victims of a chemical attack). An obvious restriction in using labelled compounds is lack of availability for a specified substance or related metabolite.[7]

This communication is devoted to the development and improvement of synthetic methods for the synthesis of deuterated derivatives of 2-(dialkylamino)ethyl chlorides, 2-(dialkylamino)ethanols and 2-(dialkylamino)ethanethiols which can be used as standards for the monitoring of CWAs such as 2-(diisopropylamino)ethanethiol, 2-(diethylamino)ethanethiol and related chlorides.

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Results and discussion

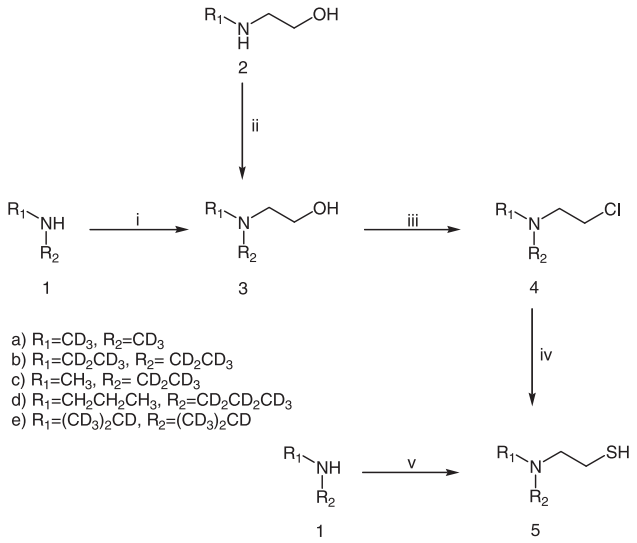
The synthesis of labelled derivatives of 2-(dimethylamino)ethanol[8–10] **3a** and 2-(diethylamino)ethanol[11] **3b** has already been reported. However, derivatives **3a** and **3b** have been prepared by a different method, moreover, the derivative **3b** has been only insufficiently characterized. For the preparation of *N,N*-disubstituted symmetrical labelled aminoethanols **3a** and **3b** we used alkylation of secondary amines **1a** and **1b** with 2-chloroethanol. Starting materials were mixed in a ratio of 1:1.2 (secondary amine vs 2-chloroethanol) and allowed to react for 18 h at elevated temperature.

In the case of the unsymmetrically labelled 2-(dialkylamino)-ethanols **3c** and **3d**, alkylation of 2-(alkylamino)ethanols **2** with the appropriate alkyl halide was the method of choice. For these alkylations we found conditions avoiding formation of undesirable quarternary salts. Bromoethane was used for the preparation of 2-(dialkylamino)ethanol **3c** instead of iodoethane and the optimal molar ratio of 2-(alkylamino)ethanol **2** and alkyl halide was adjusted to between 1:1.1 and 1:1.2. The reaction was carried out in an aprotic solvent (benzene, toluene).

Labelled 2-(dialkylamino)ethanols **3a–d** were converted into corresponding chlorides **4a–d** using thionylchloride in chloroform. Reactants were mixed at −10°C, the reaction mixture was allowed to reach ambient temperature and finally refluxed for 2.5 h. Yields were within the range of 67–76%. Using this procedure we have also increased the yield of chloride **3a** from the previously described 42[10] to 76%.

With regard to yields, two strategies were used for the preparation of 2-(dialkylamino)ethanethiols **5a–e**. Symmetrically labelled 2-(dialkylamino)ethanethiol derivatives **5a** and **5b** were furnished by the treatment of totally deuterated secondary amine **1** with ethylene sulfide. This method[12,13] was improved to avoid generation of polymers by using a 10% excess of secondary amine **1**. Yields ranged between 55 and 56%.

Other 2-(dialkylamino)ethanethiols **5c–e** have been prepared according to the protocol utilizing reaction of thiourea and appropriate 2-(dialkylamino)ethyl chloride **4c–e** resulting in the formation of isothiouronium salts which have not been isolated but *in situ* converted to corresponding 2-(dialkylamino)ethanethiols **5c–e** using alkaline hydrolysis with sodium hydroxide. Aminoethanethiol **5e** has been prepared from already reported compounds[14,15]; hence the starting compounds **3e** and **4e** are not characterized in the experimental part (Scheme 1, (i) 2-chloroethanol; (ii) RX; (iii) $SOCl_2$; (iv) thiourea, isothiouronium salt alkalized with NaOH; and (v) ethylene sulfide).



