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New Synthetic Approaches to Condensed Pyridazinones: Alkylpyridazinyl Carbonitriles as Building Blocks for the Synthesis of Condensed Pyridazinones

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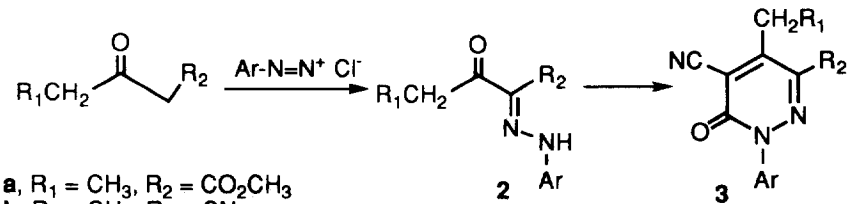
Abstract.— The pyridazinyl-5-carbonitriles (**3a-d**) were prepared via condensing the aryl hydrazones **2a-d** with ethyl cyanoacetate. Similar condensation of **2a** with malononitrile gives the pyrido[2,3-c]pyridazine derivative (**8**). Compounds **3a-d** reacted with elemental sulphur in refluxing ethanolic solutions in the presence of triethylamine to yield the thieno[3,4-*d*]pyridazinones **9a-d**. The 1,3,4-thiadiazaacenaphthene **12** was prepared via reacting **9e** with diethyl fumarate. In contrast, only the phthalazines **14a-c** were produced from the reaction of **13a-c** with **9e**. Compounds **9a-c** reacted with acrylonitrile to yield the 1,3,4-thiadiazaacenaphthenes **18a, b**. Compound **3a** condensed with benzaldehyde to yield **19a**. Condensation of **3a, c, d** with dimethylformamide dimethylacetal afforded **19b-d**. Compound **19b** cyclized into **20b** when refluxed in acetic acid in the presence of ammonium acetate. This same product was obtained from the reaction of the amide **3g** with formaldehyde in refluxing pyridine. The reaction of **3a, c** with arylidenemalononitrile (**23a, b**) gives the tetrahydrophthalazines **25a-c**. The pyridazin-4-ones **26a-d** were prepared from the reaction of **2a-d** with dimethylformamide dimethylacetal in refluxing dioxane. The crystal and molecular structure of compound **18a** was solved by X-ray analysis.

INTRODUCTION

Fused pyridazinones comprise a very interesting class of compounds because of their significant biological and pharmaceutical activities.[1-5] As part of our studies aimed at developing simple and efficient syntheses of polyfunctional heteroaromatics from readily obtainable starting materials,[6-8] we have previously reported the synthesis of 4-methyl-6-oxopyridazine-5-carbonitrile derivatives via condensation of active methylene nitriles with ethyl 2-arylhydrazono-3-oxobutyrates.[6,8] The synthesized pyridazinones were shown to be excellent precursors for the synthesis of condensed polyfunctionally substituted pyridazinones.[6]

RESULTS AND DISCUSSION

In conjunction with our studies aimed at exploring the synthetic potentials of alkyl-6-oxopyridazin-5-carbonitriles, we report here on the synthesis and reactivity of the 4-ethyl-6-oxopyridazine-5-carbonitrile derivatives **3a-d**. In addition, a new route for the synthesis of 5-methyl-4-pyridazinones is reported. The work has resulted in developing the synthesis of a variety of polyfunctionally substituted condensed pyridazines that looks interesting for utility in further chemical transformations as well as for biological evaluation. Thus, we have found that **2a-d**, prepared in excellent yields via coupling **2a, b** with aromatic diazonium salts, condensed readily with ethyl cyanoacetate to yield **3a-d** in good yields. This is a further extension of our pyridazine synthesis from the reaction of **2e** with active methylenenitriles.[7-9]



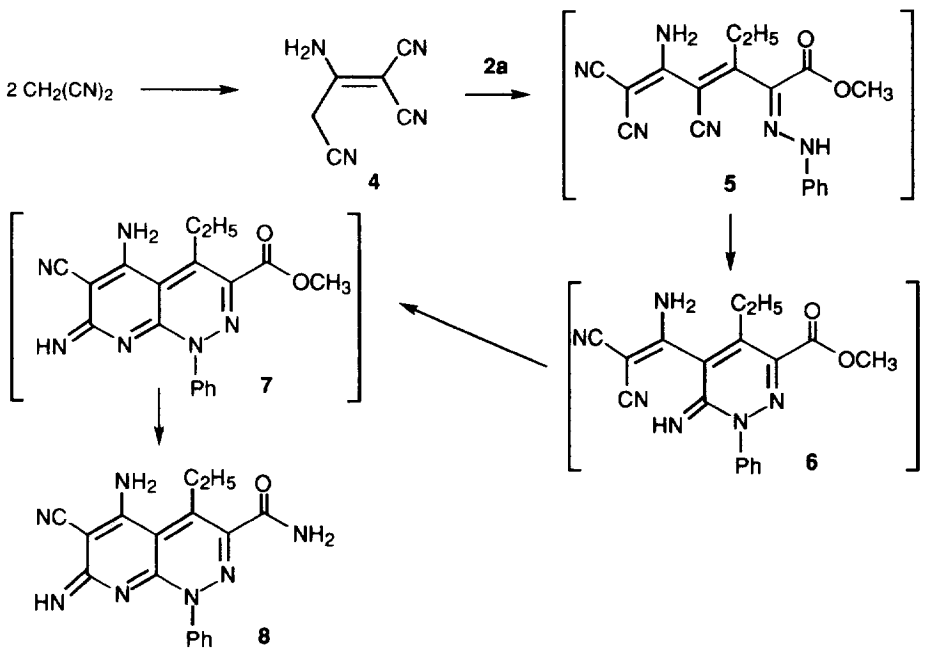
1a, $R_1 = CH_3$, $R_2 = CO_2CH_3$
1b, $R_1 = CH_3$, $R_2 = CN$
1c, $R_1 = H$, $R_2 = CO_2C_2H_5$

2

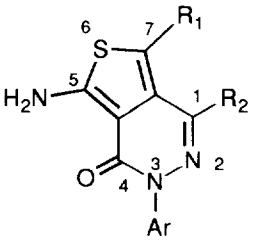
3

2, 3a, $R_1 = CH_3$, $R_2 = CO_2CH_3$, $Ar = C_6H_5$
2, 3b, $R_1 = CH_3$, $R_2 = CO_2CH_3$, $Ar = C_6H_4CH_3$-*p*
2, 3c, $R_1 = CH3$, $R_2 = CO_2CH_3$, $Ar = C_6H_4CH_3$-*p*
2, 3d, $R_1 = CH_3$, $R_2 = CN$, $Ar = C_6H_5$
2, 3e, $R_1 = H$, $R_2 = CO_2C_2H_5$, $Ar = C_6H_4OCH_3$-*p*
2, 3f, $R_1 = CH_3$, $R_2 = CO_2H$, $Ar = C_6H_5$
2, 3g, $R_1 = CH_3$, $R_2 = CONH_2$, $Ar = C_6H5$

However, in contrast to the reported formation of 6-amino-5-cyano-4-methyl-1-phenylpyridazinium-3-carboxylate from the reaction of ethyl 2-phenylhydrazono-3-oxobutyrate (**2e**) and malononitrile, the reaction of **2a** with malononitrile in the presence of ammonium acetate, afforded a product with a molecular formula $C_{17}H_{15}N_7O$. This was thus considered to be **8**. Formation of this product is assumed to result from condensation of **2a** with the initially formed **4**, resulting from dimerization of malononitrile in the presence of ammonium acetate, to yield **5** that readily afforded **6**, and subsequently the ester **7**. The latter, then reacts with ammonia yielding the final product **8**. Self condensation of two molecules of malononitrile in the presence of ammonium acetate to yield **4** has been reported earlier.[10] The difference in the behaviour between **2a** and **2e** is a result of decrease in reactivity of carbonyl group in **2a** as compared to that of **2e**, thus allowing initial self reaction of malononitrile.

