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SYNTHESIS OF N-(2-CHLOROPHENYLSULFONYL)-N'-(4-METHOXY-6-METHYL-1,3,5-TRIAZIN-2-YL)-UREA WITH A RADIOACTIVE LABEL

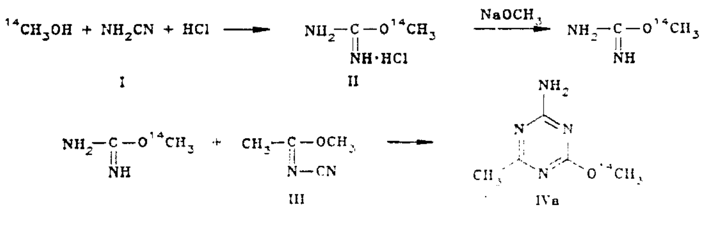
G. D. Sokolova and P. S. Khokhlov

UDC 547.491.8'495.2:07:632.954

Methods for the introduction of a radioactive ^{13}C label into N-(2-chlorophenylsulfonyl)-N'-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)urea, which has herbicidal activity, are described.

N-(2-Chlorophenylsulfonyl)-N'-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)urea (chlorosulfone, DPKh-4189, Glin) is one of the highly active herbicides that are of interest for agriculture [1, 2]. The aim of the present research was to synthesize the labeled (in various positions) herbicide that is necessary for the study of its behavior in environmental subjects.

The following reaction scheme was used to introduce a radioactive label into the methoxy group of the substituted aminotriazine [3, p. 84; 4]:



When equimolar amounts of methanol and cyanamide (I) are used in the first step of the synthesis, the yield of O-methylisourea hydrochloride (II) varies markedly, probably because

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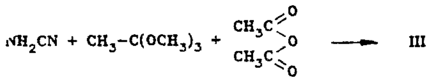
of the side reactions that take place under reaction conditions that are difficult to control when working with microquantities of the substances.

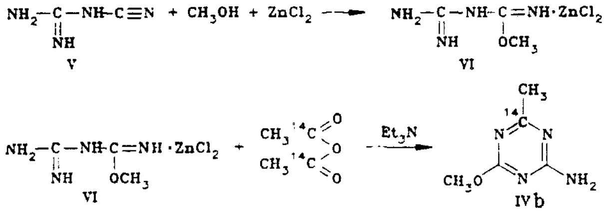
More stable results were obtained when a threefold excess of methanol was used. The excess radioactive methanol can be removed by distillation at the end of the reaction and used a second time.

The following reaction [4] was tested for the introduction of the label into the triazine ring:

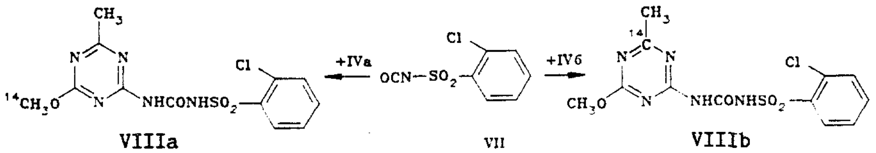


However, no more than 0.2% of the radioactivity of the acetic anhydride is transferred into the final product in this case.

The synthesis of triazine IV via the scheme in [5, 6] proved to be more successful:



The reaction of the synthesized labeled products IV with 2-chlorophenylsulfonyl isocyanate (VII) [7], prepared via the scheme in [8-10], made it possible to obtain herbicide VIII with a ^{14}C label in the methoxy group or in the triazine ring:



EXPERIMENTAL

The ^{14}C methanol and 1-^{14}C-acetic anhydride were obtained from the All-Union Association "Izotop" and were used without additional purification. Chromatography of the substances was carried out on Silufol UV-254 plates with subsequent radioscanning with a PP-8 radiometer with a T25BFL end-window counter. The radioactivities of the labeled compounds were measured with an SL-4000 scintillation spectrometer (France). The mass spectra were recorded with an LKB-2091 chromatographic mass spectrometer (Sweden) at an ionizing-electron energy of 20 eV using a system for direct introduction of the samples into the ion source at 60-140°C.

O—^{14}C-Methylisourea Hydrochloride (II). A 0.034-g (0.823 mmole) sample of cyanamide was dissolved in 0.1 ml (2.47 mmole) of ^{14}C-methanol with an overall radioactivity of 200 Mbq and gaseous hydrogen chloride was then passed through a capillary above the surface of the resulting solution, allowing no spraying to occur, until the increase in weight was 0.04 to 0.05 g. The reaction mixture was sealed with a stopper and allowed to stand for 16 h. The excess ^{14}C-methanol was then removed by distillation into a receiver cooled with a mixture of dry ice and acetone. In the residue we obtained 0.082 g [90% (based on cyanalmide)] of II with mp 122-124°C (mp 122-124°C [3]).

