SYNTHESIS AND CARDIOTONIC ACTIVITY OF 5-(2-SUBSTITUTED THIAZOL-4-YL)-2-PYRIDONES AND THIAZOLO[4,5-f]QUINOLINONES

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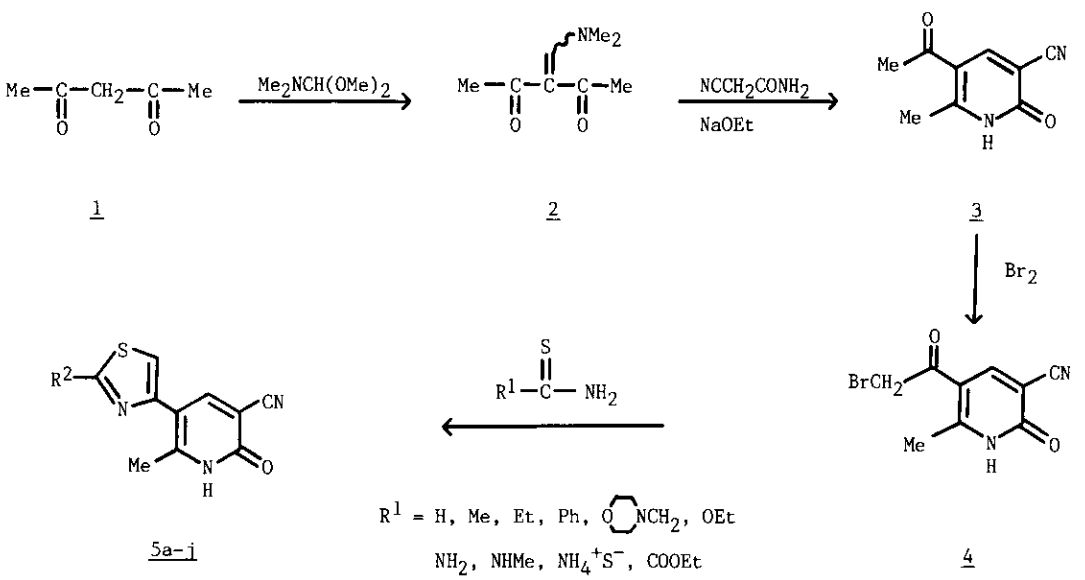
Abstract ——— A variety of 5-(2-substituted thiazol-4-yl)-2-pyridones and thiazolo[4,5-f]quinolinones were synthesized and tested *in vitro* for cardiotonic activity. Several compounds of these series showed good positive inotropic activity.

Although cardiac glycosides have major clinical utility in the treatment of congestive heart failure, the use is rather limited mainly because of their arrythmogenic liability. The general lack of safe, orally effective cardiotonics has stimulated the development of new positive inotropic agents[1,2] as substitutes for cardiac glycosides.
As part of our effort in search of potent cardiotonics, we undertook the preparation of thiazolylpyridones, and their cyclized derivatives. The present paper reports the preparation of 5-(2-substituted thiazol-4-yl)-2-pyridones and thiazolo[4,5-f]quinolinones and their cardiotonic activity.

