IMIDAZOLE SULPHONAMIDES AND RELATED COMPOUNDS[1]

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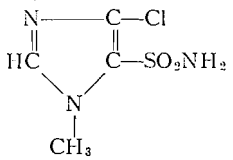
ABSTRACT

The preparations of a number of imidazole sulphonamides and related compounds are described.

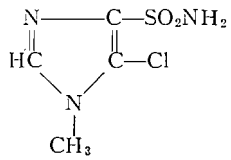
INTRODUCTION

The interest in heterocyclic sulphonamides as diuretic agents (1) prompted us to prepare a number of imidazole sulphonamides and related compounds for investigation. The syntheses of those compounds which have not been previously reported are described in this communication.

4-Chloro-1-methylimidazole (2) and 5-chloro-1-methylimidazole (3) were chlorosulphonated with chlorosulphonic acid and the sulphonyl chlorides were converted into the sulphonamides (I) and (II) with concentrated ammonia. 4(5)-Bromo-5(4)-sulphamylimidazole (4) was converted into the acetylsulphonamide (III) with acetic anhydride, in the usual way.



(I)



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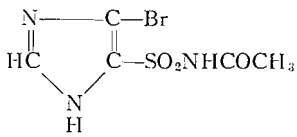
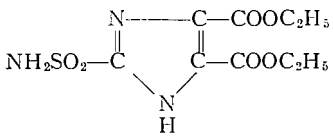


(III)

The halo compounds could not be converted into amines by treatment with alcoholic ammonia at an elevated temperature in a sealed tube. Bennett and Baker (4) showed similar inertness of the bromine atom in 4(5)-bromo-5(4)-sulphamylimidazole.

4,5-Bis(ethoxycarbonyl)-2-mercaptoimidazole (5) was converted into the sulphonyl chloride by oxidative chlorination in dilute hydrochloric acid. A brief treatment with concentrated ammonia gave the sulphonamide (IV). This ester on standing in concentrated ammonia or hydrazine for several hours was converted into the diamide (V) and the dihydrazide (VI).



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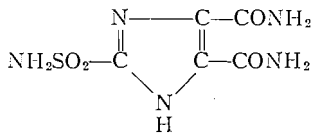
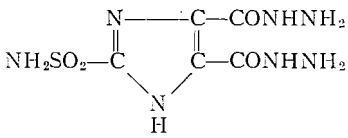


(V)



(VI)

Attempted conversion of the diamide into a xanthine with alkaline hypobromite (6) was unsuccessful. The dihydrazide with dilute hydrochloric acid gave a substance of undetermined structure rather than the expected dihydroxypyridazine (7).

The acid chloride of 5-carboxy-1-methyl-4-nitroimidazole (8) with hydroxylamine gave the expected hydroxamic acid (VII). However, with hydrazine under a variety of

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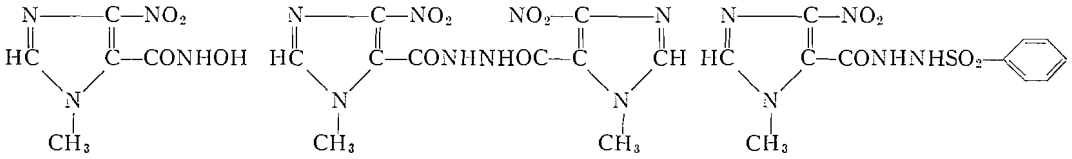
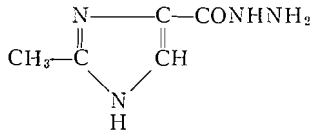
conditions only the 1,2-disubstituted hydrazine (VIII) could be isolated. Reaction with benzenesulphonylhydrazine gave the normal benzenesulphonylhydrazide (IX).



(VII) (VIII) (IX)

4(5)-Ethoxycarbonyl-2-methylimidazole (9) refluxed with hydrazine in methanol gave the hydrazide (X).



