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SYNTHESIS OF NEW CONDENSED PYRIMIDINES : III

Mohamed Y. Ebeid * , Sayed A. Lashine , Nageh A. Abou-Taleb and Lubna M. Abdel-Aziz

PHARACEUTICAL CHEMISTRY DEPARTMENT , FACULTY OF PHARMACY , *CAIRO UNIVERSITY AND ZAGAZIG UNIVERSITY

ABSTRACT

Acylation of the o-aminonitrile (enaminonitrile) derivatives of certain pyrimido- [1, 6-a] indole, with acid anhydrides or acid chlorides was achieved yielding a tetracylic structure, pyrimido- [4',5' : 4,5] pyrimido [1,6-a] indole. The chlorine atom in the chloroalkyl moiety was replaced by different amines or condensed with thiourea and the formed salts were hydrolyzed to give the mercapto alkyl compounds. Moreover, enaminonitriles were reacted with oxalyl chloride to afford the 3-chlorocarbonyl derivatives from which esters and amides were prepared. The 3-carboxylic acid derivtives were also prepared and subjected to decarboxylation . Some of the prepared compounds were tested for their pharmacological activties .

INTRODUCTION

The bridged nitrogen system , pyrimido [1,6-a] indoline [I] was obtained, by the addition of 2-dicyanomethrlidino indoline to alkyl isocyanates [1] . O-acylaminonitriles are of considerable interest[2] .

They are converted either by acid[3] or base[4] to condensed pyrimidines. Several reports have been considered for this conversion[5].

EXPERIMENTAL

All melting points were uncorrected and were determined by open capillary method. Microanalysis were performed by the Microanalytival Center , University of Cairo. IR spectra were determined on perkin-

Elmer PE-298 Spectrophotmeter using KBr discs. ^{1}Hnmr ws carried out in Faculty of Pharmacy, Cairo University , using JEOL FXQ 90 MHZ NMR Spectrometer .

3,5-Dialkyl-12 , 12a-dihydropyrimido [4', 5', : 4,5] pyrimido [1,6-a] indole - 1,6 (2H,5H) dione - (II-III) :

A mixture of I (0·01 mole) , acetic anhydride (15 ml) was refluxed for 4 hours . The reaction mixture was evaporated to dryness under vacuum and the residue was triturated with ethanol , the separated crystals were filtered and recrystallized from ethanol . (Yield 72%) .

5-Alkyl-3-phenyl or Substituted phenyl-12 , 12a-dihydro pyrimido [4', 5', :4,5] pyrimido 1,6 (2H,5H) dione . (IV-VII) :

A mixture of I (0.01 mole), benzene (10 ml) , the appropriate acid chloride (0.011 mole) and 2 drops of triethylamine was refluxed for 3 hours , the separated crystals obtained after cooling were filtered, washed with water and recrystallized from ethanol (Yield 71%) .

5-Alkyl-3-(chloromethyl) - 12,12a-dihydropyrimido [4', 5', 4,5] pyrimido [1,6 -a] indole - 1,6 (2H, 5H) dione (VIII - IX) :

A mixture of I (0.015 mole) , dry benzene . (15 ml) and chloro-acetyl chloride (0.017 mole) was left to stand overnught) . The separated crystals were filtered and recrystallized from absolute ethanol .

5-Alkyl - 3 -methylaminomethyl-12,12 a-dihydro pyrimido [4', 5', :4,5] pyrimido [1,6-a] indole 1,6 (2H,5H) dione (X-XI) :

A mixture of VIII or IX (0.01 mole) and methylamine in alcoholic solution (10 ml) was left to stand overnight and the solution was extract was dried over sodium sulphate , filtered, evaporated to dryness under vacuum and recrystallized from absolute ethanol (Yield 65%) .

5-Alkyk-3-diethylaminomethyl - 12,12a-dihydropyrimido - [4', 5', : 4,5] pyrimido [1,6-a] indole-1,6 (2H,5H) dione (XII - XIII) :

A mixture of VIII or IX (0.01 mole) and alcoholic diethylamine (10 ml) was refluxed for 4 hours . The reaction mixture was evaporated to dryness, water (10 ml) was dded and the mixture was extracted three times with chloroform , the combined chloroformic extract was dried over anhydrous sodium sulphate, filtered , evaporated to dryness under vacuum and the residue was crystallized from aqueous ethanol .

