

Preparation of 1,3,4-Thiadiazole and its [2-D], [2,5-D₂], [2-¹³C], and [3-¹⁵N] Isotopic Species

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The compounds mentioned in the title were prepared to provide the necessary material for infrared, Raman, and microwave investigations carried out in this laboratory.¹ High purity of the preparations was desired and, where ever possible, sufficient quantities to permit Raman studies.

1,3,4-Thiadiazole (I) was prepared by a modified Goerdeler procedure.² 20.6 g (125 mmole) 2-Br-1,3,4-thiadiazole was dissolved in 45 ml water and placed with 32.7 g zinc-dust (500 mmole) in a reaction vessel with mechanical stirrer. After cooling to 0°C an aqueous solution of acetic acid (from 12.8 g (CH₃CO)₂O and 85 ml water) was added dropwise over a period of 15 min, the temperature being kept between 0°C and 5°C. Titration of the bromide ion showed the reaction to be complete. After filtering and washing (20 ml water) the aqueous solution was extracted continuously for 5 h by 250 ml ether. An unidentified precipitate was filtered off, the ethereal solution neutralized by 50 g Na₂CO₃, filtered, dried (MgSO₄), and evaporated to dryness *in vacuo* at -60°C. The residue, heated to room temperature, was only partially crystalline. The crystals were isolated by suction, the mother-liquor cooled (-10°C) and a second crop of crystals obtained. Both samples were dried in an evacuated desiccator over KOH. Yield 3.2 g (38 mmole). M.p. of both samples 41-42°C, after one sublimation *in vacuo* 42-43°C, the same as in literature.² However, in the infrared spectrum of both samples, recorded by us, the line at 1040 cm⁻¹, recorded by Goerdeler,² was missing. The proton magnetic resonance (PMR) spectrum of our preparations showed one line at 9.38 ppm, relative to tetramethylsilane (TMS) in chloroform solution (conc: 12 %). Combustion

analysis: 27.4 % C (calc. 27.9), and 2.3 % H (calc. 2.35).

1,3,4-[2-D]-thiadiazole (II). 30 g (182 mmole) 2-Br-1,3,4-thiadiazole was dissolved in 45 ml D₂O with 50 g zinc-dust added. External conditions as above. 20 ml (CH₃CO)₂O (200 mmole) was reacted with 45 ml D₂O to a solution of CH₃COOD in D₂O. This solution was added dropwise to the reaction mixture as indicated for (I), but this time under careful exclusion of atmospheric moisture. Continuous extraction by 150 ml ether for 5 h *etc.* produced 2.6 g crystals. Repeated extraction by ether for 9 h produced 1.7 g crystals. The two crystalline yields were identical as seen from their infrared spectra. Their m.p., 41.5-42.5°C, showed their high purity. Their *isotopic* purity was estimated by means of recorded infrared and PMR spectra. They contained ca. 10 % [2,5-D₂]-, 75 % [2-D]-, and 15 % (I). The total yield 4.3 g (49 mmole), is about as high as for (I). 37 ml D₂O was recovered. Its isotopic purity was close to 99 %.

1,3,4-[2,5-D₂]-thiadiazole (III). 30 g (123 mmole) of 2,5-dibromo-1,3,4-thiadiazole (preparation, *vide infra*) was powdered and added to 125 g zinc-dust, dispersed in 75 ml D₂O, under the same external conditions as above. 30 ml (CH₃CO)₂O (300 mmole) was reacted with 50 ml D₂O to a solution of CH₃COOD in D₂O which was added dropwise to the reaction mixture. Proceeding as indicated for (I) and (II), two crystalline crops weighing 1.6 and 0.3 g, respectively, were obtained. The two fractions were identical (infrared spectra) with high m.p. (41-42°C). Their isotopic purity was estimated as above. They contained 65 % (III), 25 % (II), and 10 % (I). 85 ml 99 % D₂O was recovered. Obviously, the undesirable exchange occurs during or after the ether extraction. The sample was of sufficient purity for microwave investigation, but not quite satisfactory for infrared and Raman work. The preparation of (III) of higher isotopic purity is planned.

1,3,4-[2-¹³C]-thiadiazole (IV). 9.87 g (50 mmole) ¹³C-enriched (52 %) BaCO₃ (= Ba*CO₃) and conc. H₂SO₄ produced 49 mmole *CO₂, which was absorbed in a solution of 3 g NaOH in 50 ml water. Dilute HCl was added until pH = 8.25. The aqueous solution of NaH*CO₃ was hydrogenated at *p* ~ 200 atm, *t* = 140°C (catalyst: palladium oxide). After 2 days the pressure was released, the solution acidified and excess *CO₂ was removed by a stream of N₂. pH was adjusted to 9.3 and water evaporated completely *in vacuo*, the final external temperature being 120°C. The residue, a mixture of H*COONa and NaCl, was brought into contact with 60 mmole dry,

