SYNTHESIS OF SOME PYRIDO[2,3-d]PYRIMIDINE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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Abstract : 2-Amino-3-cyano-4,6-disubstituted pyridines were condensed with carbondisulfide, thiourea, urea and formamide to obtain 5,7-disubstituted pyrido[2,3-d]pyrimidine-2,4(1H,3H)dithiones, 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidin-2(1H)thiones, 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidin-2(1H)-ones and 4-amino-5,7-disubstituted pyrido-[2,3-d]pyrimidines, respectively. Structural assignments were made on the basis of analytical and spectral data. All the synthesized compounds were screened for their antimicrobial evaluation against a number of bacteria and fungi and were found to be moderately active.

Introduction

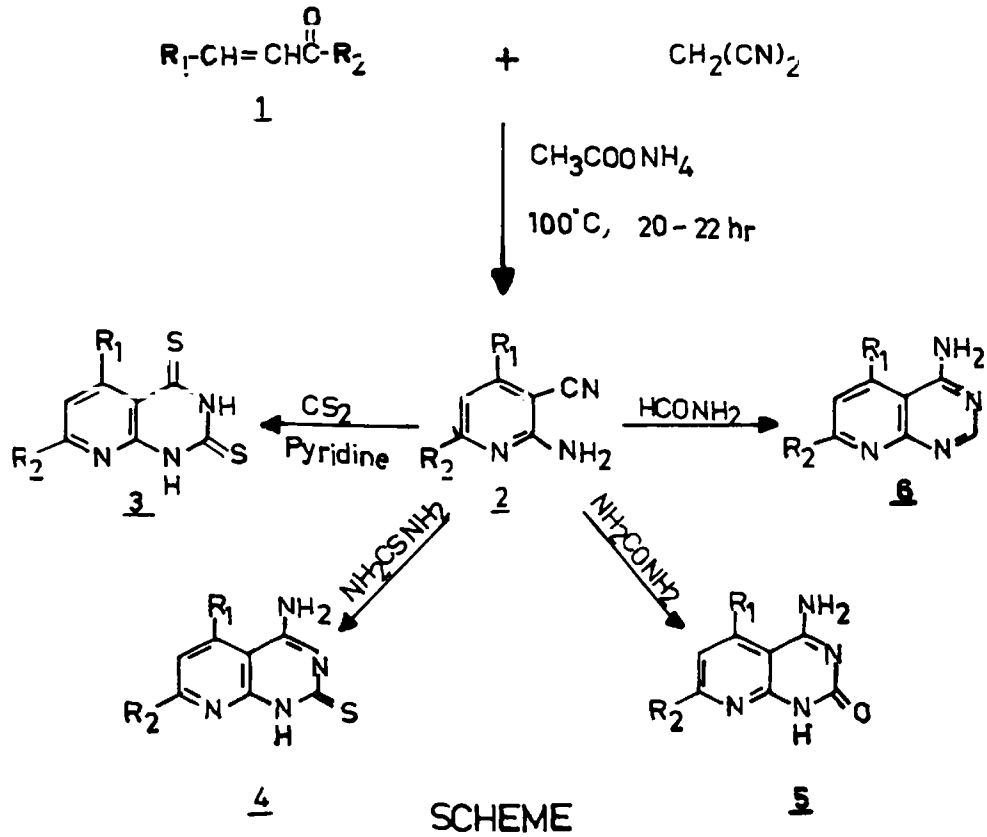
On account of the growing assets of pyrido[2,3-d]pyrimidines, they have been largely synthesized in the recent years. They are known to possess a wide spectrum of biological activities (1-6). Viewing this, some newer 5,7-disubstituted pyrido[2,3-d]pyrimidin-2,4(1H,3H)dithiones 3, 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidin-2(1H)thiones 4, 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidin-2(1H)ones 5 and 4-amino-5,7-disubstituted pyrido[2,3-d]pyrimidines 6 were synthesized.

Experimental

Melting points were determined in sealed, evacuated capillary tubes and are uncorrected. The IR spectra were recorded by means of pressed KBr disks on a Perkin-Elmer 577 grating IR spectrophotometer. The ^1H NMR spectra were obtained from FX90Q Jeol type spectrophotometer (at 90 MHz) using TMS as an internal standard.

