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SOME REACTIONS OF 3-CYANO-4-P-CHLOROPHENYL-6-[1′-(2′-METHOXY NAPHTHALENYL)] -2-THIOPYRIDONE AND 2-METHYL-(b)-2-[α-B-METHOXY NAPHTHALENYL)-4-P-CHLOROPHENYL-3′, 4′-DIHYDROPYRIDYL] AZACHROMONE

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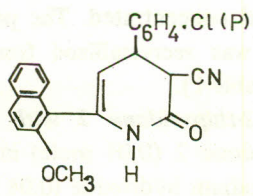
Reactions of 3-cyano-4-P-chlorophenyl-6-[1 '-(2 '-methoxy naphthalenyl)] -2-thiopyridone (2) with alkylating agents, acrylonitrile and formaldehyde in the presence of appropriate amine have been investigated. Thus treatment of 3-cyano-2-thiopyridone **2** with ethyl iodide and/or chloroacetic acid gave the corresponding S-alkylated derivatives **3a** and **3b** respectively. Reaction of **2** with acrylonitrile gave compound **3c**. Hydrolysis of **3c** with sodium hydroxide gave compound **4**. Oxidation of **3a** with $KMnO_4$ in the presence of sulphuric acid gave sulphone derivative 5.

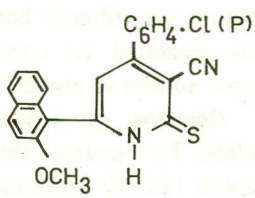
Thione **2** underwent Mannich reaction to give compounds **6a** and **6b**. 2-Methyl azachromone (**7**) condensed with phthalic anhydride in the presence of fused sodium acetate to give phthalide derivative (**8**). Heating **8** with aniline gave **7** and N-phenyl phthalimide. Hydrolysis of **8** with NaOH gave phthalic acid and compound **9**; Refluxing **8** with alcoholic CH_3ONa gave compound **10**. The aim of the present investigation is to synthesise some new pyridine derivatives. Their antimicrobial action was also studied.

INTRODUCTION

Treatment of 3-cyano-4-P-chlorophenyl-6-[1 ' (2 '-methoxy naphthalenyl)] -2- oxo- 1,2,3,4-tetrahydropyridine **1** with phosphorous pentasulphide [1] in dry xylene effected thionation together with dehydrogenation to give 3-cyano-4-P-chlorophenyl -6-[1 '-(2 '-methoxy naphthalenyl)] -2-thiopyridine **2**.



1



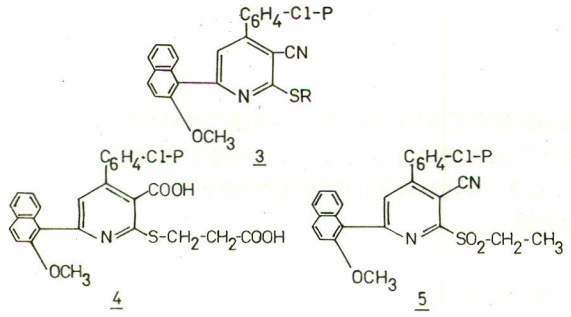
2

The IR spectrum of 3-cyano-2-thiopyridone derivative **2** showed C=S at ν 1285 cm^{-1}, C=N at ν 2240 cm^{-1} and NH at ν 3350 cm^{-1}.

3-cyano-2-thiopyridine **2** is readily alkylated on the exocyclic sulphur atom when treated with ethyliodide and chloroacetic acid giving the corresponding S-alkylated derivatives 3a and 3b. This shows that the 3-cyano-2-thiopyridone **2** is reactive as thiol in solution [2].

The infrared spectra of the S-alkylated products **3** revealed the absence of NH at ν 3350 cm^{-1} and C=S at ν 1285 cm^{-1} , the infrared spectrum of **3b** showed, in addition to the disappearance of the above mentioned bands, the presence of absorption bands characteristic for C=O (1710 cm^{-1}) and OH (3230 cm^{-1}) of the carboxyl group.