Scheme 1

Experimental

Melting points were determined on a Boetius stage and are uncorrected. The IR spectra were recorded in KBr wafers on an ATI Unicam Genesis FTIR instrument. The NMR spectra were recorded on a Bruker Avance 300 MHz DRX spectrometer; chemical shifts are reported in ppm, the coupling constants *J* in Hz. Elemental analyses were performed with an EA 1108 Elemental Analyser (Fison Instruments). Mass spectrometric experiments were performed using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA). All prepared compounds are characterized as hydrochlorides.

2-(Dimethyl-d_6-amino)ethanol hydrochloride (**3a**): To a stirred cooled solution (5°C) of dimethylamine hydrochloride **1a** (5.0 g, 57.0 mmol) in water (8 ml) was added NaOH (2.28 g, 57.0 mmol). After 2 min, 2-chloroethanol (5.5 g, 68.3 mmol) was added and the reaction mixture was allowed to reach ambient temperature in a sealed vial. Subsequently, the temperature was increased to 90°C and kept constant for 18 h. After cooling, the reaction mixture was extracted with ether (2 × 4 ml) and then made alkaline with NaOH (2.3 g). 2-(Dimethylamino)ethanol **3a** was extracted with ether (5 × 5 ml) from the alkaline water layer, combined ether extracts were dried over $MgSO_4$, and the ether was removed under reduced pressure. An oily residue was dissolved in ethanol and acidified with concentrated (35%) HCl (1 ml) to convert free amine **3a** to hydrochloride and then volatiles were removed under reduced pressure. The residue was dried over KOH under reduced pressure to constant weight to give **3a** (1.03 g, 14%) as a white solid. The sample for analysis was recrystallized from a mixture of ethanol and ether: m.p. 94–98°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 3.12 (t, J = 5.4 Hz, 2H), 3.72 (t, J = 5.4 Hz, 2H), 5.41 (brs, 1H (OH)), 10.43 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 41.5 (brs), 55.2, 58.1. IR (KBr): 3400, 2953, 2699, 1633, 1386, 1086 cm^{-1}. MS-ESI (*m/z*): 96.2 [M+H$^+$]. Calculated for $C_4H_6D_6ClNO$ (131.6): C, 36.50; H, 13.77; N, 10.64. Found: C, 36.23; H, 14.02; N, 10.33.

2-(Diethyl-d_{10}-amino)ethanol hydrochloride (**3b**): Diethylamine **1b** (1.0 g, 12.0 mmol) and 2–chloroethanol (1.16 g, 14.4 mmol) were mixed together in a sealed vial. The temperature of the reaction mixture was raised to 90°C and kept constant for 18 h. Then the reaction mixture was cooled, diluted with water (2.5 ml) and worked up analogously as the derivative **3a**, yielded a white solid (1.1 g, 56%). The sample for analysis was recrystallized from a mixture of ethanol and ether: m.p. 132–135°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 3.10–3.13 (m, 2H), 3.75 (t, J = 5.1 Hz, 2H), 5.41 (brs, 1H (OH)), 10.37 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 7.9 (brs), 46.4 (brs), 53.4, 55.8. IR (KBr): 3400, 2957, 2695, 1635, 1443, 1091. MS-ESI (*m/z*): 128.2 [M+H$^+$]. Calculated for $C_6H_6D_{10}ClNO$ (163.7): C, 44.02; H, 16.00; N, 8.56. Found: C, 43.85; H, 16.35; N, 8.46.

