Heterodiene Synthesis. Synthesis of Fused Thiopyrano[2,3-*d*]thiazole, [1]Benzopyrano[3′,4′:4,5]thiopyrano[2,3-*d*]thiazole and Thiazolo[3,4-*c*]triazine Derivatives

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5-Salicylidenethiazolidine-2,4-dithione (**1**) reacts with acrylonitrile, *N*-phenylmaleimide and dimethyl acetylenedicarboxylate to afford the fused thiopyrano[2,3-*d*]thiazolidinethione derivatives **2, 4** and **6**, respectively. The salicylidene derivative **1** reacts with ethyl acrylate and malononitrile to afford the fused [1]benzopyrano[3′,4′:4,5]thiopyrano[2,3-*d*]thiazoles **3** and **9**, respectively. 4-Phenylhydrazono-2-thiazolidinethione (**11**) reacts with ethyl bromoacetate and/or phenacyl bromide to yield the fused thiazolo[3,4-*c*]triazines **13** and **14**.

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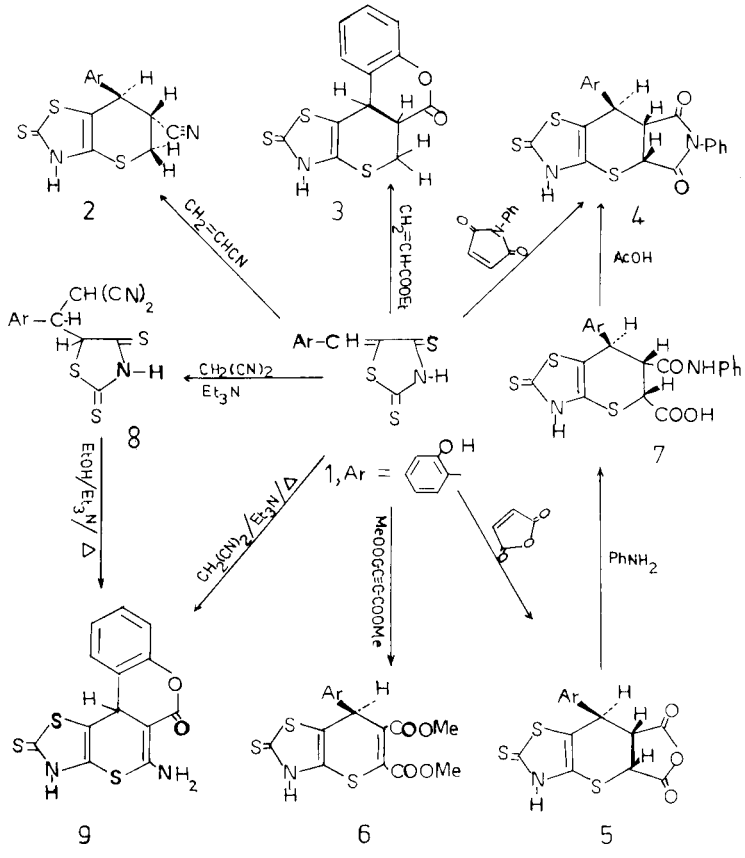
The biological and medicinal activities of substituted thiazolidines have been well reviewed [1,2]. The use of thiopyrano derivatives as antimalarial drugs [3,4] has prompted us to synthesize compounds having both thiazolidine and thiopyrano moieties.

The reaction of the highly coloured 5-salicylidenethiazolidine-2,4-dithione (**1**) [5] and acrylonitrile at room temperature, in acetic acid, afforded a colourless 1:1 adduct, as inferred from its analytical data. The ^{1}H-nmr data of the adduct can be readily interpreted in terms of 6-cyano-7-*o*-hydroxyphenyl-5,6-dihydrothiopyrano[2,3-*d*]thiazolidine-2-thione (**2**). The regiochemical assignment was based on proton chemical shift, which is in agreement with the favourable interaction between the sulphur atom of the heterodiene component, >C=(C)-(C-)=S, and the β-carbon atom of the dienophile [6]. On the other hand, when **1** was reacted with either acrylonitrile and/or ethyl acrylate in refluxing acetic acid, one and the same product was obtained; as fused[1]benzopyrano[3′,4′:4,5]thiopyrano[2,3-*d*]-thiazole-2-thioxo-(6*H*)-one (**3**) as inferred from its analytical and spectral data. The formation of **3** is assumed to proceed through cycloaddition followed by loss of ethanol.

