

Preparation of Some Perhydrothiazolo[3,2-a][1,3,5] triazine-2,4-diones

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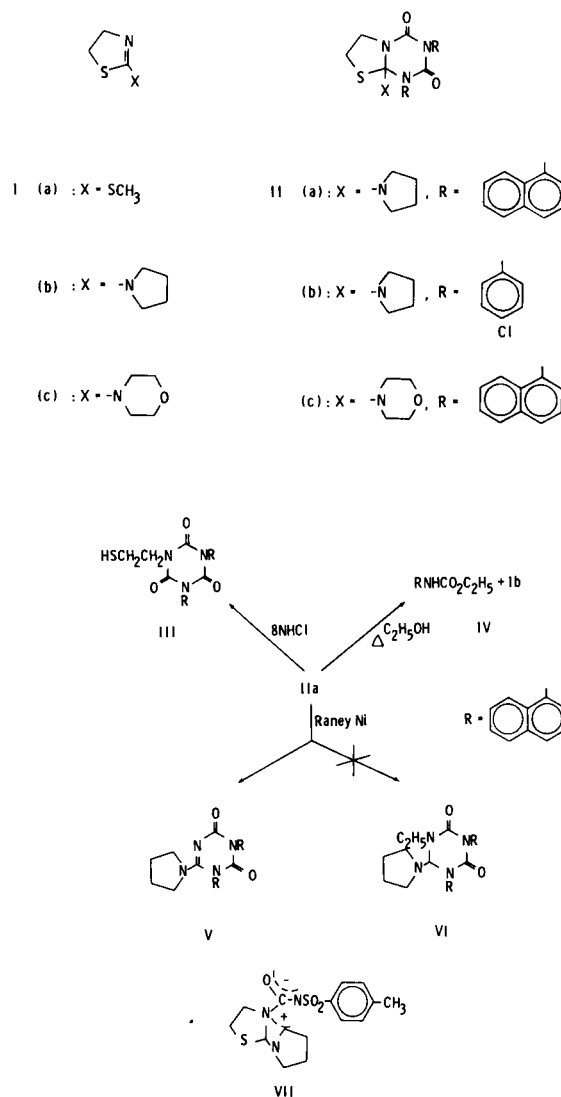
2-Dialkylamino- Δ^2 -thiazolines were found to react with aryl isocyanates to give 1,3-diaryl-8a-dialkylaminoperhydrothiazolo[3,2-a][1,3,5]triazine-2,4-diones (IIa-c), while *p*-toluenesulphonyl isocyanate gave a 1:1 adduct (VII). No reaction was observed with alkyl or aryl isothiocyanates.

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1,4-Dipolar cycloadditions involving isocyanates and carbon-nitrogen double bonds are well established routes to 1,3,5-triazines (1-5). More recently it has been shown that amidines, guanidines, and other carbonimidic acid derivatives undergo similar cycloadditions, and a number of novel bridged- and fused-ring triazines have been prepared in this way (6-10). There is, however, only one report of thiazolo[3,2-a][1,3,5]triazines prepared by such 1,4-dipolar cycloadditions (11), although related compounds have been obtained by reactions of 2-aminothiazole, and its derivatives, with alkoxy carbonyl isothiocyanates (12-14). Thus, Penner and Conklin (11) have described the reaction of 2-substituted- Δ^2 -thiazolines (I; X = alkyl, aryl) with isocyanic acid to give the saturated thiazolo[3,2-a][1,3,5]triazine diones (II; X = alkyl, aryl; R = H).

We wish to report that the cycloaddition reported by Penner and Conklin (11), which is restricted to isocyanic acid, can be extended to aryl isocyanates if the thiazoline bears a sufficiently strong electron-donating group at the 2-position. Thus, while 2-methyl- Δ^2 -thiazoline (I; X = CH₃) and 2-methylthio- Δ^2 -thiazoline (Ia) failed to undergo cycloaddition with aryl isocyanates, even under forcing conditions, treatment of 2-pyrrolidino- Δ^2 -thiazoline (Ib) with 1-naphthyl isocyanate or 4-chlorophenyl isocyanate gave 1,3-diaryl-8a-pyrrolidinoperhydrothiazolo[3,2-a][1,3,5]triazine-2,4-diones (IIa, IIb) in high yield at room temperature. The 2-morpholinothiazoline (Ic) similarly gave a thiazolo[3,2-a][1,3,5]triazine (IIc) on treatment with 1-naphthyl isocyanate, but only under more vigorous conditions (100°).