gaseous HCl which liberated H^*COOH . Excess HCl was removed by distillation *in vacuo* at -80°C . H^*COOH was collected *in vacuo* at room temperature. Yield 1.60 g (35 mmole). The purity of the product was satisfactorily demonstrated by recording the PMR spectrum, showing the characteristic splitting of the 'aldehydic' proton resonance (at 8.33 ppm in HCOOH) into two components at 6.66 and 10.0 ppm, respectively, in H^*COOH , relative to TMS (external). The whole quantity of H^*COOH was reacted with 2.03 g (22.4 mmole) thiosemicarbazide for 2 h at 85°C . The crystals formed were thoroughly crushed, washed with 10 ml water, filtered, and dried over CaCl_2 in a desiccator. Yield 2.17 g (18.5 mmole) [^{13}C -formyl]-thiosemicarbazide, m.p. $175-178^\circ\text{C}$.² The infrared spectrum showed no non-isotopic impurities. The whole of the semicarbazide quantity was converted³ to 2-amino-1,3,4-[^{13}C]-thiadiazole (V). Yield 1.40 g (14 mmole) of correct m.p. ($190-192^\circ\text{C}$) and a satisfactory infrared spectrum. The whole quantity of (V) was dissolved in 28 ml 40% aqueous HBr and cooled to -10°C . 3 ml Br_2 (54 mmole) was added to the slurry, producing the new compound 2-amino-5-bromo-1,3,4-thiadiazole which was immediately diazotized *in situ* by dropwise addition of a solution of 2.55 g NaNO_2 (37 mmole) in 6 ml water, maintaining the temp. below -10°C . After 30 min at 0°C and 90 min at room temp. the reaction mixture was made alkaline by slowly adding 50 ml 30% NaOH, controlling that $t < 15^\circ\text{C}$. After continuous ether extraction for 30 min, drying (Na_2SO_4), and evaporation of ether *in vacuo*, 2.3 g (9.5 mmole) of a product, mainly consisting of 2,5-dibromo-1,3,4-[^{13}C]-thiadiazole (VI) was obtained. The observed m.p., $80-96^\circ\text{C}$, was lower than in the literature³ (111°C), but the infrared spectrum indicated a 90-95% purity, allowing the use of (VI) for the next preparation without further purification. The 30 g portion of 2,5-dibromo-1,3,4-thiadiazole (m.p. $108-110^\circ\text{C}$) used for the preparation of (III) was prepared from 2-amino-1,3,4-thiadiazole as indicated above.

The whole quantity of (VI) was dissolved in 30 ml methanol. 4 ml $(\text{C}_2\text{H}_5)_3\text{N}$ and 150 mg PtO_2 catalyst was added. At the catalytic reduction, a slight excess hydrogen pressure was maintained until the theoretical quantity of hydrogen had reacted. After evaporation of methanol and excess $(\text{C}_2\text{H}_5)_3\text{N}$ *in vacuo*, the residue was extracted by ether, the ethereal solution dried (Na_2SO_4), filtered, and the ether evaporated *in vacuo*. Final purification by sublimation *in vacuo*. Yield 440 mg (5.1 mmole)

(IV). As judged by the infrared absorption, no non-isotopic impurities were present. A following microwave investigation confirmed that the sample consists of about equal parts of (IV) and (I).

1,3,4-[^{15}N]-thiadiazole (VII). At reduced pressure (430 mm Hg), a solution of 20 g NaOH in 20 ml water was dropwise added to 20 g (250 mmole) of ^{15}N -enriched (30%) NH_4NO_3 ($=^*\text{NH}_4\text{NO}_3$), dissolved in 20 ml water. Evolution of $^*\text{NH}_3$ started at room temperature and was brought to completion by gradually raising the temperature to 100°C . $^*\text{NH}_3$ passed a column of KOH before condensing in a trap (-190°C). After pumping at -190°C for removal of atmospheric gasses, $^*\text{NH}_3$ was absorbed in 21 ml water. A ca. 20% aqueous solution of $^*\text{NH}_3$ was obtained (VIII). A solution of 1.13 g (10 mmole) hydroxylamine-O-sulphonic acid³ in 30 ml water was added to (VIII), half of the ammonia water was distilled off (into 6 N HCl to collect $^*\text{NH}_3$), and the residue was acidified by 2 ml conc. H_2SO_4 , producing 713 mg (5.5 mmole) of hydrazinium sulphate (IX). $^*\text{NH}_3$ in the filtrate was liberated as above and recovered as $^*\text{NH}_4\text{Cl}$. Total amount of recovered $^*\text{NH}_4\text{Cl}$: 12.7 g (237 mmole) which was used for a second synthesis of (IX), yielding 671 mg (IX). Recovered $^*\text{NH}_4\text{Cl}$: 12 g. The combined quantities of (IX), 1.38 g, were added to a solution prepared from 0.5 g Na in 10 ml abs. ethanol. After 3 days at room temperature (stirring), Na_2SO_4 was separated by filtering, and the filtrate (X) stored. Gaseous H_2S was bubbled to an ice-cooled solution of 2.45 g Na in abs. ethanol for 15 min. Hereafter, (X) and 3.5 ml CHCl_3 (42 mmole) was added. The reaction mixture was boiled for 24 h in a nitrogen atmosphere (bubbling), NaCl was filtered off, and ethanol removed *in vacuo* at a final external temperature of 45°C . The residue was dissolved in 10 ml water, acidified, and left for 10 min at room temperature. After neutralization, filtration, and continuous extraction for 5 h by boiling ether, the ether solution was dried (Na_2SO_4) and evaporated *in vacuo etc.* Yield of sublimed product 162 mg (1.9 mmole). As judged from its infrared spectrum this sample contained no non-isotopic impurities. A following microwave investigation confirmed that it consists of 30% (VII) 70% (I).

1. To be published.
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3. Sommer, F. *Z. anorg. Chem.* **147** (1925) 142.

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