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Synthesis of some pyridinethione derivatives and their biological activity

Jehane A. A. Miky[1] and Samir A. M. Zahkoug[2]

[1]Chemistry Deaprtment, Faculty of Science (Girls)
[2]Zoology Department, Faculty of Science Al-Azhar University, Nasr City 11884, Cairo, Egypt

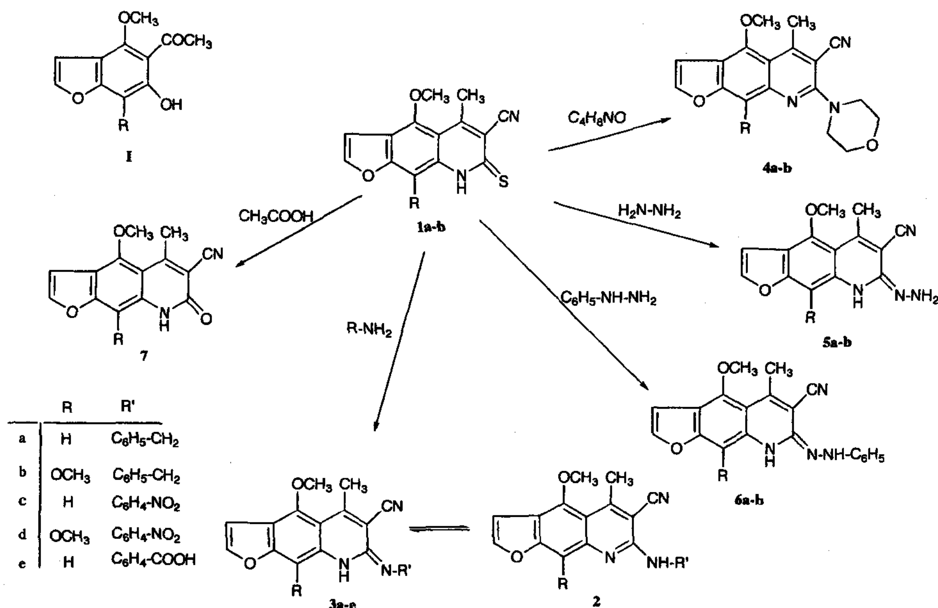
Abstract – Aminolysis, hydrazinolysis and alkylation of 4-methoxy and 4,9-dimethoxy-6-cyano-7-thione-5-methyl-7H furo [3,2-g] [1] benzopyridine (1 a-b) yielded 7-N-substituted furobenzopyridine derivatives (2 a-e or the possible isomers 3 a-e and 4 a-b), (5 a,b and 6 a,b) and the ester (8 a,b). Hydrolysis of (1a) with acetic acid gave the corresponding pyridone derivatives (7). Furobenzopyridinyl-7-thioacetyl hydrazide (9 a,b) have been prepared via alkylation of furobenzopyridine thione (1 a-b) with ethyl chloroacetate followed by condensation with hydrazine hydrate. Schiff base (11) was prepared by reacting (9a) with p. N,N-dimethyl aminobenzaldehyde in boiling ethanol. Treatment of (8a) with anthranilic acid gave the corresponding 7-substituted-4H-3,1-benzoxazine-4-one (10). We found that compound (11) increased bleeding, coagulating time, the total count of white blood cells, blood glucose level (cause hyperglycemia), enzymes (GOT, GPT) activities, concentration of urea and creatinine. On the other hand it decreased red blood cells number, haemoglobin content and haematocrite value.

Keywords – Liver and kidney function tests, amminolysis, hydrazinolysis and alkylation of pyridinethione derivatives.