2-[Ethyl-d_5-(methyl)amino]ethanol hydrochloride (**3c**): Bromoethane-d_5 (5.0 g, 43.9 mmol) was added over 3 min into a cooled stirred solution of 2-(methylamino)ethanol **2c** (2.7 g, 36.0 mmol) in benzene (4 ml). The reaction mixture was then stirred at

ambient temperature for 1 h. After that, the temperature was increased to 60°C and kept for 10 h. The benzene layer was removed from the cooled reaction mixture and the rest was dissolved in water (3.5 ml). This solution was extracted with ether (3 × 3 ml) to remove the remaining starting material then alkalized with NaOH (1.8 g); the separated free amine was extracted with ether (3 × 3 ml). The combined ether extracts were dried over $MgSO_4$ and ether was removed under reduced pressure. The oily residue was dissolved in ethanol (4 ml), acidified with concentrated (35%) HCl to convert the free amine **3c** to hydrochloride and then volatiles were removed under reduced pressure. The solid remaining was dried over KOH under reduced pressure to constant weight to give **3c** (2.05 g, 39%) as a white solid. The sample for analysis was recrystallized from a mixture of ethanol and ether: m.p. 100–102°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.71 (s, 3H), 3.10–3.15 (m, 2H), 3.75 (t, J = 5.6 Hz, 2H), 5.40 (brs, 1H (OH)), 10.43 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 8.3 (brs), 39.5, 50.1 (brs), 55.7, 56.6. IR (KBr): 3400, 2961, 2707, 1629, 1466, 1071 cm^{-1}. MS-ESI (*m/z*): 109.2 [M+H$^+$]. Calculated for $C_5H_9D_5ClNO$ (144.7): C, 41.52; H, 13.23; N, 9.68. Found: C, 41.32; H, 13.44; N, 9.61.

2-(Dipropyl-d_7-amino)ethanol hydrochloride (**3d**): A solution of 2–(propylamino)ethanol **2d** (1.05 g, 10.12 mmol) and iodopropane-d_7 (2.0 g, 11.3 mmol) in benzene (2 ml) was stirred at 70°C for 16 h. A reaction mixture was worked up analogously as the derivative **3c**, yielded a white solid (1.44 g, 75%). The sample for analysis was recrystallized from a mixture of ethanol and ether: m.p. 85–87°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 0.89 (t, J = 7.5 Hz, 3H), 1.67 (hx, J = 7.5 Hz, 2H), 2.95–3.06 (m, 2H), 3.10–3.12 (m, 2H), 3.75 (t, J = 7.0 Hz, 2H), 5.36 (brs, 1H (OH)), 10.30 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 10.4 (brs), 11.3, 15.7 (brs), 16.8, 53.6 (brs), 54.4, 54.6, 55.8. IR (KBr): 3400, 2965, 2657, 1637, 1474, 1060 cm^{-1}. MS-ESI (*m/z*): 153.3 [M+H$^+$]. Calculated for $C_8H_{13}D_7ClNO$ (188.7): C, 50.91; H, 14.41; N, 7.42. Found: C, 50.69; H, 14.68; N, 7.37.

General synthesis of 2-(dialkylamino)ethyl chlorides hydrochlorides (**4**): To a cooled solution (−10°C) of an appropriate 2-(dialkylamino)ethanol **3** (5.0 mmol) in chloroform (8 ml) was added dropwise a solution of thionylchloride (7.0 mmol) in chloroform (2 ml). The reaction mixture was then allowed to reach ambient temperature, refluxed for 2.5 h and cooled. Methanol (5 ml) was added into the stirred reaction mixture and after 15 min volatiles were removed under reduced pressure. After recrystalization from a mixture of acetone and diethylether the product was dried at 60°C for 1.5 h *in vacuo* to furnish a white crystalline compound.

2-(Dimethyl-d_6-amino)ethyl chloride hydrochloride (**4a**): Prepared from the alcohol **3a** (0.63 g, 4.8 mmol), yielded (0.55 g, 76%): m.p. 197–206°C (ref.[11] 184–204°C). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.92 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 10.71 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 37.4, 41.2 (brs), 56.3. IR (KBr): 2973, 2904, 2860, 2673, 1446, 1123, 778, 735 cm^{-1}. MS-ESI (*m/z*): 114.1 [M+H$^+$]. Calculated for $C_4H_5D_6Cl_2N$ (150,1): C, 32.01; H, 11.41; N, 9.33. Found: C, 31.96; H, 11.30; N, 9.41.

