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Synthesis and Biological Activity of 2-methyl-3-nitropyridine Derivatives

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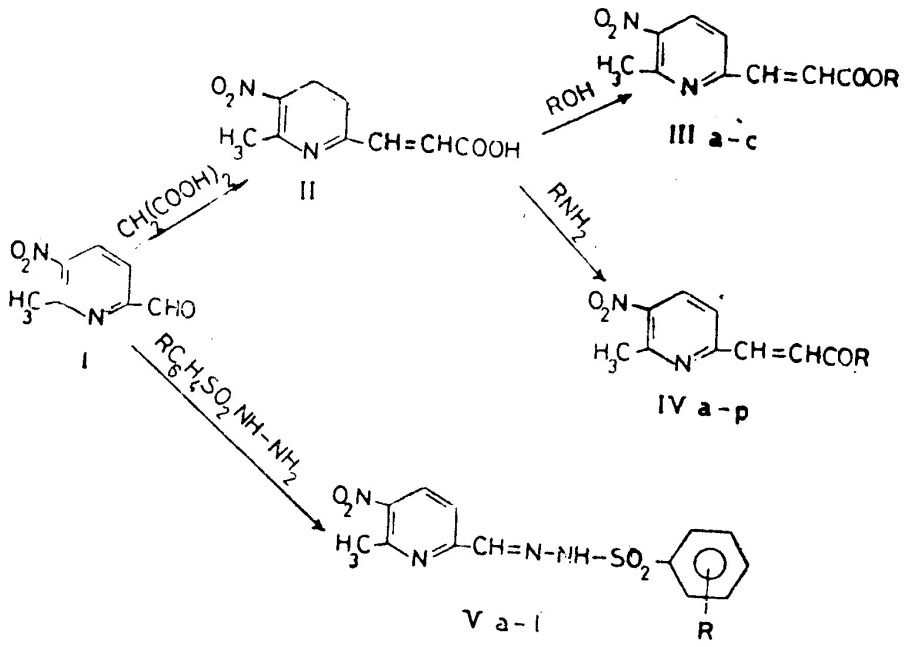
CONDENSATION of 2-methyl-3-nitropyridyl-6-carboxal dehyde(I) with malonic acid under the conditions of Knoevenagel reaction yielded mixture of cis and trans acrylic acids in the ratio of ca. 1 : 2. The mixture was used for the preparation of the acid derivatives. Condensation of the aldehyde (I) with benzenesulphonyl hydrazines is stereoselective and the syn configuration was assigned to the main product of the reaction. The hydrazones were evaluated against poultry helminth, Ascaridia galli and against S. aureus and E. coli. The esters and amides of acrylic acid were tested as antiparasitic agents against E. histolytica and B. coli.

The biochemical effect of pyridine homologues on binding to cytochrome P- 450 and diminishing the respiratory rate of bovine heart mitochondria were reported [1,2]. At the same time little is reported in the literature about the nitropyridine homologues as biologically active compounds. 2-Acylamino-5nitropyridines elicited trichomonostatic activity weaker than the nitrothiazole analogues [3,4]. Anticoccidial activity was assigned to-2-methyl-5-nitronicotinamide derivatives [5]. N-alkylidenyl (arylidenyl)-2-methyl-3-nitropyridine-6- carboxaldehyde hydrazones and N-acyl-2-methyl-3-nitropyridine-6-carboxaldehyde hydrazones were recently synthesized in our laboratories and some of these derivatives revealed activity equal to that of sulphanilamide against S. aureus and E. coli [6]. Study of structure activity relationship of certain nitrofuryl acrylamides [7,8] and certain pyridine derivatives [9] showed that the ethylene (-CH = CH-) and the azomethine (-CH = N-)moieties are essential substituents in the αposition to elicit antiparasitic activity. Moreover, some N-benzenesulphonyl-2-(4-nitropyridyl) formyl hydrazones were recently reported to possess antineoplastic activity[10,11]. This report deals with the synthesis and preliminary study of the antibacterial and antiparasitic potentialities of the 2-methyl-3-nitro-6-pyridyl moiety. Two series were prepared; a) acrylic acid esters III and amides IV, and b) hydrazone derivatives V:

Experimental

Melting points were determined on Electrothermal melting point apparaturs and are uncorrected. Microanalyses were performed at Microanalytical Centre, Cairo University and El-Nasr Pharm. Chem. Co.



