Studies with Condensed Aminothiophenes: Further Investigation on the Reactivity of Condensed Aminothiophenes Toward Electron Poor and Acetylenes under Microwave Heating

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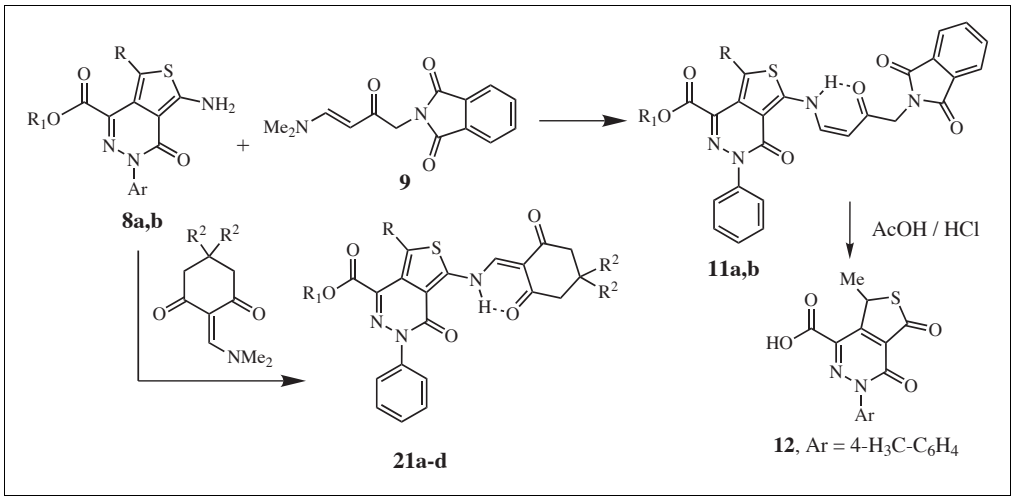

The reaction of aminothienopyridazines **8a,b**, aminothienocoumarin **13** and aminothienonaphthopyran **14** with enaminones **9**, **17** and **20a,b** under microwave irradiation affords either a mixture of both condensations C-1 alkylation products **15** and **16** or amino moiety alkylation and diethylamine elimination or only one of these products depending on nature of substituents on the thiophene ring. On the other hand reaction of these condensed aminothiophenes with 3-dimethylaminoacrylaldehyde afforded **24** and **25**.

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Introduction.

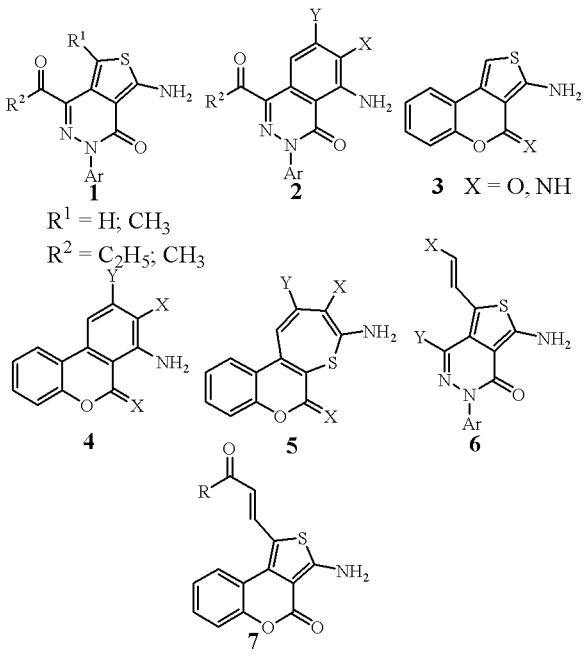
The exact pattern of reactivity of condensed aminothiophenes toward electron poor olefins and acetylenes is not completely defined. Initially Elnagdi *et. al.,* [1,2] reported that despite the fact that thiophenes are highly inactive as electron rich dienes, condensed aminothienopyridazines **1** are highly reactive and do add electron poor olefins to yield products of 4+2 cycloaddition that readily lose hydrogen sulphide to yield phthalazienes **2** in a novel rout to this ring system. Subsequently Döpp *et.al.*, [3] reported that the thienocoumarin **3** has also added electron poor olefins in a similar fashion yielding dibenzopyranones **4**. The reaction with dimethylacetylenedicarboxylate with that thienocoumarin afforded thiepines **5** [5], *via* a rearrangement of the initially formed cycloadducts. Al-Omran *et.al.*, [5,6] have also claimed thiepine formation in reactions of several condensed aminothiophenes with electron poor acetylenes. On the other hand Elnagdi *et.al.,* [7] have noted that enaminones, ω-nitrostyrene and phenyl vinyl ketone reacts with **1** and **2** to yield products of C-1 alkylation **6**, **7** [7] that are believed to be formed *via* a dipolar cycloaddition mechanism. In light of this finding Elnagdi *et.al.*,[8] has reinvestigated the behaviour of **2** towards acetylenes and could show that the products initially claimed to be thiepins are really C-1 alkylation products (Scheme I).

Results and Discussion.

In conjugation of this work we report here results of our further work in this area. It has been found that **8a,b** [9] reacts with the enaminone **9** recently prepared by Al-Mousawi *et.al.*, [10] to yield products of condensation *via* dimethylamine elimination for which structures **10** or **11a,b** seemed possible. Structure **11a,b** was established for this product based on the ^{1}H NMR and IR spectral data that revealed involvement of aminofunction in the reaction. Further confirmation of this structure assignment was obtained *via* successful conversion of **11b** into the thiophene **12** through hydrolysis of the alkylated amino moiety (Scheme II).

Typical for primary enaminone compound **11** existed solely in *Z* form as this form is fixed by hydrogen bond and this preferred over sterically and stereoelectronically fixed *E* form. The *Z* structure was readily concluded based on considering *J* values for olefinic protons. Assignment of ^{1}H and ^{13}C NMR signal was made based on HMQC - 2D spectroscopy.