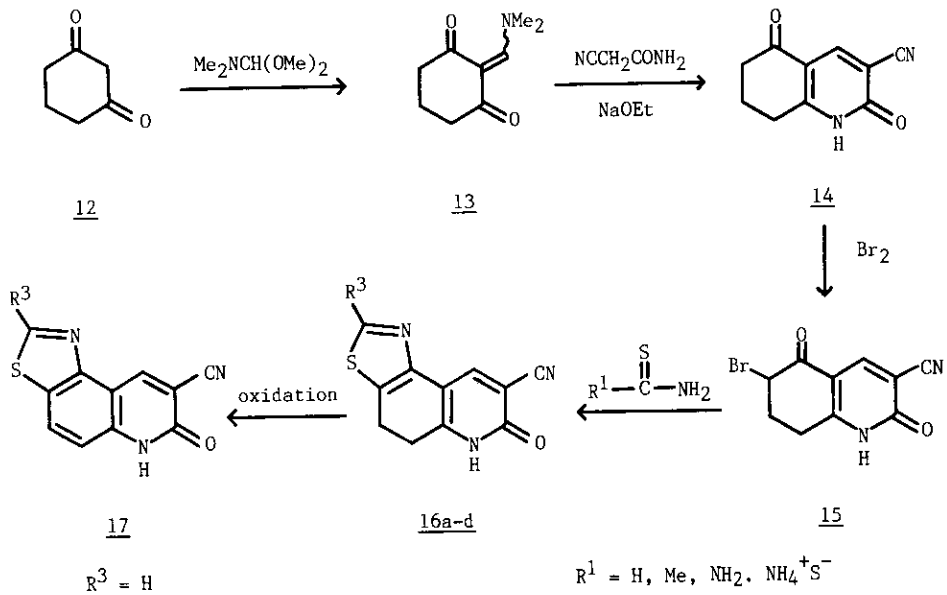
In the synthesis of 5-(2-substituted thiazol-4-yl)-2-pyridones, 5-bromoacetyl-3-cyano-6-methyl-2-pyridone (4) was selected as a key intermediate, since the bromomethyl keto function was convertible into a thiazol-4-yl moiety by the Hantzsh synthesis[3] using thiocarbonylamino compounds as outlined in Scheme 1. The key intermediate 4 was prepared by bromination of 5-acetyl-3-cyano-6-methyl-2-pyridone[4], which was readily prepared from acetylacetone *via* the enamine 2. Thioamides, the counterpart of the bromoacetyl derivative 4 in the thiazole synthesis, were either purchased or prepared. The preparation of thioamides was performed conveniently from the corresponding amides and phosphorus pentasulfide in tetrahydrofuran or pyridine at room temperature. Formation of the thiazole ring by the reaction of 4 with the thiocarbonyl derivatives proceeded smoothly in DMF at room temperature. Thus, the thiazolylpyridones were prepared from 4 and the corresponding thiocarbonyl functions; 5a-e and 5i from the thioamides 5f and 5g from the thioureas; 5h from ammonium dithiocarbamate; and 5j from ethyl thiooxamate as shown in Scheme 1. The resulting 2-mercaptothiazole (5h) and 2-ethoxycarbonylthiazole (5j) derivatives were used for further derivatization. Methylation of 5h gave the 2-methylthiothiazole derivative 6.

Oxdation of 6 with either one or two equimolar equivalent of hydrogen peroxide produced the sulfoxide 9 and the sulfone 10, respectively. Compound 7 carrying an alkoxy group at the 2-position of the thiazole ring was prepared by displacement of the methylsulfonyl group of 10 with the corresponding alcohol in the presence of sodium hydride. The carbamoyl-substituted derivatives 8a-d in the 2-position of the thiazole ring were prepared by aminolysis of the corresponding ethoxycarbonyl compound 5j with appropriate amines. As transformation of another position, the cyano group of compound 5a in the 3-position of the pyridone ring was hydrolyzed to amide, which was subjected to the Hofmann reaction to yield 3-amino-6-methyl-5-(thiazol-4-yl)-2-pyridone (11). The thiazolo[4,5-f]quinolinones 16a-d, having a ring system bridged with two carbon units between the 5-position of the thiazole ring and the 6-position of the pyridone ring of the above thiazolylpyridone, were synthesized according to the Scheme 2. Cyclohexane-1,3-dione reacted with DMF acetal to give the enamine 13, which was condensed with cyanoacetamide in the presence of sodium ethoxide to afford the bicyclic ketone 14. Bromination of 14 followed by cyclization with thiocarbamoyl functions gave 16a-d in a similar fashion described in the synthesis of the thiazolylpyridones (steps 3 through 5). Dehydrogenation of 16a was effected by aeration in the presence of DBU in refluxing ethanol to afford the aromatized derivative 17. Conversion of the cyano groups of compound 16a and 17 into amino group was carried out as described above to give compounds 18 and 19.



1 2 3 4 5a-j

Scheme 1

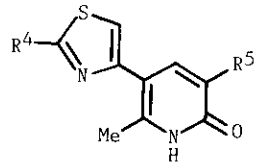


Scheme 2

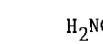
The 5-(2-substituted thiazol-4-yl)-2-pyridones and thiazolo[4,5-f]quinolinones thus prepared were tested for positive inotropic activity (PIA) on the isolated guinea pig papillary muscle, and the effects on heart rate were recorded by using the right atrium.