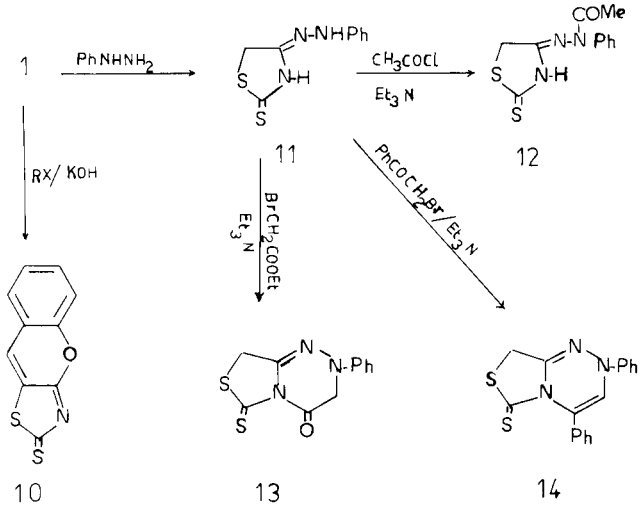


The reaction of **1** with *N*-phenylmaleimide, maleic anhydride and dimethyl acetylenedicarboxylate in acetic acid, afforded the colourless 1:1 adducts **4, 5** and **6**, respectively. The gross structures of compounds **4, 5** and **6** were assigned on the basis of their analytical and spectral data; the stereochemical assignment of **4** and **5** rests on the proton coupling constants. Subjecting the anhydride **5** to the action of aniline in benzene afforded the amide **7**, which is readily dehydrated by the action of acetic acid containing anhydrous sodium acetate to afford **4**.

The behaviour of **1** toward the action of malononitrile has also been investigated. Thus, treatment of **1** with malononitrile, at room temperature, in absolute ethanol, and in the presence of triethylamine afforded the colourless adduct **8**. The structure of **8** was based on its analytical and spectral data, besides its unambiguous synthesis, by the reaction between thiazolidine-2,4-dithione [7] and salicylidenemalononitrile. On the other hand, when the reaction of **1** with malononitrile was carried out in refluxing ethanol, a fused benzopyrano[3′,4′:4,5]thiopyrano[2,3-*d*]-thiazole-2-thione derivative **9** was obtained. The structure of **9** was based on its analytical and spectral data; furthermore, compound **9** was found to be identical with the product obtained by refluxing **8** in absolute ethanol in the presence of triethylamine.

Attempts to *S*-alkylate the potassium salt of **1** by the action of methyl iodide, ethyl bromoacetate and/or phenacyl bromide were unsuccessful, and instead, one and the same product was isolated. Structure **10** was assigned for the product based on its analytical and ir data; besides, its alkaline hydrolysis afforded 3-mercaptocoumarine, proved to be identical *via* its *S*-benzyl derivative with an authentic sample [8].

The reaction of **1** with phenylhydrazine at room temperature, effected salicylidene group cleavage, with the formation of 4-phenylhydrazono-2-thiazolidinethione (**11**) [9]. The reaction of **11** with acetyl chloride afforded 4-*N*^{1}-acetylphenylhydrazono-2-thiazolidinethione (**12**). Subjecting **11** to the action of ethyl bromoacetate and phenacyl bromide, in refluxing ethanol, and in the presence of triethylamine, afforded the fused thiazolo[3,4-*c*]triazine derivatives **13** and **14**, respectively. The structures of **12, 13** and **14** were based on their analytical and spectral data; besides, the acid hydrolysis of **12** and **13** yielded 4-thiazolidinone-2-thione [10]. This is in analogy with the reported behaviour of 2-phenylhydrazono-4-thiazolidinone derivatives toward the action of the same reagents [11].



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) using a Pye-Unicam SP 1100 spectrophotometer. The ^{1}H-nmr were recorded on a Varian EM-390 spectrometer in DMSO-d_6, using TMS as an internal indicator and chemical shifts are expressed as δ ppm.

Reaction of **1** with Acrylonitrile, *N*-Phenylmaleimide, Maleic Anhydride and Dimethyl Acetylenedicarboxylate to Give **2, 4, 5** and **6**. General Procedure.

A solution of equimolecular amounts (0.01 mole) of **1** and acrylonitrile, *N*-phenylmaleimide, maleic anhydride or dimethyl acetylenedicarboxylate in acetic acid (50 ml) was mechanically stirred at room temperature for one hour. The white solid so formed was filtered off and crystallised from the appropriate solvent.