5-Alkyl -3- (substituted aminomethyl) 12 ,12a- dihydropyrimido [4', 5', : 4,5] pyrimido [1,6-a] indole -1,6 (2H,5H) dione (XIV - XIX) :

A mixture of VIII or IX (0.015 mole) , benzene (15 ml) and the approptiate secondary amine (0-017 mole) was refluxed in dilute hydrochloric acid and filltered . The filtrate was rendered dilute hydrochloric to dryness . The residue was dissolved in dilute hydrochloric acid and filltered . The filterate was rendered alkaline with ammonia , extracted three times each with 15 ml chloroform ; the combined chloroformic exteact was washed with water , dried over anhydrous sodium sulphate , filtered and evaporated to dryness under vacuum and the residue was crystallized from absolute ethanol .

5-Alkyl -3 (S-alkylthiouronium chloride) - 12, 12a - dihydropyrimido [4', 5', :4,5] pyrimido [1,6 - a] indole - 1,6 (2H, 5H) dione (XX-XXI) :

A mixture of VIII or IX (0.015 mole) and thiourea (0.015 mole) in ethanol (15 ml) was refluxed for 3 hours . After cooling the separated crystals were filtered and recrystallized from ethanol .

5- Alkyl -3- mercaptoalky - 12,12a - dihydro - pyrimido [4', 5', :4,5} pyrimido [1,6- a] indole - 1,6 (2H, 5H) dione (XXII - XXIII) :

Compound XX or XXI was dissolved in an ice - cooled 10% sodium hydroxide (20%) . The alkaline solution was acidified with hydrochloric acid to pH 4 when a precipetate was formed , filtered , washed with water and recrystallized from absolute ethanol .

5- Alkyl -3- chlorocarbonyl - 12,12a - dihydro - pyrimido [4', 5', :4,5} pyrimido [1,6- a] indole - 1,6 (2H, 5H) dione (XXIV - XXV) :

Oxalyl chloride (0.005 mole) was added to a mixture of I (0.005 mole) and dry benzene (15 ml) . The reaction mixture was kept at room temperture for 5 hours and the solvent was evaporated to drynees under vacuum , and used without separation for the following reactions.

Alkyl -5- Alkyl- 1,2,5,6,12,12a -hexahydro - 1,6- dioxopyrimido [4', 5', :4,5} pyrimido [1,6- a] indole - 3- carboxylate (XXVI - XXXI) :

To the reaction products XXIV - XXV , the appropriat measure of alcohol (20 ml) . was added and the reaction mixture was refluxed for two houts . The separted crystals were filtered and recrystallized from ethanol (Yield 85%) .

5- Alkyl-3-morpholinocarbonyl-12,12a -dihydropyrimido [4', 5', : 4,5} pyrimido [1,6- a] indole - 1,6 (2H, 5H) dione (XXXII - XXXIII) :

Morpholine (9.0 ml , 0.011 mole) and dry benzene (10 ml) were added to the 3 - chlorocarbonyl derivatives , XXIV or XXV. The reaction mixture was allowed to stand over night, then evaporated under vacuum . The residue was triturated with ethanol , filtered , washed with water and crystallized from ethnol (Yield 58%) .

5- Alkyl -1,2,5,6,12.12a - hexahydro -1,6 -dioxopyimido [4', 5', :4,5} pyrimido [1,6- a] indole - 3 - carboxylic acid (XXXIV- XXXV) :

A mixture of XXVI or XXVII (0.01 mole) and 10 % sodium carbonate solution (20 ml) was stirred untill completed dissolution wea obtained . The alkaline solution was filtered , acidified with hydricholric acid , the separated crustals were filtered , washed with water and recrystallized from ethanol . (Yield 80%) .

5- Methyl -12,12a - dihydropyrimido [4', 5', :4,5] pyrimido [1,6- a] indole -1,6 (2H, 5H) dione (XXXVI) :

A suspension of XXXIV (1.5 g) in 0.5 N hydrochloric cod (20 ml) was refluxed for 6 hours , cooled and filtered . The residue was washed with aqueous solution of sodium bicarbonate and crystallized from chloroform / absolute ethanol (Yield 70%)

Pharmacological Screening :

Compounds VIII, XVIII, XXIII and XXXIV were evaluated for their analgetic and antiinflammatory activities .