Table I shows the PIA of the 5-(2-substituted thiazol-4-yl)-2-pyridones 5a-j, 6, 7, 8a-d, 9, 10 and 11. Compounds 5a, 5b, 5i and 7 having a hydrogen, a methyl, an ethoxy and a 2-morpholinoethoxy group, respectively, at the 2-position of the thiazole, and having a cyano group in common at the 3-position of the pyridone were the most active, being as active as milrinone at 10^{-4}M. Reduction of activity was noted when either the alkyl side-chain on the thiazole(compound 5b) was extended to ethyl or the cyano group of 5a was transformed to an amino group. The resulting compounds 5c and 11, and other 2'-substituted derivatives(5e, 5f, 5g, 6, 8b, 8c, 8d and 9) showed weak to intermediate activity, while the remaining compounds showed no significant activity. The PIA of the thiazolo[4,5-f]quinolinone derivatives 16a-d, 17, 18 and 19 are shown in Table II. Compounds 16a(R^6=H, R^7=CN, 4-5 bond=saturated) and 19(R^6=H, R^7=NH_2, 4-5 bond=double) were as active as milrinone at 10^{-4}M. It is interesting to note that the cyano compound 16a was more active than the amino analog 18 in the 4-5 bond saturated series, whereas the activities were reversed, 19(R^7=NH_2) > 17(R^7=CN) when the 4-5 bond was unsaturated. Conpounds 16b, 16c, 17 and 18 exhibited weak to intermediate activity.

Table I. Preliminary Screening of 5-(Thiazol-4-yl)-2-pyridones



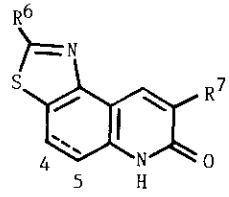
Compound[a]	R^4	R^5	Mp (°C)	Yield (%)	Formula	Analysis(%) Calculated(Found) C	H	N	S	Contractile Force[b]	Heart Rate[b]
5a	H	CN	280-282	40.0	$C_{10}H_7N_3OS$	55.29	3.25	19.34	14.76	+++	+
						(55.15	3.08	19.39	14.83)		
5b	Me	CN	299-302	74.8	$C_{11}H_9N_3OS$	57.13	3.92	18.17	13.86	+++	+
						(57.15	3.88	18.17	13.90)		
5c	Et	CN	252-256	65.8	$C_{12}H_{11}N_3OS$	58.76	4.52	17.13	13.07	++	+
						(58.64	4.39	17.18	13.01)		
5d	Ph	CN	276-280	80.3	$C_{16}H_{11}N_3OS$	65.51	3.78	14.32	10.93	±	-
						(65.27	3.69	14.35	10.98)		
5e		CN	190-194	32.1	$C_{15}H_{16}N_4O_2S \cdot HCl \cdot H_2O$	48.58	5.16	15.10	8.64	+	±
						(48.84	4.87	14.98	8.64)		
5f	H_2N	CN	>300	60.2	$C_{10}H_8N_4OS$	51.71	3.47	24.12	13.81	+	±
						(51.71	3.34	24.05	13.81)		
5g	MeNH	CN	244(decomp)	73.0	$C_{11}H_{10}N_4OS$	53.64	4.09	22.75	13.02	++	+
						(53.57	4.09	22.46	12.64)		
5h	HS	CN	>300	59.9	$C_{10}H_7N_3OS \cdot 0.25MeOH$	47.84	3.13	16.33	24.92	±	-
						(47.84	2.93	16.36	24.83)		
6	MeS	CN	247-252	88.0	$C_{11}H_9N_3OS$	50.17	3.44	15.96	24.35	+	±
						(50.14	3.33	15.84	24.33)		
9	MeSO	CN	247	73.0	$C_{11}H_9N_3O_2S$	47.30	3.25	15.04	22.96	++	+
						(47.14	2.95	14.96	22.87)		