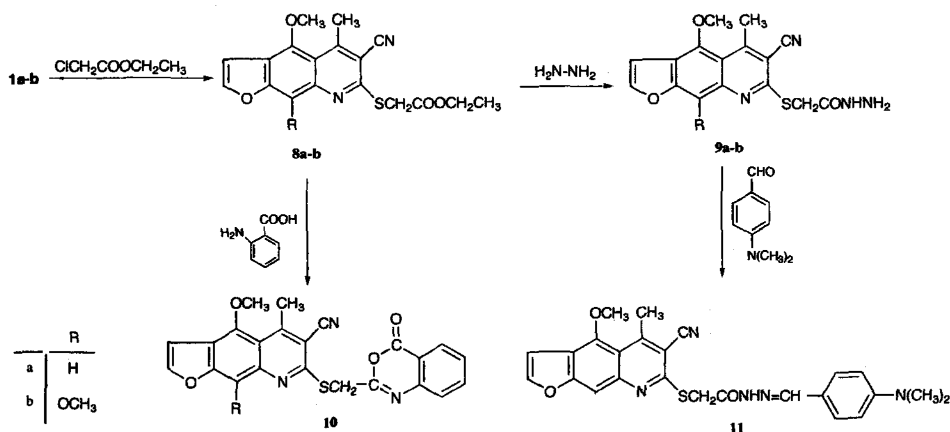
Introduction

It is well known that pyridine derivatives possess acaricidal (Treb *et al.*, 1970), insecticidal (Rigterink *et al.*, 1968). herbicidal (Driscoll, *et al.*, 1970) and antibacterial (Seydel *et al.*, 1964) activities. The interest in the chemistry of benzofuran derivatives was extended to develop synthetic approaches for polyfunctionally substituted benzofuranyl pyridine derivatives. Several analogs of the naturally occuring of benzofuran derivatives have been found to possess antibacterial properites (Hishmat *et al.*, 1977 and Hishmat *et al.*, 1983, Nomura *et al.*, 1979) and effective fungicides (Takasugi *et al.*, 1979, Chamberlain *et al.*, 1982). We report here the synthesis of new derivatives of furobenzopyridine-7-thione and their biological activity. The ethanolic solution of 4-methoxy- and 4,9-dimethoxy-6-cyano -7-thione-5-methyl-7H-furo [3,2-g] (1) benzopyridine (1 a-b) with amines gave N-substituted-7-amino-4-methoxy and 4,9-dimethoxy-6-cyano-5-methyl-7H-furo [3,2-g] (1) benzopyridine (2 a-e or the possible isomers 3 a-e and 4 a-b) (Saleh *et al.*, 1991) (Scheme 1, cf. Table 1). A similar reaction of (1 a-b) with hydrazine hydrate and phenyl hydrazine afforded the corresponding 7-hydrazino- and 7-phyenylhydrazino-6-cyano-5-methyl furobenzopyridine derivatives (5 a-b) and (6 a-b) respectively, (Scheme 1, cf. Table 1). When 1a was refluxed with acetic acid, the thione group at position 7 was hydrolysed to the corresponding 6-cyano-4-methoxy-5-methyl-7H-furo [3,2-g] (1) benzopyridine-7-one (7) (cf. Table 1). Compound (7) was also obtained by

[1]Author for correspondence.



Scheme 1.



Scheme 2.

treating visnagione (I) with cyanoacetamide in the presence of ammonium acetate (Hishmat *et al.*, 1983) (m.p. and mixed m.p.). Alkylation of (1 a-b) with ethyl chloroacetate in the presence of sodium acetate in dry acetone (Sharmah *et al.*, 1982) formed furobenzopyridine-7-ylthioacetic ester derivatives (8 a-b), (Scheme 2, cf. Table 1). Condensation of the ester (8 a-b) with hydrazine hydrate (99%) in absolute ethanol resulted in the formation of furobenzopyridine-7-ylthioacetyl hydrazide (9 a-b) (Scheme 2, cf. Table 1). When compound (9a) was condensed with p.N, N-dimethyl aminobenzaldehyde in absolute ethanol an orange-red crystalline material was obtained (compound 11) in a 75% yield. The reaction of 8a with anthranilic acid gave the corresponding-7-substituted-4H-3,1-benzoxazine-4-one (10) (Soliman *et al.*, 1990), (Scheme 2, cf. Table 1).

