Synthesis of New Bicyclic β-Lactams

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Two new bicyclic β-lactams have been synthesised by the addition reaction of phthalimidoacetyl chloride with 2-methyl- Δ^2 -oxazoline and 2-phenyl 4-H-5.6-dihydro- Δ^2 -1.3-thiazine bases.

SHEEHAN and RAYAN 1,2 reported the addition reaction of phthalimidoacetyl chloride with a Schiff base giving a simple β -lactam, and with a thiazoline derivative giving a fused bicyclic β -lactam. We have extended this reaction to the synthesis of two new bicyclic β-lactams (I) and (II). Reaction of phthalimidoacetyl chloride in the presence of triethylamine with 2-methyl- Δ^2 oxazoline (Wenker³) gave (I) and with 2-phenyl-4-H, 5,6-dihydro- Δ^2 -1,3-thiazine (Pinkus ⁴) gave (II). Heterocyclic bases were taken in slight excess over phthalimidoacetyl chloride to yield (I) and (II) free from a 2,4-dioxopiperidine derivative, a probable side product² of the keteneimine type of interaction, which is probably the mechanism involved. The use of nonequivalent proportions also simplifies the working up.



The infrared spectra of compounds (I) and (II) taken respectively in KBr disc and chloroform solution on a

¹ J. C. Sheehan and J. J. Rayan, J. Amer. Chem. Soc., 1951, 73, 1204. 4 N

Perkin-Elmer Infracord instrument reveal the following significant peaks: 3400, 2900, 1780 (5.62 µ), 1650-1680 cm.⁻¹ in (I) (KBr discs), and 1780 (5.62 μ), 1650-1680 cm.⁻¹ in (II) (CHCl₃). The absorption at 1780 cm.⁻¹ (5.62 μ) in (I) and (II) is characteristic of a β -lactam structure whereas the broad band at 1650-1680 cm.-1 is due to a carbonyl group of the phthalimide moiety. The additional peak at 2900 cm.⁻¹ in compound (I) (KBr) which is characteristic of -CH stretching provides additional evidence for the β -lactam structure of (I). The two spectra can be compared with the one given by Sheehan and Rayan² for α -phthalimido-2-phenyl-2-thiazolidineacetic acid β -lactam and all three spectra agree in respect of β-lactam structure. The analytical results also support these structures.

The absorption at 3400 cm.⁻¹ in compound (I) (KBr is presumably due to hydrogen-bonded OH in the absence of an -NH group. Hence the presence of a molecule of water of crystallisation is indicated, as is confirmed by analysis. This is perhaps due to the fact that 2-methyl- Δ^2 -oxazoline, from which (I) is obtained,

² J. C. Sheehan and J. J. Rayan, J. Amer. Chem. Soc., 1951, 73, 4367.

 ³ H. Wenker, J. Amer. Chem. Soc., 1953, 57, 1079.
⁴ G. Pinkus, Ber., 1893, 26, 1077.

is a hygroscopic liquid and a water molecule seems to persist even in the final compound and is very difficult to remove.

EXPERIMENTAL

a-Phthalimido-2-methyloxazolidine-2-acetic Acid B-Lactam (I).-To a 2-necked flask, with mechanical stirrer and pressure-equalising dropping funnel, containing dry pure 2-methyl- Δ^2 -oxazoline ³ (2.5 g., 0.0249 mole) and triethylamine (3 g., 0.0298 mole) in dry pure benzene (60 ml.), was added during 40 min. phthalimidoacetyl chloride⁵ (5.4 g., 0.0241 mole) in dry pure benzene (100 ml.) at room temperature. Turbidity appeared and triethylamine hydrochloride gradually separated. Stirring was continued for 2 hr. The precipitate was then filtered off, washed twice with two 25 ml. portions of dry benzene, dried, and (3.5 g.) treated with distilled water (10 ml.), and the residue filtered under suction and washed twice with 5 ml. portions of water. 1 g. of the required product, m. p. 138-140°, was obtained.

Benzene filtrate and washings were collected and the solvent was removed under suction. The pasty mass obtained was triturated with dry benzene (20 ml.), and the insoluble solid was filtered off and washed several times with dry benzene, yielding a further 0.7 g. of product, m. p. 135°. The total yield (1.7 g.) (26%) was recrystallised from benzene-light petroleum and had m. p. 144° (Found: C, 57.4; H, 4.6; N, 10.1. C₁₄H₁₂N₂O₄,H₂O requires C, 57.9; H, 4.8; N, 9.7%). Benzene washings on concentration gave a paste which could not be purified.

a-Phthalimido-2-phenyl-2-thiazaneacetic Acid β -Lactam (II).-2-Phenyl-4-H-5,6-dihydro- Δ^2 ,1,3-thiazine. Dry thiobenzamide 6 (5 g., 0.0364 mole) and dry 1-chloro-3-bromo-

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propane (32 ml., 0.33 mole) were gently heated under reflux; a clear solution was obtained and fumes of HCl were given off. Heating was discontinued after nearly 45 min. as the product started decomposing. The mixture was cooled and treated with water. The aqueous layer was separated, thrice extracted with ether to remove traces of dihalogenopropane and thiobenzamide if any, and basified with saturated sodium carbonate solution, whereupon a heavy oil separated which was extracted with ether. The ethereal solution was dried (K₂CO₃) and solvent was finally removed at room temperature. On cooling, the oily residue gradually solidified to give crystalline thiazine base, m. p. 46° (lit.,4 m. p. 45-46°).

Addition of phthalimidoacetyl chloride to 2-phenyl-4-H, 5,6-dihydro- Δ^2 -1,3-thiazine. The details are similar to the addition of phthalimidoacetyl chloride to 2-methyl- Δ^2 -oxazoline in presence of triethyl amine. The starting materials were 2-phenyl-4-H, 5,6-dihydro- Δ^2 -1,3-thiazine (4 g., 0.0226 mole), phthalimidoacetyl chloride (4 g., 0.0179 mole), and triethylamine (4 ml., 0.0179 mole). The crude product was crystallised from benzene-chloroform (yield 3.5 g., 43%), m. p. 219-221° (Found: C, 65.6; H, 4.4; N, 8.03. C₂₀H₁₆N₂O₃S requires C, 65.9; H, 4.4; N, 7.7%).

We thank Professor G. B. Singh, Head of the Chemistry Department, for facilities, and U.G.C., New Delhi, for a Junior Research Fellowship (A. K. M.).

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⁵ J. C. Sheehan and V. S. Frank, J. Amer. Chem. Soc., 1949,

71, 1856. ⁶ A. E. S. Fairful, J. L. Lowe, and D. A. Peak, J. Chem. Soc., 1952, 742.