# NITRO- AND AMINO-IMIDAZOLESULPHONAMIDES[1]

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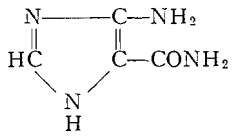
ABSTRACT

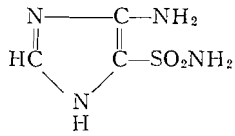
Several 4(5)-nitro- and 4(5)-amino-5(4)-sulphamylimidazoles have been synthesized as potential antagonists to 4(5)amino-5(4)-carbamylimidazole.

## INTRODUCTION

There has recently been considerable interest in the role of 4(5)-amino-5(4)-carbamylimidazole (I) and related compounds in the biosynthesis of purines (1, 2, 3, 4). However, the preparation of imidazole analogues as potential antagonists has not been widely investigated (5). In this work compounds related to 4(5)-amino-5(4)-sulphamylimidazole (II) were synthesized for biological testing.[2]



(I)

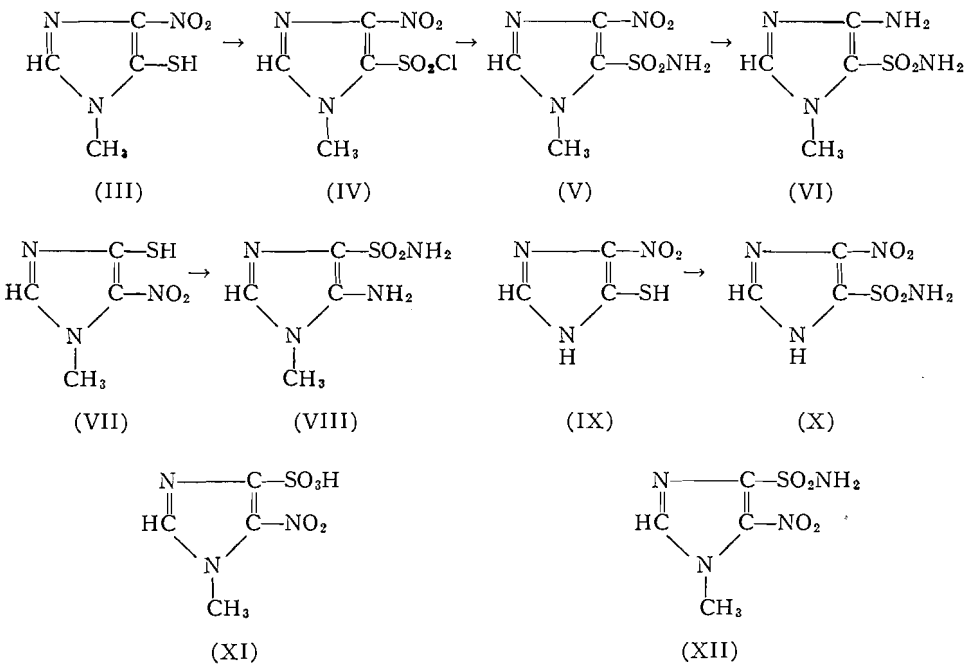


(II)

A number of unsuccessful attempts to prepare compounds of this type have been reported, e.g. chlorination of imidazole sulphonic acids, chlorosulphonation of nitro- or acylamino-imidazoles, amination of bromo-imidazoles, and conversion of imidazolethiols to sulphenamides followed by oxidation (5, 6, 7). 4(5)-Bromo-5(4)-sulphamylimidazole was prepared by chlorosulphonation of 4(5)-bromoimidazole (5), but it failed to react with ammonia.

The most attractive approach was the oxidative chlorination of the thiols, a general method described by Sprague and Johnson (8) and later used for the preparation of 2-sulphamylimidazoles (9, 10). 5-Mercapto-1-methyl-4-nitroimidazole (III) (5) was converted to the sulphonyl chloride (IV) by oxidative chlorination in dilute hydrochloric acid. The sulphonyl chloride with concentrated aqueous ammonia yielded 1-methyl-4-nitro-5-sulphamylimidazole (V). Catalytic reduction of this compound gave 4-amino-1-methyl-5-sulphamylimidazole (VI). In a similar manner 5-amino-1-methyl-4-sulphamylimidazole (VIII) was obtained from 1-methyl-4-mercapto-5-nitroimidazole (VII). 4(5)-Mercapto-5(4)-nitroimidazole (IX) (5) was converted to 4(5)-nitro-5(4)-sulphamylimidazole (X) but attempted catalytic reduction caused gross decomposition.

