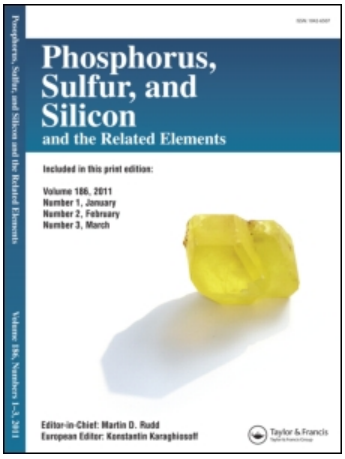

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SYNTHESIS AND SOME REACTIONS OF 4-[(2',3'- DIPHENYL-6' -METHOXY-5' -BENZOFURANYL) METHYLENE] -2-PHENYLTHIAZOLIN-S-ONE

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SYNTHESIS AND SOME REACTIONS OF 4-[(2′,3′-DIPHENYL-6′-METHOXY-5′-BENZOFURANYL) METHYLENE]-2-PHENYLTHIAZOLIN-5-ONE

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4-[(2′,3′-Diphenyl-6′-methoxy-5′-benzofuranyl)methylene]-2-phenylthiazolin-5-one (**I**) was allowed to react with several reagents to get new benzofuran derivatives that have different heterocyclic and/or acyclic moieties at position 5. The assigned structures for the prepared compounds were established through elemental analysis, spectral data and when possible by alternative synthetic routes.

Key words: Benzofuranylmethylenethiazolidinone; substituted benzofuran derivatives; active nitriles.

The synthesis of thiazolidinone compounds possessing heterocyclic moieties such as thiazole, benzothiazole, pyridine and several other aromatic systems have been reported.[1] Most of these compounds possess significant bactericidal and fungicidal activities. Although the synthesis and antimicrobial[2] activities of benzofuran derivatives are well documented, meager data are available for the synthesis and pharmacological studies of the thiazolidinone derivatives possessing such moiety.

Since the 4-thiazolidinone itself is pharmacologically active, the presence of both moieties in the same compound may augment its potency. In continuation of our earlier work on benzofuran derivatives,[3,4] we report here, the synthesis and uses of 4-[(2′,3′-diphenyl-6′-methoxy-5′-benzofuranyl)methylene]-2-phenylthiazolin-5-one (**I**) as a key intermediate for preparation of new benzofuran derivatives of extended and/or improved biological activity.

4-[(2′,3′-diphenyl-6′-methoxy-5′-benzofuranyl)methylene]-2-phenylthiazolin-5-one (**I**) was prepared via condensation of 2,3-diphenyl-5-formyl-6-methoxybenzofuran[5] with thiobenzoyl glycine[6] in presence of acetic anhydride and sodium acetate.

In addition to elemental analysis, compound **I** showed in the IR spectrum two absorption bands at 1645 and 1690 cm^{-1}, characteristic for C=N and C=O of γ-thiolactone moiety.[7,8] The ^{1}H-NMR spectrum ($CDCl_3$) exhibited signals at δ 3.9 ppm (3H, s, OCH_3), 6.5 ppm (1H, s, C-4), 6.7–7.25 ppm (16H, m, aromatic) and at 7.4 ppm (1H, s, C-7).

Hydrolysis of **I** with sodium hydroxide afforded 2,3-diphenyl-6-methoxy-5-benzofuranylpyruvic acid (**IIa**) which was unchanged upon oxidation. Esterification of the acid **II** afforded the ester (**IIb**). The thiazolone **I** reacted with hydrazine hydrate to yield α-thiobenzamido-β-(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylohydrazide (**III**), which upon treatment with nitrous acid, gave α-thiobenzamido-β-(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylic acid azide (**IV**). The latter compound when