Scheme I

Abou-Zaabal, Cairo. Infrared spectra were recorded on Pye Unicam SP 1000 Infrared spectrophotometer in kBr discs. NMR spectra were deter mined on T 60 ANMR spectrometer (VARIAN). Mass spectra were run on Finnigan 3200 Gas chromatography -Mass spectrometer.

3-(2-*Methyl*-3*nitro*-6-*pyridyl acrylic acid* (*II*)

The acid was prepared from (I) ([12]) and malonic acid under the conditions of knoevenagel reaction.

3-2-(*Methyl*-3- *nitro*-6-*pyridyl*) *acrylic acid esters* (*III a-c*)

The following general procedure was adopted:

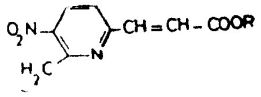
The acid II (2·08 g,0·01 mole) was dissolved in the appropriate alcohol (40ml) conc. sulphuric acid (3 ml) was slowly added and the mixture was refluxed for 5 hr. After cooling, the mixtures was neutralized to litmus with 10%sodium carbonate solution and the separated mass was filtered and recrystallized from the appropriate solvent (Table 1).

3-(2-*Methyl*-3- *nitro*-6- *pyridyl*) *acrylamide* (*IVa*)

To the suspension of III b (lg, 0·042 mole) in water (5ml),conc. ammonia solution (30ml) was added. After 24 hr a stream of ammonia gas was

Table 1. 3-(2-Methyl-3-nitro-6-pyridyl) acrylic acid esters

(III)



III	R	Yield %	M.P.°C	Solvent of Crystallization	Mol. Formula	Microanalysis: Calc. /found		
						%C	%H	%N
a	CH_3	63	126—7	isopropanol and pet ether (60—80)	$C_{10}H_{10}N_2O_4$	54.05 53.90	4.50 4.80	12.61 12.68
b	C_2H_5	79	94—5	ethanol	$C_{11}H_{12}N_2O_4$	55.93 56.30	5.08 5.10	11.86 11.92
c	$CH(CH_3)_2$	71	82—4	ethanol	$C_{12}H_{14}N_2O_4$	57.60 57.40	5.60 5.10	11.20 11.34

passed in the reaction mixture, while keeping the temperature below 5°C, till saturation and the mixture was left in the refrigirator for 5 days. The precipitate was filtered and recrystallized from a mixture of isopropanol and pet. ether (Table 2).

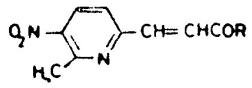
N-substituted 3-(2-*methyl*-3-*nitro*-6-*pyridyl*) *acrylamides* (*IVbp, Table* 2):

To the suspension of II (2·08 g, 0·01 mole) in methylene chloride (20ml), dicyclohexylcarodiimide (2·06g, 0·01 mole) and the appropriate amine (0·01 mole) were added and the mixture was left overnight in the refrigirator. The reaction mixute was then processed by either procedure A or B.

Procedure A

the reaction mixture was filtered, washed with methylene chloride. The afiltrate and washings were evaporated to dryness and the residue was triturated with 2N H Cl (25 ml), filtered, washed successively with water (50 ml), 5% $NaHCO_3$ solution (25 ml) and then with water.

Table 2 3-(2-Methyl-3-nitro-6-pyridyl) acrylamides (IV)



