The Intramolecular Acylation of Enamine-acids

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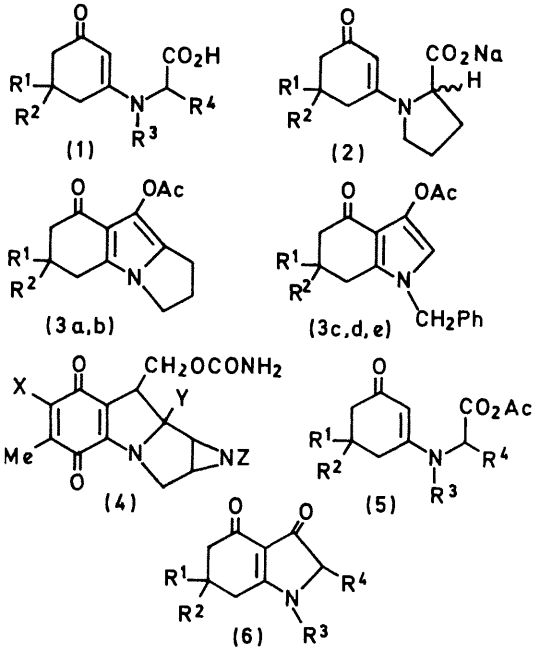
Summary Enamine-acids or their salts, available from condensation of cyclohexane-1,3-diones and secondary amino-acids, their salts and their esters, are transformed, *via* treatment with acetic anhydride, to 3-acetoxy-4,5,6,7-tetrahydro-4-oxoindoles.

PROMPTED by the recent report of Bobbitt and Dutta[1],† on the intramolecular condensation of enamine-aldehydes to afford tetrahydro-oxoindoles, and by the emerging utility of derivatives of the latter as analgaesics,[2a] antipsychotic, and anti-anxiety agents,[2b] we report our results of a study of a related reaction. We find that the enamine-acids (**1**) and the salts (**2a,b**) are transformed on exposure to an excess of hot acetic anhydride to 3-acetoxy-4,5,6,7-tetrahydro-4-oxoindoles (**3**) in good to moderate yields. The novel tricyclic tetrahydro-oxoindoles (**3a,b**) are of interest because their skeletal similarity to the natural mitomycin antibiotics (**4**)[3] suggests that a suitably functionalized derivative of (**3a**) might have synthetic value.

The enamine-acids (**1**) are synthesized by condensation of the appropriate cyclohexane-1,3-diones with ethyl *N*-benzyl-α-aminoacetate[4] or ethyl prolinate,[5] followed by mild hydrolysis of the ester function. The enamine-acid salts (**2**) result from condensation of the 1,3-diones with sodium prolinate in hot *NN*-dimethylformamide solution.[6,7]

Ring closure was effected on a preparative scale by treatment of the acids with hot neat acetic anhydride for periods of 12—45 min., followed by isolation of (**3**) by elution or dry-column[8] chromatography. The acid salts (**2a,b**) were cleanly converted into the tricyclic tetrahydro-oxoindoles (**3a,b**), no chromatographic purification being required.

Presumably, the sequence (**1**) or (**2**) → (**5**) → (**6**) → (**3**) takes place. Evidence for this comes from the observation (n.m.r.) that (**1c**), on treatment with a deficient amount of acetic anhydride, is readily converted into at least one intermediate, whose singlet methylene resonances (adjacent



(1) (2) (3a,b) (3c,d,e) (4) (5) (6)

	R^1	R^2	R^3	R^4
(a)	Me	H	$-(CH_2)_2-$	
(b)	Me	Me	$-(CH_2)_2-$	
(c)	Me	Me	CH_2Ph	H
(d)	Me	H	CH_2Ph	H
(e)	H	H	CH_2Ph	H

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to nitrogen) at τ 6·11 and 5·27 p.p.m. are consistent with those expected for (**5c**) or (**6c**).

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