Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 92, No. 1, January 1983, pp. 99–106.

Addition products of dimethyl acetylenedicarboxylate to thioureas—studies on 2-(*p*-bromophenyl) imino-3-methyl-5-carbomethoxymethylidenethiazolidin-(4)-one†

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MS received 27 September 1982

Abstract. N-(*p*-bromophenyl)-N′-methylthiourea (1) undergoes addition to acetylenedicarboxylic acid (3) and its dimethyl ester (4) to form 2-(*p*-bromophenyl) imino-3-methyl-5-carboxymethylidenethiazolidin-(4)-one (5) and its methyl ester (6) respectively. Alkaline hydrolysis of (6) leads to a mixture of (5) and 2-(*p*-bromophenyl) imino-3,4-dihydro-3-methyl-4-oxo-2H (1,3)-thiazine-6-carboxylic acid (7). Several reactions of (5) and (7) are described. The structures of (5) and (7) are established by x-ray crystallographic and ^{13}C NMR studies.

Keywords. Thiazolidinone; thiourea; addition products; dimethyl acetylenedicarboxylate.

1. Introduction

Dinucleophiles like thioureas undergo facile regioselective, sometimes regiospecific addition to acetylenedicarboxylic esters. The structures of the products have been the subject of controversy (Vögeli *et al* 1978; Acheson and Wallis 1981), only a few having been solved by x-ray crystallographic studies (Cameron *et al* 1970; Adman *et al* 1975; Mckillop *et al* 1978). We have demonstrated earlier (Vögeli *et al* 1978; Nagarajan *et al* 1979) for the first time that ^{13}C NMR spectroscopy was ideally suited to provide satisfactory answers in this area, by studying the products from a number of dinucleophiles, mostly thioureas. In one case, *viz.* that of the addition product (6) of N-(*p*-bromophenyl-N′-methylthiourea) (1) and dimethylacetylenedicarboxylate (4), we had undertaken x-ray crystallographic studies as well. We wish to present in this paper results of these studies and incidental interesting chemical observations which demonstrated facile conversion of thiazolidones to thiazinones.

2. Addition of thiourea (1) to acetylenedicarboxylic acid derivatives to form thiazolidones (5) and (6)

The reaction of thiourea (1) with diester (4) provided the thiazolidinone (6) in 60% yield as slender, yellow needles. During attempts to grow crystals suitable for x-ray studies, nice crystals were obtained by the fortuitous use as solvent, of acetone

† Contribution No. 596 from CIBA-GEIGY Research Centre.
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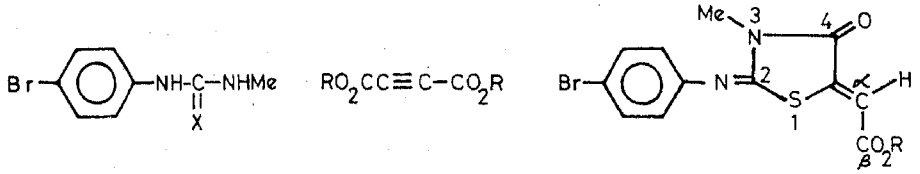
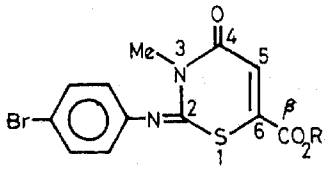


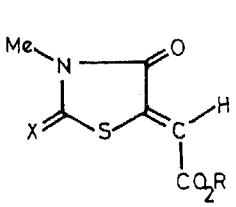
(1) X = S
(2) X = O

(3) R = H
(4) R = Me

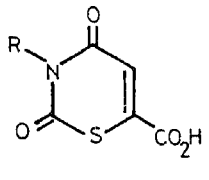
(5) R = H
(6) R = Me



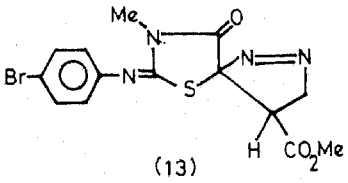
(7) R = H
(8) R = Me



(9) X = O ; R = H
(10) X = MeN ; R = Me



(11) R = Me
(12) R = p-Br-C_6H_4-



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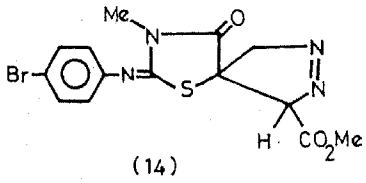