10	$MeSO_2$	CN	>300	84.7	$C_{11}H_9N_3O_3S$	44.73	3.07	14.23	21.71	±	±
						(44.72	2.86	14.15	21.85)		
5i	EtO	CN	244(decomp)	54.9	$C_{12}H_{11}N_3O_2S$	55.16	4.24	16.08	12.27	+++	+
						(54.97	4.10	15.89	12.34)		
7		CN	213-215	84.1	$C_{16}H_{18}N_4OS \cdot HCl$	50.19	5.00	14.63	8.38	+++	+
						(50.12	4.92	14.57	8.26)		
5j	EtO_2C	CN	252-254	68.4	$C_{13}H_{11}N_3O_3S$	53.97	3.83	14.52	11.08	±	±
						(53.67	3.78	14.58	10.87)		
8a	H_2NCO	CN	259	87.6	$C_{11}H_8N_4O_2S \cdot 0.5H_2O$	49.06	3.37	20.81	11.91	±	±
						(50.01	3.28	20.67	11.70)		
8b	$H_2N(CH_2)_2NHCO$	CN	262-263	81.1	$C_{13}H_{13}N_5O_5S \cdot HCl$	45.95	4.15	20.61	9.44	+	-
						(45.94	3.99	20.31	9.29)		
8c	$Me_2N(CH_2)_2NHCO$	CN	252-255	95.2	$C_{15}H_{17}N_5O_2S \cdot HCl \cdot 0.5H_2O$	47.81	5.08	18.58	8.51	+	±
						(47.73	4.85	18.25	8.30)		
8d		CN	182-184	42.2	$C_{17}H_{19}N_5O_3S \cdot 2HCl$	45.75	4.74	15.69	7.18	++	±
						(45.62	4.78	15.74	7.09)		
11	H	NH_2	233	58.0	$C_9H_9N_3OS \cdot 0.25H_2O$	51.05	4.52	19.84	15.14	++	±
						(50.78	4.43	19.87	14.83)		
amrinone										+	±
milrinone										+++	+

[a] All compounds exhibited ir and nmr spectra consistent with the structures.

[b] Percent increase in the contractile force and the heart rate were expressed as scores, respectively : no significant ± ; 25-50% + ; 50-75% ++ ; 75-100% +++.

Table II. Preliminary Screening of Thiazolo[4,5-f]quinolinones



Compound[a]	R^6	R^7	4-5 Bond	Mp (°C)	Yield (%)	Formula	Analysis(%) Calculated (Found) C	H	N	S	Contractile Force[b]	Heart Rate[b]
16a	H	CN	saturated	273-280	49.0	$C_{11}H_7H_3OS$	57.63	3.08	18.33	13.99	+++	+
							(57.38	2.93	18.31	13.63)		
16b	Me	CN	saturated	>300	53.6	$C_{12}H_9N_3OS$	58.17	3.86	16.96	12.94	+	±
							(58.56	3.60	16.97	12.73)		
16c	H_2N	CN	saturated	>300	51.5	$C_{11}H_8N_4OS$	53.11	3.44	22.52	12.89	+	±
							(53.40	3.18	22.27	12.75)		
16d	HS	CN	saturated	288-293	79.0	$C_{11}H_7N_3OS$	48.07	3.11	15.29	23.33	±	-
							(48.10	2.97	15.14	23.10)		
18	H	NH_2	saturated	265-268	25.1	$C_{10}H_9N_3OS$	50.62	4.67	17.71	13.51	++	±
							(50.18	4.27	17.61	13.22)		
17	H	CN	double	270-275	85.4	$C_{11}H_5N_3OS$	58.14	2.22	18.49	14.11	+	±
							(57.96	2.13	18.35	14.09)		
19	H	NH_2	double	245-250	30.8	$C_{10}H_7N_3OS \cdot 0.5H_2O$	53.09	3.56	18.57	14.17	+++	±
							(53.39	3.26	18.63	14.14)		
amrinone											+	±
milrinone											+++	+

[a,b] See footnotes a and b in Table I.

Compounds which showed good activity similar to milrinone were further evaluated to confirm the activity. The results are summarized in Table III. The pyridone derivatives 5i and 7, and the thiazolo[4,5-f]quinolinone derivative 19 were the most active of these analogs with 10^{-6}M levels of ED_{25} values, although somewhat less active than milrinone. Compound 19 having less effect on heart rate gave the greatest HR/FC ratio of the three. Thus, this study clarified that the thiazolylpyridones and the tricyclic analogs showed good cardiotonic activity in guinea pigs.

