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

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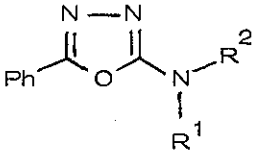
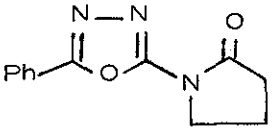
The sodium salt of 2-acetamido-5-phenyl-1,3,4-oxadiazole can be alkylated using activated bromides. Alkylation by an unactivated halide takes place intramolecularly. The N-substituted compounds and derivatives thus prepared were essentially inactive in a screening system for CNS activity.

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 acylated[2] and Gehlen has shown[3] that the 2-acetamido compound (I, $R^1 = H$, $R^2 = Ac$) forms a sodium salt which can be alkylated with dimethyl



(I)

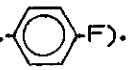


(II)

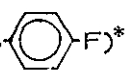
or diethyl sulphate; the reaction with simple alkyl halides, however, was very slow.

† 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 $NaBH_4$ in MeOH gave two products. The least soluble in CH_2Cl_2 was identified as the ethanolamine (I, R^1 = H, R^2 = CH_2 CHOH.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-fluoro-butyrophenone to give a p-fluorobutyrophenone (I, R^1 = H, R^2 = $(CH_2)_3$ CO.  -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 $(CH_2)_3Cl$),* 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 SiO_2 with PII solvent [6].

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

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4 N.C. Misra and K.K. Patraik, J. Inst. Chemists (India), 1972, 44, 5, claim to have prepared a substance with this structure. We have repeated their work and shown that the product is recovered starting material, 2-amino-5-phenyl-1,3,4-oxadiazole.

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