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NEW CONDENSED PYRIMIDINES AS POTENTIAL ANALGETICS

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ABSTRACT

New O-aminonitriles (enaminonitriles) namely, pyrimido[1,6-a] indole were prepared by addition of 2-dicyanomethylidinoindoline- obtained from oxindole- to various isothiocyanates . The obtained enaminonitriles were acylated using chloroacetylchloride yielding methylchloride derivatives of the condensed pyrimidines, pyrimido[4,5 :4,5]pyrimido[1,6-a]indole. The chlorine atom was substituted by different amines or condensed with thiourea and the formed salts were hydrolyzed to give mercaptoalkyl compounds. Some of the prepared compounds were tested for their analgetic activities.

INTRODUCTION

Some pyrolopyrimidine [1-6] and pyrimido-azepine [7,8] derivatives have been reported to possess analgetic activities. Accordingly, oxindole was used in this work to prepare a series of 6-thio-pyrimido[4',5':4,5]pyrimido [1,6-a]indole in order to investigate the chemical and pharmacological properties of this heterocyclic fused system.These compounds are shown in scheme 1.

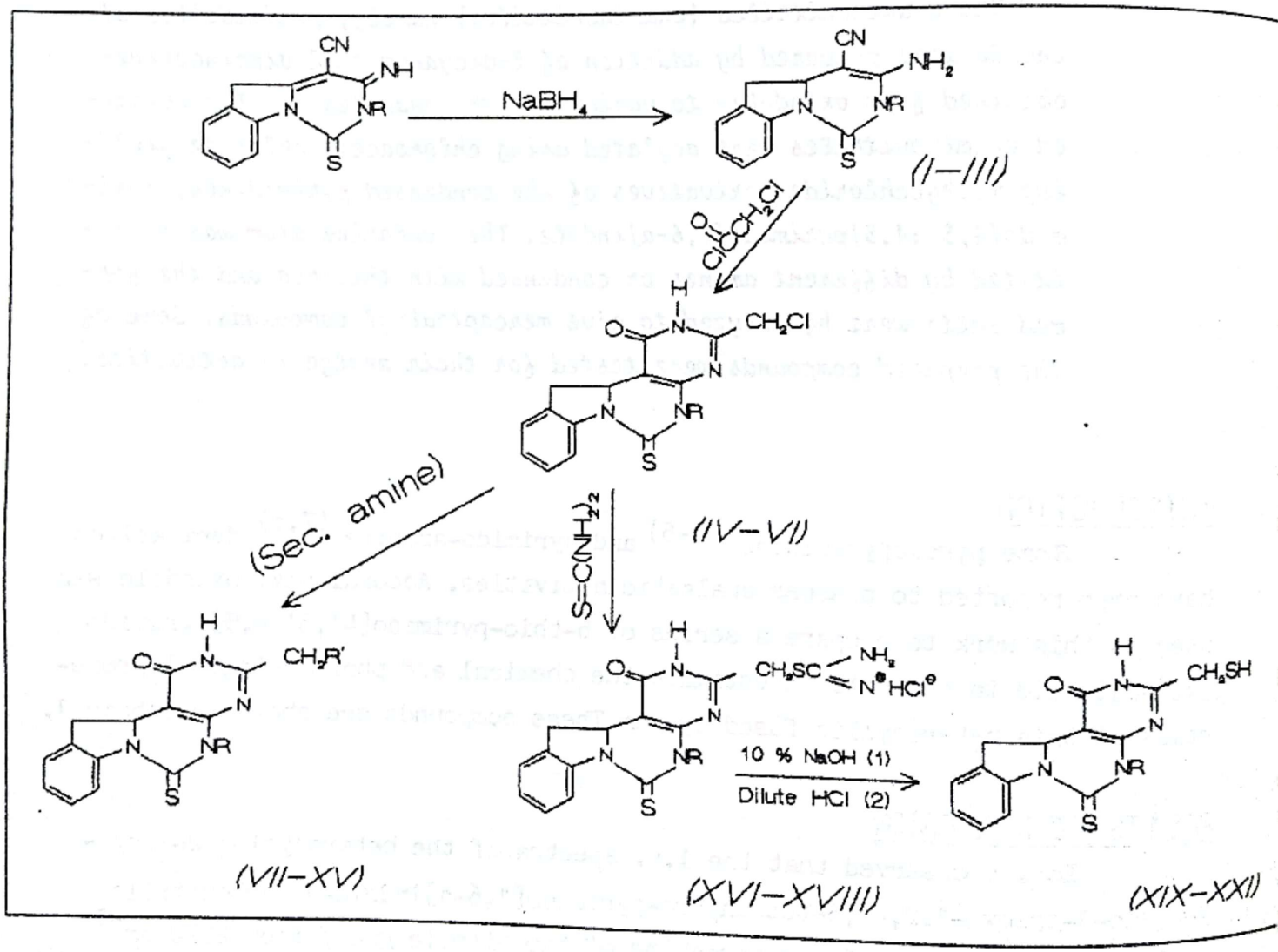
RESULTS AND DISCUSSION

It was observed that the i.r. spectra of the heterocycles 2-alkyl-3-amino-1-thioxo-1,2,4a,5-tetrahydro-pyrimido[1,6-a]indole-4-carbonitrile (I-III) show lowering of the streching of the nitrile group from 2220 cm^{-1} (typical for α,β unsaturated nitriles) to 2190 cm^{-1}, this lowering of 30 cm^{-1} can only be attributed to the conjugation of the amino group through the carbon-carbon double bond.

Chloroacylation of (I-III) proceeded at room temperature to afford crystalline compounds of concordant microanalytical data with the expected

chloroacylated compounds as confirmed by i.r. spectral analysis which revealed the absence of the nitrile band[2,9-11]. This acylation reaction provides a simple mean of preparation of substituted alkyl halides, thus after acylation of (I-III) at room temperature the tetracyclic structure 5-alkyl-3-chloromethyl-1-oxo-6-thio-12,12a-dihydropyrimido[4',5':4,5]pyrimido[1,6-a]2H,5H-indole(IV-VI) were obtained through acylation of the amino group and formation of oxazine intermediate, which undergoes rearrangement by acid liberated in the reaction[2].

