Acetylaranotin. Displacement Reactions at the Disulphide Linkage

By K. C. MURDOCK* and R. B. ANGIER

(*Organic Chemical Research Section, Lederle Laboratories, American Cyanamid Company, Pearl River, New York* 10965)

Summary The disulphide linkage of the antiviral antibiotic acetylaranotin is shown to be highly reactive, undergoing novel insertion reactions with elemental sulphur and hydrogen cyanide and cleavage reactions with hydrogen sulphide and dimethyl disulphide.

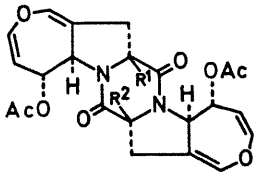
ACETYLARANOTIN (I), an antiviral metabolite produced by *Aspergillus terreus* and *Arachniotus aureus* (Eidam) Schroeter has been shown[1,2] to share the same epidithiadiketopiperazine moiety present in gliotoxin (XII) and sporidesmin.[3] The chemical reactivity of this moiety is of special interest because the antiviral and antibacterial activities of these compounds were not present in related compounds lacking the disulphide linkage,[3–5] a likely site for reaction with enzymatic thiol groups.

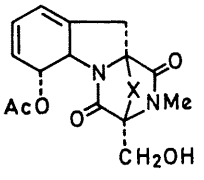
Under mild conditions (pyridine solution, 25°) (I) was reduced rapidly and cleanly with an excess of methanethiol to give dithiol (II) [92%, m.p. 252—254°; *SS*-diacetyl derivative (III) m.p. 140—144°]. Reaction presumably[6] proceeds *via* an unsymmetrical methyl disulphide (IV) which then reacts with more methanethiolate ion to give (II). Under the same conditions reaction with excess dimethyl disulphide gave the bis(methyl disulphide) (V) (64%, m.p. 128—131°). Surprisingly, catalysis[6] by an added thiol was uot required, though a little methanethiol might have been present in the dimethyl disulphide. More surprisingly, elemental sulphur was readily inserted into the disulphide linkage of (I) without requiring addition of dithiol (II) or any other thiol catalyst (*cf.* ref. 7). With a large excess of sulphur only two equivalents reacted, forming the tetrasulphide (VI) (81%). A tetrasulphide (XIII) of gliotoxin (XII) was prepared by the same method: 71%, m.p. 194—196° (decomp.). With just one equivalent of sulphur, acetylaranotin formed both the tetra- and tri-sulphides [(VI) and (VII)]. A more clean-cut synthesis of the trisulphide resulted from the action of sulphur dichloride on dithiol (II). Unique peaks in the spectra of the trisulphide showed that it was not a fortuitous mixture of the di- and tetra-sulphides [*i.e.* i.r. (KBr) 5·85, 5·89 and 5·91 μm (amide) and n.m.r. ($CDCl_3$) δ 2·00, 2·11, and 2·17 p.p.m. (acetate) for (I), (VII) and (VI), respectively].[8]

Acetylaranotin and an excess of hydrogen cyanide gave a 1 : 1 adduct [i.r.(KBr) 5·82,5·73,3·12μm] lacking the i.r. peak near 4·7 μm expected for thiocyanate (VIII). It gave an n.m.r. spectrum [*i.e.* two acetate peaks, at δ 1·97 and 2·00 and NH at δ 8·80 p.p.m. in $CDCl_3$–$(CD_3)_2SO$)] showing a molecular dissymmetry which would be unexpected in iminodithiocarbonate (IX), a possible cyclization product from (VIII). This adduct is believed to be the dithiocarbamate (XI), a cyclization product which would be expected to form after a preliminary rearrangement[9] of thiocyanate (VIII) to isothiocyanate (X). In contrast with the above reaction, in acyclic systems disulphide linkages bound to fully substituted carbon atoms did not react with cyanide ion.[10]

All of the above reactions proceeded readily in pyridine solution at *ca.* 25°. The marked reactivity of the disulphide linkage in acetylaranotin is in accord with *X*-ray crystallographic data[1b] showing a considerable angular constraint in this bridged-ring molecule, where the system C–S–S–C defines a dihedral angle of only 15 to 18°. This contrasts with a preferred angle near 100° in linear disulphides.[11]

The antiviral activities† of tetra- and tri-sulphides (VI) and (VII) *in vivo* were comparable with those of acetylaranotin. The tetrasulphide (XIII) from gliotoxin was active only *in vitro*; the other compounds were inactive.





(I)	R^1, R^2 = S–S
(II)	$R^1 = R^2$ = SH
(III)	$R^1 = R^2$ = SAc
(IV)	R^1 = SH, R^2 = S–SMe
(V)	$R^1 = R^2$ = S–SMe
(VI)	$R^1 + R^2$ = S–S–S–S
(VII)	$R^1 + R^2$ = S–S–S
(VIII)	R^1 = SH, R^2 = SC≡N
(IX)	$R^1 + R^2$ = S(C=NH)S
(X)	R^1 = SH, R^2 = N=C=S
(XI)	R^1, R^2 = S(C=S)–NH

(XII)	X = S–S
(XIII)	X = S–S–S–S

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