Table 1. Physical, analytical data for compouds

Compound (Colour)	M. P (℃) (Solvent)	Yield (%)	Molecular Formaula (Mol. Wt.)	Analysis Calcd/Found			
				C	H	S	N
2a	110	50	$C_{21}H_{17}N_3O_2$	73.47	4.96		12.24
(yellow)	(p.E.40-60)		(343)	73.2	5.0		12.4
2b	140	60	$C_{22}H_{19}N_3O_3$	70.78	5.09		11.26
(brown)	(n.hexane)		(373)	71.0	5.1		11.3
2c	160	80	$C_{20}H_{14}N_4O_4$	64.17	3.74		14.97
(yellow needless)	(p.E.60-80)		(374)	64.3	3.8		15.0
2d	150	65	$C_{21}H_{16}N_4O_5$	62.38	3.96		13.86
(colorless)	(n.hexane)		(404)	62.5	4.0		14.0
2e	130	70	$C_{21}H_{15}N_3O_4$	67.56	4.02		11.26
(yellow)	(p.E.60-80)		(373)	67.8	3.9		11.0
4a	120	55	$C_{18}H_{17}N_3O_3$	66.87	5.26		13.00
(yellow)	(n.hexane)		(323)	67.0	5.4		13.00
4b	190	50	$C_{19}H_{19}N_3O_4$	64.59	5.38		11.90
(brown)	(Ethanol)		(353)	64.6	5.4		12.0
5a	135	80	$C_{14}H_{12}N_4O_2$	62.69	4.47		20.9
(yellow)	(p.E.80-110)		(268)	62.8	4.5		21.0
5b	180	70	$C_{15}H_{14}N_4O_3$	60.40	4.7		18.8
(yellow)	(Ethanol)		(298)	60.5	4.6		19.0
6a	140	85	$C_{20}H_{16}N_4O_2$	69.77	4.65		16.28
(brown)	(n.hexane)		(344)	70.0	4.7		16.4
6b	165	80	$C_{21}H_{18}N_4O_3$	67.38	4.81		14.97
(yellow)	(Ethanol)		(374)	67.5	5.0		15.0
7	305	83	$C_{14}H_{10}N_2O_3$	66.14	3.94		11.02
(brown)	acetone		(254)	65.9	4.0		11.0
8a	218-220	75	$C_{18}H_{16}N_2O_4S$	60.63	4.49	8.98	7.86
(brown)	(Ethanol)		(356)	60.7	4.4	9.0	8.0
8b	160	70	$C_{19}H_{18}N_2O_5S$	59.03	4.66	8.29	7.25
(yellow)	(n.hexane)		(386)	58.9	4.7	8.2	7.4
9a	106	60	$C_{16}H_{14}N_4O_3S$	56.10	4.09	9.35	16.36
(yellow)	(p.E.40-60)		(342)	56.3	3.9	9.4	16.5
9b	113-114	60	$C_{17}H_{16}N_4O_4S$	54.80	4.29	8.59	15.04
(yellow)	(p.E.60-80)		(372)	55.0	4.4	8.7	15.0
10	150	85	$C_{23}H_{15}N_3O_4S$	64.33	3.49	7.45	9.79
(white)	(n.hexane)		(429)	64.1	3.5	7.5	10.0
11	190	75	$C_{25}H_{23}N_5O_3S$	63.42	4.86	6.76	14.79
(orange) Red	(Ethanol)		(473)	63.5	4.9	7.0	15.0

Experimental

Melting points are uncorrected. Mass spectra were recorded on a Varian Mat CH-4B spectrometer. IR spectra were run in KBr on Pye- Unicann sp. 1100 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO on a varian 1M-3901 spectrometer at 90, 200 or 270 MHZ using TMS as internal standard.

Preparation of N-substituted-7-amino-6-cyano-5-methyl-4-methoxy-and 4,9-dimethoxy-7H-furo [3,2-g] (1) benzopyridine (2 a-e or the possible isomer 3 a-e and 4 a-b)－A solution of (1 a-b) (Miky, 1995) (0.01 mol) and amine [benzylamine, p-nitroaniline, p-aminobenzoic acid and morpholine] (0.01 mol) in ethanol (50 ml) was heated under re-

flux for 8hr. The product obtained filtered and crystallized from appropriated solvent (cf. Table 1). All compounds gave a negative ferric chloride test. Compound 2c: IR (Kbr, cm^{-1}) showed bands at 3216 (NH), 2190 (C≡N), 1631 (C=N) and 1394 (NO_2). PMR (DMSO) δ 2.1 (s, 3H, CH_3), 3.26 (s, 3H, OCH_3), 6.2 (br., 1H, NH), 6.54 (d, J=7.2Hz, 2Haromatic), 6.62 (d, J=2.5Hz, 1H, H_3 furan moiety), 6.72 (s, 1H, H_9 of benzofuran) and 7.93-7.97 (m, 3H, 2H aromatic and H_2 furan moiety); MS (m/z): 374 (M^+), 237 (M^+-$C_6H_5N_2O_2$), 222 (M^+-$C_7H_8N_2O_2$).

