SYNTHESIS OF 5-HYDROXY-4,5-DIHYDRO-6H-1,3-THIAZINE-4,4-DICARBOXYLATE DERIVATIVES

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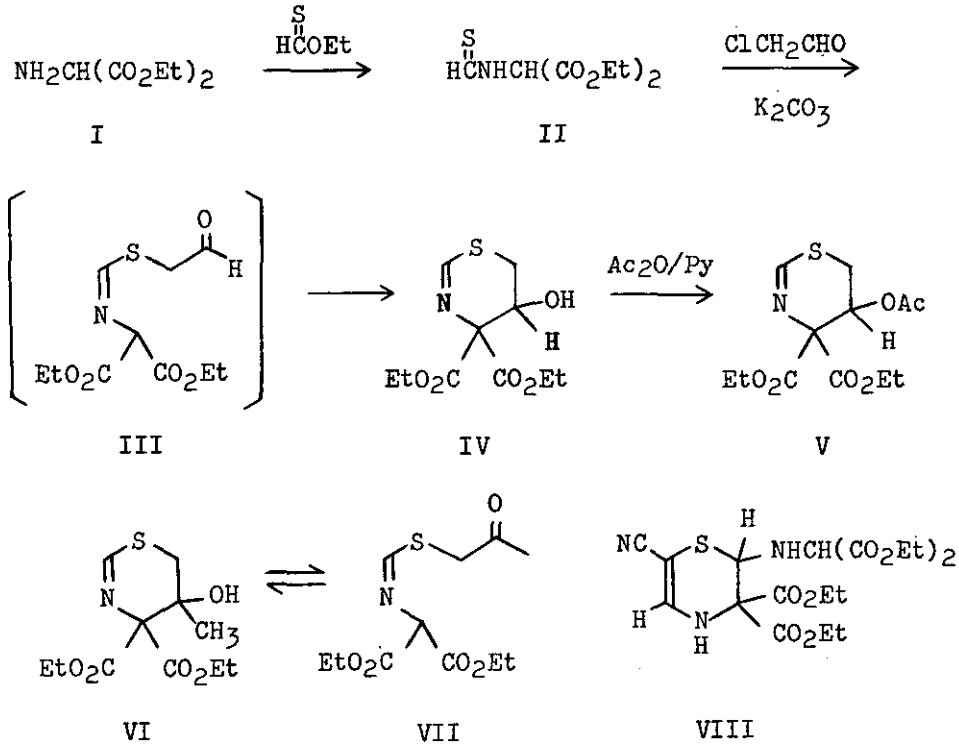
Dihydro-1,3-thiazines, the title compounds (IV-VI), were prepared as possible intermediates for cephalosporin synthesis. The process involves a few steps starting from diethyl aminomalonate(I).

Although numerous 1,3-thiazine derivatives have been reported, 1,3-thiazines bearing no substituent at the 2-position are seldom mentioned in the literature. The 2-unsubstituted 1,3-thiazines seem to be less accessible possibly because of their susceptibility to hydrolysis and other nucleophilic reactions at the 2-position. Recently Ratcliffe and Christensen[1] have succeeded in obtaining 2-unsubstituted 6H-1,3-thiazine derivatives for the synthesis of cephalosporin derivatives. In connection with synthetic studies on the β-lactam antibiotics,[2,3] it was our intention to synthesize 2-unsubstituted 1,3-thiazines which may be of value as intermediates for cephalosporin synthesis. The title

compounds were synthesized with the hope that the activated methine carbon of an aminomalonate derivative (III) might facilitate its cyclization reaction with the carbonyl group to give a dihydro-1,3-thiazine derivative.

Thioformylation of diethyl aminomalonate[4] was carried out by treatment of the hydrochloride with triethylamine and ethyl thioformate in carbon tetrachloride at room temperature. The thioformamide thus formed was reacted with freshly prepared chloroacetaldehyde in the presence of powdered potassium carbonate in acetone for 14 hr at room temperature. The crude product was purified by dry column chromatography on silica gel (1:1 benzene-AcOEt) to give diethyl 5-hydroxy-4,5-dihydro-6H-1,3-thiazine-4,4-dicarboxylate as an unstable oil (IV, Yield 54%, NMR($CDCl_3$) δ: 1.30(t, J=7.5 Hz, 2 x $CH_2C\underline{H}_3$), 3.04(d-d, J=13.5, 5.5 Hz, C_6-H), 3.41(d-d, J=13.5, 3.2 Hz, C_6-H), 4.28(q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.33 (q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.61(d-d, J=5.5, 3.2 Hz, C_5-H), 8.45(s, C_2-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430(OH), 1735(ester)). The hydroxyl compound IV was acetylated with excess acetic anhydride in pyridine (room temp., 15 hr). The reaction mixture was poured into ice-water and extracted with AcOEt, and the residue obtained from the extract was purified by preparative TLC (4:1 benzene-AcOEt) to afford an acetate (V, Yield 74%, MS m/e: 303(M^+), NMR ($CDCl_3$) δ: 1.21(t, J=6.8 Hz, 2 x $CH_2C\underline{H}_3$), 1.98(s, $COC\underline{H}_3$), 3.04(d-d-d, J=14.0, 4.2, 1.5 Hz, C_6-H), 3.59(d-d, J=14.0, 3.0 Hz, C_6-H), 4.18(q, J= 6.8 Hz, $C\underline{H}_2CH_3$), 4.32(q, J=6.8 Hz, $C\underline{H}_2CH_3$), 5.70(d-d, J=4.2, 3.0 Hz, C_5-H), 8.42(bs, C_2-H)). Similarly the thioformamide II was treated with chloroacetone in the presence of K_2CO_3 in acetone



to yield approximately a 1:1 mixture of a dihydro-1,3-thiazine derivative (VI) and acyclic imine (VII). NMR($CDCl_3$) δ: VI, 1.37 (s, CH_3), 2.71, 3.31(AB-q, J=12.5 Hz,2xC_6-H), 8.37(s, C_2-H); VII, 2.23(s, $COCH_3$), 3.79(s, SCH_2), 4.72(s, NCH), 8.28(s, CH=N). The two components of the product appeared to be readily interconvertible and in equilibrium.

Similar treatment of the thioformamide II with chloroacetonitrile and K_2CO_3 in acetone (room temp., 24 hr) did not yield the corresponding 1,3-thiazine, but instead a dihydro-1,4-thiazine (VIII, Yield 32%, mp 100-101° (from isopropyl ether), MS m/e: 443 (M^+), NMR($CDCl_3$) δ : 1.28(t, J=7.5 Hz, 4 x $CH_2\underline{CH}_3$), 2.63(d-d, J=

13.0, 5.6 Hz, NH), 4.23, 4.25, 4.30, 4.32 (4 x q, J=7.5 Hz, 4 x $C\underline{H}_2CH_3$), 4.27(d, J=5.6 Hz, NHC$\underline{H}$), 5.03(d, J=13.0 Hz, C_6-H), 6.18 (d, J=6.4 Hz, NH), 7.14(d, J=6.4 Hz, C_3-H)).

The reactions of the 1,3-thiazine V with azidoacetyl chloride failed to yield the desired cepham compound under the usual reaction conditions. A previous paper[3] implies that the [2 + 2] cycloaddition reaction of a 1,3-thiazine-4-carboxylate occurred on the opposite side of the C_4-carboxylate group. In this case, the additional carboxylate group appears to have prevented an azidoketene addition to the C=N bond. The following paper, however, indicates that glycine ester can be utilized as the starting material for 1,3-thiazine and cephalosporin synthesis.

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