[1]*Manuscript received November 29, 1960.*
*Contribution from the Research Department, Merck and Co. Ltd., Montreal, Que.*
[2]*The compounds are being screened for anticancer activity at the Sloan-Kettering Institute for Cancer Research.*




The oxidative chlorination of the 4-thiol (VII) yielded variable products. The desired sulphonyl chloride was obtained when the reaction temperature was maintained below 40° and the rate of addition of chlorine carefully controlled. Too rapid addition of chlorine at 20° or above resulted in the formation of 1-methyl-5-nitroimidazole-4-sulphonic acid (XI). Best results were obtained when the chlorine was added rapidly at 0° until the bright yellow starting material became white. The preparation was further complicated because the sulphonamide (XII) was isolated in two forms melting at 149° and 159°. Catalytic reduction of either form yielded the same amine. The oxidative chlorination of the other thiols (III) and (IX) gave good yields of the sulphonyl chlorides at 20°–30° and 0° respectively.

There was a pronounced difference in stability between the amines. 4(5)-Amino-5(4)-sulphamylimidazole was so unstable that it was neither isolated as the base nor a salt. 4-Amino-1-methyl-5-sulphamylimidazole (VI) was an unstable base and formed a moderately stable hydrochloride. 5-Amino-1-methyl-4-sulphamylimidazole (VIII) was stable either as the base or as the hydrochloride.

## EXPERIMENTAL

*1-Methyl-4-mercapto-5-nitroimidazole (VII)*

4-Chloro-1-methyl-5-nitroimidazole (11) (10 g) was suspended in a warm solution of water (67 ml) and concentrated ammonia (33 ml). Hydrogen sulphide gas was passed into the stirred mixture until a clear, dark red solution was obtained (20 minutes). The ammonium salt of the product crystallized on standing (9 g), m.p. 139°–140°. Recrystallization by the addition of three volumes of isopropanol to a solution in a minimum volume of water yielded dark orange needles, m.p. 140°–141°. Found: C, 27.4; H, 4.5; N, 31.1; S, 18.3. Calc. for $C_4H_8N_4O_2S$: C, 27.3; H, 4.5; N, 31.8; S, 18.2%.

*4(5)-Nitro-5(4)-sulphamylimidazole (X)*

The ammonium salt of 4(5)-mercapto-5(4)-nitroimidazole (5) (1 g) was suspended in 1 *N* hydrochloric acid (10 ml) and cooled in an ice bath. Chlorine gas was passed into the stirred mixture until the suspended solids became buff colored (35 minutes). The sulphonyl chloride produced (m.p. 180°–183°) was collected, washed with a little ice water, and dissolved in concentrated ammonia (10 ml). After 15 minutes the excess of ammonia was evaporated *in vacuo* and the residual solution was acidified with hydrochloric acid. The sulphonamide, which precipitated, was collected and crystallized from water as jagged white needles (0.4 g), m.p. 261°–262°. Found: C, 18.8; H, 2.1; N, 29.3; S, 16.9. Calc. for $C_3H_4N_4O_4S$: C, 18.8; H, 2.1; N, 29.2; S, 16.7%.

*1-Methyl-5-nitro-4-sulphamylimidazole (XII)*

The ammonium salt of 4-mercapto-1-methyl-5-nitroimidazole (VII) (5.0 g) treated in a similar manner yielded the sulphonyl chloride (m.p. 104°), which was converted into the sulphonamide (3 g), m.p. 158°–159°. Found: C, 23.3; H, 2.9; N, 27.5; S, 15.7. Calc. for $C_4H_6N_4O_4S$: C, 23.3; H, 2.9; N, 27.2; S, 15.5%. The product was also isolated in another form, m.p. 149°–150°. Found: C, 23.4; H, 3.0; N, 26.6; S, 15.5%.

From a similar experiment in which the temperature was allowed to reach 50° there was isolated the ammonium salt of *1-methyl-5-nitroimidazole-4-sulphonic acid (XI)* m.p. 260°–265° (decomp.). Found: C, 21.4; H, 3.5; N, 25.0; S, 14.4. Calc. for $C_4H_8N_4O_5S$: C, 21.4; H, 3.6; N, 25.0; S, 14.3%. Acidification of a solution of the ammonium salt in water precipitated the acid m.p. 299°–300°. Found: C, 23.3; H, 2.4; N, 20.0; S, 15.5. Calc. for $C_4H_5N_3O_5S$: C, 23.2; H, 2.4; N, 20.3; S, 15.5%.