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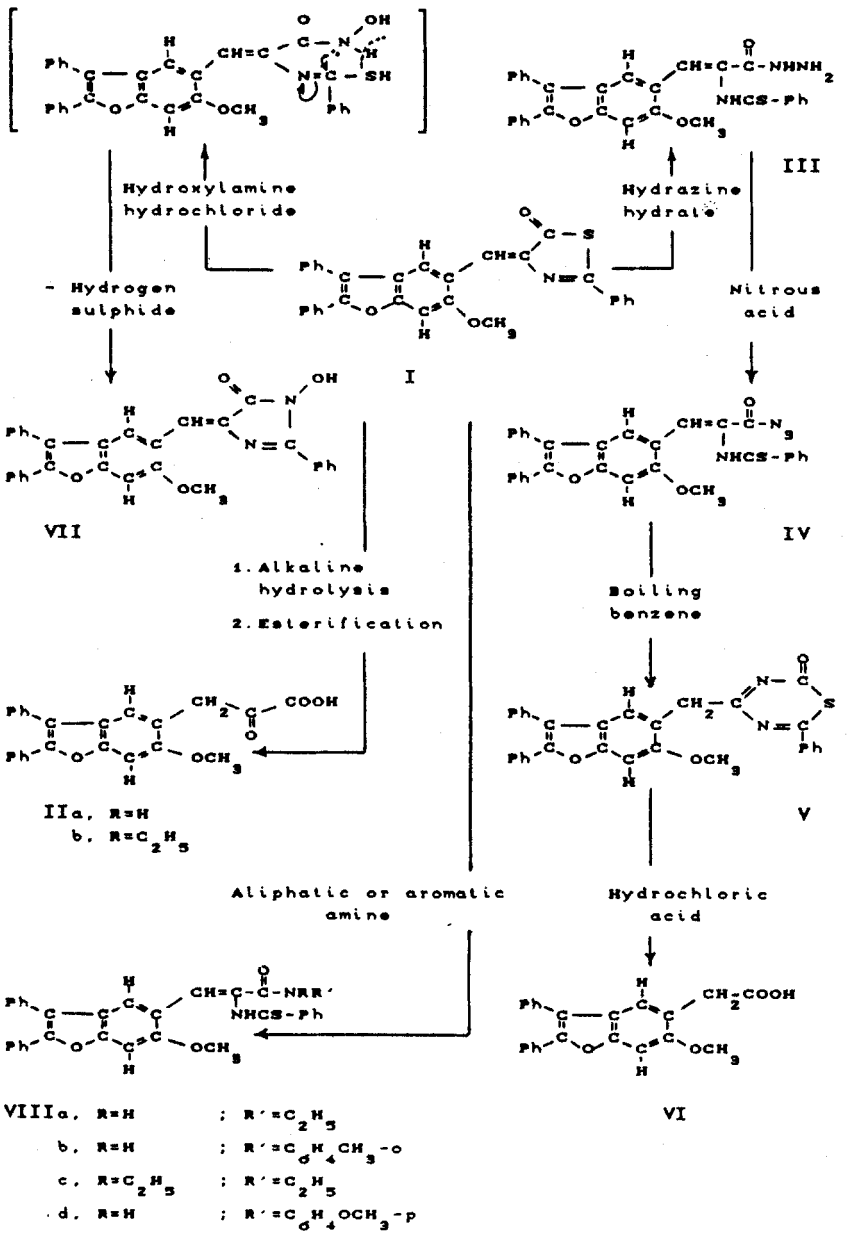
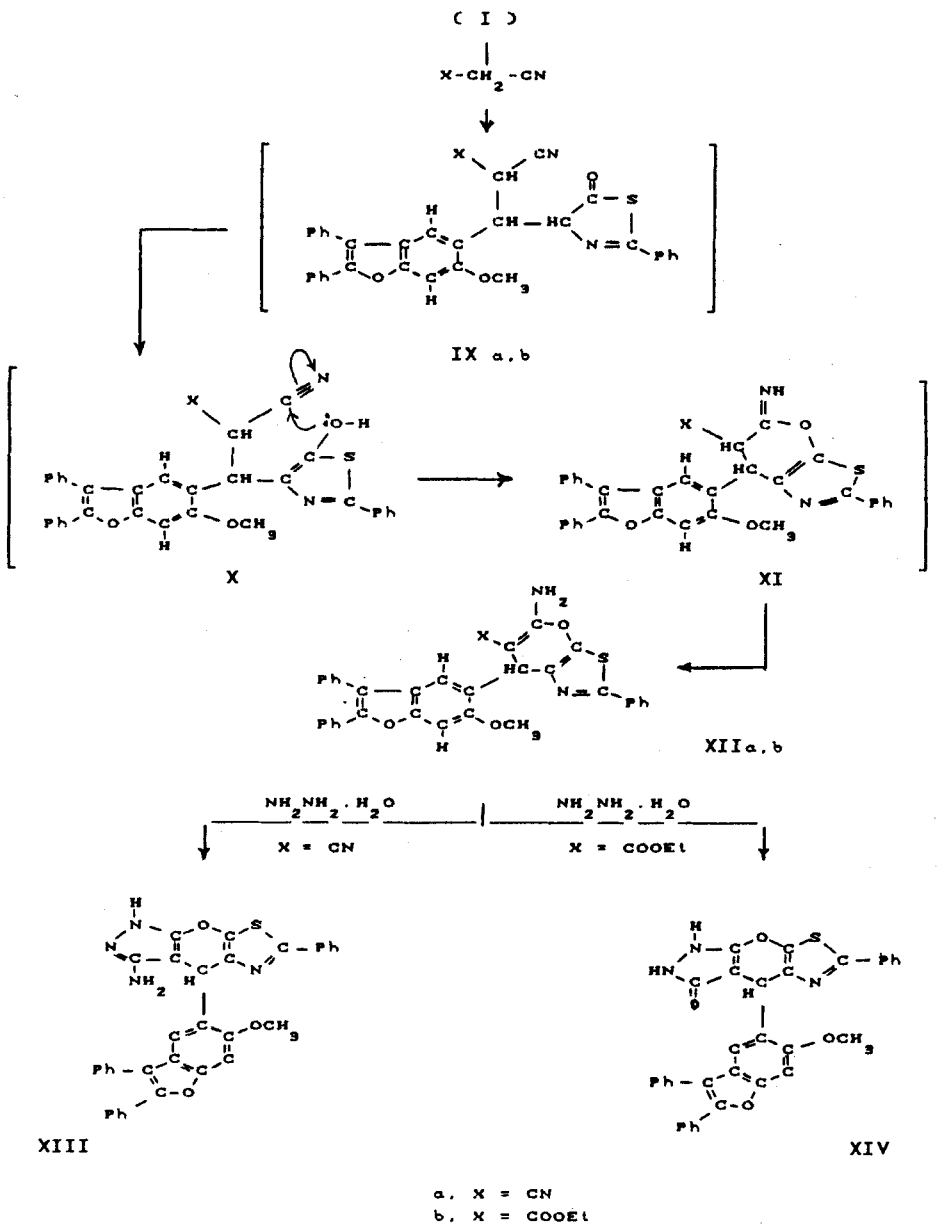