The products gave pmr spectra consistent with structure II, and satisfactory microanalyses; the infrared spectra



showed two strong peaks near 1700 cm^{-1} characteristic of carbonyl absorptions in 1,3,5-triazines (15). The assigned structure was confirmed by hydrolysis of IIa in 8*N* hydrochloric acid to the isocyanurate (III), and by solvolysis in ethanol to a mixture of α -naphthylurethane (IV) and 2-pyrrolidino- Δ^2 -thiazoline (Ib). An attempted Raney nickel desulphurisation led to V by elimination of thiirane, rather than the expected product (VI). A related, thermally-induced, elimination has been reported by Feinauer (16).

The nature of the heterocumulene is also important in determining whether reaction will occur, and the nature of the products obtained. Hence, aryl and alkyl isothiocyanates failed to react even with 2-pyrrolidino- Δ^2 -thiazoline at 100° for 18 hours. *p*-Toluenesulphonyl isocyanate, on the other hand, reacted exothermally with Ib to give a 1:1 adduct (VII), which is not unexpected in view of the high degree of charge delocalisation involved (17).

EXPERIMENTAL

Melting points were determined using a Büchi capillary melting-point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 157 spectrometer using sodium chloride plates. Pmr spectra were recorded at 60 MHz using a Varian A-60 or Perkin-Elmer R-12 spectrometer, and 100 MHz spectra were recorded using a Varian HA 100D spectrometer. Mass spectra were determined on an AEI-MS902 instrument, and microanalyses were carried out on a Carlo Erba Elemental Analyser Model 1104. Column chromatography was carried out using silica gel (60-120 mesh) from B.D.H. Ltd., or Woelm neutral alumina (activity 3).

2-Methylthio- Δ^2 -thiazoline (Ia).

A solution of 2-mercaptothiazoline (11.9 g., 0.1 mole) and iodomethane (15 g., 0.106 mole) in acetone (150 ml.) was refluxed for 3 hours. The yellow suspension was cooled, filtered, and the resulting white crystalline solid washed with acetone (50 ml.), and dried *in vacuo* to give 22.6 g. (87%) of Ia as the hydriodide, m.p. $115\text{--}117^\circ$, lit. (18) $112\text{--}114^\circ$; pmr (DMSO- d_6): δ 2.78 (s, 3, CH₃), 4.07 (A₂B₂, 4, thiazoline ring).

Anal. Calcd. for C₄H₈INS₂: C, 18.4; H, 3.08; N, 5.36. Found: C, 18.7; H, 3.1; N, 5.3.

2-Pyrrolidino- Δ^2 -thiazoline (Ib).

A solution of 2-methylthio- Δ^2 -thiazoline (73 g., 0.55 mole) (prepared from the hydriodide by treatment with dilute aqueous sodium hydroxide) and pyrrolidine (42 g., 0.6 mole) in ethanol (100 ml.) was refluxed for 48 hours. Evaporation of the excess pyrrolidine and solvent left a light orange liquid which on distillation gave 77.2 g. (90%) of Ib as a colourless oil, b.p. $118^\circ/2.5\text{ mm}$; ir (liquid film): 1610 cm^{-1} (C=N); pmr (deuteriochloroform): δ 1.8 (m, 4, N-C-CH₂), 3.3 (m, 6, pyrrolidine -CH₂N- + -CH₂S-), 3.98 (t, 2, -CH₂N=); mass spectrum: *m/e* 156 (M⁺).

Anal. Calcd. for C₇H₁₂N₂S: C, 53.8; H, 7.74; N, 17.9. Found: C, 54.0; H, 7.5; N, 18.3.

2-Morpholino- Δ^2 -thiazoline (Ic).

A similar procedure to that described above gave Ic as a white crystalline solid in 88% yield, m.p. $62\text{--}64^\circ$ (b.p. $85\text{--}91^\circ/0.5\text{ mm}$); ir (nujol): 1610 cm^{-1} (C=N); pmr (deuteriochloroform): δ 3.65

(m, 10), 4.1 (t, 2, CH₂-N=C).

Anal. Calcd. for C₇H₁₂N₂OS: C, 48.8; H, 7.02; N, 16.3. Found: C, 48.8; H, 7.1; N, 16.1.

1,3-Bis(1-naphthyl)-8a-pyrrolidinoperhydrothiazolo[3,2-*a*][1,3,5]-triazine-2,4-dione (IIa).