Scheme I



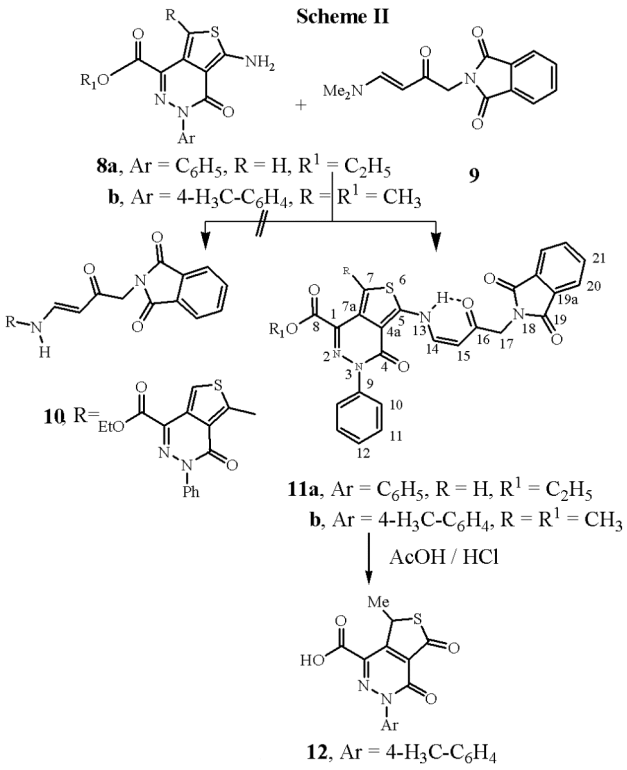
Moreover these were also found very similar to assignment of a simulated spectroscopy using ACD LABS. It is of value to report here that enaminone **9** could be prepared in our laboratory *via* reacting of dimethylformamide dimethylacetal (DMFDMA) with phthalimidoacetone in a microwave oven at 840W for 60 seconds. Yield of this synthesis is 74 % much higher than that obtained by literature procedure [10].

The reaction of the thienocoumarin **13** and the benzothienocoumarin **14** with enaminone **9** has afforded only C-1 alkylation products **15** and **16** respectively (Scheme III), as indicated from ^{1}H NMR that revealed amino signal at δ 8.68 ppm and *trans* olefinic protons at ~ δ 6.3 and 8.3 (J = 15 Hz). This find parallel to reported C-1 alkylation of thienocoumarins and thienonaphtho-benzopyran on reaction with enaminones [7]. Further confirmation of structure was obtained *via* HMQC - 2D spectroscopy that enabled assignment of ^{13}C NMR spectra.

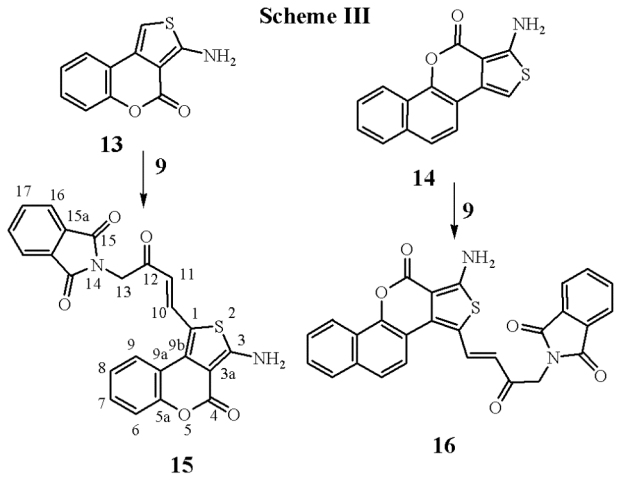
The reaction of enaminone **17** [11], prepared here *via* microwave heating of a mixture of benzylideneacetone with DMFDMA, with **8a,b** and **14** has afforded **18a,b** and **19** (Scheme IV). The *cis-trans* diene structures **18a,b** and **19** were assigned based on ^{1}H NMR that revealed *cis* olefinic proton doublet of doublet as well as a *trans* olefinic doublet. Assignment of ^{13}C NMR was made after inspection of HMQC – 2D spectra of the reaction product.

Compounds **8a,b**, **13** and **14** reacted with the enaminones **20a,b** [12] to yield the N-alkylated products **21a-d, 22a,b** and **23a,b** as indicated from ^{1}H NMR that showed low field NH signal at δ *ca.*13 ppm (Scheme V).

Scheme II



Scheme III

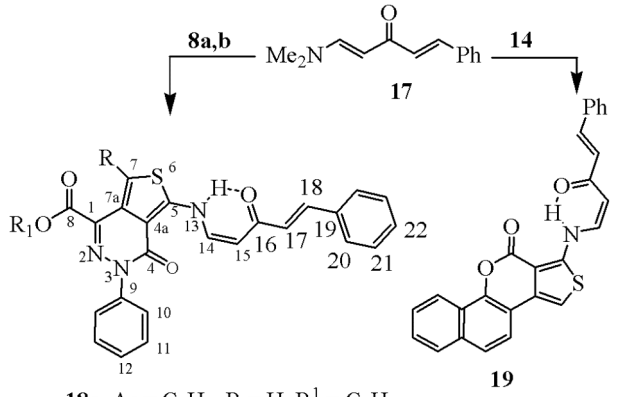


In contrast to this compound **13** reacted with 3-dimethylaminoacrylaldehyde to afford products of cyclo-addition and dimethylamine elimination. This was assigned structure **24** and was also formed from reaction of **13** with acrolein. Similarly, compound **14** reacted with 3-dimethylaminoacrylaldehyde or acrolein to yield **25**. Possible formation of C-1 alkylation products could be readily eliminated based on ^{1}H NMR that revealed absence of the two olefinic proton doublet (Scheme VI).