5,7-Disubstituted pyrido[2,3-d]pyrimidin-2,4-(1H,3H)dithiones 3a-b (Scheme)

A mixture of 2-amino-3-cyano-4,6-disubstituted pyridine 2 (0.01 mole) and carbondisulfide (0.04 mole) in pyridine (15 ml) was refluxed on a water bath for 10-15 hr. After cooling, the excess of pyridine was removed by distilling under reduced pressure. The product was washed with water, saturated sodium bicarbonate solution and cold ethanol. It was recrystallized from DMF-ethanol (1:2) to obtain 3.



SCHEME

4-Amino-5,7-disubstituted pyrido[2,3-d]pyrimidin-2(1H)thione 4a-b (Scheme)

A mixture of 2 (0.01 mole) and thiourea (0.02 mole) was heated on oilbath at 120°-130° for 2 hr with constant stirring. The temperature was raised to 180° and finally the mixture was heated at 230° for 2 hr. The product so obtained was washed with water, saturated sodium bicarbonate solution and cold ethanol. It was recrystallized from DMF-ethanol (1:2) to obtain 4.

The compounds 5a-b were prepared from 2 by its treatment with urea by the same method as reported for the compounds 4a-b.

4-Amino-5,7-disubstituted pyrido[2,3-d]pyrimidines 6a-b (Scheme)

A mixture of 2 (0.01 mole) and formamide (0.04 mole) was refluxed on oilbath for more than 15 hr. After cooling, the reaction mixture was poured into the crushed ice. The product obtained was washed with water and recrystallized from DMF-ethanol (1:2) to obtain 6.

The characterization data of the synthesized compounds are given in the table 1.

Antimicrobial activity

All of the synthesied compounds were screened against the gram positive bacteria Staphyloccoccus aureus and the gram negative bacteria Escherichia coli. The fungi used for the antifungal evaluation of the synthesized compounds were Aspergillus niger, Aspergillus flavus, Curvularia lunata, Fusarium moniliformae and Alternaria tenuis. Disk diffusion method was employed. Streptomycin and Mycostatin were used as the standard compounds for antibacterial and antifungal evaluation respectively (7) (Table 2).

Results and Discussion

Cyclization of chalcone with dicyanomethane in 1:1 molar ratio in the presence of ammonium acetate gave 2-amino-3-cyano-4,6-disubstituted pyridine 2 through Michael reaction (8).

Compound 2 was condensed with carbondisulfide, thiourea, urea and formamide to obtain compounds 3, 4, 5 and 6 respectively. These condensation products were characterized with the help of elemental analyses, IR & ^{1}H NMR spectral data.

The IR (KBr) spectra of 2 had a sharp band at 2180-2160 cm^{-1}. This band completely vanished from the spectra of the compounds 3-6 indicating the completion of the reaction. The compounds 3 & 4 showed C=S group frequency in the region 1220-1160 cm^{-1} and 1220-1180 cm^{-1} respectively. The C=O group in the compound 5 caused absorption in the region 1690-1680 cm^{-1}. The compounds 4 & 5 showed the stretching vibrations of the NH_2 group in the region 3400-3320 cm^{-1} and that of NH group in the region 3160-3010 cm^{-1}.

The ^{1}H NMR spectra of the compound 2 showed a broad singlet of NH_2 protons in the region δ 7.28-8.26 ppm and the aromatic protons caused a multiplet in the region δ 6.82-8.56 ppm. In the compound 4 and 5 the NH protons occurred in the range δ8.3-9.0 ppm. In the compound 3, a complex multiplet of aromatic protons was found in the region δ6.86-8.10 ppm and the NH protons caused singlet in the range δ8.3-8.5 ppm. The compound 6 gave a multiplet of aromatic and NH_2 protons in the range δ6.96-8.30 ppm.

