STUDIES ON POLYAZAINDENES SYNTHESIS OF SEVERAL NEW CONDENSED PYRIDAZINE DERIVATIVES

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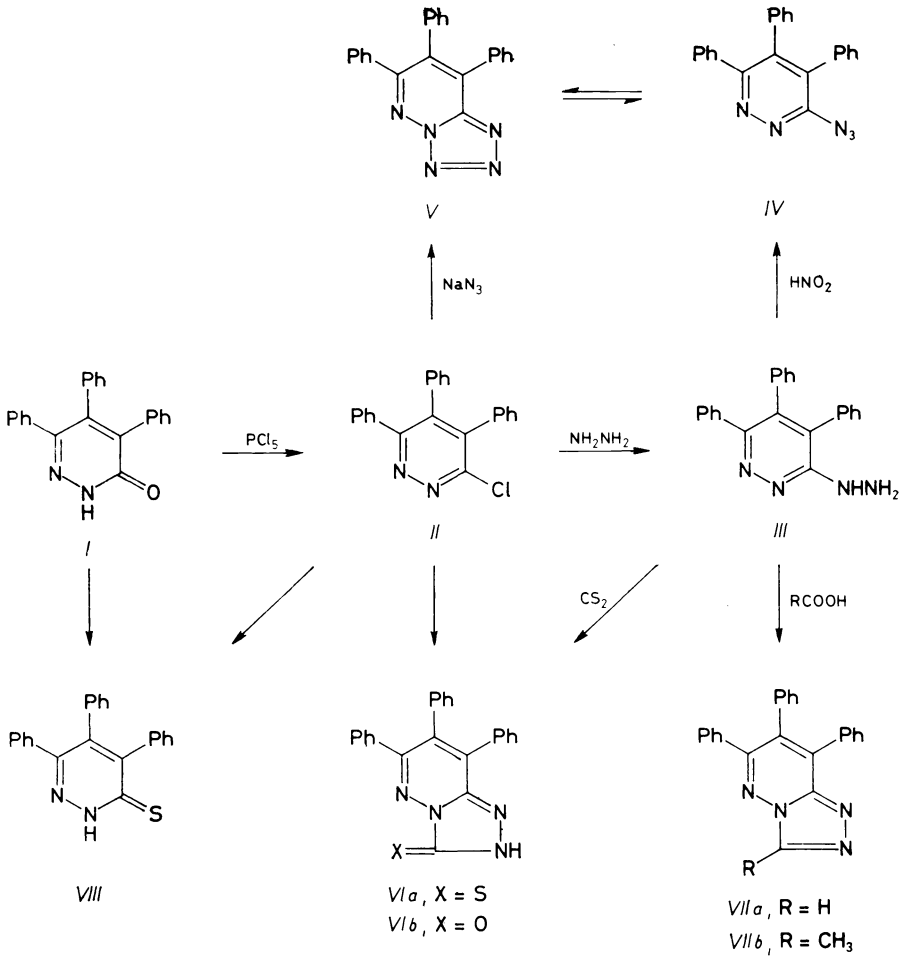
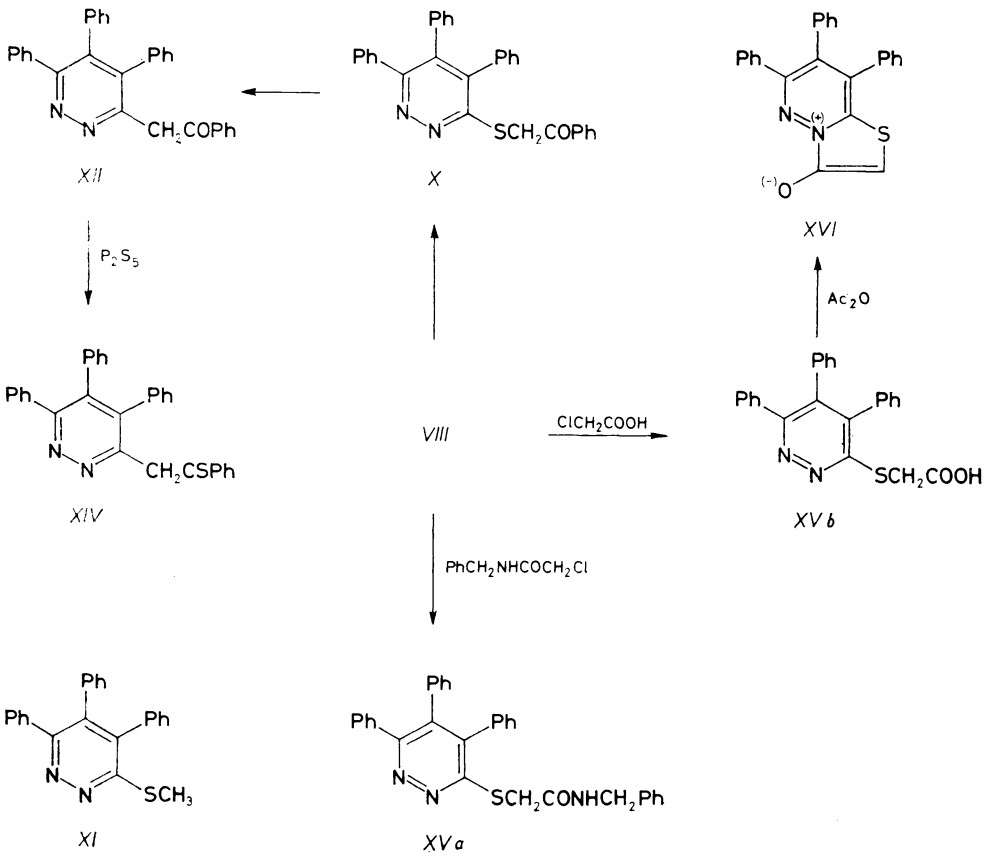
Polyazaindenes are purine analogues and as such may act as antimetabolites in purine biochemical reaction[1-3]. In the last few years we were involved in program aimed