6-Cyano-7-(*o*-hydroxyphenyl)-5,6-dihydrothiopyrano[2,3-*d*]thiazolidine-2-thione (**2**).

This compound formed colourless crystals from ethanol, mp 215°, yield 55%; ir: 3350 cm^{-1} (OH), 3200 cm^{-1} (NH) and 2220 cm^{-1} (C≡N); nmr: 11 (s, 1H, -O*H* phenolic), 10 (s, 1H, N*H*), 7.3-6.7 (m, 4H, Ar), 4.75 (d, 1H, J = 6 Hz, C-7 proton), 3.75-4.0 (m, 1H, C-6 proton) and 3.35-3.6 (m, 2H, C-5 proton).

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 50.98; H, 3.29; N, 9.15; S, 31.34. Found: C, 51.01; H, 3.30; N, 9.31; S, 31.64.

7-(*o*-Hydroxyphenyl)-*N*-phenyl-5,6-dihydrothiopyrano[2,3-*d*]thiazoldine-2-thione-5,6-dicaroximide (**4**).

This compound formed colourless crystals from acetic acid, mp 255°, yield 50%; ir: 3340 cm^{-1} (br, OH), 3200 cm^{-1} (NH) and 1720 cm^{-1} (C=O); nmr: 10.8 (s, 1H, -O*H* phenolic), 10.0 (s, 1H, N*H*), 7.7-6.8 (m, 4H, Ar), 5.2 (d, 1H, J = 9 Hz, C-7 proton), 4.8 (d, 1H, J = 6 Hz, C-5 proton) and 4.3-4.0 (dd, 1H, J = 6, 9 Hz, C-6 proton).

Anal. Calcd. for $C_{20}H_{14}N_2O_3S_3$: C, 56.34; H, 3.31; N, 6.57; S, 22.52. Found: C, 56.71; H, 3.33; N, 6.46; S, 22.67.

7-(*o*-Hydroxyphenyl)-5,6-dihydrothiopyrano[2,3-*d*]thiazolidine-2-thione-5,6-dicarboxylic Acid Anhydride (**5**).

This compound formed colourless crystals from benzene, mp 240°, yield 50%; ir: 3340 cm^{-1} (br, OH), 3180 cm^{-1} (NH) and 1780 and 1710 cm^{-1} (anhydride C=O); nmr: 10.5 (s, 1H, -O*H* phenolic), 10.0 (s, 1H, N*H*), 7.4-6.8 (m, 4H, Ar), 5.4 (d, 1H, J = 9 Hz, C-7 proton), 4.8 (d, 1H, J = 6 Hz, C-5 proton) and 4.3-3.9 (dd, 1H, J = 6, 9 Hz, C-6 proton).

Anal. Calcd. for $C_{14}H_9NO_4S_3$: C, 47.87; H, 2.58; N, 3.99; S, 27.33. Found: C, 48.03; H, 2.61; N, 4.14; S, 27.61.

Dimethyl 7-(*o*-Hydroxyphenyl)thiopyrano[2,3-*d*]thiazolidine-2-thione-5,6-dicarboxylate (**6**).

This compound formed colourless crystals from benzene-petroleum ether, mp 132°, yield 56%; ir: 3340 cm^{-1} (br, OH), 3180 cm^{-1} (NH) and 1770 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{13}NO_5S_3$: C, 48.60; H, 3.29; N, 3.54; S, 24.30. Found: C, 48.81; H, 3.30; N, 3.61; S, 24.27.

Reaction of **1** with Acrylonitrile and/or Ethyl Acrylate to Give 2-Thioxo-2,3,5,5a,6,11b-hexahydro[1]benzopyrano[3',4':4,5]thiopyrano[2,3-*d*]thiazol-6-one (**3**).

A solution of equimolecular amounts (0.01 mole) of **1** and acrylonitrile and/or ethyl acrylate in acetic acid (50 ml), was refluxed for 30 minutes, left to cool and the solid, so formed, was filtered off and recrystallised from acetic acid as colourless crystals, mp 265°, yield 45%; ir: 3200 cm^{-1} (NH) and 1740 cm^{-1} (C=O); nmr: 9.8 (s, 1H, N*H*), 7.6-7.1 (m, 4H, Ar), 4.5 (d, 1H, J = 8 Hz, C-7 proton), 4.1-3.8 (ddd, 1H, J = 6, 6, 9 Hz, C-6 proton) and 3.5 (d, 2H, J = 6 Hz, C-5 protons).