*1-Methl-4-nitro-5-sulphamylimidazole (V)*

The ammonium salt of 5-mercapto-1-methyl-4-nitroimidazole (5) (22 g) by similar oxidative chlorination at 20°–30° yielded the sulphonyl chloride (m.p. 106°–107°), which was converted into the sulphonamide (16.5 g), m.p. 176°–177°. Found: C, 23.4; H, 3.0; N, 27.0; S, 15.3. Calc. for $C_4H_6N_4O_4S$: C, 23.3; H, 2.9; N, 27.2; S, 15.5%. The acetyl derivative was prepared by refluxing the sulphonamide for 1 hour in an excess of acetic anhydride. Crystallization from water yielded white needles m.p. 219°–220° (decomp.). Found: C, 29.0; H, 3.3; N, 22.7. Calc. for $C_6H_8N_4O_5S$: C, 29.0; H, 3.2; N, 22.6%.

*4-Amino-1-methyl-5-sulphamylimidazole (VI)*

A suspension of 1-methyl-4-nitro-5-sulphamylimidazole (5 g) and Adams' platinum catalyst (0.1 g) in dry ethanol (250 ml) was hydrogenated at room temperature and atmospheric pressure. The theoretical volume of hydrogen was absorbed in 1 hour and a white solid was precipitated. The solid and the catalyst were collected, washed with ether, and suspended in ethanol (125 ml). Concentrated hydrochloric acid (5 ml) was added, the amine was dissolved, and the catalyst was filtered off immediately with the aid of filtercel. The hydrochloride salt of the product crystallized on standing as cream needles (1.9 g), m.p. 180° (decomp.), with sintering at 140°–150°. Found: C, 20.6; H, 4.0; Cl, 15.6; N, 23.9; S, 14.0. Calc. for $C_4H_8N_4O_2S,HCl,H_2O$: C, 20.8; H, 4.8; Cl, 15.4; N, 24.3; S, 13.9%. Attempts to obtain the base were unsuccessful and the hydrochloride salt itself darkened and finally decomposed on long standing.

*5-Amino-1-methyl-4-sulphamylimidazole (VIII)*

Catalytic reduction of 1-methyl-5-nitro-4-sulphamylimidazole (5 g) in a similar manner yielded the hydrochloride salt of the product as white needles (4.2 g), m.p. 185°–187°

(decomp.). Found: C, 22.6; H, 4.2; N, 26.3; S, 15.4. Calc. for $C_4H_8N_4O_2S$, HCl: C, 22.6; H, 4.2; N, 26.3; S, 15.0%.

An aqueous solution of the hydrochloride salt on addition of an excess of ammonia precipitated the base as white needles m.p. 208°–210° (decomp.).

*Reduction of 4(5)-nitro-5(4)-sulphamylimidazole (X)*

Catalytic reduction of 4(5)-nitro-5(4)-sulphamylimidazole with Adams' platinum catalyst was attempted in both dry ethanol and in a mixture of glacial acetic acid and acetic anhydride. In each case the solution became dark brown as hydrogen was absorbed. No crystalline products were isolated.

*Infrared Spectra*

The infrared spectrum of each of the compounds reported was examined. The nitroimidazole sulphonamides showed bands in the regions of 1540 and 1350 $cm^{-1}$ characteristic of the nitro-group and bands in the regions of 1300 and 1175 $cm^{-1}$ characteristic of the sulphonamide group. Reduction of the nitro-compounds caused a disappearance of the bands in the regions of 1540 and 1350 $cm^{-1}$. The spectra of the aminoimidazole sulphonamides showed two bands in the regions of 3385 and 3315 $cm^{-1}$ characteristic of primary amine stretching absorptions and a band in the region of 1660 $cm^{-1}$ characteristic of primary amine deformation vibrations. The bands in the regions of 1300 and 1175 $cm^{-1}$ characteristic of sulphonamides were still evident.

The determination and interpretation of the infrared spectra was carried out by Professor A. Taurins, Department of Chemistry, McGill University.

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