CINNAMOYLACETONITRILE ARYLHYDRAZONES IN HETEROCYCLIC SYNTHESIS: SIMPLE SYNTHESIS OF PYRIDAZINES AND THEIR CONDENSED DERIVATIVES

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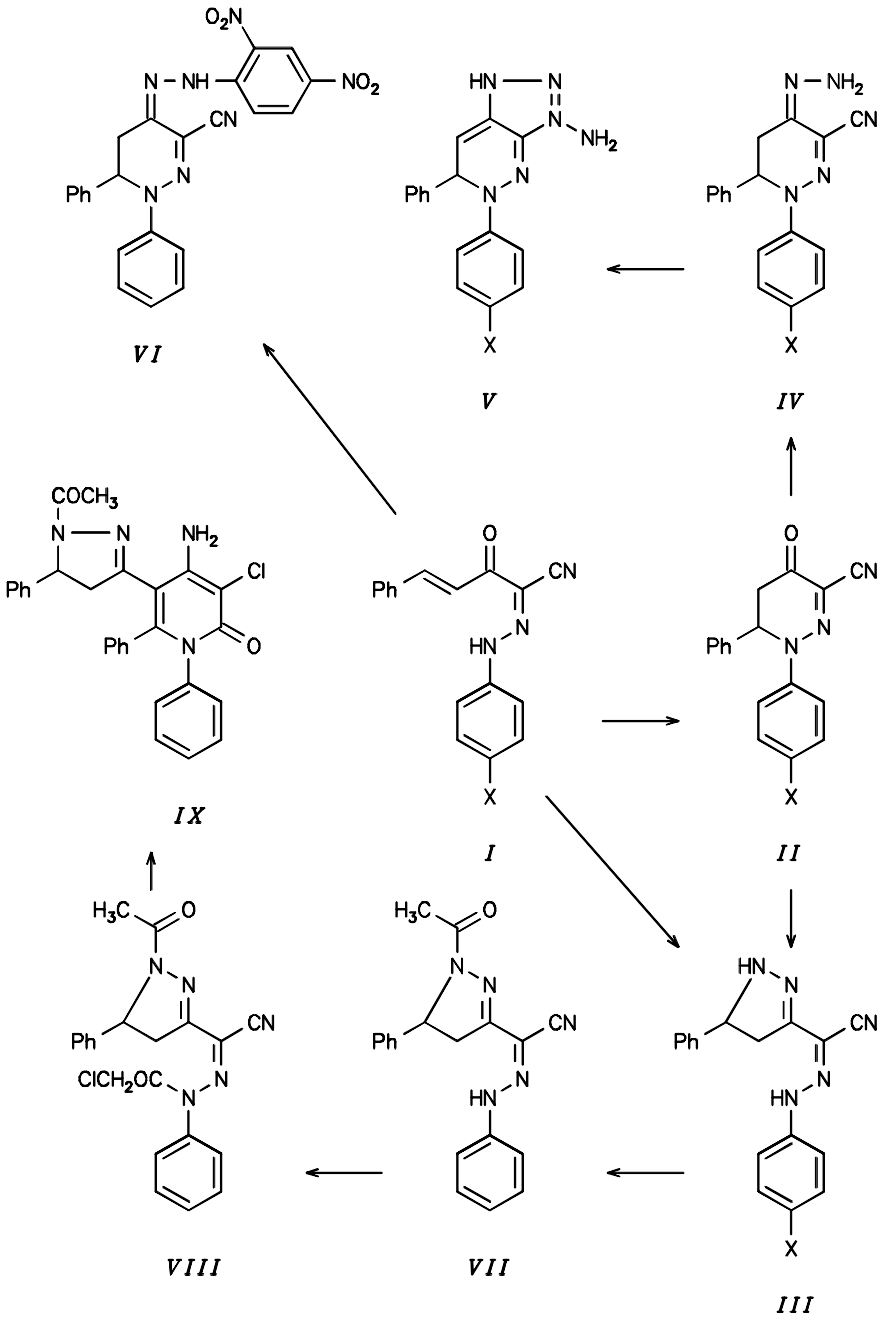
A new route for the synthesis of the title ring systems starting with the cinnamoylacetonitrile arylhydrazones (*Ia*, *Ib*) is described. It involves the self-cyclization of *I* which was found to be pH dependent.