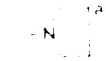
IV	R	Yield %	M.P.°C	Solvent of crystallization	Mol.Formula	Microanalysis: Calc./found		
						%C	%H	%V
a	$-NH_2$	57	214—5	iso propanol/ pet ether (60-80)	$C_9H_9N_3O_3$	52.17 52.80	4.35 4.80	20.29 20.70
b	$-N^{a}(CH_3)_2$	85	175—6	ethanol	$C_{11}H_{13}N_3O_3$	56.17 56.30	5.53 5.90	17.87 17.95
c	$-N^{a}(C_2H_5)_2$	64	177—9	isopropanol/pet. ether	$C_{13}H_{17}N_3O_3$	59.32 59.50	6.46 6.50	15.97 15.82
d	$-NHCH_a(CH_3)_2$	83	130—2	" "	$C_{12}H_{15}N_3O_3$	57.83 57.40	6.02 6.10	16.87 17.04
e	$-NHC_4H_9(n)a$	81	145—6	" "	$C_{13}H_{17}N_3O_3$	59.32 59.00	6.46 6.30	15.97 15.90
f	$-NHC_6H_{11}a$	92	145—6	" "	$C_{15}H_{19}N_3O_3$	62.28 62.80	6.57 6.70	14.53 14.80
g		71	189—90	isopropanol	$C_{13}H_{15}N_3O_3$	59.77 59.50	5.74 6.10	16.09 15.84
h		60	109—11	isopropanol/ pet ether (60-80)	$C_{14}H_{17}N_3O_3$	61.09 61.50	6.18 6.30	15.27 15.26
i		94	148—9	H_2O	$C_{13}H_{15}N_3O_4$	56.31 56.27	5.41 5.19	15.16 14.83
j	$-NHC_6H_5b$	98	152—4	ethyl acetate	$C_{15}H_{13}N_3O_3$	63.60 53.30	4.59 5.00	14.84 13.86
k	$-NHC_6H_4Cl(o)a$	92	180—1	ethanol	$C_{15}H_{12}ClN_3O_3$	56.68 57.10	3.78 4.10	13.22 12.99

TABLE 2. (Cont.)

IV	R	Yield	M.P.°C	Solvent of Crystallization	Mol. Formula	Microanalysis:Calc/foud		
						%C	%H	%N
l	-NHC$_6$H Br(p)b	52	226—7	isopropanol/ ethano	$C_{15}H_{12}BrN_3O_3$	49.72 50.00	3.31 3.60	11.60 11.30
m	-NHC$_6$H$_4$CH a(o)	70	149—51	ethyl acetate	$C_{16}H_{15}N_3O_3$	64.65 64.90	4.05 5.00	14.14 14.21
n	-NHC$_6$H$_4$CH$_3$ (p)b	77	191—2	ethanol	$C_{16}H_{15}N_3O_3$	64.65 64.60	5.05 5.40	14.14 14.11
o	-NHC$_6$H$_4$NO$_2$ a(o)	50	189—90	*ethanol* acetate	$C_{15}H_{12}N_4O_5$	54.88 54.90	4.66 3.90	17.07 17.07
	-NHC$_6$H$_4$NO$_2$ a(p)	46	272 (dec.)	ethanol/dioxane	$C_{15}H_{12}N_4O_5$	54.88 55.00	3.66 3.90	17.07 16.93

a) Isolated according to procedure (A). b) Isolated according to procedure (B)

Procedure B

The dicyclohexylurea floating on the surface of the reaction mixture was removed as much as possible by decantation and the remaining suspension was dried by distillation of the solvent. The residue was triturated with 2N HCl (25ml) and filtered, the residue washed with water (50 ml), 5% $NaHCO_3$ (25ml) and finally with water.

General method for synthesis of N-benzenesulphonyl-2- methyl- -3-nitropyridine-6-carboxaldehyde hydrazones (*V*a -l)

To the ice cooled solution of aldehyde I (8·3 g, 0·05 mole) in methanol (15ml), the solution of the appropriate benzene sulphonyl hydrozine ([3]) (0·06 mole) in methanol (50ml) was added with stirring. The mixuure was allowed to warm to room temperature and stirring was continued for further one hour. The reaction mixture was left overnight in a refrigirator. The solid separated was filtered , washed with cold methanol, dried and recrysta llized from the appropriate silvent (Table 3).

Thin layer chromatography of compound V c

Adsorbent : neutral alumina

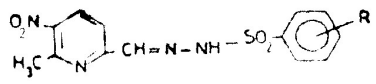
The systems used for separation and the R_f values :

1- Benzene - ethyl acetate (4:96), R_f =0·5.

2- Methanol- water (1:99), R_f = 0·55.

3- Methanol- water -acetic acid (5:4:1), R_f=0·58.