Scheme 1



Finally the chlorine atom in the 3-chloromethyl derivatives was replaced with different amines to afford the substituted aminoalkyl derivatives (VII-XV), or it was condensed with thiourea to afford S-alkyl thiouronium salts(XVI-XVII), and the 3-mercaptoalkyl compounds(XIX-XXI) were obtained from the thiouronium salts by decomposition with alkali[7,12-14].

PHARMACOLOGICAL SCREENING

Four of the newly prepared compounds VI,IX,XI and XXI were screened for their analgesic properties.

Analgesic effect

The analgesic activity was determined using the writhing method according to Witkin et al[15]

p-Benzoquinone is given intraperitoneally in dose of 0.2-0.25 ml of 0.02% solution in normal saline 24 hours before the test, the mouse which exhibits writhing is considered sensitive to this method.

Mice weighing 20-30 g were assigned into 6 groups (10 mice each), 4 groups were used for test compounds VI, IX,XI and XXI in polyethylene glycol intraperitoneally in a molar ratio doses (51,51,51 and 50 mg/100 g) respectively. One group was used as control and the last group was given the standard (novalgin in a dose 45 mg/100 g). One hour later mice were given p-benzoquinone (0.2-0.25 ml of 0.02% solution in normal saline) intraperitoneally. Mice of each group were placed in aseparate glassy cage for observation and the number of protected animals were determined in each group. The results are shown in table (1) .

Table (1) The absolute and relative analgesic activity of the tested compounds to novalgin.

Compound	Absolute% protection of writhing	Relative% protection of writhing	Relative% potancy to novalgin
Novalgin	80	100	1.0
VI	60	75	0.8
IX	70	87.5	0.9
XI	70	97.5	0.9
XXI	80	100	1.0

Conclusion

It was found that compounds VI, IX and XI possess moderate analgesic activity while compound XXI has analgesic activity equal to that of novalgin .

EXPERIMENTAL

All melting points are uncorrected and determined by open capillary method using Cole Parmer digital apparatus. IR spectra were performed using Perkin- Elmer PE-298 spectrophotometer as KBr discs. Microanalysis was performed at the Microanalytical Center, Cairo University. ^{1}H NMR spectra were recorded on Varian T-60 spectrophotometer using $CDCl_3$ as solvent. Oxindole is available from Sigma Chemical Company .