3-Oxoalkanonitriles are versatile reagents and their chemistry has received considerable attention[1]. Several heterocyclic compounds could be prepared on utilizing benzoylacetonitrile[2,3]. When cinnamoylacetonitrile was used instead of the benzoyl derivative, a broader variety of heterocycles were synthesized also through simple methods[4,5]. Recently, we have reported a novel approach to the synthesis of pyrano[2,3-*d*]pyridazines starting with the hydrazones *Ia* and *Ib*. We became interested in proving that these available hydrazones can be utilized as convenient precursors for the synthesis of pyridazines annulated with various five and six membered heterocycles.

Thus, we were able to synthesize our previously reported pyridazine derivatives *IIa* and *IIb* in a better yield and simpler procedure by keeping solutions of the hydrazones *Ia* and *Ib* in tetrahydrofuran at 25 °C for 48 h in presence of catalytic amounts of concentrated sulfuric acid: an acid induced self-cyclization occurred affording compounds *IIa* and *IIb*. On reacting of compound *Ia* with hydrazine hydrate in boiling ethanol, only a complicated mixture was formed. On the other hand, when the reaction was conducted at room temperature (25 °C) a product of a molecular formula $C_{17}H_{15}N_5$ (*m*/*z* 289) was obtained. Two structures seemed possible for this product (cf. structures *IIIa* and *IVa* in Scheme 1). Structure *IIIa* was confirmed by the spectral data and chemical behaviour. The ^{1}H NMR spectrum revealed a pyrazoline ring (H-5) signal at δ 4.9 ppm. If the product was the pyridazine derivative *IV*a one would expect the same proton signal (H-6) at downfield shift[6]. In accordance with this view, the same pyrazoline product *IIIa* was obtained when the pyridazine derivative *IIa* was allowed to react with hydrazine hydrate at 25 °C.

Similarly, the pyrazoline *IIIb* was obtained in satisfactory yield from the reaction of hydrazine hydrate with either *Ib* or *IIb* on applying the above mentioned experimental



In formulae *I* – *V* : *a*, X = H; *b*, X = Cl

SCHEME 1

TABLE I
Yields, melting points and analytical data of compounds *III – X*, *XIII*, and *XVI*

Compound	Yield, %	M. p., °C solvent	Formula (M. w.)	Calculated/Found			
				% C	% H	% Cl	% N
IIIa	75	90 ether	$C_{17}H_{15}N_5$ (289.3)	70.57 70.39	5.23 5.02	– –	24.20 23.95
IIIb	70	99 ether	$C_{17}H_{14}ClN_5$ (323.8)	63.06 62.87	4.36 4.20	10.95 10.52	21.63 21.37
IVa	60	218 – 220 dioxane	$C_{17}H_{15}N_5$ (289.3)	70.56 70.41	5.22 4.97	– –	24.21 24.00
IVb	63	224 dioxane	$C_{17}H_{14}ClN_5$ (323.8)	63.06 62.79	4.36 4.13	10.95 10.63	21.63 21.40
Va	45	250 – 252 dioxane	$C_{17}H_{15}N_5$ (289.3)	70.56 70.36	5.22 5.00	– –	24.21 23.86
Vb	45	263 dioxane	$C_{17}H_{14}ClN_5$ (323.8)	63.06 62.74	4.36 4.07	10.95 10.59	21.63 21.40
VI	70	128 dioxane	$C_{23}H_{17}N_7O_4$ (455.4)	60.66 60.43	3.76 3.51	– –	21.53 21.24
VII	65	215 ethanol	$C_{19}H_{17}N_5O$ (331.4)	68.87 68.77	5.17 5.00	– –	21.13 20.87
VIII	60	183 ethanol	$C_{21}H_{18}ClN_5O_2$ (407.9)	61.84 61.61	4.45 4.35	8.69 8.40	17.17 16.85
IX	55	194 dioxane	$C_{21}H_{18}ClN_5O_2$ (407.9)	61.84 61.74	4.45 4.12	8.69 8.48	17.17 17.00
Xa	70	220 methanol	$C_{17}H_{16}N_4O_2$ (308.3)	66.22 66.19	5.23 5.01	– –	18.17 17.95
Xb	63	228 methanol	$C_{17}H_{15}ClN_4O_2$ (342.8)	59.57 59.28	4.41 4.30	10.34 9.98	16.34 16.00
XIIIa	40	255 dioxane	$C_{17}H_{13}N_4O$ (289.3)	70.58 70.36	4.53 4.37	– –	19.37 19.03
XIIIb	35	267 dioxane	$C_{17}H_{12}ClN_4O$ (323.8)	63.07 62.79	3.74 3.56	10.95 10.61	17.30 17.17
XVIa	50	>300 ethanol	$C_{23}H_{17}N_7O$ (407.4)	67.80 67.63	4.21 4.00	– –	24.06 23.65
XVIb	53	>300 ethanol	$C_{23}H_{16}ClN_7O$ (441.9)	62.52 62.40	3.65 3.37	8.02 7.71	22.19 21.78