It can thus be concluded that outcome of reaction of aminothienocoumarins with electron poor olefins and acetylenes is dependent on nature of reagents used.

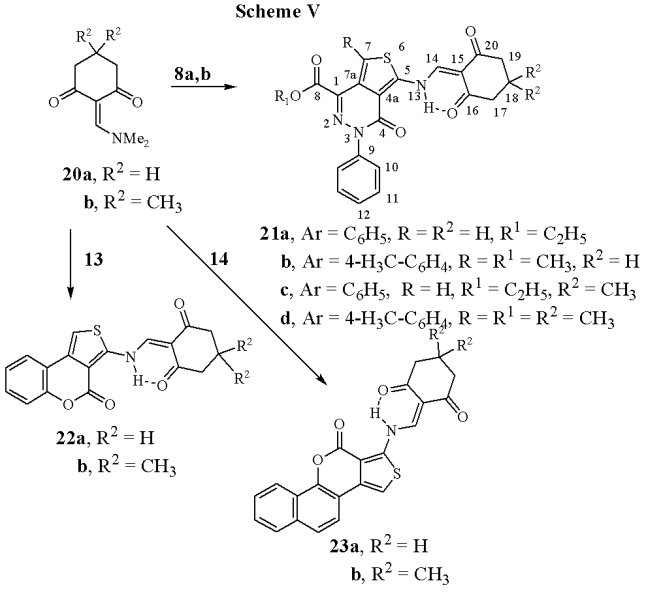
Aminofunction, C-1 as well as the diene system are all possible sites of attack. However, in no case thiepins has resulted from such additions as has been claimed earlier [13].

Scheme IV



18a, Ar = C_6H_5, R = H, R^1 = C_2H_5
b, Ar = 4-H_3C-C_6H_4, R = R^1= CH_3

Scheme V



20a, R^2 = H
b, R^2 = CH_3

21a, Ar = C_6H_5, R = R^2 = H, R^1 = C_2H_5
b, Ar = 4-H_3C-C_6H_4, R = R^1 = CH_3, R^2 = H
c, Ar = C_6H_5, R = H, R^1 = C_2H_5, R^2 = CH_3
d, Ar = 4-H_3C-C_6H_4, R = R^1 = R^2 = CH_3

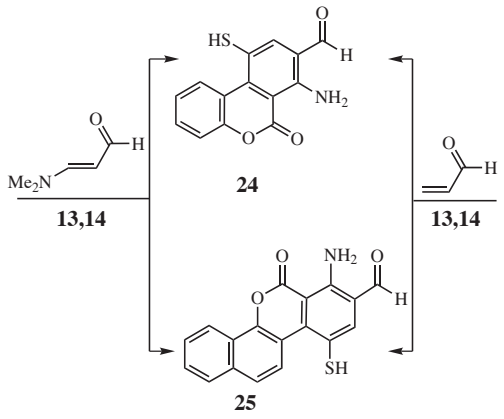
22a, R^2 = H
b, R^2 = CH_3

23a, R^2 = H
b, R^2 = CH_3

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DPX 400, 400MHz super-conducting NMR spectrometer in deuteriochloroform or dimethylsulfoxide-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS). Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. Microwave experiments were conducted in a microwave oven DAEWOO, edition II (KOR-8667). Compounds **13** and **14** were prepared following published procedure [5].

Scheme VI



General Procedure for the Preparation of Compounds **11a,b**, (**15**) and (**16**).

A mixture of each of **8a,b**, **13** and **14** (10 mmole) and compound **9** (2.58 g, 10 mmoles) in the presence of few drops of acetic acid was irradiated in a microwave oven at 690W for 120 sec. The solid products obtained were crystallized from ethanol/dioxane (1:3).

Ethyl 5-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-oxobut-1-enyl-amino]-4-oxo-3-phenyl-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (**11a**).

Compound **11a** was obtained as buff crystals 1.76 g (33%), mp. 269-271°, ir (KBr): 3420 (NH), 1778, 1720, 1661 (CO) cm^{-1}; ms: m/z = 528 (M^+, 100), 486 (78), 326 (38), 277 (15), 160 (41), 104 (39), 77 (41); ^{1}H nmr (deuteriochloroform): δ 1.41 (t, 3H, J = 8 Hz, CH_3), 4.43 (q, 2H, J = 8 Hz, CH_2), 4.58 (s, 2H, CH_2), 5.58 (d, 1H, J = 8 Hz, olefinic-H), 7.02 (d,d, 1H, J = 8 Hz, olefinic-H), 7.28 (t, 1H, J = 7.2 Hz, phenyl-H), 7.39 (t, 2H, J = 7.6 Hz, phenyl-H), 7.55 (d, 2H, J = 8 Hz, phenyl-H), 7.70 (s, 1H, thiophene-H), 7.72-7.75 (m, 2H, arom-H), 7.85-7.87 (m, 2H, arom-H), 12.88 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuterio-chloroform): δ 192.2, 168.3, 163.4, 158.4 (CO), 153.6 (C-5), 142.1 (C-1), 140.8 (C-9), 134.7 (C-14), 133.4 (C-21), 132.8 (C-19a), 129.4 (C-7), 128.8 (C-7a), 128.4 (C-11), 126.7 (C-12), 126.2 (C-10), 124.1 (C-20), 110.5 (C-4a), 98.3 (C-15), 62.7 (ester CH_2), 46.4 (C-17), 14.8 (ester CH_3).

Anal. Calcd. For $C_{27}H_{20}N_4O_6S$ (528.54): C, 61.36; H, 3.81; N, 10.60; S, 6.07. Found C, 61.25; H, 3.92; N, 10.81; S, 5.88.

Methyl 5-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-oxobut-1-enylamino]-7-methyl-4-oxo-3-p-tolyl-3,4-dihydrothieno[3,4-d]-pyridazine-1-carboxylate (**11b**).