SCHEME 1

at developing of new antischistosomal drugs. Schistosomiosis is one of the most difficult diseases to treat and is a national problem in this country. As pyrazolo[1,5-*a*]-pyrimidines has been reported to have middle activity against schistosoma mosire, we became interested in synthesizing new analogues of these compounds which may be less toxic and more active. As a part of this program, samples of certain azino-pyridazines were required. Synthetic approach is represented in Schemes 1 and 2.



SCHEME 2

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were determined in $(CD_3)_2SO$ on a Varian 60 MHz spectrometer with TMS as internal standard and chemical shifts are expressed as δ (ppm). IR spectra were obtained on a Pye Unicam SP-1100 spectrophotometer (KBr). Analytical data were provided by the Microanalytical centre, Cairo University.

Compound *I* (m.p. 270°C), and compound *II* (m.p. 150°C) were obtained according to reported procedures[4].

3-Hydrazino-4,5,6-triphenylpyridazine *III*

To a solution of *II* (3·4 g, 0·01 mol) in butanol (30 ml) hydrazine hydrate (0·5 ml) was added and the reaction mixture was refluxed for 4 h. After removal of the solvent in vacuo, the residue obtained was crystallized from butanol to give *III* (yield 60%), m.p. 235–236°C. For $C_{22}H_{18}N_4$ (338·4) calculated: 78·08% C, 5·36% H; found: 78·00% C, 5·31% H. IR spectrum (cm^{-1}): 3 475, 3 350, 3 200 (NH_2 and NH); 1 620 (—C=N—); 1 560 (—C=C—). ^1H NMR: 5·8–6·1 m, 3 H $NHNH_2$); 7·5–7·7 m, 15 H (3 Ph).

6,7,8-Triphenyltetrazolo[1,5-*b*]pyridazine *V*

Method A: To a suspension of *III* (3·38 g, 0·01 mol) in a mixture of water (4 ml) and acetic acid (5 ml), a solution of sodium nitrite (150 mg) in water (2 ml) is added dropwise at 0°C. The mixture is left for 2 h at room temperature. The precipitate formed was collected by suction, crystallized from acetic acid and gave *V* (yield 75%), m.p. 225–226°C. For $C_{22}H_{15}N_5$ (349·4) calculated: 75·62% C, 4·32% H; found: 75·70% C, 4·28% H. IR spectrum (cm^{-1}): 1 640 (—N=N—), 1 600 (—C=N—). ^1H NMR: 7·4–7·8 m, 15 H (3 Ph).

Method B: To a solution of *II* (3·4 g, 0·01 mol) in dimethylformamide (20 ml) a solution of sodium azide (1 g) in water (5 ml) was added and the reaction mixture was refluxed for 3 h. After removal of the solvent in vacuo an oily residue was obtained, which repeatedly washed with water and recrystallized from acetic acid gave *V* (yield 45%).

6,7,8-Triphenyltriazolo[4,3-*b*]pyridazine-3-thione *VIa*

A solutions of *III* (3·38 g, 0·01 mol) in carbon disulfide (20 ml) was refluxed for 2 h. After removal of the solvent in vacuo, the residue obtained was crystallized from methanol to give *VIa* (yield 60%), m.p. 260–261°C. For $C_{23}H_{16}N_4S$ (380·4) calculated: 72·61% C, 4·24% H; found: 72·65% C, 4·30% H. IR spectrum (cm^{-1}): 3 150 (NH), 1 650 (C=N), 1 480 (C=S).

