Simple and Effective Synthesis of Pyrido[2,1-*b*]thiazines

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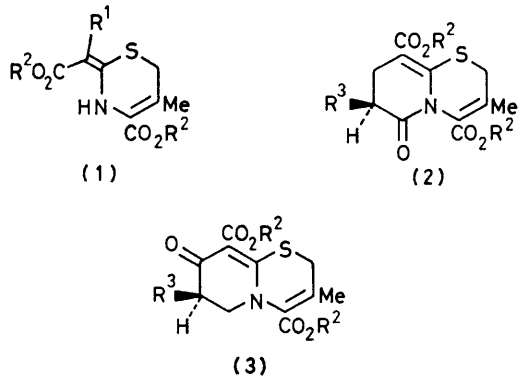
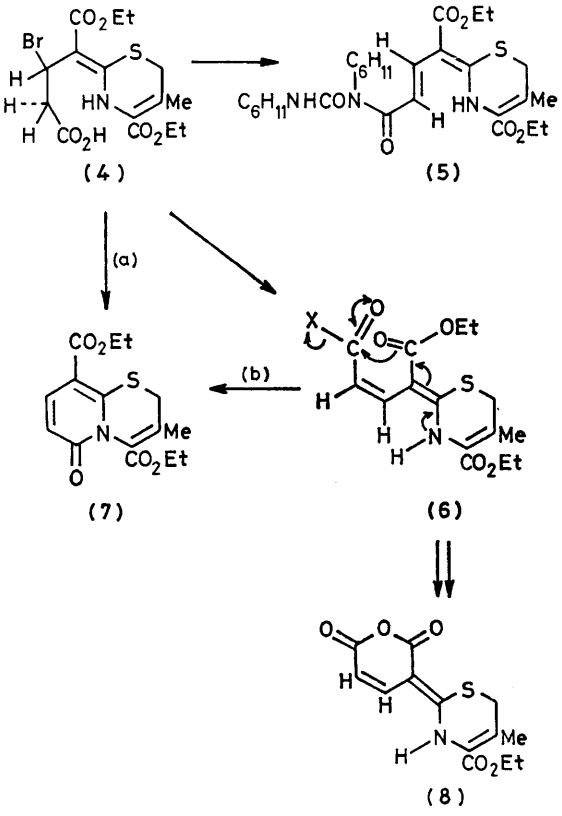
Summary One-step annelation of the 1,3-thiazine derivatives (**1**, $R^1 = H$) is achieved using substituted acrylic acids under peptide coupling conditions; use of sterically hindered acrylic acids results in an anomalous reaction and the thiazine derivative (**1**, $R^1 = R^2 = Et$) gives an interesting rearrangement.

THE chemistry of 1,3-thiazines is of considerable interest because this ring system is present in the bicyclic compounds which make up the cephalosporin group of antibiotics. We report herein a simple effective synthesis of bicyclic compounds containing this ring system by treating substituted acrylic acids with the thiazine derivatives (**1**, $R^1 = H$)[1] under peptide condensation conditions.

When the acid chloride of 2-phthalimidoacrylic acid[2] was treated with the dihydrothiazine (**1**; $R^1 = H$, $R^2 = CH_2Ph$), a product, $C_{33}H_{26}N_2O_7S$ (λ_{max} 313 nm†), was obtained in 30% yield. The yield was improved to 92% when the phosphazo-method[3] of coupling was used. The spectra were in keeping with structure (**2**; R^3 = phthalimido, $R^2 = PhCH_2$). The alternative structure (**3**) was ruled out since no absorption occurred to lower field than δ_C 167 p.p.m. in the ^{13}C n.m.r. spectrum. When the diethyl ester (**1**; $R^1 = H$, $R^2 = Et$)† was prepared from ethyl 3-methyl-2-oxobut-3-enoate[4] and α-ethoxycarbonylthioacetamide[1] the phosphazo-method gave a 66% yield of (**2**; R^3 = phthalimido, $R^2 = Et$)†. Use of 2-phenylacetamidoacrylic acid[5] in the synthesis by the phosphazo-method gave (**2**; $R^3 = PhCH_2CONH$, $R^2 = PhCH_2$) and (**2**; $R^3 = PhCH_2CONH$, $R^2 = Et$)† in 80 and 82% yields, respectively, whilst use of acrylic acid gave a 56% yield of (**2**; $R^3 = H$, $R^2 = PhCH_2$).†