conditions. Based on these data, it could be deduced that the self-cyclization of the hydrazones *I* to form pyridazines *II* is a pH dependent reaction and the N(1)–C(6) bond in these pyridazines splits with remarkable ease at alkaline pH as we have previously reported[6]. To make use of this behaviour, we have carried out the reaction of the pyridazines *IIa* and *IIb* with hydrazine hydrate in presence of sulfuric acid as a catalyst. The hydrazonopyridazines *IV*a and *IVb* were obtained in this case instead of the pyrazoles *IIIa* and *IIIb*. Structure *IV* was established through elemental analyses and spectral data (cf. Table I).

Cyclization of compounds *IVa* and *IVb* could be achieved by heating at 220 °C to afford the aimed pyrazolo[4,3-*c*]pyridazines *Va* and *Vb*, respectively. Their structures were established based on elemental analyses and spectral data; the IR spectra showed the absence of the C≡N group.

In accordance with these results, the hydrazone *Ia* condensed readily with 2,4-dinitrophenylhydrazine in presence of sulfuric acid to give a deep red product of molecular formula $C_{23}H_{17}N_7O_4$ (*m*/*z* 455) which could be formulated as the hydrazono- pyridazine derivative *VI* according to elemental analysis and spectral data (cf. Table I). Several attempts for the cyclization of *VI* in order to prepare the corresponding pyrazolo[4,3-*c*]pyridazine derivative were carried out but none of them was successful.

Continuing our interest in the synthesis of pyridazines, compound *IIIa* was acetylated with acetic anhydride affording the N-acetylpyrazole *VII* which could be further acylated with chloroacetyl chloride in presence of one equivalent of sodium hydride to give the N,N′-diacylpyrazole derivative *VIII*. Structures of compounds *VII* and *VIII* were established based on their elemental analyses and spectral data (cf. Table I). The chemical behaviour of compound *VIII* was also in full accordance with the N,N′-diacyl structure. Thus, when it was boiled under reflux in xylene in the presence of one equivalent of sodium hydride, a product with a molecular formula $C_{21}H_{17}ClN_5O_2$ (*m*/*z* 406) was obtained. The 3-(3-pyrazolyl)pyridazine structure *IX* was suggested for this product on the basis of elemental analysis and spectral data. Its ^{1}H NMR spectrum showed a pyrazoline protons pattern similar to that present in the parent compound in addition to a (D_2O) exchangeable signal at δ 4.8 ppm attributable to the amino group protons. While the IR spectrum revealed the absence of the cyano group absorption and showed a broad absorption at 3 300 – 3 200 cm^{-1} assigned to the amino group absorption plus two carbonyl group absorptions at 1 650 and 1 680 cm^{-1} attributable to the acetyl and pyridazine carbonyl groups absorptions, respectively.