2e: IR (Kbr, cm^{-1}): 3457 (OH), 3196 (NH), 2204 (C≡N), s1661 (C=O of acid); PMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 4.22 (s, 3H, OCH_3), 5.88 (s, 1H, NH), 6.6 (d, J=7.2Hz, 2H, aromatic), 7.1 (d, J=2.5Hz, 1H, H_3 furan moiety), 7.4 (s, 1H, H_9 benzofuran), 7.9 (d, J=7.4Hz, 2 H, aromatic), 8.1 (d, J=2.5Hz, 1H H_2 furan moiety), 9.2 (br., 1H, OH, exchangeable with D_2O).

Compound 4a: MS (m/z): 324 (M^++1), 237 (M^+-C_4H_8NO).

Preparation of 7-Hydrazino/7-phenylhydrazion-6-cyano-5-methyl-4-methoxy-(and 4,9-dimethoxy) -7H furo-[3,2-g] (1) benzopyridine (5 a-b and 6 a-b) – A solution of (1 a-b) (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) in ethanol (50 ml) was heated under reflux for 6hr. The product obtained was filtered and crystallized from suitable solvent (cf. Table 1). All compounds gave no colour reaction with aqueous ferric chloride solution and a brown colour with concentrated sulphuric acid. The IR spectrum of 5a (Kbr, cm^{-1}) appeared 3342, 3259 and 3155 (NH_2 and NH), 2193 (C≡N) and 1617 (C=N).

Compound 6a: IR (Kbr, cm^{-1}) showed 3245, 3177 (NH), 2197 (C≡N), 1596 (C=N); PMR (DMSO): δ 2.15 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.54 (s, 1H, NH), 6.67 (d, J=2.4Hz, 1H, H_3 furan moiety), 7.01-7.14 (m, 5H, aromatic), 7.87 (d, J=2.35Hz), 1H, H_2 furan moiety), 8.16 (s, 1H, H_9 benzofuran) and 9.17 (s, 1H, NH).

Preparation of 6-cyano-4-methoxy-5-me thyl-7H-furo [3,2-g] (1) benzopyridine-7-one (7) – Compound 7 was obtained in 83% yield as brown crystals by refuluxing 1a (1 g) with glacial acetic acid (10 ml) for 2 hours. (cf. Table 1). The IR spectrum of 7 revealed bands at 3134 (NH), 2200 (CN) and 1726 (C=O pyridone)

Preparation of Ethyl-6-cyano-5-methyl-4-methoxy-and (4,9-dimethoxy)-7H-furo [3, 2-g] (1) benzopyridine-7-ylthioacetic ester (8 a-b) – A mixture of (1 a-b) (0.01 mol) ethyl chloroacetate (0.01 mol) and fused sodium acetate (0.03 mol) in dry acetone (40 ml) was refluxed on a water bath for 8hr. The reaction mixture was cooled and poured into water. The resultant solid was filtered, washed with water, dried and recrystallized from suitable solvent (cf. Table 1).

The IR spectra of 8a and 8b (KBr, cm^{-1}) showed bands at 2193, 2210 (C≡N) and 1750, 1762 (C=O ester) respectively. The molecular weight determination (MS) of 8a corresponded to $C_{18}H_{16}N_2SO_4$ (m/z-356).