TABLE 3. N-(substituted benzenesulphonyl)-2-methyl-3-6-pyridyl formyl hydrazones (V)



V	R	Yield %	M.P.°C	Solvent of crystallization	Mol. Formula	Microanalysis: Calc./ found		
						%C	%H	%N
a	H	83	130—2	ethyl acetate	$C_{13}H_{12}N_4O_4S$	48.75 48.60	3.75 3.70	17.50 18.00
b	p-CH_3	75	125	Benzene	$C_{14}H_{14}N_4O_4S$	50.29 50.40	4.10 4.20	16.76 16.90
c	p-OCH_3	6	120—2	ethanol	$C_{14}H_{14}N_4O_5S$	48.00 48.30	4.00 3.60	16.00 15.70
d	m-OCH_3	50	108	ethyl acetate	$C_{14}H_{14}N_4O_5$	48.00 48.00	4.00 3.80	16.00 15.30
e	p-NO_2	95	185	" "	$C_{13}H_{11}N_5O_6S$	40.27 40.30	3.01 3.10	19.15 19.30
f	m-NO_2	82	136	" "	$C_{13}H_{11}N_5O_6S$	40.27 41.10	3.01 2.90	19.15 18.60
g	p-Cl	65	128—30	" "	$C_{13}H_{11}ClN_4O_4S$	44.01 44.40	3.10 3.30	15.79 16.00
h	m-Cl	80	119—21	ethyl acetate	$C_{13}H_{11}ClN_4O_4S$	44.01 44.40	3.10 3.20	15.79 15.68
i	p-Br	60	128—30	" "	$C_{13}H_{11}N_4O_4S$	39.10 38.90	2.75 2.90	14.04 14.50
j	m-Br	91	124—6	" "	$C_{13}H_{11}BrN_4O_4S$	39.10 39.10	2.75 2.40	14.04 14.10
k	p-NH $COCH_3$	70	152—4	" "	$C_{15}H_{15}N_5O_5S$	47.74 47.30	3.97 4.30	
l	p-Coo Et	91	130—2	" "	$C_{10}H_{10}N_4O_6S$	48.90 48.50	4.08 4.10	14.28 13.57

The experiments were carried out at room temperature and the separated spot was recognized by its faint yellow colour.

Preparation of Cu (II) complex (VI)

To the solution of the hydrazone Vc (0.3 g, 0.001 mole) in methanol(15ml), the solution of Cu (II) acetate (0.182) g, 0.001 mole) in methanol (50 ml) was added. The mixture was stirred for 48 hr at room temperature. The produced precipitate was purified by repeated washing with hot methanol. Preparative TLC was applied using DMF/H_2O (1:99) system for complete purification. Yield 0.47 g (90%). m.p. 176C(decompn). Analysis required by the formula $C_{18}H_{20}N_4O_9S$ Cu: % C 40.6, % H 3.7, % N 10.5. Found values are % C 41.8, %H 3.8, % N 10.8.

Biological screening

A) Antiparasitic activity of acid II, esters III a,c, and amides IV a-g were determined against Entamoeba histolytica and Balantidium coli.

B) Antiparasitic activity of hydrazones Va, b,e,g, and l (Table 3) was evaluated against Ascaridia galli by two methods :

(1) *In vitro testing*

Materials and method

— Alcoholic solutions 0.8% w/v of the tested compounds (solution a).

— Aqueous sloutions of ethanolamine salts of the test compounds in concentration 0.8% w/v (equivalent to the tested compound (solutdion b)

— Worms used were Ascaridia galli of poultry isolated from naturally infected groups.

Method: The petri dish method [14] was applied for testing the antiparasitic activity. The worms of Ascardia galli were washed with saline immediately after removal from the intestine of poultry. The aliquotes of 1,2,3ml of solution (a) and that of solution (b) were added to 20 ml of saline. To this mixture, in each petri dish, two worms (freshly isolated and washed with saline) were added. The time elapsed to induce relaxation or complete death of the parasite was recorded.

(2) *In vivo testing*

Materials

Suspensions of 3% w/v of the same compounds tested in vitro in 1% carboxymethylcellulose were prepared.

Dose 300 mg/kg (10 ml suspension) was used.

- Naturally infected chickens each of about 1 kg body weight were used.

Method : Each infected chiken was given orally a single dose of 300 mg/kg for three successive days. After each day, the stool was examined. At the end of the third day, the chicken was sacrificed and examined for presence of Ascaris worms. If worms were present, they were immediately placed in saline to examine their vitality.