The behaviour of the arylhydrazones *Ia* and *Ib* towards hydroxylamine hydrochloride was also investigated under different experimental conditions. Thus, it has been found that *Ia* could react with hydroxylamine hydrochloride in presence of pyridine to yield a product of a molecular formula $C_{17}H_{16}N_4O_2$ (*m*/*z* 308). Its IR spectrum showed the absence of the cyano group and the presence of a carbonyl absorption at 1 650 cm^{-1} beside a broad absorption band at 3 150 – 3 250 cm^{-1} assignable to an amino group.

Moreover, the ^{1}H NMR spectrum showed ABX system, attributable to the CH_2–CH moiety; this characteristic protons pattern was previously observed in our report on tetrahydro-4-oxopyridazine derivatives[6] and accordingly structure *Xa* was given for the product. An analogous result was obtained from the reaction of *Ib* with hydroxylamine hydrochloride affording *Xb* under the same experimental conditions (see Scheme 2). It is assumed that the formation of *X* occurred via the intermediacy of the pyridazine *II* which subsequently reacted with hydroxylamine to afford the final product. In accordance with this view, compound *Xa* was obtained when the pyridazine *IIa* was allowed to react with hydroxylamine hydrochloride under similar reaction conditions.

If the hydrazones *I* reacted with hydroxylamine prior to its cyclization, other types of cyclizations would be expected to compete with the proposed structure as observed when the reaction was carried out in presence of aqueous potassium hydroxide. Instead of the pyridazines isoxazolopyridazines *XIIIa* and *XIIIb* were obtained. The IR spectrum of *XIIIa* showed absence of the cyano group absorption which ruled out the possible formation of the isoxazole derivative corresponding to the pyrazole structure *III*. Moreover, its ^{1}H NMR spectrum revealed two doublets at δ 5.9 (J = 8 Hz) and δ 6.3 (J = 8 Hz) attributable to the pyridazine H-6 and H-5, respectively. It is assumed that the formation of *XIIIa* and *XIIIb* occurred via the intermediacy of the hydroxyimino derivatives *XIIa* and *XIIb* with subsequent cyclization.