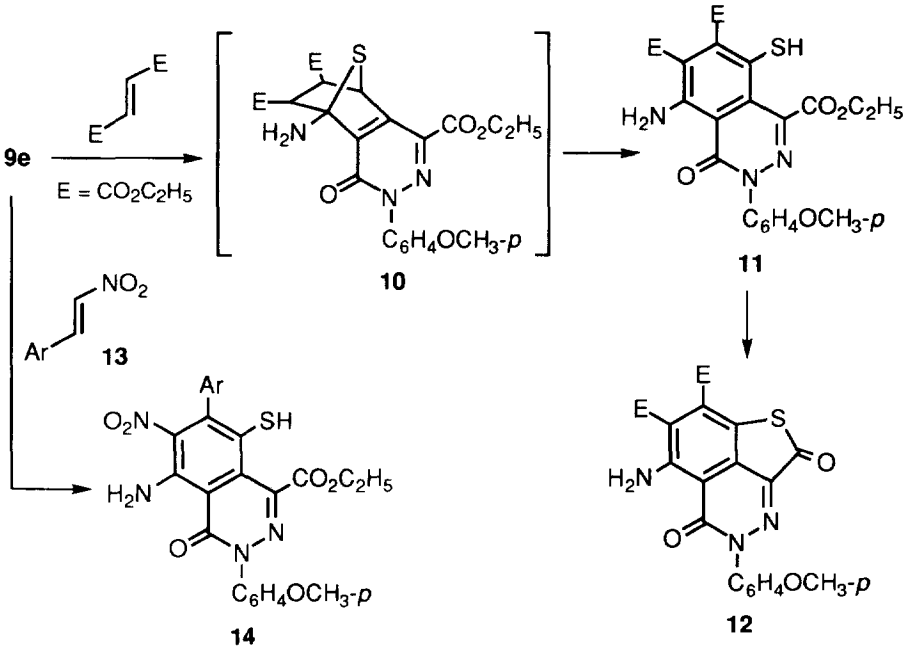


Compound **3a-d** reacted with elemental sulphur to yield the thieno[3,4-*d*]pyridazines **9a-d**. The formation of **9a-d** is a further demonstration of the scope of our thienoazine synthesis.[6]

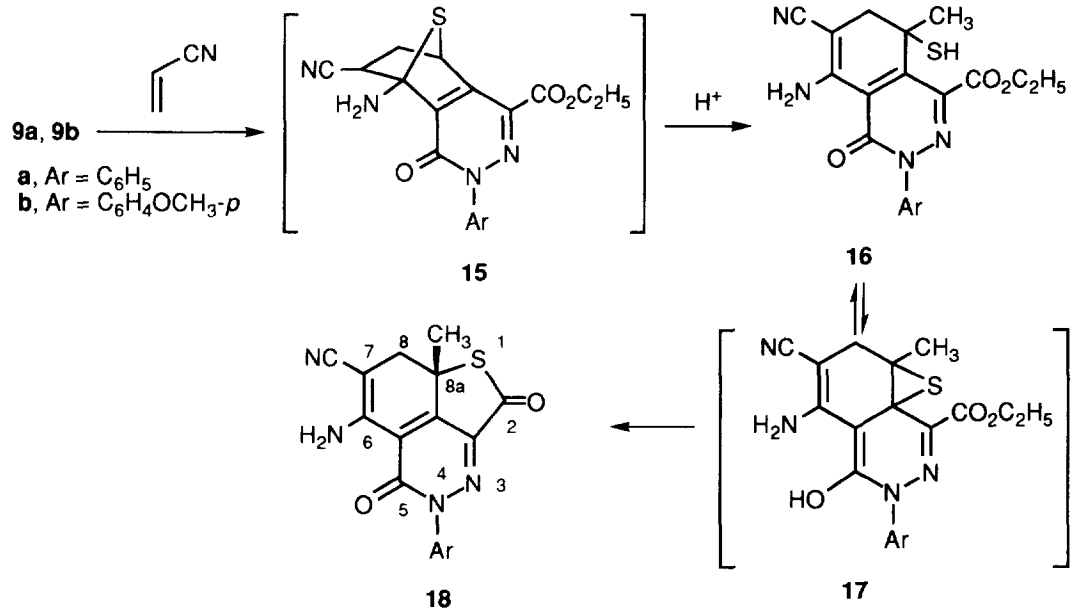


9a, $R_1 = CH_3$, $R_2 = CO_2CH_3$, Ar = C_6H_5
9b, $R_1 = CH_3$, $R_2 = CO_2CH_3$, Ar = $C_6H_4CH_3$-*p*
9c, $R_1 = CH_3$, $R_2 = CO_2CH_3$, Ar = $C_6H_4OCH_3$-*p*
9d, $R_1 = CH_3$, $R_2 = CN$, Ar = C_6H_5
9e, $R_1 = H$, $R_2 = CO_2C_2H_5$, Ar = $C_6H_4OCH_3$-*p*
9f, $R_1 = H$, $R_2 = CO_2C_2H_5$, Ar = C_6H_5

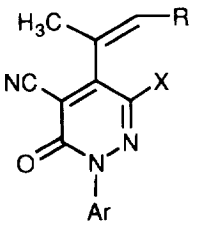
In previous work we have shown that the thienopyridazine derivative **9e** readily adds electron poor olefins to yield cycloadducts that readily decompose into phthalazines via elimination of hydrogen sulphide or hydrogen molecule, depending on both nature of olefin and applied reaction conditions.[6,11] To our knowledge, this was the first successful cycloaddition of electron poor olefins and acetylenes to amino condensed thiophenes. Recently, Döpp *et al.*[12] have reported a second example of such addition. The reaction of aminothienobenzopyranimine with diethyl fumarate proceeded in a way similar to that reported by us.[6] However, the reaction of this thienobenzopyranimine with dimethyl acetylenedicarboxylate resulted in rearrangement of the formed cycloadduct into thiepinobenzopyran.[10] In order to see if such rearrangement can also occur with our systems we have investigated further the behavior of **9a-e** toward electron poor olefins. The work enabled the development of a synthesis of polyfunctionally substituted 1,3,4-thiadiazaacenaphthene derivatives **12** and **18a, 18b** via a new, previously unreported, reaction pathway. Thus, reacting **9e** with diethyl fumarate, in refluxing dioxane in the presence of acetic acid, gave **12** in a moderate yield. Compound **12** is assumed to be formed via intermediacy of the cycloadduct **10** which first rearranges into **11** then undergoes autooxidation and cyclizes into **12** via loss of ethanol. In contrast, **9e** reacted with the nitrostyrene derivatives **13a-c** to yield the phthalazines **14a-c**. Trials to isolate the product of the decomposition of the intermediary formed [4 + 2] cycloadduct with loss of hydrogen sulfide, as has been reported earlier, failed.[11]



Compounds **9a-d** were recovered unreacted when refluxed with acrylonitrile in dioxane solution in the presence of acetic acid for two hours. In contrast to this, **9e** has been reported to add smoothly acrylonitrile under similar conditions.[6] Although the introduction of methyl function at C7 of **9a-d** is expected to raise the HOMO-LUMO energy of the system, this same function interacts sterically with the substituents on the olefin, thus raising the energy needed to attain the transition state for the reaction. This seems to be the controlling factor.



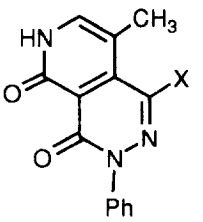
Compounds **9a**, **9b** reacted with acrylonitrile when refluxed in acetic acid solution for twenty hours, to yield products of addition and methanol elimination. These are assigned structure **18**, and are assumed to be formed via rearrangement of the initially formed cycloadduct **15** to **16**. The latter is perhaps in equilibrium with **17**. Cyclization of **16** via loss of methanol yields **18**. This is different to the reported behaviour of **9e**, **9f** toward acrylonitrile where ready elimination of hydrogen sulfide or autooxidation of the formed cycloadduct has been observed.[6] This difference in behaviour is the result of steric factors. Thus, if **17** would lose hydrogen sulphide to yield a phthalazine, the methyl and ester function in this product would experience large steric interactions. The structure proposed for compounds **18a**, **b** was established with certainty by X-ray diffraction of a crystal of **18a** (see later on). Furthermore ^{1}H NMR showed an AB multiplet near δ 3.00 ppm for CH_2 protons at position 8.



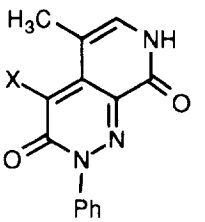
19a, R = Ar = C_6H_5, X = CO_2H
19b, R = $N(CH_3)_2$, Ar = C_6H_5, X = CO_2CH_3
19c, R = $N(CH_3)_2$, Ar = $C_6H_4OCH_3$-*p*, X = CO_2CH_3
19d, R = $N(CH_3)_2$, Ar = C_6H_5, X = CN

Similar to the reported ready condensation of **3e** with aromatic aldehydes to yield the styryl derivative **19a** was formed on reacting **3a** with benzaldehyde. Water separated during the condensation effects hydrolysis of methyl ester. Compound **19a** was also formed from reaction of **3f** with benzaldehyde. Compound **3f** has been prepared by hydrolysis of **3a** with acetic acid in the presence of hydrochloric acid.

