Synthesis of Spiro-pyrazole-3,3'-thiopyrano[2,3-*b*]pyridines and Azolo[*a*]pyrido[2',3':5,6]thiopyrano[3,4-*d*]pyrimidines as New Ring Systems with Antifungal and Antibacterial Activities

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Reactions of 2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine with aldehydes and with DMF-DMA furnished the 3-benzylidene and 3-(*N*,*N*-dimethylamino)-methylene derivatives. The latter products afforded spiro-pyrazolo-3,3'-thiopyrano[2,3-*b*]pyridines and new tetra- and penta-heterocyclic ring systems when treated with nitrilimines and aminoazoles, respectively. A number of the products showed high antifungal and antibacterial activities.

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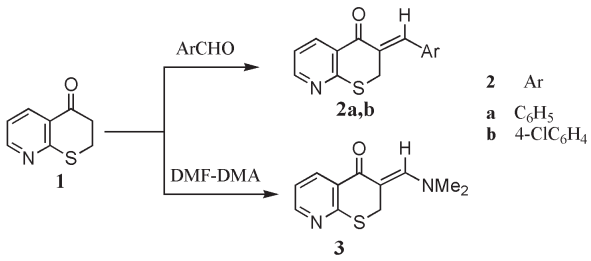
Some of 4-oxothiopyrano[2,3-*b*]pyridine derivatives were recently reported as potential antihypertensive agents [1,2]. Pyrazole derivatives have also exhibited diverse pharmacological properties [3]. In addition, many investigations concerning the synthesis of spiro heterocycles utilizing nitrilimines were discussed [4-7]. We have previously described several routes to fused polyheterocyclic ring systems [8-10], we here intend to report our results on the synthesis of the so far unreported 3-benzylidene-4-oxothiopyrano[2,3-*b*]pyridines **2a,b** and their 3-(*N*,*N*-dimethylamino)-methylene analog **3** as well as their applications in the synthesis of the novel spiro-pyrazolo-3,3'-thiopyrano[2,3-*b*]pyridines **6a,b**, 6*H*-2-phenylpyrazolo[1,5-*a*]pyrido[2',3':5,6]thiopyrano[3,4-*d*]pyridine (**12**) and 7*H*-pyrido[2'',3'':6',5']thiopyrano[4',3':4,5]pyrimido-[1,2-*a*]benzimidazole (**14**) as new ring systems. The biological activities of the obtained products were investigated and some of them showed high antifungal and antibacterial activities.

2,3-Dihydro-4-oxothiopyrano[2,3-*b*]pyridine (**1**) was prepared from the reaction of 2-mercaptopyridine-3-carboxylic acid with 3-bromopropionic acid in aqueous potassium hydroxide solution as reported in the literature [1]. Treatment of compound **1** with aromatic aldehydes in ethanol, in the presence of a catalytic amount of piperidine, at 90 °C afforded the corresponding 3-benzylidene derivatives **2a,b** as shown in Scheme 1. Compound **1** reacted also with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene and furnished a single product that was identified as 3-(*N*,*N*-dimethylamino)methylene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**3**) (Scheme 1). Elemental and spectral analyses were in complete accordance with the assigned structures **2** and **3**. The ^{1}H nmr spectrum of compound **3** revealed three singlet signals at δ 3.18, 4.11 and 7.59 characteristic for the *N*,*N*-dimethylamino, the methylene α to sulfur atom and the exocyclic C=CH protons, respectively. The products **2a,b** and **3** were assigned the *E*-configuration based on their ^{1}H nmr spectra which revealed the exocyclic C=CH proton signal around δ 7.5, for *Z*-isomers of analogous structures were reported to appear around δ 6.9 [11]. For compound **3**, NOE correlations were observed from C=CH proton to the NMe_2 protons, and from the thiopyran-SCH_2 protons to the NMe_2 protons but there was no correlation from C=CH proton to the thiopyran-SCH_2, as shown in Figure 1. These NOE's confirm the absolute *E*-configuration of structure **3**.

