Isothiocyanates and Their Synthetic Producers. XII. Preparation of 3,5-Disubstituted Tetrahydro-1,3,5-thiadiazine-2--thiones Labeled with ^{14}C and ^{35}S

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The preparation of 3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione-^{35}S by isotopic substitution with ^{35}S is described. Also the preparation of 3-(4--bromophenyl)-5-benzyltetrahydro-1,3,5-thiadiazine-2-thione-^{35}S from 4-bromophenyl isothiocyanate-^{35}S and of 3-benzyl-5-carboxymethyltetrahydro--1,3,5-thiadiazine-2-thione-^{14}C from glycine-^{14}C is described.

In the last few years the interest in substances from which biologically active isothiocyanate can be liberated has markedly increased. These compounds have been useful mainly owing to their antibacterial activity. An important group of substances possessing similar properties are derivatives of thiadiazine.

For their studies of organ distribution and detoxication *in vivo Martin* and *Venker* [1] prepared 3-benzyl-5-(β-hydroxyethyl)tetrahydro-1,3,5-thiadiazine-2-thione-^{35}S, where both the heterocyclic and the thione sulfur were radioactive, from benzylamine, carbon disulfide-^{35}S, formaldehyde and 2-ethanolamine. This method is, however, not suitable for the preparation of thiadiazines from amines bearing electron withdrawing substituents or from those liable to amino-imino tautomerism. Here we describe the synthesis of 3,5-disubstituted thiadiazines labeled with ^{35}S from isothiocyanates-^{35}S and, alternatively, by direct exchange of sulfur in thiadiazines with ^{35}S. The preparation of thiadiazines bearing ^{14}C-substituents in the 5-position of the heterocyclic ring is also described.

Experimental

Throughout all the experiments reagent grade solvents (Lachema, n.e.) were used. Crystalline elemental sulfur ^{35}S (5—1 mCi/mg) and glycine-2-^{14}C (0.07 mCi/mg) were obtained from Institute for Research, Production and Uses of Radioisotopes, Prague. 4-Bromophenyl isothiocyanate-^{35}S (0.23 mCi/mg) was prepared by direct exchange of sulfur in 4-bromophenyl isothiocyanate with elemental sulfur ^{35}S, as described earlie [2].

The purity of the components and the kinetics of the substitution were determined by thin-layer chromatography on Silica gel G precoated aluminum foils (Silufol, Lachema, n.e.) irrigated with benzene—chloroform 1 : 1. The components were located by spraying with a solution of silver nitrate (thiadiazine, dithiocarbamate, thiourea), silver nitrate—

—ammonium hydroxide (isothiocyanate), ninhydrine (thiadiazine, after decomposition into an amine with acetic acid). The radioactivity was determined on Frieske and Hoepfner FHT apparatus equipped with a methane flow-tube.

3,5-Dibenzyltetrahydro-1,3,5-thiadiazine-2-thione-^{35}S

Preliminary experiments were run in the following manner: Sealed test tubes containing an equimolar amount of 3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione and crystalline sulfur ^{35}S in xylene (0.025 M) were heated in an oil bath for four hours. Periodically, the test tubes were withdrawn and the reaction mixture was chromatographed. Two parallel thin layers were run, one being checked radiometrically for the degree of substitution and the other for identification purposes. The degree of substitution (expressed in % of the overall radioactivity found in thiadiazine) was at 100, 115, 130, and 140°C 1.4, 3.4, 7.2, and 21.9%, respectively. With increasing temperature the thermal decomposition of thiadiazine and formation of ^{35}S-labeled decomposition products became more pronounced.

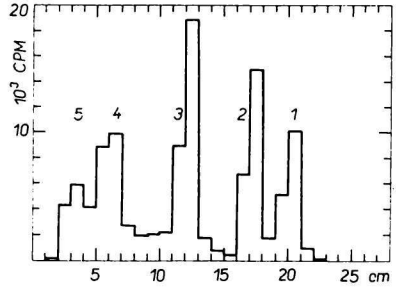

Fig. 1. Radiochromatogram of the reaction mixture after isotope exchange between 3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione and elemental sulfur ^{35}S.
1. elemental sulfur ^{35}S; *3.* thiadiazine; *2.*, *4.*, *5.* decomposition products.