Preparation of 6-cyano-5-methyl-4-methoxy-(4,9-dimethoxy)-7H-furo [3,2-g] (1) benzopyridine-7-ylthioacetylhydrazine (9 a-b) – A mixture of (8 a-b) (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 6hr. The solid obtained was crystallized from suitable solvent (cf Table 1). The IR spectrum of 9a (Kbr, cm^{-1}) appeared bands at 3357, 3261, 3196 (NH_2, NH), 2204 (C≡N), 1661 (C=O amide) and 1601 (C=N). Its ^{1}H-NMR spectrum (DMSO) showed δ 2.3 ppm (s, 3H, CH_3), 4.14 (s, 3H OCH_3), 5.86 (s, 2H, CH_2), 6.73 (s, 3H, 1H, H_9 benzofuran and 2H of NH), 7.19 (d, J=2.2Hz, 1H, H_3 furan moiety), 7.8 (d, J=2.35Hz, 1H, H_2 furan moiety), and 11.4 (s, 1H, NH).

Preparation of 6-cyano-5-methyl-4-methoxy-(4,9-dimethoxy)-7H-furo [3,2-g] (1) benzopyridine-7-yl-thiomethyl-4H-3,1-benzoxazine-4-one (10) – A solution of 8a (0.01 mol) and anthranilic acid (0.01 mol) in ethanol (40 ml) and few drops of Ac_2O was heated under reflux for 15hrs. The solid that separated on cooling, was filtered and crys-

tallized (cf Table 1). IR spectrum of (10): 2225 (C≡N), 1760 (oxazinone C=O), 1670 (amide C =O). The PMR spectrum (DMSO): showed signals at δ 2.2 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.4 (s, 2H, CH_2), 6.6-7.9 (m, 7H, 4H aromatic 1H benzofuran and 2H furan). The mass spectrum of (10) showed a molecular ion M^+ (m/z) at 429.

Preparation of Schiff base (11) – A mixture of (0.005 mol) of 9a and P-N,N-dimethyl aminobenzaldehyde (0.05 mol) in absolute ethanol (40 ml) and two drops of piperidine was refluxed for 4hr then left to cool and crystallized (cf. Table 1). The IR spectrum of 11 (Kbr, cm^{-1}) showed 3179 (NH), 2220 (C≡N) and 1667 (C=O) and molecular weight determined (MS) corresponded to $C_{25}H_{23}N_5O_3S$ (m/z=473).

Bleeding and coagulatine time

Materials and methods – Male albino rats (Rattus morvigicus) of same age and weight (120-140 gm) were sued in this study. Five groups (5 rats each) were given the tested compounds orally by using the stomach tube. The experimental animals were received food and water adlibitium. These animals were deprived of the food and water before given the tested compound by 2 hours.

LD_{50}'s of the tested compounds – LD 50's of the compounds 2d, 5a, 7, 8a, 9a, 11, 1a and 1b were estimated in the experimental rats, percentage mortality for each group was recorded at 24 hours after administration. Tested animals were observed for alterations in vilality, behavioural response and any other symptoms. Sublethal dose 0.1 of the LD_{50}'s for each group of the above compounds were tested for 10 days without the control group. At the end of the experiment, a piece from ear of the rat was cut for estimation the bleeding time (Ivy *et al.*, 1940). Then, animals were sacrificed by decapitation and the blood was collected in dry and clean tubes for estimation the coagulating time (Lee et al., 1955).

LD_{50}'s – Main symptoms were observed, such as muscle fasciculations, salivation, vomiting, Nausea and accelerate the respiratory rate. The results shown in Table 2 revealed that compound 11 had more toxic effect to the tested animals probably due to the presence of cyano, sulphur and ter amine group while the remaining compounds had a less toxic effect on the body of the tested animals.

Bleeding and coagulating time – The results presented in Table 3 indicated that the compound 5a and 11 had an inverse effect on the intrinsic coagulation mechanism (Factor I to XIII) or platelets, thrombin and calcium ion probably due to the presence of cyano and amino groups. Also the compounds 11, 9a and 1a increase the clotting time probably due to defecieincies of some blood coagulation factors which are often associated with severe derangement of haemostasis des-

Table 2. The LD_{50} value of the tested compounds mg/kg of the body weight of rats

	Control	Tested compound							
		2d	5a	7	8a	9a	11	1a	16
LD_{50}s	-	270	300	260	200	250	150	200	250

Table 3. Bleeding and coagulating time, minutes of blood of rats

	Control	Tested compound							
		2d	5a	7	8a	9a	11	1a	1b
Bleeding time (min.)	4	8	10	7	7	8	10	8	7
Coagulating time (min.)	5	7	8	8	7	9	10	9	8

pite normal primary arrest of haemorrhage.