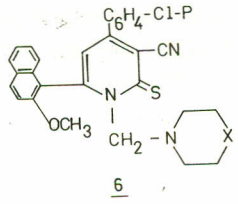
Cyanoethylation of heterocyclic nitrogen systems has recently received much attention but considerable confusion exists regarding the structure of addition of acrylonitrile to tautomeric compounds present in a large number of heterocyclic systems. In the reaction of 3-cyano-2-thiopyridone **2** with acrylonitrile [3], cyanoethylation took place exclusively on the exocyclic sulphur giving **3c**. Hydrolysis of **3c** with sodium hydroxide gave the corresponding dicarboxylic acid **4**. Oxidation of **3a** with potassium permanganate in the presence of sulphuric acid gave the ethyl sulphone derivative **5**.



a, $-C_2H_5$; b, $-CH_2-COOH$; c, CH_2-CH_2-CN

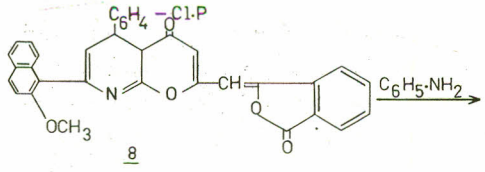
The IR spectrum of **3c** showed absorption bands in the region ν 2230 – 2220 cm^{-1} due to C≡N with disappearance of bands due to C=S and NH. The IR spectrum of **5** revealed the presence of strong absorption band in the region 1330 – 1325 cm^{-1} due to C-S asymmetric stretching in sulphones.

The thione **2** reacted with formaldehyde and the appropriate amine to afford Mannich bases **6a** and **6b**. The IR spectra of **6** showed C=N in the region (ν 2230 – 2225 cm^{-1}) and C=S in the region (ν 1290 – 1280 cm^{-1}).

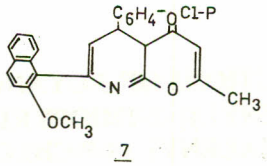


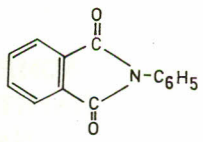
a, O; b, CH_2

The reaction between 2-methyl -1,4-B-naphthopyrone and phthalic anhydride has been investigated by Kamal [4]. We found that the 2-methyl azachromone **7** when fused with phthalic anhydride in the presence of fused sodium acetate gave the phthalide derivative **8**. The elemental analyses and infrared spectrum of **8** showing C=O lactonic at ν 1750 cm^{-1}, C=O azachromone at ν 1700 cm^{-1}, C=C at ν 1620 cm^{-1} and C=N at ν 1640 cm^{-1} were in conformity with the assigned structure. The phthalide derivative **8** upon heating with aniline at 180° gave the original 2-methyl azachromone **7** and N-phenyl phthalimide.



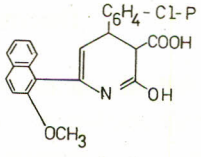
Hydrolysis of **8** with aqueous sodium hydroxide gave

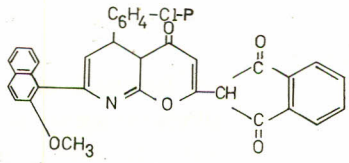




phthalic acid and pyridine derivative **9**.

The phthalide **9** underwent rearrangement to the phthalone derivative **10** upon refluxing with alcoholic sodium methoxide.





The infrared spectrum of **9** showed well defined absorption bands at 3350 cm^{-1}, 1695 cm^{-1} and 1620 cm^{-1} and attributed to OH, C=O carboxylic and C=N respectively. The IR spectrum of the phthalone derivative **10** exhibited a band at 1650 cm^{-1} due to α' B-unsaturated > C=O as well as another band at 1690 cm^{-1} attributed to the proper > C=O groups. The spectrum reveals no lactonic > C=O band.

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra in KBr were taken on a Unicam Sp 1200 spectrophotometer (ν max in cm^{-1}).