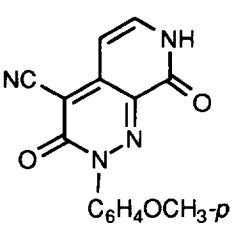
Compounds **3a**, **3c** and **3d** condensed with dimethylformamide dimethylacetal to yield the condensation products **19b-d**. The reaction of **19d** with acetic acid-hydrochloric acid mixture afforded a product that may be formulated as **20a** or **21a**. In order to establish the structure of this product, the amide **3g** was synthesized via refluxing **3a** with concentrated ammonia in DMF at 100°C for thirty minutes. This amide reacted with formaldehyde, in refluxing pyridine. However, instead of isolating **21a**, an amide was formed. Thus, this amide may again be either **20b** or **21b**. In an other approach compound **3a** was treated with dimethylformamide dimethylacetal and the product formed (**19b**) was treated with acetic acid in the presence of ammonium acetate. Again, the same amide was formed. Structure **20** was established for the reaction product **20a**, **b** based on UV spectra which showed a pattern completely different to that of **22**, recently obtained in our laboratory via reacting **3e** with dimethylformamide dimethylacetal and treatment of the product with aniline.[13] Thus, whereas **22** is a red compound with strong UV maxima at 430 nm, compounds **20a**, **20b** are yellow ones and do not absorb at above 400 nm. Their UV showed maxima at 371 and 365 nm, respectively.



20a, X = CN
20b, X = $CONH_2$

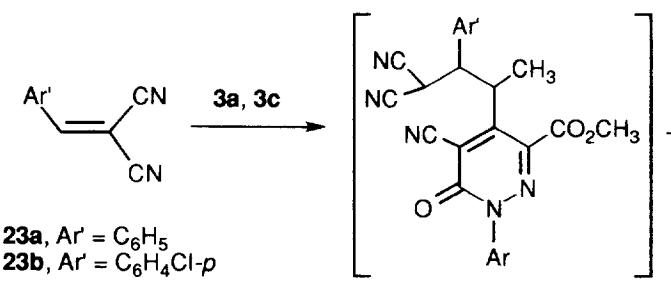


21a, X = CN
21b, X = $CONH_2$



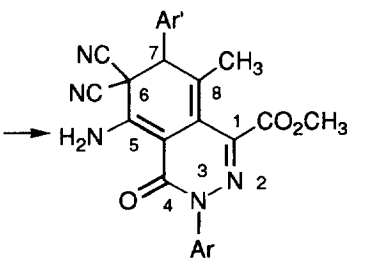
22

The reaction of **3a**, **3c** with arylidenemalononitrile **23a**, **23b** afforded 1:1 adducts which may be formulated as **24** or **25**. The tetrahydrophthazine structure **25** is established based on IR and ^1H NMR which revealed the presence of an amino group and the absence of CH multiplets in the range of δ 2-4 ppm other than the one for H-7, which would be present in the spectrum of **24**. Formation of **25** from **23a**, **b** and **3a**, **c** is assumed to occur via initial formation of Michael adducts **24**. Similar mechanism has been proposed earlier to account for the formation of phthalazines via reaction of **3e** with **23**.[6,14-16] In contrast to this report, the formed adduct did not aromatize by losing hydrogen cyanide. It seems that the adducts **25** are more stable than the products of hydrogen cyanide elimination as in the latter products, several functional groups should be in one plane, and as such should experience strong steric interaction.



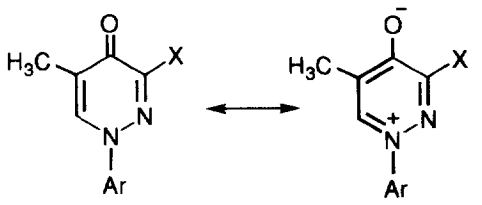
23a, Ar' = C_6H_5
23b, Ar' = C_6H_4Cl-*p*

24



25a, Ar = Ar' = C_6H_5
25b, Ar = C_6H_5, Ar' = C_6H_4Cl-*p*
25c, Ar = $C_6H_4OCH_3$-*p*,
Ar' = C_6H_4Cl-*p*

In order to investigate the activity of alkyls in pyridazin-4-ones, we have developed a new synthesis of 5-methylpyridazin-4-ones. Thus, reacting **2a-d** with dimethylformamide dimethylacetal gives the pyridazinones **26a-d** in good yield. The IR spectra of **26a-d** did not show any band for ring CO above 1650 cm^{-1}. This may indicate the importance in this compound of the resonance form **27**. We have found that the methyl function in **26a-d** is inactive toward aldehydes.



27

26a, Ar = C_6H_5, X = CO_2CH_3
26b, Ar = $C_6H_4CH_3$-*p*, X = CO_2CH_3
26c, Ar = $C_6H_4OCH_3$-*p*, X = CO_2CH_3
26d, Ar = C_6H_5, X = CN

X-Ray Crystallographic Study of Compound **18a**.

The molecular structure and the numbering scheme is depicted in Fig. 1. The dihydrothiophene ring displays a similar pattern of bond distances and angles to that of thiophthalide (a dihydrobenzo[*b*]thiophenone, CSD refcode: THOPHT),[17] the only similar ring reported so far. The observed distances in the 2-phenylpyridazinone are in good agreement with the mean values we have calculated from five structures containing this group (FEWBAK, GAXVIK, KUPNOY, PACVOE and PYRZON). The heteroring adopts a rather flat distorted boat conformation (Table 1) probably as a consequence of the fused rings as it happens in the PYRZON where a benzothiepine ring is sharing the C(3)-C(4) bond. The conformation of the dihydrothiophene ring as well as the other six-membered ring is defined by the ring puckering parameters,[18] the rings show a distorted envelope and a 1,3-diplanar conformations respectively (Table 1).

The formation of the N-H intramolecular hydrogen bond to the carbonyl O6 atom weakens the C=O, displaying a length of 1.220(3) Å which aids π electron delocalization of the electron lone pairs giving rise to a C5-C6 bond shorter than the tabulated Csp^2-Csp^2 of 1.465(18) Å in C=C-C(=O)(-C) fragments.[19a] The phenyl ring, that makes an angle of 47.9(1)° with the pyridazinone one, allows the formation of the C19-H19···O6 interaction. The NH_2 group is involved in a bifurcated hydrogen bond (Table 2) with two O6 atoms giving rise to dimers (Fig 2) through symmetry centers. These dimers form piles along the **c** axis by means of weak C-H···O interactions. The crystal is built up of these piles that do no bear any interaction between them other than the van der Waals ones.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer (for compound **18a** a Varian Gemini 200 spectrometer was used) with [$^2H_6$]DMSO as solvent and TMS as an internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on GS/MS INCOS XL Finnigan MAT. Microanalyses were performed on LECO CHNS-932. Compounds **3e** and **9e** were prepared using our recently published procedures.[14,15]

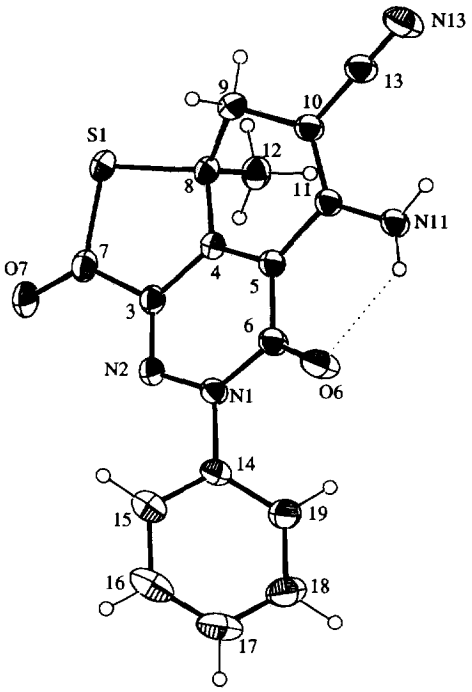


Fig.1 .-Molecular structure showing the displacement parameters drawn at the 30% level. Hydrogen atoms are shown as spheres of arbitrary radii. Dotted line means hydrogen bond.

Table 1. Selected geometrical parameters (Å,°).