(Scheme 1)

refluxed with dry benzene, decomposed with evolution of nitrogen gas to give 4-[(2′,3′-diphenyl-6′-methoxy-5′-benzofuranyl)methyl]-6-phenyl-2*H*-1,3,5-thiadiazin-2-one (**V**). With hydrochloric acid, compound **V** gave 2,3-diphenyl-6-methoxy-5-benzofuranylacetic acid (**VI**).

Authentic samples of compounds **IIa,b** and **VI** were prepared according to a



(Scheme 2)

previously reported method[9] and were found to be identical (melting and mixed melting points).

Structures **III** and **V** were inferred by analytical and spectral data. The IR spectrum of **III** exhibited two bands at 1680 and 1625 cm^{-1} assigned for the CONH and C=C groups, respectively. The ^{1}H-NMR spectrum ($CDCl_3$) of **III** revealed a signal of δ 3.7 ppm (3H, s, OCH_3). The aromatic protons appeared as a multiplet

at 7.20–7.80 ppm overlapped with protons of the hydrazide moiety. The IR spectrum of **V** showed bands at 2960, 1690, 1650 and 1620 cm^{-1} attributed to CH, C=O, C=N and C=C groups, respectively.

Treatment of **I** with hydroxylamine hydrochloride afforded 4-[(2′,3′-diphenyl-6′-methoxy-5′-benzofuranyl)methylene]-1-hydroxy-2-phenylimidazolin-5-one (**VII**). The IR spectrum of **VII** showed absorption bands at 3400, 1740, 1650 and 1625 cm^{-1} assigned to the OH, C=O, C=N and C=C groups, respectively. The ^{1}H-NMR spectrum ($CDCl_3$) of **VII** gave signals at δ 3.8 ppm (3H, s, methoxy), 6.00 ppm (1H, s, C-4), 6.5–7.4 ppm (16H, m, aromatic and O*H*) and at δ = 7.90 ppm (1H, s, C-7).

