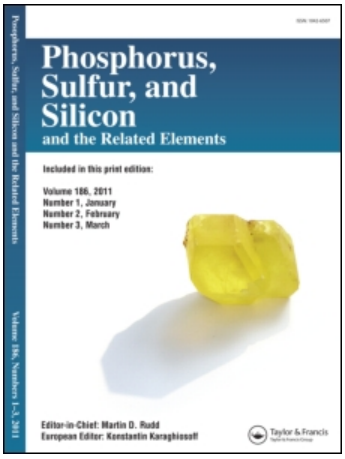

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Bakhite, E. A. , Geies, A. A. , El-Dean, A. M. Kamal and El-kashef, H. S.(1995) 'SYNTHESIS AND SOME REACTIONS OF PYRROLO[1",2":1',6']PYRAZINO-[2', 3': 4, 5]THIENO[2, 3-b]QUINOLINES; A NEW FUSED PYRAZINE RING SYSTEMS', Phosphorus, Sulfur, and Silicon and the Related Elements, 104: 1, 143 — 149
To link to this Article: DOI: 10.1080/10426509508042586
URL: http://dx.doi.org/10.1080/10426509508042586

Phosphorus, Sulfur, and Silicon, 1995, Vol. 104, pp. 143–149
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SYNTHESIS AND SOME REACTIONS OF PYRROLO[1″, 2″:1′,6′]PYRAZINO-[2′, 3′: 4, 5]THIENO[2, 3-b]QUINOLINES; A NEW FUSED PYRAZINE RING SYSTEMS

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(Received November 15, 1994; in final form March 3, 1995)

Ethyl 3-amino-4-(4-chlorophenyl)-5, 6, 7, 8-tetrahydrothieno[2, 3-b]quinoline-2-carboxylate (**1**) was converted into the corresponding 3-(1-pyrrolyl) derivative **2**. Various derivatives of **2** were prepared. The synthesis of the title compounds and other related heterocyclic systems are reported.

Key words: Pyrazine ring, fused ring, heterocycle, thienopyrozine.

INTRODUCTION

Benzothienopyrazine derivatives have received little attention. The synthesis of [1]benzothieno[2, 3-e]pyrrolo[1, 2-a]pyrazines were reported by Robba *et al.*[1,2] In continuation of our program devoted to the synthesis of aza- and diaza-analogues of the heterocyclic systems, the synthesis of pyrrolo[1″, 2″: 1′, 2′]pyrazino[6′, 5′: 4, 5]thieno[2, 3-c]pyridazine derivatives[3] has been reported.

The present paper deals with the synthesis of the title compounds of anticipated biological activity.

The amino ester[4] **1** was allowed to interact with 2, 5-dimethoxy-tetrahydrofuran in boiling acetic acid to give the pyrrolyl ester **2**. The reaction of the latter compound with hydrazine hydrate gave the hydrazide 3 which in turn was converted into azide **4**. Curtius rearrangement of **4** in boiling alcohols, amines or hydrazine hydrate gave the corresponding carbamates **5**, **6**, ureas **7–11** or semicarbazide **12** respectively. The arylidene semicarbazide derivatives **13–16** were obtained when compound **12** was reacted with the appropriate aromatic aldehydes in boiling ethanol. When Curtius rearrangement was carried out by heating **4** in an inert high-boiling point solvent such as xylene, the 4-oxopyrazine, 12-(4-chlorophenyl)-4, 5, 8, 9, 10, 11-hexahydro-4-oxo-pyrrolo[1″, 2″:1′, 6′]pyrazino[2′, 3′: 4, 5]thieno[2, 3-b]quinoline (**17**), was obtained. Thiation of **17** using phosphorus pentasulfide in boiling pyridine gave the corresponding thioxo derivative **18**.

It is worth mentioning that we have to reconsider the nomenclature we gave to our recently published pyrrolo[1″, 2″:1′, 2′]pyrazino]6′, 5′:4, 5]thieno[2, 3-

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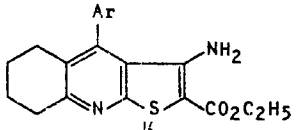
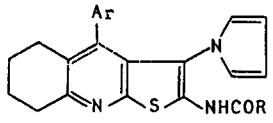
c]pyradazine system.[3] A more correct name should be given as pyrrolo[1″, 2″: 1′, 6′]pyrazino-[2′, 3′: 4, 5]thieno[2, 3-c]pyridazine.