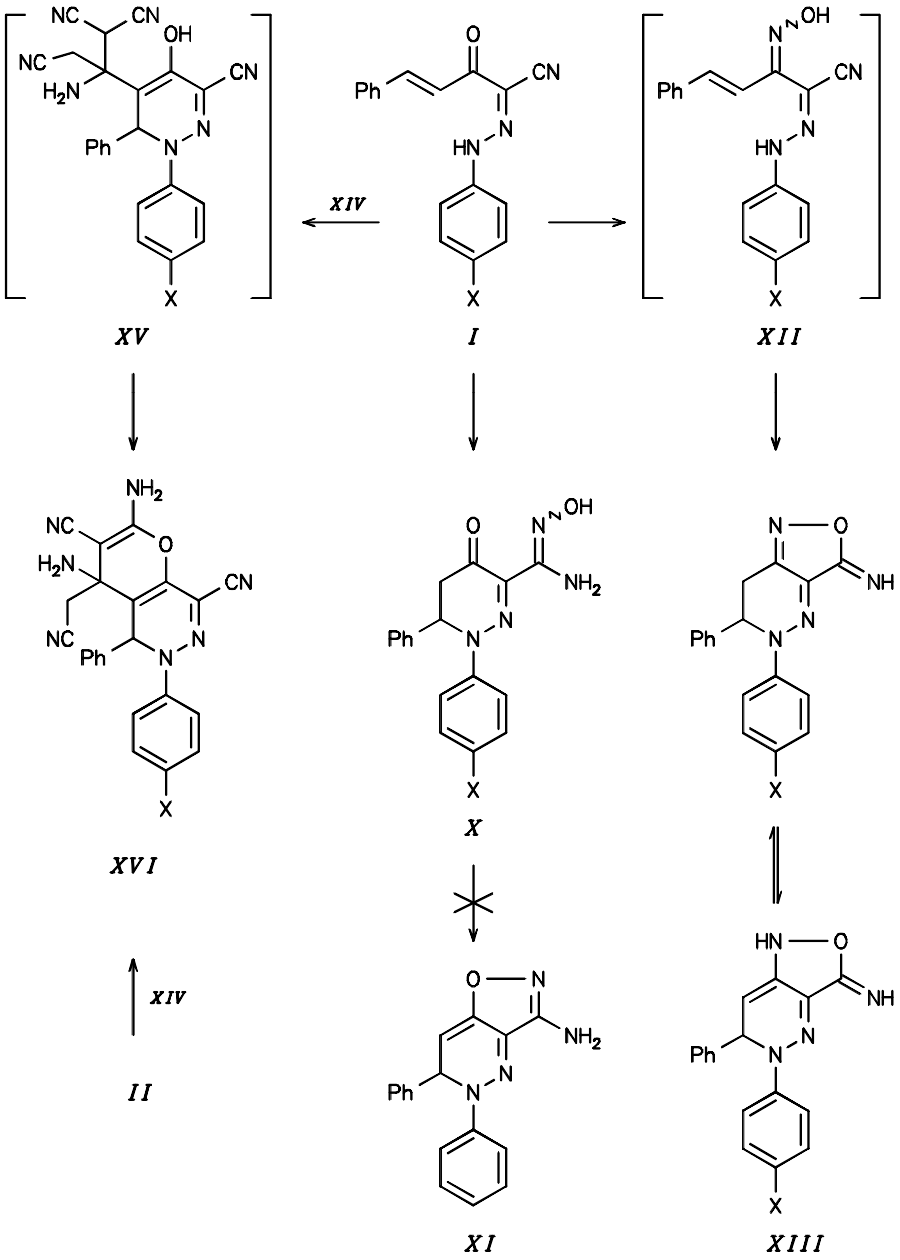
Attempts for the preparation of the isoxazolopyridazine *XI* were carried out by refluxing of *Xa* in different solvents in presence of dehydrating agents. However, none of them was fruitful and the starting material was always recovered unchanged.

New pyrano[2,3-*d*]pyridazine tricarbonitrile derivatives *XVIa* and *XVIb* could be prepared by refluxing compounds *Ia* and *Ib* with the enaminonitrile *XIV* in ethanol in presence of piperidine. Structure *XVI* was assigned to the product based on elemental analyses, spectral data and analogy with published data[7]. Thus the ^{1}H NMR spectrum of *XVIa* revealed only two singlets at δ 3.4 and δ 6.9 ppm assignable to the cyanomethyl group protons and the pyridazine H-6, respectively, beside the aromatic protons signals at δ 7.3 – 7.7 ppm and the amino group protons signals at δ 7.1 and 8.6 ppm. Compounds *XVIa* and *XVIb* were also the only isolable products obtained when the pyridazines *IIa* and *IIb* were used instead of the hydrazones *Ia* and *Ib* in their reaction with the nitrile *XIV*.

Accordingly, it could be concluded that the conveniently available cinnamoylacetonitrile hydrazones *I* are good precursors for the synthesis of the difficulty accessible pyridazines and their condensed derivatives through simple methods.

EXPERIMENTAL

All melting points were uncorrected. The IR spectra were recorded in KBr with a Pye–Unicam SP-1000 spectrometer; wavenumbers are given in cm^{-1}. The ^{1}H NMR spectra were run on a Varian EM 390 (90 MHz) and Gemini-200 spectrometers, using tetramethylsilane as an internal reference.



In formulae *XII*, *XIII*, *XV* and *XVI*:*a*, *X* = *H*; *b*, *X* = *Cl*

SCHEME 2

Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The mass spectra were recorded with a Varian MAT 311 A mass spectrometer (70 eV).

1-Aryl-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridazine-3-carbonitriles (*IIa*, *IIb*)

A solution of the hydrazone *Ia*, *Ib* (0.01 mol) in tetrahydrofuran (30 ml) in presence of concentrated sulfuric acid (1 ml) was left overnight at 25 °C. The precipitate formed was collected and crystallized from the proper solvent[6].