2-Alkyl-3-amino-1-thioxo-1,2,4a,5-tetrahydro-pyrimido[1,6-a]indole-4-carbonitrile (I-III)

To a stirred mixture of 2-alkyl-3-imino-1-thioxo-1,2,3,4,4a,5-hexahydro-pyrimido[1,6-a]indole-4-carbonitrile [1] (0.1 mole) in absolute ethanol (20 ml), sodium borohydride (0.06 mole) was added in portions, and the stirring was continued for one hour. The reaction mixture was left to stand overnight at room temperature, the separated crystals were filtered, washed with water and recrystallized from ethanol (Table 2)

Table (2)

No	R	M.P°C	M.f & M.wt.		Microanalysis Calcd	Found
I	CH_3	163	$C_{13}H_{12}N_4S$ (256)	C	60.93	60.6
				H	4.68	4.4
				N	21.87	21.8
II*	C_2H_5	171	$C_{14}H_{14}N_4S$ (270)	C	62.22	62.5
				H	5.18	5.3
				N	20.74	20.7
III	C_4H_9	203	$C_{16}H_{18}N_4S$ (298)	C	64.43	64.6
				H	6.04	6.2
				N	18.79	18.7

* ^{1}H nmr (ppm) : 1.25 (t, 3H, CH_3); 3.15 (q, 2H, CH_2); 2.8 (d, 2H, CH_2); 3.7 (t, 1H, CH); 4.9 (s, br, 2H, NH_2); 6.9-7,3 (m, 4H, aromatic Protons).

5-Alkyl-3-chloromethyl-1-oxo-6-thio-12,12a-dihydropyrimido[4,5:4,5]pyrimido-[1,6-a]-2H,5H-indole (IV-VI)

A mixture of I-III (15 mmol), dry benzene (15 ml) and chloroacetyl chloride (17 mmol) was left to stand overnight at room temperature. the separated crystals were filtered and recrystallized from absolute ethanol (Table 3)

5-Alkyl-3-(disubstituted aminomethyl)-1-oxo-6-thio-12,12a-dihydropyrimido [4,5:4,5] pyrimido[1,6-a]-2H,5H-indole (VII-XV)

A mixture of IV-VI (15 mmol), benzene (15 ml) and appropriate disubstituted amine (17 mmol) was refluxed for 8 hours and then evaporated to dryness. The residue was dissolved in dilute hydrochloric acid and filtered. The filtrate was rendered alkaline with ammonia,extracted three times each with 15 ml chloroform; the combined chloroformic extract was washed with water and dried with anhydrous sodium sulphate, then evaporated in vacuum. The residue was recrystallized from absolute ethanol (Table 3)

5-Alkyl-3-(S-methylthiouronium chloride)-1-oxo-6-thio-12,12a-dihydropyrimido-[4;5': 4,5]pyrimido[1,6-a]-2H,5H-indole (XVI-XVIII)

A mixture of IV-VI (15 mmol) and thiourea (15 mmol), in ethanol (15 ml) was refluxed for 3 hours. After cooling the separated crystals were filtered and recrystallized from ethanol (Table 3).

5-Alkyl-3-mercaptomethyl-1-oxo-6-thio-12,12a-dihydropyrimido[4;5': 4,5]pyrimido[1,6-a]-2H,5H-indole (XIX-XXI)

Compounds XVI-XVIII were dissolved in an ice-cooled 10% sodium hydroxide (20 ml). The alkaline solution was acidified with hydrochloric acid to pH 4, the formed preciptate was filtered, washed with water and recrystallized from absolute ethanol (Table 3)

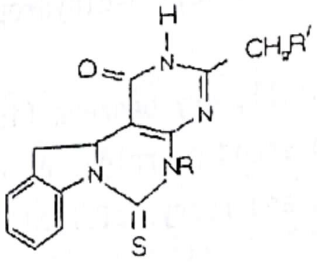
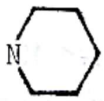
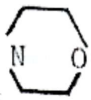
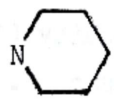
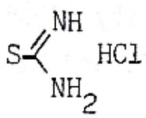
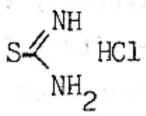
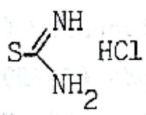


Table (3)