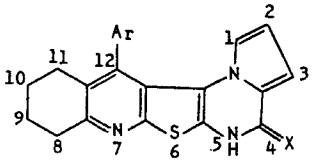
The thioxopyrazine **18** has served as a point of departure into several alkylated mercaptopyrazines **19–22** and hydrazinopyrazine **23**. Reaction of **18** with some halocompounds such as; methyl iodide, phenacyl bromide and ethyl chloroacetate produced the corresponding S-substituted mercaptopyrazines **19–21**. The acethy-



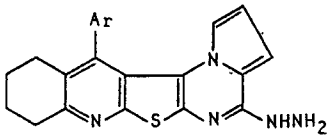
1, Ar=C_6H_4-4-Cl



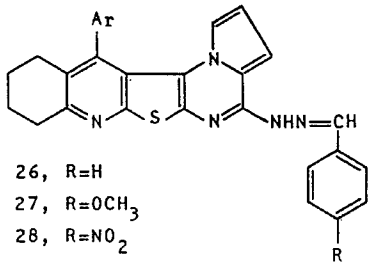
7, R=$NH(CH_2)_2OH$
8, R=$NHCH_2C_6H_5$
9, R=NHC_6H_5
10, R=1-piperidinyl
11, R=1-morphorlinyl
12, R=$NHNH_2$



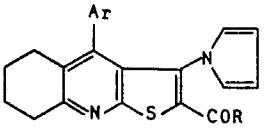
17, X=O
18, X=S



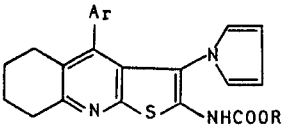
23



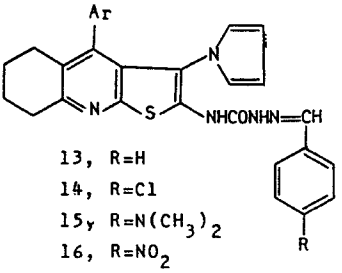
26, R=H
27, R=OCH_3
28, R=NO_2



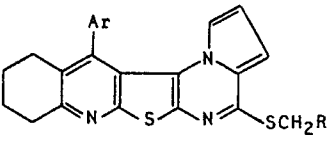
2, R=OC_2H_5
3, R=$NHNH_2$
4, R=N_3



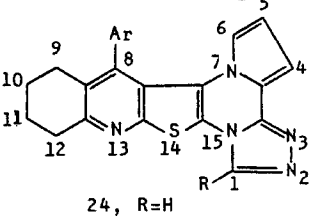
5, R=C_2H_5
6, R=$CH(CH_3)_2$



13, R=H
14, R=Cl
15, R=$N(CH_3)_2$
16, R=NO_2



19, R=H
20, R=COC_6H_5
21, R=$CO_2C_2H_5$
22, R=$CONHNH_2$



24, R=H
25, R=CH_3

drazide derivative **22**, however, was obtained by hydrazinolysis of ester **21**. Compounds **18** could be easily converted into **23** by heating with an excess amount of hydrazine hydrate. The latter compounds (**23**) was converted to the triazolo derivatives **24** and **25** by interacting with formic and acetic acids respectively. When **23** was reacted with aromatic aldehydes, the corresponding hydrazones **26–28** were obtained.

EXPERIMENTAL

Melting points are uncorrected and were measured on a MeI-Temp II melting point apparatus. IR spectra were recorded on a Pye-Unicam SP-3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM 360L 60 MHz NMR spectrometer in the suitable deuterated solvent using TMS as an internal standard. Elemental analysis were determined on a Perkin-Elmer 240 C microanalyser.