3-(Arylhydrazono)cyanomethyl-5-phenyl-4,5-dihydropyrazole[3] (*IIIa*, *IIIb*)

Compounds *Ia*, *Ib* or *IIa*, *IIb* (0.01 mol) in tetrahydrofuran (15 ml) were treated each with 99% hydrazine hydrate (0.3 g, 0.01 mol) at 25 °C: precipitation occurred immediately after addition and the solid products were filtered off and crystallized.

Compound IIIa. IR spectrum: 3 400 – 3 200 (2 × NH); 2 200 (C≡N). ^{1}H NMR spectrum: 3.0 dd, 1 H (pyrazoline H-4 axial, J = 15, J = 12); 3.6 dd, 1 H (pyrazoline H-4 equatorial, J = 15, J = 10); 4.9 dd, 1 H (pyrazoline H-5, J = 12, J = 10); 7.0 – 7.7 m, 10 H (aromatic protons); 12.2 s, 4 H (NH); 12.7 brs, 1 H (NH).

Compound IIIb. IR spectrum: 3 800 – 3 200 (2 × NH); 2 200 (C≡N). ^{1}H NMR spectrum: 3.1 dd, 1 H (pyrazoline H-4 axial, J = 15, J = 12); 3.8 dd, 1 H (pyrazoline H-4 equatorial, J = 15, J = 10); 5.1 dd, 1 H (pyrazoline H-5, J = 12, J = 10); 7.0 – 7.7 m, 9 H (aromatic protons); 12.7 brs, 1 H (NH); 15.2 s, 1 H (NH).

1-Aryl-4-hydrazono-6-phenyl-1,4,5,6-tetrahydropyridazine-3-carbonitriles (*IVa*, *IVb*)

Compounds *IIa*, *IIb* (0.01 mol) in tetrahydrofuran (30 ml) were treated each with 99% hydrazine hydrate (0.3 g, 0.01 mol) in presence of concentrated sulfuric acid (3 ml) at 25 °C with stirring for 48 h. Hexane (20 ml) was then added to the reaction mixture forming so two layers: the hexane layer was discarded while the tetrahydrofuran one was partially concentrated and the solid product thus obtained was crystallized.

Compound IVa. IR spectrum: 3 400 – 2 860 (NH–NH_2 and NH_2); 2 220 (C≡N). ^{1}H NMR spectrum: 2.7 – 3.4 m, 2 H (pyridazine H-5); 5.8 – 6.0 m, 1 H (pyridazine H-6); 7.0 – 7.6 m, 10 H (aromatics); 11.2 brs, 1 H (NH_2); 12.1 brs, 1 H (NH).

Compound IVb. IR spectrum: 3 400 – 2 860 (NH–NH_2 and NH_2); 2 210 (C≡N).

3-Amino-5-aryl-6-phenyl-1*H*-pyrazolino[4,3-*c*]pyridazines (*Va*, *Vb*)

Compounds *IVa*, *IVb* (0.01 mol) were each fused at 220 °C for 6 h in an oil bath. The oil obtained was triturated with methanol and the solid thus formed was collected and crystallized.

Compound Va. IR spectrum: 3 300 – 3 150 (NH_2 and NH). ^{1}H NMR spectrum: 3.8 brs, 1 H (NH); 5.8 m, 1 H (pyrazolinopyridazine H-6); 7.1 – 7.6 m, 11 H (aromatic protons and pyrazolinopyridazine H-7); 11.3 brs, 1 H (NH).

Compound Vb. IR spectrum: 3 300 – 3 150 (NH_2 and NH). ^{1}H NMR spectrum: 4.0 brs, 2 H (NH_2); 5.8 m, 1 H (pyrazolinopyridazine H-6); 7.1 – 7.6 m, 10 H (aromatic protons and pyrazolinopyridazine H-7); 11.5 brs, 1 H (NH).