6,7,8-Triphenyltriazolo[4,3-*b*]pyridazine-3-one *VIb*

To a solution of *II* (3·4 g, 0·01 mol) in acetonitrile (30 ml) ethyl hydrazinoformate (1·04 g, 0·01 mol) was added and the mixture was refluxed for 3 h. After removal of the solvent in vacuo, the residue obtained was crystallized from acetic acid to give *VIb* (yield 65%), m.p. 280–281°C. For $C_{23}H_{16}N_4O$ (364·4) calculated: 75·81% C, 4·42% H; found: 75·79% C, 4·41% H. IR spectrum (cm^{-1}): 3 200 br (NH), 1 690 (C=O). ^1H NMR: 6·4 br,s, 1 H (NH); 7·4–7·7 m, 15 H (3 Ph).

6,7,8-Triphenyltriazolo[4,3-*b*]pyridazine *VIIa*

A solution of *III* (3·38 g, 0·01 mol) in formic acid (30 ml) was refluxed for 4 h. After removal of the solvent in vacuo, the residue obtained was crystallized from benzene to give *VIIa* (yield 65%), m.p. 255–256°C. For $C_{23}H_{16}N_4$ (348·4) calculated: 79·29% C, 4·62% H; found: 79·30% C, 4·58% H. ^1H NMR: 6·2 s, 1 H (H7); 7·4–7·7 m, 15 H (3 Ph).

3-Methyl-6,7,8-triphenyltriazolo[3,4-*b*]pyridazine *VIIb*

A solution of *III* (3·38 g, 0·01 mol) in acetic acid (30 ml) was refluxed for 4 h. After removal of the solvents in vacuo, the residue obtained was crystallized from benzene to give *VIIb* (yield 75%), m.p. 265—266°C. For $C_{24}H_{18}N_4$ (362·4) calculated: 79·54% C, 5·00% H; found: 79·60% C, 4·91% H. ^{1}H NMR: 2·3 s, 3 H (CH_3); 7·5—7·8 m, 15 H (3 Ph).

4,5,6-Triphenyl-2*H*-pyridazine-3-thione *VIII*

Method A: To a solution of *I* (3·24 g, 0·01 mol) in pyridine (20 ml) was added phosphorus pentasulfide (4·4 g). The reaction mixture was heated under reflux for 4 h. The resulting solution was poured into crushed ice (400 g) containing HCl (70 ml). The yellow solid product obtained was filtered off and crystallized from acetic acid to give *VIII* (yield 55·5%), m.p. 250—251°C. For $C_{22}H_{16}N_2S$ (340·4) calculated: 77·64% C, 4·11% H; found: 77·70% C, 4·10% H. ^{1}H NMR: 3·25 s, 1 H (SH); 7·78 m, 15 H (3 Ph).

Method B: Thiourea (1·14 g, 15 mmol) was added to a solution of *II* (3·4 g, 10 mmol) in 25 ml of absolute ethanol and the reaction mixture was stirred at 20°C for 3 h. The light yellow deposit thus obtained was filtered and treated with 2·5 M sodium hydroxide (14 ml) and refluxed for 1 h. The reaction mixture was concentrated to half of its volume, cooled in an ice bath and acidified with hydrochloric acid (pH 2). The yellow product thus obtained was filtered and recrystallized from acetic acid to give *VIII* (yield 70%).

3-Benzylmethylthio-4,5,6-triphenylpyridazine *X*

To a solution of *VIII* (3·48 g, 0·1 mol) and sodium ethoxide (0·35 g of sodium) in ethyl alcohol (30 ml), freshly prepared phenacylbromide (2 g, 0·01 mol) was added. The reaction mixture was refluxed for 2 h. A crystalline matter was separated and recrystallized from ethanol to give *X* (yield 62%), m.p. 215—216°C. For $C_{30}H_{22}N_2OS$ (458·6) calculated: 78·57% C, 4·83% H; found: 78·50% C, 4·79% H. IR spectrum (cm^{-1}): 1 690 (C=O), 1 620 (C=N). ^{1}H NMR: 3·8 s, 2 H (CH_2); 7·7—7·9 m, 20 H (4 Ph).

3-Methylthio-4,5,6-triphenylpyridazine *XI*

To a solution of *VIII* (3·48 g, 0·01 mol) in ethanol (30 ml) was added aqueous sodium hydroxide (0·5 mol l^{-1}, 10 ml) and methyl iodide (0·4 g). The reaction mixture was stirred for 2 h at 20°C. The light yellow deposit thus obtained was extracted with dichloromethane. The dichloromethane was removed in vacuo and the residue was crystallized from ethanol to give *XI* (yield 75%), m.p. 230—231°C. For $C_{23}H_{18}N_2S$ (354·5) calculated: 77·93% C, 5·11% H; found: 77·87% C, 5·09% H. IR spectrum (cm^{-1}): 1 580 (C=N), 1 500 (C=C). ^{1}H NMR: 3·52 s, 3 H (SCH_3); 7·5—7·3 m, 15 H (3 Ph).