C—*Antibacterial activity* : Solutions of compounds Va-c,e,g,i, k and l (Table 3) in dimethylformamide in 1 mg/ml conc. were tested against S. aureus and E. coli by the disc-agar diffusion method.

Discussion

a) *Chemical*

The conditions of knoevenagel reaction were adopted for the synthesis of 3-(2-methyl-3-nitro-6-pyridyl) acrylic acid (II) from aldehyde (I) and malonic acid. This reaction may yield exclusively trans or mixture of cis and trans isomers([15]) In a previous work ([16]), investigation by n.m.r. spectroscopy revealed the abundance of both cis and trans isomers of (II) in the ratio of ca. 1:2 respectively([16]). The mixture of isomers was used for further synthesis of the esters (III) and the amides (IV) listed in Tables 1 and 2 respectively. The esters were prepared from the acid (II) in presence of sulphuric acid as a catalyst. The substituted amides (IV) were prepared by reacting equivalents of the acid, amine and dicyclohexylcarbodimide under conventional conditions (scheme 1). The hydrazones (V) listed in Table 3 were prepared via the condensation of the aldehyde (I) and the appropriate benzenesulphonyl hydrazines. The i.r. spectra of these compounds revealed the characteristic vibrational bands ν 3260-3280 cm^{-1} (NH), ν 1560-1580 cm^{-1} (C = N), ν 1520-1540 cm^{-1} (NO_2), ν 1320-1370 cm^{-1} (NO_2), ν 1360-1380 cm^{-1} (SO_2), ν 1160- 1180 cm^{-1} (SO_2). The compounds Vk and VI showed in addition the bands at 1685 and 1705 cm^{-1} respectively assigned to (C=O) group. The n.m.r. spectrum of the compound (V g), taken as a model, showed signals at δ 2.75 (singlet; 3H: 2-CH_3), δ 3.2 (singlet; 1 H/6-CH), δ 7.8 (multiplet; 6H : 2,3,5 6-H of benzne + 5-H of pyridine + SO_2 NH). On addition of D_2O the NH proton disappeared and the multiplet centered at δ 7.8 was integrated by five protons only. The 4-H of pyridine shows up as a AX doublet at 8.4.

The mass spectral data for the representatives V c and g are given in Tables 4-6. As a common pattern, the molecular ion peaks of these compounds could not be identified. This may be attributed to the instability of their molecular ions under the effect of the electron impact. The fragmentation patterns of these compounds can be represented by schemes (2-6). The fragment A was identified in the m.s. spectra of all the investigated compounds. The residue of the molecule after cleavage of A retains an m/e value dependent on the nature of R. where R = Cl the fragment B was identified together with A. On the otherhand, C and A were detected in cases of R=OCH_3.

The apparent difference in the fragmentation of the compound V g (R = Cl) and compounds V c & VI (R = OCH_3) to give fragments B and C respectively may be correlated wih electron donating potential of

the substituent R as expressed in R values; Cl = -0 16 and OCH_3 = -0·5. [11] when the strong electron donating group is conjugated with the moiety – CH =$NNHSO_2$, the C—N and the N—S bonds are cleaved spontaneously.

Table 4. Fragment ions from part A.

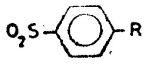
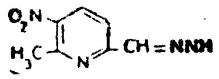


TABLE 4. **Fragment ions from part A.**

Compound No.	R	Fragment ion	m/e*	Relative abundance*
Vc	OCH_3			
		$C_7H_7O_3S$	171	100.0
		$C_7H_8O_3S$	170	38.7
		$C_6H_5O_3S$	157	25.8
		$C_6H_4O_3S$	156	3.2
		C_6H_4O	92	4.8
		C_6H_5	77	4.8
		C_6H_4	76	16.1
		C_5H_4	64	6.0
		C_4H_3	51	12.9
		C_3H_3	39	32.3
Vg	Cl			
		$C_6H_4ClO_2S$	175 (177)	55.8 (18.6)
		C_6H_4ClOS	159 (161)	76.8 (25.6)
		C_6H Cls	143 (145)	27.9 (9.3)
		C_6H_5Cl	112 (114)	74.4 (25.1)
		C_6H_4Cl	111 (113)	79 1 (26.5)
		C_6H_5S	108	27.9
		C_6H_5	77	100.0
		C_6H_4	76	27.9
		C_4H_3	51	60.4
IV	OCH_3			
		$C_7H_7O_3S$	171	18.8
		$C_6H_4O_2S$	156	15.7
		C_6H_4S	108	56.3
		C_6H_4O	92	25.0
		C_6H_5	77	37.5
		C_5H_5	65	100.0
		C_5H_4	64	31.3
		C_5H_3orCu	63	37.5
		C_4H_3	51	31.3
		C_3H_3	39	56.2

* Values between brackets correspond to ^{37}Cl.