Anal. Calcd. for $C_{13}H_9NO_2S_3$: C, 50.82; H, 2.95; N, 4.56; S, 31.26. Found: C, 50.71; H, 2.89; N, 4.66; S, 31.50.

Reaction of the Anhydride **5** with Aniline to Afford the Amide **7**.

To a solution of **5** (0.01 mole) in benzene (50 ml), was added dropwise, while stirring, a solution of aniline (0.01 mole) in benzene (10 ml). The precipitated solid was filtered off and crystallised from ethanol as colourless crystals, mp 222°, yield 45%; ir: 3400-2800 cm^{-1} (br, OH carboxylic), 1680 cm^{-1} (br, C=O amide and carboxylate).

Anal. Calcd. for $C_{20}H_{16}N_2O_4S_3$: C, 54.06; H, 3.63; N, 6.31; S, 21.60. Found: C, 54.10; H, 3.66; N, 6.25; S, 21.84.

Cyclization of the Amide **7** to Give **4**.

To a suspension of **7** (0.01 mole) in acetic acid (50 ml) was added fused sodium acetate (1.0 g). The reaction mixture was heated on a steam bath for one hour, left to cool, then poured over water. The solid, so formed, was filtered off, washed with water and crystallised from acetic acid as colourless crystals, found to be identical (mp and mixed mp) with **4**.

Reaction of **1** with Malononitrile to Afford 5-[*o*-Hydroxyphenyl(dicyanomethyl)methyl]thiazolidine-2,4-dithione (**8**).

A solution of equimolecular amounts (0.01 mole) of **1** and malononitrile in ethanol (100 ml), containing few drops of triethylamine, was mechanically stirred at room temperature, until the colour of the reacion mixture faded away and a complete precipitation of a colourless solid took place (one hour). The solid product was collected by filtration and crystallised from ethanol as colourless crystals, mp 175°, yield 75%; ir: 3400 cm^{-1} (OH), 3180 cm^{-1} (NH) and 2200 cm^{-1} (C≡N); nmr: 10.6 (s, 1H, O*H*), 7.1-6.8 (m, 4H, Ar), 6.5 (s, 1H, N*H*), 3.4 (d, 1H, -C*H*-C=S), 3.0 (t, 1H, Ar-(-C*H*)- and 1.4 (d, 1H, >C*H*-C≡N).

Anal. Calcd. for $C_{13}H_9N_3OS_3$: C, 48.91; H, 2.84; N, 13.16; S, 30.06. Found: C, 49.11; H, 2.90; N, 13.45; S, 30.33.

Compound **8** was also obtained and identified (mp and mixed mp) by the reaction between thiazolidine-2,4-dithione and salicylidenemalononitrile under the same reaction conditions described above.

Reaction of **1** with Malononitrile to Give 5-Amino-2-thioxo-3*H*,11b*H*-dihydro[1]benzopyrano[3',4':4,5]thiopyrano[2,3-*d*]thiazol-6-one (**9**).

A solution of equimolecular amounts (0.01 mole) of **1** and malononitrile in ethanol (50 ml), containing few drops of triethylamine, was refluxed for one hour then left at room temperature overnight. The solid product so obtained was filtered off and recrystallised from ethanol to afford **9**, mp 300°, yield 45%; ir: 3300, 3280 cm^{-1} (NH_2), 3100 cm^{-1} (NH) and 1700 cm^{-1} (C=O); nmr: 11.1 (br, 2H, NH_2), 3100 cm^{-1} (NH) and 1700 cm^{-1} (C=O); nmr: 11.1 (br, 2H, NH_2), due to deshielding of the C=C group, 9.8 (s, 1H, N*H*), 7.8-7.0 (m, 4H, Ar) and 4.3 (s, 1H, C 11b proton).

Anal. Calcd. for $C_{13}H_8N_2O_2S_3$: C, 48.76; H, 2.52; N, 8.75; S, 29.97. Found: C, 48.55; H, 2.41; N, 8.61; S, 29.64.

[1]Benzopyrano[2,3-*d*]thiazole-2-thione (**10**).

