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THE REARRANGEMENT OF 3-ACYLAMINOAZETIDINONES[1]

C. W. BIRD

Queen Elizabeth College, London, W.8

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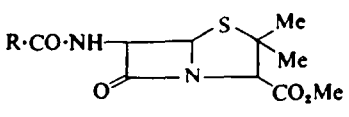
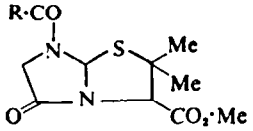
Abstract—3-Acylamino-1,4-diphenylazetidin-2-ones rearrange to 3-acyl-1,2-diphenyliminazolid-5-ones on refluxing in xylene with a trace of iodine. A mechanism is proposed for this rearrangement.

REARRANGEMENTS involving the azetidinone ring have been encountered in the chemistry of the penicillins,[2,3] but few have been observed in simpler systems. A particular example is the rearrangement of methyl benzylpenicillinate (Ia) to methyl benzylpenillonate (IIa) on heating in xylene with a trace of iodine or sulphuric acid.[4] The same product is also obtained from methyl benzylpenicillenate (III) under these conditions. Methyl n-amylpenicillenate (Ib) also appears to rearrange but methyl anhydrobenzylpenicillin (IV)[5] does not.

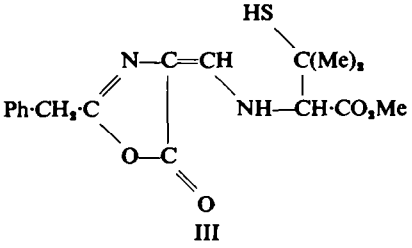


I

(a) R = CH_2·Ph
(b) R = n-C_5H_{11}



II



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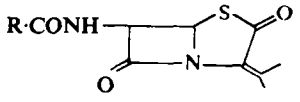
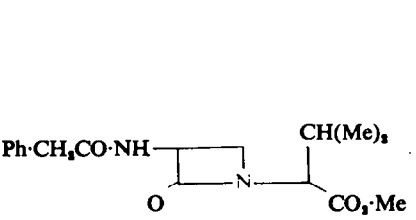


IV

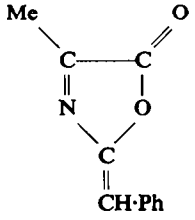
In the case of monocyclic azetidinones methyl desthiobenzylpenicillinate (V) is reported to be converted in refluxing anisole into the oxazolone (VI), which is also obtained from the azetidinone (VIIa) under the same conditions.[6] These reactions probably proceed through formation of the oxazolone (VIII), followed by elimination

[1] For a preliminary communication see *Tetrahedron Letters* 609 (1964).
[2] *The Chemistry of Penicillin* (Edited by H. J. Clarke, J. R. Johnson and R. Robinson). Princeton University Press, N.J. (1949).
[3] A. H. Cooke, *Quart. Revs.* 2, 203 (1948).
[4] Ref. 2., pp. 158–161 and 188–194.
[5] S. Wolfe, J. C. Godfrey, C. T. Holdrege and Y. G. Perron, *J. Amer. Chem. Soc.* 85, 643 (1963).
[6] Ref. 2, p. 977 onwards.

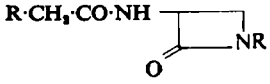
of amine and rearrangement of the resulting methyleneoxazolone into the pseudo-oxazolone (VI), which is unreactive to attack by amine. Support for this pathway



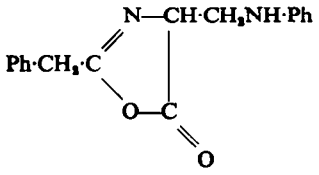
V



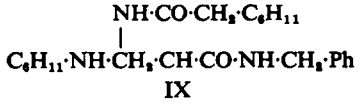
VI



VII (a) R = Ph
(b) R = C_6H_{11}



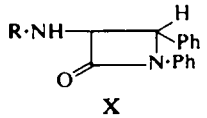
VIII



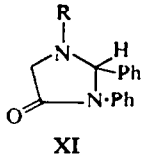
IX

is provided by the conversion of 3-cyclohexylacetamido-1-cyclohexylazetidin-2-one (VIIb) into the propionamide derivative (IX) by successive treatment with hydrogen chloride in chloroform and benzylamine.[6] The marked contrast in behaviour between the bicyclic and monocyclic series suggested the ensuing work, which was directed towards the realisation of a penicillin–penillonic acid type rearrangement of a monocyclic azetidinone and clarifying its mechanism.

Mechanistic considerations (*vide infra*) suggested investigation of acyl derivatives of the readily accessible[7] 3-amino-1,4-diphenylazetidin-2-one. The phenylacetyl compound (Xa) when refluxed with a trace of iodine in xylene gave an 80% yield of the iminazolidone (XIa). The IR spectrum of this compound showed carbonyl bands at 1695 and 1665 cm^{-1} consistent with the assigned structure. The absence of bands due to N—H excluded formulations analogous to IX. As anticipated acid hydrolysis of XIa gave phenylacetic acid, benzaldehyde and aniline.