2-Amino-4-^{14}C-methoxy-6-methyl-1,3,5-triazine (IVa). A 0.082-g (7.41 mmole) sample of O-^{14}C-methylisourea hydrochloride was added to a solution of 7.41 mmole of sodium methoxide in 7.41 ml of methanol, the mixture was stirred for a few minutes, the precipitate was removed by filtration, and the filtrate was added to 0.083 g (7.41 mmole) of methyl N-cyanoacetimidate (III). The reaction mixture, in which a precipitate began to develop after a few minutes, was washed on the filter with 0.5 ml of methanol to give 0.062 g (59.7%) of product IVa with mp 255°C (dec.) (mp 257-259°C [4]) and R_f 0.2 [acetone—toluene (1:1)]. Mass spectrum: 140 (71) $[M]^+$, 126 (7) $[M - CH_2]^+$, 110 (67) $[M - OCH_2]^+$, 69 (100).

N-(2-Chlorophenylsulfonyl)-N'-(4-^{14}C-methoxy-6-methyl-1,3,5-triazin-2-yl)urea (VIIIa). A 0.062-g (0.443 mmole) sample of triazine IVa was suspended in 4.5 ml of methylene chloride, 0.096 g (0.443 mmole) of VII was added, and the mixture was allowed to stand for 16 h. The undissolved IVa was removed by filtration (it can be resubjected to reaction with isocyanate (VII)), and the filtrate was evaporated. The residue was triturated with ether to give 0.086 g (57%) of sulfonylurea VIIIa with mp 174-176°C (mp 174-178°C [2]) and R_f 0.5 [acetone—toluene (1:1)], 0.75 [benzene—acetone (1:1)], and 0.45 [ethyl acetate—benzene (1:1)]. In the mass spectrometer under electron impact the substance did not give a molecular ion. The radiochemical purity was 98%, and the specific radioactivity was 170 MBq. To increase the purity the substance was subjected to column chromatography: 0.013 g of VIIIa was dissolved in 2 ml of methylene chloride and applied to a column (30 by 1 cm) packed with 4 g of L 40/100μ silica gel (Czechoslovakia SSR) suspended in methylene chloride. Successive elution with 10 ml of methylene chloride and acetone—toluene (1:1) gave 0.01 g of VIIIa with a radiochemical purity of 99.5%.

Methyl N-Cyanoacetimidate (III). A 0.0174-g (0.414 mmole) sample of cyanamide, 0.052 ml (0.414 mmole) of trimethyl orthoacetate, and 0.08 ml (0.828 mmole) of 1-^{14}C-acetic anhydride with an overall radioactivity of 60 MBq were placed in a microapparatus for distillation, and the mixture was heated on a bath until methyl acetate began to be removed by distillation. Heating was then regulated in such a way that the reaction did not take place too violently but also did not stop, gradually raising the temperature to 135-150°C. The mixture was maintained at this temperature for ~1 h. The residual liquid was distilled at 85-90°C (18 mm) to give 0.0212 g (52%) of III. The substance was used for the synthesis of triazine IV and sulfonylurea VIII via the methods described above. This procedure gave 0.014 g of sulfonylurea VIII with a specific radioactivity of 0.23 MBq/g.

Complex (VI) of O-Alkyl-1-amidinourea with Zinc Chloride. A mixture of 8.5 g (0.101 mole) of dicyanodiamide and 16.3 g (0.1 mole) of $ZnCl_{12} \cdot 1.5H_2O$ in 25 ml of methanol was refluxed with stirring for 2 h, after which it was cooled, and the precipitate was removed by filtration and washed with 5 ml of methanol to give 17.77 g (70%) of complex VI with mp 230°C (dec.).

2-Amino-4-methoxy-6-methyl-1,3,5-triazine-6-^{14}C (IVb). A 0.059-ml (0.424 mmole) sample of triethylamine was added with stirring to a suspension of 0.0534 g (0.212 mmole) of complex VI in 0.85 ml of acetonitrile, and a solution of 0.02 ml (0.212 mmole) of 1-^{14}C-acetic anhydride with an overall radioactivity of 80 MBq in 0.43 ml of acetonitrile was added dropwise, after which the mixture was refluxed for 2 h. The precipitate was removed by filtration in the hot form and washed with 0.5 ml of hot acetonitrile to give 0.029 g (98%) of triazine IVb.

N-(2-Chlorophenylsulfonyl)-N'-(4-methoxy-6-methyl-1,3,5-triazin-2-yl-6-^{14}C)urea (VIIIb). This compound was obtained in 52% yield by a procedure similar to that used to obtain VIIIa. The specific radioactivity was 162.8 MBq/g, and the radiochemical purity was 80%.