Liver and Kidney function tests

Materials and Methods – Animals: white (albino) rats of (140-160 gm) body weight were obtained from the animal house colony from Helwan culture for experimental animals.

These rats kept on standard laboratory diet and water was provided *ad libituim*. Animals were divided into two groups (each group has 5 animals), one group for tested and the other for control. Tested compound was given using stomach tube, percentage mortility was recorded at 24 hours after administration. Tested amimals were observed for alterations behavioral response and any toxic symptoms. After estimation LD_{50} sublethal dose (0.1 LD_{50}) of the compound 11 which was 150 mg/kg. The oral administration was given in fasting at least 2 hours for 10 days. At the end of the experiment, animals were decapitated, blood samples were collected in clean and dry tube.

To determine some biochemical parameters liver and kidney function tests such as serum glutamic oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), total protein (T. protein), albumin, globulin, albumin/globulin ratio, glucose, blood picture, urea and creatinine. (SGOT) and (SGPT) activities were determined by measuring the liberated oxaloacetate and pyruvate respectively according to method of (Reitman, *et al.*, 1957). Total protein was determined according to the method (Lowry *et al.*, 1951), albumin was determined using technique of (Doumas *et al.*, 1971). The globin value was obtained by substracting the albumin value from the total protein of the sample. The glucose was determined by the method of (Trinder *et al.*, 1969). Serum urea concentration was measured according to method of (Chaney *et al.*, 1962). Also serum creatinine concentration was estimated according to (Husdan *et al.*, 1968) using Jafe's reaction.

Some haematological parameters were also estimated such as Red, White blood corpuscles and haemoglobin by using the method of (Dacie *et al.*, 1984 and Drabkin *et al.*, 1932) and haematocrite values were estimated using the technique of (Sanders *et al.*, 1961). Results were analyzed statistically using student's t-test.

Results and Discussion

The growth rate was depressed and the animals gained less weight than controls after oral administration for 10 days with compound (11). Many symptoms were observed few minutes after being doses such as tremor, muscle fasciculation, salivation, nausea, increase respiratory and heart beat rate.

The data presented in Table 4 showed that administration of compound (11) lead to the increase of blood glucose level from 115 to 150 mg/dL. The increase in serum glucose (hyperglycemia) may be due to glycogenolysis (the formation of glucose from glycogen) or from gluconeogenesis (the formation of glucose from non carbohydrate sources such as proteins or fat) activity in the liver (Ganong *et al.*, 1983). The present finding of occurrence of some increase in serum glucagon may be interpreted in terms of the role of glucagon in the process of glycogenolysis to increase blood glucose (diabetes). The effect of compound (11), due to the presence of cyano, sulphur and $N(CH_3)_2$ on adrenal cortex of adrenal gland may increase the level of glucocorticied hormone (corticosteron) which causes an increase in liver glycogen and adereare in the rate of oxidation of glucose. Also may cause increase formation of glucose from other sources. Statistical analysis induced a significant increase in glucose of blood serum of tested compound in experimental animals as compared to control animals. Liver is the seat of production of most plasma proteins, with administration of compound (11) as indicated in Table 4. The total proteins showed a decreasing tendency. The

Table 4. Effect of 0.1 LD_{50} of compound (11) administration on some biochemical parameters of blood serum of rats

bservation number	Glucose mg/dL		Total protein gm/dL		Albumin mg/dL		Globulin mg/dL		A/G Ratio	
	Control	Treated	Control	Treated	Contrl	Treated	Control	Treated	Control	Treated
	80	115	7.5	6	5.0	3.5	2.5	1.5	2.0	2.3
1	90	148	7.5	6.3	5.3	4.0	2.2	1.3	2.4	3.1
2	89	129	7.0	6.0	4.9	4.3	3.1	1.7	2.3	2.5
3	92	138	6.9	5.5	5.0	4.6	1.9	1.6	2.6	2.7
4	100	150	6.5	5.8	4.9	4.6	1.6	1.3	3.1	3.5
5	90.2	136	7.08	5.52	5.02	4.06	2.06	1.46	2.48	2.81

Where total protein=Albumin+Globulin

compound (11) may be loss or lower the appetite (decrease of protein synthesis) due to the presence of CN, which may cause many diseases to the liver such as acute hepatitis and cirrhosis (Talaat et al., 1955).