To a solution of **1** (0.01 mole) in ethanolic potassium hydroxide (20 ml; 10%) was added either methyl iodide, ethyl bromoacetate or phenacyl bromide (0.01 mole). The reaction mixture was refluxed for 30 minutes and left to cool. The separated crystals were filtered off, washed with water and then crystallised from acetic acid as colourless crystals. The product in all cases was proved to be one and the same, mp 190°, yield 42%.

Anal. Calcd. for $C_{10}H_5NOS_2$: C, 54.80; H, 2.30; N, 6.39; S, 29.20. Found: C, 55.11; H, 2.27; N, 6.51; S, 29.66.

Alkaline Hydrolysis of **10** to Give 3-Mercaptocoumarin.

A suspension of **10** (1.0 g) in aqueous sodium hydroxide (30 ml, 10%) was refluxed for one hour, cooled and poured over diluted hydrochloric acid. The white solid, so obtained, was filtered off, washed with water to give the crude 3-mercaptocoumarin, mp 110°. The identity of 3-mercaptocoumarin was established through its *S*-benzyl derivative which was found to be identical (mp and mixed mp) with an authentic sample [8].

Action of Phenylhydrazine on **1** to Afford 4-Phenylhydrazono-2-thiazolidinethione (**11**).

Equimolecular amounts (0.01 mole) of **1** and phenylhydrazine were mixed together at room temperature until the odour of hydrogen sulphide ceased. The reaction mixture was then triturated with ethanol and the solid, so obtained, was filtered off and crystallised from methanol, mp 138°, proved to be identical (mp and mixed mp) with an authentic sample [9].

4-*N*^{1}-Acetylphenylhydrazono-2-thiazolidinethione (**12**).

To a cold solution of **11** (0.01 mole) in methylene chloride (50 ml) containing triethylamine (0.03 mole), was added acetyl chloride (0.01 mole) dropwise with mechanical stirring, and allowed to warm to 30°. Stirring was continued for three hours and the solid precipitated was filtered off. The filtrate was evaporated and the solid product, so obtained, was collected and crystallised from ethanol as colourless crystals, mp 223°, yield 40%; ir: 3200 cm^{-1} (NH) and 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{11}N_3OS_2$: C, 49.81; H, 4.18; N, 15.84; S, 24.12. Found: C, 50.18; H, 4.12; N, 16.12; S, 24.00.

Reaction of **11** with Ethyl Bromoacetate and Phenacyl Bromide to Give **13** and **14**. General Procedure.

To a solution of **11** (0.01 mole) in ethanol (50 ml) contining few drops of triethylamine, was added ethyl bromoacetate and/or phenacyl bromide. The reaction mixture was refluxed for three hours then allowed to cool. The solid product, so obtained, was filtered off and recrystallised from ethanol.

6-Thioxo-3,4,6,8-tetrahydro-2-phenyl-2*H*-thiazolo[3,4-*c*]-1,2,4-triazin-4-one (**13**).

This compound formed colourless crystals, mp 260°, yield 55%; ir: 1730 cm^{-1} (C=O); nmr: 7.1 (s, 5H, Ph), 4.3 (s, 2H, S-CH_2-C=) and 3.6 (s, 2H, N-CH_2-CO).

Anal. Calcd. for $C_{11}H_9N_3OS_2$: C, 50.19; H, 3.45; N, 15.97; S, 24.31. found: C, 50.55; H, 3.39; N, 16.00; S, 24.50.

6,8-Dihydro-2,4-diphenyl-2*H*-thiazolo[3,4-*c*]-1,2,4-triazine-6-thione (**14**).

This compound formed colourless crystals, mp 170°, yield 50%; nmr: 7.4-6.8 (m, 10H, 2Ph), 6.4 (s, 1H, C*H*=C-Ph) and 4.2 (s, 2H, S-CH_2-C=).

Anal. Calcd. for $C_{17}H_{13}N_3S_2$: C, 63.15; H, 4.05; N, 13.00; S, 19.80. Found: C, 63.11; H, 4.10; N, 13.23; S, 20.00.

Action of Ethanol-Hydrochloric Acid Mixture on **12** and **13**.

A solution of **12** and/or **13** (1.0 g) in a mixture of ethanol (20 ml) and hydrochloric acid (4 ml) was refluxed for two hours, allowed to cool and diluted with water. The solid product, so obtained, was filtered off and recrystallised from ethanol, mp 167°, proved to be identical (mp and mixed mp) with 4-thiazolidinone-2-thione [10].

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