The thiazolone **I** reacted with amines, namely, aniline, o-toluidine, diethylamine and p-anisidine to give α-thiobenzamido-β-(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylamide derivatives (**VIIIa–d**), respectively. Assignment of structures **VIIIa–d** was based on correct analytical data and IR spectra which showed two absorption bands at 3030 and 1680 cm^{-1} assigned to the NH and CO groups respectively. The ^{1}H-NMR spectrum of **VIIId** ($CDCl_3$) gave signals at δ 1.6 ppm (2H, broad, two NH), 6.7 ppm (1H, s, C-4), 6.85–7.60 ppm (20H, m, aromatic), 7.7 ppm (1H, s, C-7) and two singlets at 3.7 and 3.85 ppm for the two OCH_3 groups.

Compound **I** with malononitrile gave a product with a molecular formula [$C_{34}H_{23}N_3O_3S$]. The IR spectrum of this product revealed the presence of absorption bands at 3400, 1700, 1650 and 1630 cm^{-1} attributable to the NH_2, CO of ester moiety (hydrogen bonded), C=N and C=C groups, respectively.

Its ^{1}H-NMR ($CDCl_3$) showed a singlet at δ 6.05 ppm assigned for the pyran proton (C-4). If this compound is the acyclic thiazolone derivative **IX**, at least two successive doublets at 3–6 ppm should have been expected, this indicates that the product is considered to have the pyrano[3,2-*d*]thiazole structure (**XIIa**).

Similarly, the thiazolone **I** reacted with ethyl cyanoacetate in presence of piperidine and gave the (1:1) adduct (**XIIb**).

In addition to analytical data, the IR spectrum of **XIIa** exhibited absorption bands at 3400, 2950, 2210, 1650 and 1620 cm^{-1} that are characteristic for the NH_2, C≡N, C=N and C=C groups respectively. The ^{1}H-NMR spectrum of **XIIa** showed the single proton of C-4 at 6.00 ppm. Thus the pyrano [3,2-*d*]thiazole structure **XIIa** was suggested for the product.

The formation of (**XIIa,b**) from the reaction of **I** with malononitrile or ethyl cyanoacetate is assumed to proceed via addition of active methylene reagent to the activated double bond in compound **I** to yield the intermediate Michael adducts **IXa,b** which cyclise under the reaction conditions to the final isolable products.

Acyclic and cyclic β-enamino-esters and β-enamino-nitrils have been recently reported to react with hydrazines and amines to give adducts which then undergo further reactions depending on the nature of the reacting enamino-ester or nitrile.[10,11] Prompted by these reports, it appeared of interest to try the synthesis of pyrazolopyrano[3,2-*d*]thiazole derivatives **XIII** and **XIV** for further biological evaluations.

Thus, treatment of the enamino nitrile **XIIa** or enamino ester **XIIb** with hydrazine hydrate under reflux afforded the corresponding products (**XIII**) and (**XIV**), respectively.

Confirmatory evidence for structures **XIIIa,b** was provided by elemental and

spectral data. The IR spectrum of **XIII** revealed intense absorption band at 3500 cm^{-1} assignable to NH_2 group, beside another band at 1630 cm^{-1} for C=N. The ^{1}H-NMR spectrum of **XIII** ($CDCl_3$) showed signals at δ 1.5 ppm (1H, broad, NH), 3.3 ppm (2H, broad, NH_2), 3.8 ppm (3H, s, OCH_3), 6.1 ppm (1H, s, CH) and at 6.55–7.50 ppm (17H, m, aromatic).

The IR spectrum of **XIV** showed bands at 3400, 1680 and 1630 cm^{-1} characteristic for NH, CONH and C=N groups, respectively. The ^{1}H-NMR spectrum of **XIV** ($CDCl_3$) showed signals at δ 1.95 ppm (1H, broad, NH), 3.5 ppm (1H, broad, CONH), 3.7 ppm (3H, s, OCH_3), 6.1 ppm (1H, s, CH) and at 6.40–7.80 ppm (17H, m, aromatic).

All reactions are given in the formula scheme. The products were characterized by elemental analysis. IR and ^{1}H-NMR spectral measurements.

EXPERIMENTAL

Melting points are not corrected. The infra-red spectra were carried out on an SP 2000 Pye-Unicam Spectrophotometer. The ^{1}H-NMR spectra were recorded on Varian EM 360 NMR Spectrometer 60 MHz with TMS as an internal standard.