When (*Z*)-3-bromoacrylic acid[6] was treated with the ester (**1**; $R^1 = H$, $R^2 = Et$) in the hope of obtaining fused pyridones, the phosphazo-method gave complex mixtures. Use of dicyclohexylcarbodi-imide in the presence of a 4 Å molecular sieve, however, did yield a compound, $C_{15}H_{17}NO_5S$ (λ_{max} 360 nm†), in 50% yield. The i.r. spectrum had absorptions characteristic of a 2-pyridone[7] and the ^1H and ^{13}C n.m.r. spectra were consistent with structure (**7**). A second compound, $C_{28}H_{41}N_3O_6S$,† was obtained in 22% yield and was obviously the *transoid* acylurea (**5**). This suggested that, in the one-step annelation reactions, Michael attack of the enethiamine on the acrylic acid preceded acylation. A third compound, $C_{13}H_{13}NO_5S$ (λ_{max} 390 nm†), was also obtained from this reaction in 14% yield. Spectroscopic data indicated that this compound was one of the two geometric isomers of the glutaconic anhydride (**8**); the i.r. spectrum contained an N–H absorption at ν 3325 cm^{-1} and other properties were as expected[8] and comparable with those for an authentic sample of an analogous compound.[9] It is likely that this compound is derived from the *cisoid* intermediate (**6**), since no analogous compounds were formed in the synthesis of the dihydropyridones (**2**). Nucleophilic attack by the oxygen of the vinylogous urethane on the activated acid in the inter-



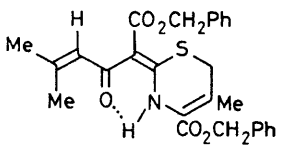
SCHEME

† All new compounds had satisfactory analytical and spectroscopic data. Where u.v. data are quoted, the solvent is MeOH and only the absorption to highest wavelength is described.

mediate (**6**) would give compound (**8**), as shown in the Scheme, and this may imply that the pyridone (**7**) is derived *via* cyclisation of the thiazine (**4**) followed by dehydrobromination, as in route (a), rather than *via* the alternative route (b).

When 3,3-dimethylacrylic acid was treated with (**1**; $R^1 = H$, $R^2 = CH_2Ph$) using the phosphazo-method a product, $C_{27}H_{27}NO_5S$ (λ_{max} 358 nm†) was obtained in 45% yield. The ^1H and ^{13}C n.m.r. spectra indicated that this was a mixture of the two geometric isomers of compound (**9**) which rapidly equilibrated at 140 °C *via* an imine intermediate. The ketonic carbonyl groups resonated at δ_C 188·6 and 189 p.p.m. in the ^{13}C n.m.r. spectrum (room temperature) and were to lower field than the amide carbonyl resonances of compounds (**2**) and (**7**). It is evident, therefore, that the annelation reaction is extremely sensitive to steric effects and that the enethiamine system undergoes 1,2-addition with 3,3-dimethylacrylic acid rather than the more usual 1,4-addition.

When $R^1 = H$ in compounds (**1**) the 'normal' synthesis would be precluded and so we prepared (**1**; $R^1 = R^2 =$ Et)† from 2-ethoxycarbonylthiobutyramide‡ and ethyl 3-methyl-2-oxobut-3-enoate.[4] This was treated with 2-phthalimidoacrylic acid using the phosphazo-method to give a 56% yield of a compound, $C_{25}H_{26}N_2O_7$ (λ_{max} 288 nm†). The ^1H n.m.r. spectrum lacked the resonance due to the CH_2S protons in compound (**2**) and exhibited a typically[10]



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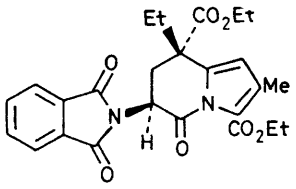

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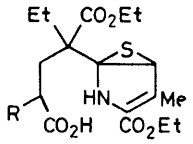

(11)

β-pyrrolic proton at δ 6·1. These and other data indicated structure (**10**), which would be formed from the initial 1,4-adduct of the 'normal' synthesis *via* an episulphide (**11**).

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