N1-N2	1.346(2)	N2-C3	1.304(2)	C3-C4	1.401(3)
C4-C5	1.355(3)	C5-C6	1.451(2)	N1-C6	1.410(3)
C6-O6	1.220(3)	C3-C7	1.490(2)	C7-O7	1.201(3)
S1-C7	1.785(2)	S1-C8	1.845(2)	C4-C8	1.500(2)
C8-C12	1.531(2)	C8-C9	1.526(3)	C9-C10	1.519(3)
C10-C13	1.416(3)	C13-N13	1.145(3)	C10-C11	1.373(2)
C11-N11	1.351(2)	C11-C5	1.471(3)	N1-C14	1.443(2)
N2-N1-C14	114.6(1)	N2-N1-C6	126.2(1)	C6-N1-C14	119.1(1)
C3-N2-N1	115.2(2)	C4-C3-N2	124.6(2)	C4-C3-C7	113.7(1)
C7-C3-N2	121.6(2)	C8-C4-C5	123.2(2)	C5-C4-C3	120.6(2)
C8-C4-C3	116.2(2)	C11-C5-C6	123.2(2)	C11-C5-C4	119.3(2)
C4-C5-C6	117.4(2)	C5-C6-N1	115.0(2)	N1-C6-O6	119.8(2)
C5-C6-O6	125.2(2)	S1-C7-C3	108.0(1)	C3-C7-O7	127.3(2)
S1-C7-O7	124.7(2)	C8-S1-C7	95.0(1)	S1-C8-C4	103.6(1)
S1-C8-C9	114.2(1)	S1-C8-C12	108.2(1)	C9-C8-C4	108.2(2)
C12-C8-C4	110.1(1)	C12-C8-C9	112.2(2)	C8-C9-C10	109.6(2)
C9-C10-C11	123.0(2)	C9-C10-C13	119.2(2)	C13-C10-C11	117.4(2)
C10-C13-N13	176.5(2)	C10-C11-C5	116.9(2)	C10-C11-N11	124.1(2)
N11-C11-C5	119.1(2)	C15-C14-C19	122.0(2)		
N1-N2-C3-C4	2.0(3)	N2-C3-C4-C5	-8.6(3)	C3-C4-C5-C6	5.2(3)
C4-C5-C6-N1	3.3(2)	C5-C6-N1-N2	-10.5(3)	C6-N1-N2-C3	7.8(2)
C3-C7-S1-C8	11.7(1)	C7-S1-C8-C4	-16.7(1)	S1-C8-C4-C3	18.6(2)
C8-C4-C3-C7	-11.2(2)	C4-C3-C7-S1	-2.6(2)	C5-C4-C8-C9	-38.8(2)
C4-C8-C9-C10	48.8(2)	C8-C9-C10-C11	-35.4(2)	C9-C10-C11-C5	3.1(3)
C10-C11-C5-C4	12.9(2)	C11-C5-C4-C8	6.8(3)	N2-N1-C14-C15	-45.3(2)

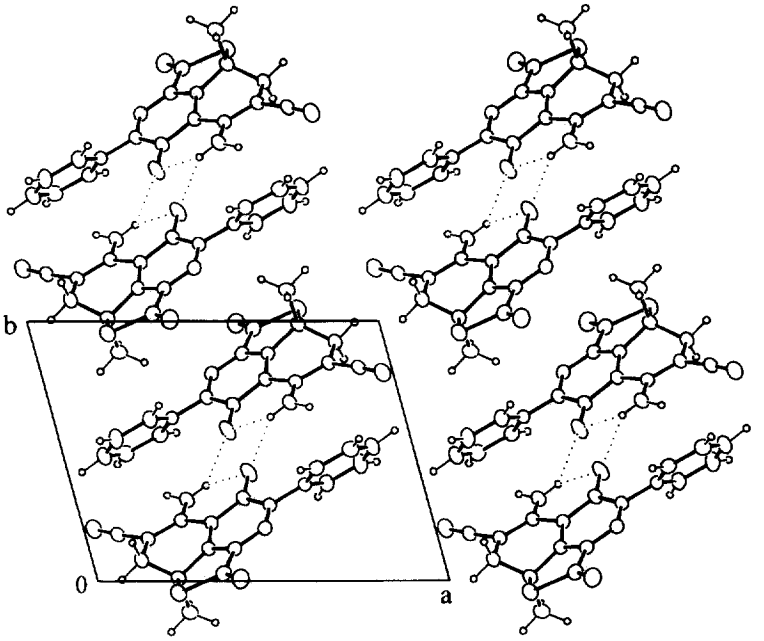


Fig.2 .-Crystal packing down the c axis.

Table 2. Hydrogen interactions. (Å,°).

X-H...Y	X-H	X...Y	H...Y	X-H...Y
N11-H111...O6	0.86(3)	2.773(2)	2.12(3)	132(3)
C19-H19...O6	0.98(3)	2.861(3)	2.60(3)	95(2)
N11-H111...O6(-x+1,-y+1,-z)	0.86(3)	3.033(2)	2.30(3)	143(3)
C12-H121...O7(x,y,z-1)	0.96(3)	3.357(2)	2.63(3)	134(2)

General procedure for the preparation of Methyl 2-arylhydrazono-3-oxopentanoates (2a-c) and 3-oxo-2-phenylhydrazonopentanonitrile (2d). To a solution of **1a** or **1b** (0.1 mol) in ethanol (100 mL) 20 sodium acetate (20.0 g, 0.3 mol) were added. The mixture was then treated gradually with stirring at room temperature with a solution of the appropriate aryldiazonium salt (prepared from 0.1 mol of aromatic amine and the appropriate quantities of hydrochloric acid and sodium nitrite). The product was separated on standing, collected by filtration and crystallised from ethanol.

Methyl 2-phenylhydrazon-3-oxo-pentanoate (2a). Compound **2a** was obtained as yellow crystals from ethanol (94%); m.p. 74°C; IR: 3500-3450 (NH), 1685 (ester CO) and 1660 cm^{-1} (acyl CO); ^1H NMR: δ 1.10 (t, 3H, CH_3, J = 7 Hz), 2.90 (q, 2H, CH_2, J = 7 Hz), 3.80 (s, 3H, OCH_3), 7.20-7.60 (m, 5 H, Ar-H) and 11.8 ppm (br, 1H, NH); MS: *m/z* 234 (M^+); Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.87; H, 6.08; N, 12.16.

Methyl 2-(*p*-methylphenylhydrazone)-3-oxopentanoate (2b). Compound **2b** was obtained as yellow crystals from ethanol (92%); m.p. 71.5°C; IR: 3450-3300 (NH), 1700 (ester CO) and 1660 cm^{-1} (acyl CO); ^1H NMR: δ 1.10 (t, 3H, CH_3, J = 7 Hz), 2.30 (s, 3H, CH_3), 2.90 (q, 2H, CH_2, J = 7 Hz), 3.80 (s, 3H, OCH_3), 7.00-7.60 (m, 4H, Ar-H) and 11.7 ppm (br, 1H, NH); Anal. Calcd. for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.88; H, 6.49; N, 11.28. Found: C, 62.87; H, 6.45; N, 11.30.

Methyl 2-(*p*-methoxyphenylhydrazone)-3-oxopentanoate (2c). Compound **2c** was obtained as red crystals from ethanol (96%); m.p. 90°C; IR: 3450-3300 (NH), 1700 (ester CO) and 1680 cm^{-1} (acyl CO); ^1H NMR: δ 1.10 (t, 3H, CH_3, J = 7 Hz), 2.95 (q, 2H, CH_2, J = 7 Hz), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.80-7.60 (m, 4H, Ar-H) and 11.8 ppm (br, 1H, NH); Anal. Calcd. for $C_{13}H_{16}N_2O_4$ (264.27): C, 59.08; H, 6.10; N, 10.60. Found: C, 58.77; H, 6.08; N, 10.63.

2-Phenylhydrazono-3-oxo-pentanonitrile (2d). Compound **2d** was obtained as yellow crystals from ethanol (73%); m.p. 127-129°C; IR: 3450-3000 (NH), 2225 (CN) and 1670 cm^{-1} (CO); ^1H NMR: δ 1.20 (t, 3H, CH_3, J = 7 Hz), 2.90 (q, 2H, CH_2, J = 7 Hz), 7.10-7.40 (m, 5H, Ar-H) and 9.65 ppm (br, 1H, NH); ^{13}C NMR: δ 195.70 (CO), 142.42, 129.89, 125.27, 116.06 (phenyl carbons), 113.47 (CN), 111.33 (C=N), 29.89 (CH_2), 8.49 (CH_3); Anal. Calcd. for $C_{11}H_{11}N_3O$ (201.22): C, 65.67; H, 5.51; N, 20.88. Found: C, 65.71; H,5.70; N, 20.85.