Antimicrobial evaluation

Table 1 : Characterization data of the synthesized compounds

Comp. No.	R_1	R_2	Yield %	m.p.	Molecular Formula	Analysis % Calcd. (Found) C	H	N
3a	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	70	225-227	$C_{21}H_{17}N_3O_2S_2$	61.9 (61.3)	4.2 (4.1)	10.3 (10.2)
3b	3,4-$(OCH_3)_2C_6H_3$	4'-ClC_6H_4	62	211-213	$C_{21}H_{16}ClN_3O_2S_2$	57.1 (57.2)	3.6 (3.2)	9.5 (9.1)
4a	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	61	197-199	$C_{21}H_{18}N_4O_2S$	64.6 (64.2)	4.6 (4.4)	14.4 (14.3)
4b	3,4-$(OCH_3)_2C_6H_3$	4'-ClC_6H_4	69	235-237	$C_{21}H_{17}ClN_4O_2S$	59.4 (59.6)	4.0 (4.3)	13.2 (13.0)
5a	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	69	192-194	$C_{21}H_{18}N_4O_3$	67.4 (67.7)	4.8 (4.9)	15.0 (14.8)
5b	3,4-$(OCH_3)_2C_6H_3$	4'-ClC_6H_4	68	258-261	$C_{21}H_{17}ClN_4O_3$	61.7 (61.5)	4.2 (4.0)	13.7 (13.5)
6a	3,4-$(OCH_3)_2C_6H_3$	C_6H_5	72	220-222	$C_{21}H_{18}N_4O_2$	70.4 (70.6)	5.0 (4.8)	15.6 (15.5)
6b	3,4-$(OCH_3)_2C_6H_3$	4'-ClC_6H_4	71	198-200	$C_{21}H_{17}ClN_4O_2$	64.2 (63.9)	4.3 (4.2)	14.3 (14.2)

Table 2 : Antimicrobial activity of the synthesized compounds

Micro-organism	Inhibition zone in mm (activity index; inhibition area of the sample/inhibition area of the standard)							
Compound No.	3a	3b	4a	4b	5a	5b	6a	6b
Bacteria								
E. coli	9.6 (1.23)	11.5 (1.35)	8.5 (1.00)	10.2 (1.20)	7.7 (0.91)	9.3 (1.09)	6.9 (0.81)	8.2 (0.96)
S. aureus	9.2 (1.15)	10.9 (1.36)	8.9 (1.11)	9.9 (1.24)	7.0 (0.88)	7.8 (0.98)	7.0 (0.88)	7.5 (0.94)
Fungi								
A. niger	8.5 (1.06)	8.9 (1.11)	7.9 (0.99)	7.7 (0.96)	8.0 (1.00)	7.2 (0.90)	6.5 (0.81)	6.8 (0.85)
A. flavus	8.8 (1.10)	8.5 (1.06)	8.2 (1.03)	8.5 (1.06)	7.3 (0.91)	7.7 (0.96)	7.5 (0.94)	7.0 (0.88)
C. lunata	7.0 (1.00)	7.9 (0.99)	6.9 (0.86)	7.0 (0.88)	6.2 (0.78)	7.0 (1.00)	6.9 (0.98)	6.5 (0.93)
F. moniliformae	7.9 (0.99)	8.9 (1.11)	8.2 (1.03)	8.8 (1.10)	6.5 (0.81)	6.7 (0.84)	6.9 (0.86)	6.5 (0.81)
A. tenuis	7.0 (1.00)	7.0 (1.00)	7.2 (1.03)	7.9 (1.13)	6.9 (0.99)	6.5 (0.93)	6.6 (0.94)	6.2 (0.89)

The synthesized compounds, when screened against the bacteria E.coli and S.aureus, and fungi A. niger, A. flavus, C. lunata, F. moniliformae and A. tenuis, were found to be only moderately active. The sulphur containing compounds, however proved to be slightly better bactericidals and fungicidals than the other ones.

Conclusions

All the synthesized compounds were obtained in the form of high melting coloured solids. The spectral data are in good agreement with, and hence support, the proposed structure. The compounds possess moderate biocidal (antifungal and antibacterial) properties.

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References

1. F. Pochat, F. Lavelle, C. Fizames and A. Zerial, Eur. J. Med. Chem. 22, 135 (1987).
2. N. Suzuki, Chem. Pharm. Bull. 28, 761 (1980).
3. M. Mohesen Ismail, J. Serb. Chem. Soc. 56 (7), 383 (1991).
4. J. Dovolli, J. Clarke and E.F. Elslager, J. Med. Chem. 15, 837 (1972).
5. J. Heider, Ger. Offen. DE 3, 320, 898 (1983); Chem. Abstr. 100, 103384 (1984).
6. K. Go, Y. Kirimoto and N. Kitamura, Eur. Pat. Appl. E.P. 243, 311 (1987); Chem. Abstr. 108, 75422 (1988).
7. J.C. Gould, J.H. Bowie, Edinb. Med. J. 59, 178 (1950).
8. A. Sakurai, H. Midorikawa, Bull. Chem. Soc. Jpn. 41 430 (1968).

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