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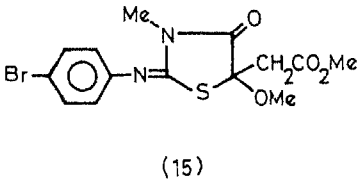

(15)

containing some dilute hydrochloric acid, but these turned out to be those of acid (5) corresponding to (6). Acid (5) was obtained directly from (1) in 70% yield by using acetylenedicarboxylic acid (3). Mild esterification of (5) employing stoichiometric amount of diazomethane afforded (6), while an excess of the reagent led to the formation of the pyrazoline (13), also obtained from (6) with excess diazomethane. Structure (13) was preferred to (14) for this product because of the appearance of signals in its ^{1}H NMR spectrum for the protons of a $-CH_2-CH-$ unit with appropriate chemical shifts. Treatment of (5) or (6) with hot hydrochloric acid in acetic acid resulted in the formation of 3-methyl-5-carboxymethylidene-thiazolidin-2,4-dione (9). This acid was also obtained by hot acid treatment of the thiazolidone (10) which was formed from N,N′-dimethylthiourea and diester (4). Rearrangement concomittant with acid hydrolysis to the thiazinone (11) had not happened, because in the ^{13}C NMR spectrum of (9), C-β was seen as a singlet, while C-2 was a quartet and C-4, a multiplet. Structure (11) would have required C-β to be a doublet with significant (~6Hz) $^3J_{CH}$ coupling (*vide infra*).

3. Alkaline hydrolysis of thiazolidone ester (6) to corresponding acid and thiazinone (7)

Interesting results were obtained when ester (6) was subjected to alkaline hydrolysis in dioxane solution. Brief treatment followed by acidification resulted in the formation of thiazolidone (5) and thiazinone (7) in nearly equal proportions. A small amount of urea (2) was also formed under these conditions, which was the sole product when hydrolysis was carried out for a longer period. The structures of (5) and (7) were established by single crystal x-ray crystallographic studies as shown later. Additional confirmation came from ^{13}C NMR spectral studies. In the carbonyl region, (6) had a

quartet for C–β due to coupling with methoxyl protons ($J = 4$ Hz) with further fine structure due to C–α H ($J = 1.1$ Hz), a multiplet for C–4, due to coupling with C–α H ($J = 5.3$ Hz) and N–CH_3 protons ($J = 2.6$ Hz). The signal due to C–4 in the analogous thiazolidone (10) was complex and was not amenable to first order analysis. But decoupling experiments allowed the extraction of the coupling constants with C–α H and N-methyl protons respectively as 6 and 2.8 Hz. In the ^{13}C NMR spectrum of acid (5), the splitting pattern seen for C–4 in (6) was retained, while C–β was a doublet ($^2J_{CH} = 1.2$ Hz). On the other hand, acid (7) exhibited a larger doublet for C–β, due to coupling with C–5 H ($^3J_{CH} = 6.3$ Hz) and 2 quartets for C–4 H, due to couplings with C–5 and N-methyl protons to 2.5 and 1.5 Hz respectively. The thiazinone structure of (7) was thus secure, although the 2 bond coupling of C–4 with C–5 H was larger than the ones we had seen for similar structures earlier.

4. Esterification of thiazinone carboxylic acid (7)

Mild esterification of (7) with diazomethane gave ester (8) which, despite its m.p. being identical with that of (6), was definitely different (mixed m.p. and spectral parameters). Unfortunately, its ^{13}C NMR spectrum did not show sufficient resolution in the C=O region (perhaps due to lack of adequate concentration). Treatment of (7) with hot acid removed the *p*-bromoaniline group to afford thiazinone (11), along with a small percentage of (12) formed presumably by rearrangement.