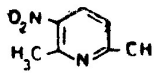
Table 5: Fragment ions from part B identified in compound



Fragment ion	m/e	Relative abundance*
$C_7H_7N_4O_6$ . .	179	9.3
$C_7H_6N_4O_5$. . .	178	55.8
$C_7H_8N_4O$ . . .	161	25.6
$C_6H_6N_3O_4$. . .	152	9.3
$C_6H_5N_3O_4$. . .	151	90.7
$C_7H_7N_3O_2$ or		
$(C_7H_5N_2O_3)$ . .	149	7.0
$C_7H_7N_3$ . . .	133	7.0

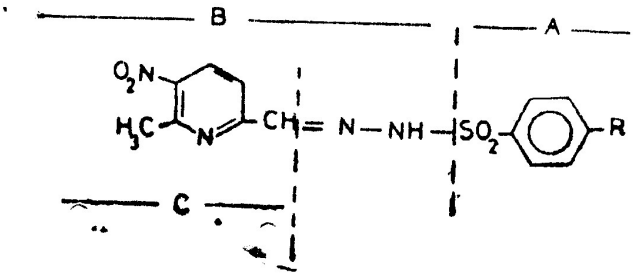
* Abundances are relative to the base peak m/e 77 table (4)

Table 6: Fragment ions from part C identified in compounds



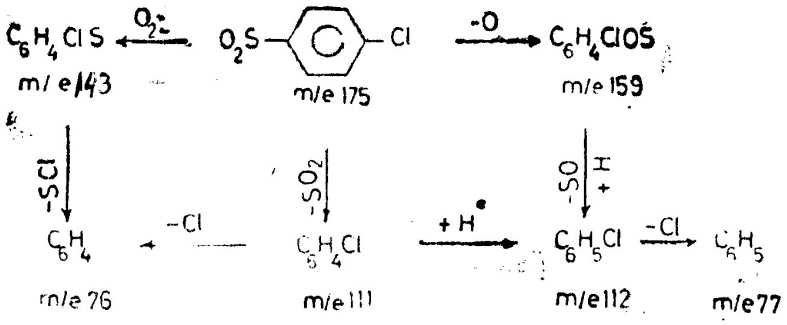
Fragment ion	m/e	Relative abundance*	
		Vc	VI
$C_7H_6N_2O_2$ . .	150	11.0	8.0
$C_7H_5N_2O$ . .	133	6.5	7.0
C_7H_6N . . .	104	5.0	4.0
C_7H_5N . . .	103	7.0	4.0
C_5H_5	77	4.8	37.5

*Abundances are relative to the base peak m/e 171 (table 4)