Based on the foregoing data, for preparative purposes the following procedure was used: 126 mg (0.4 mmole) of 3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione and 6.4 mg (0.2 mgatom) of elemental sulfur in xylene (1.5 ml) was heated in a sealed test tube at 140°C. After 5 1/2 hours (for composition of the reaction mixture see Fig. 1) the reaction mixture was cooled, put on the top of a silica gel column (1 × 7 cm) and the elemental sulfur was eluted with *n*-hexane (until the test for radioactivity of the effluent was negative). Thiadiazine was eluted with chloroform and the solvent was evaporated *in vacuo*. The oily residue thus obtained crystallized upon seeding. The crystals were redissolved in methanol and the yellow solution was decolourized with charcoal. Water was added and upon cooling there was obtained chromatographically pure crystalline material. M.p. 101°C, yield 61 mg (48%), specific activity 0.0225 mCi/mg.

3-(4-Bromophenyl)-5-benzyltetrahydro-1,3,5-thiadiazine-2-thione-^{35}S

To a solution of 214 mg (0.001 mmole) of 4-bromophenyl isothiocyanate-^{35}S (0.19 mCi/mg) in methanol (6 ml) an equimolar amount of sodium hydrogen sulfide in water was added. The solution of sodium dithiocarbamate thus obtained was cooled and treated

with 0.001 M benzylamine sulfate in water, which produced the benzylammonium salt. The crystalline material was separated and suspended in chloroform, then 0.002 mole of formaldehyde in water was added and the reaction mixture was vigorously stirred for 30 minutes. After cooling the crystalline material was separated and recrystallized from ethanol—chloroform. Yield 197 mg (52%) of chromatographically pure thiadiazine, m.p. 172°C, specific activity 0.103 mCi/mg.

3-Benzyl-5-carboxymethyl-^{14}C-tetrahydro-1,3,5-thiadiazine-2-thione

A solution of sodium carbonate (2 ml, 0.1 M) was stirred with 107 mg (0.001 mmole) of benzylamine and 76 mg (0.001 mmole) of carbon disulfide was added. The temperature of the reaction mixture was kept at 35°C for 30 minutes and then formaldehyde in water (0.002 mmole) was added. An oil which separated was centrifuged off and the clear supernatant was treated with 76 mg (0.001 mmole) of glycine-^{14}C (0.7 mCi/mg) in water. The pH of the reaction mixture was adjusted to 3—4 by addition of 1 N hydrochloric acid, the white precipitate was separated, dried under diminished pressure and recrystallized from ethanol. Yield 162 mg (58%), m.p. 150°C (decomposition), specific activity 0.00237 mCi/mg.

Discussion

In the previous paper [3] the preparation of thiadiazines from isothiocyanates was described. Here this method was applied to prepare labeled 3-(4-bromophenyl)-5-benzyltetrahydro-1,3,5-thiadiazine-2-thione-^{35}S, using 4-bromophenyl isothiocyanate-^{35}S as the starting material. As the reaction of an isothiocyanate with sodium hydrogen sulfide produces as an intermediate *N*-monosubstituted dithiocarbamate where both sulfur atoms are equivalent, in the final thiadiazine both sulfur atoms are radioactive. The same result is obtained when a thiadiazine is synthesized from an amine and carbon disulfide-^{35}S [1].

To explore the possibility of preparation of thiadiazines labeled with ^{35}S by direct exchange of the sulfur atoms in thiadiazines with elemental sulfur ^{35}S we have studied the course of the substitution reaction at different temperatures. The exchange of sulfur in 3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione with ^{35}S, under the conditions described in the Experimental Section, took place only at temperatures exceeding 100°C. At such temperatures, however, the formation of decomposition by-products containing radioactive sulfur was observed. It has been known that sulfur in a heteroatomic ring cannot be directly exchanged by elemental sulfur ^{35}S. In the case of thiadiazines only the thione sulfur should have been replaced and thus the sulfur in the 2-position of the ring would remain, generally speaking, intact. As far as our experiments are concerned, however, the possibility of partial labeling of the heterocyclic sulfur with ^{35}S cannot be excluded. This labeling can take place by resynthesis of a thiadiazine molecule from degradation products, labeled with ^{35}S. This explanation is supported by previous observation [4] that in an *N*-monosubstituted dithiocarbamate the sulfur can be exchanged even at room temperature. The fact that under certain conditions the decomposition of thiadiazines proceeds through an *N*-monosubstituted dithiocarbamate, *i.e.* through a compound which actually is the intermediate in its synthesis, has previously been [5] substantiated.

When ^{35}S-labeled thiadiazines are to be made on a preparative scale it is necessary, in view of the different stability of differently *N*-substituted substances, that the

optimum reaction conditions for the direct exchange reaction should be determined for each group of compounds. This, together with the case with which thiadiazines may during the exchange reaction undergo decomposition, makes synthetic procedures more advantageous.

References

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