Table III. Positive Inotropic Activity and Effect on Heart Rate

Compound	Contractile Force ED_{25}(M)[a]	Heart Rate ED_{25}(M)[a]	HR/FC
5a	1.15×10^{-5}	4.52×10^{-5}	3.95
5b	2.99×10^{-5}	1.84×10^{-4}	6.15
5i	3.56×10^{-6}	3.84×10^{-6}	10.79
7	4.24×10^{-6}	1.63×10^{-5}	3.84
16a	2.08×10^{-5}	3.12×10^{-5}	1.50
19	3.70×10^{-6}	1.10×10^{-4}	29.73
amrinone	4.81×10^{-4}	1.77×10^{-3}	3.68
milrinone	1.26×10^{-6}	3.85×10^{-6}	3.0

[a] ED_{25} values were calculated from the linear portion of the dose-response curve for each preparation via least-squares analysis(n=4-9).

EXPERIMENTAL

Melting points were determined by using a Mitamura Riken micromelting point aparatus and are uncorrected. Ir spectra were recorded with a JASCO A-102 spectrophotometer. Nmr spectra were recorded with a Hitachi R-40 spectrometer with tetramethylsilane as an internal standard.

5-ACETYL-3-CYANO-6-METHYL-2-PYRIDONE (3)

A mixture of acetylacetone (20.5 ml, 0.2 mol) and DMF dimethylacetal (53.1 ml, 0.4 mol) in THF (100 ml) was stirred for 3 h at room temperature. The solvent was removed in vacuo to give an oily residue (crude 2), which was added to a solution of sodium ethoxide prepared from 6.9 g (0.3 g atom) of sodium metal, and cyanoacetamide (16.8 g, 0.2 mol) in absolute EtOH (300 ml). The mixture was refluxed for 1 h with stirring, and then cooled. The resulting crystalline

precipitates (sodium salt of 3) were collected by filtration and dissolved in water (500 ml). The solution was adjusted to pH 5.5 with 3N HCl. The resulting precipitates were collected and crystallized from DMF-MeOH to give 3 (30.3 g, 86%), mp 232-4°C, lit.[4] 231°C(decomp). Ir (KBr) : 2220 (C≡N), 1680 (C=O), 1650 cm^{-1}. Nmr (DMSO-d_6) δ : 2.48 (3H, s, CH_3), 2.58 (3H, s, CH_3), 8.62 (1H, s, pyridone-H), 13.05 (1H, br, pyridone-NH).

5-BROMOACETYL-3-CYANO-6-METHYL-2-PYRIDONE (4)

To a solution of 3 (29.6 g, 0.168 mol) in AcOH (900 ml) was added a few drops of bromine at 60°C. When the colour of bromine disappeared, the solution was cooled to 20°C. To the stirred solution was added dropwise a solution of bromine (8.7 ml, 0.168 mol) in AcOH (50 ml) over 0.5 h at 20-25°C, and then stirred for an additional 1 h at the same temperature. The precipitates were collected by filtration, thoroughly washed with ether, and recrystallized from DMF-MeOH to give 4 (37 g, 86.4%), mp 224°C (decomp). Ir (KBr) : 2220 (C≡N), 1700 (C=O), 1660 cm^{-1}. Nmr (DMSO-d_6)δ: 2.60 (3H, s, CH_3), 4.75 (2H, s, CH_2Br), 8.70 (1H, s, pyridone-H), 13.20 (1H, br, pyridone-NH). Anal. Calcd for $C_9H_7N_2O_2Br$: C, 42.38 ; H, 2.77 ; N, 10.98. Found : C, 42.66 ; H, 2.59 ; N, 10.84.

3-CYANO-6-METHYL-5-(THIAZOL-4-YL)-2-PYRIDONE (5a)

To a solution of 4 (2.55 g, 10 mmol) in DMF (30 ml) was added thioformamide (0.733 g, 12 mmol) and the mixture was left overnight at room temperature. The mixture was poured into water (300 ml) and adjusted to pH 5 with aqueous sodium bicarbonate. The resulting precipitates were collected by filtration and crystallized from DMF-MeOH to give 5a (0.868 g, 40%), mp 280-282°C. Ir (KBr) : 2220 (C≡N), 1655 cm^{-1}. Nmr (DMSO-d_6) δ : 2.52 (3H, s, CH_3), 7.83 (1H, d, J=2 Hz, thiazole C5-H), 8.35 (1H, s, pyridone-H), 9.16 (1H, d, J=2 Hz, thiazole C2-H), 12.80 (1H, br, pyridone-NH). Compound 5b-5j were prepared in a similar manner. Compound 5e were crystallized from MeOH as hydrochloride.