Compound **11b** was obtained as buff crystals 2.67 g (49%), mp. 248-250°, ir (KBr): 3460 (NH), 1767, 1716, 1656 (CO) cm^{-1}; ms: m/z = 542 (M^+, 100), 500 (40), 371 (25), 340 (28), 291 (14), 160 (28), 104 (22), 91 (18), 77 (10); ^{1}H nmr (deuteriochloroform): δ 2.36 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2), 5.52 (d, 1H, J = 8 Hz, olefinic-H), 6.93 (d,d, 1H, J = 8 Hz, olefinic-H), 7.17 (d, 2H, J = 8.3 Hz, p-tolyl-H), 7.37 (d, 2H, J = 8.3 Hz, p-tolyl-H), 7.72-7.74

(m, 2H, arom-H), 7.85-7.87 (m, 2H, arom-H), 12.88 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): 200.5, 197.2, 164.5, 158.0 (CO), 148.0, 146.5, 138.5, 137.9, 135.9, 130.5, 130.2, 129.9, 126.3, 126.2, 125.5, 124.1, 116.4, 111.0, 53.8 (OCH_3), 51.2 (CH_2), 29.9, 15.8 ($2CH_3$).

Anal. Calcd. For $C_{28}H_{22}N_4O_6S$ (542.56): C, 61.98; H, 4.09; N, 10.33; S, 5.91. Found C, 61.81; H, 4.30; N, 10.31; S, 5.79.

2-[4-(3-Amino-4-oxo-4*H*-5-oxa-2-thiacyclopenta[*a*]naphthalen-1-yl)-2-oxo-3-butenyl] isoindole-1,3-dione (**15**).

Compound **15** was obtained as orange crystals (2.79 g, 65%), mp.> 300°, ir (KBr): 3438 and 3328 (NH_2), 1770, 1713, 1637 (CO) cm^{-1}; ms: m/z = 430 (M^+,22), 270 (100), 241 (18), 160 (10), 115 (12), 77 (15); ^{1}H nmr (dimethylsulfoxide-d_6): δ 4.88 (s, 2H, CH_2), 6.39 (d, 1H, J = 15 Hz, *trans* olefinic-H), 7.33-7.38 (m, 2H, coumarinyl-H), 7.51 (t, 1H, J = 7.6 coumarinyl-H), 7.89-7.96 (m, 4H, arom-H), 8.10 (d, 1H, J = 8.0 Hz, coumarinyl-H), 8.33 (d, 1H, J = 15 Hz, *trans* olefinic-H), 8.68 (br s, 2H, NH_2, D_2O exchangeable), ^{13}C nmr (dimethylsulfoxide-d_6): δ 191.6, 168.6, 159.2 (CO), 167.6 (C-3), 153.0 (C-5a), 136.3 (C-1), 136.1 (C-10), 135.8 (C-17), 132.5 (C-9b), 131.9 (C-15a), 127.3 (C-9), 126.0 (C-8), 124.3 (C-16), 119.4 (C-7), 118.7 (C-6), 118.6 (C-9a), 113.0 (C-11), 101.9 (C-3a), 46.6 (CH_2).

Anal. Calcd. For $C_{23}H_{14}N_2O_5S$ (430.43): C, 64.18; H, 3.28; N, 6.51; S, 7.45. Found C, 63.94; H, 3.41; N, 6.85; S, 7.22.

2-[4-(17-Amino-12-oxo-12H-11-oxa-16-thiacyclopenta[*a*]phenanthren-15-yl)-2-oxo-3-butenyl]isoindole-1,3-dione (**16**).

Compound **16** was obtained as orange crystals (2.78 g, 58%), mp. > 300°, ir (KBr): 3427 and 3320 (NH_2), 1772, 1716, 1637 (CO) cm^{-1}; ms: m/z = 480 (M^+, 25), 417 (26), 320 (100), 292 (18), 267 (21), 160 (20), 83 (22); ^{1}H nmr (dimethylsulfoxide-d_6): δ 4.89 (s, 2H, CH_2), 6.40 (d, 1H, J = 15 Hz, *trans* olefinic-H), 7.68-7.70 (m, 2H, arom-H), 7.84–7.99 (m, 6H, arom-H), 8.10 (d, 1H, J = 8.8 Hz, arom-H), 8.31 (d, 1H, J = 9 Hz, arom-H), 8.39 (d, 1H, J = 15 Hz, *trans* olefinic-H), 7.75 (br s, 2H, NH_2, D_2O exchangeable),. ^{13}C nmr (dimethylsulfoxide-d_6): δ = 191.5, 168.6, 158.9 (CO), 148.9, 140.0, 136.3, 135.8, 134.6, 132.6, 129.4, 128.8, 128.5, 125.6, 124.3, 124.1, 123.2, 123.0, 119.0, 114.1, 112.8, 111.6, 46.7 (CH_2).

Anal. Calcd. For $C_{27}H_{16}N_2O_5S$ (480.49): C, 67.49; H, 3.36; N, 5.83; S, 6.67. Found C, 67.16; H, 3.63; N, 5.98; S, 6.37.

7-Methyl-4,5-dioxo-3-*p*-tolyl-3,4,5,7-tetrahydrothieno[3,4-*d*]-pyridazine-1-carboxylic acid (**12**).

A solution of compound **11b** (5.42g, 10 mmol) in acetic acid / hydrochloric acid (10 mL, 3:1 by volume) was refluxed for 3 hrs, then allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol. Compound **12** was obtained as yellow crystals 2.82 g (89%), mp. 232°, ir (KBr): 3445 (OH), 1749, 1701, 1642 (CO) cm^{-1}; ms: m/z = 316 (M^+, 100), 372 (30), 243 (10), 165 (10), 107 (88), 91 (31), 77 (15); ^{1}H nmr (dimethylsulfoxide-d_6): δ = 1.72 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.45 (br, 1H, OH, D_2O exchangeable), 5.46 (q, 1H, J = 6.8 Hz, thiophenone-H), 7.34 (d, 2H, J = 8.3 Hz, p-tolyl-H), 7.43 (d, 2H, J = 8.3 Hz, p-tolyl-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 192.3, 164.4, 161.5 (CO), 155.8, 139.7, 139.1, 134.6, 130.3, 129.9, 126.8, 44.7 (thiophenone-C), 22.4, 21.7 ($2CH_3$).

