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Synthesis of 1-Ethylsulphonylnaphthalene-4-(^{35}S)-sulphonamide, a murine bladder carcinogen

R. TURNER and H. G. DEAN
Departments of Experimental Pathology and Cancer Research, and Pharmacology, School of Medicine, Leeds LS2 9 NL,
England.
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SUMMARY

Diazotisation of 1-ethylsulphonyl-4-naphthylamine followed by treatment with sulphur dioxide-^{35}S in acetic acid and then cupric chloride gave 1-ethylsulphonylnaphthalene-4-(^{35}S)-sulphonyl chloride. This gave the title compound by reaction with aqueous ammonia. Total time required was three days.

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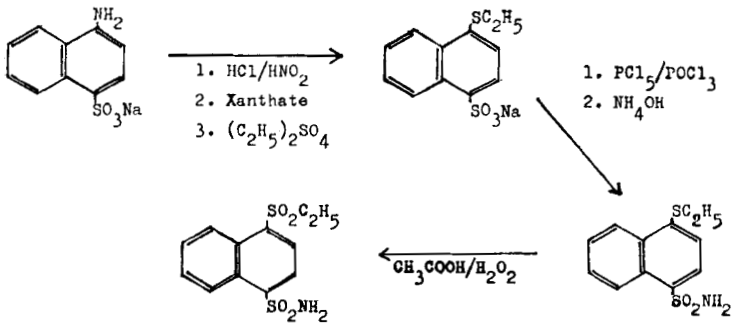
INTRODUCTION.

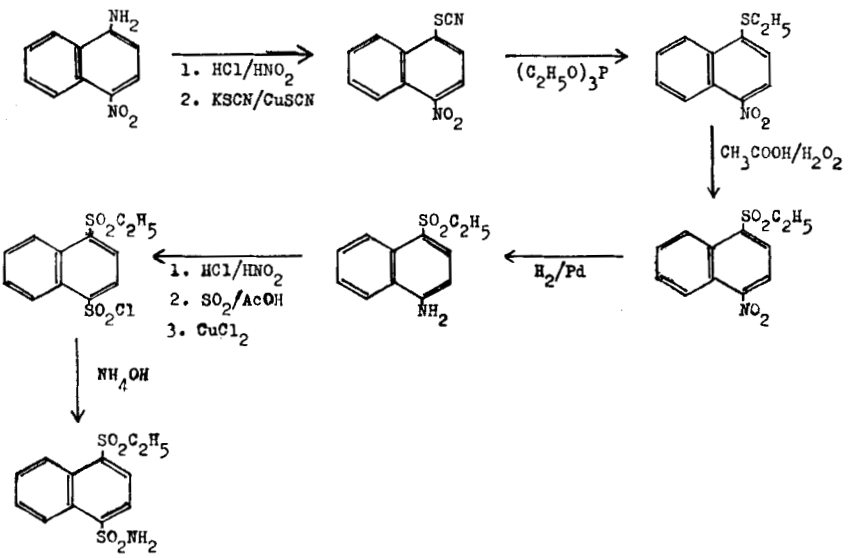
A single oral dose of 1-ethylsulphonylnaphthalene-4-sulphonamide induces a proliferative response, and repeated administration cancer, in the mouse bladder. Studies relating to its metabolism and mode of action being pursued in this department indicated a need for the title compound. The low chemical yields which were obtained following the original method of Brimelow and Vasey [1] (Scheme 1) for the preparation of 1-ethylsulphonylnaphthalene-4-sulphonamide made this method unsuitable for a small scale synthesis. Furthermore it would have necessitated the introduction of the label at an early stage giving correspondingly lower radiochemical yield. It therefore appeared preferable to introduce the sulphonamide group at as late a stage as possible.

With this in view the preparation of 1-ethylsulphonyl-4-naphthylamine was attempted (Scheme 2). Pilgram and Korte [2] had reported the preparation of 1-ethylsulphonyl-4-nitronaphthalene and reduction of this compound gave the required amine. An alternative route to this compound from 1-chloro-4-nitronaphthalene is as outlined in Scheme 3 [3]. Following the method of Meerwein *et al.* [4] 1-ethylsulphonyl-4-naphthylamine was diazotised, the diazonium salt allowed to react with sulphur dioxide-^{35}S to give 1-ethylsulphonyl-4-naphthalenesulphonyl(^{35}S) chloride, ammonolysis of which gave the desired labelled sulphonamide.