1,6-Diphenyl-4-(2,4-dinitrophenylhydrazono)-1,4,5,6-tetrahydropyridazine-3-carbonitrile (*VI*)

A solution of *Ia* (2.75 g, 0.01 mol) in tetrahydrofuran (30 ml) was treated with 2,4-dinitrophenylhydrazine (1.38 g, 0.01 mol) in the presence of concentrated sulfuric acid (1 ml). The reaction mixture

was left at 25 °C for 48 h, the precipitated solid product was collected, washed with water thoroughly and crystallized from dioxane as deep red crystals. IR spectrum: 2 210 (C≡N). ^{1}H NMR spectrum: 2.8 – 3.3 m, 2 H (pyridazine H-5); 6.2 m, 1 H (pyridazine H-6); 7.0 – 7.5 m, 10 H (aromatic protons); 7.8 d, 1 H (dinitrophenyl H-6, *J*(6,5) = 9); 8.3 dd, 1 H (dinitrophenyl H-5, *J*(5,6) = 9, *J*(5,3) = 3); 8.8 d 1 H (dinitrophenyl H-3, *J*(3,5) = 3); 11.1 s, 1 H (NH).

1-Acetyl-3-(phenylhydrazono)cyanomethyl-5-phenyl-4,5-dihydropyrazole (*VII*)

A solution of *IIIa* (2.9 g, 0.01 mol) in acetic anhydride (30 ml) was boiled under reflux for 1 h, cooled, poured into ice water and left overnight. The obtained oil was triturated with acetone to give a solid product crystallizable from ethanol as yellow crystals. IR spectrum: 3 400 (NH); 2 200 (C≡N); 1 650 (C=O). ^{1}H NMR spectrum: 2.2 s, 3 H (CH_3); 3.1 dd, 1 H (pyrazoline H-4 axial); 3.5 dd, 1 H (pyrazoline H-4 equatorial); 5.4 dd, 1 H (pyrazoline H-5); 7.0 – 7.5 m, 10 H (aromatic protons); 11.7 s, 1 H (NH).

1-Acetyl-3-[(N-chloroacetylphenylhydrazono)cyanomethyl]-5-phenyl-4,5-dihydropyrazole (*VIII*)

A solution of *VII* (3.3 g, 0.01 mol) in dry benzene (30 ml) in presence of sodium hydride (0.24 g, 0.01 mol) was stirred at 25 °C for 30 min. Chloroacetyl chloride (1.13 g, 0.01 mol) in dry benzene (5 ml) was added dropwise to the stirred solution over a period of 15 min. Stirring was kept for further 3 h, then the solvent was evaporated and the oil residue washed with 4 M hydrochloric acid then triturated with methanol. The resulting solid product was collected and crystallized from ethanol as pale yellow crystals. IR spectrum: 2 210 (C≡N); 1 665 (C=O); 1 650 (C=O). ^{1}H NMR spectrum: 2.3 s, 3 H (CH_3); 2.7 s, 2 H (CH_2–Cl); 3.2 dd, 1 H (pyrazoline H-4 axial); 3.5 dd, 1 H (pyrazoline H-4 equatorial); 5.6 dd, 1 H (pyrazoline H-5); 7.0 – 7.6 m, 10 H (aromatic protons).

4-Amino-5-chloro-3-[3-(1-acetyl-5-phenyl)-4,5-dihydropyrazolyl]-1-phenylpyridazine-6-one (*IX*)

Compound *VIII* (1.02 g, 0.005 mol) was boiled under reflux in xylene (25 ml) in presence of sodium hydride (0.12 g, 0.005 mol) for 6 h. The reaction mixture was then partially concentrated, cooled and the solid formed was dissolved in water then neutralized with dilute hydrochloric acid. The solid product, thus obtained, was collected and crystallized from dioxane as yellow crystals. IR spectrum: 3 300 – 3 200 (NH_2); 1 680 (C=O); 1 650 (C=O). ^{1}H NMR spectrum: 2.2 s, 3 H (CH_3); 3.2 dd, 1 H (pyrazoline H-4 axial); 3.5 dd, 1 H (pyrazoline H-4 equatorial); 4.8 brs, 2 H (NH_2); 5.5 dd, 1 H (pyrazoline H-5); 7.1 – 7.8 m, 10 H (aromatic protons).