Ethyl 3-amino-4-(4-chlorophenyl)-5, 6, 7, 8-tetrahydro-thieno-[2, 3-b]quinoline-2-carboxylate (**1**): This compound was prepared according to a reported method.[4]

Ethyl 4-(4-chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydro-thieno[2, 3-b]quinoline-2-carboxylate (**2**): A mixture of **1** (3.8 g, 0.01 mol) and 2,5-dimethoxytetrahydrofuran (1.6 g, 0.01 mol) in glacial acetic acid (40 ml) was heated under reflux for one hour. The product, precipitated while hot, was filtered off and recrystallized from acetic acid as white crystals.

4-(4-Chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydrothieno-[2, 3-b]quinoline-2-carbohydrazide (**3**): A mixture of ester **2** (4.4 g, 0.01 mol) and hydrazine hydrate 99% (2 ml, 0.04 mol) in pyridine (20 ml) was heated under reflux for 5 h. After cooling and dilution with ice-cold water, the resultant solid was filtered off, washed with water and recrystallized from ethanol as white crystals.

4-(4-Chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydrothieno-[2, 3-b]quinoline-2-oyl azide (**4**): To a chilled suspension of **3** (8.6 g, 0.02 mol) in glacial acetic acid (150 ml), a cold solution of sodium nitrite (10 ml, 33%) was added dropwise, with stirring. After completion of addition, stirring was continued for 1 h. The solid product thus formed was filtered, washed with water, air dried and applied in the next reactions without purification.

Alkyl-N-[4-(4-(4-chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydro-thieno[2, 3-b]quinoline-2-yl]carbamates (**5**, **6**): Compound **4** (0.3 g) was heated under reflux in the respective alcohol (25 ml) for 2 hrs. The reaction mixture was then filtered while hot, concentrated and allowed to cool. The crystalline precipitate was filtered and recrystallized from the same alcohol as pale yellow needles of **5**, **6**.

Reaction of azide **4** *with the different amines; preparation of compounds* **7–11**: *General procedure*: A mixture of azide **4** (0.4 g, 0.001 mol) and an excess of the respective amine (0.02 mol) was gently heated under reflux for 20 minutes. The reaction mixture was then triturated with ethanol (10 ml) and allowed to cool. The solid precipitate was collected by filtration and recrystallized from ethanol as white crystals of **7–11**.

4-[4-(4-Chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydro-thieno[2, 3-b]quinolin-2-yl]semicarbazide (**12**): A mixture of azide 4 (2 g) and hydrazine hydrate (20 ml) was heated under reflux for 30 minutes. The white solid thus precipitated was filtered, washed with water and recrystallized from ethanol as white crystals of **12**.

N^1-Arylidene-N^4-[4-chlorophenyl)-3-(1-pyrrolyl)-5, 6, 7, 8-tetrahydro-thieno[2, 3-b]quinoline-2-yl]semicarbazides (**13–16**): *General procedure*: Equimolar amounts (0.001 mol) of the semicarbazide **12** (0.4 g) and the appropriate aldehyde in ethanol (20 ml) was heated under reflux for one hour and left to cool. The precipitate was filtered and recrystallized from ethanol.

12-(4-Chlorophenyl)-4, 5, 8, 9, 10, 11-hexahydro-4-oxo-pyrrolo-[1", 2": 1', 6']pyrazino[2', 3": 4, 5]thieno[2, 3-b]quinoline (**17**): Compound **4** (3.0 g) in dry xylene (20 ml) was heated under reflux for 2 hrs. After cooling, the solid thus precipitated was collected and recrystallized from DMF in the form of buff crystals of **17**.