5. Alkali-promoted interconversion of 5 and 7

Surprisingly, although alkali induced a partial rearrangement of thiazinone (7) to thiazolidone (5) (NMR, isolation and identification), the latter did not suffer a similar transformation, being recovered totally under mild conditions or affording urea (2) under stress. It appeared possible that during alkali treatment, (6) partially isomerised to (8) by attack of the nucleophile at the lactam C=O group and cyclisation at the ester terminus. Addition of (1) to (4) in the presence of dry potassium hydroxide, 4-dimethylaminopyridine or a trace of sodium methoxide always led to (6), with no sign of formation of (8). Efforts to isomerise (6) at least partly to (8) using the above bases or insufficient quantity of aqueous alkali in methanol or dioxane were unsuccessful. In the presence of a larger quantity of sodium methoxide, (6) was partly transformed to (15) by the addition of methoxide to the unsaturated ester group at C-5 (NMR, mass). We are thus obliged to postulate that only in the presence of aqueous alkali (6) is isomerised to (8), which undergoes instant hydrolysis to (7).

6. Spectral studies on thiazolidones and thiazinones

The study provided us with pairs of thiazolidone and thiazinone derivatives (5) and (7), (6) and (8) and (9) and (11), for which UV, IR, ^{1}H and ^{13}C NMR and mass spectral data are presented in the experimental section. While there are differences between pairs, except by the use of ^{13}C NMR data, it appears doubtful whether an unambiguous structural assignment can be made when only one isomer is available. In the UV, the 2-iminothiazolidones (5), (6) and (10) had λ^{max} at 307–310 nm and the 2-oxoimidazolidinone (9) at 302 nm while the 2-iminothiazinones (7) and (8) showed

maxima at 271–275 nm and the 2-oxothiazinones (11) and (12) at 293 and 285 nm respectively. In the mass spectra of thiazolidinones (5) and (6) as also of the thiazinones (7) and (8), the radical ions due to N–(*p*-bromophenyl)–N′–methyl carbodimide (m/e 208, 210) were very prominent.

7. Conclusions

That study confirmed our earlier contention (Vögeli *et al* 1978) that the primary products of addition of thioureas and acetylene-dicarboxylic acid derivatives are thiazolidones, which may isomerise to thiazinones. Further thiazolidones and thiazinones of the type handled here tend to interconvert under alkaline and in some cases also under acidic conditions and structure assignments using chemical correlations have to be treated with caution.

8. X-ray crystallographic studies

Crystals of (5) and (7) were studied by single crystal x-ray diffraction methods. Both structures were solved by the heavy atom method and the atomic parameters refined by least squares techniques to the usual R index less than 6%. The structural and conformational details are shown in figures 1 and 2.

9. Experimental

M.p.s are uncorrected. UV spectra were recorded with a Beckman DK 2A spectrophotometer for solution in aqueous ethanol (95%). IR spectra were recorded on nujol mulls with Perkin-Elmer Infra cord and model 421 IR spectrophotometers. ^{1}H NMR

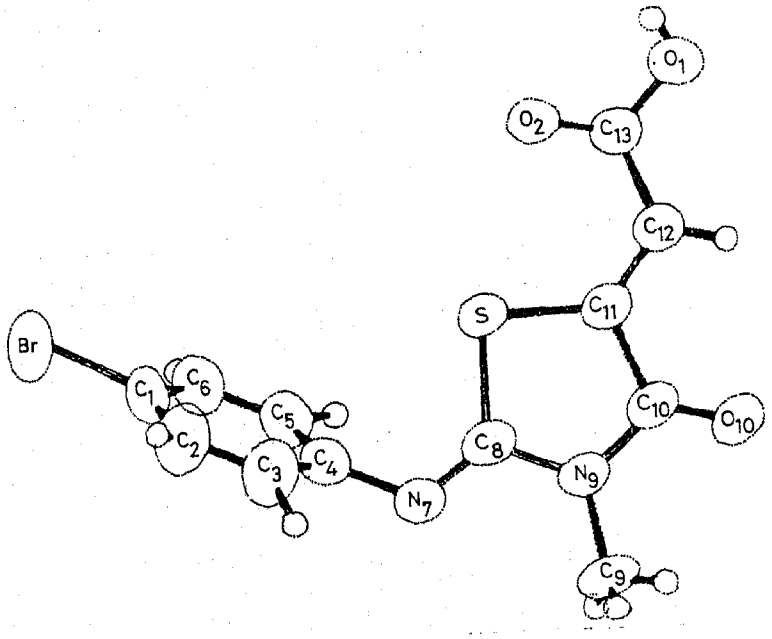

Figure 1. Crystal structure of 2-(*p*-bromophenyl-imino)-5-carboxymethylidenethiazolidin-4-one (5).