Anal. Calcd. For $C_{15}H_{12}N_2O_4S$ (316.33): C, 56.95; H, 3.82; N, 8.86; S, 10.14. Found C, 56.68; H, 3.99; N, 8.93; S, 10.07.

General Procedure for the Preparation of Compounds **18a,b** and **19**.

A mixture of each of **8a,b** and **14** (10 mmol) and compound **17** (2.01 g, 10 mmol) in acetic acid / dioxane (6 ml, 2:1 by volume) was irradiated in a microwave oven at 560W for 90 sec. The solid products so formed were crystallized from dioxane / ethanol.

Ethyl **4**-oxo-5-(3-oxo-5-phenylpenta-1,4-dienylamino)-3-phenyl-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (**18a**).

Compound **18a** was obtained as buff crystals 2.80 g (59%), mp. 222-224°, ir (KBr): 3450 (NH), 1719, 1663 (CO) cm^{-1}; ms: m/z = 471 (M^+,22), 397 (100), 315 (32), 172 (22), 131 (50), 103 (40), 77 (30); ^{1}H nmr (deuteriochloroform): δ 1.43 (t, 3H, J = 7.2 Hz, CH_3), 4.45 (q, 2H, J = 7.2 Hz, CH_2), 5.74 (d, 1H, J = 8 Hz, *cis* olefinic-H), 6.80 (d, 1H, J = 16 Hz, *trans* olefinic-H), 7.11 (d,d, 1H, J = 8 Hz, *cis* olefinic-H), 7.38-7.40 (m, 5H, arom-H), 7.45-7.57 (m, 3H, arom-H), 7.68 (d, 2H, J = 8 Hz, arom-H), 7.70 (s, 1H, thiophene-H), 7.73 (d, 1H, J = 16 Hz, *trans* olefinic-H), 13.73 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ = 190.0, 164.5, 158.5, (CO), 154.0 (C-5), 142.5 (C-18), 141.8 (C-1), 136.6 (C-9), 133.4 (C-14), 130.8 (C-19), 129.5 (C-7), 129.3 (C-22), 128.9 (C-20), 128.7 (C-21), 128.6 (C-7a), 128.3 (C-11), 127.1 (C-12), 126.7 (C-17), 126.5 (C-10), 110.0 (C-15), 102.9 (C-4a), 62.6 (ester CH_2), 14.8 (ester CH_3).

Anal. Calcd. For $C_{26}H_{21}N_3O_4S$ (471.53): C, 66.23; H, 4.49; N, 8.91; S, 6.80. Found C, 66.25; H, 4.57; N, 9.07; S, 6.61.

Methyl 7-methyl-4-oxo-5-(3-oxo-5-phenylpenta-1,4-dienylamino)-3-*p*-tolyl-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (**18b**).

Compound **18b** was obtained as buff crystals 2.58 g (53%), mp.214-216 ir (KBr): 3440 (NH), 1736, 1656 (CO) cm^{-1}; ms: m/z = 485 (M^+,42), 426 (78), 329 (100), 270 (42), 131 (80), 91 (72); ^{1}H nmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 5.68 (d, 1H, J = 8 Hz, *cis* olefinic-H), 6.77 (d, 1H, J = 16 Hz, *trans* olefinic-H), 7.01 (d,d, 1H, J = 8 Hz, *cis* olefinic-H), 7.23 (d, 2H, J = 8.2 Hz, p-tolyl-H), 7.37-7.39 (m, 3H, arom-H), 7.48 (d, 2H, J = 8.2 Hz, p-tolyl-H), 7.55-7.62 (m, 2H, arom-H), 7.70 (d, 1H, J = 16 Hz, *trans* olefinic-H), 13.69 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 189.7, 164.8, 158.4 (CO), 150.1 (C-5), 142.6 (C-18), 142.2 (C-7), 138.3 (C-1), 135.7 (C-9), 132.8 (C-12), 130.5 (C-14), 129.8 (C-19), 129.5 (C-11), 128.9 (C-22), 128.7 (C-20), 127.2 (C-21), 126.5 (C-17), 126.1 (C-10), 123.8 (C-7a), 112.3 (C-15), 102.5 (C-4a), 53.6 (ester CH_3), 21.7 (p-tolyl CH_3), 15.3 (thieno CH_3).

Anal. Calcd. For $C_{27}H_{23}N_3O_4S$ (485.55): C, 66.79; H, 4.77; N, 8.65; S, 6.60. Found C, 66.47; H, 4.80; N, 8.84; S, 6.42.

17-(3-Oxo-5-phenylpenta-1,4-dienylamino)-11-oxa-16-thiacyclopenta[*a*]phenanthren-12-one (**19**).

Compound **19** was obtained as buff crystals 3.36 g (79%), mp. 290-292°,. ir (KBr): 3298 (NH), 1715, 1655 (CO) cm^{-1}; ms: m/z = 423 (M^+,84), 345 (58), 267 (64), 170 (38), 130 (76), 77 (42); ^{1}H nmr (deuteriochloroform): δ 5.81 (d, 1H, J = 8 Hz, *cis* olefinic-H), 6.85 (d, 1H, J = 16 Hz, *trans* olefinic-H), 6.96 (s, 1H, thiophene-H), 7.12 (d,d, 1H, J = 8 Hz, *cis* olefinic-H), 7.41-7.43 (m, 3H, arom-H), 7.54-7.65 (m, 4H, arom-H), 7.70-7.82 (m, 3H, arom -H), 7.82 (d, 1H, J = 16 Hz, *trans* olefinic-H), 8.56

(d, 1H, J = 8.1 Hz, arom-H), 13.59 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 190.2, 157.4 (CO), 142.7, 141.7, 135.6, 134.7, 134.5, 130.7, 130.3, 129.5, 129.4, 128.9, 128.7, 128.2, 127.9, 127.6, 127.2, 125.0, 124.5, 123.1, 120.5, 112.7, 10.3.2, 102.0.