TABLE I

Physical and spectral data of compounds **2–28**

Compd. No.	Mp/°C (Yield/%)	Mol. formula[a] (MW)	IR (cm^{-1})	^{1}H-NMR (δ; ppm)
2	211-2 (84)	$C_{24}H_{21}ClN_4O_2S$ (464.96)	1690(CO)	($CDCl_3$): 1.15(t,3H,CH_3); 1.85(m,4H, CH_2-CH_2); 2.40(t,2H,CH_2); 3.15(t,2H, CH_2); 4.20(q,2H,OCH_2); 5.85(m,2H,2CH pyrrolyl); 6.25(m,2H,2CH pyrrolyl); 7.00(dd, 4H, arom.).
3	222-3 (78)	$C_{22}H_{19}ClN_4OS$ (422.93)	3440-3100 ($NHNH_2$); 1630(CO)	
4	322[dec.] (81)	$C_{22}H_{19}ClN_5OS$ (436.93)	2150(N_3); 1680(CO)	($CDCl_3$): 1.90(m,4H,CH_2-CH_2); 2.50(t,2H, CH_2); 3.25(t,2H,CH_2); 5.95(m,2H,2CH pyrrolyl); 6.30(m,2H,2CH pyrrolyl); 7.00(dd, 4H, arom.).
5	241-2 (73)	$C_{24}H_{22}ClN_3O_2S$ (451.96)	3390(NH); 1730(CO); 2960(CH)	($CDCl_3$): 1.20(t,3H,CH_3); 1.85(m,4H, CH_2-CH_2); 2.40(t,2H,CH_2); 3.15(t,2H, CH_2); 4.20(q, 2H, OCH_2); 5.95(m, 2H, 2CH pyrrolyl); 6.20(m, 2H, 2CH pyrrolyl); 7.00(dd, 4H, arom.).
6	235-6 (76)	$C_{25}H_{24}ClN_3O_2S$ (465.99)	3300(NH); 1700(CO)	(DMSO-d_6): 1.45(d,6H,$2CH_3$); 2.00(m,4H, CH_2-CH_2); 2.60(t,2H,CH_2); 3.30(t,2H, CH_2); 5.20(m, 1H, CH); 6.15(m, 2H, 2CH pyrrolyl); 6.45(m, 2H, 2CH pyrrolyl); 7.30(dd, 4H, arom.); 7.75(s, 1H, NH).
7	223-4 (76)	$C_{24}H_{23}ClN_4O_2S$ (466.98)	3540-3300 (2NH,OH); 1630(CO); 2950(CH)	(DMSO-d_6): 1.85(m,4H,CH_2-CH_2); 2.40 (t,2H,CH_2); 3.00-3.60(m,6H,$3CH_2$); 4.40(s,1H,OH); 6.05(m,2H,2CH pyrrolyl); 6.45(m,2H,2CH pyrrolyl); 7.10(dd,4H, arom.); 7.95(s,1H,NH).
8	248-9 (81)	$C_{29}H_{25}ClN_4OS$ (513.05)	3380,3130 (2NH);1630 (CO);2940(CH)	
9	218-20 (68)	$C_{28}H_{23}ClN_4OS$ (499.02)	3370,3110 (2NH);1640 (CO)	(DMSO-d_6): 1.75(m,4H,CH_2-CH_2); 2.30 (t,2H,CH_2); 3.10(t,2H,CH_2); 6.15(m,2H, 2CH pyrrolyl); 6.50(m,2H,2CH pyrrolyl); 7.30(m,9H, arom.).
10	131 (56)	$C_{27}H_{27}ClN_4OS$ (491.05)	3600-3200 (NH);1630 (CO)	

TABLE I (*Continued*)