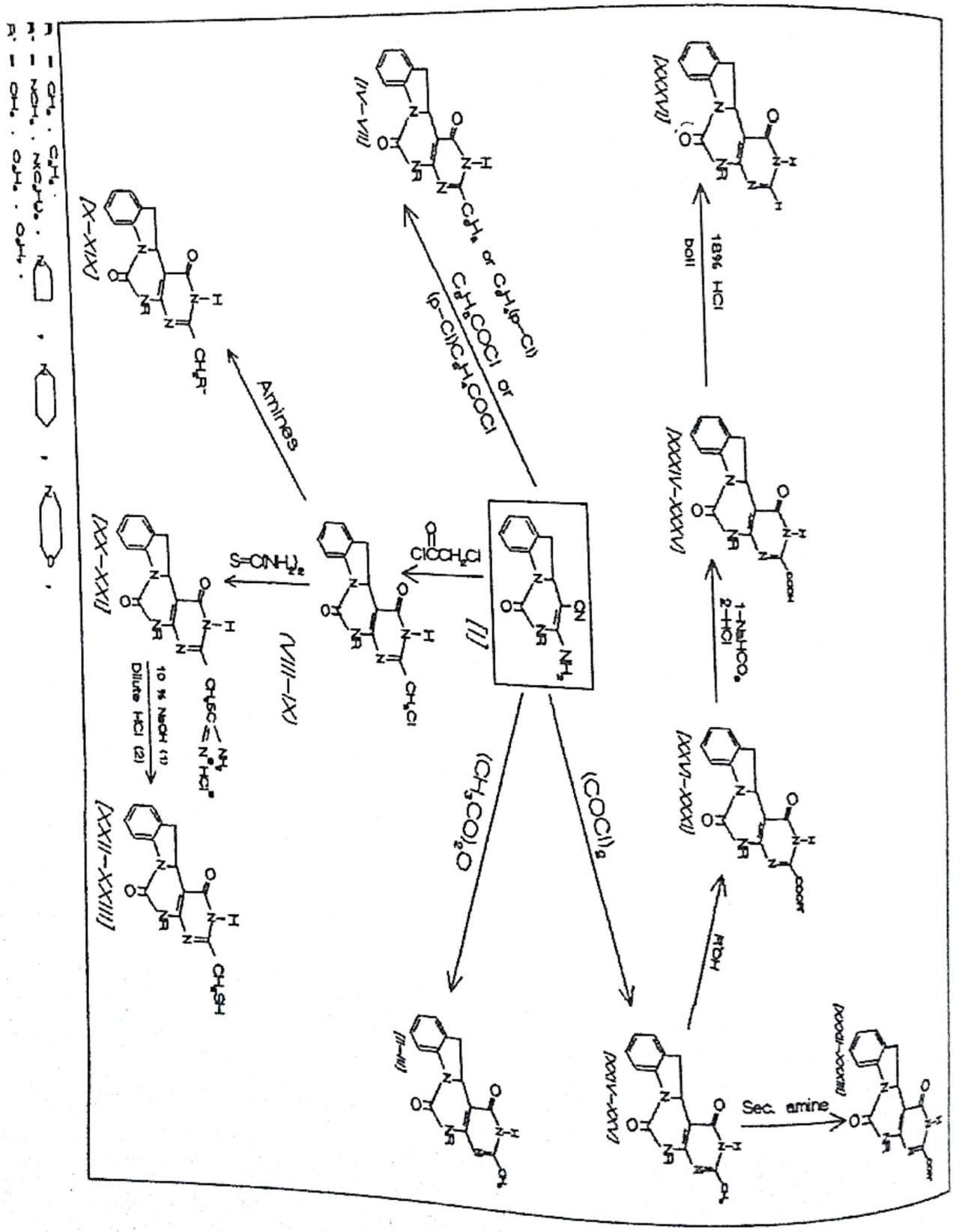
(1) Analgetic Effect :

The analgetic activity was determined using the writhing test carried out according to Witkin et al[11] method . Mice weighing 20-30 g were assigned into five groups (10 mice each) . The test compounds and antipyine were given orally as suspension in 5% gum acacia in molar ratio doses (135, 156, 140, 133 and 80 mg/kg), respectively . After one and half , mice were intraperitoneally injected with p-Benzoquinone (0.2 ml of 0.02% in normal saline) .

Mice of each group were placed in a seprate glass cage for obsevation and the number of the protected animals in each group was calculated (Table 1) .

