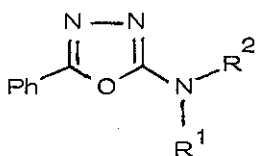


2-SUBSTITUTED-AMINO-5-PHENYL-1,3,4-OXADIAZOLES†

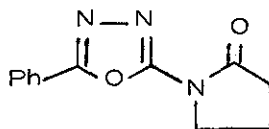
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The sodium salt of 2-acetamido-5-phenyl-1,3,4-oxadiazole can be alkylated using activated bromides. Alkylation by an unactivated halide takes place intramolecularly. The N-substituted compounds and derivatives thus prepared were essentially inactive in a screening system for CNS activity.

The amino group of the sedative and muscle relaxant,¹ 2-amino-5-phenyl-1,3,4-oxadiazole (I, $R^1 = R^2 = H$), is only a weakly reactive centre in comparison with that of a normal aromatic amine. It may however be acylated² and Gehlen has shown³ that the 2-acetamido compound (I, $R^1 = H$, $R^2 = Ac$) forms a sodium salt which can be alkylated with dimethyl



(I)



(II)

or diethyl sulphate; the reaction with simple alkyl halides, however, was very slow.

† Dedicated to Professor R.B. Woodward on the occasion of his sixtieth birthday.

We have now shown that the sodium salt formed from the amide ($I, R^1 = H, R^2 = Ac$) with one equivalent of NaOEt in EtOH, will react readily with activated halides in situ. Thus ethyl bromo acetate yielded at reflux the glycine ester ($I, R^1 = H, R^2 = CH_2COOEt$), ^{4*} m. 123-6° (52%), cleavage of the N-acetyl group taking place during reaction. Subsequent base treatment gave the amino acid ($I, R^1 = H, R^2 = CH_2COOH$)*, m. 168-169° (66%). Reaction of the sodium salt of the amide ($I, R^1 = H, R^2 = Ac$) with phenacyl bromide at R.T. gave, without N-acetyl cleavage, the substance ($I, R^1 = Ac, R^2 = CH_2COPh$)*, m. 124-5° (43%). Brief treatment of the compound with excess NaBH₄ in MeOH gave two products. The least soluble in CH₂Cl₂ was identified as the ethanolamine ($I, R^1 = H, R^2 = CH_2CHOH.Ph$)*, m. 174-6° (19%), while the second more soluble product was identified by n.m.r. spectroscopy as the O-acetyl derivative ($I, R^1 = H, R^2 = CH_2.CHOAc. Ph$)*, m. 180-181° (42%). An acyl migration had apparently taken place during the reduction, to leave the anionic centre stabilised on the nitrogen atom adjacent to the oxadiazole ring.

In confirmation of Gehlen's work ³, the sodium salt of the amide ($I, R^1 = H, R^2 = Ac$) would not react with 4-chloro-p-fluorobutyrophenone to give a p-fluorobutyrophenone ($I, R^1 = H, R^2 = (CH_2)_3 CO.-\text{C}_6\text{H}_4-F$). On the basis that a reaction which fails on an intermolecular basis may succeed if effected intramolecularly, the amine ($I, R^1 = R^2 = H$) ⁵ was converted to the amide ($I, R^1 = H, R^2 = CO (CH_2)_3 Cl$)*, m. 172-6° (89%) with 4-chlorobutyryl chloride. The latter amide contains an unactivated chlorine atom disposed in an intramolecular situation; as predicted, treatment of the amide ($I, R^1 = H, R^2 = CO (CH_2)_3 Cl$) with one equivalent NaOEt in

* All new compounds gave satisfactory spectroscopic and analytical data.

EtOH at R.T. led to rapid formation of the lactam (II)* m. 122-123° (52%), as the major product. Reaction of an ethereal suspension of the lactam (II) with 1.2 equivalents of p-fluorophenylmagnesium bromide at R.T. illustrated the enhanced reactivity of the carbonyl group in lactam (II) and gave, as the only product, the desired compound (I, $R^1 = H$, $R^2 = (CH_2)_3$ CO--F)*, m. 182-3° (12%) separated from unchanged lactam (II) by preparative t.l.c. on SiO₂ with PII solvent⁶.

Compounds prepared during this work were essentially inactive in general CNS screens.

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Received, 28th March, 1977