Compd. No.	Mp/°C (Yield/%)	Mol. formula[a] (MW)	IR (cm^{-1})	^{1}H-NMR (δ; ppm)
11	135 (60)	$C_{26}H_{25}ClN_4O_2S$ (493.01)	3600-3200 (NH);1630 (CO)	($CDCl_3$): 1.70(m,4H,CH_2-CH_2); 2.40(t,2H, CH_2); 2.90-3.60(m,10H, 5xCH_2); 3.90 (s,br,1H,NH); 5.80(m,2H,2CH pyrrolyl); 6.15(m,2H,2CH pyrrolyl); 6.80(dd,4H, arom.).
12	222-3 (69)	$C_{22}H_{20}ClN_5OS$ (437.94)	3360-3120 (2NH,NH_2); 1630(CO)	-
13	321-2 (93)	$C_{29}H_{24}ClN_5OS$ (526.05)	3260,3110 (2NH);1660 (CO)	-
14	324-5 (95)	$C_{29}H_{23}Cl_2N_5OS$ (560.50)	3250,3100 (2NH);1650 (CO).	(DMSO-d_6): 1.90(m,4H,CH_2-CH_2); 3.30 (t,2H,CH_2); 4.50(s,2H,2NH); 6.15(m,2H, 2CH pyrrolyl); 6.45(m,2H,2CH pyrrolyl); 7.35(m,8H, arom.); 7.90(s,1H,N=CH).
15	335-7 (96)	$C_{31}H_{29}ClN_6OS$ (569.12)	3300,3100 (2NH);1660 (CO)	-
16	294-6 (93)	$C_{29}H_{23}ClN_6O_3S$ (571.04)	3260,3110 (2NH);1650 (CO)	-
17	>360 (81)	$C_{22}H_{16}ClN_3OS$ (405.90)	3200-2400 (NH);1630 (CO)	(CF_3CO_2D): 2.10(m,4H,CH_2CH_2); 2.90 (t,2H,CH_2); 3.40(t,2H,CH_2); 6.30(m, 1H,CH pyrrolyl); 6.95(m,2H,2CH pyrrolyl); 7.60(dd, 4H, arom.).
18	302 (76)	$C_{22}H_{16}ClN_3S_2$ (421.96)	3200-2400 (NH)	(CF_3CO_2D): 2.15(m,4H,CH_2-CH_2); 2.95 (t,2H,CH_2); 3.40(t,2H,CH_2); 6.30(m,1H, CH pyrrolyl); 6.95(m,2H,2CH pyrrolyl); 7.70(dd, 4H, arom.).
19	183-5 (80)	$C_{23}H_{18}ClN_3S_2$ (435.99)	1600(C=N)	($CDCl_3$): 1.80(m,4H,CH_2-CH_2); 2.50(t,2H, CH_2); 2.90(s,3H,SCH_3); 3.15(t,2H,CH_2); 5.75, 6.25,6.80(3m,3H,3CH pyrrolyl); 7.25(dd, 4H, arom.).
20	148-9 (89)	$C_{30}H_{22}ClN_3OS_2$ (540.09)	1675(CO)	-
21	225-6 (85)	$C_{26}H_{22}ClN_3O_2S_2$ (508.04)	1730(CO)	($CDCl_3$): 1.30(t,3H,CH_3); 1.80(m,CH_2-CH_2); 2.60(t,2H,CH_2); 3.15(t,2H,CH_2); 4.25 (m,4H,SCH_2 and OCH_2); 5.75,6.25,6.80 (3m,3H,3CH pyrrolyl); 7.30(dd,4H,arom.).

TABLE I (*Continued*)

Compd. No.	Mp/°C (Yield/%)	Mol. formula[a] (MW)	IR (cm^{-1})	^{1}H-NMR (δ; ppm)
22	205-6 (77)	$C_{24}H_{20}ClN_5OS_2$ (494.02)	3600-3000 ($NHNH_2$); 1660(CO)	-
23	>360 (64)	$C_{22}H_{18}ClN_5S$ (419.93)	3300,3200 (NH_2); 3100-2400 (NH);1630 (C=N).	(DMSO-d_6): 1.80(m,4H,CH_2-CH_2); 3.00 (t,2H,CH_2); 4.50(s,br,2H,NH_2); 6.25 (m,1H,CH pyrrolyl); 6.90(m,2H,2CH pyrrolyl); 7.35(dd, 4H, arom.), 8.00 (s,1H,NH).
24	>360 (72)	$C_{23}H_{16}ClN_5S$ (429.93)	1620(C=N)	-
25	>360 (69)	$C_{24}H_{18}ClN_5S$ (443.95)	1625(C=N)	(CF_3CO_2D): 2.10(m,4H,CH_2-CH_2); 2.85 (s,3H,CH_3); 3.00(t,2H,CH_2); 3.40(t,2H, CH_2); 6.30(m,1H,CH pyrrolyl); 6.95 (m,2H,2CH pyrrolyl); 7.70(dd,4H,arom.).
26	349-50 (87)	$C_{29}H_{22}ClN_5S$ (508.04)	3200-2400 (NH);1630 (C=N)	-
27	341-2 (91)	$C_{30}H_{24}ClN_5OS$ (538.06)	3200-2400 (NH);1630 (C=N)	(CF_3CO_2D): 2.00(m,4H,CH_2-CH_2); 2.85 (t,2H,CH_2); 3.55(t,2H,CH_2); 4.00(s,3H, OCH_3); 6.30(m,1H,CH pyrrolyl); 6.95 (m,2H,2CH pyrrolyl); 7.70(m,8H,arom.); 8.40(s,1H, N=CH).
28	>360 (90)	$C_{29}H_{21}ClN_6O_2S$ (553.03)	3200-2400 (NH);1630 (C=N).	-

a) Statisfactory microanalyses were obtained: C, ±0.24; H, ±0.19; N, ±0.20; S, ±0.29; Cl, ±0.31.