No	R	R'	M.P°C	M.f & M.wt.	Microanaylsis	Calcd.	Found
IV**	CH_3	Cl	217	$C_{15}H_{13}ClN_4OS$ (332.5)	C	54.13	54.3
					H	3.90	3.7
					N	16.84	16.8
V	C_2H_5	Cl	174	$C_{16}H_{15}ClN_4OS$ (346.5)	C	55.41	55.5
					H	4.32	4.3
					N	16.16	16.1
VI	C_4H_9	Cl	278	$C_{18}H_{19}ClN_4OS$ (374.5)	C	57.67	57.8
					H	5.07	5.0
					N	14.95	14.9
VII***	CH_3		192	$C_{19}H_{21}N_5O_2S$ (383)	C	59.53	59.7
					H	5.48	5.5
					N	18.27	18.2
VIII	CH_3		185	$C_{19}H_{21}N_5OS$ (367)	C	62.12	62.3
					H	5.72	5.6
					N	19.07	19.1
IX	CH_3		198	$C_{20}H_{23}N_5OS$ (381)	C	62.99	63.3
					H	6.03	6.1
					N	18.37	18.5

** ^1H nmr (ppm) : 2.90 (s, 3H, CH_3); 4.1 (s, 2H, CH_2Cl); 2.7 (d, 2H,CH_2); 3.5 (t, 1H, CH); 10.2 (s,br, 1H, NH); 7-7.4 (m, 4H, aromatic protons)

*** ^1H nmr (ppm) : 2.7 (m, 4H, CH_2-N-CH_2); 3.3 (s, 2H, $\rangle$-CH_2); 3.8 (m, 4H, CH_2-O-CH_2); 2.90 (s, 3H, CH_3); 10.2 (s, br, 1H, NH) .

No	R	R'	M.P°C	M.f & M.wt.	Microanalysis	
					Calcd	Found
X	C_2H_5		210	$C_{20}H_{23}N_5O_2S$ (397)	C 60.45	60.7
					H 5.79	5.5
					N 17.63	17.6
XI	C_2H_5		207	$C_{20}H_{23}N_5OS$ (381)	C 62.99	63.2
					H 6.03	6.2
					N 18.37	18.4
XII	C_2H_5		217	$C_{21}H_{25}N_5OS$ (395)	C 63.79	63.9
					H 6.32	6.2
					N 17.72	17.7
XIII	C_4H_9		222	$C_{22}H_{27}N_5O_2S$ (425)	C 62.11	62.6
					H 6.35	6.1
					N 16.47	16.5
XIV	C_4H_9		213	$C_{22}H_{27}N_5OS$ (409)	C 64.54	64.8
					H 6.60	6.4
					N 17.11	17.1
XV	C_4H_9		208	$C_{23}H_{29}N_5OS$ (423)	C 65.24	65.6
					H 6.85	6.6
					N 16.54	16.4
XVI	CH_3		218	$C_{16}H_{17}ClN_6OS_2$ (408.5)	C 47.00	47.3
					H 4.16	4.0
					N 20.56	20.5
XVII	C_2H_5		230	$C_{17}H_{19}ClN_6OS_2$ (422.5)	C 48.28	48.4
					H 4.49	4.4
					N 19.88	19.9
XVIII	C_4H_9		226	$C_{19}H_{23}ClN_6OS_2$ (450.5)	C 50.61	50.9
					H 5.10	5.3
					N 18.64	18.4

No	R	R'	M.P°C	M.f & M. wt.	Microanalysis Calcd	Found
XIX	CH_3	-SH	165	$C_{15}H_{14}N_4OS_2$ (330)	C 54.54	54.9
					H 4.24	4.1
					N 16.96	16.9
XX	C_2H_5	-SH	115	$C_{16}H_{16}N_4OS_2$ (344)	C 55.81	55.9
					H 4.65	4.8
					N 16.27	16.4
XXI	C_4H_9	-SH	136	$C_{18}H_{20}N_4OS_2$ (372)	C 58.06	58.3
					H 5.37	5.5
					N 15.05	15.1

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مشتقات جديدة للبريميدنيات المكثفة يحتمل أن يكون لها تأثير مسكن

السيد منصور لاشين
قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة الزقازيق

فى هذا البحث تم تحليل مشتقات بريميدنية مكثفة جديدة تسمى بيريميد و (١ و ٦-١) أندول ، وقد تم الحصول من هذه المركبات على مشتقات جديدة من سلاسل كلوريد الألكيل تسمى بيريميد و (٤و٥ : ٤و٥) بيريميدو (١و ٦-١) أندول التى إشتق منها الأمينات ومركبات الثيويوريا .

وقد تم إختبار بعض المركبات المحضرة كمسنات للألم .