(X)

EXPERIMENTAL

4-Chloro-1-methyl-5-sulphamylimidazole (I)

4-Chloro-1-methylimidazole (8 g) dissolved in chlorosulphonic acid (48 ml) was refluxed for 2 hours. The solution was cooled and poured on to ice. The sulphonyl chloride was collected, washed with a little water, and dissolved in concentrated ammonia. After 15 minutes the excess of ammonia was evaporated and the solution was acidified with hydrochloric acid. The product was collected and crystallized from water as white needles (2.1 g), m.p. 164–165°. Found: C, 24.5; H, 3.22; N, 21.4; S, 16.4. Calc. for $C_4H_6ClN_3O_2S$: C, 24.6; H, 3.07; N, 21.5; S, 16.4%.

5-Chloro-1-methyl-4-sulphamylimidazole (II)

This compound was prepared from 5-chloro-1-methylimidazole (12 g) in a similar manner. Recrystallization from water gave white needles (5.4 g), m.p. 188–189°. Found: C, 24.9; H, 3.24; N, 21.3; Calc. for $C_4H_6ClN_3O_2S$: C, 24.6; H, 3.07; N, 21.5%.

4(5)-Acetylsulphamyl-5(4)-bromoimidazole (III)

4(5)-Bromo-5(4)-sulphamylimidazole (5 g) and acetic anhydride (50 ml) were refluxed for 1 hour and then cooled. The solid which crystallized was collected and recrystallized from water as white needles (2.4 g) m.p. 247–248°. Found: C, 22.3; H, 2.3; N, 15.4; S, 11.9. Calc. for $C_5H_6BrN_3O_3S$: C, 22.4; H, 2.2; N, 15.7; S, 12.0%.

4,5-Bis(ethoxycarbonyl)-2-sulphamylimidazole (IV)

4,5-Bis(ethoxycarbonyl)-2-mercaptoimidazole (1 g) was suspended in 2 *N* hydrochloric acid (10 ml) and cooled in an ice bath. Chlorine gas was passed gently through the solution for 25 minutes. The sulphonyl chloride was collected, washed with a little water, and dissolved in concentrated ammonia (10 ml). After 10 minutes the excess of ammonia was evaporated and the solution was acidified with hydrochloric acid. The product was collected and crystallized from water as white needles (0.65 g), m.p. 235–236°. Found: C, 37.4; H, 4.47; N, 14.4; S, 11.1. Calc. for $C_9H_{13}N_3O_6S$: C, 37.1; H, 4.96; N, 14.4; S, 11.0%.

4,5-Dicarbamyl-2-sulphamylimidazole (V)

4,5-Bis(ethoxycarbonyl)-2-sulphamylimidazole (0.4 g) was dissolved in concentrated ammonia (10 ml) and allowed to stand at room temperature for 3 days. The excess of

ammonia was evaporated and the solution was acidified with hydrochloric acid. The product was collected and crystallized from a large volume (100 ml) of water as white needles (0.2 g), m.p. >300°. Found: C, 25.5; H, 3.05; N, 29.6; S, 13.9. Calc. for $C_5H_7N_5O_4S$: C, 25.8; H, 3.01; N, 30.1; S, 13.8%.

4,5-Bis(hydrazinocarbonyl)-2-sulphamylimidazole (VI)

4,5-Bis(ethoxycarbonyl)-2-sulphamylimidazole (2.5 g) was dissolved in 30% hydrazine (50 ml) and allowed to stand at room temperature for 1 day. The solution was evaporated almost to dryness then diluted with water and acidified with glacial acetic acid. The product was collected and crystallized from water as small white needles (1.5 g), m.p. >300°. Found: C, 23.0; H, 3.45; N, 37.5; S, 12.3. Calc. for $C_5H_9N_7O_4S$: C, 22.8; H, 3.42; N, 37.2; S, 12.2%.