Scheme 1



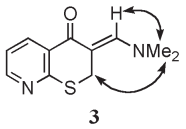


Figure 1. NOE Correlations are shown by arrows

Reaction of the 3-benzylidene derivative **2a** with the nitrilimine **5** [prepared *in situ via* treatment of *N*-phenylbenzenecarbohydrazonyl chloride (**4**) with triethylamine] under reflux in benzene, resulted in the formation of a single product as examined by TLC. Mass spectrum and elemental analysis showed that the reaction product has the molecular formula $C_{28}H_{21}N_3OS$. In the ^{1}H NMR spectrum of the reaction product, the singlet signal at δ 3.97 corresponding to the methylene protons of **2a** was not observed. Instead, two doublets were observed at δ 3.23 and 3.64 with *J* value of 14.6 Hz that each integrates for one proton. In addition, the olefinic sp^2 CH-proton of the benzylidene moiety, resonating at δ 7.50 in the ^{1}H NMR

spectrum of compound **2a**, was observed at δ 5.01 in the reaction product, which is consistent with an sp^3 CH-proton. The latter chemical shift is consistent with the pyrazoline-4H proton and not with the pyrazoline-5H-proton which appears at lower chemical shift [12,13]. Also, the ^{13}C NMR spectrum of compound **6a** revealed three sp^3 carbon signals at δ 36.87, 50.90 and 76.53. The signal at δ 76.53 corresponds to the spiro carbon and is similar to data reported for the reaction of 3-benzylidene-4-chromanones with the hydrazonoyl chloride **4** [14,15]. Moreover, the conjugated carbonyl absorption observed at 1616 cm^{-1} in the ir spectrum of compound **2a** is observed at the increased value of 1675 cm^{-1} for the reaction product. The aforementioned spectral data provides firm support for the regioselective addition of the nitrilimine **5** to the benzylidene olefinic moiety of compound **2a** to give the spiro pyrazoline-5,3'-thiopyrano[2,3-*b*]-pyridine derivative **6a** and rules out the other regio isomer **7a** (Scheme 2).

The foregoing results were supported by repeating a similar reaction using 3-(4-chlorobenzylidene)-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**2b**) with nitrilimine **5** under the same experimental conditions to give the spiro pyrazoline-5,3'-thiopyrano[2,3-*b*]pyridine structure **6b**. All spectral data agree completely with the assigned structure (*cf.* Experimental section).

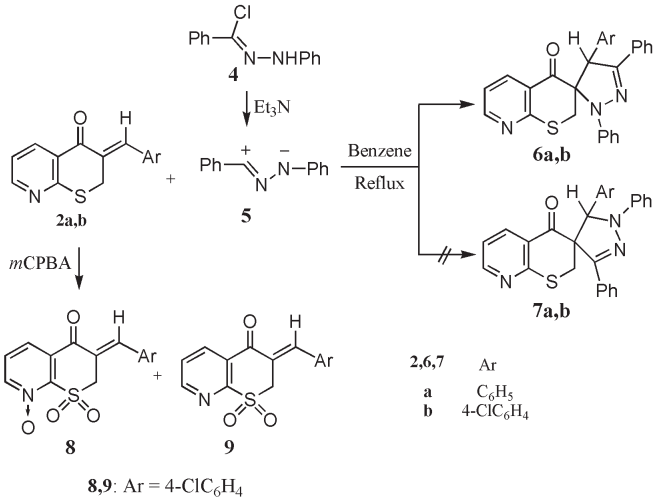
Treatment of the 3-benzylidene derivative **2b** with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane at room temperature resulted in the formation of two products as examined by TLC. One of them is 4-oxo-thiopyrano[2,3-*b*]pyridine-1,1,8-trioxide derivative **8** and the second one is its 1,1-dioxide analoge **9** (Scheme 2) as established from the elemental analysis and spectral data (IR, MS, ^1H NMR and ^{13}C NMR) of the reaction products.