Anal. Calcd. For $C_{26}H_{17}NO_3S$ (423.48): C, 73.74; H, 4.05; N, 3.31; S, 7.57. Found C, 73.35; H, 4.17; N, 3.56; S, 7.36.

General Procedure for the Preparation of Compounds **21- 23**.

A mixture of each of **8a,b**, **13** and **14** (10 mmoles) and compound **20a,b** (10 mmoles) in acetic acid / dimethylformamide (4 ml, 3:1 by volume) was irradiated in a microwave oven at 840W for 60 sec then left to cool to room temperature. The solid products obtained were crystallized from dimethylformamide.

Ethyl 5-[(2,6-dioxocyclohexylidenemethyl)amino]-4-oxo-3-phenyl-3,4-dihydrothieno[3,4-*d*]pyridazine -1-carboxylate (**21a**).

Compound **21a** was obtained as buff crystals 2.01 g (46%), mp. 252-254 ir (KBr): 3405 (NH), 1715, 1668 (CO) cm^{-1}; ms: m/z = 437 (M$^+$,78), 364 (35), 315 (100), 226 (38), 91 (62), 77 (58); ^{1}H nmr (deuteriochloroform): δ 1.36 (t, 3H, J = 7.2 Hz, CH_3), 2.01-2.08 (m, 2H, CH_2), 2.60 (t, 4H, J = 6.3 Hz, $2CH_2$), 4.50 (q, 2H, J = 7.1 Hz, CH_2), 7.37 (t, 1H, J = 7.4 phenyl-H), 7.47 (t, 2H, J = 7.9 phenyl-H), 7.64 (d, 2H, J = 8.2 phenyl-H), 8.02 (s, 1H, thiophene-H), 8.31 (d, 1H, J = 13.2 Hz, ethylenic-H), 14.39 (d, 1H, J = 13.2 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 201.0, 197.5, 163.2, 158.0 (CO), 150.6 (C-5), 148.7 (C-14), 140.6 (C-1), 133.4 (C-9), 129.3 (C-7), 128.8 (C-11), 128.6 (C-12), 126.6 (C-7a), 115.5 (C-10), 115.2 (C-4a), 112.5 (C-15), 62.9 (ester CH_2), 38.6 (C-19), 38.4 (C-17), 19.7 (C-18), 14.8 (ester CH_3).

Anal. Calcd. For $C_{22}H_{19}N_3O_5S$ (437.47): C, 60.40; H, 4.38; N, 9.61; S, 7.33. Found C, 60.42; H, 4.56; N, 9.72; S, 7.08.

Ethyl 5-[(4,4-dimethyl-2,6-dioxocyclohexylidenemethyl)amino]-4-oxo-3-phenyl-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (**21b**).

Compound **21b** was obtained as buff crystals 2.96 g (63%), mp. 260-262º, ir (KBr): 3390 (NH), 1713, 1669 (CO) cm^{-1}; ms: m/z = 465 (M$^+$,60), 392 (56), 315 (100), 299 (42), 226 (58), 91 (78), 77 (60); ^{1}H nmr (deuteriochloroform): δ 1.09 (s, 6H, $2CH_3$), 1.47 (t, 3H, J = 7.2 Hz, CH_3), 2.52 (s, 2H, CH_2), 2.91 (s, 2H, CH_2), 4.46 (q, 2H, J = 7.2 Hz, CH_2), 7.37-(t, 1H, J = 7.4 phenyl-H), 7.46 (t, 2H, J = 7.8 phenyl-H), 7.61 (d, 2H, J = 8.2 phenyl-H), 8.00 (s, 1H, thiophene-H), 8.29 (d, 1H, J = 13.2 Hz, ethylenic-H), 14.38 (d, 1H, J = 13.2 Hz, NH), ^{13}C nmr (deuteriochloroform): δ = 200.6, 197.1, 163.2, 158.1 (CO), 150.7, 148.0, 140.6, 133.5, 129.6, 129.3, 128.6, 126.2, 115.4, 115.1, 111.2, 62.9 (ester CH_2), 52.2 (cyclohexane carbon), 32.5, 32.0 (cyclohexane $2CH_2$), 29.2 (CH_3), 14.7 (ester CH_3).

Anal. Calcd. For $C_{24}H_{23}N_3O_5S$ (465.52): C, 61.92; H, 4.98; N, 9.03; S, 6.89. Found C, 61.71; H, 5.22; N, 8.79; S, 6.62.

Methyl 5-[(2,6-dioxocyclohexylidenemethyl)amino]-7-methyl-4-oxo-3-*p*-tolyl-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (**21c**).

Compound **21c** was obtained as yellow crystals 2.40 g (53%), mp. 254º, ir (KBr): 3430 (NH), 1729, 1663 (CO) cm^{-1}; ms: m/z = 451 (M$^+$,95), 392 (25), 329 (78), 270 (38), 254 (42), 105 (65), 91 (42), 60 (22); ^{1}H nmr (deuteriochloroform): δ 2.02-2.07 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.56 (t, 4H, J = 6.4 Hz, $2CH_2$), 2.63 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.24 (d, 2H, J = 8.3 Hz, p-tolyl-H), 7.47 (d, 2H, J = 8.3 Hz, p-tolyl-H), 8.22 (d, 1H, J = 13.2 Hz, ethylenic-H), 14.39 (d, 1H, J = 13.2 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 200.7, 197.6, 164.5, 158.0 (CO), 148.7, 146.4, 138.5, 135.9, 130.2, 129.6, 126.3, 125.5, 124.2, 116.5, 112.3, 53.8 (OCH_3), 39.4, 38.4 (cyclohexane $2CH_2$), 21.7 (CH_3), 19.8 (cyclohexane CH_2), 15.7 (CH_3).