2-(Diethyl-d_{10}-amino)ethyl chloride hydrochloride (**4b**): Prepared from the alcohol **3b** (0.8 g, 4.9 mmol), yielded (0.61 g, 68%): m.p. 206–212°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 3.36–3.45 (m, 2H), 4.05 (t, J = 7.2 Hz, 2H), 11.18 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 7.8 (brs), 37.8, 46.0 (brs), 51.9. IR (KBr): 2964, 2920, 2908, 2707, 2644, 1437, 1183, 1040 cm^{-1}. MS-ESI (*m/z*): 146.1 [M+H$^+$]. Calculated for $C_6H_5D_{10}Cl_2N$ (182.2): C, 39.56; H, 13.82; N, 7.69. Found: C, 39.71; H, 13.94; N, 7.53.

2-[Ethyl-d_5-(methyl)amino]ethyl chloride hydrochloride (**4c**): Prepared from the alcohol **3c** (1.5 g, 10.4 mmol), yielded (1.13 g, 67%): m.p. 174–178°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.73 (s, 3H), 3.43–3.50 (m, 2H), 4.04 (t, J = 7.0 Hz, 2H), 11.22 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 7.9 (brs), 37.8, 39.0, 49.9 (brs), 55.1. IR (KBr): 2965, 2937, 2757, 2741, 2671, 1461, 1071, 933 cm^{-1}. MS-ESI (*m/z*): 127.1 [M+H$^+$]. Calculated for $C_5H_8D_5Cl_2N$ (163.1): C, 36.82; H, 11.12; N, 8.59. Found: C, 36.65; H, 11.30; N, 8.68.

2-(Dipropyl-d_7-amino)ethyl chloride hydrochloride (**4d**): Prepared from the alcohol **3d** (1.1 g, 5.8 mmol), yielded (0.86 g, 71%): m.p. 116–119°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 0.90 (t, J = 7.5 Hz, 3H), 1.7 (hx, J = 7.5 Hz, 2H), 2.96–3.07 (m, 2H), 3.37–3.45 (m, 2H), 4.07 (t, J = 7.0 Hz, 2H), 11.17 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 10.1 (brs), 11.3, 15.3 (brs), 16.7, 37.8, 52.8 (brs), 53.0, 53.9. IR (KBr): 2947, 2924, 2757, 2670, 2594, 1460, 1435, 1373, 1075 cm^{-1}. MS-ESI (*m/z*): 171.1 [M+H$^+$]. Calculated for $C_8H_{12}D_7Cl_2N$ (207.2): C, 46.38; H, 12.64; N, 6.76. Found: C, 46.33; H, 12.54; N, 6.60.

2-(Dimethyl-d_6-amino)ethanethiol hydrochloride (**5a**): To a chilled solution (−5°C) of dimethylamine **1a** (1.0 g, 19.6 mmol) in anhydrous benzene (1.5 ml) was added ethylene sulfide (1.07 g, 17.8 mmol). The solution, placed in a sealed vial, was allowed to reach ambient temperature and then heated at 55°C for 12 h. Subsequently, the benzene was distilled off under atmospheric pressure and a distillation fraction between 150 and 160°C (temperature of an oil bath) was collected, dissolved in ether (20 ml) and converted with ethanolic HCl to hydrochloride. The precipitate (1.7 g) was recrystallized from a mixture of anhydrous ethanol and diethylether to furnish a white solid (1.48 g, 56%): m.p. 157–159°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.83 (t, J = 8.4 Hz, 2H), 3.10 (brs, 1H), 3.14–3.22 (m, 2H), 11.07 (brs, 1H, (NH)). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 17.8, 40.9 (brs), 58.5. IR (KBr): 2913, 2631, 1432, 1058 cm^{-1}. MS-ESI (*m/z*): 112.1 [M+H$^+$]. Calculated for $C_4H_6D_6ClNS$ (147.7): C, 32.53; H, 12.28; N, 9.48; S, 21.71. Found: C, 32.71; H, 12.14; N, 9.46; S, 21.91.

