Can. J. Chem. Downloaded from www.nrcresearchpress.com by 129.12.216.55 on 11/09/14
For personal use only.

CARBOXYMETHYLMERCAPTO AND CARBOXYMETHYLSULPHONYL DERIVATIVES OF NITROIMIDAZOLE[1]

M. H. Fisher, W. H. Nicholson, and R. S. Stuart

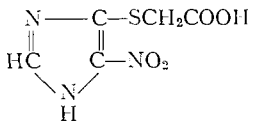
ABSTRACT

Several carboxymethylmercapto and carboxymethylsulphonyl derivatives of nitroimidazole were prepared for biological testing. Reduction or reductive cyclization of these compounds was unsuccessful.

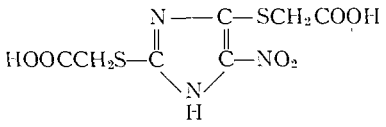
INTRODUCTION

In a previous communication (1) the syntheses of a number of nitro- and amino-imidazolesulphonamides as potential antimetabolites were described. This work has now been extended to the related carboxymethylmercapto compounds and oxidized derivatives. It was hoped that the nitro compounds could be reduced and cyclized but all attempts led to the formation of colored reaction mixtures from which no pure compounds could be isolated.

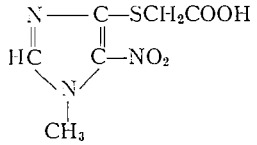
4(5)-Bromo-5(4)-nitroimidazole (2), 2,4(5)-dibromo-5(4)-nitroimidazole (2), 4-chloro-1-methyl-5-nitroimidazole (3), and 5-chloro-1-methyl-4-nitroimidazole (3) on treatment with thioglycolic acid in ammoniacal solution gave the carboxymethylmercapto compounds (I), (II), (III), and (IV).



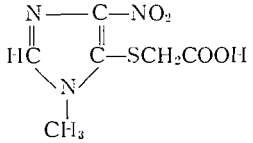
(I)



(II)

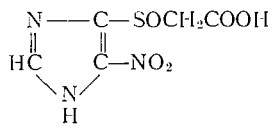


(III)

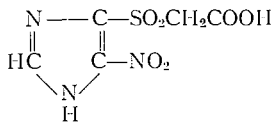


(IV)

Oxidation with hydrogen peroxide in glacial acetic acid yielded the sulphones (V), (VI), and (VII). The disulphide (II) gave an oil which could not be crystallized. The non-methylated compound (I) was somewhat more resistant to oxidation than the others. An intermediate sulphoxide (VIII) was isolated and further oxidized to the sulphone under more vigorous conditions.



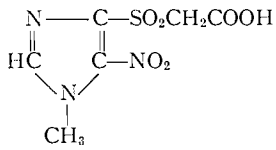
(VIII)

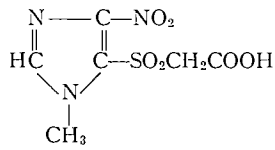


(V)

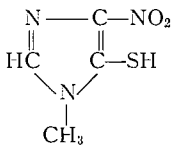
[1]*Manuscript received December 27, 1960.*
Contribution from the Research Department, Merck & Co. Ltd., Montreal, Que.

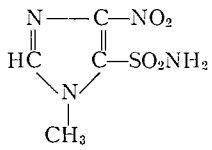
Can. J. Chem. Vol. 39 (1961)


(VI)


(VII)

Treatment of the sulphide (IV) or the sulphone (VII) with bromine yielded mixtures containing some brominated material. Either mixture with hydrogen sulphide in ammoniacal solution gave 5-mercapto-1-methyl-4-nitroimidazole (IX) (4) as the major product.


(IX)


(X)

It was subsequently found that hydrogen sulphide readily displaced the carboxymethylmercapto, the carboxymethylsulphonyl, or the sulphonamide groups from compounds (IV), (VII), or (X). In each case the thiol (IX) was produced in good yield.

EXPERIMENTAL

Carboxymethylmercapto Compounds

2,4(5)-Bis-(carboxymethylmercapto)-5(4)-nitroimidazole (II)

Thioglycolic acid (11 ml) was added to a solution of 2,4(5)-dibromo-5(4)-nitroimidazole (20 g) in water (100 ml) and concentrated ammonia (50 ml). The mixture was allowed to stand at room temperature for 64 hours. Addition of isopropyl alcohol (300 ml) precipitated the yellow ammonium salt (12 g), m.p. 136°.

The ammonium salt was converted to the free acid with Amberlite resin IR-120(H^+). Crystallization from water gave yellow needles, m.p. 212–213°. Found: C, 28.5; H, 2.38; N, 14.1; S, 21.9. Calc. for $C_7H_7N_3O_6S_2$: C, 28.6; H, 2.39; N, 14.3; S, 21.8%.

4-Carboxymethylmercapto-1-methyl-5-nitroimidazole (III)

Thioglycolic acid (7.5 ml) was added dropwise with stirring to a suspension of 4-chloro-1-methyl-5-nitroimidazole (15 g) in water (100 ml) and concentrated ammonia (50 ml). After storage at 5° for 16 hours the ammonium salt was collected as yellow needles (18.5 g), m.p. 185°.

The ammonium salt was converted to the free acid by precipitation from water with hydrochloric acid. Crystallization from ethanol gave pale yellow needles, m.p. 163–164°. Found: C, 33.2; H, 3.26; N, 18.6; S, 14.7. Calc. for $C_6H_7N_3O_4S$: C, 33.2; H, 3.22; N, 19.3; S, 14.7%.