(2) Antiinflammatory Effect :

The antiinflammatory activity of the selected compounds was determined using the rat hand paw oedema method[12] . Male rats weighing 120-180 g were divided into six groups (six rats each) .
Four groups received the tested compounds VIII, XVIII, XXIII and XXXIV intraperitoneally in propylene glycol in molar ratio doses (93, 107, 96, and 92 mg/kg), respectively . The remaining two groups , one was used as control group and received propylene in a dose of 55 mg/kg.


Amines
ClCOCH2Cl
S=C(NH2)2
(CH3CO)2O
(COCl)2
18% HCl
1-NaHCO3
2-HCl
ROH
Sec. amine
10 % NaOH (1)
Dilute HCl (2)

SCHEME I

Table (1): The absolute and relative analgetic activity of the tested compounds to antipyrine .

compound	absolute% of protection of writhing	Relative% protection of writhing	Relative% potancy to antipyrine
Antipyrine	90	100	1.0
VIII	60	67	0.7
XVIII	70	78	0.8
XXIII	70	78	0.8
XXXIV	80	89	0.9

Table (2): the absolute and relative antiinflammatory activity of the tested compounds to antipyrine.

Compound	Volume of oedema (mmhg)	%Volume of oedema	Absolute % inhibition of oedema	Relative% inhibition of oedema	Relative % potency to antipyrine
control	± 3.8	100.0	0.00	0.0	0.00
Antipy-rine	± 2.6	68.4	31.6	100	1.0
VIII	± 2.6	68.4	31.6	100	1.0
XVIII	± 3.4	89.5	10.5	33	0.33
XXIII	± 3.4	89.5	10.5	33	0.33
XXXIV	± 2.8	73.7	26.5	84	0.84

One and half hour after injection of the tested compounds , rats were subcutaneously injected with 100 ul of formalin solution (3.5 %) in the supplanter region of the right hand paw of each animal . A 100 ul saline solution was similarly injected in the left hand paw was measured using mercury plethysmograph immediately and four and half hours after injection of formalin was considered the volume of oedema and the value of inflmmation . The volume of oedema in the control group was considered as 100% .

RESULTS AND DISCUSSION

O-Aminonitrile derivative of pyrimido- [1,6-a] indoline [1] -, were reacted with different acylating agents such as acetic anhydride, benzoyl or p-chlorobenzoyl chloride and chloroacetyl chloride(6).

In no case the acyl derivative was isolated . However crystalline compounds were obtained , in high yield, the ir spectra of which were found to be lacking the nitrile absorption . This fact together with the elemental analysis indicated that the acyl derivatives underwent intramolecular cyclization(6-9) .

This facile acylation and intramolecular cyclization to the tetracyclic condensed pyrimidines was illustrated by chloroacetylation, carried out at room temperature in benzene. The crystalline compounds obtained quantitatively from this reaction were found to be missing the nitrile absorption in their ir spectra, which appeared at 2185 cm-1 in the ir spectrum of [I] indicating the formation of chloromethyl derivatives of the tetracyclic pyrimidines , presumed to have taken place through an acylaminonitrile intermediate followed by an acid catalyzed intramolecular rearrangement (during the work up) to carboxamide which is known to undergo readily intramolecular dehydration to a fused pyrimidone system (6-10).

In addition, the ir and elemental analysis data , found to be in concordance with our conclusion , the ^{1}Hnmr of 3,5-dimethyl-12,12a-dihydropyrimido [4',5': 4,5] pyrimido [1, 6-a] indole-1,6-[2H,5H] -dione (II) showed at δ 2.75 (s, 3H, CH3 at position 3) ; 3.65 (s, 3H, N-CH3) ;

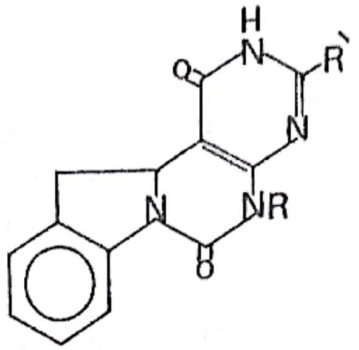
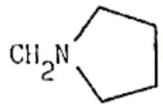
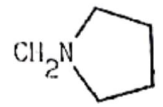
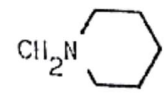
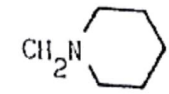
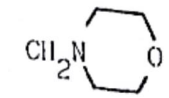
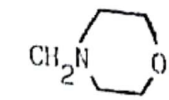
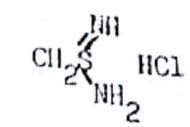


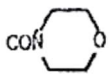
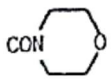
Table (3):

