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The Synthesis of 4-Acetylaminoimidazole-5-sulfonamide and 1-Acetyl-5-acetylimidazole-4-sulfonamide

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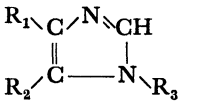
Synopsis. The synthesis of mono- and di-, *N*-acetyl derivatives of 5-aminoimidazole-4-sulfonamide, from 5-nitroimidazole-4-sulfonamide, as analogues of 5-amino-1'-ribonucleotyl)imidazole-4-carboxamide, is described.

The l-ribonucleotides of several imidazoles are well-established[1] as intermediates in purine ribonucleotide anabolism, but as yet few structurally related compounds have received attention as potential anti-viral or oncolytic agents. Since one of the intermediates in *de novo* nucleic acid synthesis is 5-amino-1-(1'-ribonucleotyl)imidazole-4-carboxamide[2] (I), we have now synthesised the di- and mono-*N*-acetyl-5-amino-4-sulfonamide derivatives (II and III respectively), which by possible *in vivo* hydrolysis of the acetyl group and l-ribonucleotylation would become bioisosteric with the above-mentioned natural ribonucleotide and thereby exibit an antimetabolite relationship.



	R_1	R_2	R_3
I	$-CONH_2$	$-NH_2$	-Ribonucleotyl
II	$-SO_2NH_2$	$-NHCOCH_3$	$-COCH_3$
III	$-SO_2NH_2$	$-NHCOCH_3$	-H
IV	$-SO_2NH_2$	$-NO_2$	-H
V	$-SO_2NH_2$	$-NH_2$	-H

Many unsuccessful attempts have been made to introduce a sulfonamide moiety into the 4-position of an imidazole ring and to prepare 5-aminoimidazole-4-sulfonamide. Attempts to prepare 4-sulfonyl chlorides as potential intermediates failed[3] when imidazole-4-sulfonic acid, 2-methylimidazole-4-sulfonic acid and 5-methylimidazole-4-sulfonic acid[4] failed to react with phosphorus pentachloride, phosphorus pentachloride–phosphoryl chloride mixtures, thionyl chloride or chlorosulfuric acid.[5] Attempts to proceed *via* the sulfenamide starting from 1-methyl-4-nitro-5-mercaptoimidazole also failed,[5] as did an attempt[5] to introduce a sulfonyl chloride group directly by chlorosulfonation of 4-acetamidoimidazole. However, 5-bromoimidazole has been successfully chlorosulfonated to give 5-bromo-4-sulfonyl chloride, which was readily converted to the corresponding amide but attempts to subsequently replace the bromo substiuent by an amino group failed.[5] although unfortunately an attempt using sodamide was not made. Attempts to catalytically hydrogenate the nitro group to an amino group in 5-nitroimidazole-4-sulfonamide (IV) led only to the formation of decomposition products,[6] probably because the amino sulfonamide (V) is unstable.

We have repeated this hydrogenation with 5-nitroimidazole-4-sulfonamide (IV), under the catalytic action of platinum, at elevated temperature and pressure, in a solution of glacial acetic acid and acetic anhydride. Instead of isolating the free amine formed, which is unstable, its diacetyl derivative (II) was formed, by boiling under reflux the reaction mixture, under the atmosphere of nitrogen gas. Aqueous hydrolysis of compound (II) afforded the monoacetyl derivative, 5-acetamidoimidazole-4-sulfonamide (III). The structure of II was confirmed by its elemental analysis and by its infrared spectrum which in particular showed two carbonyl functions. The structure of III was established by its high resolution mass spectral analysis and by its infrared spectrum which showed only one carbonyl function.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were recorded (solids as mulls in Nujol) with a Perkin-Elmer model 237 spectrophotometer, mass spectra were recorded with AEI MS-12 (low resolution) and MS-9 (high resolution) spectrometers.

5-Nitroimidazole-4-sulfonamide (IV). This compound was synthesised by the known method.[6]

5-Acetamido-1-acetylimidazole-4-sulfonamide (II). A mixture of IV (250 mg) and finely divided platinum (100 mg) in glacial acetic acid (5 ml) and acetic anhydride (15 ml), was hydrogenated at 50 p. s. i./50—60 °C. After hydrogen uptake had ceased (4 h), nitrogen was passed through the reaction mixture, the catalyst was rapidly removed by filteration and the filtrate was boiled under reflux for 1.5 h. After decolorisation (charcoal) the excess acetic acid and acetic anhydride were evaporated to afford a pale-yellow oil (50 mg) which crystallised from methanol to afford 5-acetamido-1-acetylimidazole-4-sulfonamide (II), as white prisms mp 250—252 °C; yield, 26 mg (8%).

Found: C, 33.9; H, 3.9; N, 22.7%. Calcd for $C_7H_{10}N_4O_4S$: C, 34.1; H, 4.0; N, 22.7%.

Mass spectrum: *m/e* 246 $(M)^+$; the infrared spectrum indicated the characteristic bands of the two carbonyl groups at 1710 and 1695 cm^{-1}.

5-Acetamidoimidazole-4-sulfonamide (III). A solution of II (25 mg) in water was boiled under reflux for 0.5 h. Evaporation of water and recrystallisation from methanol/ether afforded 5-acetamidoimidazole-4-sulfonamide (III) as white prisms; mp 220—221 °C; yield, 9 mg; 43%. High resolution mass spectral analysis showed a molecular ion at *m/e* 204.0319. Calcd for $C_5H_8N_4O_3S$ 204.031 the infrared spectrum indicated a characteristic band of a carbonyl group at 1675 cm^{-1}. The site of acetylation in this product is based[5] upon the similar partial hydrolysis of 1-

acetyl-4-acetamidoimidazole which affords 4-acetamidoimidazole.

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