A Simple Synthesis of γ-Anisylidene-substituted αβ-Unsaturated γ-Lactams

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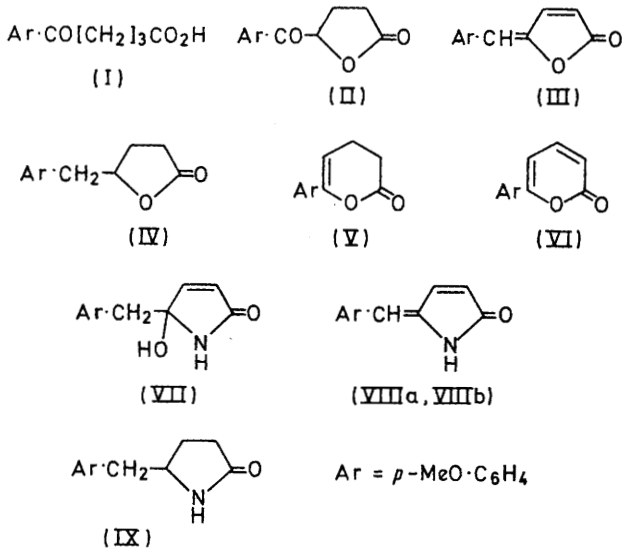
Summary The unsaturated lactams (VIIIa) and (VIIIb) have been prepared from the keto-acid (I) *via* four steps including an unusual dehydration of (II) to (III).

IN connection with our synthetic work on anisomycin[1] we have developed a convenient method of synthesizing the unsaturated lactams (VIIIa) and (VIIIb).

The keto-acid (I),[2] on treatment with bromine in an ether–dioxan solution, was converted into the keto-lactone (II),† m.p. 122—124°, ν_{max} 1790 and 1685 cm.$^{-1}$, in 87% yield. The keto-lactone (II) was kept under reflux for 48 hr. in acetic anhydride and toluene-*p*-sulphonic acid, and the resulting mixture, after evaporation of the acetic anhydride, was chromatographed on silicic acid to afford a yellow compound (III),† m.p. 116—118° (58%). The structure (III) for the dehydro-compound was assigned on the spectral evidence [ν_{max} 1795 (weak) and 1765 cm.$^{-1}$; λ_{max} 360 (ϵ 29,000) and 241 nm (11,000); δ (CCl_4) 5·83 (1H, s) and 6·70 (2H, AB-type quartet, J 6·0 Hz); M^+ 202] and chemical properties: (III) was converted into a saturated γ-lactone (IV),† m.p. 49—51° (ν_{max} 1775 cm.$^{-1}$, M^+ 206) on catalytic hydrogenation (10% Pd–C).

In order to exclude the possibility that the yellow compound is an α-pyrone derivative (VI) which would be formed from (II) *via* the acid-catalysed cleavage of the γ-lactone ring, followed by recyclization, the keto-acid (I)

† Satisfactory analytical data were obtained for all the new compounds. Unless otherwise stated, the i.r. and u.v. spectra were taken in chloroform and in ethanol, respectively.



was converted by heating in acetic anhydride into an enol-lactone (V), which was dehydrogenated under reflux with 10% Pd–C in *p*-cymene[3] to afford the α-pyrone (VI),† m.p. 99—101° [ν_{max} 1730 cm.$^{-1}$; λ_{max} 352 (ε 19,000) and 257 nm (9100)], clearly different from (III).

On standing in an aqueous ethanolic solution saturated with ammonia, the unsaturated lactone (III) was almost quantitatively transformed into a lactam (VII),†‡ m.p. 138—139°; ν_{max} 1710 cm.$^{-1}$.

The lactam (VII) was readily dehydrated with toluene-*p*-sulphonic acid in refluxing benzene to give a mixture of two unsaturated lactams, which could be separated by t.l.c. on silica gel G (solvent, CH_2Cl_2–EtOH, 9 : 1) : (VIIIa),†§ m.p. 146—148°, ν_{max} 1690 cm.$^{-1}$, λ_{max} (H_2O–EtOH, 1 : 9), 363 (ε 25,000) and 247 nm (11,000); and (VIIIb),†§ m.p. 151—152°, ν_{max} 1690 cm.$^{-1}$, λ_{max} (H_2O–EtOH, 1 : 9), 355 (ε 35,000) and 241 nm (11,000).

Both (VIIIa) and (VIIIb) afforded a saturated lactam (IX),† m.p. 77—78° (ν_{max} 1690 cm.$^{-1}$) on catalytic hydrogenation.

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‡ The open-chain form (*viz.* $ArCH_2{\cdot}CO{\cdot}CH:CH{\cdot}CONH_2$) is also conceivable. Although decisive evidence for the cyclic structure (VII) was not obtained, the lactam form seems most likely, since: (i) on heating in benzene, (VII) could be dehydrated to give the lactams, (VIIIa) and (VIIIb); (ii) a sharp singlet (1H, δ 3·10, OH) and a broad signal (1H, δ *ca.* 7·5, ·CONH·) in the n.m.r. spectrum disappeared on addition of D_2O; (iii) the $M^+ - H_2O$ peak (*m/e* 201) was a base peak in the mass spectrum.

§ The absorption maxima of (VIIIa) and (VIIIb) were not affected by variation of the pH of the solutions; however, the absorption intensities of (VIIIb) were dependent on the pH value of the solutions: (VIIIa); λ_{max} (0·01N-HCl–EtOH, 1 : 9), 363 (ε 25,000) and 247 nm (11,000); λ_{max} (0·01-N-NaOH–EtOH, 1 : 9), 363 (ε 27,000) and 247 nm (11,000). (VIIIb); λ_{max} (0·01N-HCl–EtOH, 1 : 9), 355 (ε 30,000) and 240 nm (9200); λ_{max} (0·01N-NaOH–EtOH, 1 : 9), 355 (ε 42,000) and 241 nm (13,000).

[1] For the synthesis of anisomycin, see: S. Oida and E. Ohoki, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 2086, 1969, **17**, 1405; C. M. Wong, J. Buccini, I. Chang, J. TeRaa, and R. Schwenk, *Canad. J. Chem.*, 1969, **47**, 2421.
[2] W. S. Johnson, A. R. Jones, and W. P. Schneider, *J. Amer. Chem. Soc.*, 1950, **72**, 2395.
[3] D. Rosental, P. Grabowich, E. F. Sabo, and J. Fried, *J. Amer. Chem. Soc.*, 1963, **85**, 3971.