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REACTION OF TRYPTOPHAN DERIVATIVES WITH PHENYLSULPHENYL CHLORIDE AND PHENYLSELENENYL BROMIDE

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Summary: Treatment of N_b protected tryptophan methyl esters with phenyl sulphenyl chloride and phenylselenenyl bromide results in substitution at the indole 2-position and not in the anticipated tetrahydropyrrolo[2,3-b]indoles.

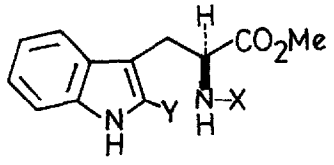
Prompted by a recent article[1] on the rearrangement of indol-3-yl sulphides to indol-2-yl sulphides under acidic conditions we report here our observations on the preparation and isolation of 2-phenylthio-and 2-phenylselenotryptophan esters by the reaction of various tryptophan derivatives with phenylsulphenyl chloride and phenylselenenyl bromide respectively.

The reaction of indole with various sulphur electrophiles leads to the formation of 3-substituted indoles whereas with 3-substituted indoles the eventual product isolated is that of substitution at the 2-position[2]. This dichotomy is probably explained by initial attack at the 3-position in both cases giving an indolenium cation followed, in the latter case, by migration of the sulphur moiety to the 2-position. Indeed the observations[3] of Plate and Ottenheim of the formation of 2-alkylthioindoles from 3-alkylthioindoles on treatment with trifluoroacetic acid are strongly supportive of such a migration. We had therefore anticipated that reaction of tryptophan derivatives with phenylsulphenyl chloride (8) or phenylselenenyl bromide (9) would lead to an indolenium species which would be trapped, intramolecularly, by the amino acid side chain leading to the diastereoisomeric tetrahydropyrrolo[2,3-b]indoles (10) and (11). Indeed such a path is followed with other electrophiles notably N-bromosuccinimide[4] and even protons[5].

We were therefore surprised to isolate the 2-phenylthiotryptophan (4) in 96% yield on reaction of (1)[6] with phenylsulphenyl chloride (8) and triethylamine in dichloromethane at room temperature. Similarly reaction of (1) with phenylselenenyl bromide (9) under identical conditions gave (5) in 87% isolated yield. Structures (4) and (5) were determined by standard spectroscopic techniques with additional confirmation of the lack of skeletal rearrangement coming from the reduction of (5) to (1) with tributyltin hydride[7] under free radical conditions. Reaction of tryptophan methyl ester (2), liberated *in situ* from its hydrochloride salt, with phenylsulphenyl chloride (8) also gave the analogous 2-phenylthioindole (6) in 72% yield. Finally given the known ability of carbamates to participate in selenolactamisations[8] and their recorded[5]

reproducible use in the formation of (11) (E = H; X = CO_2Me) from (3) with phosphoric acid we turned to the reaction of (3) with phenylselenenyl bromide (9). Once again however the only observed product (7) was that of overall substitution at the indole 2-position.

Clearly reaction of tryptophan derivatives with (8) and (9) either proceeds directly at the 2-position or takes place via initial attack at the 3-position followed by rapid rearrangement of the intermediate indolenium ion to give the observed products. Given the known reactions of (1) with N-bromosuccinimide and phosphoric acid we would favour the latter option.



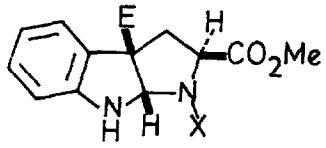
(1) X = Ac, Y = H
(2) X = H, Y = H
(3) X = CO_2Me, Y = H
(4) X = Ac, Y = SPh
(5) X = Ac, Y = SePh
(6) X = H, Y = SPh
(7) X = CO_2Me, Y = SePh

PhSCl

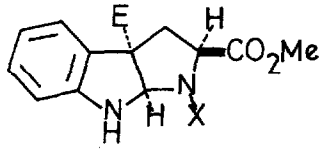
(8)

PhSeBr

(9)



(10)



(11)

E = SPh or SePh; X = H, Ac or CO_2Me

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