4[(2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-2-phenylthiazolin-5-one (**I**). A mixture of 2,3-diphenyl-5-formyl-6-methoxybenzofuran[5] (4.0 g, 0.012 mol), thiohippuric acid (8.0 g, 0.04 mol), anhydrous sodium acetate (4 g) and acetic anhydride (25 ml) was heated on a sand bath for two hours, cooled and diluted with ethanol (100 ml) and left overnight. The precipitated solid was filtered and recrystallized from ethyl acetate as yellowish orange needles, m.p. 271°C in 70% yield.
Analysis; Calcd. for $C_{31}H_{32}NSO_3$: C, 76.40; H, 4.31; S, 6.57.
Found: C, 76.73; H, 4.12; S, 6.41.

2,3-Diphenyl-6-methoxy-5-benzofuranylpyruvic acid (**IIa**). A mixture of **I** (1.0 g, 0.002 mol), pyridine (25 ml) and sodium hydroxide (20 ml; 10%) was boiled under reflux until the thiazolone dissolved completely. The solvent was removed under vacuum and the residue was treated with cold dilute hydrochloric acid and then warmed on a steam bath at 60°C for 1.5 h. In this manner, the pyruvic acid derivative separated in a granular form and was easily filtered. The benzoic acid remained in solution. The product (**IIa**) was crystallized from chloroform as colorless crystals, m.p. 268°C in 70% yield.
Analysis: Calcd. for $C_{24}H_{18}O_5$: C, 74.61; H, 4.66.
Found: C, 74.30; H, 4.40.

This compound was found to be identical with an authentic sample which was prepared according to a previously reported method[9] (m.p. & m. m.p.).

Oxidation of **IIa** (1.0 g) in aqueous potassium hydroxide (5 ml; 10%) at 0°C with hydrogen peroxide (20 ml; 100 Vol.) gave unchanged product (m.p. and m. m.p.).

Esterificiation of 2,3-diphenyl-6-methoxy-5-benzofuranylpyruvic acid (**IIa**). *Formation of the ester* (**IIb**). To compound **IIa** (1.0 g, 0.0025 mol) dissolved in absolute ethanol (20 ml), was added concentrated sulfuric acid (0.5 ml) and the mixture was refluxed on a water bath for two hours then cooled. The solid product that formed was crystallized from ethanol as colorless crystals, m.p. 183°C in 84% yield (literature m.p. 182°C).[9]

α-Thiobenzamido-β-(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylohydrazide (**III**). To a solution of **I** (5.0 g, 0.01 mol) in pyridine (40 ml), hydrazine hydrate (5 ml) was added. The reaction mixture was refluxed for three hours and left to cool. The solid that separated was filtered and recrystallized from dioxane to give compound **III** as brownish yellow crystals, m.p. 143°C in 80% yield.
Analysis: Calcd. for $C_{31}H_{25}N_3SO_3$: C, 71.68; H, 4.82.
Found: C, 71.61; H, 4.77.

4-[(2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-6-phenyl-2H-1,3,5-thiadiazin-2-one (**V**). An ice-cold solution of sodium nitrite (0.3 g) in the minimum amount of water was added slowly to a solution of **III** (1.0 g, 0.002 mol) in glacial acetic acid (40 ml). The temperature was kept below 10°C. After 30 min stirring, the yellow crystalline precipitate of the azide (**IV**) was filtered off, washed with water and dried in air, (dec. at 156°C).

The crude azide **IV** (1.0 g) was extracted with boiling benzene (50 ml) using soxhlet apparatus, then concentrated and cooled. The benzene extract deposited a product which on recrystallization from toluene gave the thiadiazine (**V**) as yellow crystals, m.p. 188°C in 75% yield.
Analysis: Calcd. for $C_{31}H_{22}N_2SO_3$: C, 74.10; H, 4.38; N, 5.58.
Found: C, 73.89; H, 4.46; N, 5.23.

2,3-Diphenyl-6-methoxy-5-benzofuranylacetic acid (**VI**). A suspension of thiadiazine **V** (2.5 g, 0.005 mol) in glacial acetic acid (30 ml) and hydrochloric acid (5 ml, 5 N) was refluxed until complete dissolution and the color of the solution discharged. Dilution with water (40 ml) precipitated the 5-benzofuranylacetic acid (**VI**) and benzoic acid. The latter was leached out with water at 60°C leaving the crude **VI** which was recrystallized from ethanol as colorless crystals, m.p. 166°C in 65% yield.
Analysis: Calcd. for $C_{23}H_{18}O_4$: C, 77.09; H, 5.03.
Found: C, 77.40; H, 4.94.