3-CYANO-6-METHYL-5-(2-METHYLTHIOTHIAZOL-4-YL)-2-PYRIDONE (6)

A mixture of 5h (1 g, 4 mmol), K_2CO_3 (0.277 g, 2 mmol) and MeI (0.57 g, 4 mmol) in DMF (20 ml) was stirred for 2.5 h at room temperature and then poured into water (100 ml). The resulting precipitates were collected, and crystallized from DMF-MeOH to give 6 (0.823 g, 78.1%), mp 247-252°C. Ir (KBr) : 2220 (C≡N), 1665 cm^{-1}. Nmr (DMSO-d_6+NaOD)δ : 2.46 (3H, s, CH_3), 2.73 (3H, s, CH_3S), 7.56 (1H, s, thiazole-H), 8.14 (1H, s, pyridone-H).

3-CYANO-6-METHYL-5-(2-N-MORPHOLINOETHOXYTHIAZOL-4-YL)-2-PYRIDONE (7)

A mixture of 10 (1 g, 3.39 mmol), 2-N-morpholinoethanol (0.62 ml, 5.07 mmol) and 50% NaH dispersed in mineral oil (0.39 g, 8.13 mmol) in DMF (10 ml) was stirred for 3 h at 50-60°C. The mixture was poured into water (60 ml) and adjusted to pH 7.5 with 6N HCl. The resulting precipitates were collected by filtration, and suspended in water (40 ml). The mixture was adjusted to pH 2.0 with 2N HCl, and then evaporated. The residue was crystallized from water-acetone to give 7·HCl (1.09 g, 84.1%), mp 213-215°C. Ir (KBr) : 2220 (C≡N), 1665 cm^{-1}. Nmr (DMSO-d_6) δ : 2.55 (3H, s, CH_3), 3.00-4.00 (10H , m, morpholino CH_2 and NCH_2), 4.92 (2H, m, CH_2O), 7.22 (1H, s, thiazole-H), 8.33 (1H, s, pyridone-H), 11.04 (1H, br, HCl), 11.84 (1H, br, pyridone-NH).

3-CYANO-5-[2-(2-N,N-DIMETHYLAMINOETHYLAMINOCARBONYL)THIAZOL-4-YL]-6-METHYL-2-PYRIDONE (8c)

A mixture of 5j (2 g, 6.9 mmol) and N,N-dimethylethylenediamine (3.04 ml, 27.6 mmol) in EtOH (150 ml) was refluxed for 18 h with stirring. The solvent was removed in vacuo, and to the residue was added acetone (50 ml). The resulting precipitates were collected by filtration, and dissolved in water (50 ml). The solution was adjusted to pH 2 with 2N HCl, and evaporated in vacuo to give a residue, which was crystallized from MeOH-acetone to afford 8c·HCl (2.42 g, 95.2%), mp 252-255°C. Ir (KBr) : 2225 (C≡N), 1650 cm^{-1}. Nmr (DMSO-d_6) δ : 2.63 (3H, s, CH_3), 2.87 (6H, s, Me_2N), 3.35 (2H, m, CH_2), 3.72 (2H, m, CH_2), 8.13 (1H, s, thiazole-H), 8.57 (1H, s, pyridone-H), 9.21 (1H, t, J=4.5 Hz, NHCO), 11.06 (1H, br, HCl), 13.02 (1H, br, pyridone-NH). The 2'-amide derivatives 8a-b and 8d were prepared from 5j in a similar fashion.

3-CYANO-6-METHYL-5-(2-METHYLSULFONYLTHIAZOL-4-YL)-2-PYRIDONE (10)

A mixture of 6 (0.7 g, 2.66 mmol) and 30% H_2O_2 (1 ml, 10 mmol) in AcOH (20 ml) was stirred overnight at 50-60°C. The solvent was removed in vacuo to give a residue, which was crystallized from aqueous MeOH to afford 10 (0.665 g, 84.7%), mp >300°C. Ir (KBr) : 2220 (C≡N), 1640 cm^{-1}. Nmr (DMSO-d_6) δ : 2.52 (3H, s, CH_3), 3.52 (3H, s, CH_3SO_2), 8.31 (1H, s, thiazole-H), 8.44 (1H, s, pyridone-H), 12.95 (1H, br, pyridone-H).