5-Carboxymethylmercapto-1-methyl-4-nitroimidazole (IV)

This compound was prepared from 5-chloro-1-methyl-4-nitroimidazole (15 g) in a similar manner. Addition of isopropanol (300 ml) and ether (150 ml) and storage for 18 hours at 5° precipitated the ammonium salt (16.5 g), m.p. 153–154°. The free acid crystallized from ethanol as jagged white lathes (8.5 g), m.p. 209–210°. Found: C, 33.5; H, 3.25; N, 19.3; S, 14.5. Calc. for $C_6H_7N_3O_4S$: C, 33.2; H, 3.22; N, 19.3; S, 14.7%.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 129.12.216.55 on 11/09/14
For personal use only.

4(5)-Carboxymethylmercapto-5(4)-nitroimidazole (I)

This compound was prepared from 4(5)-bromo-5(4)-nitroimidazole (9 g) in a similar manner. The ammonium salt (9.2 g) was collected after 1 hour. After crystallization from methanol it had a melting point of 193–194°. The free acid crystallized from water as yellow needles (6.7 g), m.p. 185–186°. Found: C, 29.6; H, 2.41; N, 20.4; S, 15.7. Calc. for $C_5H_5N_3O_4S$: C, 29.6; H, 2.48; N, 20.6; S, 15.8%.

Oxidations with Hydrogen Peroxide

4(5)-Carboxymethylsulphoxy-5(4)-nitroimidazole (VIII)

4(5)-Carboxymethylmercapto-5(4)-nitromidazole (2 g) in glacial acetic acid (10 ml) and 30% hydrogen peroxide (10 ml) was heated for 1 hour at 75°. The solution was cooled and the product crystallized as white needles (1.6 g), m.p. 219–220° (decomp.). Recrystallization from water raised the m.p. to 220–221° (decomp.). Found: C, 27.3; H, 2.26; N, 18.8; S, 14.8. Calc. for $C_5H_5N_3O_5S$: C, 27.4; H, 2.28; N, 19.2; S, 14.6%.

4(5)-Carboxymethylsulphonyl-5(4)-nitroimidazole (V)

The sulphoxide (VIII) (1 g) in glacial acetic acid (5 ml) and 30% hydrogen peroxide (5 ml) was heated for 4 hours at 90° until a clear solution was obtained. Evaporation to dryness yielded the product (0.8 g), m.p. 284–286°. Recrystallization from water gave white needles, m.p. 295–296°. Found: C, 25.0; H, 2.20; N, 18.0; S, 13.8. Calc. for $C_5H_5N_3O_6S$: C, 25.5; H, 2.12; N, 17.9; S, 13.6%.

4-Carboxymethylsulphonyl-1-methyl-5-nitroimidazole (VI)

Similar oxidation of 4-carboxymethylmercapto-1-methyl-5-nitroimidazole (5 g) for 1 hour at 85° yielded the product (4 g), m.p. 181–182° (decomp.) as white needles from water. Found: C, 28.9; H, 2.83; N,16.5; S, 13.0. Calc. for $C_6H_7N_3O_6S$: C, 28.9; H, 2.81; N, 16.8; S, 12.8%.

5-Carboxymethylsulphonyl-1-methyl-4-nitroimidazole (VII)

Similar oxidation of 5-carboxymethylmercapto-1-methyl-4-nitroimidazole (2 g) for 1 hour at 80° yielded the product (1.25 g), m.p. 170–171° (decomp.) as white needles from water. Found: C, 29.1; H, 2.81; N, 16.8; S, 13.0. Calc. for $C_6H_7N_3O_6S$: C, 28.9; H, 2.81; N, 16.8; S, 12.8%.

Brominations

5-Carboxymethylmercapto-1-methyl-4-nitroimidazole (0.01 mole) or 5-carboxymethylsulphonyl-1-methyl-4-nitroimidazole (0.01 mole) in 1 *N* sodium hydroxide (10 ml) was treated with bromine (0.012 mole). In both cases the precipitated product was a difficultly separable mixture of partially brominated materials.

Displacements with Hydrogen Sulphide

The partially brominated mixtures, 5-carboxymethylmercapto-1-methyl-4-nitroimidazole, 5-carboxymethylsulphonyl-1-methyl-4-nitroimidazole, or 1-methyl-4-nitro-5-sulphamylimidazole (1) were each dissolved in 5 *N* ammonia (1 g in 10 ml) and hydrogen sulphide passed through for 10 minutes. In each case the product was the ammonium salt of 5-mercapto-1-methyl-4-nitroimidazole.

Reductions

Each of the nitroimidazoles was reduced either with hydrogen and Adams platinum catalyst in ethanol or glacial acetic acid or with powdered zinc and glacial acetic acid. In all cases the solutions became highly colored and only dark brown tars could be isolated.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 129.12.216.55 on 11/09/14
For personal use only.

REFERENCES

1. M. H. FISHER, W. H. NICHOLSON, and R. S. STUART. Can. J. Chem. In press.
2. I. E. BALABAN and F. L. PYMAN. J. Chem. Soc. **121**, 947 (1922).
3. J. SARASIN and E. WEGMANN. Helv. Chim. Acta, **7**, 713 (1924).
4. L. L. BENNETT, JR. and H. T. BAKER. J. Am. Chem. Soc. **79**, 2188 (1957).

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 129.12.216.55 on 11/09/14
For personal use only.