Albumin as shown in Table 4 was decreased in prolonged malnutrition due to inadequate dietary intake of proteins. It was noticed in case of nephrities or neophrosis due to excretion of albumin in urine.

Albumin was also decreased in case of inability of the body to synthesis of albumin in urine.

Albumin was also decreased in case of inability of the body to synthesis of albumin in case of liver cirrhosis.

Globulin as indicated in Table 4 was increased as a result of antigenic stimulation, this infecious process produced a rise in this component due to the presence of CN, S and $N(CH_3)_2$ groups in compound (11).

In many diseases there was a constant association between decreased albumin and increased globulin e.g. nerphrosis, acute rheumatic fever and typhus fever. When liver cells were damaged serum globulin increased especially α-globulin but serum albumin fell. The present investigation showed that the tested compound (11) on experimental animals (albino rats) induced no changes in albumin/globulins ratio. Statistical analysis (Student's t-test) performed on total proteins, albumin, globulin and albumin/globulin ratio had no significant in blood serum of animals tested with compound (11) as compared to control animals.

The data found in Table 5 showed that the treated of adult male albino rats with tested compound (11) for 10 days with sublethal dose (0.1 LD_{50}) on haematological parameters, a significant decrease of red blood cells count from 7.96 (mean) in control animals to 4.1 (mean) in the experimental animals tested with compound (11). The decrease in red blood cells count due to the effect of this compound on liver and cause liver disease where liver had an important role in the regeneration of erythrocytes (it is a store of iron and globin), this decrease due to congenital haemolytic anaemia. This anaemia may be occurred as a result of haemolytic anaemia (hemolysis of red blood cells in the live). Anaemia occured if the bone marrow (the manufacture of red blood cells) was destroyed by chemicals, (Weekly *et al.*, 1981).

The data presented in Table 5 showed an increase in white blood corpuscles count from 10.2×10^3 cell/mm^3 to 13.5×10^3 cell/mm^3 (leucocytosis, due to the effect of the cyano, and trimethyl amine groups found in the tested compound (11) which cause an acute inflammation (Weekley *et al.*, 1981). Also data found in Table 5 showed a decrease in haemoglobin concentration (gm %) from 16.1 to 12.66 gm% in case of haemolytic Jaundice or may be due to the malnutrition (Globin and

Table 5. Effect of 0.1 LD_{50} of compound (11) administration on some haematological parameters of rats

Criteria / observation number	R.B.Cs $\times 10^6$ cell/mm^3		Haemoglobin gm %		Haematocrite value %		W.B.Cs $\times 10^3$ cell/mm^3	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
1	8.0	4.5	16.0	13.0	50	40	8.0	10.5
2	7.5	4.8	17.0	14.0	48	42	8.0	13.5
3	8.0	3.5	16.0	11.3	46	38	9.5	15.0
4	7.8	3.6	16.0	12.2	47	38	8.0	12.0
5	8.5	4.2	15.5	13.3	46	43	8.5	14.0
Mean	7.96	4.10	16.1	12.8	47.4	40.2	8.4	13.0
S.D.	0.36	0.56	0.55	1.04	1.67	2.28	0.67	1.76
S.E.	0.16	0.25	0.25	0.47	0.75	1.02	0.30	0.79

R.B.Cs.=Red blood corpuscles. W.B.Cs=White blood corpuscles. S.D.=Standard Deviation. S.E.=Standard Error.

Table 6. Effect of 0.1 LD_{50} of compound (11) adminstration on some biochemical parameter of rat blood

	SGOT (iu/L)		SGPT (iu/L)		Urea (mg/dL)		Creatinine (mg/dL)	
Animals	Control	Treated	Control	Treated	Control	Treated	Control	Treated
1	50.0	90.0	30.0	50.0	15.5	26.5	0.4	1.6
2	50.0	79.0	25.0	48.0	16.5	28.9	0.6	2.0
3	60.0	68.0	30.0	45.0	16.0	25.6	0.7	2.1
4	45.0	75.0	31.0	54.0	15.8	28.0	0.5	1.8
5	50.0	88.0	28.0	50.0	15.0	32.0	0.4	1.9
Mean	51.0	80.0	28.8	49.4	15.8	28.2	0.5	1.9
S.D.	4.9	8.2	2.1	2.9	0.5	2.2	0.1	0.2

iron defeciency), or may be due to vomiting or diarrhea which occured after administration of the tested compound (11).