The reactivity of 3-(*N*,*N*-dimethylamino)methylene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**3**) with some nitrogen nucleophiles was also conducted. Thus, reaction of the enamine derivative **3** with phenylhydrazine in refluxing ethanol, catalyzed with a few drops of piperidine, afforded one isolable product that was identified as 4*H*-1-phenylpyrazolo[3',4':4,5]thiopyrano[2,3-*b*]pyridine (**10**) (Scheme 3). The structure elucidation was based on elemental analysis and spectral data (IR, MS, and ^1H NMR) of the reaction product. Its ^1H NMR spectrum revealed singlet signals at δ 4.37 due to the methylene group of the thiopyran moiety and at δ 9.17 due to the pyrazole-3H proton in addition to the aromatic multiplets.

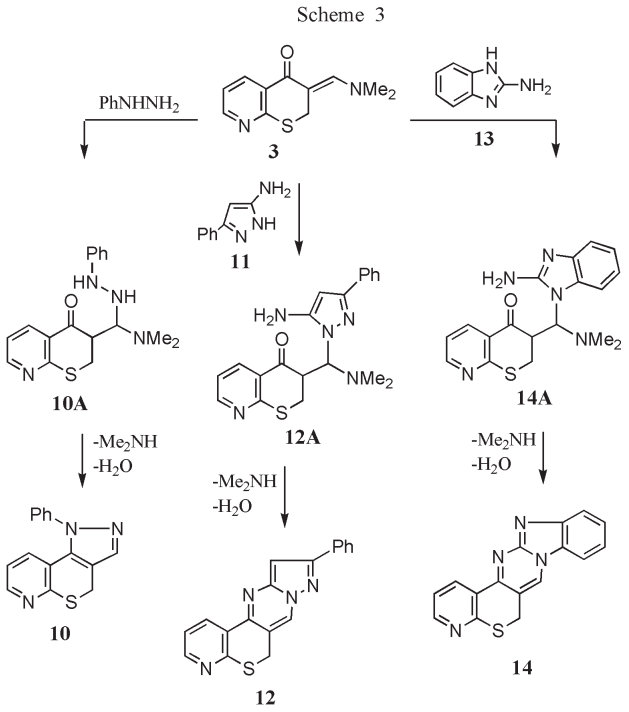
The exocyclic-enamine derivative **3** reacted also with 3-phenyl-5-amino-1*H*-pyrazole (**11**) under similar reaction conditions to afford a yellow colored product in 74% yield. The structure of the obtained product was established as the new tetra-heterocyclic ring system; 6*H*-2-phenylpyrazolo[1,5-*a*]pyrido[2',3':5,6]thiopyrano[3,4-*d*]pyridine (**12**) (Scheme 3) on the basis of its elemental analysis and spectral data. Its IR spectrum was free of carbonyl function and its ^1H NMR was free of *N*,*N*-dimethylamino protons and showed a characteristic singlet at δ 4.29 due to the methylene group at position 2 of the thiopyran ring.

Similarly, treatment of compound **3** with 2-aminobenzimidazole (**13**) resulted in the formation of a yellow-colored product that was identified as 7*H*-pyrido[2",3":6',5']-thiopyrano[4',3':4,5]pyrimido[1,2-*a*]benzimidazole (**14**), Scheme 3. The latter structure is a new heterocyclic ring system and was substantiated from elemental analysis and spectral data (IR, MS, and ^1H and ^{13}C NMR) of the reaction product (see Experimental section). Formation of the new hetero-

Scheme 2



Scheme 3



cyclic ring systems **12** and **14** is assumed to take place *via* the initial attack of the most nucleophilic endocyclic-NH of the aminoazoles **11** and **13** [16,17] to the exocyclic enamine moiety of **3** followed by the loss of dimethylamine and water molecules from the intermediates **12A** and **14A**, Scheme 3.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The nuclear magnetic resonance spectra were determined in dueteriochloroform or dimethysulfoxided$_6$ at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV Elemental analyses and the biological activities were carried out at the Microanalytical center of Cairo University. 4-Oxothiopyrano[2,3-*b*]pyridine (**1**) [1], hydrazonoyl chloride **4** [18] and 3-phenyl-5-aminopyrazole (**10**) [19] were prepared as reported in the literature procedures.