2-(Diethyl-d_{10}-amino)ethanethiol hydrochloride (**5b**): To a chilled solution (0°C) of diethylamine **1b** (1.0 g, 12.0 mmol) in anhydrous benzene (2 ml) was added ethylene sulfide (0.61 g, 10.9 mmol). The solution, placed in a sealed vial, was allowed to reach an ambient temperature and then heated at 100°C for 18 h. Subsequently, the benzene was distilled off at atmospheric pressure and the remaining thiol was distilled under reduced pressure (75°C oil bath, 20 mmHg) and worked up analogously as the derivative **5a**, yielded a white solid (1.01 g, 55%): m.p. 174–176°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.79–2.91 (m, 2H), 3.11–3.31 (m, 3H), 10.95 (brs, 1H, (NH)). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 7.3 (brs), 17.6, 45.2 (brs), 53.1. IR (KBr): 2915, 2684, 2468, 1436, 1037 cm^{-1}. MS-ESI (*m/z*): 144.2 [M+H$^+$]. Calculated for $C_6H_6D_{10}ClNS$ (179.8): C, 40.09; H, 14.57; N, 7.79; S, 17.84. Found: C, 40.29; H, 14.48; N, 7.95; S, 17.98.

General synthesis of 2-(dialkylamino)ethanethiol hydrochlorides (**5c–5e**): A stirred solution of 2-(dialkylamino)ethyl chloride hydrochlorides **4c–4e** (7.94 mmol) and thiourea (0.604 g, 7.94 mmol) in water (2.6 ml) was heated at 95°C for 7 h. Then a solution of NaOH (0.635 g, 15.88 mmol) in water (3 ml) was added to the cooled reaction mixture under continuous stirring. After 10 min the thiol was separated and extracted with diethylether (3 × 2 ml). The combined diethylether extracts were dried over $MgSO_4$; solvent was removed and the oily residue was distilled. The thiol was dissolved in diethylether (30 ml), converted with ethanolic HCl to hydrochloride and recrystallized

from a mixture of anhydrous ethanol and diethylether to furnish a white solid.

2-[Ethyl-d_5-(methylamino)]ethanethiol hydrochloride (**5c**): Prepared from the chloride **4c** (1.10 g, 6.74 mmol), yielded (0.13 g, 12%): m.p. 121–126°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.68 (s, 3H), 2.78–2.92 (m, 2H), 2.95–3.20 (m, 3H), (brs, 1H, (NH)). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 8.6 (brs), 17.6, 38.3, 49.8 (brs), 56.6. IR (KBr): 2941, 2684, 2662, 2478, 1479, 1022 cm^{-1}. MS-ESI (*m/z*): 125.1 [M+H$^+$]. Calculated for $C_5H_9D_5ClNS$ (160.7): C, 37.37; H, 11.91; N, 8.71; S, 19.95. Found: C, 37.24; H, 12.11; N, 8.85; S, 19.61.

2-(Dipropyl-d_7-amino)ethanethiol hydrochloride (**5d**): Prepared from the chloride **4d** (2.06 g, 9.9 mmol), yielded (0.52 g, 25%): m.p. 102–103°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 0.89 (t, $J = 7.2$ Hz, 3H), 1.69 (hx, $J = 7.2$ Hz, 2H), 2.86 (brs, 2H), 2.97 (t, $J = 7.2$ Hz, 2H), 3.10–3.25 (m, 3H), 10.95 (brs, 1H, (NH)). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 9.7 (brs), 10.8, 14.9 (brs), 16.3, 17.5, 52.4 (brs), 53.2, 54.3. IR (KBr): 2938, 2623, 2460, 1432, 1060 cm^{-1}. MS-ESI (*m/z*): 169.1 [M+H$^+$]. Calculated for $C_8H_{13}D_7ClNS$ (204.8): C, 46.91; H, 13.28; N, 6.84; S, 15.66. Found: C, 47.01; H, 13.17; N, 6.71; S, 15.51.

2-(Diisopropyl-d_{14}-amino)ethanethiol hydrochloride (**5e**): Prepared from the chloride **4d** (1.70 g, 7.94 mmol), yielded (0.88 g, 53%) m.p. 127–128°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.79–2.93 (m, 2H), 3.11–3.23 (m, 2H), 3.30 (brs, 1H), 10.95 (brs, 1H, (NH)). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 16.0 (brs), 20.6, 49.4, 53.1 (brs). IR (KBr): 2919, 2707, 2608, 2434, 1432, 1016 cm^{-1}. MS-ESI (*m/z*): 176.3 [M+H$^+$]. Calculated for $C_8H_6D_{14}ClNS$ (211.9): C, 45.35; H, 16.16; N, 6.61; S, 15.14. Found: C, 45.47; H, 16.07; N, 6.82; S, 15.23.

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