Compound **VI** was found to be identical with an authentic sample which was prepared according to literature[9] (m.p. and m. m.p.).

4-[(2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-1-hydroxy-2-phenylimidazolin-5-one (**VII**). To a solution of **I** (1.0 g, 0.002 mol) in pyridine (30 ml) was added hydroxylamine hydrochloride (1.0 g) in water (5 ml). The reaction mixture was refluxed for five hours, left to cool and poured on a cold dilute hydrochloric acid solution. The solid so obtained was filtered and recrystallized from ethanol as yellow crystals, m.p. 151°C in 72% yield.
Analysis: Calcd. for $C_{31}H_{22}N_2O_4$: C, 76.54; H, 4.53.
Found: C, 76.81; H, 4.24.

α-Thiobenzamido-β-(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylamides (**VIIIa–d**). A mixture of **I** (4.9 g, 0.01 mol) and the amine (0.03 mol) in pyridine (25 ml) was refluxed for five hours. The reaction mixture was cooled and poured onto cold dilute hydrochloric acid. The obtained solid were filtered off and recrystallized from the suitable solvent.

VIIIa was crystallized from ethanol as yellow crystals, m.p. 167°C in 65% yield.
Analysis: Calcd. for $C_{37}H_{28}N_2SO_3$: C, 76.55; H, 4.83; N, 4.83.
Found: C, 76.81; H, 4.59; N, 4.51.

VIIIb was crystallized from ethanol as yellow crystals. m.p. 170°C in 71% yield.
Analysis: Calcd. for $C_{38}H_{30}N_2SO_3$: C, 76.77; H, 5.05; N, 4.71.
Found: C, 76.53; H, 5.20; N, 4.94.

VIIIc was obtained as brownish-yellow crystals from ethanol, m.p. 110°C in 69% yield.
Analysis: Calcd. for $C_{35}H_{32}N_2SO_3$: C, 75.00; H, 5.71; S, 5.71.
Found: C, 75.24; H, 5.56; S, 5.83.

VIIId was produced as yellow crystals from ethanol, m.p. 125°C in 77% yield.
Analysis: Calcd. for $C_{38}H_{30}N_2SO_4$: C, 74.75; H, 4.92.
Found: C, 74.90; H, 4.71.

Reaction of **I** *with active methylene nitriles. Formation of pyrano[3,2-d]thiazoles* (**Xa,b**). Equimolar quantities of the active methylene nitriles (0.01 mol) and the thiazole derivative **I** were refluxed in absolute ethanol (50 ml) in presence of piperidine (0.5 ml) for 120–200 min. Cooling the reaction mixture followed by removal of solvent under vacuum and triturating the residue with water and dilute hydrochloric acid gave a solid product which was recrystallized from the proper solvent.

Xa was obtained as yellow crystals, m.p. 185°C from methanol in 80% yield.
Analysis: Calcd. for $C_{34}H_{23}N_3SO_3$: C, 73.78; H, 4.16; N, 7.59.
Found: C, 74.70; H, 4.01; N, 7.73.

Xb was produced as yellowish-orange crystals, m.p. 205°C from ethanol in 84% yield.
Analysis: Calcd. for $C_{36}H_{28}N_2SO_5$: C, 72.00; H, 4.67; N, 4.67.
Found: C, 72.35; H, 4.53; N, 4.93.

Reaction of pyrano[3,2d]thiazoles (**Xa,b**) *with hydrazine hydrate. Formation of* **XIII** *and* **XIV**. A mixture of compound **Xa,b** (0.01 mol in each case) and hydrazine hydrate (20 ml; 80%) was heated on a water bath for three hours. The reaction mixture was triturated with ethanol and the obtained solid was crystallized from the suitable solvent.

Compound **XIII** was obtained as brown crystals, m.p. 197°C from ethanol in 70% yield.
Analysis: Calcd. for $C_{34}H_{24}N_4SO_3$: C, 71.83; H, 4.23.
Found: C, 71.69; H, 4.47.

Compound **XIV** was formed as brownish-yellow crystals, m.p. > 300°C from methanol in 65% yield.
Analysis: Calcd. for $C_{34}H_{23}SO_4$: C, 71.70; H, 4.04.
Found: C, 71.49; H, 4.21.

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