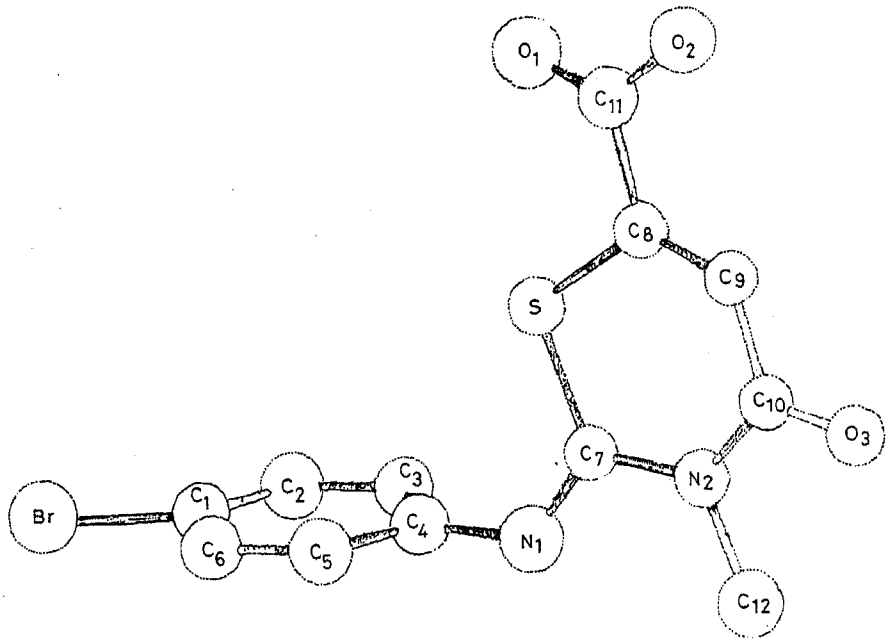

Figure 2. Crystal structure of 2-(*p*-bromophenyl-imino)-3,4-dihydro-3-methyl-4-oxo-2H-(1,3)-thiazine-6-carboxylic acid (7).

spectra were run on a Varian A60 or Bruker WH 90 spectrometer, with tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained from the latter instrument at 22.63 MHz. Mass spectra were recorded with a Varian Mat CH 7 mass spectrometer. X-ray diffraction data were collected first on a manual GE XRD5 machine and later remeasured on an automated ENRAF Nonivus CAD4 diffractometer.

9.1 *2-(p-Bromophenylimino)-5-carbomethoxymethylidenethiazolidin-4-one (6)*

To a warm solution of N-(*p*-bromophenyl)-N′-methyl thiourea (1) (9.8 g, m.p. 145°, from *p*-bromoaniline and methylisothiocyanate in boiling benzene) in MeOH (70 ml) was added dimethyl acetylenedicarboxylate (4) (5.7 g). A yellow precipitate appeared within 15 minutes. The product was filtered off after 16 hr and recrystallized from acetone-MeOH to give (6) (8.6 g) as bright, yellow needles, m.p. 138–140° (Found: C, 43.81; H, 3.34; N, 7.95. $C_{13}H_{11}BrN_2O_3S$ requires C, 43.96; H, 3.12; N, 7.89%); λ_{max} 243, 308 nm (log ϵ 4.14; 4.16); γ 1730, 1650, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 2H, ArH); 6.91 (s, 1H, C–α.H), 6.85 (m, 2H, ArH); 3.81 (s, 3H, OMe), 3.42 (s, 3H, N–Me); ^{13}C NMR ($CDCl_3$): δ 165.8 (m, C–β); 164.4 (m, C–4); 118.2 (d, C–α), 52.4 (q, O$\underline{C}H_3$), 29.4 (q, N$\underline{C}H_3$); m/e at 356, 354 (M^+); 212, 210 (ArN=C=NCH_3)$^+$.