Compound 9 was prepared from 6 by the same procedure except for with the use of one equimolar H_2O_2.

3-AMINO-6-METHYL-5-(THIAZOL-4-YL)-2-PYRIDONE (11)

A solution of 5a (3 g, 13.8 mmol) in concentrated HCl (60 ml) was heated overnight at 40-60°C, and then diluted with water (300 ml). The solution was adjusted to pH 7 with aqueous sodium bicarbonate, and the resulting precipitates were collected by filtration to give 3-carbamoyl-6-methyl-

5-(thiazol-4-yl)-2-pyridone (2.52 g, 77.6%), mp >300°C. Ir (KBr) : 3300, 1650 cm^{-1}. Nmr (DMSO-d_6+NaOD) δ : 2.40 (3H, s, CH_3), 7.50 (1H, s, thiazole C5-H), 8.30 (1H, s, pyridone-H), 9.10 (1H, s, thiazole C2-H). To a sodium hypobromite solution prepared from 2N NaOH (20 ml, 40 mmol) and bromine (0.4 ml, 7.65 mmol) under cooling was added 3-carbamoyl-6-methyl-5-(thiazol-4-yl)-2-pyridone (1.5 g, 6.4 mmol) ,and the mixture was heated for 3 h at 70°C with stirring. The mixture was adjusted to pH 7 with 6N HCl. The resulting precipitates were collected by filtration, and crystallized from MeOH to give 11(0.43 g, 32.5%), mp 232°C. Ir (KBr) : 3380 (NH_2), 1630, 1600 cm^{-1}. Nmr (DMSO-d_6) δ : 2.32 (3H, s, CH_3), 4.93 (2H, s, NH_2), 6.90 (1H, s, thiazole C4-H), 7.57(1H, s,pyridone-H), 9.13 (1H, s, thiazole C2-H), 11.70 (1H, br, pyridone-NH).

3-CYANO-5-OXO-5,6,7,8-TETRAHYDRO-2(1H)-QUINOLINONE (14)

Cyclohexane-1,3-dione (22.4 g) was reacted via the enamine 13 with cyanoacetamide in a similar manner described for 3 to yield 14 (26.7 g, 70.9%), mp 269-270°C. Ir (KBr) : 2220 (C≡N), 1680, 1650 cm^{-1}. Nmr (DMSO-d_6) δ : 2.09 (2H, m, C7-H), 2.52 (2H, t, J=7 Hz, C6 or C8-H), 2.93 (2H, t, J=7 Hz, C6 or C8-H), 8.83 (1H, s, C4-H), 11.15 (1H, br, NH).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82 ; H, 4.29 ; N, 14.89. Found : C, 63.60 ; H, 4.25 ; N, 14.81.

6-BROMO-3-CYANO-5-OXO-5,6,7,8-TETRAHYDRO-2(1H)-QUINOLINONE (15)

Bromination of 14 (26.5 g) as described for 4 gave 15 (35.8 g, 85.2%), mp 213-214°C. Ir (KBr) : 2220 (C≡N), 1650 cm^{-1}. Nmr (DMSO-d_6) δ : 2.50 (2H, m, C7-H), 3.00 (2H, t, J=7 Hz, C8-H), 4.95 (1H, t, J=5 Hz, C6-H), 8.45 (1H, s, C4-H), 13.15 (1H, br, NH). Anal. Calcd for $C_{10}H_7N_2O_2Br$: C, 44.97 ; H, 2.64 ; N, 10.49. Found : C, 45.18 ; H, 2.47 ; N, 10.45.

8-CYANO-7-OXO-4,5,6,7-TETRAHYDROTHIAZOLO[4,5-f]QUINOLINE (16a)

Compound 15 (20 g, 74.9 mmol) was reacted with thioformamide (5.49 g, 89.9 mmol) as described for 5a to give 16a (8.4 g, 49%), mp 273-280°C. Ir (KBr) : 2210 (C≡N), 1620 cm^{-1}. Nmr (DMSO-d_6) δ : 3.11 (4H, s, CH_2CH_2), 8.33 (1H, s, C9-H), 8.99 (1H, s, C2-H), 13.10 (1H, br, NH). Compound 16b-d were prepared by the same procedure.