1-Methyl-4-nitroimidazole-5-hydroxamic acid (VII)

The acid chloride of 5-carboxy-1-methyl-4-nitroimidazole (11 g) dissolved in chloroform (25 ml) was added dropwise with stirring at 0–5° to a solution of hydroxylamine hydrochloride (5 g) and sodium hydroxide (9 g) in water (50 ml). The dark red solution was acidified at 0° with hydrochloric acid. The product which precipitated was collected and crystallized from "cellosolve" as white needles (3.5 g), m.p. 200° (sintered), 308° (decomp.). Found: C, 32.5; H, 3.31; N, 30.6; Calc. for $C_5H_6N_4O_4$: C, 32.3; H, 3.23; N, 30.2%.

1,2-Bis(1-methyl-4-nitro-5-imidazolylcarbonyl)-hydrazine (VIII)

The acid chloride of 5-carboxy-1-methyl-4-nitroimidazole (18 g) dissolved in chloroform (180 ml) was added dropwise, with stirring and cooling, to a solution of 95% hydrazine (7 ml) in chloroform (180 ml). After 30 minutes the orange product was collected, dissolved in water, and acidified with hydrochloric acid yielding white needles (10 g), m.p. 308°. Found: C, 36.1; H, 3.46; N, 33.6; Calc. for $C_{10}H_{10}N_8O_6$: C, 35.6; H, 2.96; N, 33.2%.

1-Methyl-4-nitro-5-phenylsulphonylhydrazinocarbonylimidazole (IX)

The acid chloride of 5-carboxy-1-methyl-4-nitroimidazole (11.1 g) dissolved in benzene (30 ml) was added dropwise, with stirring, to phenylsulphonylhydrazine (10 g) in pyridine (25 ml). After 10 minutes the solution was poured into an excess of ice-cold dilute hydrochloric acid to precipitate the product (10.5 g). Recrystallization from "cellosolve" gave small white needles, m.p. 248° (decomp.). Found: C, 40.7; H, 3.45; N, 21.4. Calc. for $C_{11}H_{11}N_5O_6S$: C, 40.6; H, 3.38; N, 21.5%.

4(5)-Hydrazinocarbonyl-2-methylimidazole (X)

4(5)-Ethoxycarbonyl-2-methylimidazole (0.7 g) was dissolved in a mixture of 85% hydrazine hydrate (5 ml) and methanol (5 ml) and refluxed for 1 hour. The solution was evaporated to dryness and the residue crystallized from methanol to give white needles (0.4 g), m.p. 210°. Found: C, 43.5; H, 5.70; N, 39.9. Calc. for $C_5H_8N_4O$: C, 42.9; H, 5.71; N, 40.0%.

The Reaction of 4,5-Dicarbamyl-2-sulphamylimidazole with Alkaline Hypobromite

4(5)-Dicarbamyl-2-sulphamylimidazole (1.17 g) was dissolved in a solution of bromine (1.6 g) and 10% sodium hydroxide (28 ml) at 0°. After 1 hour at 0° the solution was acidified with glacial acetic acid and the precipitate was collected. After several crystallizations from water the product was obtained as pale buff needles (0.15 g), m.p. >300°. Found: C, 20.6; H, 2.58; N, 24.8; S, 11.3; residue, 14.23%.

The Reaction of 4,5-Bis(hydrazinocarbonyl)-2-sulphamylimidazole with Hydrochloric Acid

4,5-Bis(hydrazinocarbonyl)-2-sulphamylimidazole (1.5 g) dissolved in 2 *N* hydrochloric acid (15 ml) was heated for 6 hours on a steam bath. The solid (0.7 g) which precipitated during the reaction was collected and purified by dissolution in dilute sodium hydroxide and precipitation with hydrochloric acid, as white needles, m.p. >300°. Found: C, 30.8; H, 2.55; N, 31.1; S, 5.29%.

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