9.2 *2-(p-Bromophenylimino)-5-carboxymethylidenethiazolidin-4-one* (5)

An aqueous solution of diacid (3) (from 1.5 g of the monopotassium salt in 20 ml water and 4.5 ml of 2N HCl) was added to a warm solution of thiourea (1) (2.45 g) in MeOH (50 ml). An orange precipitate appeared 30 min. The mixture was set aside overnight and filtered to give acid (5) as orange crystals (2.4 g) (from MeOH–Et_2O), m.p. 216–220° (Found: C, 42.15; H, 2.81; N, 8.57; M^+ at m/e 340, 342. $C_{12}H_9BrN_2O_3S$ requires C, 42.25; H, 2.60; N, 8.21%; M, 340, 342).

9.3 *Alkaline hydrolysis of adduct* (6) *to* (5) *and* (7)

To a solution of (6) (3 g) in dioxane (20 ml) was added 10% aqueous NaOH (20 ml) with stirring. After 1 min, water (50 ml) was added and the clear solution was acidified to give a solid (2.3 g) which was essentially a mixture of the thiazolidone (5) and thiazinone (7) acids in the ratio of 6:5 (^{1}H NMR); m.p. 180–190°. Slow evaporation of an acetone solution and manual separation of orange and yellow crystals gave (5) and (7) respectively. A small amount of the urea (2) was also obtained as white crystals, m.p. and mixed m.p. with authentic sample, 216–8°, M^+ at m/e, 228, 230. This was the sole product when the hydrolysis was carried out for 1 hr.

Acid (5) (from acetone–Et_2O), m.p. 216–220° was identical with the earlier sample (Found: C, 42.50; H, 3.02; N, 8.52%); λ_{max} 245 (sh), 307 nm (log ϵ 4.23, 4.14); γ 1730, 1680, 1640, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50 (m, 2H, ArH); 6.95 (s, 1H, C-α H); 6.85 (m, 2H, ArH); 3.43 (s, 3H, N–CH_3); ^{13}C NMR ($CDCl_3$ + DMSO-d_6), δ 167.1 (d, C-β); 165.0 (m, C-4); 122.7 (d, C-α); 29.2 (q, N–$\underline{C}H_3$); m/e 342, 340 (M^+), 212, 210 $(ArN{=}C{=}NCH_3)^+$.

Acid (7) (from acetone–Et_2O) had m.p. 177–80° (Found: C, 42.46; H, 3.03; N, 8.57%); λ_{max} 242 (sh), 275 nm (log ϵ 4.39, 4.04); γ 1700, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 7.47 (m, 2H, ArH); 7.17 (s, 1H, C-5H); 6.75 (m, 2H, ArH); 3.56 (s, 3H, N–CH_3); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 162.8 (d, C-β); 162.5 (m, C-4); 121.1 (d, C-5); 30.6 (q, N–$\underline{C}H_3$); m/e at 342, 340 (M^+), 298, 296 (M^+–CO_2), 212, 210 $(ArN{=}C{=}NCH_3)^+$.

9.4 *Reaction of acid* (5) *with diazomethane*

(i) Acid (5) (0.35 g, 1 mmole) in MeOH (5 ml) was treated with diazomethane (1 mmole) in Et_2O (10 ml) for 2 hr. The solvents were evaporated and the residue separated into the methyl ester (6) (0.15 g) and recovered acid (5) (0.1 g) by column chromatography over silica gel, (6) and (5) being eluted by $CHCl_3$ and $CHCl_3$–3% MeOH respectively. The ester thus obtained had m.p. 138–140° and was identical with the earlier sample (mixed m.p., tlc).