General procedure for the preparation of methyl 1-aryl-5-cyano-4-ethyl-1,6-dihydro-6-oxopyridazin-3-carboxylates (3a-c) and 4-ethyl-1,6-dihydro-6-oxo-l-phenyl-pyridazin-3,5-dicarbonitrile (3d). In a 100 mL flask, a suspension of **2a-d** (0.01 mol) in benzene (50 mL) was treated with ammonium acetate (5.0 g) and acetic acid (2.0 mL). The reaction flask was then provided with a device for continual elimination of water, then heated under reflux for 6 h. The benzene layer was then evaporated. The resulting solid product was triturated with ethanol then collected by filtration and crystallized from ethanol.

Methyl 5-cyano-1,6-dihydro-4-ethyl-6-oxo-1-phenylpyridazin-3-carboxylate (3a). Compound **3a** was obtained as pale yellow crystals (85%); m.p. 139.2°C; IR: 2225 (CN), 1730 (ester CO) and 1670 cm^{-1} (ring CO); ^1H NMR: δ 1.13 (t, 3H, CH_3, J = 7 Hz), 3.00 (q, 2H, CH_2, J = 7 Hz), 3.90 (s, 3H, OCH_3) and 7.50-7.60 ppm (m, 5H, Ar-H); ^{13}C NMR: δ 162.18 (ester CO), 156.06 (C-4), 155.54 (C-1), 136.11 (C-6), 140.14,

129.22, 128.89, 125.61 (phenyl carbons), 114.20 (CN), 112.95 (C-5), 53.00 (OCH_3), 25.26 (CH_2), 13.33 (CH_3); MS: *m/z* 283 (M^+); Anal. calcd. for $C_{15}H_{13}N_3O_3$ (283.28): C, 63.59; H, 4.63; N, 14.83. Found: C, 63.64; H, 4.63; N, 14.83.

Methyl 5-cyano-1,6-dihydro-4-ethyl-1-(*p*-methylphenyl)-6-oxopyridazine-3-carboxylate (3b). Compound **3b** was obtained as pale yellow crystals from ethanol (81%); m.p. 133-134°C; IR: 2225 (CN), 1730 (ester CO) and 1680 cm^{-1} (ring CO); ^1H NMR: δ 1.30 (t, 3H, CH_3, J = 7 Hz), 2.40 (s, 3H, CH_3), 3.00 (q, 2H, CH_2, J = 7 Hz), 3.90 (s, 3H, OCH_3), and 7.20-7.50 ppm (m, 4H, Ar-H); Anal. calcd. for $C_{16}H_{15}N_3O_3$ (297.30): C, 64.63; H, 5.09; N, 14.14. Found: C, 64.88; H, 5.02; N,14.05.

Methyl 5-cyano-1,6-dihydro-4-ethyl-1-(*p*-methoxyphenyl)-6-oxopyridazine-3-carboxylate (3c). Compound **3c** was obtained as orange crystals from ethanol (90%); m.p. 109°C; IR: 2225 (CN), 1730 (ester CO) and 1680 cm^{-1} (ring CO); ^1H NMR: δ 1.30 (t, 3H, CH_3, J = 7 Hz), 3.00 (q, 2H, CH_2, J = 7 Hz), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), and 7.10-7.50 ppm (m, 4H, Ar-H); Anal. calcd. for $C_{16}H_{15}N_3O_4$ (313.30): C, 61.33; H, 4.83; N, 13.51. Found: C, 61.24; H, 4.88; N, 13.51.

1,6-Dihydro-4-ethyl-6-oxo-1-phenylpyridazine-3,5-dicarbonitrile (3d). Compound **3d** was obtained as violet crystals from ethanol (50%); m.p. 145-147°C; IR: 2225 (CN) and 1680 cm^{-1} (ring CO); ^1H NMR δ 1.40 (t, 3H, CH_3, J = 7 Hz), 2.95 (q, 2H, CH_2, J = 7 Hz), and 7.20-7.50 (m, 5H, Ar-H); Anal. calcd. for $C_{14}H_{10}N_4O$ (250.25): C, 67.19; H, 4.03; N, 22.19. Found: C, 67.33; H, 4.48; N, 21.89.

Preparation of 5-amino-6-cyano-7,8-dihydro-4-ethyl-7-imino-1-phenylpyrido[2,3-*c*]pyridazine -3-carboxamide (8). A mixture of **2a** (0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (5.0 g) was heated at 180° for 30 min. The solid product formed on cooling, was triturated with water, collected by filtration and crystallized from ethanol. Compound **8** was obtained as violet crystals (45%); m.p. > 200°C; IR: 3600-3400 (NH and NH_2), 2225 (CN) and 1665 cm^{-1} (amide CO); ^1H NMR: δ 1.20 (t, 3H, CH_3, J = 7 Hz), 2.95 (q, 2H, CH_2, J = 7 Hz), 7.30-7.60 (m, 10H, Ar-H, NH and NH_2); Anal. calcd. for $C_{17}H_{15}N_7O$ (333.35): C, 61.25; H, 4.53; N, 29.41. Found: C, 61.30; H, 4.64; N, 29.30.

Preparation of methyl 5-amino-3-aryl-3,4-dihydro-7-methyl-4-oxothieno[3,4-*d*]pyridazine-1-carboxylate (9a-c) and 5-amino-3,4-dihydro-7-methyl-3-phenyl-4-oxothieno[3,4-*d*]pyridazine-1-carbonitrile (9d). To a suspension of **3a-d** (0.05 mol) in dioxane (30 mL), elemental sulfur (0.05 mol) and few drops of triethylamine were added. The reaction mixture was refluxed for 3 h then poured onto water. The solid product, so formed,was then collected by filtration and crystallized from ethanol.

Methyl 5-amino-3,4-dihydro-7-methyl-4-oxo-3-phenylthieno[3,4-*d*]pyridazine-1-carboxylate (9a). Compound **9a** was obtained as brown crystals from ethanol (77%); m.p. 186°C; IR: 3550-3300 (NH_2), 1730 (ester CO) and 1640 cm^{-1} (ring CO); ^1H NMR: δ 2.30 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.20-7.60 ppm (m, 7H, Ar-H and NH_2); ^{13}C NMR: δ 164.02 (ester CO), 160.07 (C-4), 158.15 (C-1), 135.92 (C-5), 140.48, 128.32, 126.96, 125.82 (phenyl carbons), 121.00 (C-7), 115.17 (C-7a), 104.04 (C-4a), 52.71 (OCH_3), 12.94 (CH_3); Anal . calcd . for $C_{15}H_{13}N_3O_3S$ (315.34): C, 57.14 ; H , 4.16 ; N, 13.33 ; S, 10.17. Found: C, 56.93; H, 4.20; N, 13.32; S, 10.15.

Methyl 5-amino-3,4-dihydro-7-methyl-3-(*p*-methylphenyl)-4-oxothieno[3,4-*d*]pyridazine-1-carboxylate (9b). Compound **9b** was obtained as brown crystals from ethanol (61%); m.p. 178°C; IR: 3500-3300 (NH_2),1730 (ester CO) and1640 cm^{-1} (ring CO); ^1H NMR: δ 2.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3) and 7.05-7.40 ppm (m, 6H, Ar-H and NH_2); ^{13}C NMR: δ 164.09 (CO), 159.99 (C-4), 158.25 (C-1), 136.36 (C-5), 138.09, 135.78, 128.78, 125.65 (phenyl carbons), 121.10 (C-7), 115.04 (C-7a), 104.22 (C-4a), 52.69 (OCH_3), 20.55 (CH_3), 12.98 (CH_3); Anal. calcd. for $C_{16}H_{15}N_3O_3S$ (329.36): C, 58.35; H, 4.59; N, 12.76. Found: C, 58.19; H, 4.72; N,12.67.

Methyl 5-amino-3,4-dihydro-7-methyl-3-(*p*-methoxyphenyl)-4-oxothieno[3,4-*d*]pyridazine-1-carboxylate (9c). Compound **9c** was obtained as golden brown crystals from ethanol (69%); m.p. 162°C; IR: 3500-3400, 3300 (NH_2), 1730 (ester CO) and 1680 cm^{-1} (ring CO); ^1H NMR: δ 2.30 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3) and 6.80-7.50 ppm (m, 6H, Ar-H and NH_2); Anal. calcd. for $C_{16}H_{15}N_3O_4S$ (345.36): C, 55.65; H, 4.38; N, 12.17; S, 9.27. Found: C, 56.08; H, 4.77; N, 12.15; S, 9.63.

5-Amino-3,4-dihydro-7-methyl-3-phenyl-4-oxothieno[3,4-*d*]pyridazine-1-carbonitrile (9d). Compound **9d** was obtained as dark crystals from ethanol (88%); m.p. 235°C; IR: 3450, 3300 (NH_2), 2225 (CN), and 1670 cm^{-1} (ring CO); ^1H NMR: δ 2.60 (s, 3H, CH_3), and 7.30-7.70 ppm (m, 7H, Ar-H and NH_2); Anal. calcd. for $C_{14}H_{10}N_4OS$ (282.69): C, 59.48; H, 3.56; N, 19.81; S, 11.34. Found: C, 59.70; H, 3.95; N, 19.60; S, 11.23.