Anal. Calcd. For $C_{23}H_{21}N_3O_5S$ (451.49): C, 61.18; H, 4.69; N, 9.31; S, 7.10. Found C, 61.23; H, 4.97; N, 9.47; S, 7.00.

Methyl 5-[(4,4-dimethyl-2,6-dioxocyclohexylidenemethyl)-amino]-7-methyl-4-oxo-3-*p*-tolyl-3,4-dihydrothieno[3,4-*d*]pyrid-azine-1-carboxylate (**21d**).

Compound **21d** was obtained as yellow crystals 2.16 g (45%), mp. 242º, ir (KBr): 3431 (NH), 1726, 1666 (CO) cm^{-1}; ms: m/z = 479 (M$^+$,100), 420 (24), 329 (30), 254 (38), 105 (52), 91 (25); ^{1}H nmr (deuteriochloroform): δ 1.08 (s, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 2.45 (s, 2H, CH_2), 2.49 (s, 2H, CH_2), 2.66 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.24 (d, 2H, J = 8.3 Hz, p-tolyl-H), 7.47 (d, 2H, J = 8.3 Hz, p-tolyl-H), 8.18 (d, 1H, J = 13.3 Hz, ethylenic-H), 14.36 (d, 1H, J = 13.1 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 200.5, 197.2, 164.5, 159.1 (CO), 148.0, 146.5, 138.6, 137.9, 135.9, 130.5, 129.9, 126.2, 124.1, 116.4, 111.2, 53.8 (OCH_3), 52.2 (cyclohexane carbon),. 32.5, 31.6 (cyclohexane $2CH_2$), 29.8, 21.7, 15.8 ($3CH_3$).

Anal. Calcd. For $C_{25}H_{25}N_3O_5S$ (479.55): C, 62.61; H, 5.25; N, 8.76; S, 6.69. Found C, 62.55; H, 5.61; N, 8.93; S, 6.64.

2-[(4-Oxo-4*H*-5-oxa-2-thiacyclopenta[*a*]naphthalen-3-ylamino)-methylene]cyclohexane-1,3-dione (**22a**).

Compound **22a** was obtained as buff crystals 1.64 g (48%), mp. 242°, ir (KBr): 3435 (NH), 1707, 1668 (CO) cm^{-1}; ms: m/z = 339 (M$^+$,84), 254 (26), 217 (100), 202 (28), 89 (22), 63 (28); ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.94-1.98 (m, 2H, CH_2), 2.74 (t, 4H, J = 6.8 Hz, $2CH_2$), 7.30-7.37 (m, 2H, coumarinyl-H), 7.43-7.48 (m, 1H, coumarinyl-H), 7.89 (s, 1H, thiophene-H), 8.05 (d, 1H, J = 7.7 Hz, coumarinyl-H), 8.12 (d, 1H, J = 13 Hz, ethylenic-H), 13.70 (d, 1H, J = 13.1 Hz, NH), ^{13}C nmr (dimethylsulfoxide-d_6): δ 201.3, 197.0, 163.3 (CO), 158.6, 154.4, 151.2, 148.8, 133.4, 130.1, 126.0, 125.1, 119.2, 117.7, 109.9, 98.7, 39.8, 38.4, 19.6 (cyclohexane $3CH_2$).

Anal. Calcd. For $C_{18}H_{13}NO_4S$ (339.37): C, 63.71; H, 3.86; N, 4.13; S, 9.45. Found C, 63.29; H, 3.90; N, 4.31; S, 9.43.

5,5-Dimethyl-2-[(4-oxo-4*H*-5-oxa-2-thiacyclopenta[*a*]naphthalen-3-ylamino)methylene]cyclohexane-1,3-dione (**22b**).

Compound **22b** was obtained as buff crystals 2.64 g (72%), mp. 274°, ir (KBr): 3480 (NH), 1709, 1678 (CO) cm^{-1}; ms: m/z 367 (M$^+$,100), 352 (38), 241 (22), 217 (80), 174 (26), 145 (22), 83 (20); ^{1}H nmr (deuteriochloroform): δ 1.10 (s, 6H, $2CH_3$), 2.50 (s, 2H, CH_2), 2.56 (s, 2H, CH_2), 7.20 (s, 1H, thiophene-H), 7.29-7.36 (m, 2H, coumarinyl-H), 7.44 (t, 1H, J = 8.4 Hz, coumarinyl-H), 7.77 (d, 1H, J = 8.8 Hz, coumarinyl-H), 8.29 (d, 1H, J = 12.8 Hz, ethylenic-H), 14.12 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 200.4, 196.9, 158.4 (CO), 154.0, 151.2, 147.8, 147.6, 134.2, 130.5, 125.2, 123.7, 118.2, 117.0, 111.3, 105.2, 52.2 (cyclohexane carbon), 32.3, 31.4 (cyclohexane $2CH_2$), 29.7 (CH_3).

Anal. Calcd. For $C_{20}H_{17}NO_4S$ (367.42): C, 65.38; H, 4.66; N, 3.81; S, 8.73. Found C, 65.17; H, 4.64; N, 3.94; S, 8.52.

2-[(12-Oxo-12*H*-11-oxa-16-thiacyclopenta[*a*]phenanthren-17-ylamino)methylene]cyclohexane-1,3-dione (**23a**).