X



XI

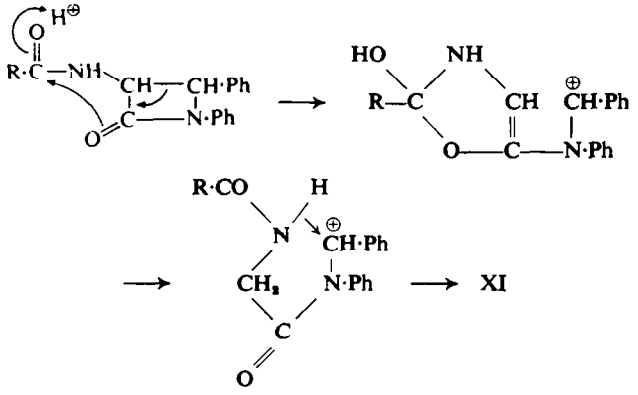
(a) R = $PhCH_2CO$
(b) R = PhCO
(c) R = p-$MeC_6H_4SO_2$

The benzoyl derivative (Xb) was also rearranged into XIb with carbonyl bands at 1700 and 1635 cm^{-1}. However, the *p*-toluenesulphonyl compound (Xc) resisted all attempts at rearrangement. The marked stability of Xc is of especial interest with

[7] J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.* **73**, 1204 (1951).

regard to the reported[8] formation of iminazolidones, e.g. XIc, from N-benzenesulphonylglycyl chloride, N-benzylideneaniline and triethylamine as it appears to exclude a mechanism involving an azetidinone intermediate.

Cogent reasons for rejecting mechanisms previously proposed[9] for the penicillin–penillonic acid rearrangement have been presented earlier.[1] The present work shows that the additional strain imposed by the thiazolidine ring is not the sole factor in controlling the occurrence of this type of rearrangement. The most plausible mechanistic sequence is depicted below.



This mechanism shows that the function of the substituent on C4 is to stabilize the intermediary carbonium ion. The participation of the N-acyl group, as in other penicillin reactions, is clearly indicated in this case by the failure of Xc to rearrange.

EXPERIMENTAL

IR spectra were recorded for Nujol mulls on a Perkin–Elmer model 137E spectrophotometer. The identity of known compounds was established by mixed m.ps and IR spectra.

Preparation of 3-acylamino-1,4-diphenylazetidin-2-ones. The *benzoyl* derivative (Xb) was prepared by treating the amine hydrochloride[7] with benzoyl chloride in pyridine, m.p. 161–162° from aqueous MeOH (Found: C, 77·2; H, 7·3; N, 7·8. $C_{22}H_{18}N_2O_2$ requires: C, 77·2; H, 5·3; N, 8·2%.) ν_{max} 3300, 1780, 1660 cm^{-1}. The *p-toluenesulphonyl* derivative (Xc) was similarly prepared, m.p. 175–176·5° from $CHCl_3$—MeOH. (Found: C, 67·5; H, 5·2; N, 7·6. $C_{23}H_{20}N_2O_3S$ requires: C, 67·3; H, 5·1; N, 7·2%.) ν_{max} 3300, 1770, 1345, 1160 cm^{-1}

Rearrangement of Xa. The Xa (3 g) and a small crystal of I_2 in xylene (100 ml) were heated under reflux for 24 hr. The product, which separated on cooling, was recrystallized from xylene to give *1,2-diphenyl-3-phenylacetyliminazolid-5-one* (XIa; 2·4 g), m.p. 220–222°. (Found: C, 77·8; H, 5·8; N, 8·0. Rast mol. wt. 348. $C_{23}H_{20}N_2O_2$ requires: C, 77·5; H, 5·6; N, 7·9%. mol. wt. 356.)

Hydrolysis of XIa. The XIa (1 g) was heated with H_2SO_4 (8 ml) and water (6 ml) under reflux for 10 min. The reaction mixture was diluted with an equal volume of water and distilled. The distillate (10 ml) was ether extracted to isolate the benzaldehyde, which was converted into its 2,4-dinitrophenylhydrazone (0·11 g). The distillation residue was then diluted with twice its volume of water and ether extracted to isolate the phenylacetic acid (0·14 g), which was purified by molecular distillation. Finally the acid solution was basified with conc. NaOH aq and distilled. The distillate (10 ml) was treated with NaOH and benzoyl chloride to convert the aniline into benzanilide (0·32 g).

Rearrangement of Xb. The Xb (1 g) and a small crystal of I_2 in xylene (20 ml) were heated under reflux for 24 hr. The *3-benzoyl-1,2-diphenyliminazolid-5-one* (XIb) crystallized out on cooling and was recrystallized from xylene (0·55 g) m.p. 240–242°. (Found: C, 76·9; H, 5·2; N, 8·2. $C_{22}H_{16}N_2O_2$ requires: C, 77·2; H, 5·3; N, 8·2%.)

[8] J. C. Sheehan and E. J. Corey, *Organic Reactions* **9**, 402 (1957).
[9] Ref. 2, p. 447.