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NEW EXAMPLES OF THE PENICILLIN-PENILLONIC ACID REARRANGEMENT

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The methyl ester of benzylpenicillin (I) undergoes molecular rearrangement to methyl benzylpenillonate (II) when heated in toluene with a trace of iodine[1]. The same product is also obtained from methyl benzylpenicillenate (III), presumably through intermediate formation of (I). Several mechanisms have been discussed[2] for the formation of (II) from (I). The observation[3] that (II) was formed by reaction of the thiazoline (IV) with the oxazalone (V) has been interpreted as supporting a sequence in which (I) is first split into the thiazoline (IV), and a keten which subsequently rearranges into (V). The condensation envisaged between (IV) and (V) to yield (II) is without precedent.

Interest[4,5] in the molecular rearrangements of small ring compounds prompted an investigation of the simpler system (VI). The rearrangement of (VIa)[6] with iodine in refluxing xylene gave the iminazolidone (VIIa)* (m.p. 220-222°; $\nu_{\text{max.}}$ 1695 and 1665 cm.$^{-1}$) in 80% yield. As anticipated

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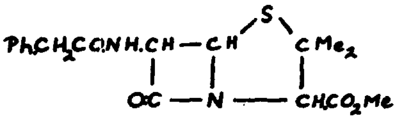
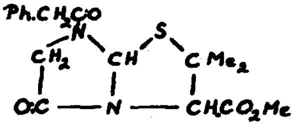
[*] All new compounds gave satisfactory elemental analyses and molecular weights.



I



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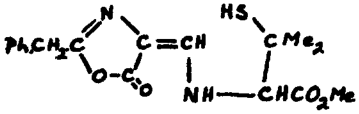

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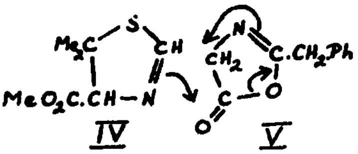

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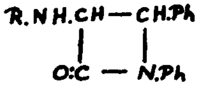
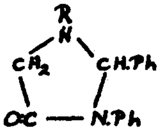


VI

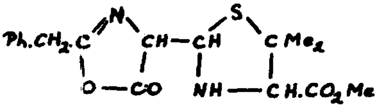


VII

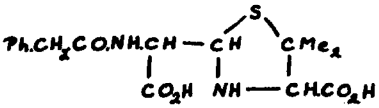
(a) $R = Ph.CH_2.CO-$

(b) $R = Ph.CO-$

(c) $R = p-Me.C_6H_4SO_2-$



VIII

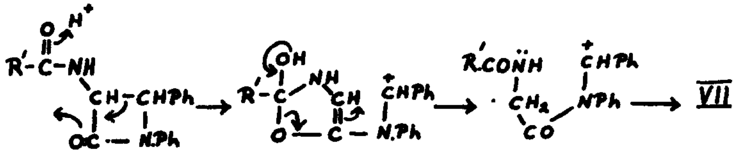


IX

acid hydrolysis of (VIIa) gave phenylacetic acid, benzaldehyde and aniline. Similarly, rearrangement of (VIb) (m.p. 161-162°; $\nu_{max.}$ 1780, 1660 cm.$^{-1}$) gave the iminazolidone (VIIb) (m.p. 240-242°; $\nu_{max.}$ 1700, 1635 cm.$^{-1}$). however, all attempts to rearrange (VIc) (m.p. 175-177°; $\nu_{max.}$ 3300, 1770, 1345, 1160 cm.$^{-1}$) to (VIIc) were unsuccessful. This suggests that the formation[7] of iminazolidones of type (VIIc) from N-benzenesulphonylglycyl chloride, N-benzylideneaniline and triethylamine does not involve an azetidinone intermediate (e.g. VIc).

The reaction of N-benzylideneaniline with the oxazolone (V) in ether was examined since, on the basis of the aforementioned scheme, they should be intermediates in the conversion of (VIa) to (VIIa). The only identifiable products which could be isolated were small amounts of the benzylidene derivative of (V) and N-phenylacetylglycine anilide. Appropriate control experiments precluded the possibility that the latter product resulted from hydrolysis of (VIIa). Thus, in this case at least, the rearrangement does not appear to follow the above path. Further efforts to realise condensations of the above type using 4,4-disubstituted oxazol-5-ones have so far been unsuccessful.

The failure of (VIc) to rearrange suggests that the N-acyl group participates in this reaction as it does in other rearrangements of (I)[2]. This feature is readily accomodated in the following scheme, which is equally applicable to the rearrangement of (I) to (II).



The result of attempts to condense *N*-benzylideneaniline with (V) suggests an alternative pathway for the genesis of (II) from (IV) and (V), via formation of (I). Addition of (V) to (IV) could lead to (VIII) which by intramolecular attack of the thiazolidine on the oxazolone would give (I) or, by elimination (III). The compound is possibly the intermediate in the conversion of (IX) into benzylpenicillin by treatment with phosphorus trichloride[8].

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