1-Naphthyl isocyanate (3.38 g., 0.02 mole) was added dropwise, with stirring, to a solution of 2-pyrrolidino- Δ^2 -thiazoline (1.56 g., 0.01 mole) in dry acetone (10 ml.). The white precipitate which formed was filtered after 18 hours, washed with acetone, and dried to give 4.3 g. (87%) of IIa, m.p. $127\text{--}128^\circ$; ir (nujol): $1720\text{ cm}^{-1} + 1680\text{ cm}^{-1}$ (C=O); pmr (DMSO- d_6): δ 1.84 (m, 4, CH₂-C-N-), 3.3 (m, 6, -CH₂N- and -CH₂S-), 3.9 (t, 2, CH₂NC(O)), 7.7 (m, 14, ArH).

Anal. Calcd. for C₂₉H₂₆N₄O₂S: C, 70.4; H, 5.29; N, 11.3. Found: C, 70.2; H, 5.2; N, 11.0.

1,3-Bis(4-chlorophenyl)-8a-pyrrolidinoperhydrothiazolo[3,2-*a*][1,3,5]-triazine-2,4-dione (IIb).

4-Chlorophenyl isocyanate (3.84 g., 0.025 mole) was added dropwise to a stirred solution of 2-pyrrolidino- Δ^2 -thiazoline (1.95 g., 0.0123 mole) in light petroleum, b.p. $60\text{--}80^\circ$ (10 ml.). The slurry was filtered after 18 hours and the white solid washed with light petroleum to give 5.0 g. (86%) of IIb, m.p. $126\text{--}128^\circ$; ir (nujol): 1710 cm^{-1} and 1670 cm^{-1} (C=O); pmr (DMSO- d_6): δ 1.7-2.0 (m, 4, CH₂-C-N), 3.1-3.5 (m, 6, -CH₂N + CH₂S-), 3.9 (t, 2, CH₂NC(O)), 7.0-7.6 (m, 8, ArH).

Anal. Calcd. for C₂₁H₂₀Cl₂N₄O₂S: C, 54.4; H, 4.35; N, 12.1. Found: C, 54.8; H, 4.4; N, 12.1.

1,3-Bis(1-naphthyl)-8a-morpholinoperhydrothiazolo[3,2-*a*][1,3,5]-triazine-2,4-dione (IIc).

A mixture of 1-naphthyl isocyanate (4.23 g., 0.025 mole) and 2-morpholino- Δ^2 -thiazoline (2.15 g., 0.015 mole) was heated at 100° for 5 hours, allowed to cool, and poured into light petroleum b.p. $60\text{--}80^\circ$ (50 ml.). Filtration gave 2.7 g. (42%) of Ic as a cream-coloured solid, m.p. $180\text{--}182^\circ$; ir (nujol): 1710 cm^{-1} and 1670 cm^{-1} (C=O); pmr (DMSO- d_6): δ 3.1-3.45 (m, 6, CH₂N- + CH₂S-), 3.45-3.75 (m, 4, CH₂O-), 3.9 (t, 2, CH₂NC(O)), 6.6-8.5 (m, 14, ArH); mass spectrum: *m/e* 425 (M-N(CH₂CH₂)₂O), 341 (M-naphthyl isocyanate), 172 (2-morpholino- Δ^2 -thiazoline), 169 (naphthyl isocyanate).

Anal. Calcd. for C₂₉H₂₆N₄O₃S: C, 68.2; H, 5.1; N, 11.0. Found: C, 68.6; H, 5.1; N, 10.7.

Attempted Reactions of Ib with Isothiocyanates.

4-Chlorophenyl, methyl, and benzyl isothiocyanates were employed. The general procedure is illustrated for benzyl isothiocyanate.

2-Pyrrolidino- Δ^2 -thiazoline (Ib) (1.95 g., 0.0125 mole) and benzyl isothiocyanate (3.73 g., 0.025 mole) were mixed and left for 4 days at room temperature. The infrared spectrum of the mixture showed strong absorption in the 2100 cm^{-1} region (N=C=S), and the pmr spectrum (deuteriochloroform) was consistent with a mixture of starting materials (e.g., the benzylic hydrogens were unchanged at 4.7 δ). The reaction mixture was heated at 100° for 18 hours and re-examined by ir and pmr spectroscopy. There was no evidence of reaction.

Reactions of 1,3-bis(1-naphthyl)-8a-pyrrolidinoperhydrothiazolo[3,2-*a*][1,3,5]triazine-2,4-dione (IIa).

(a) Hydrolysis.

