Isomerization of Tinidazole† involving a Novel *N*-Alkyl Group Migration

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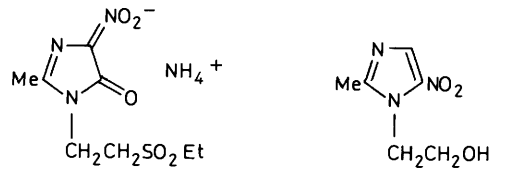
Tinidazole undergoes base-catalysed *N*-alkyl group migration in almost quantitative yields to give its 4-nitro isomer, an observation which may lead to a better understanding of the metabolism of this drug.

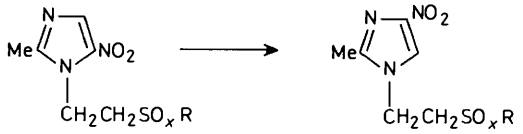
Tinidazole (**2a**) is one of a group nitroimidazoles which are active antiprotozoal agents.[1] A recent publication reporting that the major urinary metabolite of tinidazole is a ring hydroxylated isomeric product (**1**) involving nitro group migration,[2] prompted us to study the previously unreported isomerization of tinidazole.

We now report that tinidazole on refluxing in water or alcohol or a mixture of both, in the presence of a catalytic amount of a base such as hydrogen carbonate, carbonate, hydroxide or alkoxide, is neatly and almost quantitatively converted into its 4-nitro isomer (**3a**).‡ Under similar conditions some other *N*-alkyl-5-nitroimidazoles, (**2b**) and (**2c**), are also converted into the corresponding 4-nitro isomers, (**3b**) and (**3c**),‡ in almost quantitative yields.



(**1**)

(**4**)



(**2**)

(**3**)

a; $x = 2$, R = Et
b; $x = 2$, R = Bu
c; $x = 2$, R = Ph
d; $x = 1$, R = Et or Bu or Ph
e; $x = 0$, R = Et or Bu or Ph

To gain insight into the mechanism of isomerization several other *N*-alkyl-5-nitroimidazoles, (**2d**), (**2e**), and metronidazole§ (**4**) were treated under the reaction conditions described above but no isomerization occurred. From this it appears that the presence of an alkyl or aryl ethyl sulphone group is essential for the isomerization. This leads us to believe that isomerization takes place *via* *N*-dealkylation-elimination of alkyl or aryl vinyl sulphone, followed by *N*-realkylation on the other nitrogen atom.

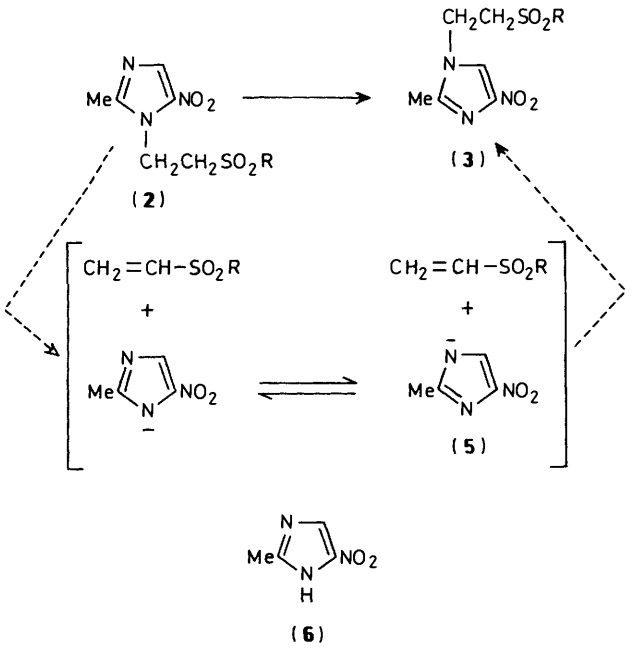
The literature report that the 4-nitro isomer is thermodynamically more stable[4,5] than the corresponding 5-nitro isomer and also that the –N– of the conjugate base (**5**) is more nucleophilic[6] should explain the neat isomerization of (**2a–c**) to (**3a–c**) respectively. As further support for this mechanism, 2-methyl-4(5)-nitro-1*H*-imidazole (**6**) has been treated with ethyl vinyl sulphone under the reaction conditions of tinidazole isomerization to give the 4-nitro isomer (**3a**) exclusively.

In the light of the findings that isomerization of tinidazole takes place through *N*-alkyl group migration, the reported isolation of tinidazole metabolite (**1**)[2] could perhaps be interpreted as arising out of *N*-alkyl group migration unless there is sufficient experimental evidence in favour of nitro group

† 1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole.

‡ Characterized by literature methods.[3]

§ 2-Methyl-5-nitroimidazol-1-ylethanol.



migration. It is also noteworthy that a ring hydroxylated metabolite of ipronidazole,*[7] where the *N*-methyl group is incapable of migration, corresponds to unisomerized product.

Experimental

1-[2-(*Ethylsulphonyl*)*ethyl*]-2-*methyl*-4-*nitro*-1H-*imidazole* (**3a**).—A mixture of 1-[2-(ethylsulphonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole (**2a**) (9.9 g), sodium hydrogen carbonate (0.4 g), and water (100 ml) was refluxed for 5 h. The reaction mixture was cooled and filtered to yield the product (**3a**) (9.0 g, 91%), m.p. 136—139 °C; 247 (M^+, 100%) and 201 (3, $M - NO_2$); $\delta_H[(CD_3)_2SO]$ 8.40 (1 H, s), 4.45 (2 H, t), 3.72 (2 H, t), 3.15 (2 H, q), 2.40 (3 H, s), and 1.25 (3 H, t). Concentration of the mother liquor afforded further product (0.4 g, 5%).

* 1-Methyl-2-(1-methylethyl)-5-nitro-1*H*-imidazole.

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