Formation of 3-cyano-4-P-chlorophenyl-6-1'-(2'-methoxy naphthalenyl) -2-thipyridone **2**. A mixture of **1** (0.02 mole) and phosphorous pentasulphide (0.02 mole) in dry xylene (100 ml) was reflux for 4 hr. The reaction mixture was filtered hot and concentrated. The product that separated on cooling was recrystallized from the proper solvent to give **2** (cf. Table 1).

Reaction of 3-cyano -2-thipyridone **2** *with Ethyl Iodide.* To 3-cyano-2-thipyridone **2** (0.01 mole) in ethyl alcohol (30 ml) was added sodium hydroxide (0.01 mole) in alcohol (5 ml) and ethyl iodide (0.01 mole) in ethyl alcohol (10 ml). The solution was then heated under reflux for 2 hr and then the solvent was evaporated, the solid obtained was filtered off and crystallized from the proper solvent to give **3a** (cf Table 1).

Reaction of **2** *with Monochloroacetic Acid.* A mixture

Table 1. Characterization of products **2**, **3a**, **3b**, **4**, **5**, **6**, **7a**, **7b**, **9**, **10** and **11**.

Compound	m.p.	Solvent yield (%)	Formula	Analysis (%) Found	Calculated
2	90	E 60	$C_{23}H_{15}N_2ClOS$	C 68.61 H 3.69 N 6.92	68.57 3.72 6.95
3a	80	E 65	$C_{25}H_{19}N_2ClOS$	C 69.72 H 4.39 N 6.48	69.68 4.41 6.50
3b	130	M 70	$C_{25}H_{17}N_2ClO_3S$	C 65.22 H 3.65 N 6.12	65.14 3.69 6.08
3c	105	M 60	$C_{26}H_{18}N_3ClOS$	C 68.53 H 3.92 N 9.38	68.49 3.95 9.22
4	180	B 70	$C_{26}H_{20}NClO_5S$	C 63.29 H 4.13 N 2.79	63.22 4.05 2.83
5	115	M 65	$C_{25}H_{19}N_2ClO_3S$	C 64.82 H 4.14 N 6.09	64.85 4.10 6.05
6a	105	M 60	$C_{28}H_{24}N_3ClO_2S$	C 67.02 H 4.75 N 8.34	66.99 4.78 8.37
6b	140	E 70	$C_{29}H_{26}N_3ClOS$	C 69.59 H 5.23 N 8.41	69.66 5.20 8.40
8	147	E 60	$C_{34}H_{22}NClO_5$	C 72.98 H 3.92 N 2.56	72.92 3.93 2.50
9	160	M 60	$C_{23}H_{18}NClO_4$	C 67.78 H 4.45 N 3.48	67.73 4.41 3.43
10	180	Bu 65	$C_{34}H_{22}NClO_5$	C 72.94 H 4.01 N 2.58	72.92 3.93 2.50

B = benzene; Bu = butanol; E = ethanol and M = methanol.

of **2** (0.01 mole) and monochloroacetic acid (0.01 mole) in aqueous sodium hydroxide (prepared from 0.02 mole sodium hydroxide in 20 ml water) was warmed (steam – bath) at 60 – 65°, for 1 hr. After cooling the reaction mixture was neutralized with 10 % aqueous HCl and the resulting precipitate was filtered off. Recrystallization from the proper solvent gave **3b** (cf. Table 1).

Reaction of **2** *with Acrylonitrile.* The compound **2** (0.01 mole) was added to a mixture of pyridine (50 ml) and water (10 ml) containing acrylonitrile (3 ml) and refluxed for 3 hr. The reaction mixture was cooled, diluted with water and the solid obtained was crystallized from the proper solvent to give **3c** (cf Table 1).

Hydrolysis of 3c, Formation of dicarboxylic Acid 4. A mixture of **3c** (0.5 g) and sodium hydroxide solution (20 ml., 20 %) was refluxed for 2 hr, cooled and filtered. The solid obtained upon dilution and acidification with hydrochloric acid was crystallized from tne proper solvent to give **4** (cf Table 1).