Compound IIa (4.0 g., 0.08 mole) was heated on a steam bath

for 4 hours in a mixture of nitromethane (30 ml.) and hydrochloric acid (40 ml. of 8*N*). The solvent was removed on a rotary evaporator and the residue suspended in acetone (ca. 40 ml.), and filtered. Evaporation of the filtrate left a brown oil which was purified by chromatography on a column of silica gel. Elution with acetone gave 3.1 g. (72%) of 5-(2-mercaptoethyl)-1,3-bis-(1-naphthyl)perhydro[1,3,5]triazine-2,4,6-trione (III) as a beige solid, m.p. 192-195° from chloroform/light petroleum b.p. 60-80°; ir (nujol): 1700 cm⁻¹ (C=O); pmr (deuteriochloroform): δ 1.41 (t, 1, SH), 2.93 (m, 2, CH₂S), 4.22 (t, 2, CH₂NC(O)), 7.5-7.85 (m, 14, ArH); mass spectrum: m/e 441 (M⁺), 382, 212, 169.

Anal. Calcd. for C₂₅H₁₉N₃O₃S: C, 68.0; H, 4.34; N, 9.52. Found: C, 67.8; H, 4.7; N, 9.2.

(b) Ethanolysis.

A suspension of IIa (1.24 g., 2.5 mmoles) in dry ethanol (20 ml.) was refluxed overnight. Evaporation of the solvent left an oil which was dissolved in chloroform and added to a column of alumina (50 g.). Elution with chloroform gave 0.9 g. (83%) of α -naphthylurethane (IV), m.p. 77-79°, lit. (19) 79°; ir (nujol): 3250 cm⁻¹ (NH), 1690 cm⁻¹ (C=O); pmr (deuteriochloroform): δ 1.38 (t, 3, CH₃), 4.3 (q, 2, CH₂), 7.0 (broad, 1, NH), 7.2-8.0 (m, 7, ArH).

Elution with chloroform/ethyl acetate gave 0.23 g. (59%) of 2-pyrrolidino- Δ^2 -thiazoline (Ib) as a colourless oil whose ir and pmr spectra were identical to those of an authentic sample.

(c) Attempted Raney Nickel Desulphurisation.

A suspension of IIb (4.94 g., 0.01 mole) and Raney nickel (ca. 35 g.) in ethanol (100 ml.) was refluxed for 48 hours. The solvent was removed by decantation and the nickel residues washed with ethanol (2 x 50 ml.). The combined ethanolic solutions were dried over magnesium sulphate and evaporated to leave a sticky solid. Trituration with ether afforded 0.8 g. (18%) of 1,2,3,4-tetrahydro-1,3-bis(1-naphthyl)-6-pyrrolidino[1,3,5]triazine-2,4-dione monohydrate (V) as a light pink solid m.p. 145°, which resolidified and melted ca. 185°; ir (nujol): 1720 cm⁻¹ and 1760 cm⁻¹ (C=O); pmr (deuteriochloroform): δ 1.4-1.8 (m, 4, CH₂-C-N), 2.95-3.4 (m, 4, -CH₂N-), 7.35-8.15 (m, 14, ArH); mass spectrum: m/e 434 (M⁺), 265 (M-naphthyl isocyanate), 169 (ArNCO).

Anal. Calcd. for C₂₇H₂₂N₄O₂·H₂: C, 71.7; H, 5.36; N, 12.4. Found: C, 71.7; H, 5.4; N, 12.4.

N-(*p*-Toluenesulphonyl)-2-pyrrolidino- Δ^2 -thiazolinio-3-carbimidate (VII).

A solution of 2-pyrrolidino- Δ^2 -thiazoline (1.56 g., 0.01 mole) in acetone (10 ml.) was added dropwise, with stirring, to *p*-toluenesulphonyl isocyanate (3.94 g., 0.02 mole) in acetone (20 ml.).

An immediate exotherm was observed, with rapid formation of a white precipitate. The suspension was filtered after 18 hours and the white solid obtained washed well with ether and dried *in vacuo* to give 3.4 g. (96% calcd. on thiazoline) of VII as a hemihydrate m.p. 121-123°; ir (nujol): 1650 cm⁻¹ and 1610 cm⁻¹ (C=O, C=N), 1140 cm⁻¹ (SO₂); pmr (DMSO-d₆): δ 1.85 (m, 4, CH₂-C-N), 2.3 (s, 3, ArCH₃), 3.3 (m, 6, CH₂S- + CH₂N-), 3.85 (m, 2, CH₂NC(O)), 7.1-7.8 (m, 4, ArH).

Anal. Calcd. for C₁₅H₁₉N₃O₃S₂·½H₂O: C, 49.7; H, 5.56; N, 11.6. Found: C, 49.6; H, 5.51; N, 11.6.

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