8-CYANO-7-OXO-6,7-DIHYDROTHIAZOLO[4,5-f]QUINOLINE (17)

A mixture of 16a (0.5 g, 2.18 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.497 g, 3.27 mmol) in EtOH (50 ml) was refluxed for 2 h, and the solvent was removed in vacuo. The residue

was crystallized from DMF-MeOH to give 17 (0.363 g, 73.7%), mp 270-275°C. Ir (KBr) : 2230 (C≡N), 1665 cm^{-1}. Nmr (DMSO-d_6) δ : 7.46 (1H, d, J=9 Hz, C4 or C5-H), 8.42 (1H, d, J=9 Hz, C4 or C5-H), 9.14 (1H, s, C9-H), 9.60 (1H, s, C2-H).

8-AMINO-7-OXO-4,5,6,7-TETRAHYDROTHIAZOLO[4,5-f]QUINOLINE (18)

The preparation of this compound was carried out as described for 11. Acid hydrolysis of compound 16a (3 g) gave the carbamoyl derivative (3.03 g, 93.9%), mp >250°C. Ir (KBr) : 3360, 1660 cm^{-1}. Nmr (DMSO-d_6) δ : 3.13 (4H, s, CH_2CH_2), 7.50 (2H, br, NH_2), 8.75 (1H, s, C9-H), 9.00 (1H, s, C2-H), 12.96 (1H, br, NH). The Hofmann reaction of the carbamoyl derivative (2 g) gave 18 (0.53 g, 29.8%), mp 265-268°C. Ir (KBr) : 1640, 1590 cm^{-1}. Nmr (DMSO-d_6) δ : 2.65-3.20 (4H, CH_2CH_2), 5.00 (2H, br, NH_2), 7.06 (1H, s, C9-H), 8.88 (1H, s, C2-H), 11.80 (1H, br, NH).

8-AMINO-7-OXO-6,7-DIHYDROTHIAZOLO[4,5-f]QUINOLINE (19)

This compound was prepared in the same way as described for 11. Acid hydrolysis of compound 17 (8.6 g) gave the carbamoyl derivative (7.4 g, 79.6%), mp >300°C. Ir (KBr) : 3420, 1625 cm^{-1}. Nmr (DMSO-d_6) δ : 7.53 and 8.39 (1H each, d, J=7.5 Hz, C4 and C5-H), 9.47 (1H, s, C9-H). The Hofmann reaction of the carbamoyl derivative (7.4 g) gave 19 (2.96 g, 45.2%), mp 245-250°C. Ir (KBr) : 3400, 1650 cm^{-1}. Nmr (DMSO-d_6) δ : 5.77 (2H, br, NH_2), 7.42 and 7.88 (1H each, d, J=9 Hz, C4 and C5-H), 7.63 (1H, s, C9-H), 9.40 (1H, s, C2-H), 12.25 (1H, br, NH).

PHARMACOLOGICAL METHODS

Hartley guinea pigs of either sex, weighing 300-500 g, were stunned with a blow on the head and exsanguinatd. The chest was opened rapidly, the heart was excised and rinsed with a modified Tyrodes solution, and the right atrium and the right ventricular papillary muscle were excised. The atrium and papillary muscle were mounted vertically in respective two-chambered vessels with an interal circulation of the the modified Tyrodes solution saturated with a gas mixture of 95% O_2 and 5% CO_2, and maintained at 30±0.3°C. The solution has the following composition (in mM): NaCl, 136.9 ; KCl, 5.4 ; NaH_2PO_4 H_2O, 0.4 ; $CaCl_2$ $2H_2O$, 2.0 ; $MgCl_2$ $6H_2O$, 1.0 ; $NaHCO_3$, 11.9 ; glucose, 5.5.

The atrium was allowed to beat spontaneously, and the papillary muscle was stimulated electrically at a rate of 1 Hz by a suprathreshold (1.5 threshold rectangular pulse 0.005 see in duration). The contractile force of the muscle was recorded isometrically by means of strain gauge transducer (Nihonkoden TB-612T) connected with an amplifer (Nihonkoden AP-621G), and the beats of the atrium

were recorded by a recticorder (Nihonkoden WT-645G). Drugs were used either as solutions in distilled water or suspensions in 0.5% CMC.

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