Compound **23a** was obtained as buff crystals 2.42 g (62%), mp. 298°, ir (KBr): 3390 (NH), 1703, 1668 (CO) cm^{-1}; ms: m/z 389 (M^+,60), 267 (100), 252 (20), 195 (22), 139 (22), 58 (32); ^1H nmr (deuteriochloroform): δ 2.09-2.15 (m, 2H, CH_2), 2.62 (t, 4H, J = 6.4 Hz, $2CH_2$), 7.23 (s, 1H, thiophene-H), 7.59-7.65 (m, 2H, arom-H), 7.74 (d, 1H, J = 6.8 Hz, arom-H), 7.86 (d, 1H, J = 6.4 Hz, arom-H), 8.11 (d, 1H, J = 6.8 Hz, arom-H), 8.33 (d, 1H, J = 12.8 Hz, ethylenic-H), 8.53 (d, 1H, J = 8 Hz, arom-H), 14.20 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 201.2, 195.6, 168.7 (CO), 148.7, 146.0, 144.8, 141.4, 139.0, 134.4, 128.3, 128.2, 127.8, 125.5, 123.0, 120.3, 114.2, 112.9, 110.0, 106.8, 38.9, 38.5, 19.7 (cyclohexane $3CH_2$).

Anal. Calcd. For $C_{22}H_{15}NO_4S$ (389.42): C, 67.85; H, 3.88; N, 3.60; S, 8.23. Found C, 67.62; H, 4.00; N, 3.82; S, 8.15.

5,5-Dimethyl-2-[(12-oxo-12*H*-11-oxa-16-thiacyclopenta[*a*]-phenanthren-17-ylamino) methylene]cyclohexane-1,3-dione (**23b**).

Compound **23b** was obtained as buff crystals 2.56 g (61%), mp.> 300°, ir (KBr): 3385 (NH), 1711, 1673 (CO) cm^{-1}; ms: m/z 417 (M^+,44), 389 (100), 267 (60), 195 (28), 139 (24), 73 (40); ^1H nmr (deuteriochloroform): δ 1.05 (s, 6H, $2CH_3$), 2.43 (s, 2H, CH_2), 2.54 (s, 2H, CH_2), 7.18 (s, 1H, thiophene-H), 7.54-7.64 (m, 2H, arom-H), 7.69 (d, 1H, J = 8 Hz, arom-H), 7.82 (d, 1H, J = 8 Hz, arom-H), 8.03 (d, 1H, J = 8 Hz, arom-H), 8.24 (d, 1H, J = 12.8 Hz, ethylenic-H), 8.49 (d, 1H, J = 8 Hz, arom-H), 14.10 (d, 1H, J = 12 Hz, NH), ^{13}C nmr (deuteriochloroform): δ 200.6, 197.2, 165.2 (CO), 158.9, 155.2, 148.0, 135.0, 134.7, 128.3, 128.2, 127.8, 125.5, 124.4, 123.0, 120.3, 112.3, 111.2, 110.3, 106.3, 52.4 (cyclohexane carbon), 31.6, 30.2 (cyclohexane $2CH_2$), 29.1 (CH_3).

Anal. Calcd. For $C_{24}H_{19}NO_4S$ (417.48): C, 69.05; H, 4.59; N, 3.36; S, 7.68. Found C, 68.85; H, 4.74; N, 3.52; S, 7.64.

General Procedure for the Preparation of Compounds **24** and **25**.

A solution of each of **13** and **14** (10 mmoles) and 3-dimethylaminoacrylaldehyde or acrylaldehyde (10 mmoles) in dimethylformamide (10 ml) was refluxed for 4 hrs. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from dioxane.

7-Amino-10-mercapto-6-oxo-6*H*-benzo[*c*]chromene-8-carbaldehyde (**24**).

Compound **24** was obtained as brown crystals 2.08 g (77%), mp. 280-282°, ir (KBr): 3426 and 3296 (NH_2), (br) 1697 (CO) cm^{-1}; ms: m/z 271 (M^+,54), 217 (100), 149 (42), 107 (88), 91 (26), 77 (28); ^1H nmr (dimethylsulfoxide-d_6): δ 7.05-7.48 (m, 4H, arom-H), 7.73 (s, 1H, SH, D_2O exchangeable), 7.79 (br, 2H, NH_2, D_2O exchangeable), 8.05 (d, 1H, J = 8 Hz, arom-H), 10.93 (s, 1H, CHO), ^{13}C nmr (dimethylsulfoxide-d_6): δ 169.6, 161.4 (CO), 159.8, 150.9, 150.6, 130.8, 130.5, 126.3, 125.8, 125.0, 118.0, 109.7, 109.4, 106.5.

Anal. Calcd. For $C_{14}H_9NO_3S$ (271.29): C, 61.98; H, 3.34; N, 5.16; S, 11.82. Found C, 61.69; H, 3.50; N, 5.32; S, 11.73.

7-Amino-10-mercapto-6-oxo-6*H*-dibenzo[*c*,*h*]chromene-8-carbaldehyde (**25**).

Compound **25** was obtained as brown crystals (2.10 g, 65%), mp. > 300°, ir (KBr): 3443 and 3307 (NH_2), 1702 (br) (CO) cm^{-1}; ms: m/z 321 (M^+,28), 267 (100), 223 (28), 105 (58), 91 (32), 60 (28); ^1H nmr (dimethylsulfoxide-d_6): δ 7.61-7.84 (m, 3H, arom-H), 7.95 (s, 1H, SH, D_2O exchangeable), 7.98 (d, 1H, J = 8.6 Hz, arom-H), 8.12 (d, 1H, J = 7.7 Hz, arom-H), 8.23 (br , 2H, NH_2, D_2O exchangeable), 8.30 (d, 1H, J = 7.7 Hz, arom-H), 8.46 (d, 1H, J = 8 Hz, arom-H), 10.98 (s, 1H, CHO).

Anal. Calcd. For $C_{18}H_{11}NO_3S$ (321.35): C, 67.28; H, 3.45; N, 4.36; S, 9.98 Found C, 67.00; H, 3.54; N, 4.51; S, 9.65.

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