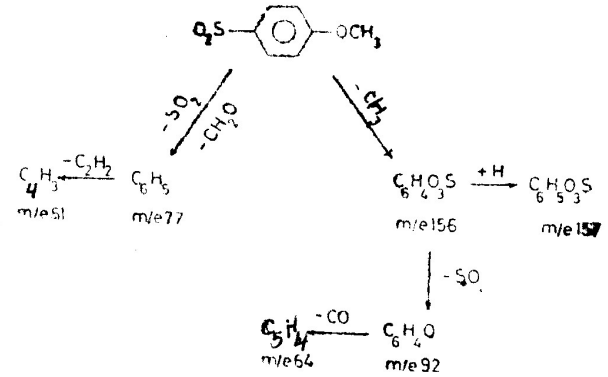


R = Cl, OCH_3

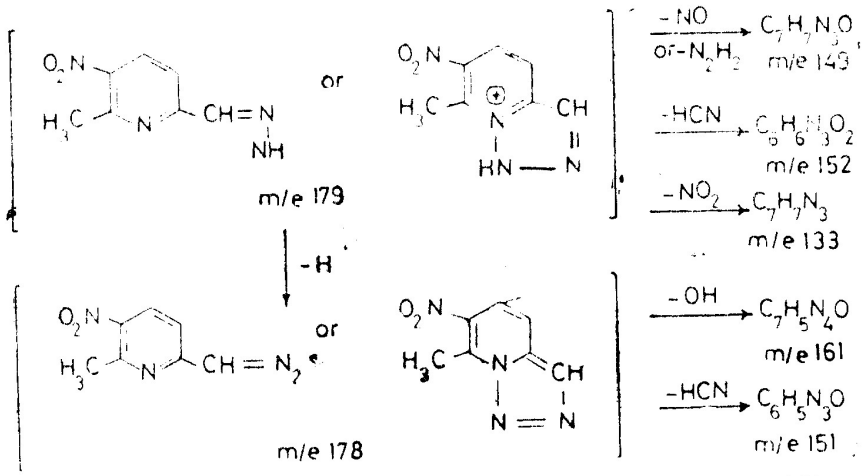
Scheme 2 : key path way of fragmentation.



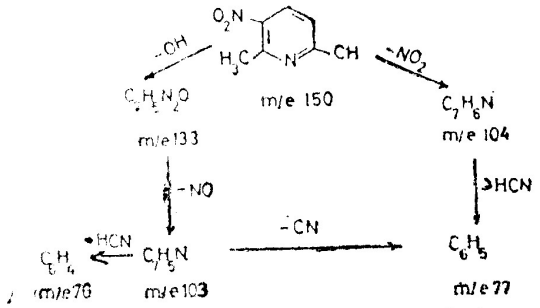
Scheme 3 : Fragmentation pattern of part A (R = Cl).



Scheme 4 : Fragmentation pattern of part A (R = OCH_3).



Scheme 5 : Fragmentation pattern of part B identified in compound V g.



Scheme 6 : Fragmentation pattern of part C identified in compounds Vc and VI

Stereoselectivity of the reaction of hydrazone formation

In principle, the reaction of aldehyde (I) and substituted benzenesulphonyl hydrazines might yield either a single configuration or mixture of syn and anti forms. Compound V-c was taken as a model and chromatographed by TLC over neutral alumina using three different systems with different polarities. The location of a single spot with all developing systems was taken as evidence for the uniformity of the compound as a single isomer. Exploitation of the high potential of the the syn isomer to form six-membered ring of metal chelate was taken to prove that the isolated compound is the syn isomer.

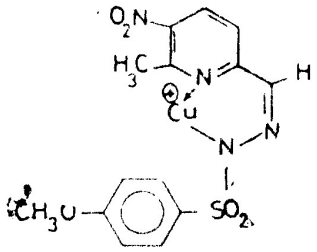
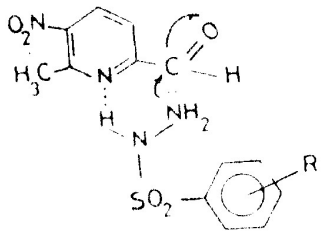


Fig. 1 : Metal chelate (VI) of the syn configuration of compound Vc.

The Cu (II) complex (VI) prepared from hydrazone V-c was identified by i.r. and m.s. spectroscopy. The i.r. bands at 2960 cm^{-1} (CH_3), 1580 cm^{-1} (C = N), 1540 cm^{-1} (NO_2) and 1380 cm^{-1} (SO_2) were recognized. The m.s. of VI showed the characteristic m/e fragments common with the fragments detected in th spectrum of compound V-c (Tables 4 and 6). The metal-ligand ratio 1 : 1 was determined by microanalysis.