3-Benzylidene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridines **2a,b**.

General Procedure.

To a solution of the 4-oxo-thiopyrano[2,3-*b*]pyridine (**1**) (3.3 g, 20 mmol) and the appropriate aromatic aldehyde (20 mmol), in ethanol (30 ml), was added a few drops of piperidine and the reaction mixture was heated at refluxing temperature for 3 hrs. After complete reaction, the reaction mixture was allowed to cool. The precipitate that formed was collected by filtration, washed with ethanol and purified by recrystallization from ethanol to afford the corresponding 3-arylmethylene derivatives **2a,b**.

3-Benzylidene-2,3-dihydro-4-oxothiopyrano[2,3-*b*]pyridine (**2a**).

Compound **2a** was obtained in 71% yield (3.6 g), mp 98-100°; ir (potassium bromide): 1616 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.97 (s, 2H, SCH_2), 7.25-7.35 (m, 5H, phenyl), 7.45 (dd, 1H, J = 8.4, 8 Hz, Ar-H), 7.50 (s, 1H, C=CH), 8.73-8.79 (m, 2H, Ar-H); ^{13}C nmr (DEPT): δ 37.53 (CH_2), 122.41, 126.46, 128.51, 129.22, 135.41, 137.02, 152.1 (CH), 128.44, 136.93, 138.0, 158.04, 179.37 (C); ms: m/z 253 (M^+), 215, 195, 127, 107, 75, 63.

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53; S, 12.66. Found: C, 71.31; H, 4.30; N, 5.79; S, 12.45.

3-(4-Chlorobenzylidene)-2,3-dihydro-4-oxothiopyrano[2,3-*b*]-pyridine (**2b**).

Compound **2b** was obtained in 80% yield (4.59 g), mp 110-112°; ir (potassium bromide): 1616 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.94 (s, 2H, SCH_2), 7.19-7.22 (d, 2H, J = 9.3 Hz, Ar-H), 7.28-7.31 (d, 2H, J = 9.3 Hz, Ar-H), 7.46-7.51 (dd, 1H, J = 9, 8.7 Hz, Ar-H), 7.54 (s, 1H, C=CH), 8.77-8.80 (m, 2H, Ar-H); ms: m/z 289 (M^++2), 288 (M^++1), 287 (M^+), 270, 252, 173, 138, 126, 115, 83.

Anal. Calcd. for $C_{15}H_{10}ClNOS$: C, 62.61; H, 3.50; N, 4.87; S, 11.14. Found: C, 62.44; H, 3.39; N, 4.75; S, 11.13.

3-(*N*,*N*-Dimethylamino)methylene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**3**).

A mixture of 2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**1**) (3.3 g, 20 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (2.66 ml, 20 mmol) in dry xylene (20 ml) was refluxed for 5 h, then allowed to cool. The yellow precipitate was collected by filtration, washed with petroleum ether (60/80 °C) and dried. Recrystallization from ethanol gave 2.99 g (68% yield) of compound **3**, mp 90-91°; ir (potassium bromide): 1637 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.18 (s, 6H, NMe_2), 4.11 (s, 2H, SCH_2), 7.10-7.14 (dd, 1H, J = 7.8, 6.3 Hz, Ar-H), 7.59 (s, 1H, C=CH), 8.30-8.33 (dd, 1H, J = 7.8, 1.0 Hz, Ar-H), 8.41-8.43 (dd, 1H, J = 6.4, 1.0 Hz, Ar-H); ^{13}C nmr (DEPT): δ, 44.28 (CH_3), 27.03 (CH_2), 120.71, 137.17, 150.39, 151.57 (CH), 99.29, 130.59, 162.36, 184.45 (C); ms: m/z, 220 (M^+), 182, 148, 126, 82.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56. Found: C, 59.88; H, 5.36; N, 12.45; S, 14.60.

Synthesis of Spiro[pyrazole-3,3'-thiopyrano[2,3-*b*]pyridine] Derivatives **6a,b**.

General Procedure.