1-Aryl-3-[(hydroxyimino)aminomethyl]-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridazines (*Xa*, *Xb*)

A suspension of *Ia*, *Ib* or *IIa*, *IIb* (0.01 mol) in dioxane (30 ml) was treated with hydroxylamine hydrochloride (0.7 g, 0.01 mol) in the presence of pyridine (1 ml). The reaction mixture was refluxed for 4 h, then left to cool. The precipitated solid product was filtered off and crystallized from the proper solvent.

Compound Xa. IR spectrum: 3 500 (OH); 3 250 – 3 150 (NH_2); 1 650 (C=O). ^{1}H NMR spectrum: 2.8 m, 2 H (pyridazine H-5); 5.9 m, 1 H (pyridazine H-6); 7.1 – 7.6 m, 11 H (10 × aromatic proton and OH); 8.6 d, 2 H (NH_2).

Compound Xb. IR spectrum: 3 500 (OH); 3 200 – 3 180 (NH_2); 1 655 (C=O).

6-Aryl-1-imino-5-phenylisoxazolo[4,3-*c*]pyridazines (*XIIIa*, *XIIIb*)

A solution of *Ia*, *Ib* (0.01 mol) in ethanol (25 ml) was treated with hydroxylamine hydrochloride (1.4 g, 0.02 mol) in presence of 10% aqueous sodium hydroxide (10 ml) at 25 °C with stirring for 6 h. The reaction mixture was neutralized with acetic acid, the solvent was then evaporated and the oil obtained was boiled under reflux in butanol (25 ml) in presence of acetic acid (5 ml) for 40 h. The reaction mixture was evaporated till dryness, ether (5 ml) was added to the obtained oil followed by a dropwise addition of petroleum ether (5 ml, b.p. 40 – 60 °C) and the reaction mixture was refrigerated overnight. The solid product formed was filtered off and crystallized.

Compound XIIIa. IR spectrum: 3 400 – 3 300 (2 × NH); 1 645 (C=N). ^{1}H NMR spectrum: 5.9 d, 1 H (isoxazolopyridazine H-5); 6.3 d, 1 H (isoxazolopyridazine H-4); 7.1 – 7.7 m, 10 H (aromatic protons); 11.0 s, 1 H (C=NH); 13.2 s, 1 H (NH).

Compound XIIIb. IR spectrum: 3 400 – 3 300 (2 × NH); 1 650 (C=N).

6-Aryl-2,4-diamino-4-cyanomethyl-5-phenyl-5*H*-pyrano[2,3-*d*]pyridazine-3,8-dicarbonitrile (*XVIa*, *XVIb*)

Compounds *Ia*, *Ib* or *IIa*, *IIb* (0.01 mol) were refluxed each with the nitrile *XIV* (1.3 g, 0.01 mol) in butanol (30 ml) in presence of piperidine (1 ml) for 8 h. The reaction mixture was evaporated till dryness, the oil formed was washed thoroughly with dilute hydrochloric acid and the solid product, thus obtained, was collected followed by crystallization.

Compound XVIa. IR spectrum: 3 370 – 3 130 (2 × NH_2); 2 200 – 2 205 (2 × C≡N). ^{1}H NMR spectrum: 3.4 s, 2 H (CH_2); 6.9 s, 1 H (pyranopyridazine H-5); 7.1 s, 2 H (NH_2); 7.3 – 7.7 m, 10 H (aromatic protons); 8.6 brs, 2 H (NH_2).

Compound XVIb. IR spectrum: 3 400 – 3 150 (2 × NH_2); 2 220 – 2 200 (2 × C≡N). ^{1}H NMR spectrum: 3.6 s, 2 H (CH_2); 6.9 s, 1 H (pyranopyridazine H-5); 7.2 s, 2 H (NH_2); 7.3 – 7.9 m, 9 H (aromatic protons); 10.2 brs, 2 H (NH_2).

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