Diethyl 6-amino-4,5-dihydro-2,5-dioxo-4-(*p*-methoxyphenyl)-1,3,4-thiadiazaacenaphthene-7,8-dicarboxylate (12). A suspension of **9e** (0.01 mol) in dioxane (30 mL) and acetic acid (5 mL) was treated with diethyl fumarate (0.01 mol). The reaction mixture was refluxed for 5 h then poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol. This compound was obtained in 62% yield as orange crystals, m.p. 192-193°C; IR: 3600-3400 (NH_2), 1720 (thiolacetone CO), 1695 (ester CO) and 1640 cm^{-1} (ring CO); ^1H NMR: δ 1.25 (t, 3H, CH_3, J = 7 Hz); 1.30 (t, 3H, CH_3, J = 7 Hz), 3.85 (s, 3H, OCH_3); 4.25 (q, 2H, OCH_2, J = 7 Hz), 4.40 (q, 2H, OCH_2, J = 7 Hz), 7.1-7.6 (m, 4H, Ar-H) and 7.70 ppm (br, 2H, NH_2); ^{13}C NMR: δ 191.85 (C-2), 169.60 (ester CO), 168.72 (ester CO), 163.45 (C-5), 163.39 (C-2a), 152.03, 143.08, 137.87, 136.16, 133.51, 131.76, 118.04, 117.56, 116.97, 115.95 (Aromatic carbons), 66.57 (CH_2), 65.85 (CH_2), 59.57 (OCH_3), 17.93 (CH_3) and 17.70 (CH_3); MS: *m/z* 470 (M^+); Anal. calcd. for $C_{22}H_{19}N_3O_7S$ (469.65): C, 56.29; H, 4.07; N, 8.98. Found: C, 56.25; H, 4.07; N, 8.98.

General procedure for the preparation of ethyl 5-amino-7-aryl-3,4-dihydro-3-(*p*-methoxyphenyl)-8-mercapto-6-nitro-4-oxophthalazine-1-carboxylates (14a-c). A suspension of **9e** (0.01 mL) in dioxane (30 mL) and acetic acid (5 mL) was treated with **13a-c**. The reaction mixture was refluxed for 6 h then poured onto water. The solid product was collected by filtration and crystallized from ethanol.

Ethyl 5-amino-3,4-dihydro-3-(*p*-methoxyphenyl)-7-(*p*-methylphenyl)-8-mercapto-6-nitro-4-oxophthalazine-1-carboxylate (14a). Compound **14a** was obtained as brown powder from ethanol (67%); m.p. 143-145°C; IR: 3560-3300 (NH_2), 1720 (ester CO) and 1650 cm^{-1} (ring CO); ^1H NMR: δ 1.16 (t, 3H, CH_3, J = 7 Hz), 2.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.30 (q, 2H, OCH_2 J = 7 Hz), 5.20 (br, 1H, SH) and 6.80-7.60 ppm (m, 10H, Ar-H and NH_2); Anal. calcd. for $C_{25}H_{22}N_4O_6S$ (506.53): C, 59.28; H, 4.37; N, 11.06. Found: C, 58.91; H, 4.72; N, 11.05.

Ethyl 5-amino-3,4-dihydro-3,7-di-(*p*-methoxyphenyl)-6-nitro-4-oxophthalazine-1-carboxylate (14b). Compound **14b** was obtained as dark brown crystal from ethanol (42%); m.p.112-114°C; IR: 3550-3400 (NH_2), 1720 (ester CO) and 1650 cm^{-1} (ring CO); ^1H NMR: δ 1.16 (t, 3H, CH_3, J = 7 Hz), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.30 (q, 2H, OCH_2 J = 7Hz), 5.20 (brs, 1H, SH) and 6.70-7.60 ppm (m, 10H, Ar-H and NH_2); Anal. calcd. for $C_{25}H_{22}N_4O_7S$ (522.53): C, 57.46; H, 4.24; N, 10.72. Found: C, 57.33; H, 4.32; N, 10.65.

Ethyl 5-amino-3,4-dihydro-3-(*p*-methoxyphenyl)-8-mercapto-4-oxo-7-phenylphthalazine-1-carboxylate (14c) .Compound **14c** was obtained as brown crystals from ethanol (61%); m.p. 190-192°C; IR: 3420-3320 (NH_2), 1710 (ester CO) and 1660 cm^{-1} (ring CO); ^1H NMR: δ 1.30 (t, 3H, CH_3, J = 7 Hz), 3.80 (s, 3H, OCH_3), 4.30 (q, 2H, OCH_2 J = 7 Hz), 5.30 (brs, 1H, SH) and 6.90-7.70 ppm (m, 10H, Ar-H and NH_2); Anal. calcd. for $C_{24}H_{20}N_4O_6S$ (492.51): C, 58.52; H, 4.09; N, 11.37; S, 6.50. Found: C, 58.70; H, 4.07; N, 11.11; S, 6.17.

General procedure for the preparation of 6-amino-4-aryl-8,8a-dihydro-2,5-dioxo-8a-methyl-1, 3,4-thiadiazaacenaphthene-7-carbonitriles (18a, b): A solution of **9a-b** (0.01 mol) in acetic acid (50 mL) was treated with acrylonitrile (0.01 mol) . The reaction mixture was refluxed for 20 h, then evaporated *in vacuo*. The remaining product was triturated with water, and the resulting solid product was collected by filtration and crystallized from dioxane.

6-Amino-8a-methyl-8,8a-dihydro-2,5-dioxo-8a-methyl-4-phenyl-1,3,4-thiadiazaacenaphthene-7-carbonitrile (18a): Compound **18a** was obtained as red crystals (90%); m.p. 224°C; IR: 3500~3250 (NH_2), 2195 (CN), 1710 (ester CO), 1665 (ring CO) and 1625 cm^{-1} (NH_2); ^1H NMR: δ 2.10 (s, 3H, CH_3), 2.81 and 3.06 (AB system, 2H, CH_2, J_{AB} = -15.5 Hz),7.35 (s, 2H, NH_2) and 7.80 ppm (m, 6H, Ar-H and OH); ^{13}C NMR: δ 193.19 (C-2), 161.28 (C-5), 153.03 (C-2a), 144.89 (C-6), 143.90, 133.29, 132.90, 130.08 (phenyl carbons), 124.02 (C-5a), 123.73 (CN), 101.17 (C-7), 75.58 (C-8a), 52.61 (C-8) and 29.54 (CH_3); Anal. calcd for $C_{17}H_{12}N_4O_2S$ (336.30): C, 60.34; H, 3.90; N, 16.77, S, 9.33. Found: C,60.71; H, 3.60; N, 16.66; S, 9.53.

6-Amino-8,8a-dihydro-2,5-dioxo-8a-methyl-4-methoxyphenyl-1,3,4-thiazaacenaphthene-7-carbonitrile (18b): Compound **18b** was obtained as red crystals (85%); m.p. 275°C; IR: 3500-3300 (NH_2), 2195 (CN), 1715 (ester CO), 1665 (ring CO) and 1640 cm^{-1} (NH_2); ^1H NMR: δ 2.90 (s, 3H, CH_3), 3.00 (s, 2H, CH_2), 7.10 (s, 2H, NH_2) and 7.2-7.5 ppm (m, 5H, Ar-H); Anal. calcd for $C_{19}H_{16}N_4O_3S$ (350.32): C, 61.51; H, 4.45; N, 16.01; S, 9.15. Found: C, 61.71; H, 4.03; N, 16.00; S, 9.15.

5-Cyano-1,6-dihydro-4-(1-methylstyryl)-6-oxo-1-phenylpyridazine-3-carboxylic acid (19a). A solution of **3a** or **3f** (0.01 mol) in pyridine (30 mL) was treated with benzaldehyde (0.01 mol) then refluxed for 6 hours. The reaction mixture was left to cool to room temperature then poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol. This compound was obtained in 69% yield as yellow crystals, m.p. 202-204°C; IR: 3500-3300 (OH dimer), 1710 (carboxylic CO) and 1675 cm^{-1} (ring CO); ^1H NMR: δ 2.20 (s, 3H, CH_3), 6.70 (s, 1H, C=CH), 7.35-7.70 (m, 10H, Ar-H) and 8.6 ppm (brs, 1H, OH); Anal. calcd. for $C_{21}H_{15}N_3O_3$ (357.36): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.63; H, 4.39; N, 12.15.