2-Chlorobenzenesulfonyl Chloride (IX). A solution of 7.35 g (106 mmole) of sodium nitrite in 15 ml of water was added at 15-20°C to a suspension of 12.75 g (100 mmole) of 2-chloroaniline in 100 ml of 20% sulfuric acid, and the mixture was allowed to stand for 15 min. The resulting solution of the diazonium salt was added dropwise at 30-40°C to a suspension of 8.54 g (50 mmole) of cupric chloride dihydrate in a mixture of 120 ml of acetic acid saturated with sulfur dioxide, 20 ml of concentrated hydrochloric acid, and 80 ml of benzene, and the reaction mixture was allowed to stand until the evolution of nitrogen ceased. It was then poured into a threefold volume of water, and the organic layer was separated, washed successively with a 1-2% solution of sodium hydroxide and water, and dried over sodium sulfate. The benzene was removed by distillation, and the residue was distilled at 140-144°C (11 mm) to give 13.04 g (61.5%) of sulfonyl chloride IX [bp 144-146°C (12 mm) [8]]. Mass spectrum: 210 (27) $[M]^+$, 175 (81) $[M - Cl]^+$, 111 (100) $[M - SO_2Cl]^+$.

2-Chlorobenzenesulfonamide (X). A 13-g (615 mmole) sample of sulfonyl chloride IX was added to 14 ml of 25% ammonium hydroxide at a rate that ensured maintenance of the temperature at no higher than 30°C, after which the mixture was heated to 80°C and maintained at this temperature for 0.5-1 h. The precipitate was removed by filtration, washed successively with water and benzene, and dried in a vacuum desiccator over P_2O_5 to give 10.18 g (86.5%) of sulfonamide X with mp 184-186°C and R_f 0.6 [acetone—toluene (1:1)]. Mass spectrum: 191 (35) $[M]^+$, 175 (31) $[M - NH_2]^+$, 127 (35) $[M - SO_2]^+$, 111 (100) $[M - SO_2NH_2]^+$.

2-Chlorophenylsulfonyl Isocyanate (VII). A 4.11-g (214 mmole) sample of sulfonamide X was dissolved in 35 ml of chlorobenzene, and traces of water were removed by azeotropic distillation. The mixture was cooled to 100°C, 0.85 g (8.6 mmole) of n-butyl isocyanate was added, the mixture was heated to the boiling point, and 5 g (50 mmole) of phosgene was passed into it in the course of 1 h. The n-butyl isocyanate and solvent were then removed by distillation, and the product was distilled in vacuo to give 4 g (86%) of isocyanate VII with bp 160-164°C (14 mm). Mass spectrum: 217 (20) $[M]^+$, 175 (54) $[M - NCO]^+$, 111 (100) $[M - SO_2NCO]^+$.

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CONDENSATION OF ETHANOLAMINE WITH CHLORO-sym-TRIAZINES

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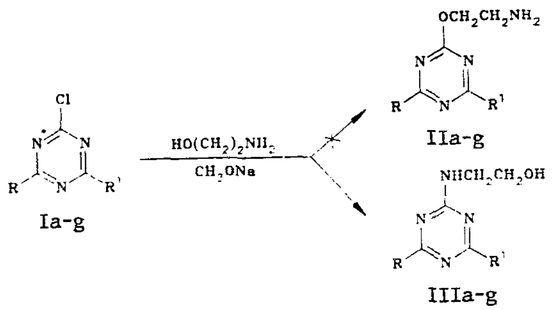
2,2-Aminoethoxy-sym-triazines have been synthesized by reduction of cyanomethoxy-sym-triazines or by the reaction of sodium 2-aminoethoxide with quaternary ammonium salts of sym-triazines. Their structures have been established by PMR and mass spectral examination.

There are conflicting literature reports concerning the structure of the products of reaction of chloro-sym-triazines I with ethanolamine. Thus, according to [1], the indicated reaction in ethanolamine medium in the presence of an equimolar amount of sodium methoxide leads to the 2-aminoethoxy derivatives (II).

By contrast, other authors [2, 3] consider that the compounds obtained are the 2-hydroxyethylamines III.



I—III a $R=OCH_3$, b $R=SCH_3$, c $R=N(CH_2)_2$, d, e $R=NHC_2H_5$, f $R=NHC_3H_7$-*iso*, g $R=N(C_2H_5)_2$; a—c $R^1=N(CH_3)_2$, d $R^1=NHC_2H_5$, e, f $R^1=NHC_3H_7$-*iso*, g $R^1=$ $=N(C_2H_5)_2$

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