The stereoselectivity of the condensation reaction between benzenesulphonyl hydrazines and aldehyde (I) can be searched in the strong hydrogen bond between the acidic hydrogen of the sulphonyl hydrazine moiety and the pyridine nitrogen. Transition state with this hydrogen bonding in consideration is favored by 5-10 K cal./mole than any other orientation lacking this electrostatic interaction. As a result the reaction will proceed keeping th N-N bond inside towards the pyridine ring with the formation of the syn isomer as the main product.



b) *Biological*

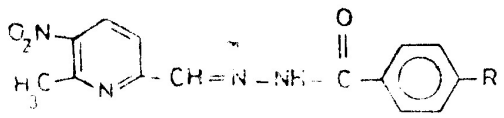
One of the primordial questions of this study was whether the 2-methyl-3-nitropyridyl moiety can conserve biological activity when it is linked to alkyl acrylates and acrylamide fragments. The acrylic acid II and its derivatives IIIa, c and IVa-g showed no activity against Entamoeba histolytica and Balantidium coli*. This illustrates that the antiparasitic activity assigned to other nitroheterocyclic acrylamides (7,8) is a subject of the whole molecular structure and can not be related specifically to th acrylic fragment.

*The experimental peocedure was carried out in the college of Pharmcy, North Dakoth State University, USA and results were supplied by personal communication with Dr. S.K. Wahba.

Five of the hydrazone derivatives Va, b,e,g and I were chosen for preliminary antiparasitic screening (in vitro) against Ascaridia galli. Three dilutions of the ethanolic solutions of the tested compounds were applied. All of the tested compounds were inactive at the level of 0.38 mg/ml, and showed an action not different from that induced by the ethanol used in th blank experiment. Compounds Vb, e and g were lethal to the parasite at concentration 0.73 mg/ml. The compound V a showed a lethal effect only at 1.04 mg/ml concentration level while V I was inactive.

Screening of the water soluble ethanolamine salts of the compounds V a, b, e, g and I under the same conditions revealed no lethal activity. This may be attributed to the inactive anionic form of the compounds in the salt formed with ethanolamine. In vivo testing using a single dose of 300 mg/kg for three successive days was of no value as antiparasitic agents in naturally infected chickens.

A second goal seemd to be of interest was how the claimed antibacterial properties of the compounds VII ([6])was affected on replacement of the CO group by isosteric SO_2 group in the prepared series of compounds V.



The compounds Va, b,c,e, g,i,k and I were tested for their antibacterial activity using the disc method. They were inactive against S. aureus and E. Coli. This allows us to conclude that the isosteric replacement of CO by SO_2 exerted a diverse action on the activity of the series VII.

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تخليق ودراسة الفعالية البيولوجية لمشتقات ٢ ـ ميثيل ـ ٣ ـ نيتروبيريدين

حسن حسن فرج ، عبد الحليم محمد عبد العليم ، عادل فوزى يوسف ، هدى يوسف ، حرية عبد المجيد وعوض عبد الحافظ

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يشتمل البحث على تخليق بعض استرات واميدات ٣ ـ (٢ ـ ميثيل ٣ ـ نيترو ـ ٦ ـ بيريديل) حمض الاكريليك بالاضافة الى تحضير بعض هيدرازونات ن ـ (بنزين سلفونيل) ـ ٢ ـ ميثيل ـ ٣ ـ نيتروبيريدين ـ ٦ ـ كاربوكس الدهيد .

ومما يجدر ذكره ان ٢ ـ ميثيل ـ ٣ ـ نيتروبيريدين ـ ٦ ـ كاربوكس الدهيد يتفاعل مع حمض المالونيك طبقا لتفاعل كنوفيناجيل للحصول على حمض الاكريليك الذى ثبت أنه عبارة عن مخلوط من النظائر الهندسية (Cis & Trans) بينما يتفاعل نفس الالدهيد مع البنزين سلفونيل هيدرازين معطيا هيدرازونات ثبت أنها عبارة عن نظير هندسى واحد وهو (Syn) واقد تأكد ذلك بواسطه كروماتوجرافيا الطبقات الرقيقة والتحليل الطيفى بالاشعة تحت الحمراء والرنين النووى المغناطيسى وطياف الكتلة لبعض الهيدرازونات المحضرة . وبدراسة الفعالية البيولوجية لبعض المركبات المحضرة وجد أن ليس لهما تاثير ضد البكتريا . ولقد وجد أن لبعض الهيدرازونات تاثير مضاد لطفيل اسكارس الدواجن خارج جسم الحيوان وليس لها تاثير داخله . هذا ولم يثبت وجود أى فعالية لاسترات واميدات حمض الاكريليك ضد طفيل الانتاميبا هستولتيكا والبلانتيديوم كرلى .