No.	R	R¯	M.P°C	M.f. & M.wt.		Microanalysis Calcd.	Found
II	CH_3	CH_3	255	$C_{15}H_{14}N_4O_2$ (282)	C	63.82	63.9
					H	4.96	4.8
					N	19.85	20.0
III	C_2H_5	CH_3	261	$C_{16}H_{16}N_4O_2$ (296)	C	64.86	64.7
					H	5.40	5.4
					N	18.91	19.0
IV	CH_3	C_6H_5	231	$C_{20}H_{16}N_4O_2$ (344)	C	69.76	69.7
					H	4.65	4.7
					N	16.27	16.4
V	C_2H_5	C_6H_5	293	$C_{21}H_{18}N_4O_2$ (358)	C	70.39	70.5
					H	5.02	5.1
					N	15.64	15.8
VI	CH_3	C_6H_4(p.Cl)	273	$C_{20}H_{15}ClN_4O_2$ (378.5)	C	63.40	63.3
					H	3.96	3.9
					N	14.79	14.8
VII	C_2H_5	C_6H_4(p.Cl)	288	$C_{21}H_{17}ClN_4O_2$ (392.5)	C	64.20	64.4
					H	4.33	4.3
					N	14.26	14.3
VIII	CH_3	CH_2Cl	205	$C_{15}H_{13}ClN_4O_2$ (316.5)	C	56.87	56.9
					H	4.10	4.1
					N	17.69	17.7
IX	C_2H_5	CH_2Cl	243	$C_{16}H_{15}ClN_4O_2$ (330.5)	C	58.09	58.3
					H	4.53	4.3
					N	16.94	17.1

Cont. Table (3)

X	CH_3	CH_2NHCH_3	210	$C_{16}H_{17}N_5O_2$ (311)	C	61.73	61.7
					H	5.46	5.5
					N	22.50	22.5
XI	C_2H_5	CH_2NHCH_3	217	$C_{17}H_{19}N_5O_2$ (325)	C	62.76	62.6
					H	5.84	5.7
					N	21.53	21.6
XII	CH_3	$CH_2N(C_2H_5)_2$	194	$C_{19}H_{23}N_5O_2$ (353)	C	64.58	64.6
					H	6.51	6.7
					N	19.83	19.8
XIII	C_2H_5	$CH_2N(C_2H_5)_2$	199	$C_{20}H_{25}N_5O_2$ (367)	C	65.39	65.4
					H	6.81	6.8
					N	19.07	19.1
XIV	CH_3		221	$C_{19}H_{21}N_5O_2$ (351)	C	64.95	65.1
					H	5.98	5.8
					N	19.94	19.9
XV	C_2H_5		238	$C_{20}H_{23}N_5O_2$ (365)	C	65.75	65.8
					H	6.30	6.4
					N	19.17	19.3
XVI	CH_3		255	$C_{20}H_{23}N_5O_2$ (365)	C	65.75	65.7
					H	6.30	6.3
					N	19.17	19.2
XVII	C_2H_5		261	$C_{21}H_{25}N_5O_2$ (379)	C	66.49	66.6
					H	6.59	6.5
					N	18.46	18.6
XVIII	CH_3		165	$C_{19}H_{21}N_5O_3$ (367)	C	62.12	62.1
					H	5.72	5.7
					N	19.07	19.1
XIX	C_2H_5		177	$C_{20}H_{23}N_5O_3$ (381)	C	62.99	62.8
					H	6.03	6.1
					N	18.37	18.4
XX	CH_3		219	$C_{16}H_{17}ClN_6O_2S$ (392.5)	C	48.91	48.8
					H	4.33	4.3
					N	21.40	21.4

Cont. table (3)

