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THE REACTION OF IMIDAZOLE WITH 2-PHENYL,4-CHLOROMETHYLENE-OXAZOL-5-ONE

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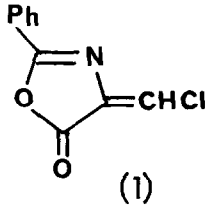
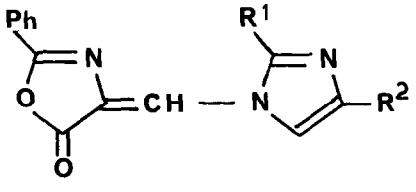
Summary: The displacement of chlorine from 2-phenyl,4-chloromethylene-oxazol-5-one by imidazole does not lead to carbon-carbon bond formation as previously reported, but involves attack by nitrogen leading to 2-phenyl,4-(imidazol-1-yl)methylene-oxazol-5-one.

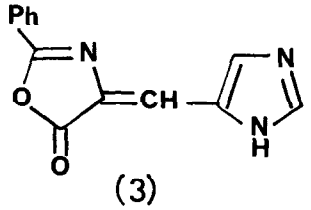
Displacement of chlorine occurs on reaction of imidazole with 2-phenyl,4-chloromethylene-oxazol-5-one (1). It might have been expected that this would involve carbon-nitrogen bond formation leading to (2), but Behringer and Duesberg[1] are emphatic in their contradiction: "Dies ist jedoch nicht der Fall"..... "Das vinyloge Saurechlorid kondensiert somit nicht am Stickstoff, sondern am Kohlenstoff in 4(5)-Stelling des Imidazols" (their emphasis). According to them, the product was (3).



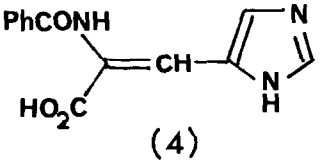
(1)



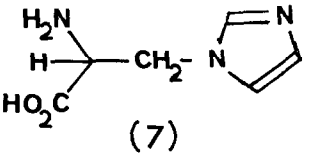
(2) $R^1=R^2=H$
(5) $R^1=Me, R^2=H$
(6) $R^1=H, R^2=Me$



(3)



(4)



(7)

The structure (3) was based[1] on the finding that mild hydrolysis gave an acid found to be identical with (4), which was prepared unambiguously according to Pyman[2] by an Erlenmeyer condensation. Since authentic (4) can be converted to histidine by hydrogenation and hydrolysis, the reaction described by Behringer and Duesberg could be the basis of a general synthesis of histidine analogues with ring substituents - indeed, they claim one such application. We were attracted to the reaction for this reason as we are currently interested in the synthesis of peptides containing modified histidines, and required a convenient general synthesis of the requisite amino-acids. When 2-methylimidazole was treated[3] with (1), however, the product was clearly of structure (5):[4] in particular, the ^{1}H n.m.r. spectrum showed no sign of an NH but had two distinct imidazole ring proton signals. Furthermore, the ^{13}C n.m.r. spectrum showed the presence of six different kinds of -CH= group. This is as required by (5), but rules out reaction at an imidazole carbon, which would have given a product with only five different kinds of -CH= group. Similarly, 4-methylimidazole gave (6), and the product from imidazole itself was found to be (2). Mild methanolysis[5], reduction and vigorous acidic hydrolysis of (2) gave the known[6] amino-acid (7), which was quite distinct from and uncontaminated by histidine.

REFERENCES AND NOTES

1. H. Behringer and P. Duesberg, Chem. Ber. 1963, 96, 381.
2. F.L. Pyman, J. Chem. Soc, 1916, 109, 186.
3. 15 min. at room temperature in dioxan; 1:1 proportions; 0.25 mmole/ml. Behringer and Duesberg used nitromethane at reflux temperature but we showed separately that the change of solvent and temperature has no detectable effect on the course of the reaction.
4. Structures (2), (5), (6) are based on elemental analysis and a full range of spectral measurements, all of which were completely consistent with purity and the structures shown. The stereochemistry about the carbon-carbon double bond in (2), (5), (6) was not investigated but all were obtained as single isomers. Melting points: (2) 231-3°, raised to 242-5° by repeated recrystallisation - cf. 233-6° reported[1] for the compound reported as (3); (5) 201°; (6) 193-5°. Yields of purified products were ca. 50%.
5. Hydrolysis of (2) as described by Behringer and Duesberg[1] did not proceed cleanly in our hands, and we were unable to isolate the crystalline acid erroneously identified by them as (4).
6. G.E. Trout, J. Med. Chem., 1972, 15, 1259.

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