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

\[
\text{(I)} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{N} \\
\text{R}^2 \\
\text{Ph} \\
\end{array}
\]

\[
\text{(II)} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{Ph} \\
\end{array}
\]

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), m. 123-6^o (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^o (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^o (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_2CHOHPh), m. 174-6^o (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_2CHOAc. Ph), m. 180-181^o (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, 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)_3CO.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) was converted to the amide (I, R^1 = H, R^2 = CO (CH_2)_3Cl), m. 172-6^o (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, R¹ = H, R² = (CH₂)₃CO.OF)*, m. 182-80 (12%) separated from unchanged lactam (II) by preparative t.l.c. on SiO₂ with PII solvent.

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

REFERENCES

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.

Received, 28th March, 1977