The haematocrite value decreased as shown in Table 5 from 47.6 to 40.2% due to red blood corpuscles count and haemoglobin concentration decreaced.

Transaminases or transferases constitute a group of enzymes which catalyzes the interconvertion of an amino-group of amino acid to ketone group of keto acids. Liver and myocardial tissues contain large amounts of transaminases. Any damage of these tissues results in elevation of these transaminases in the blood serum. Estimation of serum enzyme activityes (SGOT and SGPT) in blood of rats tested with compound (11), induced a rise in their activites.

Table 6 demonestrate changes in serum urea and cratinine concentrations in rats tested with sublethal dose 0.1 LD_{50} for 10 days. Main urea concentration mg/dL increases from 15.8 mg/dL of control to 28.2 mg/dL for tested rats also the concentration of serum creatinine significantly increases from 0.52 to 1.9 mg/dL for control and tested animals respectively.

Conclusion

The present data show that administration of single acute dose (o.1 LD_{50}) of compound (11) into rats induced significant elevation in SGPT and SGOT activities.

The level of increase in both enzyme activities was observed transaminases (SGPT and SGOT) represent a group of enzymes that are present within the cytoplasm of the living cells with the highest concentration of GPT found in liver tissue, lower concentrations present in the heart muscle and relatively small amounts are present in brain, kidney and serum (Kozma *et al.*, 1969 and Kachman *et al.*, 1976). GOT was found to have its highest concentration in a variety of tis-

sues including liver, Kidney, brain skeletal anc cardiac muslces. It was generally established that marked elevation in SGPT and SGOT indicated the infections or toxic liver damage (Friedman *et al.*, 1964 and Zakin *et al.*, 1982). Therefore the rise in SGOT and SGPT observed in the present study may reflect a damage effect of compound (11) on the liver tissue due to the presence of NH, S and $N(CH_3)_2$ groups in this compound. However it would be also suggested that the elevation in SGPT and SGOT activities observed in the present study might be due to a toxic damage of other tissues since it had been shown previously that there were two enzymes elevated when some tissues other than liver were damaged, particularly the myocardium (Rudolph *et al.*, 1957 and Rusgsegger *et al.*, 1959).

Anhydride of creatine (creatinine) was in large part synthesised endogenously in muscle tissue and liberated into the circulation. Serum creatinine concentration reflects total body supplies of creatine constancy of endogenous creatinine production and its release into the body fluids at a constant rate and constancy of its blood levels over the 24 hr of a day made it a useful endogenous substance whose concentration in serum was most useful measure in evaluating renal function (Widann *et al.*, 1973). Increase in serum creatinine had been clinically ragarded as a diagnostic indicator of chronic renal failure (Grunfeld, 1979 and Kachmar *et al.*, 1987). These data suggested the renal tissue of rats was susceptible to a toxic damage by compound (11) and this damage apparently altered the kidney function.

In the present study a significant rise in blood urea was found, and this was concomitant to a significant increased in serum creatinine levels as well. Determination of these non-protein nitrogen compounds was almost commonly ordered tests of the ability of kidney of excrete metabolic wastes (Treseler *et al.*, 1988).

The increase in these values was used as indicators of renal failure. The significant elevation in blood urea may be due to the presence of CN, S and N $(CH_3)_2$ in compound (11). The metabolic products of protein metabolism (urea and creatinine) had been considered for a long time as an essential measured in clinical diagnosis of functional alteration in different organs induced with varius disease or toxic materials (Champbell *et al.*, 1986). We mention before; that benzofuran derivatives show antibacterial activity as well as antiparasitic properties. On the other hand substituted pyridines show acaricidal, herbicidal and antibacterial activities. Therefore, we synthesised new compounds having both pyridine and benzofuran moieties, also some of them have CN, S and N $(CH_3)_2$ groups which make them possess higher marked biological activity.

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