Oxidation of **3a**; *Formation of Ethyl Sulphone Derivative* **5.** To **3a** (0.01 mole) dissolved in chloroform (10 ml) were added ice and 5 N sulphuric acid (10 ml), the mixture was cooled at O° and potassium permanganate (0.01 mole) added solwly in portions. When the addition was complete the mixture was allowed to reach room temperature, made alkaline, decolourised with sulphur dioxide, and extracted with chloroform.

The dried magnesium sulphate chloroform extract was evaporated to dryness, and the residue obtained recrystallized from the proper solvent to give **5** (cf. Table 1).

Formation of the Mannich Bases **6a** *and* **6b.** To a suspension of thione **2** (0.01 mole) and morpholine or piperidine (0.02 mole) in methanol, aqueous formaldehyde (35%, 2.5 ml) was added. The reaction mixture was heated (steam-bath) for 15 min. The solid obtained recrystallized from the proper solvent to give **6a** and **6b** (cf. Table 1).

Reaction of 2-Methyl Azachromone **7** *with Phthalic Anhydride Formation of Phthalide Derivative* **8.** A mixture of **7** (0.015 mole), phthalic anhydride (0.015 mole) and anhydrous sodiumacetate (0.02 mole) was heated at 240° for 15 min. After cooling, the reaction mixture was triturated with water and the product was crystallized from the proper solvent to give **8** (cf. Table 1).

Reaction of Phthalide Derivative **8** *with Aniline.* A mixture of **8** (1 g) and excess of aniline was heated at 180 – 190° for 15 min. After cooling, the reaction mixture was triturated with ether, the product was filtered off to give 0.5 g N-phenylphthalimide (m.p and mixed m.p). Acidification of the mother liquor with dilute hydrochloric acid and extraction with ether gave 0.25 g **7**.

Action of Aqueous Sodium Hydroxide on **8.** A mixture of **8** (0.3 g) and 10 % aqueous sodium hydroxide (10 ml) was refluxed for ½ hr. The reaction mixture was allowed to cool, acidified with dilute sulphuric acid and the product filtered off to give 0.1 g of pyridine derivative **9**, extraction of the filterate with ether gave 0.1 g phthalic acid.

Rearrangement of the Phthalide **8** *to the Phthalone Derivative* **10.** A solution of the phthalide **8** (0.2 g) in methanol (8 ml) was treated with sodium methoxide solution (from sodium metal, 0.2 g, and methanol 10 ml) and the mixture was heated under reflux for 1 hr. The cold reaction mixture was diluted with water then acidified with cold dilute H_2SO_4 and the obtained solid was collected. Recrystallization of the product from the proper solvent gave **10** (cf. Table 1).

Antimicrobial Activity. A number of nitrohetrocyclic drugs are unusual in that their action is selectively toxic towards micro-organisms. Therefore, our interest was directed to study the microbial toxicity of some new heterocyclic organic compounds against several bacteria and yeasts.

The screening results have indicated that 2-chloro-3-cyano-4-phenyl pyridine, 2-hydroxy-3-carboxy-4-phenyl pyridine, 3-cinnamoyl-4-phenyl-2-pyridone, 3-acyl-2-pyriodine, pyrazoline, 3-cyano-2-thiopyridone and 3-cyano-S-alky-2-pyridine thiol derivatives had generally higher inhibitory effect against *Candida utilis, Candida albicans, Saccharomyces cereviseae, Escherichia coli, Micrococcus species, Bacillus subtilis, Mycobacterium phlei and Sarcina species.*

REFERENCES

1. G.F. Duffin and J.D. Kendall. J. Chem. Soc., 3789 (1959).
2. Kiichi Arakawa, C.A. 80, 120981 u (1974).
3. B. Stanovnik and M. Croate Tisler, Chem. Acta, **36**, 81 (Eng) (1964).
4. S.E.M. Kamel, M.Sc. Thesis, Faculty of Science, Ain Shams University, Cairo, 1971.