To a mixture of the hydrazonoyl chloride **4** (2 mmol) and the appropriate 3-arylidene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]-pyridine **2a** or **2b** (2 mmol) in dry benzene (20 ml), triethylamine (0.2 ml) was added and the reaction mixture was refluxed for 20 h, then left to cool to room temperature. After the reaction was complete, the reaction mixture was passed through a silica gel chromatography column using hexane-ethyl acetate mixture (7:1) as eluent. The collected fractions were evaporated under reduced pressure then the yellow colored products were further purified by recrystallization from ethanol to afford the corresponding spiro-heterocycles **6a,b**.

2,4,5-Triphenyl-4'-oxo-spiro[3*H*,4*H*-pyrazole-3,3'-thiopyrano-[2,3-*b*]pyridine] (**6a**).

Compound **6a** was obtained in 57% yield (0.51 g); mp 147-8°; ir (potassium bromide): 1675 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.23 (d, 1H, J = 14.6 Hz, SCH_2), 3.64 (d, 1H, J = 14.6 Hz, SCH_2), 5.01 (s, 1H, pyrazoline-4H), 7.07-7.59 (m, 15H, Ar-H), 7.73-7.78 (m, 2H, Ar-H), 8.42 (d, 1H, J = 6.8 Hz, Ar-H); ^{13}C nmr (DEPT): δ 36.87 (CH_2), 50.90, 118.65, 121.34, 123.26, 127.34, 128.29, 128.71, 128.80, 128.97, 131.77, 135.92, 153.05 (CH), 76.53, 120.15, 128.21, 133.30, 142.47, 147.16, 157.87, 192.50 (C); ms: m/z 447 (M^+), 338, 287, 252, 173, 126, 77.

Anal. Calcd. for $C_{28}H_{21}N_3OS$: C, 75.14; H, 4.73; N, 9.39; S, 7.16. Found: C, 74.93; H, 4.55; N, 9.65; S, 7.08.

4-(4-Chlorophenyl)-2,5-diphenyl-4'-oxo-spiro[3*H*,4*H*-pyrazole-3,3'-thiopyrano[2,3-*b*]pyridine] (**6b**).

Compound **6b** was obtained in 60% yield (0.58 g); mp 154-5°; ir (potassium bromide): 1680 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.17 (d, 1H, J = 14.01 Hz, SCH_2), 3.68 (d, 1H, J = 14.01 Hz, SCH_2), 5.03 (s, 1H, pyrazoline-4H), 7.06-7.30 (m, 9H, Ar-H), 7.40-7.63 (m, 6H, Ar-H), 7.79-7.82 (d, 1H, J = 7.75 Hz, Ar-H), 8.43 (d, 1H, J = 6.78 Hz, Ar-H); ^{13}C nmr (DEPT): δ 36.65 (CH_2), 50.80, 119.0, 121.11, 123.21, 126.20, 128.68, 128.74, 128.91, 129.48, 131.88, 135.99, 153.07 (CH), 76.53, 120.07, 126.89, 129.81, 133.16, 142.72, 148.38, 158.44, 192.73 (C); ms: m/z 482 (M^++1), 481 (M^+), 356, 344, 233, 204, 165, 125, 77.

Anal. Calcd. for $C_{28}H_{20}ClN_3OS$: C, 69.77; H, 4.18; N, 8.72; S, 6.65. Found: C, 69.52; H, 4.02; N, 8.46; S, 6.61.

3-(4-Chlorobenzylidene)-2,3-dihydro-4-oxothiopyrano[2,3-*b*]-pyridine-1,1,8-trioxide (**8**) and its 1,1-Dioxide Derivative **9**.

To a stirred solution of 3-(4-chlorobenzylidene)-2,3-dihydro-4-oxothiopyrano[2,3-*b*]-pyridine (**2b**) (0.287 g, 1 mmol) in

dichloromethane (10 ml), *m*-chloroperbenzoic acid (mCPBA) (0.3 g) was added. The reaction mixture was stirred at room temperature for 6 h, then treated with aqueous sodium carbonate solution. The organic layer was separated and dried over anhydrous sodium sulfate then evaporated under vacuum. The reaction product was found to be a mixture of two components as examined by TLC. Fractional crystallization from dioxane/ethanol gave 150 mg of compound **8** (45% yield) and 100 mg compound **9** (32% yield).