12-(4-Chlorophenyl)-4, 5, 8, 9, 10, 11-hexahydro-4-thioxo-pyrrolo-[1", 2": 1', 6']pyrazino[2', 3": 4, 5]thieno[2, 3-b]quinoline (**18**): A mixture of compound **17** (4.06 g, 0.01 mol) and phosphorus pentasulfide (2.3 g, 0.01 mol) in dry pyridine (50 ml) was heated under reflux for 5 hrs. The cooled reaction mixture was poured into 200 ml of cold water and acidified with diluted acetic acid. The yellow precipitate that separated was filtered and crystallized from acetic acid to give yellow needles of **18**.

12-(4-Chlorophenyl)-4-substituted thio-8, 9, 10, 11-tetrahydro-pyrrolo[1", 2": 1', 6']pyrazino[2', 3': 4, 5]thieno[2, 3-b]quinolines (**19–21**): *General procedure*: A mixture of compound **18** (0.42 g, 0.001 mol), respective halocompound (methyl iodide, phenacyl bromide or ethyl chloroacetate) (0.001 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for one hour. The crystalline products which separated after cooling were filtered and recrystallized from ethanol as pale yellow needles of **19–21**.

12-(4-Chlorophenyl)-8, 9, 10, 11-tetrahydro-pyrrolo[1", 2": 1', 6']-pyrazino[2', 3': 4, 5]thieno[2, 3-b]quinoline-4-ylthio acethydrazide (**22**): An equimolar (0.002 mol) mixture of **21** (1.0 g) and hydrazine

hydrate 99% (0.1 ml) in ethanol (15 ml) was refluxed for 2 hrs. The product precipitated on cooling was collected and recrystallized from ethanol as white crystals.

12-(4-Chlorophenyl)-4-hydrazino-8, 9, 10, 11-tetrahydro-pyrrolo-[1", 2": 1', 6']pyrazino[2', 3': 4, 5]thieno[2, 3-b]quinoline (**23**): Compound **18** (2.0 g) in hydrazine hydrate 99% (20 ml) was heated under reflux for 2 hrs. Ethanol (30 ml) was then added and the reaction mixture was further heated under reflux for 2 hrs where hydrogen sulfide gas seased to evolve. The solid product that separated on cooling was filtered and recrystallized from dioxane as white crystals.

8-(4-Chlorophenyl)-9, 10, 11, 12-tetrahydro-[1, 2, 4]triazolo-[4", 3": 4', 5']pyrrolo[1", 2": 1', 6']pyrazino[2', 3': 4, 5]thieno[2, 3-b]-quinoline (**24**): A suspension of **23** (0.4 g) in formic acid (20 ml) was heated under reflux for 5 hrs. The reaction mixture was then concentrated in vacuo and the solid product was filtered and recrystallized from dioxane as pale yellow needles.

8-(4-Chlorophenyl)-1-methyl-9, 10, 11, 12-tetrahydro-[1, 2, 4]-triazolo[4", 3": 4', 5']pyrrolo[1", 2":1', 6']pyrazino[2', 3': 4, 5]-thieno[2, 3-b]quinoline (**25**): This compound was prepared following a procedure similar to that of compound **24** using acetic acid instead of formic acid. The product was recrystallized from dioxane as pale yellow crystals.

4-Arylidenehydrazino-12-(4-chlorophenyl)-8, 9, 10, 11-tetrahydro-pyrrolo[1", 2": 1', 6']pyrazino[2', 3': 4, 5]thieno[2, 3-b]quinolines (**26–28**): A mixture of **23** (0.432 g, 0.001 mol) and the respective aromatic aldehyde (0.001 mol) in dioxane (25 ml) was heated under reflux for 3 hrs and left to cool. The solid product was collected and recrystallized from dioxane to give compounds **26–28**.

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