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THE SYNTHESIS AND REARRANGEMENT OF 1,3-OXAZINES

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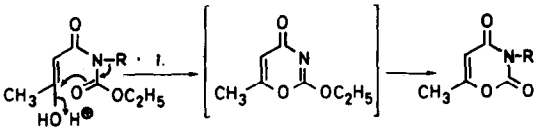
A recent report[1] on the synthesis of 2,4-dioxo-6-methyl-2,3-dihydro-4H-1,3-oxazine (IIIa) prompts us to report some related investigations in this field. Our approach to the synthesis of 1,3-oxazines was from the cyclisation of β-keto-acylurethanes or their enol-ethers, and is based on our previous synthesis[2,3] of 1,3-thiazines from acyldithourethanes.

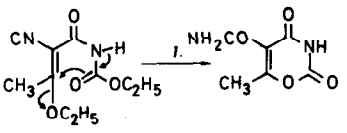
N-Acetyacetyl urethane[4] (Ia) was treated at room temperature for 24 hours with conc. sulphuric acid*, then diluted with ice and water, to form the 6-methyl-1,3-oxazine (IIIa), m.p. 237-238°C, reported[1] 231-2°C, in 24% yield. This structure was supported by elemental analysis, spectral data (λ_{max} EtOH 230 mμ; ν_{CO} (Nujol) 1690, 1775 cm^{-1}; N.M.R., see table) and by conversion into the N-methyl derivative (IIIb), m.p. 111°C, reported[5] m.p. 108-9°C, on treatment with alkaline dimethylsulphate.

*Refluxing trifluoroacetic acid gave inferior yields.



I II III

a) R = H b) R = CH_3



IV V

1. H_2SO_4

That the ring-oxygen atom of the 1,3-oxazine originated from the urethane carbonyl-group via the intermediate (II), and not by direct displacement of the urethane ethoxyl group, is supported by the finding that N-acetoacetyl-N-methylurethane* (Ib) in which no lactam-lactim tautomerism is possible, formed no 1,3-oxazine. On the other hand, the urethane (IV) in which keto-enol, but not lactam-lactim tautomerism is suppressed was readily converted into 5-carbamoyl-6-methyl-2,4-dioxo-2,3-dihydro-4H-1,3-oxazine (V), yield 94%, m.p. 195-6°C decomp.

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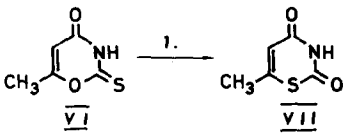
*Formed from N-methylurethane and diketene in acetic acid, b.p. 96°C/0.35 mm. The N.M.R. and i.r. data were consistent with the proposed structure, and further support was obtained from its chemical conversion into 1,3,6-trimethyluracil on heating with 40% aqueous methylamine.

(λ_{max} EtOH 237 mμ, ν_{CO} (Nujol) 1660, 1705, 1765 cm^{-1}). In this case the reaction was accompanied by additional hydrolysis of the cyano-group to the amide.

6-Methyl-4-oxo-2-thio-2,3-dihydro-4H-1,3-oxazine (VI)[1], m.p. 201-203°C, $\lambda_{max.}$ (EtOH) 216, 267 mμ, undergoes an interesting isomerisation to 2,4-dioxo-6-methyl-2,3-dihydro-4H-1,3-thiazine (VII)[3], m.p. 182°C, $\lambda_{max.}$ (EtOH) 212, 268 mμ, on solution in concentrated sulphuric acid*, but not in trifluoroacetic acid alone. Pyridine also does not effect rearrangement. The interconversion was followed by N.M.R.**, and the best results were obtained using a mixture of 20% conc. sulphuric acid in trifluoroacetic acid ($t_{\frac{1}{2}}$(33°) = 24 hr.). On a preparative scale the reaction was complete after heating under reflux for 3 hours; work up gave VII in 75% yield.



VI VII

1. H_2SO_4 (conc)

We have reinvestigated the rearrangement of 3-benzyl-6-methyl-4-oxo-2-(N-phenylimino)-2,3-dihydro-4H-1,3-oxazine (VIII) into 3-benzyl-6-methyl-1-phenyluracil (IX) using N.M.R.

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*An unidentified solid was also deposited in small amounts.

**In this solvent mixture the $C_{(5)}$-H of the 1,3-thiazine (VII) appears 27 cps downfield from the $C_{(5)}$-H of the 1,3-oxazine (VI). The similarity of the u.v. spectra of VI and VII precluded its use in following this isomerisation.

TABLE 1

N.M.R. τ Values[8] of 1,3-Oxazines and Derived Products

Compound	Solvent	$C_{(5)}$-H	$C_{(6)}$-CH_3	Other Resonances[+]
IIIa	D_6-DMS	4.13	7.85	
IIIb	$CDCl_3$	4.22	7.79	N-CH_3, 6.68
V	D_6-DMS	-	7.64	
VI	D_6-DMS	3.86	7.79	
VI	Pyridine	4.01	8.02	
VII	Pyridine	3.60	7.93	
VII	D_6-DMS	3.57	7.74	
VIII	$CDCl_3$	4.42	8.06	Benzyl CH_2, 4.80
VIII	Pyridine	4.25	8.18	" , 4.65
IX	$CDCl_3$	4.24	8.16	" , 4.87
IX	Pyridine	4.13	8.27	" , 4.68
X	$CDCl_3$	4.25	7.87	" , 4.99
XI	D_6-DMS	4.35	8.22	

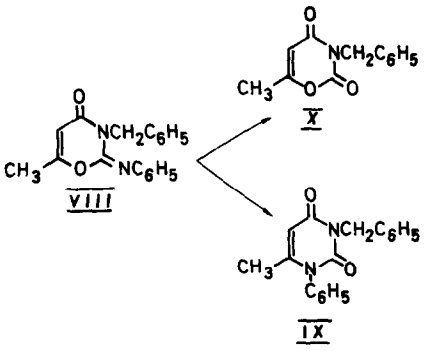
[+]Phenyl protons appeared as complex multiplets.

techniques to analyse and monitor the reaction. Our results are different from those reported by Lacey[5]. We have found that concentrated hydrochloric acid rapidly destroyed the imino-1,3-oxazine (VIII) and after 1-2 min. formed the 1,3-oxazine (X), 45-50%, and the uracil (IX)*, 35-40%. Dilute hydrochloric acid (1.7 N) slowly decomposed (VIII) to form the same products. The imino-1,3-oxazine** was very soluble in trifluoroacetic acid and was quite stable in this solvent even after prolonged refluxing.

*This structure was confirmed by unambiguous synthesis from 6-methyl-1-phenyluracil[4] (XI), by benzylation in alkaline methoxyethanol.

**We have also studied the related 2-imino-4-oxo-1,3-4H-thiazines and these results will be reported at a later date.

An aqueous solution of this acid (1:1) converted (VIII) mainly into the 1,3-oxazine (85%). Refluxing (VIII) in pyridine, collidine or trichlorobenzene had no effect, while concentrated sulphuric acid caused extensive decomposition. The uracil (IX) was slowly formed from (VIII) on refluxing with benzene containing p-toluene sulphonic acid.



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