5-Cyano-1,6-dihydro-4-ethyl-6-oxo-1-phenylpyridazine-3-carboxylic acid (3f). A solution of **3a** (0.01 mol) in acetic acid-hydrochloric acid (2:1) mixture (30 mL) was refluxed for 1 h, then poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol. This compound was obtained in 91% yield as yellow crystals; m.p. 230-231.5°C; IR: 3500-3350 (OH dimer), 2225 (CN), 1760 (carboxylic CO) and 1660 cm^{-1} (ring CO); ^1H NMR: δ 1.30 (t, 3H, CH_3, J = 7 Hz), 3.00 (q, 2H, CH_2, J = 7 Hz) 4.00 (brs, 1H, OH) and 7.60 ppm (m, 5H, Ar-H); Anal. calcd. for $C_{14}H_{11}N_3O_3$ (269.25): C, 62.45; H, 4.12; N, 15.61. Found: C, 62.56; H, 4.18; N, 15.68.

Reaction of 3c, 3d with dimethylformamide dimethylacetal. A solution of **3c, 3d** (0.01 mol) in acetic anhydride (30 mL) was treated with dimethylformamide dimethylacetal (0.01 mol). The reaction mixture was then refluxed for 10-15 min. After cooling down to room temperature it was poured onto water. The solid precipitate was collected by filtration and crystallized from ethanol.

Methyl 5-cyano-1,6-dihydro-4-[2-(*N*,*N*-dimethylamino-1-methylethenyl)]-6-oxo-1-(*p*-methoxyphenyl)pyridazine-3 carboxylate (19c). Compound **19c** was obtained as dark brown crystals from ethanol (70%); m.p. 169-170°C; IR: 2225 (CN), 1730 (ester CO) and 1656 cm^{-1} (ring CO); ^1H NMR: δ 1.95 (s, 3H, CH_3), 3.00 (s, 6H, $N(CH_3)_2$), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.85 (s, 1H, C=CH) and 7.00-7.60 ppm (m, 4H, Ar-H); Anal. calcd. for $C_{19}H_{20}N_4O_4$ (368.39): C, 61.94; H, 5.47; N, 15.20. Found: C, 61.72; H, 5.52; N, 14.73.

1,6-Dihydro-4-[2-(*N*,*N*-dimethylamino-1-methylethenyl)]-6-oxo-1-phenyl-pyridazine-3,5-dicarbonitrile (19d). Compound **19d** was obtained as red crystals from ethanol (71%); m.p. 205°C; IR: 2225 (CN) and 1660 cm^{-1} (ring CO); ^1H NMR: δ 2.25 (s, 3H, CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 7.10 (s, 1H, C=CH); and 7.30-7.70ppm (m, 5H, Ar-H); Anal. calcd. for $C_{17}H_{15}N_5O$ (305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.93; H, 4.89; N, 22.92.

5-Cyano-1,6-dihydro-4-ethyl-6-oxo-1-phenylpyridazine-3-acetamide (3g). To **3a** (0.05 mol) dissolved in DMF, an excess of ammonia was added. The mixture was refluxed for 30 min, then kept at room temperature overnight. The mixture was then poured onto water and the solid product, so formed, was filtered and crystallized from ethanol. Compound **3g** was obtained as colorless crystals (83%); m.p. 187-189°C, IR: 3375-3205 (NH_2), 2230 (CN) and 1670-1650 (ring and amide CO); ^1H NMR: δ 1.28 (t, 3H, CH_3, J = 7 Hz), 2.95 (q, 2H, CH_2, J = 7 Hz) and 7.2-8.2 ppm (m, 7H, Ar-H and NH_2); Anal. calcd. for $C_{14}H_{12}N_4O_2$ (268.27): C, 62.68; H, 4.51; N, 20.89. Found: C, 62.60; H, 4.59; N, 21.03.

4,5-Dioxo-8-methyl-3-phenyl-3,4,5,6-tetrahydropyrido[3,4-*d*]pyridazine-1-carbonitrile (20a). A solution of **19e** (0.01 mol) was added to a mixture acetic acid- hydrochloric acid (2:1) (30 mL). The reaction mixture was refluxed for 1 h then poured onto water. The solid product, so formed,was then collected by filtration and crystallized from ethanol. Compound **20a** was obtained as yellow crystals (78%); m.p. 268°C; IR: 3435-3220 (NH), 2225 (CN) and 1703, 1673 cm^{-1} (ring CO); ^1H NMR: δ 2.30 (s, 3H, CH_3), 7.30-7.75 (m, 5H, Ar-H), 7.80 (s, 1H, ring H-7) and 11.6 ppm (brs, 1H, NH); Anal. calcd. for $C_{15}H_{10}N_4O_2$ (278.27): C, 64.74; H, 3.62; N, 20.13. Found: C, 64.70; H, 3.82; N, 19.89.

Preparation of 4,5-dioxo-8-methyl-3-phenyl-3,4,5,6-tetrahydropyrido[3,4-*d*]pyridazine-1-carboxamide (20b). *Method A*: A suspension of **3g** (0.01 mol) in pyridine (30 mL) was treated with formaldehyde (0.01 mol). The mixture was refluxed for 4 h and left to cool, then poured onto water. The so formed product was filtered and crystallized from ethanol. *Method B*: A suspension of **3a** (0.01 mol) in dioxane (30 mL) was treated with dimethyl formamide dimethylacetal (0.01 mol) and refluxed for 30 min. Then, to the refluxed solution, acetic acid (0.01 mol) and ammonium acetate were added and the solution was further refluxed for 2 hours. When cooled, the solution was poured onto water and the solid product, so formed, was filtered and crystallized from ethanol. Compound **20b** was obtained as brown crystals (85%); m.p. 235°C; IR: 3460-3260 (NH_2); 1699 (amide CO); 1662 cm^{-1} (ring CO); ^1H NMR: δ 2.35 (s, 3H, CH_3); 7.30 (s, 1H, ring H-7), 7.60 (s, 7H, Ar-H and NH_2), and 11.50 (brs, 1H, NH); Anal. Calcd. for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.80; H, 4.08; N, 18.91. Found: C, 60.83; H, 4.26; N, 18.79.

General procedure for the preparation of methyl-5-amino-3,7-diaryl-6,6-dicyano-8-methyl-4-oxo-3,4,6,7-tetrahydrophthalazine-1-carboxylate (25a-c). A solution of **3a, c** (0.01 mol) in pyridine (20 mL) was treated with **23a, b** (0.01 mol). The reaction mixture was refluxed for five hours then poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol.

Methyl 5-amino-6,6-dicyano-8-methyl-4-oxo-3,7-diphenyl-3,4,6,7-tetrahydrophthalazine-1-carboxylate (25a). Compound **25a** was obtained as brown powder from ethanol (63%); m.p. 243°C; IR: 3420-3300 (NH_2), 2225 (CN), 1745 (ester CO) and 1660 cm^{-1} (ring CO); ^1H NMR: δ 1.90 (s, 3H, CH_3), 2.50 (m, 1H, phthalazine H-7), 3.90 (s, 3H, OCH_3), 7.20-7.70 (m, 10H, Ar-H) and 8.00 ppm (brm, 2H, NH_2); Anal. calcd. for $C_{25}H_{19}O_3N_5$ (437.45): C, 68.64; H, 4.37; N, 16.01. Found: C, 68.98; H, 4.40; N, 15.91.

Methyl 5-amino-7-(*p*-chlorophenyl)-6,6-dicyano-8-methyl-4-oxo-3-pheny-3,4,6,7-tetrahydrophthalazine-1-carboxylate (25b). Compound **25b** was obtained as gray crystals from methanol (57%); m.p. 185°C; IR: 3500-3450 (NH_2), 2200 (CN) and 1660-1640 cm^{-1} (ester and ring CO); ^1H NMR: δ 1.60 (s, 3H, CH_3), 2.50 (m, 1H, phthalazine H-7), 3.80 (s, 3H, OCH_3) and 7.20-7.80ppm (m, 11H, Ar-H and NH_2); Anal . calcd . for $C_{25}H_{18}ClN_5O_3$ (471.89) : C, 63.63; H, 3.84; N, 14.84 . Found: C, 63.91; H, 5.08; N, 14.93.