XXI	C_2H_5	$CH_2S(NH)NH_2$ HCl	235	$C_{17}H_{19}ClN_6O_2S$ (406.5)	C H N	50.18 4.67 20.66	50.2 4.7 20.7
XXII	CH_3	CH_2SH	166	$C_{15}H_{14}O_2N_4S$ (314)	C H N	57.32 4.45 17.83	57.4 4.5 17.9
XXIII	C_2H_5	CH_2SH	143	$C_{16}H_{16}O_2N_4S$ (328)	C H N	58.53 4.87 17.07	58.7 4.6 17.1
XXVI	CH_3	$COOCH_3$	266	$C_{16}H_{14}N_4O_4$ (326)	C H N	58.89 4.29 17.17	58.9 4.2 17.1
XXVII	C_2H_5	$COOCH_3$	234	$C_{17}H_{16}N_4O_4$ (340)	C H N	60.00 4.70 16.47	60.2 4.8 16.5
XXVIII	CH_3	$COOC_2H_5$	243	$C_{17}H_{16}N_4O_4$ (340)	C H N	60.00 4.70 16.47	60.1 4.6 16.6
XXIX	C_2H_5	$COOC_2H_5$	214	$C_{18}H_{18}N_4O_4$ (354)	C H N	61.01 5.08 15.81	61.2 5.2 15.8
XXX	CH_3	$COOC_3H_7$	173	$C_{18}H_{18}N_4O_4$ (354)	C H N	61.01 5.08 15.81	61.1 5.2 15.9
XXXI	C_2H_5	$COOC_3H_7$	162	$C_{19}H_{20}N_4O_4$ (368)	C H N	61.95 5.43 15.21	61.9 5.5 15.3
XXXII	CH_3		249	$C_{19}H_{19}N_5O_4$ (381)	C H N	59.84 4.98 18.37	59.9 4.9 18.3
XXXIII	C_2H_5		221	$C_{20}H_{21}N_5O_4$ (395)	C H N	60.75 5.31 17.72	60.9 5.2 17.9
XXXIV	CH_3	COOH	235	$C_{15}H_{12}N_4O_4$ (312)	C H N	57.69 3.84 17.94	57.8 3.9 17.9
XXXV	C_2H_5	COOH	223	$C_{16}H_{14}N_4O_4$ (326)	C H N	58.89 4.29 17.17	58.8 4.2 17.1
XXXVI	CH_3	H	228	$C_{14}H_{12}N_4O_2$ (268)	C H N	62.68 4.47 20.89	62.8 4.4 20.9

4.7 (s, br, 1H, NH); 2.9 (d, 2H, CH2); 3.3 (t, 1H, CH) ; 7.4 (m, 4H, aromatic protons), while ^{1}Hnmr of compound [VIII] appeared at δ 4.1 (s, 2H, CH_2-C1) .

Finally the chlorine atom in the chloromethyl moiety was substituted with different amines to afford the correspnding substituted aminomethyl derivatives or condensed with thiourea and the formed salts were hydrolyzed to give mercaptomethyl compounds .

Oxalyl chloride similar to other acid chlorides gave from its reaction with 3-amino derivatives [I] the corresponding acid chloride derivratives [XXIV-XXV] which were used without separation to prepare a series of esters [XXVI-XXXI] and amides [XXXII-XXXIII] . In addition, the parent acids [XXXIV-XXXV] were readily obtained from the corresponding esters [XXVI-XXXI] by alkaline hydrolysis. Decarboxylation was accomplished by boiling with 0.5N hydrochloric acid giving the corresponding compound 5-alkyl-12,12a-dihydropyrimido- [4' , 5', :4,5] pyrimido [1,6-a] indole-1,6 [2H,5H] dione [XXXVI] .

CONCLUSION

From the previously mentioned preliminary pharmacological data it could be concluded that the tested compounds possess moderate analgetic activity while compounds VIII and XXXIV demonstrate a marked antiinflammatory activity compared to antipyrine .

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تخليق بيريميدينيات مكثفة جديدة :٣

محمد عبيد* - السيد لاشين - ناجح ابو طالب - و لبنى عبد العزيز
- قسم الكيمياء الصيدلية -كلية الصيدلة - *جامعة القاهرة - و جامعة الزقازيق

تم فى هذا البحث أسترة مشتقات الاينامينونيتريل لبعض بيريميدو (٦،١ - أ) اندول باستخدام حامض الخليك اللامائى و كلوريدات الاحماض و نتج عن ذلك مركبات رباعية الحلقات و هى بيريميدو (٥،٤ : ٥،٤) بيريميدو (٦،١ -أ) اندول. و قد تم احلال ذرة الكلور فى هذة المركبات ببعض الأمنيات أو التكثيف مع الثيويوريا. و قد تم كذلك تفاعل الاينامينونيتريل مع كلوريد حامض الاكساليك للحصول على ناتج التفاعل على مركبات مختلفة.

و قد تم اجراء اختبارات أقربا زينية أولية على ٤ مركبات من هذة المركبات و قد ظهر لها تأثير كمسكنات و مضادات للالتهابات بالمقارنة بعقار الأنتيبيرين.