(ii) Acid (5) (0.15g) in MeOH (10 ml) was treated with excess diazomethane (from 5 g nitrosomethyl urea) in Et_2O (20 ml). After 16 hr, the solution was evaporated and the residue crystallized from CH_2Cl_2–hexane to give pyrazoline (13) (0.1 g) as white crystals, m.p. 115–117° identical with the sample below. (Found: N, 14.15. $C_{14}H_{13}BrN_4O_3S$ requires N, 14.11%).

9.5 *Pyrazoline* (13) *from ester* (6)

Ester (6) (0.5 g) in MeOH (10 ml) and CH_2Cl_2 (5 ml) was treated with excess diazomethane (from 5 g nitrosomethylurea) in Et_2O (20 ml) for 16 hr to afford pyrazoline (13) (0.5 g), white crystals (from Et_2O), m.p. 118–120°C (Found: C, 42.49; H, 3.63; N, 14.27. $C_{14}H_{13}BrN_4O_3S$ requires C, 42.33; H, 3.30; N, 14.11%); ν 1720, 1650; ^{1}H NMR ($CDCl_3$): δ 7.46 (m, 2H, ArH), 6.85 (m, 2H, ArH), 5.05 (d, J = 7Hz; CH_2); 3.68 (s, 3H, OCH_3); 3.62 (t, J = 7Hz, 1H, C$\underline{H}$–CO_2Me); 3.41 (s, 3H, NCH_3); m/e at 370, 368 ($M^+ - N_2$), 338, 336 (M^+–N_2–MeOH), 311, 309 (M^+–N_2–CO_2Me), 212, 210 $(ArN{=}C{=}NCH_3)^+$.

9.6 *Esterification of acid (7)*

Acid (7) (0.51 g, 1.5 mmole) in MeOH (5 ml) was treated with diazomethane (3 mmoles) in ether (20 ml) overnight. The ester (8) (60 mg) was obtained along with unreacted acid (0.15 g) and separated by chromatography on silica gel. Crystallisation from CH_2Cl_2–hexane gave pale yellow crystals of (8), m.p. 138–140°, which depressed the m.p. of (6) upon admixture (Found: C, 44.10; H, 3.30; N, 7.82%); λ_{max}243, 271 (log ϵ4.26, 4.08); γ 1720, 1685, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H, ArH), 7.13 (s, 1H, C–5H); 6.73 (m, 2H, ArH); 3.87 (s, 3H, OCH_3); 3.55 (s, 3H, N–CH_3); ^{13}C NMR ($CDCl_3$): δ 162.2 (m, C–β), 161.7 (m, C–4); 122.1 (d, C–5); 53.6 (q, O$\underline{C}H_3$); 30.9 (q, N–$\underline{C}H_3$); m/e at 356, 354 (M^+), 212, 210 (ArN=C=NMe)$^+$.

9.7 *Treatment of ester (6) with sodium methoxide*

Ester (6) (0.5 g) in MeOH (40 ml) containing sodium methoxide (from 50 mg sodium) was left overnight at 25°, made just acidic with 2N HCl and concentrated to 10 ml to give recovered starting material (0.2 g). The mother liquor was evaporated to dryness and the residue treated with water and a few drops of MeOH to give (15) as a white solid, m.p. 110°; ^{1}H NMR ($CDCl_3$); δ 7.56 (m, 2H, ArH); 7.17 (m, 2H, ArH); 3.61 (s, 3H, CO_2CH_3); 3.43 (s, 3H, OCH_3); 3.35 (s, 3H, NCH_3); 3.17 (d, J = 18 Hz, C–α H); m/e at 388, 386 (M^+), 357, 355 (M^+–OMe), 315, 313 (M^+–CH_2CO_2Me).

9.8 *Hydrolysis of acid (5) to (9)*

Acid (5) (0.35 g) in acetic acid (10 ml) was heated under reflux with 4N HCl (10 ml) for 3 hr. The solution was concentrated to about 6 ml and cooled. Colourless crystals of (9) separated and were filtered off; 0.2 g, m.p. 188–190° (from Et_2O-hexane) identical with other samples obtained as shown below. The acidic filtrate was made basic with 10% NaOH to give *p*-bromoaniline (0.1 g), m.p. and mixed m.p. 65°. Acid (9) (Found: C, 38.35; H, 2.96; N, 7.55. $C_6H_5NO_4S$ requires C, 38.51; H, 2.69; N, 7.49%).