Methyl 5-amino-7-(*p*-chlorophenyl)-6,6-dicyano-8-methyl-3-(*p*-methoxyphenyl)-4-oxo-3,4,6,7-tetrahydrophthalazine-1-carboxylate (25c). Compound **25c** was obtained as dark green crystals from ethanol (69%); m.p. 192°C; IR: 3500-3400 (NH_2), 2220 (CN) and 1750 cm^{-1} (ester CO); ^1H NMR: δ 2.10 (s, 3H, CH_3), 2.50 (m, 1H, phthalazine H-7), 3.80 (s, 3H, OCH_3), 6.90-7.90 ppm (m, 8H, Ar-H) and 8.30 ppm (brm, 2H, NH_2); Anal. calcd. for $C_{26}H_{20}ClN_5O_4$ (501.92): C, 62.21; H, 4.01; N, 13.95. Found: C, 61.74; H, 4.17; N, 14.07.

General procedure for the preparation of methyl 1-aryl-1,4-dihydro-5-methyl-4-oxopyridazine-3-carboxylate (26a-c) and 1,4-dihydro-5-methyl-4-oxo-1-phenyl-pyridazine-3-carbonitrile (26d). A solution of **2a-d** (0.01 mol) in dioxane (30 mL) was treated with dimethylformamide dimethylacetal (0.01 mol). The reaction mixture was refluxed for 10 h then the solvent was evaporated. The solid product so formed was washed and crystallized from ethanol.

Methyl 1,4-dihydro-5-methyl-4-oxo-1-phenylpyridazine-3-carboxylate (26a). Compound **26a** was obtained as yellow crystals (86%); m.p. 161°C; IR: 1735 cm^{-1} (ester CO); ^1H NMR: δ 2.1 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.30-7.60 (m, 5H, Ar-H) and 8.30ppm (s, 1H, pyridazine H-6); Anal. calcd. for $C_{13}H_{12}N_2O_3$ (244.24): C, 63.85; H, 4.95; N, 11.47. Found: C, 63.56; H ,5.20; N,11.36.

Methyl 1,4-dihydro-5-methyl-1-(*p*-methylphenyl)-4-oxopyridazine-3-carboxylate (26b). Compound **26b** was obtained as yellow crystals (90%); m.p. 138-140°C; IR: 1730 cm^{-1} (ester CO); ^1H NMR: δ 2.0 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.20-7.70 (2d, 4H, Ar-H) and 8.8 ppm (s, 1H, pyridazine H-6); Anal. calcd. for $C_{14}H_{14}N_2O_3$ (258.27): C, 65.10; H, 5.46; N, 10.86. Found: C, 65.02; H, 5.46; N,10.84.

Methyl 1,4-dihydro-1-(*p*-methoxyphenyl)-5-methyl-4-oxopyridazine-3-carboxylate (26c). Compound **26c** was obtained as orange crystals (85%); m.p. 142-144°C; IR: 1730 cm^{-1} (ester CO); ^1H NMR: δ 2.05 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.00-7.50 (2d, 4H, Ar-H) and 8.8 ppm (s, 1H, pyridazine H-6); ^{13}C NMR: δ 167.40 (C-4), 164.02 (ester CO), 159.43 (C-3), 146.28 (C-6), 139.28, 136.61, 130.96, 114.99 (phenyl carbons), 123.06 (C-5), 55.95 (OCH_3), 52.81 (OCH_3), 39.28 (CH_3); Anal. calcd. for $C_{14}H_{14}N_2O$ (274.26): C,61.31; H,5.14; N,10.21. Found: C, 61.11; H, 5.13; N, 10.26.

1,4-Dihydro-5-methyl-4-oxo-1-phenylpyridazine-3-carbonitrile (26d). Compound **26d** was obtained as violet crystals (65%); m.p. 201°C; IR: 2225 cm^{-1} (CN); ^1H NMR: δ 2.10 (s, 3H, CH_3), 7.40-7.70 (m, 5H, Ar-H) and 9.00 ppm (s, 1H, pyridazine H-6); Anal. calcd. for $C_{12}H_9N_3O$ (211.22): C, 68.23; H, 4.31; N, 19.72. Found: C, 68.06; H,4.31, N,19.72.

X ray Analysis.- A summary of data collection and refinement process is given in Table 3. All non-hydrogen atoms were found by direct methods (SIR92)[19b] and the structure was refined with a full matrix least-squares procedures on Fobs using anisotropic displacement parameters. All hydrogens were located on a difference Fourier synthesis and included and refined isotropically in the last cycles. The scattering factors were taken from the International Tables for X-Ray Crystallography.[20] Table 4 lists the final atomic coordinates and equivalent thermal factors for non-hydrogen atoms. The calculations were carried out with the XTAL,[21] PESOS[22] and PARST[23] set of programs running on a VAX 6410 computer.

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Table 3. Crystal analysis parameters at room temperature.

Crystal data

Chemical formula	$C_{17}H_{12}N_4O_2S$	Crystal system	Triclinic
Mr	336.367	Space group	*P-1*
a (Å)	12.5258(13)	α (°)	98.761(4)
b (Å)	9.7370(8)	β (°)	83.463(4)
c (Å)	6.6076(3)	γ (°)	105.775(7)
Z	2	*Dx* (gr/cm³)	1.46
V (Å³)	764.26(8)	Radiation	CuKα
Wavelength (Å)	1.5418	No. of reflections for	
θ range for lattice parameters (°)	3-45	lattice parameters:	62
Absorption coefficient (cm^{-1})	20.4	Temperature (K)	295
Crystal colour	Deep red	Crystal description	Prism
Crystal size (mm)	0.50 x 0.17 x 0.23		

Data collection

Diffractometer type	Philips PW1100, four circle. Graphite oriented monochromator.		
Measurement time	1 min./reflection	Detector apertures (°)	1 x 1
Collection method	ω/2θ scans	θ_{max} (°)	65
No. of standard reflections (interval)	2 (90 min.). No decay	Scan width (°)	1.5
No. of independent reflections	2612	No. of observed reflections, I>2σ(I)	2452

Refinement

Treatment of hydrogen atoms	See experimental part	Refinement: Least-Squares on *Fo*. Full matrix	
Secondary extinction correction (10^4)	0.23(2)		
R	0.038	No. of parameters refined	266
wR	0.044	Degrees of freedom	2186
$(\Delta\rho)_{max}$ (e/Å³)	0.32	Ratio of freedom	9.2
<Shift/error>	0.001	Max. thermal value (Å²)	U33[C22]=0.122(2)

Weighting scheme: Empirical as to give no trends in $<\omega\Delta^2F>$ vs. <|Fobs|> and $<\sin\theta/\lambda>$.

Table 4. Final atomic coordinates and $Ueq=(1/3)\Sigma[Uij\cdot a_i^*\cdot a_j^*\cdot a_i\cdot a_j\cdot\cos(a_i,a_j)]\times10^3$

Atom	x	y	z	Ueq	Atom	x	y	z	Ueq
S1	0.21947(4)	-0.04618(5)	0.65086(7)	49.6(2)	C10	0.1755(1)	0.1618(2)	0.1737(3)	42.7(6)
N1	0.5481(1)	0.2933(2)	0.3932(2)	39.9(5)	C11	0.2836(1)	0.2342(2)	0.1251(3)	39.7(5)
N2	0.5162(1)	0.2031(2)	0.5372(2)	40.7(5)	N11	0.3161(1)	0.3131(2)	-0.0329(2)	46.7(5)
C3	0.4140(1)	0.1236(2)	0.5331(2)	39.4(5)	C12	0.2375(2)	-0.1175(2)	0.2333(3)	48.9(6)
C4	0.3404(1)	0.1244(2)	0.3889(2)	37.6(5)	C13	0.0927(2)	0.1792(2)	0.0578(3)	49.0(6)
C5	0.3678(1)	0.2240(2)	0.2563(3)	39.1(5)	N13	0.0291(2)	0.2002(2)	-0.0371(4)	71.5(8)
C6	0.4788(1)	0.3205(2)	0.2586(3)	44.8(6)	C14	0.6636(1)	0.3728(2)	0.3896(3)	41.7(5)
O6	0.5140(1)	0.4197(2)	0.1558(3)	71.2(6)	C15	0.7090(2)	0.4359(2)	0.5722(4)	53.4(7)
C7	0.3629(2)	0.0290(2)	0.6945(3)	45.5(6)	C16	0.8214(2)	0.5082(3)	0.5656(5)	70.7(9)
O7	0.4075(1)	0.0078(2)	0.8340(2)	59.4(5)	C17	0.8847(2)	0.5177(3)	0.3814(5)	76.5(10)
C8	0.2316(1)	0.0117(2)	0.3942(2)	41.0(5)	C18	0.8380(2)	0.4517(3)	0.2008(5)	74.1(10)
C9	0.1403(1)	0.0803(2)	0.3592(3)	45.3(6)	C19	0.7267(2)	0.3774(2)	0.2032(3)	54.6(7)

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