3-(4-Chlorobenzylidene)-2,3-dihydro-4-oxothiopyrano[2,3-*b*]-pyridine-1,1,8-trioxide (**8**).

Compound **8** was obtained in 45% yield (150 mg), mp 175-177°; ir (potassium bromide): 1667 (C=O) 1315, 1108 (SO_2), 1245 (N=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 4.02 (s, 2H, SCH_2), 7.00 (s, 1H, C=CH), 7.17 (d, 2H, J = 8.4 Hz, Ar-H), 7.34 (d, 2H, J = 8.4 Hz, Ar-H), 7.74 (dd, 1H, J = 7.9, 6.42 Hz, Ar-H), 8.53 (d, 1H, J = 8.07 Hz, Ar-H), 8.99 (d, 1H, J = 6.42 Hz, Ar-H); ^{13}C nmr ($CDCl_3$): δ 35.97 (CH_2), 127.83, 129.24, 130.76, 133.61, 137.09, 13722, 154.59 (CH), 125.43, 128.13, 129.69, 130.05, 133.09, 133.52, 143.31, 156.04, 178.24 (C); MS m/z, 337 (M^++2), 336 (M^++1), 335 (M^+), 309, 279, 227, 165, 149, 123, 83, 58.

Anal. Calcd. for $C_{15}H_{10}ClNO_4S$: C, 53.66; H, 3.00; N, 4.17; S, 9.55. Found: C, 53.49; H, 2.72; N, 3.90; S, 9.51.

3-(4-Chlorobenzylidene)-2,3-dihydro-4-oxothiopyrano[2,3-*b*]-pyridine-1,1-dioxide (**9**).

Compound **9** was obtained in 32% yield (100 mg) mp 150-151°; ir (potassium bromide): 1680 (C=O), 1320, 1115 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.98 (s, 2H, SCH_2), 6.75 (s, 1H, C=CH), 7.29 (d, 2H, J = 7.25 Hz, Ar-H), 7.36 (d, 2H, J = 7.25 Hz, Ar-H), 7.54 (m, 1H, Ar-H), 7.92 (d, 1H, J = 8.07 Hz, Ar-H), 8.55 (d, 1H, J = 6.43 Hz, Ar-H); ms: m/z, 321 (M^++2), 320 (M^++1), 319 (M^+), 270, 255, 220, 156, 139, 111, 84, 58.

Anal. Calcd. for $C_{15}H_{10}ClNO_3S$: C, 56.34; H, 3.15; N, 4.38; S, 10.03. Found: C, 56.13; H, 3.24; N, 4.17; S, 10.11.

4*H*-1-phenylpyrazolo[3',4':4,5]thiopyrano[2,3-*b*]pyridine (**10**), 6*H*-2-phenylpyrazolo[1,5-*a*]pyrido[2',3':5,6]thiopyrano[3,4-*d*]-pyridine (**12**) and 7*H*-pyrido[2",3":6',5']thiopyrano[4',3':4,5]-pyrimido[1,2-*a*]benzimidazole (**14**).

General Procedure.

To a mixture of 3-(*N*,*N*-dimethylamino)methylene-2,3-dihydro-4-oxo-thiopyrano[2,3-*b*]pyridine (**3**) (0.220 g, 1 mmol) and phenylhydrazine or the aminoheterocycles **11** or **13** (1 mmol) in ethanol (20 ml), was added few drops of piperidine. The reaction mixture was heated at refluxing temperature for 12 h, then left to cool to room temperature. The solid product that formed was collected by filtration and was then recrystallized from ethanol/DMF to give the corresponding fused polyheterocyclic ring systems **10, 12** and **14**, respectively.

4*H*-1-phenylpyrazolo[3',4':4,5]thiopyrano[2,3-*b*]pyridine (**10**).