Reaction of XI *with hydrazinehydrate*: To a solution of *XI* (3·5 g, 0·01 mol) in ethanol (30 ml), hydrazine hydrate (0·5 ml) was added and the reaction mixture was refluxed for 6 h. After removal of the solvent in vacuo the residue obtained was crystallized from butanol to give *III* (yield 80%) which was identified by a comparison of its physical properties with that from the former experiment.

3-Benzoylmethyl-4,5,6-triphenylpyridazine *XII*

A solution of *X* (1 g, 2 mmol) in pyridine (15 ml) was refluxed for 30 min. The reaction mixture was poured into cold diluted HCl. A solid matter was separated and crystallized from methanol

to give *XII* (yield 55%), m.p. 260–261°C. For $C_{30}H_{23}N_2O$ (427·5) calculated: 84·28% C, 5·42% H; found: 84·21% C, 5·45% H. IR spectrum (cm^{-1}): 1 685 (C=O), 1 550 (C=C). ^1H NMR: 3·2 s, 2 H (CH_2); 7·4–7·8 m, 20 H (4 Ph).

3-Thiobenzoylmethyl-4,5,6-triphenylpyridazine *XIV*

To a solution of *XII* (2 g, 4 mmol) in dry xylene (50 ml), phosphorous pentasulfide (3·1 g, 0·014 mol) was added. The reaction mixture was refluxed for 2 h, filtered hot, the filtrate was concentrated, orange crystals separated and recrystallized from benzene to give *XIV* (yield 45%), m.p. 280–281°C. For $C_{30}H_{22}N_2S$ (442·6) calculated: 81·41% C, 5·01% H; found: 81·37% C, 4·92% H. IR spectrum (cm^{-1}): 1 560 (C=C), 1 475 (C=S). ^1H NMR: 3·1 s, 2 H (CH_2); 7·6 to 7·9 m, 20 H (4 Ph).

3-Benzylaminocarbonylmethylthio-4,5,6-triphenylpyridazine *XVa*

A mixture of *VIII* (3·48 g, 0·01 mol), potassium carbonate (1 g), and monochlorobenzyl amide (1·83 g, 0·01 mol) was refluxed in dry acetone for 12 h. After removal of the solvent in vacuo, water (20 ml) was added, and reaction mixture extracted with ether (3 × 50 ml). The extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from methanol to give *XVa* (yield 62%), m.p. 198–199°C. For $C_{31}H_{25}N_3OS$ (487·6) calculated: 76·35% C, 5·16% H; found: 76·40% C, 5·09% H. IR spectrum (cm^{-1}): 3 150 (br, NH), 1 700 (C=O).

3-Carboxymethylthio-4,5,6-triphenylpyridazine *XVb*

To a solution of *VIII* (3·48 g, 0·01 mol) in acetic acid (30 ml), chloroacetic acid (0·94 g, 0·01 mol), and sodium acetate (3 g) were added. The reaction mixture was refluxed for 5 h. After removal of the solvent in vacuo, an oily residue was obtained which was repeatedly washed with water and recrystallized from methanol to give *XVb* (yield 60·6%), m.p. 155–156°C. For $C_{24}H_{18}N_2O_2S$ (398·5) calculated: 72·34% C, 4·55% H; found: 72·28% C, 4·51% H. IR spectrum (cm^{-1}): 3 100 (OH), 1 725 (C=O). ^1H NMR: 3·9 s, 2 H (CH_2); 7·4–7·6 m, 15 H (3 Ph); 12·1 s, 1 H (OH).

6,7,8-Triphenyl-1,3-thiazolo 2,3-*b* pyridazinium-3-one *XVI*

Acetic anhydride (10 ml) was added at room temperature to a solution of *XVb* (1 g, 2 mmol) in pyridine (10 ml). The reaction mixture was immediately warmed on a steam-bath for 5 min. The colour of the solution quickly changed from light to deep yellow and finally to redish brown when the reaction was virtually complete. The mixture was immediately cooled down to room temperature and the excess of acetic anhydride decomposed with 95% ethanol (10 ml). The pale yellow mesoionic *XVI* separated on keeping the reaction mixture for 2 h in the cold-bath, was crystallized from ethyl acetate (yield 13%), m.p. 95–96°C. For $C_{24}H_{17}N_2OS$ (381·5) calculated: 75·56% C, 4·49% H; found: 75·51% C, 4·41% H. IR spectrum (cm^{-1}): 1 670 (C=O), 1 600 (C=C).

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