9.9 Acid (9) from ester (6)

Hydrolysis of ester (6) (0.5 g) as before gave acid (9) (0.2 g), m.p. and mixed m.p. 188–190°.

9.10 *Acid (9) from ester (10)*

A solution N,N′-dimethylthiourea (2.6 g) in MeOH (20 ml) was left with diester (4) for 10 min to afford the thiazolidone ester (10) (4.5 g), m.p. 152–4° (from CH_2Cl_2–Et_2O) (Found: C, 45.17; H, 5.09; N, 12.80. $C_8H_{10}N_2O_3S$ requires C, 44.86; H, 4.71; N 13.08%); λ_{max} 310 nm (log ϵ 4.15); γ 1720, 1700, 1660, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 1H, C–α H); 3.85 (s, 3H, OCH_3); 3.30, 3.29 (2s, 3H each, N–CH_3); ^{13}C NMR ($CDCl_3$ + DMSO–d_6); δ 166.2 (m, C–β); 164.7 (m, C–4); 115.3 (d, C–α), 52.2 (q, O$\underline{C}H_3$);

38.8 (q, $\underline{C}H_3$N=C); 29.1 (q, C–N–$\underline{C}H_3$); m/e at 214 (M^+); 183 (M^+–OMe), 155 (M^+–CO_2Me), 144 (M^+–MeN=C=NMe).

The above ester (2.1 g) in acetic acid (20 ml) was hydrolysed as before with 4N HCl (60 ml) under reflux to give acid (9) (1.8 g), m.p. 188–190° (from Et_2O) (Found: C, 38.79; H, 3.00; N, 7.58%); λ_{max} 249, 302 nm (log ϵ 3.94, 3.89); γ 1755, 1700, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 6.92 (s, 1H, C-αH); 3.17 (s, 3H, N-CH_3); ^{13}C NMR: δ 169.0 (q, C-2); 166.3 (s, C-β); 164.8 (m, C-4); 120.2 (d, C-α), 27.4 (q, N-$\underline{C}H_3$); m/e at 187 (M^+), 130 (M^+-MeNCO).

9.11 *Acidic hydrolysis of acid (7)*

Acid (7) (1.6 g) in acetic acid (20 ml) was heated under reflux with 4N HCl (45 ml) for 30 min. The initially yellow solution became colourless and deposited crystals. The mixture was cooled and filtered to give the *p*-bromophenylthiazinone (12) (70 mg), m.p. >300° (decomp.) (Found: C, 40.44; H, 2.05. $C_{11}H_6BrNO_4S$ requires C, 40.27; H, 1.84%); λ_{max} 285 nm (log ϵ 3.97); γ (KBr) 1780, 1700, 1635 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.64 (m, 2H, ArH), 7.22 (m, 2H, ArH); 7.09 (s, 1H, C-5H); m/e at 329, 327 (M^+), 301, 299 (M^+-CO), 199, 197 (ArN=C=O)$^+$.

The filtrate was concentrated to a small volume, diluted with 50% aqueous MeOH and the solution passed through a column of Dowex-50 (20–50 mesh; H^+ form). The column was eluted further with 50% aqueous MeOH. The combined eluates were evaporated to dryness and the residue crystallised from CH_2Cl_2–Et_2O to give (11) (0.15 g), m.p. 158° (Found: C, 38.79; H, 2.95; N, 7.71%); λ_{max} 293 nm (log ϵ 3.68); γ (KBr) 1700, 1640 cm^{-1}; ^1HNMR ($CDCl_3$+DMSO-d_6): δ 7.24 (s, 1H, C-5H); 3.40 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 164.7 (q, C-2), 163.6 (m, C-β), 162.7 (m, C-4), 121.8 (d, C-5), 28.3 (q, N-$\underline{C}H_3$), m/e at 187 (M^+); 144 (M^+CO_2), 130 (M^+-MeNCO).

Acknowledgement

We thank Dr S Selvavinayakam and his associates for analytical and spectral data.

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