Compound **10** was obtained in 55% yield (0.14 g); mp 195-197°; ir (potassium bromide): 1598 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.37 (s, 2H, SCH_2), 7.39-7.53 (m, 5H, Ar-H), 7.97-8.56 (m, 3H, Ar-H), 9.17 (s, 1H, pyrazole-3H) ; ms: m/z 257 (M^++1), 256 (M^+), 189, 148, 104, 77.

Anal. Calcd. for $C_{15}H_{11}N_3S$: C, 67.90; H, 4.18; N, 15.84; S, 12.09. Found: C, 67.77; H, 4.26; N, 15.57; S, 12.11.

6*H*-2-phenylpyrazolo[1,5-*a*]pyrido[2',3':5,6]thiopyrano[3,4-*d*]-pyridine (**12**).

Compound **12** was obtained in 74% yield (0.23 g); mp 286-288°; ir (potassium bromide): 1605 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.29 (s, 2H, SCH_2), 7.43-7.60 (m, 5H, Ar-H), 8.40-8.79 (m, 4H), 8.97 (s, 1H, pyrimidine-4H); ms: m/z 317 (M^++1), 316 (M^+), 177, 148, 109, 82, 51.

Anal. Calcd. for $C_{18}H_{12}N_4S$: C, 68.33; H, 3.82; N, 17.71; S, 10.14. Found: C, 68.26; H, 3.63; N, 17.49; S, 10.16.

7*H*-pyrido[2",3":6',5']thiopyrano[4',3':4,5]pyrimido[1,2-*a*]benzimidazole (**14**).

Compound **14** was obtained in 60% yield (0.17 g); mp 230-232°; ir (potassium bromide): 1597 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.36 (s, 2H, SCH_2), 7.42-7.60 (m, 3H, Ar-H), 7.86 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.26 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.57 (m, 1H, Ar-H), 8.73 (dd, 1H, *J* = 7.9, 1.7 Hz, Ar-H), 9.62 (s, 1H, pyrimidine-4H); ^{13}C nmr (DMSO-d_6): δ 27.04, 100.87, 111.70, 112.38, 119.25, 121.64, 126.25, 126.25, 127.04, 128.78, 132.39, 135.34, 144.51, 149.72, 151.71, 155.67, 159.87; ms: m/z 291 (M^++1), 290 (M^+), 257, 145, 129, 102, 77, 63.

Anal. Calcd. for $C_{16}H_{10}N_4S$: C, 66.19; H, 3.47; N, 19.30; S, 11.04. Found: C, 66.11; H, 3.34; N, 19.13; S, 11.20.

Biological Activity.

The antibacterial and antifungal activities were carried out in the Microanalytical Center of Cairo University, using the diffusion plate method [20-22]. A bottomless cylinder containing a measured quantity of the sample is placed on a plate containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium) which has been heavily seeded with the spore suspension of the test organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism. All measurements were done in chloroform as a solvent. The obtained results were compared with some reference antibiotics that were purchased from Egyptian markets. As shown in Table 1, the 4-oxothiopyrano[2,3-*b*]pyridine-1,1,8-trioxide derivative **8** was found be highly active against both *Bacillus Cereus* and *Fusarium Oxysporium* microorganisms with respect to the used reference. The antifungal activity of com-

Table I

Antibacterial and Antifungal Activities of the Synthesized Compounds

Comp. No.[a]	Antibacterial activity [b] Inhibition %	Antifungal activity [c] Inhibition %
3	10	--
6b	19	11
8	56	78
9	32	--
$CHCl_3$ (Solvent)	--	--
Reference Drugs		
Duricef	93	80
Ampicillin	35	35
Ultragriseofolvin	--	47.5

[a] The biological activity of all other compounds cited in this paper were also examined, however no inhibition activities were observed; [b] The tested microorganism was *Bacillus Cereus*; [c] The tested microorganism was *Fusarium Oxysporium*.

pound **8** was found to be similar to Durecif and much higher than both of Ampicillin and Ultragriseofolvin.

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