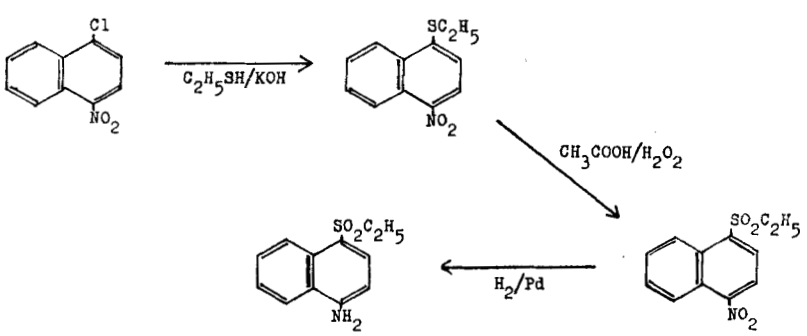
Scheme 1.



Scheme 2.



Scheme 3.



METHODS AND RESULTS.

Synthesis of 1-ethylsulphonyl-4-naphthylamine.

1-Ethylsulphonyl-4-nitronaphthalene (1.43 g) was suspended in ethanol (500 ml) and hydrogenated at 3 atmospheres pressure using 5 % palladium on charcoal (0.4 g) as catalyst. The catalyst was removed by filtration and the solution concentrated to a small volume. The crystals (75 %) obtained had m. pt. 154-156° C.

Analysis :

Calculated C 61.28 %, H 5.53 %, N 5.96 %. Found C 61.39 %, H 5.72 %, N 5.95 %.

Synthesis of 1-ethylsulphonylnaphthalene-4-(^{35}S)-sulphonamide.

1-Ethylsulphonyl-4-naphthylamine (0.118 g, 0.5 mM) was warmed with 10N hydrochloric acid (1.0 ml). This solution was cooled to 0-5° C diazotised with sodium nitrite solution (1.0 ml of 10 %) and allowed to stand for 0.5 hours. A break-seal ampoule containing 1.51 mmoles of sulphur dioxide (5.1 mCi.) was sealed on to the reaction vessel which was itself connected to a high vacuum manifold via a cold trap. Glacial acetic acid (0.3 ml) was put into the reaction vessel which was then sealed with a septum and cooled in liquid nitrogen. After whole apparatus had been evacuated to 10^{-5} mm and isolated, the ampoule was broken and the sulphur dioxide-^{35}S condensed into the acetic acid. Repeated cooling and warming of the reaction vessel ensured a uniform mixture of the sulphur dioxide-^{35}S and acetic acid. With the reaction vessel held at −78° C the system was filled with nitrogen and the diazonium salt solution added through the septum. This was followed immediately by addition of cupric chloride solution (0.2 ml of 50 % $CuCl_2$, $2H_2O$). The flask was cooled to −196° C, evacuated to about 30 mm and the system isolated. The reaction vessel was then allowed to warm to room temperature. After 18 hours the system was brought to atmospheric pressure with nitrogen, the excess sulphur dioxide-^{35}S being absorbed in $K_2Cr_2O_7$. The aqueous residue was separated from the solid residue adhering to the sides of the flask, with a pipette. The crude sulphonyl chloride which remained was dissolved in acetone (5 ml) and ammonia solution (17N 5 ml) and the mixture allowed to stand for 1 hour. The product was then separated by freeze drying at 10^{-3} mm dissolved in a small volume of acetone and purified by preparative layer chromatography on 1 mm silica gel (Silica Gel H. Merck) using toluene-ethyl acetate (4 : 1) as developing solvent. The 1-ethylsulphonylnaphthalene-4-(^{35}S)-sulphonamide band was located under U. V. light (pale blue fluorescence), scraped from the plate and eluted with acetone. Further purification was effected by thin layer chromatography on silica gel (as above) using benzene-ethanol (4 : 1). This

procedure gave 0.0978 g of 1-ethylsulphonylnaphthalene-4-(^{35}S)-sulphonamide m. p. 198° C (Literature [1], 198° C).

Chemical yield 65.4 % from amine.

Radiochemical yield 16.6 % from $^{35}SO_2$.

Specific activity as determined by scintillation counting was 2.57 mCi/mmole.

The ^{35}S-labelled material was identical with authentic unlabelled chemical in numerous paper chromatographic and T. L. C. systems.

The total time involved in the preparation using the radioactive compound was three days.

DISCUSSION.

In the method outlined above a two mole excess of sulphur dioxide was found to be essential. Sulphur dioxide-^{35}S is, however relatively cheap and the low radiochemical yield is more than compensated by the economics of the procedure when compared with the method of Brimelow and Vasey [1] in which the chemical yield based on xanthate was only 7.5 % on the semi-molar scale.

From the results obtained it appears that this procedure could be usefully applied to the synthesis of other ^{35}S-labelled aromatic sulphonyl chlorides and their derivatives.

ACKNOWLEDGEMENTS.

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